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Integrating health-related quality of life in neuro-oncology

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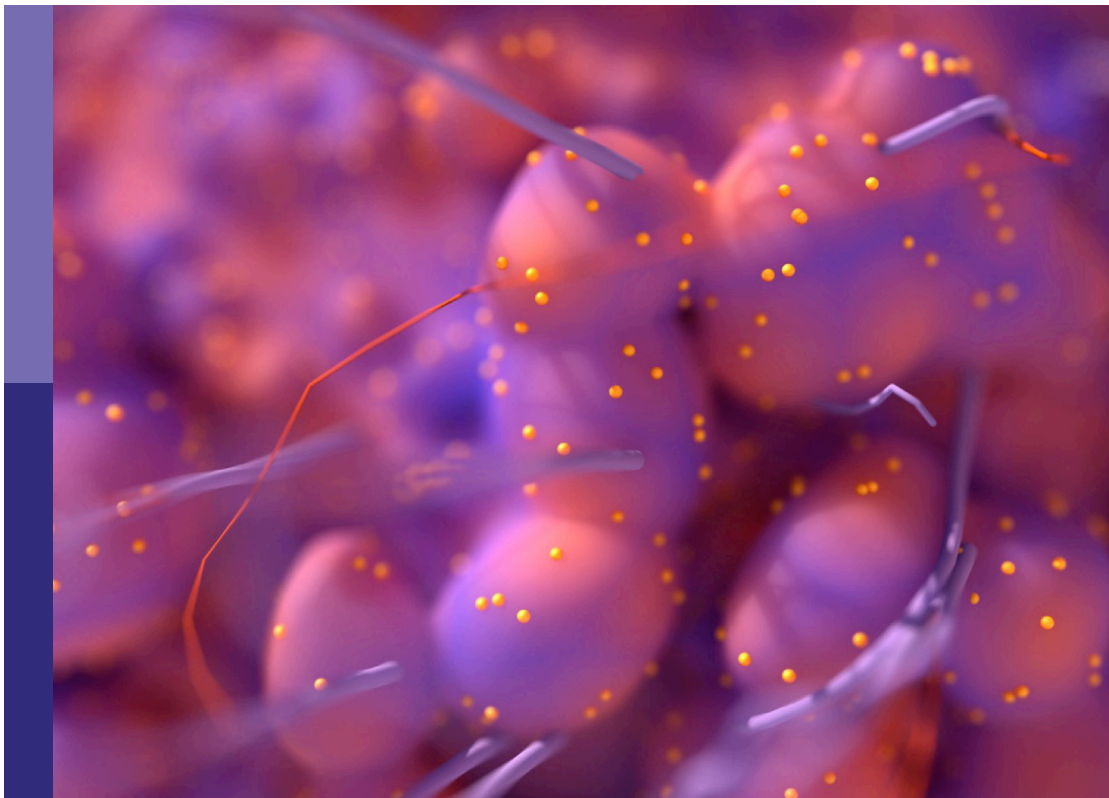

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Integrating health-related quality of life in neuro-oncology

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Editorial: Integrating health-related quality of life in neuro-oncology

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HRQoL, mental health, distress, brain tumor, glioma, pediatric tumors, peripheral nerve tumor

Editorial on the Research Topic
Integrating health-related quality of life in neuro-oncology

This present Research Topic includes eleven articles contributed by 70 authors. Our aim was to give an up-to-date overview of health-related quality of life (HRQoL) in adult and pediatric patients spanning diverse neuro-oncological diseases. The HRQoL-related articles of the Research Topic provide a multifaceted overview of HRQoL-related topics, ranging from research on patients with brain metastases and gliomas to peripheral nerve tumors. Here, we summarize a selection of these articles.

The study "Psycho-oncological burden in patients with brain metastases undergoing neurological surgery" by Araceli et al. demonstrates the high prevalence of psycho-oncological distress among patients with surgically treated brain metastases (BM). The use of the Hornheider screening instrument (HSI) and Distress Thermometer (DT) allowed for the identification of a significant percentage of patients needing immediate intervention. The study further detected independent risk factors for high psycho-oncological burden, such as synchronous BM, female gender, and low KPS. This study emphasizes the need for routine psycho-oncological screening and interventions and the importance of addressing these psychological needs to improve overall BM patient care. The identification of specific risk factors allows for more targeted screenings and interventions.

In line with this, Staub-Bartelt et al., in their study "Influence of neuropathological diagnosis on psychooncological distress in neurooncological patients - a retrospective cross-sectional analysis," address the psycho-oncological impact of glioblastoma (GB) as a life-changing disease. Although overall distress levels were similar between GB and grade 2 glioma patients, GB patients experienced significantly higher levels of depression. This highlights that even with similar overall distress, the ability to cope with specific mental health challenges depends on the type of tumor diagnosis. Using validated and robust scales (Hospital Anxiety and Depression Scale, Karnofsky Performance Score), the authors showed not only higher depression but also significantly greater physical impairment in GB patients. This study emphasizes the importance of early screening for depression and

the need for targeted interventions tailored to the specific mental health needs of GB patients, in the context of comprehensive care beyond mere tumor treatment.

The study "Sexual life in adults treated for brain tumors: a retrospective study" by Leonetti et al. addresses a previously largely neglected aspect of HRQoL: While objectifiable sexual dysfunction is relatively uncommon, a substantial portion of patients experience a subjective decline in sexual well-being, often linked to relationship changes and treatment side effects. Based on its considerable impact on HRQoL, this study advocates more comprehensive HRQoL assessments and suggests the development of appropriate interventions to improve patients' sexual well-being.

With their study on the "Preoperative subjective impairments in language and memory in brain tumor patients", Rybka et al. provide important insights into the impact of cognitive difficulties on patients' daily lives and emphasizes the need for assessments measures of cognitive function.

Duffau extend the field of attention towards creative functions, presenting an illustrative case of a drastic and largely inconscient change of creative behavior after resection of a right frontal low grade oligodendroglioma, titled "When art is faced with brain surgery: acute change in creative style in a painter after glioma resection".

Especially the last-mentioned studies highlight the trend towards a progressively more comprehensive view on determining the functional limits of resection, most importantly in low grade glioma patients. This paradigm change might prove at least similarly meaningful in pediatric populations which suffer heavily from long-term treatment effects on quality of life, as Joh-Carnella et al. impressively illustrate with their case report titled "Pediatric low-grade gliomas: a fine balance between treatment options, timing of therapy, symptom management and quality of life". The case unravels the complex challenge of managing low grade gliomas in children, highlighting the need for individualized treatment strategies and comprehensive, multidisciplinary care to balance disease control against the risk of long-term toxicity and, hence, symptom burden. Further research is needed to improve the prediction of treatment-related long-term effects and to optimize treatment strategies with regard to patient well-being in pediatric populations.

Sperl at al. systematic review shows that skull base tumor surgery temporarily reduces quality of life (QoL), which usually recovers. QoL is significantly affected by patient age, gender, tumor characteristics, surgical approach, resection extent, and pre-operative status. Radiotherapy and recurrent surgeries worsen QoL. Personalized care and early psychological intervention are crucial for optimal outcomes.

Savic et al. highlight the importance of individualized treatment for patients with peripheral nerve tumors (PNTs) due to their varied presentations. Grübel et al.'s large-scale, multicenter study ("Health-related quality of life in patients with peripheral nerve tumors: results from the German multicentric Peripheral Nerve Tumor Registry") demonstrates that early surgical intervention at specialized centers significantly improves health-related quality of life (HRQoL). This improvement is seen across various subdomains, including pain relief, as measured by the EQ-5D-5L and EQ-VAS validated instruments. Therefore, early surgical treatment of PNTs is crucial for pain control and optimizing HRQoL.

Focusing more specifically on neurofibromatosis 1 (NF1), the study "Quality of life of patients with neurofibromatosis 1-Physical disability does not necessarily result in poor mental health" by Bäzner et al. suggests that symptomatic management should be considered even for severely affected patients to enhance their HRQoL.

In conclusion, the studies compiled in this Research Topic converge on several key topics: the importance of HRQoL assessments and interventions in neuro-oncology practice and science; the need for multidisciplinary approaches; the value of early interventions; and the role of specialized centers in improving outcomes. While each study focuses on a specific aspect, the overarching message is the crucial need to consider the overall patient integrity, addressing physical, psychological and social well-being alongside tumor control.

Author contributions

MP: Writing – original draft, Writing – review & editing. MM-J: Writing – review & editing. CJ: Writing – original draft. PH: Writing – review & editing. CW: Writing – original draft, Writing – review & editing.

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The author(s) declare that no Generative AI was used in the creation of this manuscript.

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Abbreviations: HRQoL, Health-Related Quality of Life; GMB, Glioblastoma; HADS, Hospital Anxiety and Depression Scale; KPS, Karnofsky Performance Score; QoL, Quality of Life; PNT, Peripheral Nerve Tumors; EQ-5D-5L, European Quality of Life- 5 Dimensions- 5 Level; EQ-VAS, European Quality of Life- Visual Analogue Scale; BM, Brain metastases; HSI, Hornheider screening instrument; DT, Distress Thermometer; NF, Neurofibromatosis 1.

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Case report: when art is faced with brain surgery: acute change in creative style in a painter after glioma resection

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Background: Strong interactions between art and health are well-known. While advances in brain surgery resulted in an improved preservation of sensorimotor, visuospatial, language and cognitive functions, creative abilities received less attention. However, creativity may represent a critical issue to resume an optimal quality of life, especially in artists. Here, a unique case of sudden change in creative style in a painter who underwent glioma resection is described. This prompts to explore further creative thinking and its clinical implications in routine practice.

Methods: A 36-year-old right-handed woman experienced inaugural seizures, allowing the discovery of a right frontal lesion. The patient was a professional painter and did not complain about any decline in her creativity. The preoperative neurological examination was normal.

Results: Surgery was achieved with a maximal tumor resection through a frontal lobectomy. A WHO grade II oligodendroglioma was diagnosed. A regular surveillance was performed without adjuvant oncological treatment. The patient did not exhibit postoperative functional deterioration and she returned to normal activities including painting during 15 years. Remarkably, even though her creative activity was judged by the patient herself to be rich and satisfying, her style drastically changed from surrealism and mysticism to cubism whereas she was not able to explain why.

Conclusion: This is the first report of acute modification of the painting style following frontal lobectomy for a low-grade glioma, supporting that brain resective surgery may impact creativity. While neglected for many decades, this complex human ability should be evaluated more regularly in neurosurgical practice, particularly in artists.

KEYWORDS

art, brain surgery, creativity, glioma, case report

Introduction

Strong links between art and medicine are well-known, as evidenced by a recent WHO review which supported a critical role of the arts in the prevention of illness, promotion of good health, and treatment of acute and chronic diseases arising across the lifespan (1). The value of artistic creativity has especially been observed in brain-damaged patients who have benefited from art-therapy in the context of neurorehabilitation (2). It also seems that cerebral injury, in turn, might have an influence on patient's creative abilities since many reports have described changes in how they approach and produce art (3). Nonetheless, even though several observations have been published for various brain disorders, such as degenerative diseases (Alzheimer's and Parkinson's disease, frontotemporal and Lewy body dementia, or corticobasal degeneration) or stroke, there is currently no report of art-related change after brain resective surgery.

Here, a unique case of acute modification of the creative style in a painter who underwent glioma removal is described. This prompts to explore further creative thinking and its clinical implications in routine practice.

Case report

A 36-year-old right-handed woman with no previous medical history experienced inaugural seizures, allowing the discovery of a right frontal lesion. The patient was a professional painter and did not subjectively complain about any decline in her creativity. The preoperative neurological examination was normal. The tumor was voluminous (105mL) and involved the frontal structures, including the medial prefrontal cortex (MPFC), the anterior cingulate cortex (ACC) and the corpus callosum (Figure 1A).

Surgery was achieved with a maximal resection of the tumor through a right frontal lobectomy (Figure 1B). A WHO grade II oligodendroglioma was diagnosed. A regular surveillance was performed without administration of adjuvant oncological treatment. The patient did not exhibit postoperative functional deterioration and she returned to normal activities including painting for 15 years. Surprisingly, even though her creative activity remained rich and was judged by the patient herself to be satisfying, her style drastically changed - whereas she was not able to explain why - from "surrealism and mysticism" (Figure 1C) to "cubism" (as defined by the artist herself) (Figure 1D).

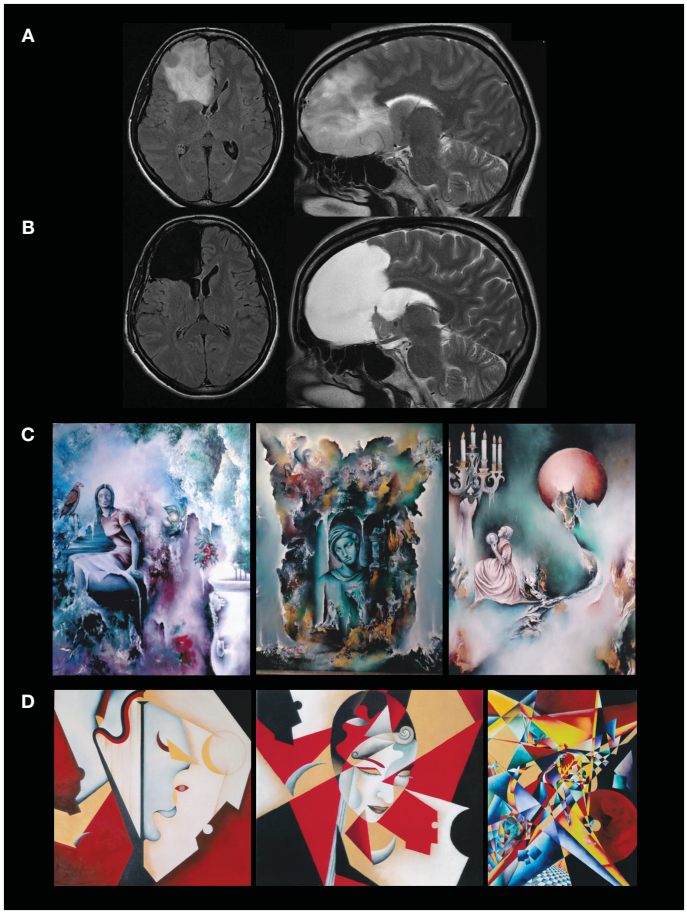

FIGURE 1
(A) preoperative axial FLAIR-weighted MRI (left) and sagittal T2-weighted MRI (right) showing a right frontal hypersignal typical for a low-grade glioma. **(B)** postoperative axial FLAIR-weighted MRI (left) and sagittal T2-weighted MRI (right) showing a right frontal lobectomy involving the DLPFC, ACC and MPFC, with a complete resection of the tumor. **(C)** Three works from her preoperative period. **(D)** Postoperative period illustrating the change in content and technique.

The study was approved by an independent institutional review board of the ethical comity of research from the French National College of Neurosurgery (N°00011687–2024/07). Works illustrating the different periods of the patient's creativity are reproduced with authorization.

Discussion

Although advances in brain surgery resulted in an improved preservation of sensorimotor, visuospatial, language and higher-order cognitive functions (4), creative abilities have received less attention. However, creativity may represent a critical issue to resume an optimal quality of life, especially in artists. Here, this is the first report of sudden change in artistic style in a painter following large resection of a right frontal glioma, even if the patient was still able to be creative.

Recent developments in neurosciences have led to preliminary hypothesis regarding the neural substrates underpinning artistic activities. From a biochemical perspective, the influence of dopamine agonists in creativity has been evoked. Lhommée et al. (5) described the case of a painter with a Parkinson's disease who experienced a change in content and technique of painting before and after deep-brain stimulation of the sub-thalamic nucleus. However, due to the role of prefrontal cortex for creativity, the authors did not rule out that the bilateral insertion into frontal lobe of microelectrodes and deep brain stimulation leads had an impact on painting. Indeed, from a connectome perspective, creative cognition has been correlated not only with cortical areas such as the dorsolateral prefrontal cortex (DLPFC) and the ACC, but also with the dynamic interaction across large-scale neural circuits (6, 7). First, the default-mode network (DMN) which mainly consists of the MPFC, posterior cingulate cortex, precuneus and temporoparietal junction, is involved in elaborative processing and self-generated thought, including mind-wandering, mental simulation, social cognition, autobiographical retrieval, and episodic future thinking – as supported by functional imaging (8). Interestingly, a recent series using stereo-electroencephalography in epilepsy patients showed that direct cortical stimulation at the level of several DMN hubs induced a decrease in creative thinking (9). Second, the executive fronto-parietal network (FPN) is also implied in creative cognition (6, 7). This control network is composed of lateral prefrontal (including DLPFC and ACC) as well as anterior inferior parietal regions, and its activity is correlated with cognitive processes which need externally-directed attention, working memory and task-set switching (10). In this integrative framework, an increased interplay between DMN and FPN has been observed during artistic performances, especially visual art (11). Moreover, the salience network which includes anterior insula and cingulate, seems to play an active role in such a DMN/FPN coupling critical for idea generation (6–8).

Whereas art-making changes have been already observed in the event of progressive neurodegeneration, this has not previously been described after brain surgical lobectomy, especially for visual art. In the case reported here, even though functional neuroimaging has not been achieved, one can hypothesize that the massive right frontal resection which involved the DLPFC, ACC and MPFC, thus with a disconnection of a part of the DMN and FPN, might have impacted the artistic style by modulating the balance across brain systems underlying creative thinking. In other words, artistic creativity should be conceived as a multidimensional entity relying on dynamics across neural circuits, in the framework of a meta-networking organization of cerebral processing, i.e., with perpetual succession of new equilibrium states within network of networks (12). By applying this concept to artists who should undergo removal for a brain glioma, it has recently been proposed to achieve awake surgery with intraoperative direct electrostimulation (DES) mapping while the patients are performing on-line multi-tasking throughout the resection into the operating room (13). This monitoring of several functional systems (e.g., sensorimotor, language, cognitive, emotional) in real-time, as a mirror of the meta-network, resulted in a tailored connectome-based resection which allowed professional musicians to resume their artistic activities following tumor resection: indeed, by preserving crucial networks subserving musical skills, learning and creativity, patients were able to not only to play music again but also to compose new pieces after brain surgery (14). One step forward, Shofty et al. (15) have suggested to use DES in awake patients performing a test of creative thinking (alternate-uses-task). They observed that stimulation at the DMN hubs elicited a reduction of creative fluency, supporting that the DMN is causally linked to creativity. Therefore, DES mapping could be helpful to preserve networks involved in creative cognition during tumor resection, especially in artists.

In summary, creativity is a complex ability mediated by integrated cognitive systems which should be conceived in a multi-demanding, delocalized and constantly-in-motion networking processing. This better understanding of the neurobiology of creative thinking may have important clinical applications, notably for brain surgery. Thus, while neglected for a long time, this unique human ability should be evaluated more regularly in routine practice, particularly in artists.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Institutional review board of the ethical comity of research from the French National College of Neurosurgery (N°00011687–2024/07). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the

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Author contributions

HD: Conceptualization, Data curation, Investigation, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing.

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Health-related quality of life in patients with peripheral nerve tumors: results from the German multicentric Peripheral Nerve Tumor Registry

Nadja Grübel[1]*, Gregor Antoniadis[1], Uerschels AK[2], Benjamin Mayer[3], Ralph König[1], Christian Rainer Wirtz[1], Andrej Pala[1], Nora F. Dengler[4] and Maria Teresa Pedro[1] on behalf of the Peripheral Nervetumor Study Group

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Objective: Peripheral nerve tumors (PNTs) are rare diseases. So far, no multicenter data on diagnostics, the efficacy of treatment, long-term outcomes, and health-related quality of life (HRQoL) exist. The establishment of the Peripheral Nerve Tumor Registry (PNTR) in 2015 allows for the systematic analysis of patients with tumors associated with peripheral nerves. The present study aims to investigate the impact of PNT on an individual's HRQoL and the effect of surgery.

Methods: HRQoL was pre- and postoperatively assessed by the Euro-Qol-5D-5L (EQ-5D-5L) and Euro-Qol visual analog scale (EQ-VAS) survey in the retrospective and prospective study arm in three active participating study centers. An index was calculated based on the EQ-5D-5L for the quantification of health state (0: worst possible state of health, 1: best possible state of health). The EQ-VAS ranges from 0% (worst imaginable health status) to 100% (best possible health status). Patient characteristics (age, sex), as well as disease (histopathological entity) and treatment (pre- and postoperative symptoms, type of treatment)-specific data, were analyzed.

Results: Data from 171 patients from three high-volume centers were included, with schwannoma (70.8%, n = 121) and neurofibroma (15.8%, n = 27) being the most prevalent histopathological diagnoses. Both the median health index value (preoperative: 0.887, n = 167; postoperative: 0.910, n = 166) and the median EQ-VAS (preoperative: 75%, n = 167; postoperative: 85%, n = 166) of the entire cohort regarding all histopathological diagnosis improved significantly after surgical therapy (p < 0.001). Preoperatively, 12.3% (n = 21) reached the highest index score of 1.0 in EQ-5D-5L and 100% in the EQ-VAS score in 5.3% (n = 9) of all patients. Postoperatively, the highest index score of 1.0 and 100% in the EQ-VAS score increased significantly and were achieved in 33.3% (n = 57) and 11.1% (n = 19) of the patients, respectively (p < 0.001).

Conclusion: For the first time, our study presents multicenter data on life quality and the effect of surgery in primarily benign peripheral nerve tumors. Early surgery at a specialized center could improve neurological outcomes and, in conclusion, better QoL. In summary, surgical therapy significantly improved the entire cohort's QoL, VAS, and analgesia.

KEYWORDS

peripheral nerve tumor, life quality, pain, malignant peripheral nerve tumor, neurofibromatosis

Introduction

Overall, peripheral nerve tumors (PNTs) are rare diseases, occurring frequently in the extremities, torso, or neck (1–3). The affected patients usually complain of pain, muscle weakness, or sensory deficits. Tumor size and the exact entity of PNT can vary substantially, leading to a large spectrum of therapeutic pathways, outcomes, and prognoses. Right from the start of treatment, the main challenge is to choose between open biopsy, surgical resection, or conservative management (3). To date, clinical trial evidence with robust epidemiological and clinical information is limited mainly to single-center results regarding schwannoma and neurofibroma, most frequent among PNTs and benign tumors (4). Other rare entities, such as perineurioma, amyloidoma, lipoma, desmoid, lymphoma, and malignant peripheral nerve sheath tumors (MPNSTs), are scarcely described (5, 6). No studies on life quality in patients with PNT have been conducted to date.

Quality of life is a complex concept combining the fields of medicine and public health to find a combined endpoint concerning diagnostic modalities, types of therapy, and life quality (7). Furthermore, the World Health Organization (WHO) described life quality as "An individual's perception of their position in life in the context of the culture in which they live and about their goals, expectations, standards, and concerns" (8). According to the revised version of the "Declaration of Geneva" in 2017, it is within the responsibility of all doctors to restore health and not impair the overall well-being of patients and to implement health aspects to treatment and decision-making in everyday clinical practice (9).

Health-related quality of life is the subject of medical care and represents only a small but important part of overall quality of life. For example, HRQoL is essential for medical decision-making and predicts treatment success and overall survival (7).

This study aims to evaluate HRQoL in patients with tumors associated with the peripheral nerves and the effect of surgical therapy on these patients and their life quality.

Methods

Study design—Peripheral Nerve Tumor Registry

The establishment of the multicentric Peripheral Nerve Tumor Registry (PNTR) in 2015 in Germany allows for the systematic analysis of patients with benign, malignant, and other rare tumor entities associated with the peripheral nerves. So far, no multicentric data on peripheral nerve tumors exist in Europe. The PNTR was divided into a retrospective (2015–2016) and prospective (since 2017) study arm. Patient characteristics (age, sex) as well as disease (affected nerve, tumor location, histopathology), surgical treatment (type of treatment, pre- and postoperative symptoms), radiological imaging, diagnosis of neurofibromatosis (NF), data on health-related quality of life (HRQoL), return to work, and long-term follow-up data were analyzed. The long-term goal is to create uniform treatment recommendations (10).

This substudy of the PNTR contains a partially retrospective and prospective analysis of HRQoL in 171 patients with benign, malignant, and rare peripheral nerve tumors that were surgically treated in either the Department for Neurosurgery in Günzburg, University Hospital Ulm; the Department for Neurosurgery in Berlin, Charité University Hospital; or the Department for Neurosurgery in Essen, University Hospital, which were treated between January 2015 and January 2023. All patients gave written permission. This study was approved by our local ethics committees in Ulm (Nr. 249/17) and Berlin (EA4/058/17) and is registered with the German Trials Registry (www.drks.de) (10).

Inclusion and exclusion criteria

All patients who were diagnosed with a tumor in association with a peripheral nerve and surgically treated in one of the high-volume recruiting study centers were enrolled.

Abbreviations: HRQoL, health-related quality of life; EQ-VAS, Euro-Qol visual analog scale; PNTs, peripheral nerve tumors; PNTR, Peripheral Nerve Tumor Registry; MPNST, malignant peripheral nerve sheath tumor; WHO, World Health Organization; MO, mobility; SC, self-care; UA, usual activities; PD, pain/discomfort; AD, anxiety/depression.

Assessment of the HRQoL

The assessment of HRQoL was conducted by the standardized preference-based questionnaire Euro-Qol-5D-5L (EQ-5D-5L) and Euro-Qol visual analog scale (EQ-VAS), which were developed by the EuroQol Group in 2005 (11). The EQ-5D-5L is a generic instrument for describing and evaluating health status by interrogating questions related to five dimensions: mobility (MO), self-care (SC), usual activities (UA), pain/discomfort (PD), and anxiety/depression (AD). Each dimension has five response levels (Table 1). The questionnaire is designed for self-completion, has been widely tested in different populations and patient samples, and is routinely used in clinical research (12).

An index value was calculated based upon the EQ-5D-5L, which reflects the quality of the health status according to the preferences of the general population of a country, in this case, Germany (0: worst possible state of health, 1: best possible state of health). Therefore, the EQ-5D-5L-Crosswalk-Index-Value-Calculator from the research by van Hout et al. was used (13). The EQ-VAS ranges from 0% (worst possible health status) to 100% (best imaginable health status) (11, 12).

Data were collected via face-to-face interviews during follow-up examinations or telephone interviews or completed at home and sent postally.

All in all, the PNTR contains to date 267 patients; for this substudy, the response rate was 64% (n = 171). In summary, the surveys were assessed at a mean of 36.9 months (SD 23 months) after surgery.

Clinical data

Detailed patient characteristics, including age and sex, as well as histopathological diagnosis, type of surgical treatment, neurological symptoms, pain, and imaging-specific data, were analyzed. Surgical therapy was performed according to established principles (14).

Statistical analysis

Dataset analysis was performed using SPSS 27.0 (SPSS, Inc., Chicago, IL, USA). Metric data were described using median, mean,

TABLE 1 Comparison of pre- and postoperative EQ-5D-5L dimension levels in the subgroup analysis regarding histopathological features.

		Overall (n = 167, n = 166 follow-up)[a]	p	Group 1 (n = 148)	p	Group 2 (n = 4, n = 3 follow-up)[a]	Group 3 (n = 15)
EQ-5D-5L dimension level % (n)							
Mobility [%, (n) with limitations][b]	T^1	32.9 (55)	<0.001	29.7 (44)	<0.001	25 (1)	33.3 (5)
	T^2	22.2 (37)		19.5 (29)		66.6 (2)	13.3 (2)
No problems	T^1	67 (112)	<0.001	66.8 (99)	0.038	75 (3)	66.6 (10)
	T^2	77.7 (129)		77.7 (115)		33.3 (1)	86.6 (13)
Slight problems	T^1	14.9 (25)	0.877	14.8 (22)	1	0 (0)	20 (3)
	T^2	14,4 (24)		14.8 (22)		33.3 (1)	6.6 (1)
Moderate problems	T^1	11.9 (20)	0.137	11.4 (17)	0.277	25 (1)	13.3 (2)
	T^2	7.2 (12)		6.7 (10)		33.3 (1)	6.6 (1)
Severe problems	T^1	5.3 (9)	0.01	6 (9)	0.01	0 (0)	0 (0)
	T^2	0.6 (1)		0.6 (1)		0 (0)	0 (0)
Extreme problems/ unable to	T^1	0.6 (1)	0.317	0.6 (1)	0.316	0 (0)	0 (0)
	T^2	0 (0)		0 (0)		0 (0)	0 (0)
Self-care [%, (n) with limitations][b]	T^1	17.3 (29)	0.002	14.1 (21)	0.487	25 (1)	33.3 (5)
	T^2	11.4 (19)		11.4 (17)		0 (0)	13.3 (2)
No problems	T^1	82.6 (138)	0.192	84.4 (125)	0.308	75 (3)	66.6 (10)
	T^2	88.5 (147)		88.5 (131)		100 (3)	86.6 (13)
Slight problems	T^1	10.1 (17)	1	8.1 (12)	0.545	0 (0)	33.3 (5)
	T^2	10,2 (17)		10.1 (15)		0 (0)	13.3 (2)
Moderate problems	T^1	4.1 (7)	0.091	4.0 (6)	0.152	25 (1)	0 (0)
	T^2	1.2 (2)		1.3 (2)		0 (0)	0 (0)

(Continued)

TABLE 1 Continued

		Overall (n = 167, n = 166 follow-up)[a]	p	Group 1 (n = 148)	p	Group 2 (n = 4, n = 3 follow-up)[a]	Group 3 (n = 15)
EQ-5D-5L dimension level % (n)							
Severe problems	T^1	2.9 (5)	0.024	3.3 (5)	0.024	0 (0)	0 (0)
	T^2	0 (0)		0 (0)		0 (0)	0 (0)
Extreme problems/ unable to	T^1	0 (0)		0 (0)		0 (0)	0 (0)
	T^2	0 (0)		0 (0)		0 (0)	0 (0)
Usual activities [%, (n) with limitations][b]	T^1	44.3 (74)	<0.001	43.2 (64)	0.03	25 (1)	60 (9)
	T^2	31.3 (52)		31.0 (46)		33.3 (1)	33.3 (5)
No problems	T^1	55.6 (93)	0.02	56.7 (84)	0.03	75 (3)	40 (6)
	T^2	68.6 (114)		68.9 (102)		66.6 (2)	66.6 (10)
Slight problems	T^1	20.9 (35)	1	20.2 (30)	1	0 (0)	33.3 (5)
	T^2	21 (35)		20.2 (30)		33.3 (1)	26.6 (4)
Moderate problems	T^1	19.1 (32)	0.013	18.9 (28)	0.032	0 (0)	26.6 (4)
	T^2	9.6 (16)		10.1 (15)		0 (0)	6.6 (1)
Severe problems	T^1	4.1 (7)	0.032	4 (6)	0.056	25 (1)	0 (0)
	T^2	0.6 (1)		0.6 (1)		0 (0)	0 (0)
Extreme problems/ unable to	T^1	0 (0)		0 (0)		0 (0)	0 (0)
	T^2	0 (0)		0 (0)		0 (0)	0 (0)
Pain [%, (n) with limitations][b]	T^1	76 (127)	<0.001	76.3 (113)	<0.001	75 (3)	73.3 (11)
	T^2	54.8 (91)		54.7 (81)		66.6 (2)	53.3 (8)
No problems	T^1	23.9 (40)	<0.001	23.6 (35)	<0.001	25 (1)	26.6 (4)
	T^2	45.1 (75)		45.2 (67)		33.3 (1)	46.6 (7)
Slight problems	T^1	28.1 (47)	0.06	25.6 (38)	0.018	50 (2)	46.6 (7)
	T^2	37.9 (63)		38.5 (57)		66.6 (2)	26.6 (4)
Moderate problems	T^1	23.9 (40)	0.018	26.3 (39)	0.003	0 (0)	6.6 (1)
	T^2	13.8 (23)		12.8 (19)		0 (0)	26.6 (4)
Severe problems	T^1	20.9 (35)	<0.001	22.2 (33)	<0.001	0 (0)	13.3 (2)
	T^2	3 (5)		3.3 (5)		0 (0)	0 (0)
Extreme problems/ unable to	T^1	2.9 (5)	0.024	2 (3)	0.082	25 (1)	6.6 (1)
	T^2	0 (0)		0 (0)		0 (0)	0 (0)
Anxiety/depression [%, (n) with limitations][b]	T^1	50.2 (84)	<0.001	52 (77)	<0.001	0 (0)	46.6 (7)
	T^2	25.9 (43)		26.3 (39)		33.3 (1)	20 (3)
No problems	T^1	49.7 (83)	<0.001	47.9 (71)	<0.001	100 (4)	53.3 (8)
	T^2	74 (123)		73.6 (109)		66.6 (2)	80 (12)
Slight problems	T^1	25.7 (43)	0.046	27 (40)	0.051	0 (0)	20 (3)
	T^2	16.8 (28)		17.5 (26)		33.3 (1)	6.6 (1)
Moderate problems	T^1	15.5 (26)	0.009	15.5 (23)	0.016	0 (0)	20 (3)
	T^2	6.6 (11)		6.7 (10)		0 (0)	6.6 (1)
Severe problems	T^1	7.7 (13)	0.025	8.1 (12)	0.017	0 (0)	6.6 (1)

(Continued)

TABLE 1 Continued

		Overall (n = 167, n = 166 follow-up)[a]	p	Group 1 (n = 148)	p	Group 2 (n = 4, n = 3 follow-up)[a]	Group 3 (n = 15)
EQ-5D-5L dimension level % (n)							
	T^2	2.4 (4)		2 (3)		0 (0)	6.6 (1)
Extreme problems/ unable to	T^1	1.1 (2)	0.156	1.3 (2)	0.156	0 (0)	0 (0)
	T^2	0 (0)		0 (0)		0 (0)	0 (0)
EQ-5D-%L index (mean +/− SD)	T^1	0.801 (0.200)	<0.001	0.800 (0.193)	<0.001	0.771 (0.400)	0.818 (0.217)
	T^2	0.907 (0.113)		0.908 (0.116)		0.879 (0.045)	0.911 (0.094)
EQ-VAS score (mean +/− SD)	T^1	72.26 (17.73)	<0.001	72.91 (17.73)	<0.001	52.5 (21.016)	71.2 (14.766)
	T^2	80.77 (15.93		80.98 (16.21)		66.67 (15.275)	81.47 (12.397)

Group 1 (n = 148) represents the benign PNST, group 2 (n = 8) the malignant tumors, and group 3 (n = 15) the rarities. EQ-5D-5L levels were dichotomized into "no limitations" (i.e., level 1) and "with limitations" (i.e., levels 2 to 5).
T^1, preoperative status; T^2, postoperative status.
[a]Missing data due to death (n = 3, follow-up n = 4) and dementia (n = 1).
[b]EQ-5D-5L dimension responses of any slight, moderate, severe, and extreme problems were grouped into the "with limitations" category.

and standard deviation; categorical data were characterized by frequency and valid percent. Mann–Whitney U, Wilcoxon, Fisher exact, McNemar, and chi-square tests were used for the analysis. The correlation was calculated using Pearson correlation. A level of significance was defined as p <0.05.

Results

Patients' characteristics

A total of 171 surgically treated patients at three high-volume centers were included in this study. Forty-five percent of patients were women (n = 77), and 55% were men (n = 94), with a mean patient age of 48.1 years (SD 13.4). Patients were surgically treated by complete tumor resection in 88.9%, by biopsy in 7%, and by partial tumor removal in 4.1%. A neurofibromatosis spectrum disease was scientifically proven in 15 patients (8.7%). The demographic and clinical characteristics of the patients are presented in Table 2.

Location

PNSTs were most often located in the brachialis plexus region in 16.4% (n = 28), in the median nerve in 15.8% (n = 27), and in the ulnar nerve in 12.3% (n = 21), respectively. The upper and lower extremities were the location of 96 (56.1%) and 75 (43.9%) tumors. Table 3 shows the distribution of the 171 peripheral nerve tumors according to their location.

Histopathology

Most of the 171 surgically treated PNSTs were benign (86.5%) and included schwannoma (n = 121) and neurofibroma (n = 27). Other histopathological diagnoses were perineurioma (n = 6), hybrid nerve sheath tumors (schwannoma/neurofibroma and schwannoma/perineurioma, n = 4), and lymphangioma (n = 2). Malignant tumors included malignant peripheral nerve sheath tumors (MPNSTs) (n = 5). Rarities were singularly represented such as cavernous hemangioma, desmoid tumor, metastasis of breast cancer, amyloidoma, plasmacellular myeloma, and B-cell lymphoma Table 4.

Pain

The prevailing preoperative symptom was pain, including stress and rest pain in 140 patients (82%), rest pain in 60 patients (35%), and stress pain, including a positive Tinel sign in 125 patients (73%). In the follow-up examination, which was in the mean 36.9 months after surgery, patients benefited significantly from surgery, reporting overall pain release (p < 0.001). Only 55 patients (32%) reported pain postoperatively (stress and rest pain altogether) Figure 1.

Neurological deficits

Preoperative motor deficits occurred in 18.7% (n = 32), which increased postoperatively to 23.4% (n = 40) but decreased in the follow-up examination to 18% (n = 31) Figure 2. In 7 of these 32 patients (21.8%), motor deficits occurred after a previous surgery or biopsy at an unspecialized center.

In the total cohort of 171 patients, 13 patients (7.6%) underwent previous surgery, including biopsies at an unspecialized center. In 7 of 13 patients (53.8%) and in 11 of 13 patients (84.6%), motor deficits and sensory deficits respectively occurred after previous surgery or biopsy at an unspecialized center. Out of 158 patients who had no previous biopsy, 28 patients presented preoperative motor deficits, while 27 cases exhibited deficits. Among the 158 cases, 7 patients (4%) experienced new motor deficits after undergoing surgery at a specialized center.

A significant correlation (p < 0.001, r = 0.744) was found between patients with preoperative motor deficits (n = 32) and patients with permanent motor deficits (n = 24).

TABLE 2 Patients' baseline characteristics.

Parameters	Cohort, n = 171		
Follow-up time	Mean 36.9 (SD 23) months	Range 3–96 months	
Age	Mean 48.1 (15–85) years	Median 48 months	
Sex	Women 45% (n = 77/171)	Men 55% (n = 94/171)	
Side	Left 51.5% (n = 88)	Centrally 1.2% (n = 2)	Right 47.4% (n = 81)
Surgical technique	Gross total resection 88.9% (n = 152) Partial resection 4.1% (n = 7) Biopsy 7% (n = 12)		

Neurofibromatosis spectrum disease 8.7% (n = 15).

The same trend is seen in sensory deficits. Preoperative sensory deficits occurred in 38.6% (n = 66), which increased postoperatively to 52.6% (n = 90) but then decreased in the follow-up examination to 38% (n = 65). In 11 of these 66 patients (16.6%), sensory deficits occurred after a previous surgery or biopsy at an unspecialized center. We found a weak correlation between the preoperative and postoperative permanent sensory deficit ($p < 0.001$, $r = 0.443$).

Health-related quality of life data from the Euro-Qol-5D-5L and the Euro-Qol visual analog scale

The median health index value of the entire cohort was 0.887 (n = 167) preoperatively and improved postoperatively to 0.910 (n = 166, $p < 0.001$). The median EQ-VAS score was 75% (n = 167) preoperatively and enhanced to 85% (n = 166, $p < 0.001$) postoperatively (Table 5).

EQ-5D-5L levels were dichotomized into "no limitations" (i.e., level 1) and "with limitations" (i.e., levels 2 to 5). The results are shown in Table 1.

Preoperatively, 12.3% of the patients reached the highest index value score of 1.0 in the EQ-5D-5L and improved postoperatively to 33.3%. In the Euro-Qol visual analog scale (EQ-VAS score), patients rated their overall health preoperatively with a median of 75%, which improved to 85% postoperatively.

TABLE 3 Location of 171 peripheral nerve tumors.

Location	Percent, frequency
Upper extremity	**56.1% (n = 96)**
Cervical plexus	1.2% (n = 2)
Suprascapularis nerve	1.2% (n = 2)
Brachial plexus	16.4% (n = 28)
Median nerve	15.8% (n = 27)
Ulnar nerve	12.3% (n = 21)
Radial nerve	2.9% (n = 5)
Cutaneous antebrachii medialis nerve	1.8% (n = 3)
Interosseus posterior nerve	1.2% (n = 2)
Lower extremity	**43.9% (n = 75)**
Lumbosacral plexus	4.1% (n = 7)
Femoral nerve	5.3% (n = 9)
Cutaneous femoral nerve	1.8% (n = 3)
Sciatic nerve	10.5% (n = 18)
Tibial nerve	7.6% (n = 13)
Peroneal nerve	10.5% (n = 18)
Saphenous nerve	2.3% (n = 4)
Others (single represented locations)	5.2% (n = 9)

Subgroup analysis

Health index values and EQ-VAS scores were compared between different subgroups (histopathological diagnosis, age, and gender). According to histopathological features, three subgroups were defined. Group 1 included benign nerve sheath tumors (schwannoma and neurofibroma), with a total of 148 patients. Group 2 included malignant tumors, including MPNST, metastasis of breast cancer, plasmacellular myeloma, and B-cell lymphoma, with a total of eight patients. In group 3, rare histopathological diagnoses were summarized, including perineurioma, hybrid nerve sheath tumors, and lymphangioma, and represented diagnoses with a total number of 15 patients.

Because of the small number of patients in groups 2 and 3, no levels of significance were calculated.

In Table 1, all pre- and postoperative EQ-5D-5L dimension levels are compared regarding the distribution in subgroups after histopathological patterns.

In the overall cohort, after surgery, the number of patients with no limitations significantly increased in the dimension's mobility, usual activities, pain, and anxiety/depression (Table 1). Additionally, the EQ-5D-%L index scores and the EQ-VAS scores improved postoperatively significantly ($p < 0.001$) in the overall cohort (Table 1).

In the further analysis of our data regarding upper and lower extremities, we did not find any significant differences in the median health index values preoperatively (upper extremity 0.887, lower extremity 0.828) and postoperatively (upper and lower extremity 0.910) and in the median EQ-VAS scores preoperatively (upper extremity 80%, lower extremity 75%) and postoperatively (85%).

TABLE 4 Distribution of histopathological diagnosis within the cohort.

Histopathology	Percent (frequency)
Schwannoma	70.8% (n = 121)
Neurofibroma	15.8% (n = 27)
Perineurioma	3.5% (n = 6)
MPNST	2.9% (n = 5)
Hybrid nerve sheath tumor	2.3% (n = 4)
Lymphangioma	1.2% (n = 2)
Cavernous hemangioma	0.6% (n = 1)
Desmoid	0.6% (n = 1)
Metastasis of breast cancer	0.6% (n = 1)
Amyloid angiopathy	0.6% (n = 1)
Plasmacellular myeloma	0.6% (n = 1)
B-cell lymphoma	0.6% (n = 1)

Discussion

Our study is the first to explore the HRQoL of surgically treated patients with peripheral nerve tumors in a multicentric setting.

The EQ-5D-5L questionnaire was able to detect significant differences between pre- and postoperative HRQoL as hypothesized. Consequently, surgery significantly improved the HRQoL as well as individual function in the dimensions, mobility, usual activities, pain, and anxiety in patients with PNT in the entire cohort.

Comparison of life quality in patients with PNT to the general German population

The mean EQ-5D-5L index score of the German general adult population was stated to be 0.88 (SD 0.18), and the overall EQ-VAS score was 71.59 (SD 21.36). Higher education, full-time work, and private health insurance were associated with a higher EQ-5D-5L index score. Female gender and higher age were associated with a lower EQ-5D-5L index score (12).

In our cohort, the median health index values were identical for the male and female genders (0.887 T^1, 0.910 T^2). Women reported a lower score (72.5%) than men (80%) only in the preoperative median EQ-VAS score. Postoperatively, the median EQ-VAS score increased in both genders to 85%. In our cohort, it can therefore be concluded that there was no gender difference in life quality.

In terms of age relevance for HRQoL, we could not find significant differences in our cohort. With a median age of 48 years, our cohort was slightly younger than the cohort described by Grochtdreis et al. with a median age of 51 years (12). Younger age according to their data was associated with better life quality. This correlation could not be found in our dataset of PNT patients.

Overall, patients in our cohort had a higher median index score postoperatively than in the German general adult population (0.91 vs. 0.88). Reduced pain and symptom control could be a possible explanation.

Among the five different dimensions that were analyzed in our cohort, the fewest restrictions were in the dimension of self-care. Nearly all patients can fend for themselves. Disabilities in patients with PNT—excluding NF patients—are mostly limited to one extremity.

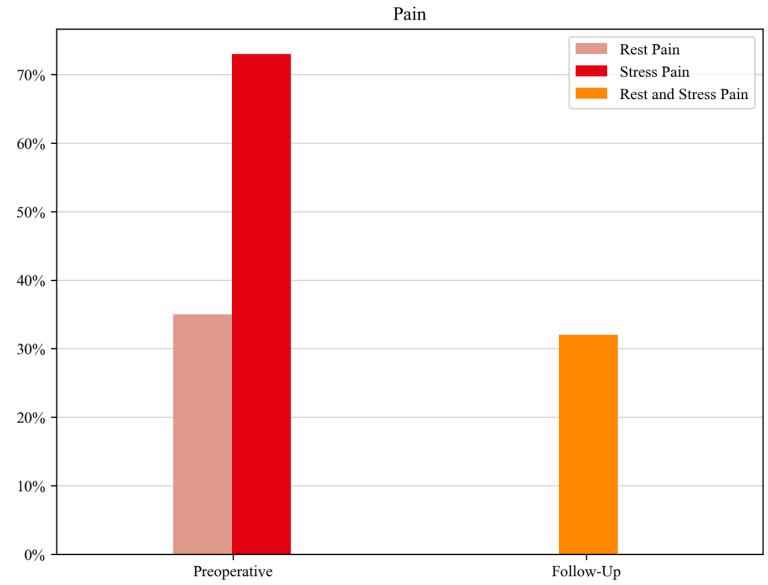

FIGURE 1
Monitoring of the lead symptom (pain) over the course of the disease.

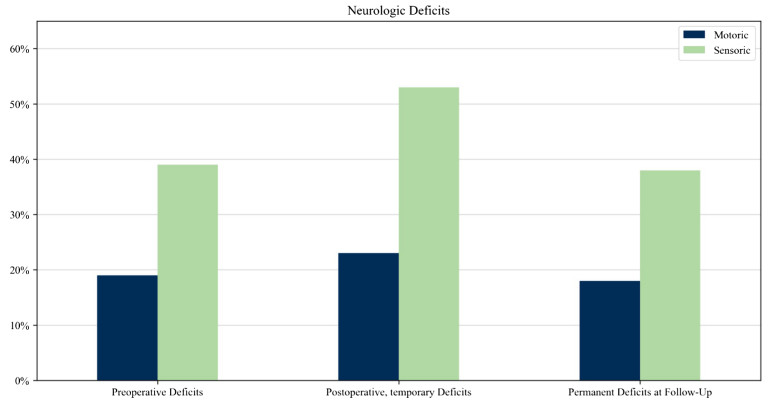

FIGURE 2
Monitoring of neurological deficits throughout the disease.

Effect of surgery on pain and neurological deficits on life quality

Our data show overall that patients improved postoperatively in HRQoL. A non-negligible percentage of motor and sensory deficits occurred after previous surgeries or needle biopsies in non-specific centers; those deficits are frequently permanent. The harm that can be caused due to surgical treatment in non-specialized centers has been shown in a recent study and supports our results (4). Overall, the key observation is that patients who presented deficits prior to surgery are more prone to experiencing permanent deficits. Because neurological deficits determine life quality, especially in the domain of mobility, self-care, and usual activities, these previous surgeries can negatively influence HRQoL. Furthermore, due to their rarity, patients often experience a long diagnostic process in the future with the potential of misdiagnosis and severe consequences (44.7%) (4).

Our study shows that preexisting neurological deficits, including pain, are risk factors for permanent deficits. This additionally supports the recommendation to perform surgery at a specialized center to prevent function and consecutively impaired life quality.

In our dataset, most restrictions occurred in the dimension of pain. In 76%, preoperative limitations (slight–extreme problems) occurred, which significantly improved postoperatively to 54.8% ($p < 0.001$). These results are mirrored in the preoperative collected data of symptoms; pain (rest and stress pain) was reported in 82% and improved postoperatively to 32%. All in all, surgery led to improved symptom control in the dimension of pain. Pain was not only the leading symptom in patients with malignant or rare PNTs but also in patients with benign PNTs like schwannoma and neurofibroma with no other neurological deficits, which is in concordance with previous studies (2, 15). For this reason, we recommend early surgery at a specialized center for symptom control and for returning to everyday life and work quickly.

Effect of histopathological diagnosis on life quality

Compared with patients with benign PNT, patients with malignant peripheral nerve tumors undoubtedly have a worse life quality (Table 1), which is, on the one hand, related to the physio-

TABLE 5 Comparison of EQ-5D-5L index values preoperatively (T^1) vs. postoperatively (T^2) of the total cohort (N = 167).

		Index value T^1	EQ-VAS score (%) T^1	Index value T^2	EQ-VAS score (%) T^2
N	**Valid**	167	167	166	166
	Missing[a]	4	4	5	5
Mean		0.801	72.26	0.907	80.77
Median		0.887	75.00	0.910	85.00
Std. deviation		0.200	17.73	0.113	15.93
Minimum		0.118	15	0.378	25
Maximum		1.000	100	1.000	100
Highest score of 1 (EQ-5D-5L) and 100% EQ-VAS, *N* (%)		21 (12.3%)	9 (5.3%)	57 (33.3%)	19 (11.1%)

T^1, preoperative status; T^2, postoperative status.
[a]Missing data due to death (n = 3, follow-up n = 4) and dementia (n = 1).

and psychological burden of the disease itself and, on the other hand, influenced by the more radical surgical treatment followed by neurological deficits and the duration of the disease. Due to the small number of patients with malignant PNT, generalized recommendations are not possible; however, due to limited life expectancy, it is even more critical to counterbalance the radicality of treatment and the QoL. Different concepts regarding the priority of neurological function preservation in contrast to surgical radicality are currently applied and must be discussed with the patient before surgery (16). Interestingly, patients in the group with rare entities had comparable pre- and postoperative index scores to the group with benign PNT (T^1 0.818, T^2 0.911).

The effect that the degree of HRQoL improvement varies according to preoperative neurological symptoms is not only shown in our data but also by Haider et al., who report this effect in patients with intracranial meningiomas (17).

Socioeconomic aspects of life quality in the working population

As diagnosis and treatment modalities have improved over time, early return to work and life quality are necessary outcome measurements in patients with PNT. Additional work and employment are essential factors in life quality, ranked right after family and partnership (18). It becomes clear that PNT concerns, in particular, the working population with a mean age of 48.1 years. With pain as the leading symptom and knowing the obstacles and the effort that occur in patients with chronic pain returning to work, including managing symptom control, work relationships, and making workspace adjustments (19), the highest goal should be treating pain immediately at the initial diagnosis. The more neurological deficits occur pre- or postoperatively, the more likely it may be that patients will not return to work as fast as patients without deficits. However, a specific analysis of return to work in patients with PNT needs to be improved. Our data show that resection at a specialist high-volume center is safe and improves symptoms and life quality after surgery.

Strengths and limitations

The strength of this study is the large cohort of patients with clearly peripheral nerve tumors; intraspinal schwannoma was not included. A second strength is the multicentric study design.

The limitations are that the results are from a retrospective analysis. The number of patients with malignant PNT and neurofibromatosis was proportionally small.

Conclusion

Preservation and, if possible, improvement of neurological function and reduction of pain are of utmost importance for individual patient's quality of life and in patients with PNT. The dimension of pain predominantly affected the overall quality of life. In summary, surgical therapy improved life quality in the entire cohort.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Ethikkomission der Universität Ulm. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

NG: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft. UAK: Data curation, Writing – review & editing. CW: Supervision, Writing – review & editing. ND: Conceptualization, Data curation, Supervision, Writing – review & editing. RK: Conceptualization, Methodology, Supervision, Writing – review & editing. AP: Conceptualization, Formal analysis, Project administration, Resources, Visualization, Writing – original draft, Writing – review & editing. GA: Conceptualization, Supervision, Writing – review & editing. BM: Formal analysis, Methodology, Writing – review & editing. MP: Conceptualization, Data curation, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Case report: Pediatric low-grade gliomas: a fine balance between treatment options, timing of therapy, symptom management and quality of life

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Introduction: Pediatric low-grade gliomas (pLGG) are the most common brain tumor in children and encompass a wide range of histologies. Treatment may pose challenges, especially in those incompletely resected or those with multiple recurrence or progression.

Case description: We report the clinical course of a girl diagnosed with pilocytic astrocytoma and profound hydrocephalus at age 12 years treated with subtotal resection, vinblastine chemotherapy, and focal proton radiotherapy. After radiotherapy the tumor increased in enhancement temporarily with subsequent resolution consistent with pseudoprogression. Despite improvement in imaging and radiographic local control, the patient continues to have challenges with headaches, visual and auditory concerns, stroke-like symptoms, and poor quality of life.

Conclusion: pLGG have excellent long-term survival; thus, treatments should focus on maintaining disease control and limiting long-term toxicities. Various treatment options exist including surgery, chemotherapy, targeted agents, and radiation therapy. Given the morbidity associated with pLGG, individualized treatment approaches are necessary, with a multi-disciplinary approach to care focused on minimizing treatment side effects, and promoting optimal quality of life for patients.

KEYWORDS

pediatric low-grade glioma, pilocytic astrocytoma, proton radiation, chemotherapy, case report

1 Introduction

Pediatric low-grade gliomas (pLGG) are one of the most common childhood brain tumors, accounting for about one-third of such tumors. The clinical behavior varies, but pLGG are indolent and carry a low risk of malignant transformation, with a 5-year overall survival (OS) as high as 97%, and 10- and 20-year OS around 90% (1, 2). Progression-free survival (PFS) is inferior, especially in those with residual tumor, where PFS has been documented as high as 45%-65% (3). These tumors can occur in deep locations such as the brainstem and suprasellar area; treatments and tumoral location may result in considerable morbidity, including vision loss, functional decline, endocrine dysfunction, motor disability, neurocognitive difficulties, and reduced quality of life (QoL). Management is aimed at long-term tumor control while minimizing tumor- and treatment-related morbidity and maintaining QoL (4, 5).

Gross total resection is the preferred treatment for pLGG when feasible (6). Unresectable tumors or those that progress require adjuvant treatment with chemotherapy, targeted agents, and/or radiation therapy (6, 7). With the emergence of molecular diagnostics suggesting most pLGG upregulate the RAS mitogen-activated protein kinase (RAS/MAPK) pathway, targeted therapies are a promising treatment option (4, 8). Early studies offer optimistic results, but long-term side effects are yet unknown; should current clinical trials report efficacious and safe treatment of pLGG, this modality has the potential to become first-line treatment of pLGG (9) Chemotherapy remains a front-line adjuvant therapy for children with progressive or unresectable pLGG. Typically monotherapy with vinblastine or carboplatin or combination treatment with carboplatin and vincristine or thioguanine, procarbazine, lomustine/CCNU and vincristine (TPCV) are utilized (10, 11). Chemotherapy is associated with a 3-year PFS of 50–80% (6), and side effects are taken into consideration (7).

Radiation therapy has become less favored as first-line therapy in young patients (i.e., those under 10 years old) due to its potential long-term effects, including neurocognitive and endocrine dysfunction as well as risk of second malignancy (7). Although developments in radiation technology, such as imaged guided intensity modulated photon and proton beam radiation, can significantly reduce side effects (12), the high OS associated with pLGG, alternative treatment options, and low likelihood of malignant transformation have resulted in less frequent use. Radiation therapy may serve as a reasonable option in older pLGG patients, those with symptomatic progression, and/or those with progressive disease despite systemic therapy.

The timing of various treatments and their potential side effects relative to morbidity associated with tumor progression and cumulative effects of other treatment options need to be carefully considered (13, 14). Herein, we report the multi-year clinical course of a 12-year-old female diagnosed with a pLGG and ultimately treated with subtotal resection, vinblastine chemotherapy, and focal proton radiotherapy. While our patient's disease was adequately treated with this combination of therapy, her QoL has significantly suffered as she continues to experience effects of the tumor itself as well as its associated treatment.

2 Case description

A 12-year-old previously healthy female presented with a 2–3-month history of intermittent headaches, dizziness, emesis, and unsteady gait. Neurological assessment revealed slow and deliberate speech, papilledema, decreased lower extremity tone, bilateral dysmetria, and ataxia. MRI brain revealed a heterogeneously enhancing mass in the fourth ventricle with obstructive hydrocephalus (Figures 1, 2A). The patient's treatment included endoscopic third ventriculostomy and subtotal tumor resection (Figure 2B). Surgical management of pediatric CNS tumors is specialized, thus centralization of care at large pediatric centers is imperative. Her post-operative course was complicated by cerebral salt wasting, ophthalmoplegia, and diplopia. Pathology was consistent with a pilocytic astrocytoma, WHO grade I; molecular testing, now considered standard of care, was not performed.

Local tumor progression was identified on surveillance imaging 5 years after initial diagnosis (Figure 2C). The patient experienced clinical progression with right-sided hearing loss. Given the tumor location, additional surgery was not feasible; she was started on vinblastine chemotherapy. Dose reduction (4mg/m2/dose) was required secondary to intolerance, specifically nausea, peripheral neuropathy, and myelosuppression. She completed a 70-week course of chemotherapy as planned, with subsequent tumor stability (Figure 2D). Throughout treatment the patient struggled with episodic headaches, ataxia, diplopia, and neuropathic pain. She completed high school but was unable to pursue further education given her functional status. Approximately 8 months post chemotherapy, the patient developed further clinical and radiographic progression with vomiting and headaches (Figure 2E). At this time, a right ventriculoperitoneal (VP) shunt was inserted which improved performance status. Subsequent treatment options were discussed and ultimately the patient proceeded with focal proton beam radiation (5220cGy/29 fractions) (Figure 3). At presentation and throughout her treatment, she was followed by allied health professionals. Medications were used to help manage pain, neuropathy, tinnitus, headaches, and nausea.

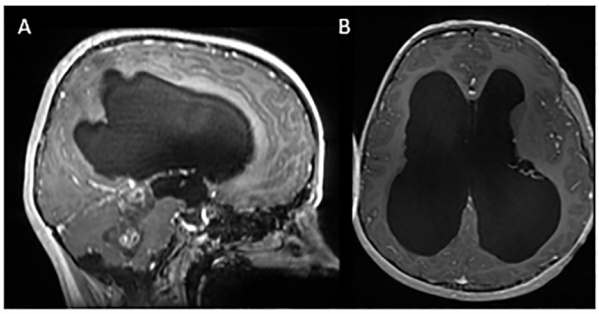

FIGURE 1
Initial MRI imaging demonstrating mass and associated hydrocephalus. Sagittal **(A)** and axial **(B)** post contrast images demonstrating fourth ventricular mass with associated hydrocephalus.

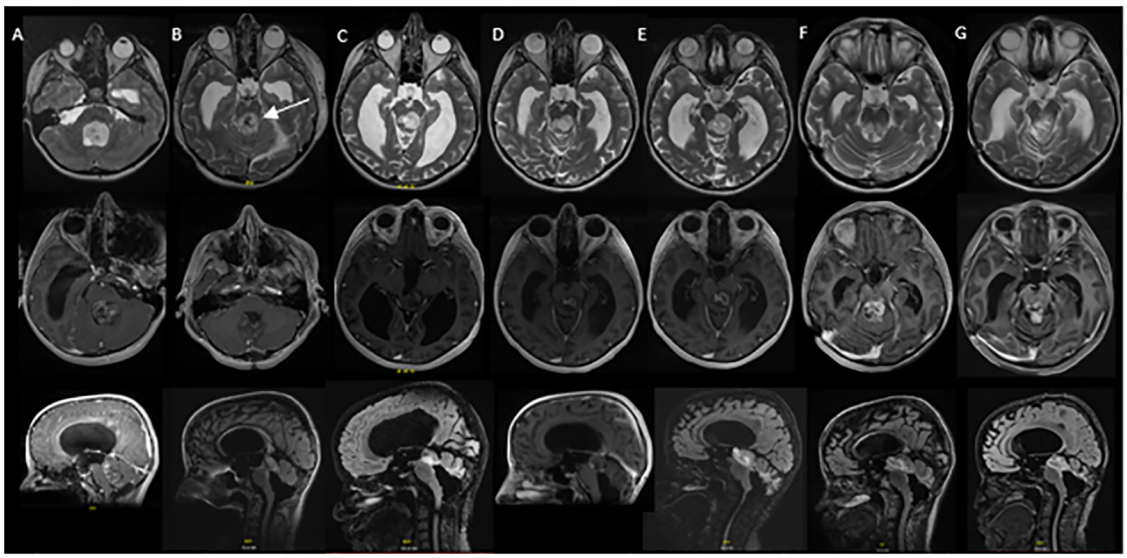

FIGURE 2
Serial MRI imaging demonstrating tumor changes over time. Axial high-resolution images on top panel, axial T1 post contrast images in middle panel and sagittal T1 post contrast images in bottom panel [**(B)** and **(C)** bottom are sagittal FLAIR images]. **(A)** Mass noted within the fourth ventricle resulting in supratentorial hydrocephalus and trans ependymal edema. **(B)** Post-operative MRI demonstrating residual tumor in the midbrain (arrow) and pons as well as roof of fourth ventricle (1 week post initial MRI). **(C)** Local tumor progression with enlargement of nodular component of dorsal midbrain mass and increased enhancement (64 months from initial diagnosis). **(D)** Completion of vinblastine chemotherapy, tumor stable on imaging (84 months from diagnosis). **(E)** Further tumor progression with increase in size of posterior midbrain mass (92 months from diagnosis). **(F)** Following radiation therapy, tumor appears stable in size although increased enhancement of the tumor was noted in the pons, midbrain and subthalamic regions (105 months from diagnosis). **(G)** Tumor stable on most recent evaluation (152 months from initial diagnosis).

Five months following completion of radiation, the patient developed worsening headaches, fatigue, unsteadiness, dizziness, word-finding difficulties, auditory symptoms, and visual symptoms, raising concern for a stroke. Neuro-imaging ruled out a stroke and demonstrated stability in tumor size, with new T2 changes and enhancement surrounding the tumor (Figure 2F). Differential included post-radiation effects, pseudoprogression, or true tumor progression. Dexamethasone was initiated, but due to myopathy was discontinued.

Ongoing surveillance over the subsequent 5 years demonstrated tumor stability and eventual improvement of the peritumoral T2 changes and enhancement (Figure 2G) suggesting the initial changes were related to pseudoprogression. The patient continued to endorse headaches, diplopia, hearing impairment, tinnitus, ataxia, and fatigue. Despite combination treatment that ultimately achieved durable tumor control, her long term QoL has been adversely affected since diagnosis.

3 Discussion

pLGG are indolent tumors described as a chronic progressive disease that may require multiple treatment modalities. The

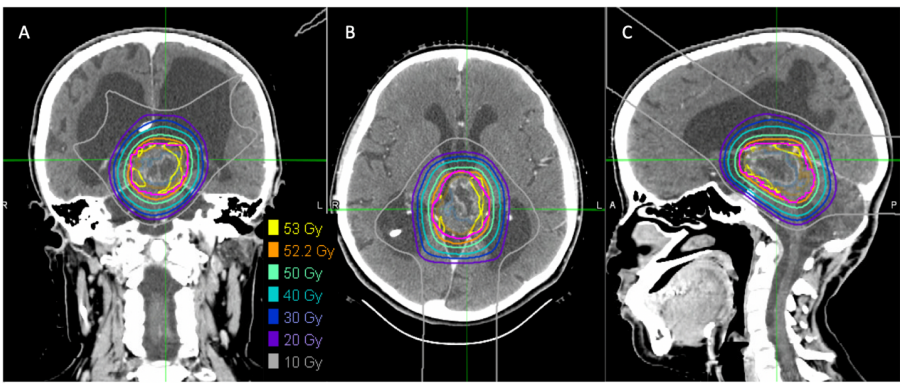

FIGURE 3
Proton radiation plan demonstrating doses administered. Coronal **(A)**, axial **(B)** and sagittal **(C)** images demonstrating proton radiation plan and doses administered.

mainstay of therapy is complete resection, when feasible (5, 6). In those with residual disease, timing of adjuvant therapy is controversial, with some suggesting a "watch and wait" approach as a quiescent period is possible and others considering more immediate treatment (3, 6). The plethora of treatment options and their associated toxicity weighed against the potential complication of tumor progression need to be taken into consideration in the management of these patients.

LGG of childhood have been recognized as distinct from those arising in older adolescents and adults (8, 15). In contrast to adult LGG, pLGG rarely undergo malignant transformation, although the precise frequency of this transformation in the absence of radiotherapy in the management of pLGG remains unknown as radiotherapy is often used at progression and repeat biopsy is seldom performed (15). In adult patients with shorter life expectancies and whose tumors are typically more aggressive than children's, early irradiation remains standard practice (16).

Historically photon radiation had been used in pLGG, in both up-front and salvage therapy, with 5-year PFS and OS of 87% and 99%, respectively (17). Radiation, albeit an effective treatment, is not without side effects, some of which greatly impact QoL (14, 18–20). Photon radiotherapy is associated with long-term side effects including neurocognitive decline, behavioral changes, increased risk of stroke, neuroendocrine deficiencies, vascular damage, growth abnormalities, and increased risk of second malignancy (Table 1) (30–34). Neuropsychiatric impacts of brain radiation need to be further explored especially in the modern era of radiotherapy.

Chemotherapy is an option in progressive or incompletely resected pLGG as a means to delay or avoid radiotherapy (6, 10, 11). The combination of carboplatin and vincristine is associated with a PFS of 68% (12). TPCV is similarly effective, but is associated with a risk of second malignancy and infertility (35). Some patients receive multiple lines of chemotherapy for recurrent disease, and their QoL and risk of treatment toxicity remains a concern.

In those patients that exhaust other therapy options, radiation becomes a treatment consideration. Newer radiation techniques, such as intensity modulated, image guided photon or proton beam radiation offer treatment with the potential of reducing radiation-associated toxicity (Table 1) (20, 30). Proton beam radiation, which our patient received, allows for improved sparing of normal brain tissue (20, 22, 30). Although data are limited, initial studies report that proton therapy is effective in pLGG at maintaining high PFS and OS while reducing radiation-induced side effects (18, 20, 30). Some series have suggested a higher risk of pseudoprogression following proton beam radiotherapy compared to photon radiotherapy; a recent systematic review suggested no difference (22, 36, 37). In our patient, there was radiographic as well as clinical deterioration following radiotherapy. While the imaging changes resolved, the clinical symptoms persisted. Although most instances of pseudoprogression are diagnosed on imaging alone, clinical symptom progression is possible (22, 38, 39).

Stereotactic radiation therapy (SRT), another highly conformal radiation approach, has also been shown to be effective in the management of pLGG (28). Similar to proton radiation therapy, the goal of SRT is to minimize the amount of normal tissue irradiated without compromising tumor management (28). Second malignant neoplasm (SMN) specifically high-grade glioma, although rare, serves as a possible late effect of radiation therapy. Chemotherapy, specifically TPCV, is also associated with a risk of SMN, specifically leukemia, and thus tends to be a less favored chemotherapy regimen (20, 35, 40). Furthermore, children with neurofibromatosis type 1 (NF-1) who are at increased risk of pLGG, also have an increased risk of SMN with one study documenting a relative risk of 3.04 of SMN after radiation therapy (41).

Although not applicable in our case, clinicians considering radiation therapy should be aware of the well-documented cranial radiation-induced vascular complications (27, 42–45). The pathophysiology of this is complex; it involves endothelial loss and ultimately results in vascular damage and abnormal endothelial proliferation involving the upregulation of pro-inflammatory and hypoxia-related genes (42, 46). Certain factors including tumor location (i.e., circle of Willis), younger age at time of irradiation, NF-1, treatment with an alkylating chemotherapy agent, and higher doses of radiation increase the risk for cerebrovascular complications (43–45, 47–50).

The emergence of molecular diagnosis allowing for targeted therapy is changing the landscape of pLGG management. These tumors frequently have somatic driver alterations that result in MAPK pathway activation (8). Initial clinical trials offer promising results but more data are needed to evaluate long-term efficacy and side effects (9). Notably, molecular diagnostics were not available for our patient at the time of presentation for consideration of radiotherapy; molecular characterization of disease is done routinely in cases of pLGG.

In most cases of residual or unresectable disease, systemic therapy is not curative and serves primarily as a radiotherapy deferral strategy particularly among younger patients who are at highest risk of long-term deficits. That said, an "avoid radiotherapy until absolutely necessary" strategy may not serve all patients well as radiation will not reverse pre-existing toxicity deficits incurred through successive rounds of tumor progression and interventions. It is unknown if proton therapy was introduced earlier in her care (i.e. at the time of first progression after surgery when the patient was age 17), in aggregate would have had a more favorable longer term therapeutic profile than the patient experienced.

QoL is an important aspect of clinical care that encompasses various aspects of a person's well-being and reflects satisfaction with life (51, 52). As a broad term it tends to be defined as an individual's sense of well-being and ability to participate in and enjoy life. QoL includes physical, psychological and functional status, as well as social and emotional wellbeing (53–57). There are various standardized questionnaire that focus on general symptoms and patients ability to function, some of these include questions pertaining to difficulties with symptoms such as headaches, anorexia, nausea, seizures, sleep disturbances, mood, social interactions or isolation, motor difficulties, cognitive abilities and one's ability to perform basic activities of daily living (57–60). QoL is impacted by patient specific factors, tumor location, treatment and side effects from the treatment and patients overall experience (53). In our case, no formal tool was used to assess QoL, instead subjective QoL was reported based on the patient's symptoms.

TABLE 1 pLGG treated with radiation therapy in the literature.

Author/Year	Mean age at RT (year; range)	Pathology	RT modality	Median RT dose (range) Gy	Patients who received chemotherapy prior to RT	Prior surgical resection/ biopsy	Outcome	Toxicity reported
Rodrigues et al., 2021 (21)	9.22 years	Astrocytoma NOS (n=249, 68%) Pilocytic astrocytoma (n=64, 17.5%) Diffuse astrocytoma (n=22, 6%) Oligodendroglioma (n=5, 1.4%) Glioma NOS (n=18, 4.9%) Mixed glioma (n=8, 2.2%)	EBRT		34/366 (9.3%)	Surgery (n=248, 67.8%)	No survival assessment in study	Secondary neoplasm 7.4% in RT treated group
Indelicato et al., 2019 (20)	10.2 (2–21) years 48.6% (n=36) of the patients were <30 years old	WHO grade I: (n=122, 70%) WHO grade II: (n=52, 30%)	Proton	129 treated with 54Gy and 45 treated with <54 Gy	74/174 (43%) 1 prior regimen (n=29, 17%), 2 prior regimens (n=23, 13%). 3+ prior regimen (n=22, 13%)	No prior surgery (n=22, 13%) STR/biopsy (n=147, 84%) GTR (n=5, 3%)	5-year PFS and OS 84% and 92%, respectively	Reduced local control in brainstem/ spinal cord tumor (62% vs 90% other locations) and in those that received dose <54 Gy (67% in <54Gy vs 91%) Nausea or vomiting (12.6%) New central hormone deficiency (22%) Pseudo progression (32%) Significant toxicity in 4% of patients; brainstem necrosis requiring corticosteroids (n=2), symptomatic vasculopathy (n=2), radiation retinopathy (n = 1), epilepsy (n = 1), and death from radiation-induced high-grade glioma (n = 1).
Ludmir et al., 2019 (22)	10 (1–17.6) years	WHO grade I (n=62, 75%) WHO grade II (n=21, 25%)	IMRT (n=32, 39%) Proton (n=51, 61%)	50.4 (45–59.4) Gy	32/83 (39%)	Biopsy (n=42, 51%) STR (n=37, 45%) GTR (n=4, 5%)	Improved local control with proton RT (HR 0.34, 95% CI: 0.10–1.18, p=0.099)	Pseudo progression (n=31, 37%); 8/32 (25%) IMRT patients and 23/51 (45%) proton (p=0.048). Higher doses of RT (>50.4Gy) were more likely to have pseudo progression (p=0.016)

(Continued)

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TABLE 1 Continued

Author/Year	Mean age at RT (year; range)	Pathology	RT modality	Median RT dose (range) Gy	Patients who received chemotherapy prior to RT	Prior surgical resection/ biopsy	Outcome	Toxicity reported
Cherlow et al., 2019 (23)	13.6 (3–21) years *(median)*	Pilocytic astrocytoma (n=66; 78%) Diffuse astrocytoma (n=12, 14%) LGG NOS (n=2, 2%) LGG oligodendroglioma (n=1, 1%)	IMRT (n=60, 71%) 3D-CRT (n=25; 29%)	54 Gy	36/85 (42%)		PFS (5-year) 71% OS (5-year) 93%	Tumor necrosis (n=1) Acute visual loss reversed with steroids (n=1) Acute diplopia reversed with steroids (n=1)
Mannina et al., 2016 (24)	10.9 (4–20) years	WHO grade I (n=15, 100%)	Proton	54 (50.4–59.4) Gy	9/15 (60%)	Biopsy only: (n=5, 33%) ≥ 1 subtotal resection: (n=10, 67%) 2 STR (n=3, 30%)	5-year OS and intervention free survival 93% and 73%, respectively	Pseudo progression (20%) Secondary malignancy, ALL (n=1), radio necrosis (n=1)
Raikar et al., 2014 (25)	9.4 years	WHO grade I (n=10, 59%) WHO grade II (n=7, 41%)	Conformal RT (n=13, 76%) CyberKnife (n=2, 12%) Gamma Knife (n=2, 12%)	50–54 Gy (CRT) 14–16Gy (GammaKnife) 21–26Gy (CyberKnife)	13/17 (76%) 1 prior regimen (n=7, 54%), 2 prior regimens (n=4, 31%), 3 prior regimens (n=1, 8%), 4 prior regimens (n=1, 8%)	Biopsy (n=7, 41%) STR (n=10, 59%) GTR (n=0)	PFS (3-year) OS (3 and 10-year) 100%	
Greenberger et al., 2014 (18)	11.0 (2.7–21.5) years	WHO grade I: (n=19, 59.4%) WHO grade II: (n=6, 18.8%)	Proton	52.2 (48.6–54) Gy	16/32 (50%)	No prior surgery: (n=5, 15.6%) Biopsy only: (n=6, 18.7%)	6-year PFS 89.7%, 8-year PFS 82.8%; OS (8-year) 100%	Decline in neurocognitive outcome in children < 7 years in age and those with higher doses to left temporal lobe/hippocampus.

(Continued)

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TABLE 1 Continued

Author/Year	Mean age at RT (year; range)	Pathology	RT modality	Median RT dose (range) Gy	Patients who received chemotherapy prior to RT	Prior surgical resection/ biopsy	Outcome	Toxicity reported
		low grade (not specified) (n=2, 6.3%), no pathology: (n=5, 15.6%)			One prior regimen (n=6, 18.8%) 2 prior (n=7, 21.9%) 3 prior (n=3, 9.4%) none (n=16,50%)	1 prior resection: (n=17, 53.1%) 2 or more resections: (n=4, 12.5%)		Higher risk of endocrinopathy in patients with mean dose of ≥40 Gy to hypothalamus, pituitary, or optic chiasm Moya moya (n=2)
Paulino et al., 2013 (26)	10 (1–17) years *(median)*	WHO grade I (n=32, 82%) WHO grade II (n=7; 18%)	IMRT	50.4 Gy (45–54Gy)	10/39 (25.6%)	STR (n=19; 48.7%)	PFS (8-year) 78.2%, OS (8-year) 93.7%	Age at time of RT was significant for PFS, with more disease progression observed in patients ≤5 years of age at time of IMRT. Moya moya (n=1) Children with centrally located tumor more likely to develop endocrine abnormalities compared to hemispheric or posterior fossa tumors, hormone deficiency (n=10)
Merchant et al., 2009 (27)	9.7 (2.2–19.8) years	WHO grade I (n=67, 86%) WHO grade II (n=11, 14%)	IMRT (n=3, 4%) 3D-CRT (n=75, 96%)	50.4 (one patient with OPG), otherwise 54Gy in all others	25/78 (32%)	Biopsy (n=30, 38%) STR (n=35, 45%) No prior surgery (n=13, 17%)	EFS 87.4% (5-year), 74.3% (10-year) OS 98.5% (5-year), 95.8% (10-year)	Vasculopathy (n=5); younger children <5yo were at greatest risk Second malignancy (n=1) Younger age associated with more marked decline in cognitive scores with most marked decline in <5yo Thyroid hormone and GH deficiencies (10-year cumulative incidence), 64% and 48.9%, respectively
Marcus et al., 2005 (28)	9 (2–26) years	WHO grade I (n=35, 70%) WHO grade II (n=15, 30%)	SRT	Mean 52.2 (50.4–58) Gy	12/50	STR (n=38, 76%)	PFS (5-year) 82.5% (8-year) 65% OS 97.8% at 5-years, 82% at 8 years	Transformation to higher grade tumor, anaplastic astrocytoma (n=2) RT induced PNET (n=1) Moya-moya (n=4)

(Continued)

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TABLE 1 Continued

Author/Year	Mean age at RT (year; range)	Pathology	RT modality	Median RT dose (range) Gy	Patients who received chemotherapy prior to RT	Prior surgical resection/ biopsy	Outcome	Toxicity reported
								No significant acute toxicity attributable to SRT
Hug et al., 2002 (29)	8.7 (2–18) years	Diffuse low grade astrocytoma (n=9, 33%) JPA (n=14, 52%), no path (n=4, 19%)	Proton	Mean 55.2 (50.4–63)	No comment on prior therapy	STR/biopsy (n=25, 92%) GTR, but residual enhancement (n=1, 4%) GTR (complete radiographic resection) (n=1, 4%)	At mean follow up 3.3 years 6/27 patients local failure, 4/27 died	Transformation to high grade GBM (n=1) New onset hypopituitarism (n=4) Moya moya (n=1)

EBRT, external beam radiation therapy; IMRT, Intensity-modulated radiation therapy; SRT, Stereotactic radiotherapy; WHO, World Health Organization; GTR, Gross total resection; STR, Sub total resection; RT, radiation; PFS, Progression free survival; OS, Overall survival.

4 Conclusion

As a chronic disease, pLGG tend to require multiple modalities of therapy. Patients' QoL can be significantly impacted both by symptoms of tumor progression as well as treatment side effects. The heterogenous nature of this disease and varying clinical course results in challenges in management. The treatment-related effects should be considered. In some circumstances, the cumulative effects of multiple lines of surgery and systemic therapy in addition to the tumoral's negative impact on function at diagnosis and at progression likely play a significant role in patients' poor health-related QoL outcomes. For some patients, earlier intervention with radiotherapy (accepting potential longer-term toxicity of this modality) with its associated durable tumor control might be the appropriate strategy to secure optimal long-term QoL as even the most advanced technical delivery of radiation typically cannot recover function that has been lost. Overall, these patients require individualized approaches to management with a focus on multi-disciplinary team involvement to reduced treatment-associated side effects, and promote QoL.

5 Patient perspective

For the past 15 years, I have struggled through surgery, chemotherapy, and radiotherapy and all of the side effects that come with all of those treatments. None of them were easy and there is no one path that I favor more than the others, they are all equally difficult to endure. Separately I don't believe they were as helpful as they were when combined altogether. I am thankful to be able to receive all of these important treatments and my long survival. Though I've been left disabled after everything, I am thankful to be alive and to be able to enjoy my life with my family. I am also thankful to all of the very knowledgeable doctors for each part that they have played in my treatment. It has been a painful and arduous journey that I've been through and it has been full of loss, and though my life is very different than that of the average person, that doesn't mean it's not enjoyable or fulfilling. Life goes on, and it doesn't have to go on the same way for everyone to be considered a good life.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

NJ-C: Writing – original draft. GB: Conceptualization, Writing – review & editing. TY: Writing – review & editing. SZ:

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Conflict of interest

GB sits on the Proton Therapy Advisory Panel for Cancer Care Ontario.

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Identification and validation of potential prognostic biomarkers in glioblastoma via the mesenchymal stem cell infiltration level

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Aims: Mesenchymal stem cells (MSCs) are key components in promoting glioblastoma (GBM) progression. This study aimed to explore new therapeutic targets and related pathogenic mechanisms based on different MSCs infiltration levels in GBM patients.

Methods: We estimated the relationship between cell infiltration and prognosis of GBM. Subsequently, key risk genes were identified and prognostic models were constructed by LASSO-Cox analysis. The risk genes were validated by five independent external cohorts, single-cell RNA analysis, and immunohistochemistry of human GBM tissues. TIDE analysis predicted responsiveness to immune checkpoint inhibitors in different risk groups.

Results: The MSCs infiltration level was negatively associated with survival in GBM patients. LOXL1, LOXL4, and GUCA1A are key risk genes that promote GBM progression and may act through complex intercellular communication.

Conclusion: This research has provided a comprehensive study for exploring the MSCs infiltration environment on GBM progression, which could shed light on novel biomarkers and mechanisms involved in GBM progression.

KEYWORDS

glioblastoma, mesenchymal stem cell, tumor microenvironment, immune checkpoint, prognostic model

Introduction

Glioblastoma (GBM) is one of the most commonly reported malignancies worldwide, and the need to improve its prognosis remains a major clinical challenge. GBM accounts for 48.6% of central nervous system malignant tumours, with a median overall survival (OS) time of 15 months (1). The tumor growth and progression effect of mesenchymal stem cells (MSCs) in GBM was demonstrated in previous studies (2, 3). However, there is a lack of analyses based on gene expression at different infiltration levels of MSCs.

MSCs have been found to migrate toward tumours, interact with the TME and promote tumor growth (2). MSCs are induced to differentiate into pericytes and promote angiogenesis in GBM. They also shift glioma stem cells (GSCs) toward a more aggressive status (4). Hossain et al. showed that MSCs isolated from fresh human brain GBM tissue can promote the proliferation and self-renewal of GSCs, thus driving the construction of an environment conducive to tumor growth. In the GBM microenvironment, about 10% of MSCs may be differentiated from GSCs (3). As a result of β-connexin phosphorylation and Wnt signalling activation in tumours, endothelial cells acquire the ability to transform into MSC-like cells and induce tumour resistance to cytotoxic treatments (2, 5).

GBM is a "cold tumor" with a tumor immune phenotype that is characterised by poor function and severe exhaustion of T cells in the TME (7–9). Considering that many immune cells and stromal cells in the TME interact to promote tumor development, we wondered whether these factors are related to cold tumours. Previous studies have observed poor T-cell function and severe exhaustion in GBM, which is characterised by upregulation of multiple immune checkpoints, T-cell hypo-responsiveness, and a low infiltration state of T cells (10). Immune checkpoint inhibitors (ICIs) promote the antitumor immune response by inducing suppressive immune checkpoint regulatory pathways and have been applied to many kinds of cancer types in the clinic (11). PD-1 blocker therapy adjuvantly enhanced local and systemic anti-tumour immune responses in glioblastoma patients, significantly increasing their overall survival (12). A study indicated that PD-L1 blockade combined with a DC vaccine can increase antitumor efficacy in a mouse model of glioma (13).

Although these tumor-promoting effects of MSCs have been observed consistently, the underlying changes in gene expression are still unknown. There is also a lack of typing studies based on MSC infiltration level indicators in GBM. This study will help identify genes that play a key role in promoting tumor progression during GBM development, screen for new therapeutic targets, and provide new ideas for the risk stratification and treatment of GBM patients.

Materials and methods

Data accessing and preprocessing

The RNA-seq data and clinical details of GBM patients were obtained from the TCGA database, GEO database and CGGA database. Samples without clinical information were excluded. The source and number of people in the training and validation cohorts are shown in Table 1. The raw counts of the training cohort (TCGA-GBM, n=158) was obtained from TCGA database. According to the requirements of the xCell website, the gene expression of the training cohort (TCGA-GBM) was normalised to transcripts per kilobase million (TPM) for xCell analysis. For subsequent differential gene analysis, the raw counts of the training cohort (TCGA-GBM) were normalised by "DESeq" function in the "DESeq2" R package (14). For validation cohort 1 (GSE74187, n=60) and validation cohort 5 (GSE16011, n=154) the data format provided by the "Series Matrix File(s)" in the GEO database was used. For validation cohort 2 (mRNAseq-325, n=137) and validation cohort 4 (mRNAseq-693, n=237), FPKM values provided by the CCGA website were used. For validation cohort 3 (mRNA-array-301, n=114), the processed format provided in the CCGA website was used.

Immune infiltration assessment and prognostic grouping

The training cohort (TCGA-GBM) was analysed by the xCell method (15). The patients were grouped according to each cell type

TABLE 1 Source and number of patients in training and validation cohorts.

Group	Source	Alive n(%)	Dead n(%)	Radiation therapy n(%)	Chemotherapy therapy n(%)
Training cohort	TCGA-GBM	29(18.4%)	129(81.6%)	69(43.7%)	56(35.4%)
Validation cohort 1	GSE74187 (GEO)	14(23.3%)	46(76.7%)	Not reported	Not reported
Validation cohort 2	mRNAseq-325(CGGA)	13(9.4%)	124(90.5%)	100(73.0%)	99(72.3%)
Validation cohort 3	mRNA-array-301 (CGGA)	17(14.9%)	97(85.1%)	97(85.1%)	61(53.5%)
Validation cohort 4	mRNAseq-693 (CGGA)	27(11.4%)	210(88.6%)	193(81.4%)	99(84.0%)
Validation cohort 5	GSE16011 (GEO)	7(4.5%)	147(95.5%)	119(77.3%)	10(6.4%)

The Table 1 shows the data sources and specific details of this study, including dataset number, survival status, radiotherapy and chemotherapy treatment.

in xCell and divided into two groups (high and low) according to the median infiltration score. Then, we evaluated the relationship between each cell type and prognosis through Kaplan–Meier (K-M) survival analysis and univariate Cox regression analysis.

Differentially expressed gene analysis and enrichment analysis

To investigate the differences in gene expression at different levels of MSC infiltration, we divided the training cohort into two groups according to the median MSC infiltration score and performed differential analysis by the "DESeq2" R package. The screening conditions were restricted to |fold change| > 2, $p < 0.05$, and adjusted $p < 0.05$. To explore the potential biological functions of the up-regulated differentially expressed gene (DEGs), we further conducted Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene Ontology (GO) enrichment analyses.

Screening for the prognostic risk genes

To screen for genes strongly associated with prognosis, we performed univariate Cox regression analysis and K-M survival analysis. The least absolute shrinkage and selection operator (LASSO) analysis was employed, followed by 10 cross-validations with the "glmnet" R package.

Establishment of the GBM prognostic model

To construct the final prognostic model and determine the independence of the genes included in the model, we performed multivariate Cox regression analysis (16). The prognostic model of GBM was as follows: Risk score = $\sum$expgenei$*$ βi, where expgenei is the expression of each chosen risk gene and βi is the regression coefficient. A risk score was calculated from this model for each patient. We separated the patients into two groups (high- and low-risk groups) according to the cutoff point of the risk score by "maxstat" R package.

Single-cell RNA analysis

The single-cell sequencing data and cell markers used were taken from files in the supplementary file of the GEO database (17). The "Seurat" package was utilised to generate objects and filter out poor quality cells while performing standard data preprocessing procedures (16). Percentages of gene count, cell count and mitochondrial content were calculated. The filtering criterion was to detect cells with less than 20 detected genes. Retained genes detected in at least 1 cell. Filter out cells with less than 100 or more than 15,000 detected genes and cells with high mitochondrial content (>20%). We scaled the UMI counts using scale.factor = 10000. After logarithmic transformation of the data, the ScaleData function in "Seurat (v4.4.0)" was used. The corrected normalised data metrics were applied to the standard analysis. The first 2000 variable genes were extracted for principal component analysis (PCA). We performed cell clustering using the FindClusters function implemented in the "Seurat" R package (resolution = 2.0). "CellChat" package is an R package that can predict intercellular communication networks from single-cell RNA sequencing data (18). By inputting gene expression, signal ligands, receptors, and their co-factors, "CellChat" package can predict intercellular communication and visualise the results, which provides more meaningful information to help us understand the concrete mechanism.

Evaluation of predictive performance

K-M survival analysis was performed to evaluate the association between GBM risk grouping and overall survival and to check the predictive capability of our model. The log-rank test was used to determine significance. The prognostic areas under the curve (AUCs) at 1, 3, and 5 years were calculated with the "timeROC" R package. The above analysis methods were applied to the training cohort and validation cohorts. We compared the expression of immune checkpoints and related ligands in all cohorts between the two groups, including PDCD1 (PD1), CTLA4, HAVCR2 (TIM-3), TIGIT, BTLA, CD274 (PD-L1), PDCD1LG2 (PD-L2), and CD80 (19), and predicted the response to ICI treatment by TIDE (http://tide.dfci.harvard.edu/). TIDE was used to assess the possibility of immune escape in tumours. Higher TIDE scores indicate an inferior treatment response to ICIs (20).

Prediction of interaction genes and functional enrichment analysis

To explore the potential mechanism, the interaction genes of model genes were predicted by GeneMANIA (http://genemania.org/) (21). In terms of biological function, the model genes and the predicted interaction genes were analysed using the KEGG pathway analysis and the GO enrichment method.

Haematoxylin and eosin and immunohistochemistry staining in GBM

With the human subjects' understanding and consent and the approval of the Ethics Committee of the Second Hospital of Harbin Medical University (approval number: KY2022-001), we collected the magnetic resonance imaging (MRI) images and pathological sections of 6 GBM patients. Three of them were patients with OS < 15 months and the other three were patients with OS ≥ 15 months. Standard HE staining was performed to observe the GBM tissue structure. To observe the expression and location of the 3 risk genes, we performed IHC staining, which was conducted on GBM paraffin sections by using an anti-LOXL1 polyclonal antibody (1:400, PB0758, Boster, China), anti-LOXL4 polyclonal antibody (1:50,

TW11440, Shanghaitongwei, China) or anti-GUCA1A antibody (1:300, E-AB-53078, Elabscience, China). ImageJ was used for semi-quantitative analyses and Graphpad prism for histograms.

Statistical analysis

Plotting and statistical analysis were performed by R (4.0.5) and SPSS. The log-rank test was used to compare the significance of differences in component K-M survival analysis. The Wilcoxon test was used to compare gene expression between the two groups. A t test was used to compare TIDE scores between the two groups. A p value < 0.05 was considered significant.

Results

Worse survival situation in the higher MSC infiltration group

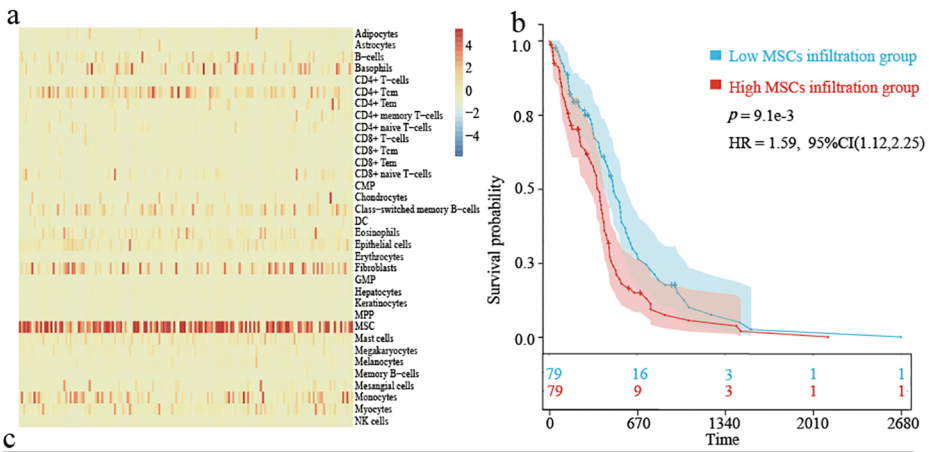
The heatmaps clearly present the first 34 cells in the xCell assessment (Figure 1A). Many immune cells were infiltrated to a lesser extent, and MSCs were more significantly infiltrated than other cells. K-M survival analysis and univariate Cox regression showed that higher MSC infiltration was significantly related to worse survival (Figures 1B, C).

Differential analysis and enrichment analysis

A total of 395 DEGs were screened between high and low MSC infiltration groups by using the "DESeq2" R package (Figures 2A, B). To explore the relevant risk pathways and details, we performed KEGG enrichment analysis. The results showed that most upregulated genes were significantly enriched in cytokine-receptor interaction processes and other signalling pathways (Figure 2C). The results of GO enrichment analysis showed that most upregulated genes mainly focused on cellular component (Figure 2D).

Establishment and validation of a 3-gene GBM prognostic risk model

After univariate Cox regression analysis and K-M survival analysis, we screened 38 prognostic genes from DEGs. When the lambda value was 0.207, we obtained three genes: LOXL4, LOXL1, and GUCA1A (Figures 2E, F). Through multivariate Cox analysis, the GBM prognostic model formula was as follows: Risk score = 0.131*LOXL1 + 0.170*LOXL4 + 0.136*GUCA1A (Figure 2G). The risk score distribution is displayed in Figures 3A–F. The prognosis was worse in the high-risk group (Figures 3G–L). The AUC value demonstrates that this prognostic model has good risk differentiation at 1,3,5 years (Figures 3M–R).



c

Cell	p.value	HR	Low 95%CI	High 95%CI	K-Mplot p.value
MSC	0.046	9.928	1.039	94.903	0.009
Epithelial cells	0.001	1.66E+13	1.51E+05	1.82E+21	0.053
Macrophages M1	0.039	936.726	1.4216	6.18E+05	0.067
Macrophages M2	0.044	519.137	1.187	2.27E+05	0.108
Monocytes	0.025	257.665	2.007	3.31E+04	0.461
NKT	0.106	20.442	0.525	795.763	0.103

FIGURE 1
Immune cell and stromal cell infiltration in TCGA-GBM patients. **(A)** Heatmap showing xCell assessment in GBM patients. **(B)** Kaplan-Meier survival analysis based on the grouping at the median value of MSCs infiltration scores in xCell. **(C)** The results obtained by univariate cox regression analysis and K-M survival based on each cell infiltration are presented by triliniear plots.

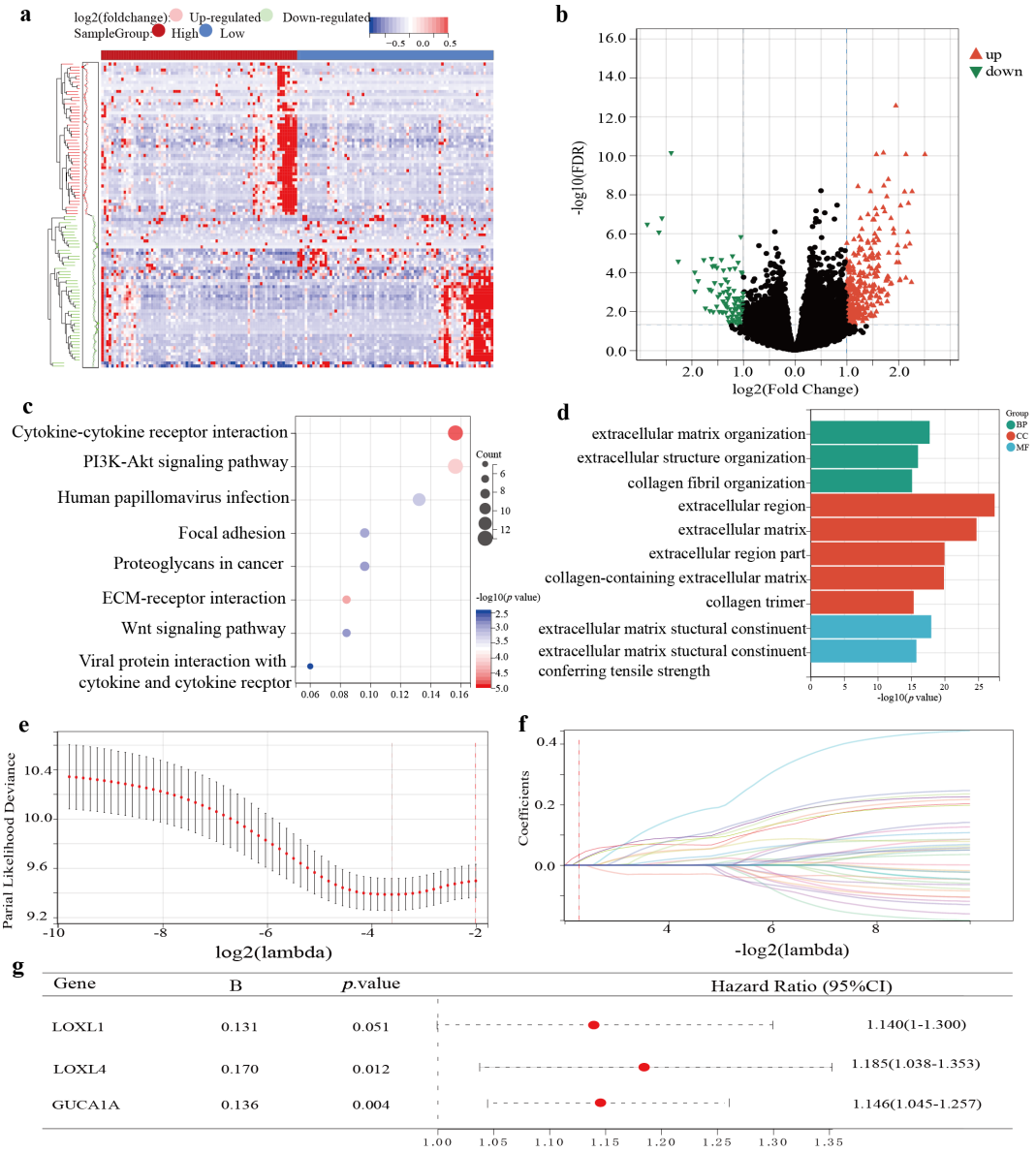


FIGURE 2
Identification and establishment of TCGA-GBM prognostic model. **(A)** The expression of DEGs based on the grouping at the median value of MSCs infiltration score is shown by heatmap. **(B)** Screening conditions for DEGs. **(C)** KEGG enrichment analysis for up-regulated DEGs. **(D)** Go enrichment analysis for up-regulated DEGs. **(E)** Partial likelihood deviation of LASSO-Cox coefficient curves. **(F)** A red dotted line painted at the value selected for 10-fold cross-validation to select the genes for the final construction of the prognostic model. **(G)** Prognostic model construction by multifactorial Cox regression analysis.

Single-cell RNA-seq analysis

Six cell clusters (myeloid cells, tumor cells, pericytes, neurons, endothelial cells, and lymphoid cells) were identified on the UMAP plot (Figure 4A). The number and strength of interactions in six cell clusters are shown in Figures 4B and C. The 3 risk genes have different expression levels in different cell clusters. Elevated expression of LOXL1, LOXL4 and GUCA1A was detected in tumour cells. In myeloid cells, increased expression of LOXL4 and GUCA1A was detected. In epithelial cells, elevated expression LOXL1 and GUCA1A was detected (Figure 4D).

Predicting the response to immune checkpoint inhibitor therapy

Box plots were used to demonstrate the expression of immune checkpoints and related ligands. Overall, immune checkpoints and related ligand molecules were more highly expressed in the high-risk groups. PDCD1LG2, PDCD1, TIGIT, and CD274 showed more significant differences in high and low risk groups across different cohorts (Figures 5A, C, E, G, I, K). In all cohorts, the high-risk groups all had higher TIDE scores, which revealed that the high-risk groups were less responsive to ICI treatment (Figures 5B, D, F, H, J, L).

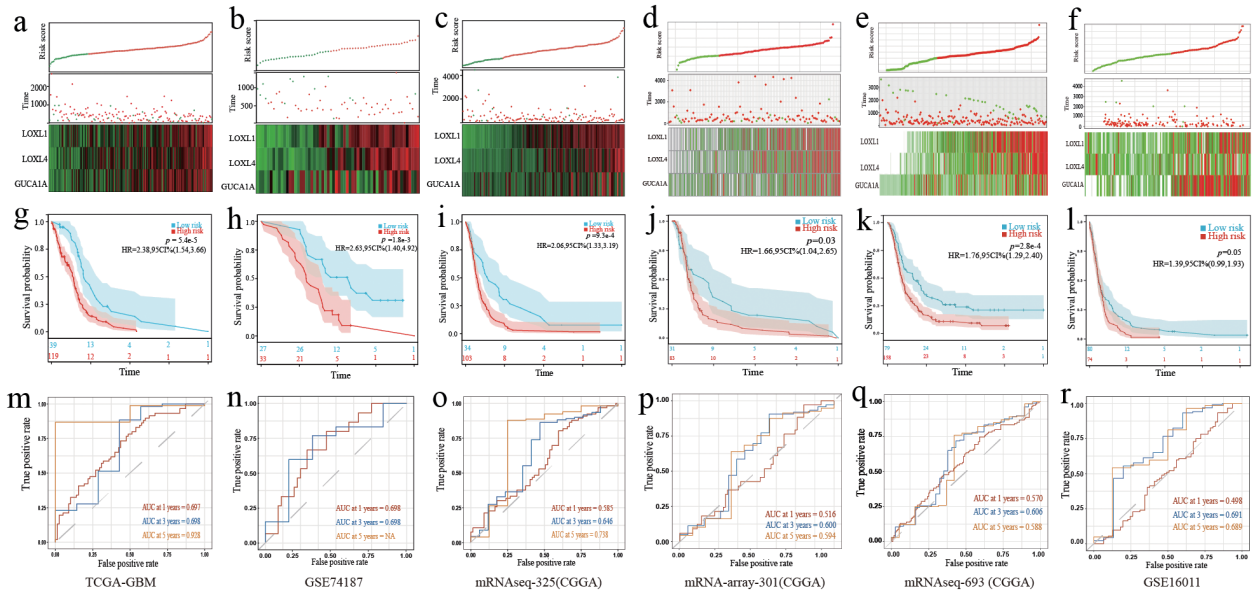


FIGURE 3
Validation of the 3-gene GBM prognostic model. **(A–F)** The distribution of the risk score, OS time, status of patients, and heatmap of the 3 risk genes expression profiles. **(G–L)** K-M curves showed survival differences in different risk groups. **(M–R)** TimeROC curves of the prognostic gene model. **(A, G, M)** Training cohort. **(B, H, N)** Validation cohort 1. **(C, I, O)** Validation cohort 2. **(D, J, P)** Validation cohort 3. **(E, K, Q)** Validation cohort 4. **(F, L, R)** Validation cohort 5.

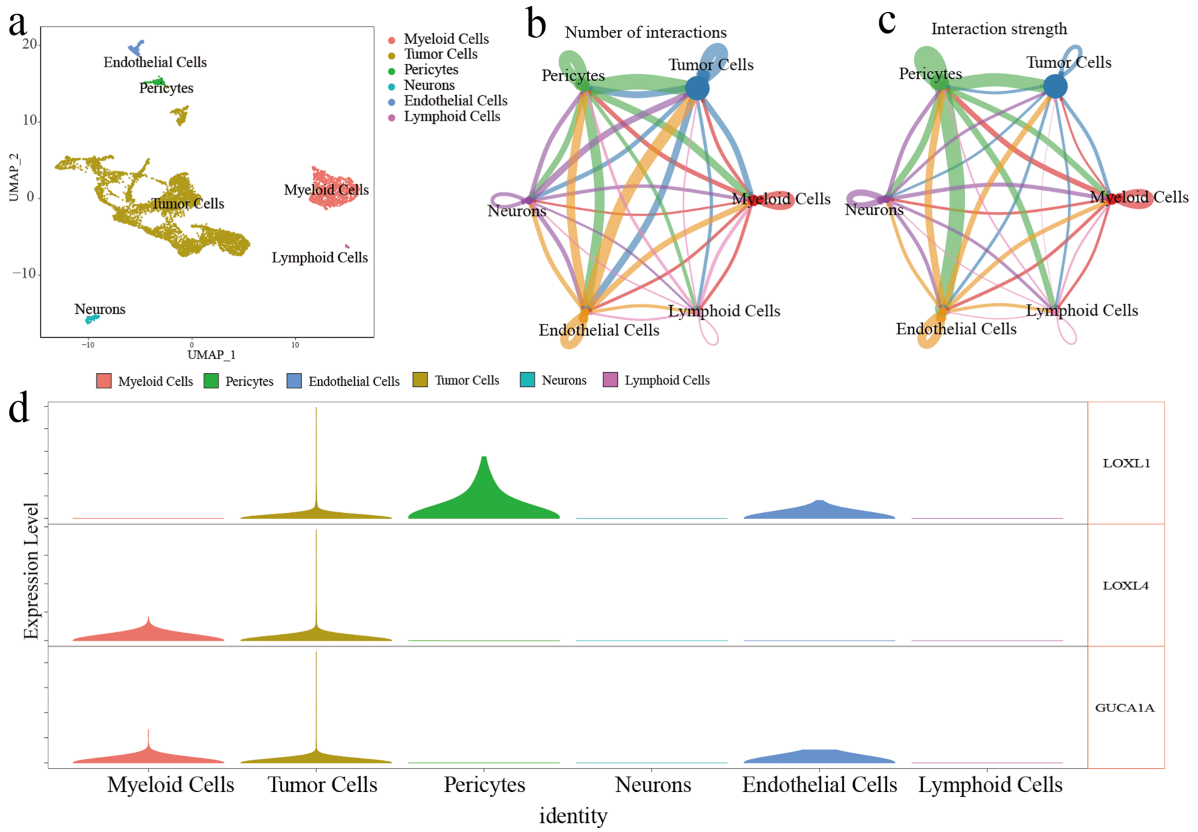


FIGURE 4
ScRNA-seq analysis of GBM. **(A)** Six cell cluster were identified on the UMAP plot. **(B, C)** The number and strength of interactions in six cell clusters **(D)** The expression level of three risk genes in six cell clusters.

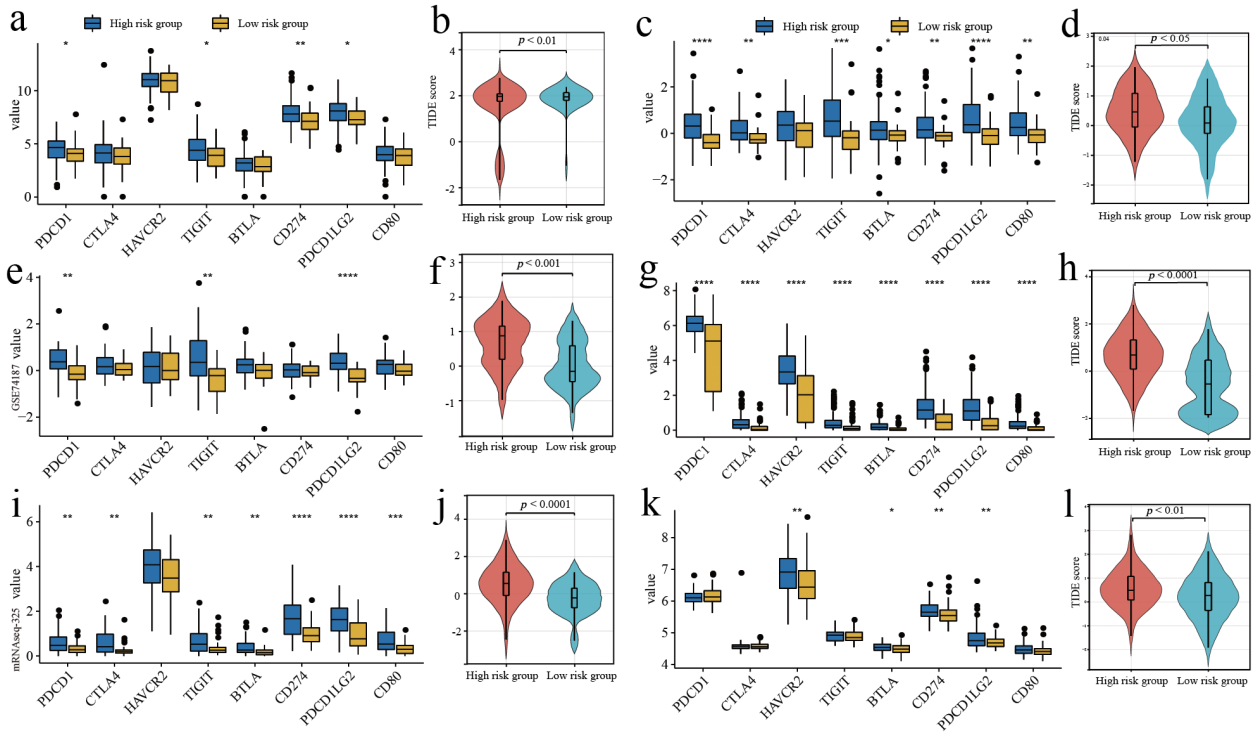


FIGURE 5
Predicting the response to immune checkpoint inhibitor therapy. **(A, C, E, G, I, K)** Comparison of the expressed amount of 8 immune checkpoint molecules. **(B, D, F, H, J, L)** Comparison of TIDE scores in different risk groups. **(A, B)** Training cohort. **(E, F)** Validation cohort 1. **(I, J)** Validation cohort 2. **(C, D)** Validation cohort 3. **(G, H)** Validation cohort 4. **(K, L)** Validation cohort 5. *p<0.05, **p<0.01, ***p<0.001 and ****p<0.0001.

Functional enrichment analysis of model genes and interaction genes

To predict the interaction genes of the 3 risk genes, we used GeneMANIA and output the visualisation results (Figure 6A). There are complex associations in physical interaction, co-expression and pathways, etc. The results of enrichment analysis displayed the model genes and interaction genes mainly participated in environmental information processing, metabolism and extracellular structure organisation, etc (Figures 6B, C).

The expression and localisation of the 3 risk genes in GBM patients

The GBM tumours located in the frontal lobe and temporal lobe (Figures 7A, C). We observed that the nuclear division of GBM cells was active. The shape of the nucleus was significantly atypical (Figures 7B, D). The positive localisation of LOXL1 was predominantly in the cytoplasm, with some nuclear plasma being expressed. The positive localisation of LOXL4 and GUCA1A was in the cytoplasm. Comparing the area fraction (%Area) of risk genes in GBM patients, it was observed that LOXL1, LOXL4, and GUCA1A were significantly elevated in patients with an OS <15 months (Figure 8).

Discussion

The tumor-promoting role of MSCs in GBM has been widely discussed in the past decade. However, the gene expression pattern of GBM based on MSC infiltration is still unclear (2, 6, 22). Based on MSC infiltration, we screened LOXL1, LOXL4, and GUCA1A as risk biomarkers for GBM to construct a prognostic model, which was further validated by external independent cohorts and IHC. MSCs contribute to the malignant progression of GBM by promoting the formation of stromal structures favourable for tumour cell dissemination and an immunosuppressive status. Our prognostic model may contribute to the risk stratification, prognosis prediction, and screening of ICI sensitivity of patients with GBM.

We found that MSCs may be the cellular component that has a significant effect on the overall survival of GBM patients. By analysing the immune and stromal cell infiltration in the GBM environment, the results showed that the GBM was in an immunosuppressed state, but MSC infiltration was very pronounced. Hossain et al. observed that MSCs isolated from fresh human GBM tissue promoted the growth and transformation of glioma stem cells into a mesenchymal phenotype, which showed more aggressive behaviour compared to other phenotypes (3). Researchers have discovered that MSCs can be recruited around tumor cells and secrete soluble proteins for tumor progression (23, 24). GBM produces large amounts of

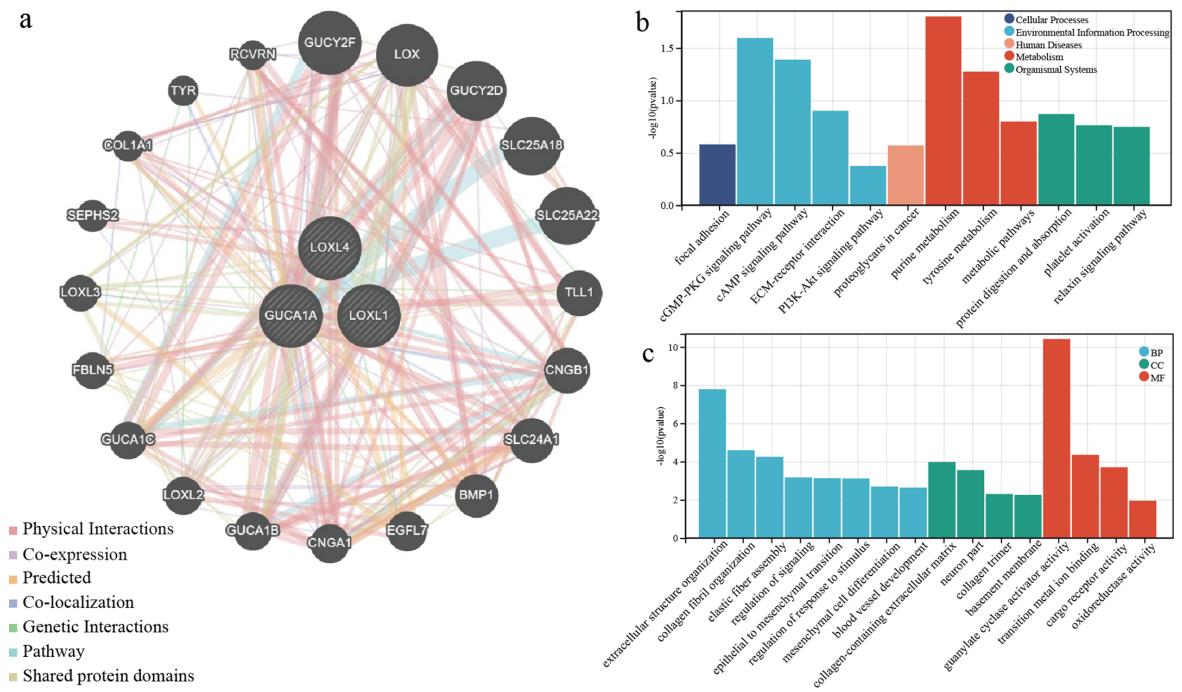


FIGURE 6
Functional enrichment analysis of model genes and interaction genes. **(A)** Prediction of interaction protein networks associated with three risk genes. **(B)** KEGG enrichment analysis for three risk genes and interaction genes. **(C)** GO enrichment analysis for three risk genes and interaction genes.

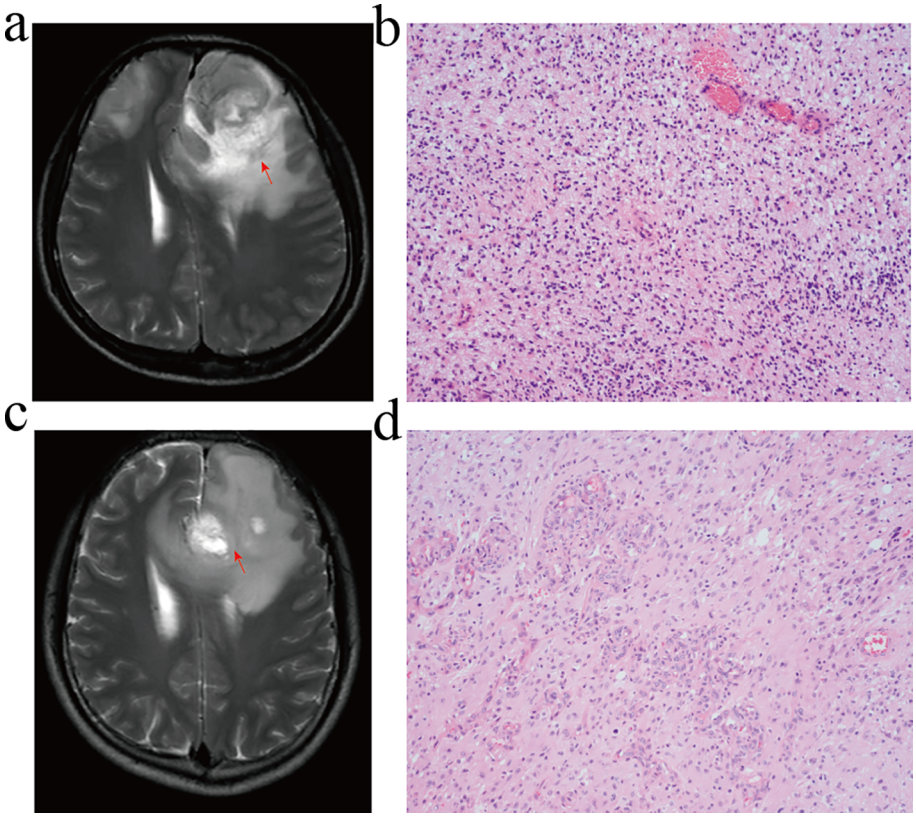


FIGURE 7
MRI and HE staining of GBM patients. **(A, B)** GBM patients with overall survival <15 months. **(C, D)** GBM patients with overall survival ≥ 15 months. **(A, C)** T2-WI; **(B, D)** HE staining, GBM cell had active nuclear division and typical nuclear morphology disappeared.

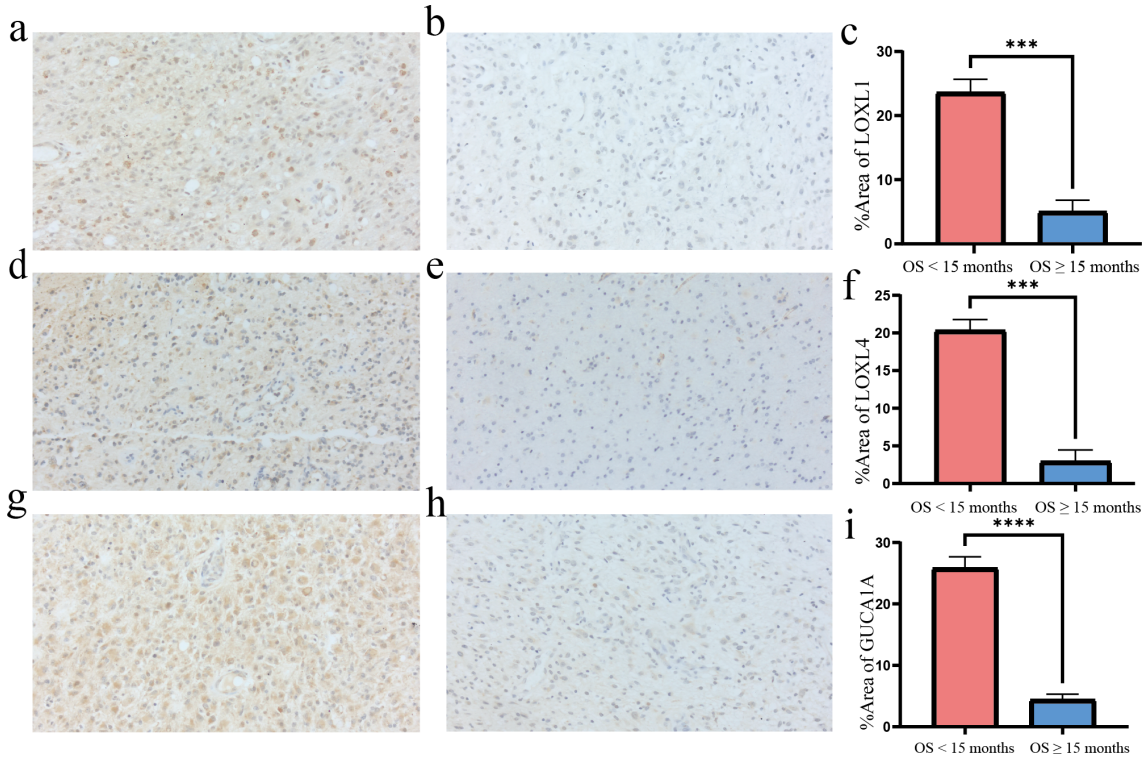


FIGURE 8
Immunohisctochemical detection of risk gene in GBM tissues. **(A, B)** LOXL1 immunohistochemistry: the positive expression was mainly in the cytoplasm and a few in the nucleus; **(C, F, I)** The %Area of risk gene in different group; **(D, E)** LOXL4 immunohistochemistry: positive localization in cytoplasm; **(G, H)** GUCA1A immunohistochemistry: positive localization in cytoplasm. Overall survival <15 months group compared to overall survival ≥15 months group ***p<0.001 and ****p<0.0001, N=3.

cytokines in the TME that recruit MSCs across the blood-brain barrier to the mesenchyme of the tumor tissue to further interact with tumor cells (2, 25–28). Mechanistic studies indicate that MSCs can migrate toward the GBM vasculature and transform into pericytes to produce shorter and more blood vessels than human epithelial cells. Cytokines secreted by tumor cells can induce the conversion of MSCs into CAFs to enhance the growth and angiogenesis of tumours. The abundance of tumor blood vessels is closely related to prognosis (4, 26, 29–31).

Bulk and single-cell RNA analyses have shown that intercellular signalling plays an important role in tumor progression. For example, the phosphatidylinositol 3-kinase (PI3K)/AKT signalling pathway, which plays an essential role in regulating the survival, proliferation, and migration of tumor cells (32, 33). In addition, it has been found that deregulated ECM may contribute to the transformation of the environment into an environment that promotes cancer (34). The upregulated DEGs primarily influence extracellular structure and communication, are involved in the robustness of extracellular collagen fibril structure, and regulate the TME into an environment more suitable for tumor cell growth (35). Collagen is at low levels in the normal brain. Up-regulation of collagen gene expression has been detected in gliomas and forms a collagen-rich matrix in the tumour microenvironment, which rapid migration of tumour cells in the brain tissue (36).

We continuously narrowed down the candidate genes through a series of analyses. A prognostic model containing three genes (LOXL1, LOXL4, and GUCA1A) was finally constructed for the risk stratification of GBM patients. The lysyl oxidase-likes (LOXLs) belong to the lysyl oxidase (LOX) family and are copper-dependent monoamine oxidases that promote the cross-linking of collagen and elastin to maintain the structural stability and rigidity of the ECM (37). As glioma malignancy increased, LOX family expression increased thereby promoting ECM stiffening. The stiffened ECM can disrupt vascular integrity and lead to the formation of a hypoxic environment, enhancing GBM malignant progression (38, 39). LOXL1 accelerates the proliferation of glioma cells by modulating the Wnt/β-catenin signalling pathway. Experiments showed that LOXL1 was upregulated by the VEGFR-Src-CEBPA axis and interacted with BAG2 proteins. LOXL1 prevented BAG2-K186 ubiquitylation and promoted tumor cell survival (40). Many studies have shown that LOXL4 is overexpressed and promotes tumor progression in some human malignancies, such as hepatocellular carcinoma and gastric cancer (41, 42). Earlier studies found that exposure of macrophages to LOXL4 induced an immunosuppressive phenotype in tumours and activated the expression of programmed death ligand 1 (PD-L1), which further suppressed CD8+ T-cell function and contributed to the formation of an immunosuppressive microenvironment (43). LOXL4, which is directly regulated by TGF-β1, is involved in vascular processes associated with vascular endothelial cell remodelling and fibrosis (44).

Guanylate cyclase activator 1A (GUCA1A) regulates the neuronal calcium sensing of the phototransduction cascade (45).

Previous studies showed that cone-rod dystrophy and macular dystrophy were associated with the GUCA1A gene mutation. In recent years, Liu et al. found that GUCA1A is significantly increased in osteoarthritis and is involved in the development and progression of osteoarthritis (46). Further research is needed to discover the molecular functions of GUCA1A to discover therapeutic targets for GBM. Although rare in-depth studies on the direct mechanism of model genes in GBM are currently available, our findings may provide a new perspective for exploring new relevant mechanisms for research in this field.

The enrichment analysis found that risk genes and interaction genes may be involved in various metabolic and environmental information processing, and may be associated with alterations in the structure of the tumor environment. Various metabolisms within brain tumours are reprogrammed to adapt to stress conditions, such as hypoxia, low glucose, low pH, or purine metabolism, maintaining tumor cell growth (47, 48).

In our study, the expression of multiple immune checkpoint molecules and their ligands was found to be generally increased in the high-risk group, with PDCD1, TIGIT, CD274, and PDCD1LG2 being significantly increased in at least five data cohorts. Combined with TIDE analysis, patients in the high-risk group were predicted to be less sensitive to ICI therapy. We therefore considered that the risk genes may be involved in regulating the process of aberrant activation of immune checkpoint molecules, which promotes the evasion of tumour cells from the surveillance of the immune system (49). Immune checkpoints are a class of immunosuppressive molecules that are expressed on immune cells to keep the level of immune system activation within the normal range and avoid overactivation of the immune system. However, in many malignant tumours, tumour cells are able to regulate the overexpression of immune checkpoints, blocking the process of antigen presentation to T cells, reducing T cell reactivity, and causing the tumour microenvironment to become highly immunosuppressive, which facilitates tumour cell survival by escaping from the surveillance of the immune system (49, 50). GBM may increase the risk of immune evasion through the regulation of risk genes and immune checkpoint molecules, leading to tumor progression (7). However, ICI has not yet achieved significant efficacy in the therapeutic application of GBM, which may be related to the existence of the blood-brain barrier, the low degree of T-cell infiltration and the complex highly immunosuppressive environment (51). However, this does not indicate that ICI therapy is completely ineffective in GBM, and a significant increase in overall survival was observed in GBM mouse models with the combination of anti-VEGF and ICI (52). In the future, the prognostic model constructed in this study will be useful for the selection of ICI treatment options and provide individualised treatment recommendations for GBM patients.

Our study is helpful for understanding the immune environment of GBM patients. MSCs have a great impact on the progression and prognosis of GBM. Here, we constructed a three-risk gene model for risk stratification and ICI application guidance in GBM patients. However, there is also the drawback of not being able to distinguish the origin of MSCs during immune infiltration assessment. Our work may provide new targets for the treatment of GBM. This is the first time that LOXL1, LOXL4 and GUCA1A have been explored as key risk genes for deteriorating the prognosis of GBM at the level of infiltration differences in MSCs. Risk genes may accelerate tumour cell growth and infiltration by promoting the formation of environmental structures more conducive to tumour cell spread and the construction of an immunosuppressive state. More in-depth research is needed to transform this conclusion into clinical practice. By assessing the expression levels of risk genes in GBM patients, it may be possible to predict the responsiveness of GBM patients to ICI therapy and provide risk stratification management and clinical treatment guidance.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: TCGA-GBM, http://cancergenome.nih.gov/. GSE74187, https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi. mRNAseq-325, mRNA-array-301, mRNAseq-693, http://www.cgga.org.cn/download.jsp. GSE16011, https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi.

Ethics statement

The studies involving humans were approved by The Ethics Committee of the Second Hospital of Harbin Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

SW: Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. SM: Data curation, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – review & editing. XFL: Data curation, Methodology, Project administration, Software, Validation, Visualization, Writing – review & editing. DY: Data curation, Formal analysis, Investigation, Project administration, Resources, Writing – review & editing. YZ: Formal Analysis, Project administration, Resources, Software, Writing – review & editing. HY: Methodology, Project administration, Software, Validation, Writing – review & editing. BL: Investigation, Project administration, Resources, Validation, Visualization, Writing – review & editing. WL: Formal analysis, Methodology, Project administration, Validation, Writing – review & editing. CL: Formal analysis, Investigation, Project administration, Supervision, Writing – review & editing. XZ: Conceptualization, Data

curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Preoperative subjective impairments in language and memory in brain tumor patients

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Background: Subjective reports can reveal relevant information regarding the nature of the impairment of brain tumor patients, unveiling potential gaps in current assessment practices. The co-occurrence of language and memory impairments has been previously reported, albeit scarcely. The aim of this study is therefore to understand the co-occurrence of subjective language and memory complaints in the preoperative state of brain tumor patients and its impact on Quality of Life (QoL).

Methods: 31 brain tumor patients (12 LGG, 19 HGG) underwent a semi-structured interview to assess subjective complaints of language deficits, co-occurrences between language and memory dysfunction, and changes in QoL. Group and subgroup analyses were conducted to provide general and tumor grade specific data.

Results: 48.4% of patients mentioned co-occurrence of language and memory impairments in reading, writing, and conversation. The HGG group reported co-occurrences in all three of these (reading: 31.6%; writing: 21.1%; conversation: 26.3%), while the LGG only described co-occurrences in reading (25%) and conversation (8.3%), although these were not statistically significant. All patients with co-occurring language and memory deficits reported these to be linked to reduced QoL (48.4%). In patients with an HGG, this number was slightly higher (52.6%) than in patients with an LGG (41.7%).

Conclusion: Language impairments co-occur with memory dysfunction as perceived in patients' daily life. Patients see these impairments as affecting their quality of life. Further attention to dedicated language and memory tasks seems necessary.

KEYWORDS

brain tumor, language, memory, subjective deficits, quality of life

1 Introduction

Evaluating multiple language functions is becoming common practice in the assessment of brain tumor patients (1–3). However, detailed evaluations of short-term and working memory (henceforth "memory") are less common [e.g. (4)]. More importantly, difficulties with memory have been previously reported (4–8) and can co-occur with language deficits (9–11). This relation between language and memory has been discussed in both healthy [for review see (12)] and clinical populations [e.g. (13–16)], suggesting, for example, that memory capacity is relevant for language production and comprehension as it relies on encoding, maintenance, recall, and manipulation of information [e.g. (17)]. Consequently, memory impairments have been associated with issues in sentence processing, reading comprehension, writing, and more generally with conversation abilities (4, 9, 11, 18–20). To illustrate, complex sentences may require a higher memory load than simpler sentences (21, 22). Damage of memory function can hence limit the ability to comprehend linguistically complex structures. Despite the co-occurrence between language and memory impairments, difficulties with memory and language are not consistently reported. Potential factors for this inconsistency may relate to patient selection (e.g., focusing on a specific tumor type, location, surgical intervention), or the use of different assessment protocols which include different tasks across centers (3, 10, 11, 23). For example, patients with tumors that grow particularly fast (e.g., high grade gliomas, HGGs) may be more severely affected in language and memory than individuals with slower growing tumors (e.g., low grade gliomas, LGGs; 4, 6, 24). Regarding protocols, survey work indicates that object naming and fluency tasks are typically used to assess brain tumor patients (2). However, other materials to assess memory are used more sparsely (3). Additionally, the tasks typically administered have often been standardized to assess stroke patients, where the sudden disease onset may cause more pronounced symptoms than in brain tumor patients (25).

The study of subjective complaints may provide complementary information to dedicated protocols, possibly unveiling potential gaps in current assessment practices. To assess subjective complaints, studies commonly use standardized Quality of Life (QoL) questionnaires. Examples are the EORTC-QLQ-C30 and BN20 (26) which address a wide range of topics to assess patient's well-being, symptom burden, and symptom management (27). However, these questionnaires often provide limited questions related to language and memory. To illustrate, the EORTC-QLQ30 and BN20 only include four questions relating to language (1x difficulty to read, 1x word finding difficulties, 1x difficulties to speak, 1x difficulty to communicate thoughts) out of a total of fifty questions. Memory disturbances are only reflected in one question.

Semi-structured interviews offer an alternative approach to these questionnaires. Previous studies employing this method highlighted the importance of language and memory and their co-occurrence for a wide variety of QoL-related factors, including work ability [e.g. (18, 28–30)], social participation and psychological distress [e.g. (31–33)]. For instance, patients with brain tumors reported a negative influence of memory disturbances on their communicative abilities that were perceived as limiting them in recollecting thoughts, the conversational content or the ongoing topic (18, 28, 34). These findings may suggest that good language performance does not only rely on an intact language system but also on other neurocognitive functions, such as memory [for discussion see (35–37)]. These findings cannot be validated using standardized questionnaires which highlights the added value of patient interviews.

Of particular interest for the study of the tumor impact itself on both language and memory functions and the consequences for QoL, preoperative assessments in brain tumor patients are indispensable, and also serve as a baseline for follow-up examinations [e.g. (2)], where treatment effects such as surgery and adjuvant therapies may have triggered (further) neurocognitive decline (1, 38, 40). Additionally, a preoperative baseline is crucial to determine the longitudinal trajectory of neurocognitive changes which can provide valuable information on the possibly differential recovery patterns across various neurocognitive functions. Indeed, some studies suggest that memory may recover more poorly after brain tumor surgery compared to language (40). Considering the above-mentioned detrimental effects of such long-term deficits on QoL, such as work ability (28, 30), these findings suggest that memory may be a crucial neurocognitive function to preserve, and requires preoperative assessment. Despite this relevance, preoperative deficits have not been as widely studied as postoperative neurocognitive deficits (11, 39, 41, 42), although patients with reduced QoL at baseline may also report QoL limitations at later stages (43). This is particularly true for qualitative studies assessing subjective neurocognitive complaints in brain tumor patients [e.g. (29, 44)]. Another aspect to consider is that these studies usually do not report the prevalence of these subjective deficits or differentiate patients based on tumor characteristics [e.g. (32)], leaving an uncertainty as to the relevance for the overall population of brain tumor patients or specific subgroups (e.g., patients with LGGs or HGGs). Differences across different tumor groups, especially in relation to tumor grades, have been previously reported, including language and memory function (6, 23, 45), mainly based on neuropsychological tests. Understanding whether this may translate to subjective dysfunctions, is necessary to improve patient consultation or neurorehabilitative measures.

The scarce literature available on preoperative subjective complaints supports the notion that language and memory dysfunction are present before treatment [e.g. (41, 46)] and limit QoL [e.g. (32)]. Considering that these studies rarely contrast patients with different tumor grades, the influence of these tumor grades on perceived preoperative impairments remains unclear. Taken together, the current information provided by these qualitative studies using interviews to assess subjective deficits, mainly hints at subjective changes particularly perceived in communication, with some observations of co-occurring memory deficits. Other difficulties, such as struggles with more specific

aspects of language such as writing or reading, are less frequently studied, causing a possible gap in the current literature.

1.1 Aims and predictions

We aim to understand the preoperative co-occurrence of subjective language and memory deficits in individuals with brain tumors and their relation to QoL. We will answer the following research questions:

1. Do language and memory deficits co-occur in preoperative subjective reports of brain tumor patients? If so, which are the most frequently reported language modalities (e.g., conversation, reading, writing) of this co-occurrence?
2. Are these deficits related to a perceived decline in QoL?
3. Do patients with LGGs differ from those with HGGs in their subjective reports?

We hypothesize that disturbances in memory and language will co-occur. Furthermore, we expect that most co-occurrences may be perceived during conversation, and that language and memory deficits contribute to reduced perceived QoL in patients. Finally, HGG patients will present with more difficulties and a higher rate of co-occurrence compared to LGG patients.

2 Materials and methods

2.1 Participants

Thirty-one patients with gliomas (mean age = 41.19, SD = 1.76, range = 22-61, male = 11, female = 20) were included. Twelve patients had a LGG and 19 had a HGG. Eligible patients were screened based on the diagnosis of a presumed glioma at the neurosurgical department of the Charité Universitätsmedizin Berlin from January 2023 until June 2024. Initial diagnosis was based on MRI scans, medical history, and physical exam. Data on demographic and tumor characteristics can be found in Table 1.

The inclusion criteria for this study were: having pathological results confirming glioma diagnosis; being a native German speaker;

TABLE 1 Demographic and tumor characteristics.

Patient	Age	Gender	Tumor diagnosis	WHO grade	Hemisphere	Location
P1	55	female	oligodendroglioma	3	left	parietal
P2	37	female	pediatric diffuse HGG	4	left	parietal
P3	57	female	diffuse LGG	1	left	temporal
P4	24	male	astrocytoma	2	left	insular
P5	47	female	glioblastoma	4	left	parietal
P6	52	male	glioblastoma	4	left	temporal
P7	25	female	astrocytoma	2	left	frontal
P8	45	female	glioblastoma	4	left	temporal
P9	27	male	oligodendroglioma	2	right	frontal
P10	34	male	astrocytoma	3	left	temporal
P11	61	female	glioblastoma	4	left	temporal
P12	38	male	oligodendroglioma	2	left	frontal
P13	51	female	diffuse LGG[1]	1/2	left	frontal
P14	45	male	glioblastoma	4	left	temporal
P15	33	female	astrocytoma	1	left	temporal
P16	61	female	astrocytoma	4	right	temporal
P17	36	male	astrocytoma	2	left	frontal
P18	35	female	astrocytoma	4	left	insular
P19	59	female	astrocytoma	3	left	parietal
P20	37	female	glioblastoma	4	right	temporal
P21	36	male	oligodendroglioma	3	left	parietal
P22	37	female	oligodendroglioma	2	left	temporal

(Continued)

TABLE 1 Continued

Patient	Age	Gender	Tumor diagnosis	WHO grade	Hemisphere	Location
P23	22	female	astrocytoma	3	left	temporal
P24	37	male	oligodendroglioma	3	right	frontal
P25	46	female	oligodendroglioma	2	left	frontal
P26	38	female	astrocytoma	3	right	parietal
P27	38	female	astrocytoma	3	right	insular
P28	39	male	astrocytoma	2	left	frontal
P29	51	male	astrocytoma	3	left	insular
P30	42	female	astrocytoma	3	left	frontal
P31	31	female	astrocytoma	2	right	frontal

[1]no further histopathology available.

and presenting with no severe language deficits, rendering the administration of the semi-structured interview impossible. Potential patients were then contacted via phone to provide information about the study and to ensure that inclusion criteria were met. Patients who were scheduled for surgery on short notice were provided with the study information during their hospital stay at least two days prior surgery. Ethical approval for this study was obtained from the Ethical Review Board of the Clinic (no. EA1/050/23). All patients consented to participate and signed a consent form.

2.2 Materials

A guide for the semi-structured interview was designed to ensure that all patients underwent the same questions and to avoid question omittance. The questions were based on findings from previous studies and deficits reported in admission and dismissal letters from the clinic. Importantly, the questions were pre-arranged into six topics to ease interview conduction as those topics evolve around the way patients use language in their daily lives, as well as to combine all relevant information for each topic for later analysis. Furthermore, if topics are used during patient consultation and screening that focus on easily identifiable topics based on daily life activities, identifying possible deficits may be facilitated for both the clinician and the patient. Topics included frequently observed language deficits (e.g., lexical retrieval deficits), topics revolving around the use of language in patients' daily lives (e.g., reading, writing, conversation), and QoL (e.g., work ability, family and social life, leisure activities). After a general question about each topic ("Have you perceived changes in writing?"), follow-up questions were posed ("Do you have problems constructing longer or more complex sentences?"). These follow-up questions were designed to capture more specific and subtle changes within each topic. To determine possible co-occurrences, the authors adhered to indicators in patient reports relating to memory, such as (problems with) recall, retention, or storage of information.

During the interview, the interviewer (LR) was allowed to ask additional questions to accommodate the patient's answers and ask for clarifications or examples, when needed. The interviewer ensured that patients had enough time to elaborate, repeat or reformulate questions, if needed. Therefore, no time limit was set for the interview. The duration of the interview questions varied between 5 and 32 minutes with a mean time of 14 minutes (SD= 9). The interview was conducted via phone call (N=5), online meeting (N=8), or in person in the clinic (N=18).

The full interview also comprised questions relating to socio-emotional functioning. These will not be reported in the current study, as they are deemed out of scope. Furthermore, patients reported a high variety of language deficits. In order to address these data in a suitable manner, especially with regard to the complexity and volume, another publication will be devoted. Here, we will report on the topics that allowed us to concentrate on the co-occurrence of language and memory deficits.

Examples of the questions are listed in Table 2 and the full series of questions included in the semi-structured interview can be found in the Supplementary Materials.

2.3 Data collection

The interviews were audio-recorded, transcribed verbatim using an automatic speech recognition system [e.g., Whisper (47),], and manually checked by a student assistant (MB) who is a native German speaker. Properties of speech, such as crying or laughing, were not transcribed, as they were not deemed relevant for the purpose of this study. After manual correction, LR extracted the relevant passages from the transcription, noted the presence or absence of a language deficit, and whether the participants reported a co-occurrence of language and memory deficits. These passages also served as citations to illustrate the impact of present deficits on the patients' lives. Based on this data, we identified those topics where patients most commonly perceived a co-occurrence of language and memory. Any doubts regarding the co-occurrence of

TABLE 2 Examples of interview questions for language (ex. 1-3) and QoL (ex. 4-7)[1].

1. Have you perceived changes in writing?
1. Do you write slower (and if, why)?
2. Do you have problems finding the right words?
3. Do you have problems compiling the text?
4. Do you have difficulties constructing sentences when reading?
2. Have you perceived changes in reading?
1. Do you read slower (and if, why)?
2. Do you have problems understanding what you read?
3. Do you have difficulties understanding sentences when reading?
3. Have you perceived changes in conversation?
1. Do you more frequently struggle to understand what another person is saying?
2. Do you have problems participating in debates?
3. Do you have problems following or understanding what others say?
4. Do you have difficulties in pursuing leisure activities?
1. If so, why? Which factors contribute to the inability to do so?
2. Have you adopted new leisure activities as a replacement? If so, why are these easier?
5. Have you perceived changes to your family life?
1. If so, why? Which factors contribute to these changes?
2. Do you perceive these changes as negative?
6. Have you perceived changes to your social life?
1. If so, why? Which factors contribute to these changes?
2. Do you perceive these changes as negative?
7. Have you perceived changes in your ability to work?
1. If so, why? Which factors contribute to these changes?
2. What has exactly changed?
3. Do you perceive these changes as negative?

[1]All questions are first followed by the prompt to give an example in case the patient does not immediately provide an example. For readability purposes, this is omitted here for every question.

language and memory deficits were checked with the senior author (AR).

2.4 Analyses

Descriptive statistics were performed to report frequency of perceived deficits. We conducted a group-level analysis that included the full cohort of this study, followed by a subgroup analysis to assess whether individuals with an LGG and those with an HGG differ from one another. Table 3 presents examples of this process (examples translated from German into English). Fisher's exact test was used to determine significant association between subgroups (LGG and HGG) and subjective co-occurrence of language and memory deficits.

3 Results

3.1 Language and memory co-occurrences

Co-occurrences of language and memory impairments were reported in the following three topics: reading, writing, and conversation. In total, 71% (n=22) of the participants reported difficulties within these three topics, with 48.4% (n=15) reporting a co-occurrence of language and memory deficits. The greatest number of co-occurrences was observed in reading (35.5%; n=14), followed by conversation (29%; n=11). Co-occurrences in writing were less frequently reported (12.9%; n=4; see Figure 1).

In reading, language deficits involved problems relating to dysgraphia and lexical retrieval, while the simultaneous presence of language and memory impairments was noted in, for example, the maintenance of information from sentences or whole passages [1,2].

> [1] I recently bought a new book. […] I did not get along with it. I did not understand the language. [Long sentences] are difficult to understand the text, I just cannot keep [them] in mind.
> [2] Even if I understand everything in terms of content, even if I look at it at short intervals, and can still understand the content of the sentence, but I can no longer keep it in the same way.

Difficulties in writing were furthermore reported due to impairments in language, such as lexical retrieval [3], but also due to co-occurring memory dysfunction [4].

> [3] When a word is missing, I especially notice that when I am writing. Then I cannot recall, for five seconds, how to write a simple word. And after the five seconds, it is immediately back again.
> [4] And I often have to think about how do I write this now and then what did I want to write?

In conversation, patients described similar problems relating to an inability to process and recall information from complex or long sentences, as well as maintaining the on-going topic [5-7].

> [5] I [sometimes] do not even understand what [someone] is saying to me. I really panicked because I thought all the words in my head did not come together to form a sentence. She repeated that to me 30 times and I was like, I do not understand. And I could not, I could not say anything. […] So, I have moments like that every now and then.
> [6] What do I want to say and which words can I logically compile for somehow making up a sentence to produce?
> [7] [When I listen to someone] the long sentences are bothering me, [it is] the length and the information density.

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TABLE 3 Examples of transcription extracts, topics and specifications.

Extract from transcript	Language deficit present?	Co-occurrence?	Topic
When I try to write, I need to think a lot about what I want to write. First, I know what I want to write, then I suddenly lose my train of thought and do not know what I wanted to write. If I then remember later on, I often cannot find the right word, or I forget what I was writing in the middle of the sentence. It sounds stupid, but sometimes I forget what I started to write at the end of a sentence.	Yes	Yes	Writing
When I talk to my partner, I need more time than before because I cannot think of the word I want to say. […] But I know what I want to say and can remember everything like before, it just takes longer because I need to think more.	Yes	No	Conversation

3.2 Language, memory, and quality of life

A reduced QoL was reported by 61.3% (n=19) of the participants. Of these, 79% (n=15; 48.4% of the overall cohort) reported their limitations in QoL to be associated with the impairments in language and memory. 10.5% (n=2; 6.5% of the overall cohort) reported reduced QoL due to language deficits only. The remaining participants (10.5%, n=2; 6.5% of the overall cohort) related these to worries and anxiety.

Changes in work ability were noticed in 12 of 31 patients (38.7%) in relation to cognitive deficits [8-11].

> [8] I could not recall everyday words that I need in the context of work. There was a meeting and I could not think of the word "brainstorming". That is a standard, being able to do this. […] That happens frequently.
> [9] I have a lot to do with processes and its steps. And processing steps also means that I need to start somewhere, opening a folder where the file is that I will need. I need to access this file and need the folder in which this information is. This has become increasingly more difficult [for 5 years]. […] And now I have written down, I get to that folder because I need that [file].
> [10] Then a few things with work colleagues. And then there were conversations again [that I could not understand], and conversations that had a little to do with legal data. And of course, you have to concentrate carefully, and remember. And there are a few things that I have to ask again.
> [11] And […] it has been much, much more strenuous for me to speak like that, to have intensive conversations. I can no longer give a speech, which I could do before. And, of course, I have always been a bit more careful about the language. But at the moment it is extremely difficult. Where do I have the common thread, where do I have to start?

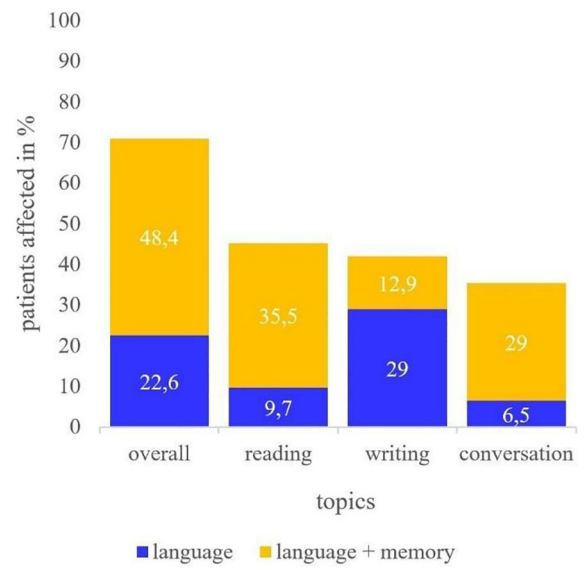

FIGURE 1
Deficits reported in reading, writing, and conversation. Report of patients perceiving language deficits only (blue) or both language and memory deficits (yellow).

Other commonly reported QoL complaints were due to increased worries, such as relating to epilepsy onset, neurocognitive deficits or surgery, affecting family life and leisure activities [12-16].

> [12] I initially had a strong fear of an epileptic seizure, so I have not dared going outside alone. So, I had a friend with me a lot. It got better because I have not had another seizure or, when [I could feel it approaching], I have developed my "calm-down-methods" and noticed that they worked.
> [13] I do not leave the area I am living in alone. [It is] too much. The seizures in my head, that I get a new seizure. Hence, I do not leave [my area] alone.
> [14] Of course you are worried. Definitely, yes. This is true for every area, especially concerning family and when it comes to the children. Well, to be completely honest, when I saw the two [children] last time, I cried bitterly.
> [15] I have taken care of many things [in case anything happens], wrote the health care proxy for my brother, insurances everything clarified, financially everything clarified, made videos […] for every single person. Today, as I said, I have written a letter to my son, today I want to write another letter to my daughter today. Because, I really worry about what is going to happen in the future, when I am not there anymore. That is a great burden. What is also a burden in addition is that I was always the strong part, who kept the family together. […] And if I do not have the opportunity anymore because I cannot walk properly, because I cannot express myself properly, yes,

that worries me a lot […]. And that I cannot be the father that I am and want to be.
[16] So, I have had great worries now and I am simply nervous and glad, when the surgery is over and the tumor is removed, because I worry due to my family history [of having brain tumors].

Besides family life, also social interaction in general was affected in those patients, partly due to their cognitive deficits [17-21].

[17] Now it is the case that I cannot think of arguments. And then I prefer to break off such a discussion because I then just get bogged down in it and then I get upset. And for example, my [partner] then thinks that I am upset with her. And then it turns into a fight, which of course I do not want. […] But I [cannot recall the arguments] at the moment.
[18] I then have to weigh up what is more important to me at that moment. Be it now when I meet for coffee and I know there will be an interesting event in the evening. How early can I have coffee? Can I estimate in advance whether it is a casual [conversation] or is it a somewhat more in-depth conversation? […] My social life also suffers a bit […] and that really gets me down.
[19] I don't exchange ideas with several of them because there is no kind of understanding. […] It [is] a bit fileted and not everything is discussed with everyone, with a few, but rather divided up a bit.
[20] Otherwise, I was often the one who could talk endlessly, without any problems, and also make people feel comfortable, so it is not like I just speak alone, but I also involve people. But now dialogues are much more difficult for me to follow and keep up with at some point and then not to leave at some point.
[21] And actually I wrote something and I thanked them. And the other one somehow replied that she was so disappointed in me. And I thought, what did I write to her then? I will have to check that again later. But I already wrote in response "I said I liked to, that I love you like the [other friends]. What was spelled wrong? I will have to take a look at that.

3.3 Differences between LGG and HGG

In reading, writing, and conversation, further differences between both groups were observed (see Figure 2).

HGG patients reported a higher number of co-occurrences of language and memory dysfunction compared to LGG patients (52.6%; n=10 vs. 41.7%; n=5). Importantly, HGG patients perceived more co-occurrences of language and memory in reading and conversation than language deficits only (reading: 31.6% vs. 26.3%; conversation: 26.3% and 15.8% respectively). Those with a LGG also described more co-occurrences in reading than language deficits only, as well (25% vs. 8.3%), but more language deficits than co-occurrences in conversation (25% vs. 8.3%). In writing, the LGG group did not report any co-occurrences. Reading, hence, seems to be most frequently affected by co-occurrences in language and memory difficulties in the full cohort, while co-occurrences in writing were only observed in the HGG group. These differences are, however, not statistically significant (p= >.05, two-tailed).

In relation to patients' QoL, 58.3% (n=7) of the LGG group reported reduced QoL, while 63.2% (n=12) of those from the HGG group perceived a reduced QoL. All patients with co-occurring language and memory deficits reported reduced QoL. For the LGG

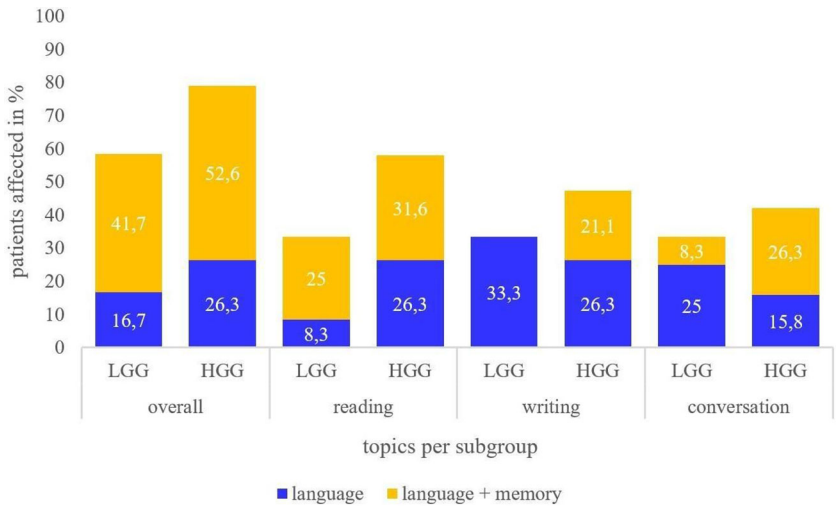

FIGURE 2
Deficits reported in reading, writing, and conversation in LGG and HGG subgroups. Report of patients perceiving language deficits only (blue) or both language and memory deficits (yellow).

group, this comprises 41.7% (n=5) of the group, and 52.6% (n=10) of the HGG group. Of the LGG patients, 16.7% (n=2) described a decline in QoL due to language deficits while they did not report co-occurring memory deficits. 10.5% (n=2) of the HGG group related their reduced QoL to their increased worries and anxiety. For HGG patients, work ability was the main QoL factor to be affected (HGG: 52.6%; n=10), while those with a LGG were similarly affected across work ability, family and social life (25% each; n=3).

4 Discussion

In the present study, we set out to assess the co-occurrence of language and memory deficits as subjectively perceived in the preoperative stage of a group of glioma patients. Analysis revealed co-occurrence of language and memory deficits in reading, conversation, and writing. While conversation and communicative abilities have been reported in previous qualitative work [e.g. (34)], the co-occurrence of language and working memory in these other domains has been seldom reported (28). To the best of our knowledge, this is the first study to explicitly focus on the co-occurrence of language and memory deficits in individuals with brain tumors.

In line with our hypotheses, individuals with brain tumors reported co-occurrences of language and memory deficits. These co-occurrences were reported by roughly 48% of our participants. Contrary to our predictions and the most frequently examined topic in the interview-based literature [e.g. (34)], conversation was not the most commonly reported topic where language and memory deficits were perceived to co-occur. Instead, co-occurrences were also frequently reported in reading (reading: 35.5%; conversation: 29%). This is an interesting finding, as reading has not yet gained as much attention in the scientific literature, as, for example, conversation. It may therefore be a relevant topic to further observe in this population considering the number of patients reporting difficulties in reading in their daily lives. Writing was the topic least affected by such co-occurrences (12.9%). Available preoperative subjective data by other authors also indicates both language and memory deficits and a negative impact on QoL [e.g. (32, 46)]. Patients in the study by Walter et al. (32) reported the greatest deficits in reading, similar to our findings, and further described deficits in writing, in addition to communicative limitations. These are three relevant topics also identified in this study. Whether the subjective complaints in Walter et al. (32) are partly related to co-occurring memory deficits cannot be determined, as this type of information was not reported. It can only be noted here, that their patient cohort also reported memory deficits.

It is interesting to see that postoperative findings in the current literature are in line with our preoperative data, as they also describe language and memory co-occurrences and the reduced QoL caused by these deficits [e.g. (18, 28)]. These studies report similar patient perceptions, such as forgetting the topic of an ongoing conversation or recalling content of conversations. Despite similar patient reports in our preoperative study, the comparison may not be as reliable considering the possible impact of treatment and adjuvant therapies in any postoperative cohorts. If we consult findings from studies employing quantitative methods to complement these results, we find that those are also in line with the present results [e.g. (9, 10, 45)] and may provide further explanations on the nature of this co-occurrence. These studies may suggest that memory function is crucial for both language comprehension and production (17, 37), including sentence processing. Patients in the present study reported, for example, subjective deficits at the sentence level. Hence, a reduced memory capacity may have partly affected language processing in production (writing, conversation) and comprehension (reading, conversation) alongside the language deficits. It seems, however, that co-occurrences of memory and language deficits are not found in all patients, requiring further studying of the precise mechanisms of these subjective impairments.

Confirming our hypothesis, language and memory co-occurrences were mentioned in relation with reduced QoL in the patients affected by these deficits. Besides work limitations, worries and changes in social and family life were related to poor QoL. This is in line with previous literature on QoL [e.g. (48, 49)], particularly in relation to issues such as return to work (20, 28, 29). Additionally, and even though this is not the main topic of the current paper, we also observed associations of language and memory complaints with increased worry and fear about the future and about social participation, which was also observed previously (18, 31, 49, 50). Consequently, deficits in language and memory have a widespread impact on many facets of QoL, and this study contributes preoperative data highlighting that QoL is already impaired preoperatively. Capturing this impact preoperatively is important to develop strategies about possible support a patient may need, including the development and deployment of new assessment tools, neurorehabilitative measures (pre- and rehabilitation), or psychooncological care for those with difficulties in their family and social life or psychological burden, especially if reduced QoL before treatment is indicative of QoL limitations at later stages (43).

Furthermore, based on the observation that co-occurring language and memory deficits were perceived as more detrimental to subjective QoL compared to those with only language dysfunction, memory may be an important neurocognitive function whose preservation is crucial to a wide variety of QoL areas, for example, regarding the ability to work which is in line with previous findings (18, 28, 30). If additionally, memory should indeed recover more poorly than language, as indicated by previous studies (40), and if this impairment causes a negative impact on QoL, as reported in this study but also suggested by previous literature (28, 34), memory may be relevant to patients' daily lives and activities, and therefore an aspect relevant to preserve. Future longitudinal studies that include such preoperative assessments (and re-assessments) at different timepoints after surgery, seem needed to determine whether memory, in addition to language, is a function that recovers poorly and therefore requires dedicated assessment perioperatively and longitudinally.

We also hypothesized that patients with a HGG would present with a higher rate of co-occurring language and memory deficits compared to those with an LGG, which could not be statistically confirmed. Consequently, these findings are not in line with previous studies that report a higher prevalence of deficits in

patients with a HGG compared to those with a LGG, especially from objective testing [e.g. (4, 6, 24)]. A comparison to previous interview data can scarcely be drawn due to the limited number of studies using this method, as those studies often did not assess differences in relation to tumor characteristics, such as tumor grade [e.g. (32, 46)] or assessed only LGG patients (49). For LGG, Antonsson et al. (49) reported 8.7% of their cohort to have difficulties in conversation, which is a lower rate than in the LGG group reported in the present study (33.3%). This may be explained by the volume and details in questions we used in our study. In consideration of these non-significant differences across subgroups, it may be suggested that language and memory co-occurrence may be of importance to brain tumor patients in general and across different topics and activities, with negative impact on QoL. This may be stressed by the observation that all LGG and HGG patients who reported co-occurring language and memory deficits reported a reduction of QoL. It needs to be highlighted here that again the professional life was particularly affected in HGG patients, with an equal limitation of LGG patients in their professional, social, and family life.

The importance of language and memory co-occurrence may require a more rigorous assessment of memory. Further work may be needed to adapt current neuropsychological test batteries to the needs and often rather mild symptoms observed in brain tumor patients, and accompany these assessments with QoL measures to determine whether a closer examination of memory in addition to language improves. This may include return to work after surgery considering limitations in professional life patients of this study already had preoperatively. If future studies have similar findings as to the relevance of memory, especially in case of deterioration after surgery, assessing memory in awake surgery may be a relevant addition to preserve this function. To date, memory and language assessments may be recommended for both HGG and LGG patients.

4.1 Limitations and future directions

The study included a heterogeneous group. Although this was intended to determine the prevalence in the overall glioma population, demographic and tumor characteristics, including tumor location, and infiltration of white matter tracts, may differentially contribute to the subjective deficits assessed in this study [e.g. (8, 51)]. This information may need to be addressed in a future study with a greater cohort. Indeed, the present cohort is rather small, especially for the LGG group (n = 12), so we should proceed with caution as these findings may not be representative of the whole population, but rather serve as an explorative study.

Even though the questions we used are partly based on previous work (18, 28, 34), it is possible that some of the difficulties mentioned also relate to psychological effects such as worries and distress, which we did not directly account for (33). Further work could add questions regarding stress and anxiety, along with the questions we proposed [e.g. (50)]. It needs to be mentioned that the responses may indicate that other functions may also contribute to deficits in language abilities, such as reduced processing speed or attentional deficits. This will require further analysis.

The high prevalence of perceived language and memory co-occurrence may also be related to the ability to create compensation mechanisms. Patients may find it easier to compensate for language deficits (34), while compensation mechanisms for memory deficits may be perceived as more effortful, for example, they may require taking further actions, such as taking notes (46, 52). Therefore, difficulties with memory (vs. language) may be perceived as triggering greater limitations in QoL in those affected by both language and memory deficits. Differences in compensation strategies in language and memory impairments may therefore deserve attention in future studies.

Furthermore, the analysis in this study focused whether or not patients perceived memory deficits. Consequently, no strict differentiation of the nature of the memory disturbance (e.g., short-term or working memory) was made. The focus of this paper is on the added value of asking additional questions relating to memory and language as perceived subjectively by patients in an interview setting, as can be done, for example, by clinicians during patient consultation. Here, questions relating to patients' daily activities was deemed to be easier understandable by the patient than questions relating to specific processing steps. An analysis using linguistic or neuropsychological models may supplement such patient-focused questions, and provide information on, for example, tasks that may be necessary to capture these subjective deficits. This was, however, considered out of scope for the present study.

Besides these limitations, the results from these semi-structured interviews provide relevant information on possible deficits and their relationship with QoL. Subjective data as provided by such interviews seems to be a powerful complement to neurocognitive assessments and questionnaires, as these alone may not provide sufficient information [e.g. (7–10, 23, 53)]. From a clinical perspective, these findings may be of further use: the topics defined in the questionnaire seem to yield various additional insights into patients' deficits, which may make these useful and informative during patient consultation, but also to support the choice of neuropsychological tasks for patient assessment or during awake brain surgeries, and possible neurorehabilitative measures. Furthermore, a more exhaustive memory assessment in addition to language tasks may allow us to objectivize these findings.

5 Conclusion

Almost half of our sample report co-occurring problems in language and memory, when asked for preoperative difficulties using a semi-structured interview. These problems are particularly perceived in reading, writing, and conversation. Patients who report problems in both language and memory more frequently report limitations in QoL, than patients that report problems in language only. Further attention to the study of memory in this population seems granted.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by ethical committee of the Charité, no. EA1/050/23. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

LR: Conceptualization, Data curation, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. RJ: Conceptualization, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. MB: Data curation, Writing – review & editing. TR: Conceptualization, Writing – review & editing. PV: Funding acquisition, Writing – review & editing. TP: Funding acquisition, Resources, Writing – review & editing. KF: Conceptualization, Funding acquisition, Supervision, Writing – review & editing. AR: Conceptualization, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2024.1475860/full#supplementary-material

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Sexual life in adults treated for brain tumors: a retrospective study

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Objective: Sexual functioning is a multifaceted aspect of human life that can be profoundly affected in patients with glioma. Most frequent symptoms include reduced sexual desire, difficulties in sexual arousal, or low satisfaction. Such symptoms may cause distress or interpersonal difficulties, inevitably resulting in negative outcomes on different domains of patients' quality of life. Despite this, sexuality is rarely addressed by medical staff and remains understudied. An important question still unanswered is whether sexual dysfunctions in glioma patients correlate with features of the tumor itself, with its treatment, or with the secondary effects of the tumor on the patient's psychological status. To answer this question, the present study aims to investigate the incidence of sexual life impairments in a very large population of patients with low- and high-grade gliomas, focusing on demographic, clinical, and treatment factors associated with their occurrence and developments.

Methods: A total of 148 patients treated for glioma were evaluated for sexual functioning, i.e., sexual dysfunction (SD), relationship status (RS), intercourse frequency (IF), and sexual satisfaction (SS), by using a specific anonymous questionnaire. Descriptive statistics were utilized to investigate participant characteristics and to evaluate the occurrence of sexual problems. Chi-squared tests were performed to detect the association between "SS" or "IF" and different clinical/demographic factors as well as between "SS" or "IF" and the "subjective–personal skills judgment".

Results: Results showed no difference between male and female patients, a very low frequency (1.4%) of SD, but a consistent percentage (25%) of subjective deterioration in sexual wellbeing. Notably, 24% of patients reported to have interrupted their relationship after the diagnosis. Chi-squared analyses reveal an association between adjuvant treatments (chemotherapy and radiotherapy) and reduction of IF. Interestingly, "SS" or "IF" was not associated with demographic, clinical, or histomolecular factors.

Conclusion: Our study showed that sexual problems in glioma patients are not uncommon, and they are especially linked to SS, RS, and IF. Specifically, intercourse frequency reduction is associated with the adjuvant treatments. Results highlight the need for improved assessment strategies and interventions tailored to the unique needs of brain tumor patients.

KEYWORDS

sex, sexual satisfaction, desire, brain tumors, quality of life

1 Introduction

Gliomas are a rare cancer disease (estimate incidence, 25.48 per 100,000) (1), with a significant impact on patient quality of life (QoL). Recent advances in imaging and surgical and adjuvant treatments (chemotherapy and radiotherapy) improve diagnosis, progression, and overall survival. For example, in patients with suspected lower-grade gliomas, the use of a functional neurosurgical approach increases the extent of resection and reduces recurrences, while improving symptoms and reducing cognitive deficit, resulting in a longer and better patient QoL. Currently, most lower-grade glioma patients are expecting to live a long, normal social and professional life (2–4), and therefore, the preservation of QoL has become a crucial issue for surgical and medical neuro-oncologists.

The burden associated with a diagnosis of glioma is dramatic for patients as individuals and for their families. The disease, its diagnosis, and the surgical and adjuvant treatments negatively affect several domains of the patient's QoL (4), among which the impact on his/her sexual life, which is often underestimated and thus ignored. Cancer patients often face symptoms of sexual life impairment from the time of diagnosis or time of treatment initiation, and these symptoms are likely to persist or even increase in the long term (5). Recent studies reported that, irrespective of the tumor type, 40% of cancer patients, especially young adults, experience sexual problem within the first 2 years following tumor diagnosis (6). The most frequently reported sexual symptoms include reduced sexual desire, difficulty in sexual arousal or orgasm, or low satisfaction with sexual life. Such symptoms may cause marked distress or interpersonal impasse with a substantial negative effect on different aspects of patients' QoL, often preventing patients from establishing or maintaining an intimate relationship or even building a family. Unfortunately, sexual health is rarely considered or addressed by an oncologist or medical staff (7–10), possibly because of lack of time and/or lack of clarity about relevant factors likely to affect patients' sexual life in their care path (11). Despite the fact that patients clearly report the need to discuss aspects of their sexual life during hospital consultation (12), uncovering an issue critical for them, the impact of the diagnosis or of its related treatments on sexual life is rarely investigated (13) or mainly limited to the investigation of brain networks potentially involved. The scarce available literature reports an association between right-side resection and difficulty in reaching orgasm and, in men, between temporal lobe resection and reduction of sexual drive and arousal (14). Independent of the specific brain areas involved, sexual symptoms most commonly reported are related to sexual desire (34%) or arousal (37.5%) (10). Such symptoms occur particularly (approximately 50%) in patients affected by LGG and in women (14–16). Limitations of these studies are the small sample size (32–50 patients only), the restriction to lower-grade patients, and the descriptive nature of the analysis.

This study aims at overcoming these limitations and at describing the incidence of sexual life impairments in a large population of glioma patients, including low- and high-grade gliomas, and also investigating the demographic, clinical, and treatment factors associated with their occurrence and developments.

2 Materials and methods

2.1 Participants and data collection

Participants were selected among patients treated for glioma at our Neurosurgical Oncology Unit.

Patients were included if they fulfilled the following criteria: (I) age ≥ 18 years; (II) absence of severe comprehension deficits affecting the ability to complete the questionnaires; (III) histomolecular diagnosis of LGGs or HGGs; the LGG group included patients with grade II and grade III IDH-mutated and grade II wild-type gliomas, and the HGG group included patients with grade IV wild-type or mutated IDH tumors; (IV) absence of motor deficits; and (V) absence of mood disorders. For each patient, the clinical records relative to tumor (type, grade, and location), medications (anti-epileptic drugs -AEDs- and steroids), and adjuvant therapies (chemotherapy and radiotherapy) were considered for the retrospective analysis, together with socio-demographic characteristics (age and level of education), personal or family history of psychiatric disorder, and current or previous treatments with psychotropic medication.

2.2 Study design

Data about sexual life were collected with a self-report questionnaire (see section 2.2.1 for details) administered within the routine neuropsychological/psychological evaluation aimed at assessing the QoL of patients treated at the Oncological Neurosurgery Unit of the IRCCS Ospedale Galeazzi-Sant'Ambrogio for brain tumor resection.

2.2.1 Questionnaire

During the routine neuropsychological/psychological evaluation, patients were assessed with a self-report questionnaire regarding sexual life divided into six sections, specifically designed to investigate the following aspects:

- *Section 1. Demographic information:* sex, sexual orientation, age, partnership status (married/cohabiting, separated/divorced, widowed, or single/never married), and current and past occupational status.
- *Section 2. Medical history and anamnestic information*: cancer diagnosis, other medical diagnosis, drugs taken, and treatment received (number of surgical interventions, adjuvant treatments, and type).
- *Section 3. Organic sexual dysfunctions*: penile erection/vaginal lubrication and ability to reach orgasm.
- *Section 4. Relationship status:* participants were asked about their relationship status before diagnosis and at the time of the questionnaire, and they were asked to indicate the reasons in case of termination of their previous relationships.
- *Section 5. Subjective impact of the disease on sexual pleasure*: the participants were asked to state whether their current sexual experience, i.e., "sexual satisfaction" (interest/desire) and "sexual performances/activities" (frequencies of sexual intercourse), has improved, deteriorated, or remained unchanged compared with the status before diagnosis. If participants reported changes, they were asked to indicate the subjective reasons.
- *Section 6. Subjective judgment about subjects' following skills*: to communicate personal feelings, to satisfy a partner, to reach orgasm, to be seductive, and to reach a satisfying level of excitement. Each item was scored on a five-point Likert scale (1 = not at all, 2 = a little, 3 = quite a bit, and 4 = very much).

2.3 Statistical analyses

Statistical analyses of the anonymized data were performed by using IBM SPSS Statistics Software 20. Descriptive statistics were performed to investigate participant characteristics and to provide occurrence of sexual problems. Chi-squared tests were performed to detect the association between "sexual satisfaction" or "frequencies of sexual intercourse" and various clinical/demographic factors (age, gender, education, IDH mutation, tumor histology, tumor grade, and affected lobe), and between "sexual satisfaction" or "sexual intercourse" and their personal skill judgment.

3 Results

3.1 Sample

For the statistical analyses, we included all patients who completed the questionnaire, i.e., 148 patients. Of the included patients, 80 (54%) were men and 68 (46%) were women (mean age, 46 ± 12.7 years). Mean interval time from diagnosis was 44.8 months (SD 25.9). Demographic and clinical characteristics of the sample are displayed in Tables 1, 2. According to the histomolecular profile and location, 100 (68%) were diagnosed with an LGG; 73 (58%) patients were operated for a left hemisphere lesion and 120 (81%) patients were also submitted to regular clinical and radiological follow-up in our center. All patients with HGG, included in this study, were submitted to the same adjuvant treatment: radiotherapy fractioned in 30 sessions with temozolomide as the chemotherapeutic agent (average, 10 cycles).

TABLE 1 Demographic characteristics.

Age, years (SD)	46 (12.7)
Educational level, years (SD)	14.3 (2.8)
Gender	
Female	80 (54%)
Male	68 (46%)
Sexual preferences	
Hetrosexual	145 (98%)
Homosexual	2 (1.4%)
Bisexual	1 (0.6%)
Pt with a relationship before tumor diagnosis	113 (76.4%)
Children	
Yes	88 (59.5%)
No	60 (40.5%)
Employment	
Office worker	47 (32%)
Manager	36 (24.3%)
Laborer	30 (20.3%)
Unemployed	15 (10%)
Retiree	12 (8%)
Student	8 (5.4%)

TABLE 2 Frequency of clinical characteristics.

Tumor grade	
LGG	100 (68%)
HGG	48 (32%)
Hemipshere laterality	
Left	73 (58%)
Right	62 (46%)
Lobe affected	
Frontal	45 (30%)
Temporal	37 (25%)
Parietal	26 (18%)
Insular	25 (17%)
Other	15 (10%)
Stage of care	
Follow-up	120 (81.1%)
Radiotherapy	15 (10.1%)
Chemotherapy	13 (8.8%)
Radiotherapy	
No	93 (63%)
Yes	55 (37%)
Chemotherapy	
No	96 (56%)
Yes	52 (35%)
No. of surgery	
1	87 (59%)
2	47 (32%)
3	9 (6%)
>3	5 (4%)
Antiepileptic drugs	
Yes	100 (68%)
No	48 (32%)
Comorbidity	
Heart disorders	12 (8%)
Urinary incontinence	9 (6%)
Prostate dysfunction	7 (10%)

3.2 Descriptive results

Descriptive analyses (percentages) were used to provide the occurrence of organic sexual dysfunction and changes in sexual life, i.e., relationship status and subjective impact of the disease on sexual pleasure, based on questionnaire responses.

3.2.1 Organic sexual dysfunction and relationship status

Only 1.4% of the patients sampled reported "Organic sexual dysfunction": 1 of 80 men reported sporadic episodes of erectile dysfunction; 1 of 68 women reported vaginal lubrication difficulties. Regarding relationship status, 23 patients (24%) reported to have interrupted their relationship after the diagnosis of a brain tumor.

3.2.2 Subjective impact of the desire on sexual pleasure

Among the 148 patients, 41% (n = 62) reported experiencing a sexual change following the diagnosis, with 25% (n = 38) reporting a subjective deterioration in sexual wellbeing and 16% (n = 25) reporting an improvement. Even though only 25% of patients reported to be dissatisfied with their sexual life, when directly asked about changes in the "frequency of intercourses", several participants (48%) reported a decrease of frequency after tumor diagnosis, especially after treatments (25% after surgery and 23% after adjuvant therapies). Specifically, the frequency of intercourse was higher before diagnosis in 82% of patients (several times a week in 38% and 2 or 4 times a month in 45%) than after diagnosis (several times a week in 15% and 2/4 times a month in 30%).

Different factors were reported to be subjectively associated with "sexual dissatisfaction" and with a "reduced frequency of intercourse". Asthenia, due to adjuvant treatments, was associated with both aspects (sexual dissatisfaction and reduced frequency of intercourse) in 47% of patients. Additionally, "relationship issues" emerging during the care path were associated with sexual dissatisfaction in 36% of patients and a reduction in the frequency of intercourse in 41% of patients. "Lack of desire", followed by "physical problems", was associated with sexual dissatisfaction in 11% of patients and a reduced frequency of intercourse in 14% of patients. Finally, "drug effects" (AEDs and corticosteroid) were associated with both sexual dissatisfaction and a reduced frequency of intercourse in 4% of patients.

The last part of the questionnaire self-evaluated the patients' personal feeling relative to their relational and sexual skills before diagnosis; one-third of participants reported a diminished capacity to "satisfy the partner" (32%), or to "reach orgasm" (32%), or "feeling sexual and attractive to others" (27%), or to be "self-confident" (27%) following the diagnosis. Patients ascribed these difficulties to different conditions: cognitive deficits (32%), asthenia (32%), drug effect (22%), alteration of self-image (17%), relationship difficulties (17%), subjective reduction of the motor abilities (15%), effect of adjuvant treatment (chemotherapy and radiotherapy, 15%), mild psychological symptoms (reactive anxiety for the prognosis, 8%), illness-related pain (8%), or loss of interest by the partner (8%).

3.3 Factors associated with sexual and relationship changes

Sexual and relationship changes were correlated with several functional and clinical features. The analysis showed that the "frequency of intercourses" was negatively associated with

adjuvant treatments ($p = 0.042$), with 55.4% of patients submitted to adjuvant treatments reporting a reduction in the frequency of intercourse, in comparison to patients submitted to the sole follow-up (39.8% of reduction). Interestingly, "sexual satisfaction" or "sexual intercourse" was not associated with any demographic, clinical, or histomolecular factors (see Table 3).

4 Discussion

In this study, a non-randomized, retrospective analysis was conducted to evaluate sexuality in a large cohort of patients surgically treated for glioma, without previous or concurrent psychiatric disorders. This is one of the largest population-based studies of sexual function ever conducted in the brain cancer population ($n = 148$). The first relevant result is the lower occurrence (1.4%) of organic sexual dysfunctions (i.e., erectile dysfunction/vaginal lubrication impairment) compared with the incidence reported in other studies (14, 16). Despite the negligible percentage of patients with organic sexual dysfunctions, a relevant percentage (25%) of patients reported a subjective deterioration in sexual wellbeing and about half of the sample (48%) reported a decrease of intercourse frequency (two to four times a month). Both changes were significantly associated with treatment (25% after surgery and 23% after adjuvant therapies). These data are also validated by the assessment of subjective perception (subjective factors) related to the worsening of the patients' quality of sexual life. Adjuvant treatments and related side effects (e.g., asthenia) are reported as determinant factors in 15% and 32% of the sample, respectively. Our results, supporting previous research (16–18), suggest that both the subjective deterioration in sexual wellbeing and the decrease of intercourse frequency experienced by our patients might be due to an indirect effect of the treatments. Treatment side effects on specific aspects of QoL, such as worsening (real or perceived) of physical conditions, lack of social support, or changes in body images mainly due to the radiotherapy, may be responsible. Patients who have undergone adjuvant treatments are at increased risk for developing mood disorders, body image disturbances, and existential concerns, all of which can adversely affect sexual desire, satisfaction, and intimacy. Furthermore, changes in physical appearance, such as hair loss, and decreases in functional independence, such as a temporary inability to drive—common side effects of radiotherapy—may alter self-perception and interpersonal relationships, contributing to sexual distress and relational difficulties. This assumption is also confirmed by the fact that 25% of patients interviewed ended the relationship after diagnosis and that most of the patients (47%) ascribe the reduction of the intercourse frequency to asthenia and relationship issues. Finally, other relevant subjective factors associated with worsening of quality of sexual life are the onset of cognitive symptoms (32%), subjective motor abilities (15%), and psychological symptoms (8%). Although the questionnaire does not allow for an objective assessment of these aspects, this finding is consistent with a recent study (4) showing the importance of functional and psychological impairments in health-related QoL of brain cancer patients. In fact, mood disorders (anxiety or depression) are frequently perceived by patients as the culprits for sexual dysfunctions, particularly in terms of sexual desire (19).

TABLE 3 Association between sexual intercourse–sexual satisfaction and demographical and clinical factors.

Factors	Prevalence of diminished SI (%)	*p*-value	Prevalence of diminished SS (%)	*p*-value
Hemisphere		0.207		0.382
Left	21		54,2	
Right	27		49	
Lobe		0.882		0.674
frontal	63.6		45.5	
parietal	50		43.8	
temporal	60		60	
Fronto-parietal-insular	57.1		71.4	
Adjuvant treatment		**0.042***		0.384
yes	55.4		55.4	
no	39.8		49.8	
Sex		0.770		0.883
Female	52.6		52.6	
Male	58.6		48.3	

In the table, the main explored factors potentially affect SI (sexual intercourse) and SS (sexual satisfaction). The asterisk (*) shows the factor statistically associated with SI. Asteriscs and bold value show the factor statistically associated with SI

No significant associations were found between the occurrence of sexual dysfunction/satisfaction and demographics (age, gender, educational level, job, etc.), clinical characteristics of the tumor (lobe, hemisphere, and histomolecular profile or the patients' stage of disease at the time of evaluation), or pharmacological treatments. Notably, this result differs from previous studies reporting tumor location (frontal) or gender (female) as factors linked to sexual dysfunctions (16). Several lines of evidence underline differences between male and female patients in their sexual needs and behavior; i.e., male cancer survivors generally were most concerned about being able to satisfy their partners, while female cancer survivors were most concerned with sex-related changes in their body image. However, gender differences have been found in studies mainly focused on women who have breast or gynecologic cancer and men who have prostate cancer, requiring more invasive and sex-specific surgical and adjuvant treatments than brain tumor.

Although the side effects of oncological treatments seem to be relevant in the emergence of patients' sexual difficulties, our data suggest that patients' self-perception may also play a crucial role in their sexual satisfaction. In fact, one-third of the patients perceived themselves as less able to "satisfy the partner" or to "reach orgasm" or "to be attractive" regardless of their physical or clinical conditions.

Taken together, our results highlight that despite the complex multidimensionality of sexual health, in brain cancer patients, some

factors clearly emerge as more relevant than others. More than actual organic dysfunctions, which actually play a minor role in the sexual impasse following the diagnosis of brain tumors, the side effects of treatment and the individual perception of sexual inadequacy relevantly impact patients' sexual life. For this reason, beside the "standard" biological and psychological aspect, an adequate oncologic care of brain cancer patients must consider important, and not underestimate, the side effects of treatments on the quality of sexual life and couple relationships, especially since the patients themselves demand attention to the problem. For this reason, a routine screening for sexual dysfunction, open communication, and a multidisciplinary collaboration to the management of sexual wellbeing in patients with brain cancer is crucial. Interventions may include psychosexual counseling, couple therapy, patient education/empowerment, and also education regarding adaptive sexual practices.

4.1 Limitation

In our study, frequency of occurrence estimation was based on self-reports. Sexual health and its vulnerability is an issue prone to stigmatization. We cannot exclude the self-reported data to be biased toward underestimation or to be a subject to "social acceptability" bias. However, precisely because of this issue, sexual problems may be even more disguised by patients in personal interviews, and assessment via self-report may provide more reliable data. Moreover, the present study includes only Italian subjects and manly adults, making it difficult to draw firm conclusions regarding other populations and patients diagnosed before the age of 30.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Comitato Etico Territoriale Lombardia 1 (MoCA Project -L2093). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

AL: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. GP: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Writing – review & editing. LG: Conceptualization, Writing – review & editing. LV: Conceptualization, Formal analysis, Writing – review & editing. MR: Conceptualization, Writing – review & editing, Data curation, Supervision. MC: Conceptualization, Writing – review & editing. TS: Conceptualization, Writing – review & editing. LF: Methodology, Writing – review & editing. GC: Conceptualization, Funding acquisition, Writing – review & editing. LB: Conceptualization, Data curation, Funding acquisition, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Quality of life of patients with neurofibromatosis 1—Physical disability does not necessarily result in poor mental health

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Introduction: Neurofibromatosis 1 (NF1) is a chronic neurocutaneous disease known to profoundly affect quality of life (QoL). We have performed an analysis of disease severity, mental and physical QoL and compare the different subclasses among patients with neurofibromatosis 1 (NF1).

Patients and methods: We conducted a prospective analysis of 89 NF1 patients between January 2016 and March 2018. Data sourced from local records including demographic information, employment status, education level, and marital status. All patients completed 36-Item Short Form Health Survey (SF-36) and additionally the numerical pain rating scale (NPS). Patients were stratified based on severity of NF1, visibility and disease severity.

Results: Among 89 patients, severity was classified as grade 4 was identified in 42 (47.2%), moderate in 17 (19.1%), mild in 23 (25.8%) and minimal in 7 (7.9%) cases. According to visibility scale, severe grade 3 was found in 28 (31.5%), moderate grade 2 in 26 (29.2%) and mild grade in 35 (39.3%) cases. SF-36 data, except for pain, showed significantly lower values, if compared to the standard German population ($P < 0.001$, physical component summary $P = 0.045$). Sex, marital status and education level did not significantly influence results. Employment was significantly associated with better mental and physical status ($P = 0.028$ and $P = 0.01$ respectively) and age >40 was linked to lower physical ($P = 0.027$) but not mental component scores ($P = 0.362$). The numerical pain rating scale indicated pain levels of 7–10 in 9 cases (10,1%), 5–6 in 10 patients (11.2%), 1–4 in 26 patients (29.2%) and no pain in 44 cases (49.4%). Physical component scores significantly differed across different NPS grades ($P < 0.001$) but not in mental component scores (P = 0.06). Finally, no significant differences were found in mental component scores across severity or visibility grades.

Conclusion: Severity and visibility grades of patients with NF1 may not necessarily result in poor mental health. Symptomatic treatment should be considered even for severely disabled patients as they may have comparable QoL to less severely affected patients with NF1. Employment was linked to better quality of life outcomes in our findings.

KEYWORDS

NF1, quality of life, SF-36, severity, visibility

Introduction

Neurofibromatosis is a heterogeneous neuro-cutaneous disease, including neurofibromatosis type 1 (NF1), neurofibromatosis type 2 (NF2) and schwannomatosis (1, 2). NF1, the most common subtype (1:2,700 births), is characterized by many typical features such as café-au-lait macules (CALM), freckling, Lisch nodules, cutaneous and plexiform neurofibromas, optic gliomas, bone deformities and in addition associated learning difficulties and attention deficits (ADHD) with different impact on quality of life (QoL) (1–3). Plexiform neurofibromas pose the risk not only for malignant transformation resulting in malignant peripheral nerve sheath tumors (MPNST) but also for visible deformities which may influence QoL (4). NF1 patients have an increased risk of developing several other tumor diseases like gastrointestinal or breast cancers, impacting the life expectancy (5, 6). These patients often undergo repetitive surgeries and develop different neurological impairments due to tumor progression, so that decision making for an aggressive treatment is difficult and the severity grade may influence the final choice.

Health related Quality of Life (QoL) encompasses physical, psychological and social wellbeing of patients and reflecting the complex and multifactorial conditions and factors affecting the patients' lives (7). The aim of this study is to identify the various aspects of QoL in patients with NF1 and to identify predictors of QoL within this population. Despite previous studies described an association between neurofibromatosis and a diminished QoL, our knowledge about the factors which influence the QoL of this group is limited (1, 3). Furthermore, we have analyzed the impact of employment, age, marital status and education level on QoL.

Patients and methods

Study design

We conducted a prospective, descriptive, observational study between 2016 and 2018 involving 89 patients. The patients were consecutively enrolled in the study. The study received approval from the local ethics committee (N 51/16) and adhered to the principles of the international Declaration of Helsinki. Informed consent was obtained from all participants (3, 8).

Collected data

A standardized, generic survey for health-related quality of life was chosen to ensure reproducibility and comparability in this topic. All patients attending the specialized NF outpatient department and providing informed consent were included in the study. The advantage of local NF outpatient department lies in interdisciplinary approach involving neurologists, neurosurgeons, dermatologists, pediatricians and genetics experts. Each patient underwent a neurological examination and received the 36-Item Short Form Health Survey (SF-36) and numerical pain rating scale (9, 10). The local records were analyzed for demographic data and patients were stratified based on severity and visibility grades as proposed by Huson et al. and Ablon et al. (3, 8).

Demographic variables including age, sex, marital status and employment status were analyzed. Two age groups with cut of >40 years were evaluated. The cut off value was based on assumption that it is the middle of life episode, typically with grounded family.

Statistical analysis

Descriptive statistics were used for data analysis, reporting mean and standard deviation for continuous variables and absolute and relative frequencies for qualitative parameters. Explorative tests between interesting subgroups were applied by the underlying parameters (ANOVA as well as T-test). Non-parametric tests were performed in the presence of non-Gaussian distribution of values (Mann-Whitney Test, Kruskal-Vallis-test). The significance level was defined as $P < 0.05$. Statistical analysis was performed using the SPSS® statistical software (IBM Company, SPSS Inc. Chicago Illinois).

Results

Demographic and general data

Detailed demographic data including severity and visibility scores and other NF1 characteristics are summarized in Table 1. Females predominated in our cohort and the majority of patients were employed. Slightly more patients are married or are living in a relationship. Approximately, half of the patients have a familial form of NF1 (Table 1).

Regarding education level, it's visible that 10.1% of the patients are without any graduation, which is more than twice as much as in the general German population (4.7%).

Severe grades were observed in nearly half of the patients ($N = 42$, 47.1%) in our study, typically correlating with increased surgeries and frequent hospitalizations.

Quality of life

Evaluating SF-36, all domains showed significantly lower scores compared to the normal population (Table 2).

Sex, marital status and education level did not significantly influence QoL (Table 3). However, employment status was significantly associated with better mental and physical status according to SF-36 (Table 3) while age >40 was linked to lower physical but not mental component (Table 3).

According to numerical pain rating scale, 7–10 were noted in 9 cases (10,1%), 5–6 in 10 patients (11.2%), 1–4 in 26 patients (29.2%) and no pain in 44 cases (49.4%). Physical component showed significant difference between different NPS grades ($P < 0.001$, Table 4) but no significant difference in mental component summery ($P = 0.06$).

No significant differences were found between different severity grades and visibility grades in mental component summery (Table 4). As expected, physical components were significantly worse in more severe cases (Table 1) and in patients with higher visibility grades.

TABLE 1 Patients'characteristics.

Sex	Male	$N = 33$ (37.1%)	$P = 0.015$
	Female	$N = 56$ (62.9%)	
Age	Mean (SD)	38.67 ± 16.12	
Inheritance	Familial	42 (47.2%)	$P = 0.596$
	Sporadic	47 (52.8%)	
Partner/Marital status	Single	42 (47.2%)	$P = 0.596$
	Partner/married	47 (52.8%)	
Level of education	None	9 (10.1%)	$P < 0.001$
	Elementary school	36 (40.4%)	
	Middle school	24 (27%)	
	High school	20 (22.5%)	
Employment	Employed	76 (78.4%)	$P < 0.001$
	Unemployed	13 (21.6%)	
Disease severity	Minimal (Grade 1)	7 (7.9%)	$P < 0.001$
	Mild (Grade 2)	23 (25.8%)	
	Moderate (Grade 3)	17 (19.1%)	
	Severe (Grade 4)	42 (47.2%)	
Visibility scale	Mild (Grade 1)	35 (39.3%)	$P = 0.471$
	Moderate (Grade 2)	26 (29.2%)	
	Severe (Grade 3)	28 (31.5%)	

TABLE 2 Results of short-form 36 health survey for patients with neurofibromatosis type 1 compared with German standard population.

	NF1, Mean ± SD ($n = 89$)	German standard population, mean ± SD ($n = 2,773$)	p
Physical component summary	48.34 ± 10.61	50.21 ± 10.24	0.045
Mental component summary	42.85 ± 7.60	51.54 ± 8.14	<0.001
Physical functioning	82.36 ± 23.25	96.61 ± 10.04	<0.001
Role: physical	70.51 ± 40.69	96.89 ± 13.88	<0.001
Bodily pain	71.54 ± 30.18	94.60 ± 14.99	<0.001
General health	61.60 ± 24.16	79.89 ± 13.66	<0.001
Vitality	54.78 ± 19.67	71.90 ± 14.31	<0.001
Social functioning	53.79 ± 10.56	94.87 ± 12.33	<0.001
Role: emotional	76.40 ± 38.99	96.89 ± 14.13	<0.001
Mental health	63.46 ± 14.51	79.16 ± 13.11	<0.001

Discussion

The QoL is one of the most relevant outcome parameters in patients with chronic diseases (11–13). Generally, all patients in our study showed reduced QoL based on SF-36. This aspect highlights the significant impact of NF1 on quality of life, which is consistent with previous studies (14, 15).

Regarding the visible aspects of this neurocutaneous disease, that contrary to previous studies, we did not observe significant differences in mental health scores across different severity groups. Chren et al. and Krueger et al. showed in contrast, that disorders that affect the skin, result in negative emotional and psychological outcomes (16, 17). Kodra et al. have found similar results in NF 1 where the changing of the appearance because of the skin abnormalities ends in an inferior QoL (7). Smith et al. reported that the female sex is especially affected by cosmetic burdens of the NF1 (18). Similarly, Hummervoll et al. noted that females had tremendously worse QoL in contrast to men (19). This is in discrepancy to our results which showed no significant difference between males and females. In a similar way to our findings, Crawford et al. haven't found gender differences nor even an influence of visibly changes of the QoL in the Australian population (20). The participants of our study may cope better with the change of the appearance or have a better body image than we have expected. Many participants cope with the visible aspects of the NF1 by concealing the skin with special clothing or avoiding activities like swimming (2). Similarly to our study, a Canadian publication also showed no significant differences in the body image scores of women compared to men (21).

Previous research has suggested visible aspects of NF1 can pose challenges in forming relationships and finding a partner is more difficult (22). We haven't found a relevant difference compared to the standard population in our study (22).

It is known that the attractiveness is positively influencing the state of employment, so it is to be expected, that the skin abnormalities of the NF1 leads to a higher number of unemployment, but in contract to former studies, the participants of our study have a normal level of employment (23, 24). The level of education is lower, which is correlating with the type of employment. Many participants in our study are manual laborers in factories or working as unskilled workers, where the visual appearance is not so important.

A recent review and meta-analysis by Crow et al. also showed that cognitive deficits in this group are widespread and significant (25). Not all areas of cognitive function are equally affected. Age, gender, education level and parental education level have no significant impact on cognitive outcomes. This underscores the need for early and continuous support of cognitive functions in patients with NF1 throughout their lifespan. Additionally, recent Finnish research indicates that NF1 is associated with lower educational attainment and a tendency to purse vocational rather than academic education. Individuals living with NF1 particularly those with cancer, developmental disorders or familial NF1 require effective student counseling and learning assistance (26).

Learning difficulties are a well-known aspect in NF1 and are often the reason for painful school experiences, including social assaults and unhappiness, leading to school refusers and a drop out of trainings (8, 22). The results of these learning difficulties are often a lack of self-confidence, missed career choices and

TABLE 3 Comparison of physical and mental component summary according to patients'characteristics.

	Level of education	Mean ± SD	*P* value
Physical component summary	None	46.59 ± 8.06	0.474
	Elementary school	48.87 ± 10.26	
	Middle school	46.77 ± 11.64	
	High school	50.04 ± 11.30	
Mental component summary	None	45.55 ± 5.27	0.693
	Elementary school	42.57 ± 8.68	
	Middle school	42.13 ± 6.72	
	High school	42.85 ± 7.60	
	Employment	**Mean ± SD**	***P* value**
Physical component summary	Employed	49.54 ± 10.17	*0.010*
	Unemployed	41.30 ± 10.77	
Mental component summary	Employed	43.62 ± 7.22	*0.028*
	Unemployed	38.40 ± 8.50	
	Partner/marital status	**Mean ± SD**	***P* value**
Physical component summary	Single	47.84 ± 11.69	0.863
	Partnered/married	48.78 ± 9.64	
Mental component summary	Single	41.84 ± 8.74	0.375
	Partnered/married	43.76 ± 6.36	
	Age (years)	**Mean ± SD**	***P* value**
Physical component summary	≤ 40	50.08 ± 11.38	*0.027*
	> 40	46.47 ± 9.49	
Mental component summary	≤ 40	43.53 ± 7.62	0.362
	> 40	42.13 ± 7.59	
	Sex	**Mean ± SD**	***P* value**
Physical component summary	Male	47.00 ± 11.93	0.530
	Female	49.12 ± 9.77	
Mental component summary	Male	43.61 ± 7.88	0.316
	Female	42.41 ± 7.46	

Italic values indicate $p < 0.05$.

TABLE 4 Comparison of physical and mental component summery between different grades of disease severity.

	Numerical rating scale	Mean ± SD	P value
Physical component summary	0	54.30 ± 7.21	*<0.001*
	1–4	46.89 ± 8.70	
	5–6	41.28 ± 6.79	
	7–10	31.21 ± 8.65	
Mental component summary	0	42.25 ± 7.81	0.064
	1–4 ($n = 26$)	45.93 ± 6.16	
	5–6 ($n = 10$)	40.96 ± 8.01	
	7–10 ($n = 9$)	39.03 ± 7.91	
	Visibility scale	**Mean ± SD**	**P value**
Physical component summary	Grade 1	53.30 ± 8.04	*<0.001*
	Grade 2	47.69 ± 10.69	
	Grade 3	42.73 ± 10.71	
Mental component summary	Grade 1	42.63 ± 7.31	0.840
	Grade 2	42.83 ± 6.98	
	Grade 3	43.16 ± 7.60	
	Disease severity	**Mean ± SD**	**P value**
Physical component summary	Grade 1 ($n = 7$)	54.90 ± 7.92	*0.006*
	Grade 2 ($n = 23$)	52.02 ± 10.21	
	Grade 3 ($n = 17$)	43.00 ± 10.78	
	Grade 4 ($n = 42$)	47.38 ± 10.16	
Mental component summary	Grade 1 ($n = 7$)	46.18 ± 2.96	0.678
	Grade 2 ($n = 23$)	41.04 ± 8.82	
	Grade 3 ($n = 17$)	42.92 ± 5.88	
	Grade 4 ($n = 42$)	43.27 ± 7.96	

Italic values indicate $p < 0.05$.

employment opportunities. In our cohort, the level of education is lower compared to the German population (27). Especially the number of people without any graduation is higher and the number of participants having a university degree is much lower. These results are in line with former studies (28). Other studies describe that older adults (born before 1970) have worse school experiences than younger ones, this may be explained by a greater awareness of NF1 and leads to a necessity of an early support and the treatment of the learning difficulties and the lack of concentration (29).

Pain is a prevalent and significant factor affecting QoL, so we used except of the SF-36 questionnaire and the patient history, the NRS to correlate the severity of the pain with the QoL. Nearly half of the population described no pain, but the physical component showed significant difference with increasing NRS. In our study, participants predominantly reported back pain or headaches, which are typical manifestations of NF1–on the one hand attributed to the typical bodily findings in the NF1 like scoliosis and poor postures, but on the other hand it can be a sign of psychological disorders like depression and maladaptive coping strategies associated with the chronic nature of the disease (30, 31).

Brar et al. published a study in 2023 that highlights the prevalence of psychiatric comorbidities in NF patients, particularly associated with male sex and for people of color. Mood disorders

and anxiety disorders were the most common, while ADHD was less prevalent than in previous studies. This further emphasizes the importance of psychological support for this patient group (32).

It's important to investigate and treat the physical restrictions in the early childhood to avoid later problems. Emphasis should be placed on implementing multidisciplinary approaches to integrate psychological therapies such as acceptance and commitment therapies (ACT), resilience and coping strategies (1, 14, 29). Furthermore, regular neuropsychological assessment with regard to visual spatial skills and attention deficits was recommended for further support and improvement of QoL in children (33). Cavallo et al. reported recently that in children population of patients with NF1 disease severity interferes with social functioning and consequently QoL (34). This may lead to stigmatization which could be less relevant in the adult population as presented in our results. The early identification of QoL in both pediatric and adult population with an early intervention and personalized treatment might improve further wellbeing of this patients cohort.

Regarding the influence of the age, many studies demonstrate a lower QoL in younger NF1 patients, a pattern observed in other chronic diseases (35, 36). Although our study did not include children, we mentioned, that the age >40 years is significantly associated with a lower physical component. Probably, possible bone abnormalities like scoliosis, plexiform neurofibromas and a higher risk of developing malignant tumors as well as associated surgeries can explain the higher physical problems of this group. Surprisingly, the mental component of QoL was not affected in this age group. Probably, the coping strategies are better and the life and family planning is completed. In addition, there are not enough investigations to report the differences between adults and children with NF1 (even separated by children and parents' reports) or long-term follow-ups, regarding the development of this population over the years.

A literature review was conducted by Domon-Archambault et al. on the social life, mental health and QoL of children and adolescents with NF1, as well as the psychosocial interventions aimed at this population (37). Compared to unaffected children and adolescents in the general population, pediatric patients with NF1 face a higher risk of experiencing social difficulties, mental health disorders, behavioral and emotional problems, and reduced QoL. There are not enough articles which discuss interventions specifically targeting the NF1 population to address these challenges. There is a pressing need to develop and evaluate psychosocial interventions for patients with NF1.

Our detailed analysis revealed that severity grade does not correlate with inferior mental status despite physical functioning in more severe cases. In former studies, the principal concerns of the participants were the cosmetic neurofibromas followed by learning difficulties and across all age groups and gender the fear of disease progression. Interestingly the measured severity of disease using the Huson scale did not directly correlate with individual perceptions of this disease. Some participants seem to cope better with their chronic disease and their acceptance of their body seems to be much better. Especially the impact of psychosocial factors, due to the lack of treatment methods and the limitations of medication in NF1 should be considered to have the opportunity to develop resiliency strategies (15).

Based on our finding and experience, an early investigation of NF1 children through specialized centers coupled with individualized therapies is essential for promoting optimal development and long-term wellbeing. Increasing awareness of the NF1 among healthcare providers and the general public is key to improving diagnosis, treatment and support services for affected individuals and their families.

Study limitations

One of the primary limitations of our study is the relatively small and heterogenous cohort of participants. The limited sample size and diversity in patient characteristics may restrict the generalizability of our findings to broader populations of individuals with NF1. Consequently, our results may not fully represent the QoL experiences of all NF1 patients, and caution should be exercised when applying these findings to larger, more diverse populations.

The detailed analysis of QoL in NF1 patients is inherently complex and influenced by multiple factors that are challenging to summarize and quantify.

The Ablon scale has certain limitations as well. While Ablon's Visibility Index measures the visibility of the disease, it does not evaluate the severity of the condition, such as the necessity for surgeries, various medications, such as chemotherapeutics or other treatments.

Quality of life encompasses physical, psychological and social dimensions, each can be affected by the multifaceted nature of NF1. As a result, our study may not fully capture the nuanced interactions and variability in QoL experiences among individuals with NF1.

The multitude of factors influencing QoL in NF1, including disease severity, symptom variability, psychosocial factors and treatment interventions, pose challenges in summarizing and interpreting study outcomes. Quantifying the impact of these diverse factors on overall QoL outcomes requires comprehensive and detailed assessments, which may not have been fully achieved in our study due to limitations in data collection and analysis.

Conclusion

The severity and visibility grade of NF1 patients may not necessarily result in poor mental health in comparison with lower grades. Employment was associated with better QoL according to our results. Based on that, it is important to support this group of patients to protect their jobs and even if the level of education was not significant for the QoL, it seems to be reasonable to support the younger patients with NF1 to minimize learning disabilities and to acquire a graduation and thereby an employment.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the University of Ulm. Written informed consent to participate in this study was provided by the patients/participants or patients/participants legal guardian/next of kin.

Author contributions

UB: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. LS: Data curation, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing – review & editing. TK: Conceptualization, Project administration, Supervision, Writing – review & editing. CW: Project administration, Supervision, Writing – original draft. AP: Data curation, Formal analysis, Methodology, Project administration, Software, Supervision, Validation, Writing – review & editing.

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The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Influence of neuropathological diagnosis on psychooncological distress in neurooncological patients - a retrospective cross-sectional analysis

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Background: Gliomas, the most common primary brain tumours, are classified based on histology and molecular genetics. Glioblastomas (GBM) are highly aggressive and are graded as WHO grade 4, while astrocytoma and oligodendrogliomas fall under WHO grades 2-3 (4). Gliomas affect 6 per 100,000 people, with a higher incidence in men. GBM has the poorest prognosis, whereas grade 2 astrocytoma and oligodendrogliomas show better outcomes. Quality of life (QoL) is now a crucial therapeutic goal alongside survival. Despite the impact of gliomas on QoL, especially given their incurability and progressive neurological deficits, research specifically comparing QoL and psycho-oncological stress in GBM versus grade 2 gliomas (glioma_2) remains limited. This study aims to fill that gap using validated measurement methods.

Methods: This retrospective, single-centre study investigated differences in QoL among neuro-oncological patients using the Karnofsky Performance Score (KPS), Distress Thermometer (DT), Hospital Anxiety and Depression Scale (HADS), and EORTC-QLQ-C30-BN20. Data were collected before chemotherapy or radiotherapy to avoid therapy impact on QoL. Out of 2258 patients screened until June 30, 2022, 639 had glioblastoma or WHO grade 2 gliomas, with 223 meeting inclusion criteria for analysis.

Results: The study included 161 GBM and 62 Glioma_2 patients, with 64% of all patients being male. The mean age was 58.11 years (SD $\pm$ 16.186). The DT did not show significant differences between GBM and glioma_2 glioma patients (median GBM:6 vs. 5 in glioma_2, p=0.480). However, the HADS-D indicates that GBM patients experience significantly more depression (median GBM 4.5 vs. 4 in glioma_2, p=0.033), though anxiety levels are similar in both groups (median GBM. 6 vs. 6 in glioma_2, p=0.867). The KPS (median GBM 70 vs. 90 in glioma_2, p<0.001) and specific aspects of the EORTC-QLQ-C30-BN20 questionnaire demonstrate that GBM patients have notably greater physical impairments than glioma_2 patients at diagnosis. Overall, GBM patients report worse quality of life compared to glioma_2 patients (median GBM 50 vs. 67 in glioma_2, p<0.001).

Conclusion: This study showed that distress is present in glioma patients regardless of their histopathological grading, even though GBM patients show higher depression levels and more physical limitations. Targeted anxiety management and early depression screening are essential for all glioma patients. Early QoL screening and making QoL a therapeutic goal benefits patient care and society.

KEYWORDS

quality of life, glioma, neurooncology, mental health, distress

Introduction

Gliomas are the most common primary brain tumours, classified based on histology and molecular genetics. The actual WHO classification of CNS tumours, updated in 2021, emphasises molecular genetic factors and their implications for tumour aggressiveness and patient survival. Glioblastomas (GBM) are characterised by rapid, aggressive, and infiltrative growth and are assigned to WHO grade 4. Molecularly, GBM is distinguished from astrocytoma WHO grade 4 by the absence of an IDH mutation. Other common glioma groups include astrocytoma and oligodendroglioma, which are assigned WHO-grade 2-3 based on histology and specific factors. Both groups typically feature an IDH mutation, with oligodendrogliomas exhibiting a 1p/19q codeletion (1). Histopathological and molecular findings are of high therapeutical consequence for the patients. Survival times vary significantly depending on tumour type and WHO grade. Globally, the incidence of glioma is approximately 6 per 100,000 individuals, with men being 1.6 times more likely to be affected than women (2). The average age for GBM patients is around 65 years, depending on the study, while for low-grade glioma (LGG) patients, the average age is significantly lower, around 45 years, varying by subtype (3, 4). GBM, the most common malignant primary brain tumour (50%), has the poorest prognosis. A statistical report from the USA for 2016-2020 indicates a median survival of 8 months for GBM patients in a cohort of over 1000.000 people during 16 years, irrespective of whether individuals received any treatment for their tumour or not (3). In contrast, patients with WHO grade 2 astrocytoma, referred to as LGG (formerly diffuse astrocytoma), have a median survival of approximately 60 months, while oligodendroglioma patients have a median survival of about 199 months. The 5-year survival rate for glioblastoma patients is 7.2%, whereas 53.5% of patients with WHO grade 2 tumours show a 5-year survival. Only 4.7% of glioblastoma patients survive for 10 years, compared to 43.1% of WHO grade 2 astrocytoma patients and 69.6% of oligodendroglioma patients (3). Numerous studies have examined the survival rates of different tumour entities, with survival traditionally being the primary factor in oncological treatment planning.

However, quality of life (QoL) is increasingly recognised as an important therapeutic goal alongside survival and has become a focus of various studies (5–9). QoL encompasses both subjective and objective aspects such as health, autonomy, and freedom and is influenced by individual and environmental factors, including character, experiences, values, personal resources such as family support, social status and region of living (10–13). The personal prerequisites for good QoL can change dynamically over a person's life. QoL can be negatively impacted by anxiety, burden, stress, distress and depression. Earlier publications proved that oncological patients commonly suffer from these negative influences, significantly reducing their QoL (14–16). Neurooncological, as a special subgroup of cancer patients, suffer from an incurable disease with increasing neurological deficits over time. Therefore, the impact on QoL is huge. Still, the burden differs between GBM and LGG patients, depending on the different therapy approaches, the different expected overall survival as well and the different life situations (regarding age, working situation, and family situation). However, literature that addresses this important and specific difference is sparse.

Few studies have analysed the impact of neuropathological tumour diagnosis on QoL and psycho-oncological stress (17–20). No study has yet used comprehensive measurement tools to compare the differences in QoL at the primary diagnosis of GBM versus LGG (WHO grade 2 gliomas). This work aims to gather previously unknown data on the burden and QoL of GBM patients and patients with WHO grade 2 gliomas using a representative study cohort and validated measurement methods and to analyse the differences in their psycho-oncological stress and QoL.

Patients and methods

This study is a retrospective, single-centre investigation conducted at the Center for Neuro-Oncology in the Department of Neurosurgery at the University Hospital of Düsseldorf. Since 2010, patients have undergone screening for psycho-oncological distress and QoL using specific questionnaires. The study was approved by the Ethics Committee of Heinrich Heine University Düsseldorf under the file number 2022-1852.

To minimise potential bias effects from adjuvant radiation and chemotherapy on QoL, data were collected before treatment. For preoperative data, patients were aware of their suspected diagnosis, which was later confirmed by neuropathological findings.

Selection criteria for patients included treatment at the Centre for Neuro-Oncology at the University Hospital of Düsseldorf, a neuropathological confirmed diagnosis of WHO tumour grade 4 (GBM) or glioma WHO tumour grade 2 (Glioma_2), and no adjuvant therapy at the time of the survey. Exclusion criteria included receiving adjuvant therapy, multiple malignancies, and incomplete questionnaires.

The specific inclusion and exclusion criteria are outlined in the table below (Table 1):

Overall, EORTC-QLQ-C30-BN20 questionnaires were available from 639 Patients diagnosed with either GBM or Glioma_2, who underwent the interview at any timepoint of diagnosis. 223 of these 639 (34.9%) patients had filled in the EORTC-QLQ-C30-BN20 questionnaire at the point of initial diagnosis and, therefore, met the predefined inclusion criteria.

Socioeconomic data such as gender, age, Karnofsky Performance Status (KPS), relationship status, psychiatric history, and others were obtained from hospital software "Medico" (CompuGroupMedical, CGM Clinical Europe GmbH).

Data collection and questionnaires - MedForm App

For data collection on the psycho-oncological burden and QoL of patients, the "MedForm App" was used. This application was developed by Mr. Frank Escher in 2020 and is utilised on Samsung Galaxy Tab A (2016) tablets. MedForm is a user-friendly application that guides patients through various input pages, requesting basic personal information such as name, date of birth, nationality, and gender, as well as socioeconomic data like education level, marital status, occupation, number of children, and psychosocial support. Further questions involve disease-specific details (date of initial diagnosis, current diagnosis, disease status, and adjuvant therapy information). At last, patients proceed to answer questions from standardised questionnaires embedded in the app, which assess QoL and psycho-oncological burden. The questionnaires integrated into MedForm are validated tools for assessing QoL and psycho-oncological burden in cancer patients.

These include:

- EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30): A standardised questionnaire for evaluating the QoL in cancer patients.

The EORTC initially was released in 1986/87 as QLQ-C36, the current version (EORTC QLQ-C30 Version 3.0) includes 30 evaluable questions covering 15 aspects of quality of life. Each aspect is scored on a scale from 0 to 100% (21). In addition to the general cancer questionnaire, there are disease-specific modules. The QLQ-BN20 was designed for brain tumour patients, featuring 20 specific questions (22, 23).

- HADS (Hospital Anxiety and Depression Scale): An instrument for assessing anxiety and depression in hospital patients.

The S3 Guideline recommends HADS for screening psychological distress alongside the Distress Thermometer (DT) (24). It consists of 14 questions without somatic symptoms. The results provide separate scores for anxiety and depression, which can also be combined to give a general distress score, though this combined score is not used in this study due to the use of DT for general distress. Scores are interpreted in three ranges: 0-7 (normal), 8-10 (borderline), and 11+ (abnormal). A cut-off score of 8 increases sensitivity but reduces specificity, capturing more at-risk patients. While HADS cannot diagnose anxiety and depression solely based on self-reported symptoms, elevated scores suggest the need for further evaluation by a specialist.

- Distress Thermometer (DT).

The DT is a multidisciplinary self-assessment screening tool developed by the National Comprehensive Cancer Network (NCCN) in the USA (25). Patients indicate their distress level over the past week, including the current day, on an analogue scale depicted as a

TABLE 1 Patient selection and inclusion/exclusion criteria.

Inclusion Criteria	*Exclusion Criteria:*
Patient treated + in the Department of Neurosurgery at the University Hospital of Düsseldorf.	Patients who had already received adjuvant therapy/recurrent disease
Age ≥18 years.	Patients with multiple malignancies.
Provided informed consent.	Patients with more than half of the questionnaires incomplete.
Neuropathologically confirmed primary diagnosis of glioblastoma WHO tumour grade 4 or glioma WHO tumour grade 2 according to the current diagnostic criteria at the time of therapy.	Lack of cognitive understanding of the questions.
For glioma WHO tumour grade 2 patients: perioperative or follow-up data collection with stable disease (no clinical or radiological indication of recurrence).	Poor health status preventing them from answering the questions.
No adjuvant therapy received at timepoint of inclusion Cognitive ability to independently complete the questionnaires.	Lack of proficiency in German.

thermometer, ranging from 0 (no distress) to 10 (extreme distress). Scores ≥ 5 are considered elevated. Its validity has been confirmed through multiple correlations with the HADS (26). This study uses the recommended cut-off value of ≥5 for neuro-oncological patients.

These questionnaires and the DT cover a broad range of dimensions, including emotional well-being, social functioning, and general physical complaints.

- KPS

For further evaluation of the physical functioning and reflection of dependence on external help of patients, the Karnofsky Performance Status (KPS) was used, which assesses the physical functioning of patients, particularly their ability to work and care for themselves. The use of KPS allows for a standardised assessment of the overall health status of patients.

For further detailed information and sample illustrations of the questionnaires used, we refer to the Supplementary Material.

Sample size and statistical analysis

The required sample size was calculated by statisticians at Heinrich-Heine University before retrospective data collection and analysis. Although a larger sample would enhance the study's power, the cohort size is acceptable given the rarity of gliomas and the specific inclusion criteria and is representative compared to other studies.

Statistical analysis aimed to compare differences in QoL aspects between patients with GBM and those with Glioma_2. Most analyses used descriptive statistics, given the comparison between two groups on various QoL aspects. Dependent variables included the DT, HADS, and EORTC-QLQ-C30-BN20. The KPS was analysed as both a dependent and independent variable.

Initially, the distribution of variables was examined, confirming normal distribution only for age. KPS, DT, HADS, and EORTC-QLQ-C30-BN20 results did not exhibit normal distribution. Despite the ordinal nature of these outcomes, median, mean and standard deviation (SD) are reported for comparability with other studies.

For non-normally distributed independent variables, differences between diagnostic groups were assessed using the Mann-Whitney U test as a non-parametric alternative to the T-test. Significance was set at p=0.05. The effect size was calculated using Pearson's correlation coefficient (r), with thresholds of 0.1-<0.3 for weak, 0.3-<0.5 for moderate, and ≥0.5 for strong effects according to Cohen's criteria. Given only two comparison groups, Bonferroni correction was not deemed necessary. Percentages are reported using valid percentages from SPSS, excluding missing data. To examine confounders, the cohort was dichotomised by gender, psychiatric history or medication, children, and relationship status, and results were compared within each diagnostic group. For example, only male or female GBM patients were analysed for differences in DT scores. Some analyses were impractical due to small subgroup sizes. Additionally, the correlation between physical condition and measurement outcomes was analysed using Pearson correlation, linking instrument results with KPS scores. All statistical analyses were conducted using IBM SPSS Statistics 28.0.1.1.

Results

The study included 161 GBM and 62 Glioma_2 patients, with 64% of all patients being male. The mean age was 58.11 years (standard deviation ± 16.186). GBM patients were, on average, 24.25 years older than Glioma_2 patients ($p < 0.005$). Administration of the EORTC-QLQ-C30-BN20 questionnaires occurred either perioperatively at initial diagnosis or during follow-up for Glioma_2 patients. Most questionnaires were completed preoperatively, with 49% of GBM patients and 10% of Glioma_2 patients participating at this stage. Follow-up assessments were more common among Gliom_2 patients. Out of the 223 surveyed patients, 34 (15%) reported having a pre-existing psychiatric condition or the use of psychotropic medication. This subset included 18 GBM patients and 16 Glioma_2 patients. Furthermore, 114 patients (51%) reported being in a partnership, while 35 patients (16%) were single or widowed. Regarding family structure, 97 patients (43%) indicated they had children, whereas 19 patients (8%) reported being childless. Table 2 summarises details of the entire cohort, displaying the two subgroups, GBM and Glioma_2.

KPS

The KPS was significantly lower in GBM patients compared to Glioma_2 patients, with median KPS scores of 70 for GBM (Mean = 75.7, SD = 12.175) and 90 for Glioma_2 (Mean = 91.13, SD = 9.599); p= < 0.001 (Figure 1A). Age significantly predicted KPS in the overall cohort ($p < 0.001$), but within each diagnosis group, age had no significant impact (GBM: $p = 0.175$; Glioma_2: $p = 0.05$). Additionally, KPS was not significantly affected by gender, survey timing, or pre-existing psychiatric conditions.

DT

Out of 213 patients, 141 (66%) reported a DT score above the cut-off value of 5. The median DT score did not differ significantly between GBM patients (median = 6; mean = 5.43; SD = 2.77) and Glioma_2 patients (median = 5; mean = 5.15; SD = 2.568); $p = 0.480$ (Figure 1B). Among GBM patients, 99 out of 152 (65.6%) had a DT score ≥5, compared to 41 out of 61 (67.2%) Glioma_2 patients, demonstrating high distress levels across both groups. Further analysis showed that gender, family situation, timing of the survey, or pre-existing psychiatric conditions did not have a significant impact on distress levels as measured by the DT.

HADS

HADS-Anxiety

No significant difference in HADS-A scores was observed between GBM and Glioma_2 patients. GBM patients had a median HADS-A score of 6 (mean = 6.72, SD = 4.993), while

TABLE 2 Provides a detailed overview of the entire cohort, distinguishing between GBM and Glioma_2 diagnosis groups.

	Total cohort n = 223	GBM n = 161	Glioma_2 n = 62
Age (mean ± SD)	58.11 ± 16.2	64.86 ± 12	40.6 ± 12
Female	79/35.40%	53/32.9%	26/41.9%
Male	144/64.6%	108/67.1%	36/58.1%
GBM	161/72.2%		
Glioma_2	62/27.8%		
Timepoint of assessment			
Pre-OP	132/59.2%	110/68.3%	22/25.5%
Post-OP	63/28.3%	51/31.7%	12/19.4%
Follow-Up	28/12.6%	0/0%	28/45.2%
Psychological precondition			
yes	97/43.5%	71/44.1%	26/41.9%
Tumour localisation			
Right	105/47.1%	76/47.2%	29/46.8%
Left	100/44.8%	68/42.2%	32/51.6%
Multiple	18/8.1%	17/10.6%	1/1.6%
Relationship status			
In a relationship	114/51.1%	85/52.8%	29/46.8%
Single	35/15.7%	22/13.7%	13/21%
Children			
Yes	97/43.5%	71/44.1%	26/41.9%
No	19/8.5%	10/6.2%	9/14.5%
KPS known	220/98.7%	158/98.15%	62/100%
DT completed	213/95.5%	152/94.4%	61/98.4%
HADS-A completed	163/73.1%	114/70.8%	49/79.0%
HADS-D completed	163/73.1%	114/70.8%	49/79.0%
EORTC completed	223/100%	161/100%	62/100%

It includes measurements of various factors and confounders: age, gender, survey timing, tumour location, relationship status, and parenthood. The table presents data on absolute numbers, means, percentages, and standard deviations (SD).

Glioma_2 patients had a median score of 6 (mean = 6.51, SD = 4.006); p = 0.867 (Figure 1C). 38.6% of GBM patients (44 out of 114 patients) reported a HADS-A score of ≥8. Of these, 14.9% (17 patients) had a HADS-A score between 8-10, and 23.7% (27 out of 114 patients) had a HADS-A score of ≥11. In the Glioma_2 group, 38.8% (19 out of 49 patients) reported a HADS-A score of ≥8. Of these, 26.5% (13 patients) had a HADS-A score between 8-10, and 12.2% (6 out of 49 patients) had a score of ≥11.

HADS-Depression

A significant difference was found in HADS-D scores between GBM and Glioma_2 patients. The median HADS-D score of the GBM group was 4.5 (mean = 5.43, SD = 4.323), whereas Glioma_2 patients had a median score of 3 (Mean = 4.18, SD = 4.410), p = 0.033 (Figure 1C). A HADS-D score of ≥8 was reported in 29.8% (34 out of 114) of GBM patients, compared to 16.3% (8 out of 49) in the Glioma_2 group. In the GBM group specifically, 19.3% (22 patients) had HADS-D scores between 8-10, 10.5% (12 patients) had scores of ≥11 and 4.1% (2 patients) among Glioma_2 patients had scores between 8-10, and 12.2% (6 patients) had scores of ≥11.

Influencing factors on HADS

Timing of survey

GBM patients surveyed preoperatively reported significantly lower depression scores compared to those surveyed postoperatively. The median HADS-D score was 4 preoperatively

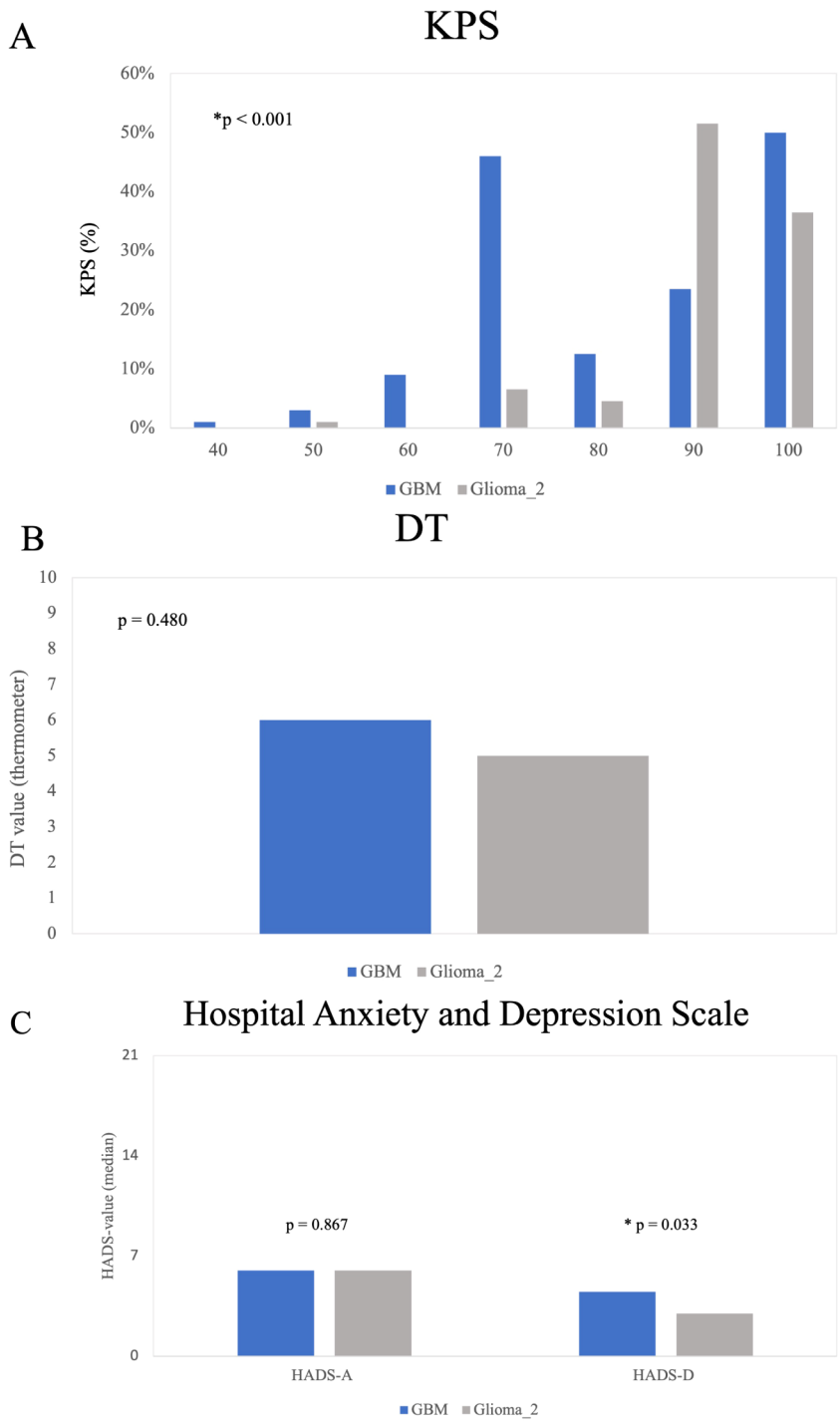

FIGURE 1
(A–C) Results from KPS **(A)**, DT **(B)** and HADS **(C)**, * indicating significant p-values in group comparison, GBM data visualised in blue, Glioma_2 data visualised in grey. **(A)**: Distribution of patients across the KPS scores from 40 to 100 (%), comparing GBM patients with Glioma_2 patients. The median KPS for GBM cohort was 70, while the median KPS for Glioma_2 patients was 90, $p < 0.001$. **(B)** Median DT results for GBM patients compared to Glioma_2 patients. While the trend indicates higher values for GBM patients, the results remained not statistically significant (p=0.480). **(C)** Median values for HADS-A (left) and HADS-D (right) in GBM patients compared to Glioma_2 patients. There was no significant difference in the median HADS-A scores between the diagnostic groups (p=0.867), while GBM patients report a higher median in HADS-D than Glioma_2 patients (p=0.033).

(mean = 4.68, SD = 3.638) versus 7 postoperatively (mean = 7.21, SD = 5.262). This difference was statistically significant (p = 0.018). Although the median HADS-D scores for both preoperative and postoperative GBM patients were below the cut-off value of 8, a smaller proportion of preoperative patients reported elevated HADS-D scores (23.8%; 19 out of 80) compared to postoperative patients (44.1%; 15 out of 34). The timing of the survey did not reveal significant differences in HADS-A scores (Figure 2A).

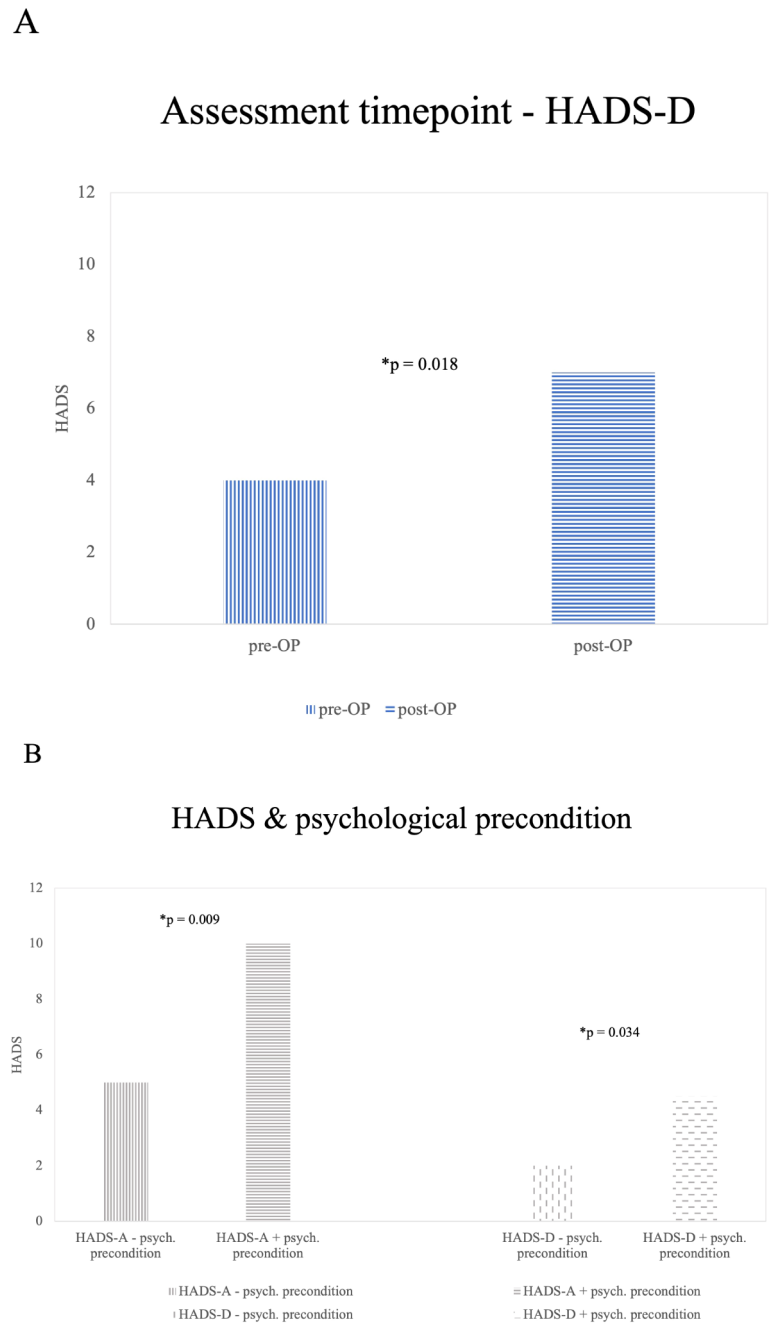

FIGURE 2
Significant (*) results from influence factors on HADS [**(A)** assessment timepoint, **(B)** psychological precondition]. **(A)** HADS-D and Survey Time Points: This graph shows the median HADS-D scores of GBM patients at different survey time points. GBM patients surveyed pre-operatively reported lower levels of depression compared to those surveyed post-operatively (p=0.018). There were no significant findings in the Glioma_2 group **(B)** Illustrates findings in the Glioma_2 patients group concerning HADS-A and HADS-D differences in patients reporting a history of psychiatric preconditions and patients without a specific history of psychiatric conditions. A significantly (*) higher number of Glioma_2 patients with a history of anxiety (p=0.009) and depression (p=0.034) are affected compared to those without such a history.

Psychological preconditions and medication

Out of the entire cohort, 34 patients (15.2%) reported a history of psychiatric conditions or ongoing psychotropic medication. HADS data were missing for 8 of these patients. Significant results could only be obtained in the Glioma_2 patients' group. No significant influence of psychiatric preconditions on HADS-A or HADS-D scores was observed in GBM patients (n=14).

Within Glioma_2 patients, HADS-D scores were significantly higher among those with a history of psychiatric conditions (median = 4.5; mean = 6.33; SD = 4.887) compared to those without (median = 2; mean = 3.49; SD = 4.073; p = 0.034. 33.3% (4 out of 12) reported HADS-D scores above the cut-off of 8, with all these patients indicating HADS-D scores ≥11. In contrast, among Glioma_2 patients without psychiatric conditions, only 10.8% (4

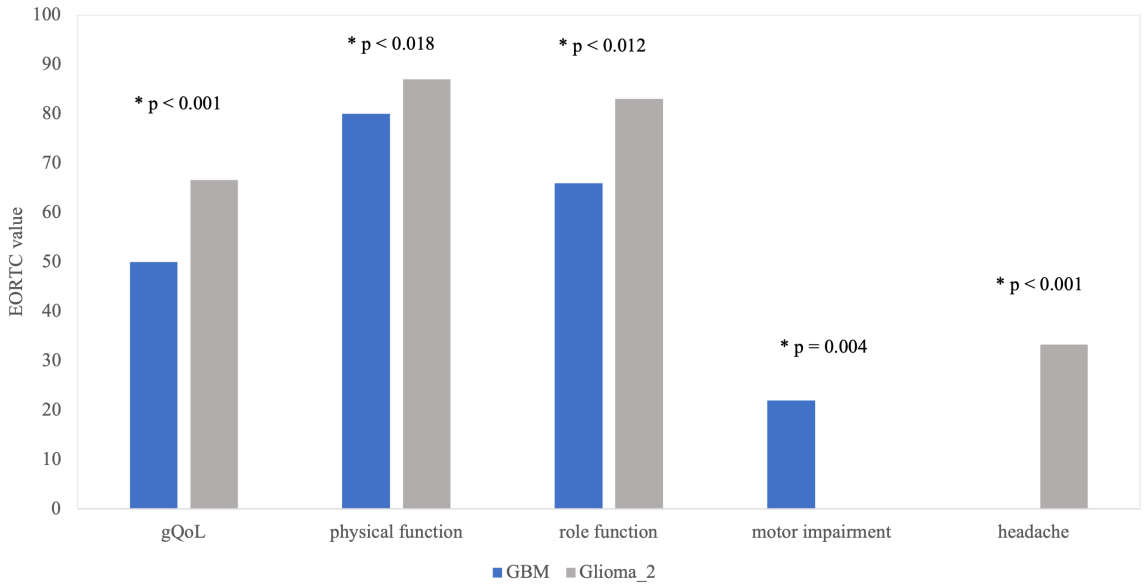

FIGURE 3
EORTC-QLQ-C30-BN20 by Diagnosis Groups: Five key quality-of-life areas with significant differences between diagnosis groups are shown. Glioma_2 patients showed significantly higher and thus better scores in gQoL ($p < 0.001$), physical functioning ($p = 0.018$), and role functioning ($p = 0.012$) compared to GBM patients. GBM patients report more motor limitations ($p = 0.004$). Headaches are the only negative aspect more common in Glioma_2 patients than in GBM patients ($p < 0.001$).

out of 37) reported HADS-D scores ≥8 (5.4% scored between 8-10, and 5.4% reported scores ≥11).

Regarding HADS-A scores among Glioma_2 patients, a history of psychiatric conditions (Median = 10; Mean = 9.33; SD = 4.376) significantly elevated scores compared to those without known psychiatric conditions (median = 5; mean = 5.59; SD = 3.468; $p = 0.009$. 66.7% (8 out of 12) reported HADS-A scores above the cut-off of 8. In contrast, among Glioma_2 patients without psychiatric conditions, 29.7% (11 out of 37) reported HADS-A scores ≥8. Of these, 24.3% (9 out of 37) scored between 8-10, and 5.4% (2 out of 37) reported scores ≥11. Results are illustrated in Figure 2B.

EORTC-QLQ-C30-BN20 domains of QoL

Significant differences were observed within the diagnostic groups. GBM patients reported significantly lower median values in the following domains of QoL: gQoL (GBM median = 50; mean = 50.57; SD = 27.496 vs. Glioma_2 median = 66.67; mean = 64.54; SD = 23.935; $p < 0.001$), physical function (GBM median = 80; mean = 69.68; SD = 31.055 vs. Glioma_2 median = 87; mean = 81.41; SD = 21.928: $p = 0.018$), role Function (median = 66; mean = 57.89; SD = 37.093 vs. Median = 83; mean = 72.25; SD = 31.496; $p = 0.012$). Furthermore, motor function impairments were significantly higher among GBM patients (median = 22; mean = 27.78; SD = 30.275) compared to Glioma_2 patients (median = 0; mean = 15.07; SD = 22.072; $p = 0.004$). Significant differences were also observed in the subscales of headache (GBM < Gliom_2, $p < 0.001$) and incontinence (GBM > Gliom_2, $p = 0.023$). In all other aspects of quality of life assessed by the EORTC-QLQ-C30-BN20, there were no statistically significant differences observed between the diagnostic groups (emotional, cognitive, and social functioning, fatigue, nausea/vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties, fear of future, visual problems, communication limitations, seizures, dizziness, hair loss, itching). Figure 3 illustrates significant findings from the EORTC-QLQ-C30-BN20 subdomains.

Influencing factors of EORTC-QLQ-C30-BN20 domains of QoL

Only the analyses yielding significant results within the GBM or Glioma_2 group are reported.

In our analysis, gender was identified as a significant factor influencing communication limitations in the GBM patients' group (women > men, median = 33; mean = 35.80; SD = 31.426 vs. median = 16.56; mean = 23.92; SD = 26.982; $p = 0.019$).

Additionally, there was a significant difference observed in physical function related to the timing of assessment (preoperative median = 86; mean = 73.97; SD = 29.378 vs. postoperative median = 73; mean = 60.44; SD = 32.819; $p = 0.01$) in GBM patients' group. Furthermore, visual problems, as a component of physical function, showed significant differences over time (preoperative median = 0; mean = 12.69; SD = 18.783 and postoperative median = 11; mean = 20.43; SD = 24.374; $p = 0.045$). Finally, pre-existing psychiatric conditions were found to significantly influence aspects of the EORTC-QLQ-C30-BN20.

In the aspect of gQoL, GBM patients with psychiatric distress exhibited significantly lower scores (median = 25; mean = 35.8; SD = 33.029) compared to those without such distress median (50; mean = 52.33; SD = 26.343; p = 0.037).

Similarly, in Glioma_2 patients, gQoL scores were significantly lower at a significance level of exactly 5% among those with psychiatric distress (median = 50; mean = 53.12; SD = 26.68) compared to those without (median = 66.67; mean = 68.51; SD = 21.822; p = 0.05).

Discussion

The question of QoL is crucial in the treatment of patients diagnosed with glioma. While the implementation of screening has been thoroughly examined in recent years, insights into the timing of necessary interventions or significant differences arising from the diagnoses of LGG compared to a GBM have not been adequately studied. Therefore, we, in this study, specifically investigated whether Glioma_2 patients, among other factors, experience better QoL and lower psycho-oncological distress due to their better prognosis and younger age at the onset of their illness compared to GBM patients. We analysed factors such as gender, psychological predisposition, marital status, and physical constitution to understand their influence.

Key conclusions that can be drawn from our data are that by using unspecific screening tools for non-specific stress in this study, the DT, no significant difference between patients with GBM and those with Glioms_2 could be found. However, concerning the domain of depression, when assessed with the HADS-D, significantly more GBM patients reported depression, whereas anxiety levels assessed using the HADS-A were similar in both groups. To evaluate the patients' physical functions, the medically assessed KPS and some of the subjectively answered aspects of the EORTC-QLQ-C30-BN20 questionnaire that were used showed that GBM patients already have significantly more physical impairments compared to Glioma_2 patients at the time of diagnosis. Among the other aspects of the EORTC-QLQ-C30-BN20 questionnaire, the overall QoL is notably worse for glioblastoma patients. The complexity of QoL could be illustrated through our study.

Integrating our results with existing published data is challenging due to the limited number of glioma studies using the EORTC-QLQ-C30-BN20 questionnaire. Few studies have referenced this questionnaire. Budrukkar's work is highly comparable, as it uses baseline data from LGG and HGG patients before adjuvant therapy. However, this study involves an Indian patient cohort with a young average age of under 40 years, presenting a demographic difference from the study presented here. Unlike the cohort analysed here, Budrukkar's patients with disabilities were assisted in answering the questions, suggesting a more varied physical and cognitive condition among the Indian patients (19). Additional sources of LGG data include the study by Gustafsson (27) and, for HGG data, the study by Osoba (28). The data collection periods in both studies align broadly with this current work. It remains unclear whether, unlike in this study, Gustafsson included patients with recurrences.

Furthermore, a comparison with EORTC-QLQ-C30 values from the general population will be conducted. The data from the United Nations Department of Economic and Social Affairs, providing age-adjusted (18-70 years) surveys of the German average population (N=1006), are particularly suitable for this purpose (29). Given the high variability in EORTC-QLQ-C30 results within the average population, the official reference values from the EORTC-QLQ-C30-BN20 manual and the survey of the German average population from Schwarz's study are also incorporated (30, 31).

Distress and emotional function in glioma patients

Glioma patients in this study report elevated levels of non-specific distress, consistent with findings in previous literature (32, 33). Using the DT to compare distress levels between different neuropathological entities, specifically GBM and lower-grade gliomas (Glioma_2), no significant difference is found in our data. This aligns with the literature suggesting the DT's limited sensitivity to tumour stage across various cancer types (34–36). Contrary to the overall results, a smaller study with a limited LGG cohort (n=8) indicates higher DT scores in HGG patients compared to LGG patients despite generally low DT values reported (37). This discrepancy may reflect the DT's variable sensitivity depending on the sample size and composition. From the crucial finding of increased stress present regardless of the grading of the diagnosis, it can be concluded that every patient newly diagnosed with a glioma, irrespective of its grading, should be offered psycho-oncological support.

In the EORTC-QLQ-C30-BN20 questionnaire, glioma patients in our cohort reported greater limitations in emotional functioning compared to age-matched controls (19, 29). Consistent with DT findings, no significant differences in emotional function are detected between the diagnosis groups within this study. However, Budrukkar's study reports better emotional function in LGG patients compared to HGG patients, possibly due to cultural influences. In the study, they observed emotional function is best among older normal population controls, suggesting age-related influences on emotional well-being, as reported by Nolte et al. (29).

GBM patients, who are typically about 25 years older than Glioma_2 patients, might initially have better emotional function relative to their younger counterparts. However, the aggressive nature of GBM potentially reduces their emotional function over time. Another significant aspect of high distress in Glioma_2 patients might be their life situation. Being generally younger, these patients are often engaged in family planning, childcare, and pursuing unfulfilled life goals, contributing to their elevated distress levels.

Anxiety

In this study, 39% of glioma patients show elevated anxiety levels, with 20% even having scores of ≥11. Compared to other studies, the prevalence of anxiety in our cohort is relatively low (10, 25, 33, 38, 39).

A study in 1999 found that anxiety levels in pre-operative brain tumour patients were 20% higher than those reported in this study, indicating potential progress in managing emotional side effects over time (40). Unlike the study, our data did not reveal significant statistical differences in HADS-A scores between different diagnostic groups. Similarly to our data, the study by Bunevicius et al. found no pre-operative differences in HADS-A scores between HGG and LGG at initial diagnosis (38). However, a study by Arnold et al. reports higher anxiety in LGG patients compared to HGG patients, citing the inclusion of many complex cases and a generally high prevalence of depression as contributing factors (41).

Depression

Unlike anxiety, depression is significantly more reported by GBM patients in this cohort than by Glioma_2 patients. This is evident in both the median HADS-D scores (4.5 vs. 3) and the percentage of patients above the cut-off (29.8% vs. 16.3%). A similar prevalence was found in a study of pre-operative patients at initial diagnosis using the same cut-off values (37% HGG; 10% LGG) (38). However, another study using objective depression screening tests did not find differences based on tumour histopathology (42). Additional studies confirm increased depression in GBM patients compared to LGG patients and other brain tumour patients (38, 40). Conversely, the study by Arnold et al., study shows higher depression scores in LGG patients than in HGG patients, but direct comparison is limited due to different measurement tools. The authors also attribute the high depression prevalence to the inclusion of many complex cases in his study (41). The elevated depression rates among GBM patients may be linked to their shorter survival times, more severe symptoms, and the burdensome adjuvant therapy they undergo.

Comparing the overall HADS-A and HADS-D results for this cohort, anxiety is more prevalent than depression, with a quarter of the patients scoring above the cut-off of ≥8. Bunevicius also observed higher perioperative anxiety compared to depression (38). Following the conclusion of a meta-analysis on glioma and depression, the prevalence in this study falls within the lower reported range (13-53%) for the risk of glioma patients developing depression (43).

Physical functioning

In this cohort, GBM patients reported significantly worse physical functioning compared to Glioma_2 patients. Similar findings are presented in Budrukkar's cited study involving HGG and LGG patients. Regardless of the diagnostic group, there is a pronounced reduction in physical function compared to the age-matched average German population (29).

The interpretation of physical limitations in GBM and Glioma_2 patients should consider the average age difference of approximately 25 years between the groups. Age-related declines in physical function are evident in the age-adapted EORTC-QLQ-C30 results for the general population. Glioma_2 patients show fewer differences in physical functioning relative to the younger average population compared to the difference observed between GBM patients and the older average population. This suggests that neuropathology influences physical function, although a statistically valid calculation to confirm this is not feasible due to the lack of literature data. The presence of more severe physical symptoms is expected, given the more rapid and aggressive tumour growth in GBM.

Supporting these results, the EORTC-QLQ-C30-BN20 questionnaire in this study indicates significantly higher scores for motor deficits among GBM patients compared to Glioma_2 patients. Budrukkar's study also reports pronounced motor deficits, with greater impairment in HGG patients compared to the LGG cohort.

Clinical assessment using the KPS

When measuring physical condition using the KPS, which is critical for immediate therapy planning, a significant difference between GBM and Glioma_2 patients is confirmed in this study. Even when only pre- and post-operative Glioma_2 patients are included in the calculation, they exhibit significantly better physical condition than GBM patients at initial diagnosis. While the results for GBM patients in this study align with the literature, Glioma_2 patients show better outcomes than previously reported in the literature (44, 45). This discrepancy may be due to early screening and the exclusion of patients undergoing adjuvant therapy or with recurrences. Regardless of the specific cause, older glioma patients and GBM patients are particularly affected by reduced KPS. In this cohort, the median KPS for Glioma_2 patients was 90, indicating normal activity with minimal or mild symptoms. In contrast, the median KPS for GBM patients was 70, suggesting that while patients can still manage self-care, normal activity or participation in the workforce is no longer possible.

Overall QoL in glioma patients

Our study results indicate a markedly lower subjective QoL for GBM patients compared to Glioma_2. This distribution of gQoL between GBM and Glioma_2 patients aligns with Budrukkar's findings. Comparing global QoL outcomes across different age groups in the general population reveals a slight decline in global QoL with increasing age. While Glioma_2 patients in this study exhibit similar global QoL levels to their age-matched general population, GBM patients show substantially lower scores than the 60–69-year-old group in the general population (29). Therefore, the diminished gQoL observed in GBM patients cannot be fully attributed to the older average age of these patients. Hickmann reports better gQoL scores for HGG patients compared to the GBM patients in this study and finds no significant difference between HGG and LGG patients, possibly due to varying disease stages within the patient cohort (11). Additionally, Osoba et al. note higher, near-normal gQoL scores for perioperatively surveyed HGG patients (28). The reason for the differences in gQoL outcomes among various HGG cohorts remains unclear.

Limitations

The challenging measurability of QoL stems from its inconsistent definition and the variety of measurement methods used. This complicates the comparison of data, exacerbated by differently defined cut-off values, various analytical methods and differing survey timings in the literature. The rarity of the disease often results in small and heterogeneous study cohorts. Furthermore, deviations in neuropathological diagnosis based on current criteria cannot be ruled out when compared with older data.

To address these limitations, this study presents results from multiple established measurement methods with precise statistical details, highlighting relevant differences found in the literature. Comprehensive data collection is not fully achieved due to the adaptation of sociodemographic questions during the data collection period. Retrospective data collection is not feasible for deceased patients, meaning that an analysis of additional potential confounders can only be conducted with new data over time. The retrospective character of this study is, therefore, one major limitation. This study cannot entirely rule out the impact of "selection bias," as patients unable to complete the questionnaires independently were excluded. The impact is considered minimal given the early survey timing and the relatively unaffected patients. It is recognised in recent publications that cognitively impaired individuals tend to report a higher QoL than their caregivers (46). Glioma patients report lower scores in the "cognitive function" aspect of the EORTC-QLQ-C30 compared to the general population, indicating that bias cannot be excluded. Furthermore, the groups were unevenly distributed, and assessment took place at different time points. These facts have to be clarified to contextualise the data. Prospective data collections are needed to reduce possible bias.

Conclusion

In this study, we analysed the complex field of QoL by analysing data from GBM and Glioma_2 patients. The initial assumption of lower QoL and higher psycho-oncological burden among GBM patients, compared to Glioma_2 patients, was substantiated in key aspects. We conclude from our data that besides a general need for psychooncological screening, especially targeted anxiety management interventions for glioma patients and early screening for depression, especially among GBM patients, should become more standard practice. The EORTC-QLQ-C30-BN20 questionnaire emerged as a comprehensive screening tool, revealing significant differences not only in physical domains but also in other aspects between GBM and Glioma_2 patients. Particularly, gQoL vividly portrayed the poorer state of GBM patients compared to Glioma_2 patients. A substantial influencing factor was a history of psychological burden, reflected in diminished global QoL and increased cognitive impairments among psychologically burdened patients.

In summary, our results advocate for early QoL screening of all glioma patients. The understanding of individual life situations offers targeted support for personal limitations. Due to the known interconnectedness between QoL and survival, QoL should be further implemented as a therapeutic goal, and the results of the present study aim to contribute to this advancement.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics committee Heinrich-Heine University Düsseldorf. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

FS: Validation, Visualization, Writing – original draft, Writing – review & editing. SO: Data curation, Formal analysis, Investigation, Validation, Writing – original draft. MS: Supervision, Writing – review & editing. MR: Conceptualization, Methodology, Project administration, Supervision, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2024.1457017/full#supplementary-material

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Psycho-oncological burden in patients with brain metastases undergoing neurological surgery

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Purpose: The development of brain metastases (BM) can significantly increase the psycho-oncological burden in cancer patients, requiring timely intervention. In addition, this aspect may negatively affect the course of the disease and treatment outcome. However, screening for psycho-oncological burden is often overlooked in clinical routine. Therefore, we analyzed the extent of psycho-oncological distress in a patient population with BM receiving neurosurgical resection and identified clinical characteristics associated with a high need for psycho-oncological intervention.

Methods: We prospectively screened 353 patients (169 female, 184 male, mean age 61.9 years) scheduled for microsurgical resection of one or more BM. Psycho-oncological screening was performed on the day of admission using the Hornheider screening instrument (HSI) and the distress thermometer (DT). Screening results were correlated with demographic and clinical data.

Results: Most patients (73.1%) completed the screening questionnaire. Patients who failed to complete the questionnaire presented more frequently with metachronous BM (74.7% *vs*. 25.3%, p=0.009), were significantly older (p=0.0018), and had a significantly lower KPS score (p=0.0002). Based on the threshold values of the questionnaires, 59.3% of the patients showed a significant psycho-oncological burden requiring immediate intervention. Univariate analysis demonstrated that synchronous BM (p=0.034), tumors in eloquent areas (p=0.001), lower KPS (p=0.031), female gender (p=0.009), and presurgical aphasia (p=0.042) were significantly associated with high psycho-oncological burden. Multivariate analysis showed synchronous BM (p=0.045), female gender (p=0.005), and lower KPS (p=0.028) as independent factors associated with high psycho-oncological burden.

Conclusion: The majority of patients with BM have a high psycho-oncological burden. Female gender, synchronous BM, and lower KPS are independently associated with a need for psycho-oncological intervention.

KEYWORDS

psycho-oncology, brain tumor, neurosurgery, psychological distress, psycho-oncological need

1 Introduction

The development of brain metastases (BM) can significantly worsen the prognosis of patients with cancer (1) and is an increasingly common complication of the primary disease (2). Patients with BM are severely burdened by metastasis-related symptoms and the exceptionally poor prognosis (3). As a life-threatening disease, cancer increases the risk of developing mental health problems, including depression, anxiety, and distress (4). These factors have been shown to be significant determinants of quality of life (QoL) (5). Depression and anxiety in particular negatively influence treatment outcome and survival (6). The National Comprehensive Cancer Network (NCCN) defines distress in cancer as "a multifactorial unpleasant experience of a psychological, social, spiritual, and/or physical nature that may interfere with one's ability to cope effectively with cancer, its physical symptoms, and its treatment" (7). Therefore, patients with a high level of distress need supportive care and psycho-oncological intervention (8). It is highly important that each individual patient in need of psycho-oncological support is identified correctly and in a timely manner (9). Two well-established tools, the Hornheider Screening Instrument (HSI) and the Distress Thermometer (DT), can be used to assess psycho-oncological distress (10–18). The HSI is an appropriate tool with high reliability and validity using the answer categories "yes" and "no" to assess the physical and mental status of patients during the initial contact between physicians and patients (19). DT is recognized as a brief, feasible, and highly sensitive screening tool when evaluated against established criteria (17, 20, 21). However, with the exception of specialized neuro-oncology centers, screening for psycho-oncological distress is not regularly established in the clinical routine of neurosurgical units, and the need for psycho-oncological support may often be underestimated (22). We hypothesized that patients with BM and high psycho-oncological needs may be identified by specific characteristics such as older age, low KPS, or focal neurological impairment. The aim of this study was therefore to analyze the subgroup of patients with BM scheduled for neurological surgery who showed increased psycho-oncological burden, in order to identify clinical parameters that predict this specific unmet medical need. Although similar studies have been performed in patients receiving radiotherapy (23–25) or systemic treatment (26), no such analysis has yet been performed in patients with BM undergoing microsurgical resection.

2 Material and methods

2.1 Study design and ethical approval

This single-center cross-sectional study prospectively enrolled patients scheduled for microsurgical resection of one or more BM at the Regensburg Brain Tumor Center between January 2015 and January 2023. After being informed about the objectives of the study and confirming the voluntary participation, patients were questioned once at first admission using the HSI or the DT and divided into two groups with and without the need for psycho-oncological care.

In accordance with German ethical and regulatory standards and the Declaration of Helsinki (7th revision, 2013), the study was approved by the Regensburg University Institutional Ethics Review Board (vote no. 20-1799-101). The data protection concept at the Brain Tumor Center Regensburg, established according to the European General Data Protection Regulation and relevant national legislation, was strictly followed.

2.2 Questionnaires

The HSI is a questionnaire designed to assess psycho-oncological needs of cancer patients. It contains 7 items that examine global health conditions, global mental conditions, burden, person of trust, burdened family member, temporary internal disturbance, and information about the disease and treatment. The individual items are aggregated into a summary score ranging from 0 to 14. The cut-off is set at 5 score points, with scores ≥ 5 points indicating the need for psycho-oncological support (11). The DT is a screening instrument developed by the NCCN Distress Management Panel to provide an initial screening of psycho-oncological distress in cancer patients. Its scale is 0 to 10, and a score greater than 4 indicates psycho-oncological need (27).

The psycho-oncological screening was performed on the day of admission. Examples of the questionnaires are attached in the Supplementary Files (Supplementary Material 1). The questionnaire given to the patients was selected according to the hospital's internal standards. The change from HSI to DT was based on a consensus decision made by the leading board of the local Comprehensive Cancer Centers network in Würzburg, Erlangen, Regensburg, and

Augsburg (CCC – WERA), aligning with the current guidelines (28). Accordingly, we have implemented this decision into our clinical practice. A value of ≥ 5 in the HSI or > 4 in the DT indicated high psycho-oncological distress.

2.3 Study population

During the patient recruitment phase, data on the entire cohort were filtered out. Inclusion criteria were admission to the neurosurgical department because of suspected brain metastasis or known primary systemic oncologic disease and presence of an intracerebral tumor mass on MRI, an appropriate recruiting time frame before neurosurgical resection, age older than 18 years, and histological confirmation of the diagnosis BM after the resection. Patients without psycho-oncological screening at admission or with ambiguous or unclear answers were excluded.

The following variables were collected from the electronic patient files of the SAP® software (SAP® Deutschland SE & Co.KG, Walldorf, Germany) and the radiological, oncological, medical, and tumor board reports: age, gender, preoperative Karnofsky Performance Status (KPS), tumor-related deficits, histology of the primary tumor, BM timing, side and location of the BM, BM status (solitary = one single BM without systemic metastases, singular = one singular BM and at least one systemic metastasis, and multiple = more than one BM), and extent of resection. Eloquent areas were defined using a widely used summary description in the literature that describes eloquent cerebral structures as brain areas with readily identifiable neurological function, where injury results in disability (29).

2.4 Statistics

For continuous data, descriptive statistics were applied (Stata/IC version 16.1, College Station, USA) using mean, median, minimum, maximum, and standard deviation. Categorical data are presented as absolute and relative frequencies. Continuous variables were compared using the Student's t-test for normally distributed data and the Mann-Whitney U test for non-normally distributed data. A multivariate analysis was performed using a multiple linear regression model, and the independence of categorical variables was tested with Pearson's chi-squared. A p-value < 0.05 was defined as statistically significant.

3 Results

3.1 Population characteristics

Our study included 353 patients (169 female and 184 male between the ages of 26.3 and 85.1 years, mean age 61.9 ± 12.2 years). 186 patients who did not meet the inclusion criteria were excluded. In the recruited population, the mean preoperative KPS was 79.5 ± 15.7 (range: 30-100). 50.4% (n=178) of the patients presented with multiple metastases, 38.8% (n=137) with singular, and 10.8% (n=38) with solitary metastasis. The majority of the patients (63.2%, n=223) were treated for metachronous metastases, and the remaining patients for synchronous metastases (36.8%, n=130). The most frequent primary tumor was lung cancer (38.2%, n=135), followed by melanoma (15.0%, n=53), and breast cancer (12.5%, n=44). Complete resection was achieved in 78.5% (n=277) of the patients, while resection was incomplete in 21.5% (n=76). 47 (13.3%) patients were affected by aphasia, 77 (21.8%) showed hemiparesis, and 49 (13.9%) had visual impairments. Regarding the anatomical site of the lesion, 113 (32.0%) were frontal, 78 (22.1%) cerebellar, 57 (16.1%) parietal, 51 (14.5%) occipital, 39 (11.0%) temporal, 9 (2.6%) frontoparietal, and 6 (1.7%) frontotemporal. In total, 155 (43.9%) lesions were located on the right side, 151 (42.8%) on the left side, and 47 (13.3%) were bilateral. 114 (32.3%) were situated in an eloquent area. The baseline data are summarized in Table 1 and partially illustrated in Figure 1.

3.2 Completion of questionnaires

Most patients (258, 73.1%) completed the screening questionnaire. This subgroup showed a mean age of 60.6 ± 12 years and a preoperative mean KPS of 81.4 ± 13.8. 152 (58.9%) patients had metachronous, and 106 (41.1%) patients had synchronous metastasis timing. Psycho-oncological screening using the HSI was performed in 241 (93.4%) patients and with the DT in 17 (6.6%) patients. 95 (26.9%) patients failed to complete the questionnaire. The characteristics of this subpopulation were as follows: mean age 65.4 ± 12.2 years, mean preoperative KPS 74.4 ± 19, 71 (74.7%) patients with metachronous presentation and 24 (25.3%) patients with synchronous presentation. Univariate analysis showed that the patients who failed to complete the questionnaire were significantly older (60.6 *vs.* 65.4, p=0.0018), presented significantly more frequently with metachronous BM (74.7 *vs.* 25.3%, p=0.009), and showed a significantly lower presurgical KPS (74.4 *vs.* 81.4, p=0.0002) than patients who filled out the questionnaire. These results are illustrated in Table 2 and Figure 2.

3.3 Psycho-oncological need

Based on the thresholds of the questionnaires, 153 (59.3%) patients showed a significant psycho-oncological burden requiring immediate intervention, while 105 (40.7%) patients did not 85 (55.6%) female and 68 (44.4%) male patients required psycho-oncological care, while 64 (60.9%) male and 41 (39.1%) female patients did not need psycho-oncological support. According to the univariate analysis psycho-oncological need was significantly higher in female gender (p=0.009). 96 (62.7%) patients with high psycho-oncological distress had BM in a non-eloquent area, while 57 (37.3%) patients had BM in an eloquent area. In contrast, 86 (81.9%) patients with a distress value below the threshold had a

TABLE 1 Baseline data.

Parameter	Value
Total population	353
Gender (m/f)	184/169 (52.1/47.9)
Age	61.9 (range: 26.3–85.1)
Preoperative KPI	80 (range: 30–100)
Metastasis status	Solitary: 38 (10.8) Singular: 137 (38.8) Multiple: 178 (50.4)
Metastasis timing	Synchronous: 130 (36.8) Metachronous: 223 (63.2)
Primary	Lung: 135 (38.2) Melanoma: 53 (15.0) Breast: 44 (12.5) Colorectal: 24 (6.8) CUP: 23 (6.5) Kidney: 13 (3.7) Stomach: 8 (2.3) Prostate: 8 (2.3) Urothelium: 7 (1.9) Endometrium: 6 (1.7) Cervix: 5 (1.4) Testis: 2 (0.6) Other: 25 (7.1)
Deficits	
- Hemiparesis - Visual impairment - Aphasia	77 (21.8) 49 (13.9) 47 (13.3)
Localization	
- Frontal - Cerebellar - Parietal - Occipital - Temporal - Frontoparietal - Frontotemporal	113 (32.0) 78 (22.1) 57 (16.1) 51 (14.5) 39 (11.0) 9 (2.6) 6 (1.7)
Side	
- Right - Left - Bilateral	155 (43.9) 151 (42.8) 47 (13.3)
Eloquent area	114 (32.3)
Complete resection (y/n)	277 (78.5)/76 (21.5)

Values are given as number of patients (%) or median (range).

non-eloquent BM, compared to the remaining 19 (18.1%) patients with BM in an eloquent area. Furthermore, 129 (84.3%) patients without aphasia and 24 (15.7%) patients with aphasia showed psycho-oncological distress values above the threshold. In comparison, 98 (93.3%) patients without aphasia and 7 (6.7%) patients with aphasia did not reach distress values above the threshold. When considering the timing of BM, 93 (60.8%) patients with metachronous BM and 60 (39.2%) with synchronous BM had above-normal distress values, in contrast to 78 (74.3%) patients with metachronous BM and 27 (25.7%) patients with synchronous BM who did not. Patients with high psycho-oncological distress had a lower KPS (80.1 ± 14.5) than the patients with a distress value below the threshold (83.3 ± 12.5). Univariate analysis thus demonstrated that tumors in an eloquent area (p=0.001), occurrence of aphasia (p=0.042), synchronous BM (p=0.034), and lower presurgical KPS (p=0.031) were significantly associated with high psycho-oncological burden (Table 3; Figure 3). The other variables did not significantly differ between the patients with or without high psycho-oncological distress. The multivariate analysis using a multiple linear regression model, showed that female gender (p=0.005), presurgical KPS (p=0.028), and synchronous BM (p=0.045) are independent factors associated with a high need for psycho-oncological support (Table 4; Figure 4).

4 Discussion

This study evaluated for the first time the psycho-oncological burden in patients with BM receiving neurosurgical resection. Based on the results of the HSI and DT screening tools, this study has shown which subgroups of patients are most at risk and therefore may require more rapid and targeted psycho-oncological intervention.

4.1 Psycho-oncological burden in study populations

A survey of 4664 cancer patients treated at 55 American Cancer Centers demonstrated a significant psychological burden in 46% of all patients included (30). In contrast, in another study by Zabora et al. (2001), the overall prevalence rate of distress in patients with all types of cancer was only 35.1% (31). Patients with pancreatic or lung cancer as the primary tumor were associated with higher psycho-oncological burden (30, 31). To the best of our knowledge, there is not head-to-head study on whether cancer patients with BM have a higher psycho-oncological burden than those without BM. However, psychological distress, depression, and anxiety may be particularly enhanced in patients with primary brain tumors as compared to patients with non-CNS tumors (32, 33). Nevertheless, the literature shows considerable heterogeneity regarding the rate of psycho-oncological burden in patients with primary brain tumors, as shown in a recent meta-analysis, in which the prevalence of distress ranged from 12.3% to 73.6% (34). This extensive variability may be associated with the type of tumors and their different grades of malignancy. For example, a study on low-grade glioma showed a significant psycho-oncological burden in only 20.8% of the patients (35), whereas a similar study performed in patients with high-grade glioma found a rate of 61.5% (36). Those results are comparable to our data of 59.3% of all BM patients with significant psycho-oncological burden.It has been reported that patients with primary brain tumors experience unmet supportive care needs, especially in the psychological domain (37). Our work indicates that patients with BM also present with a high level of psycho-oncological distress that requires adequate intervention. Tumor-induced symptoms and impairments as well as tumor-targeted treatments may affect one's ability to carry out daily routine tasks,

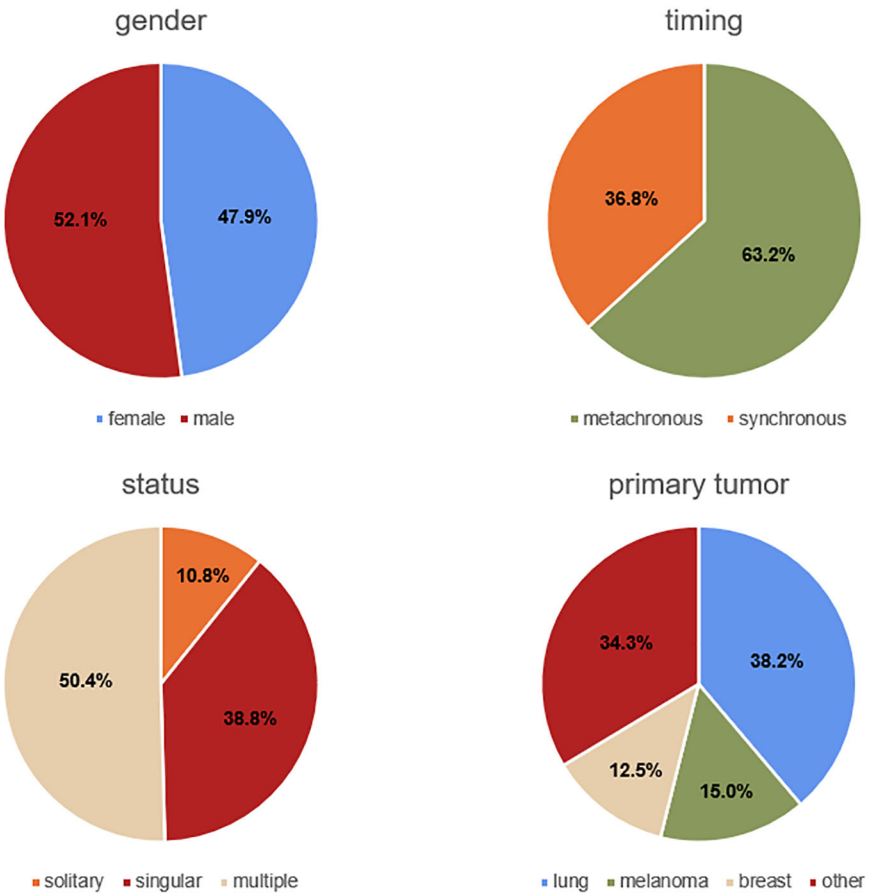

FIGURE 1
Pie charts showing part of baseline data.

resulting in increased functional dependency, significant emotional distress, and anxiety about the future (38). Distress in cancer is a multifactorial unpleasant experience that results in the loss of the patient's coping strategies (39). This statement indicates that the topic of psycho-oncological support comprises a comprehensive set of complex issues that require multidisciplinary, disease-specific experience. Our purpose, however, was to evaluate correlations between psycho-oncological needs and specific aspects to identify patients most in need of support in a well-defined study population.

There is widespread evidence that physical symptoms of specific types of cancer may contribute to depression (40). Among all preoperative functional symptoms, only aphasia was shown to be significantly associated with higher levels of psycho-oncological distress in our data. In our univariate analysis, the other factors related to higher psycho-oncological burden were synchronous metastasis, tumors in eloquent areas, lower KPS, and female gender. Concerning the role of the KPS, some authors did not find any correlation between KPS and psycho-oncological needs (10, 37), while other studies are in line with our data (41, 42). In our study, age was no relevant factor for psycho-oncological burden, which is consistent with similar reports (10). The relationship between age and psychological burden in cancer patients is controversial in the literature: some studies have shown that younger patients are more likely to experience psychological issues and have a higher frequency of anxiety symptoms than older patients (43, 44). However, other studies have indicated that cancer patients over 85 years of age are more likely to develop depression than younger patients (45, 46).

TABLE 2 Influence of BM timing on questionnaire completion.

Metastasis timing	Screening failure		p-value
	no = 258 (73.1)	yes = 95 (26.9)	
Synchronous	106 (41.1)	24 (25.3)	**0.009**
Metachronous	152 (58.9)	71 (74.7)	

Values are given as number of patients (%). The p-value is highlighted in bold.

Excluding possible confounders, synchronous metastasis timing, KPS, and female gender were factors associated with a higher risk of psycho-oncological burden. The fact that patients with synchronous metastasis have a higher psycho-oncological distress seems reasonable, considering that the impact of a diagnosis of brain metastasis in patients who have already known about the primary tumor for at least 3 months may be different from that in patients who receive a diagnosis of BM and a diagnosis of primary tumor at the same time or within a very short interval.

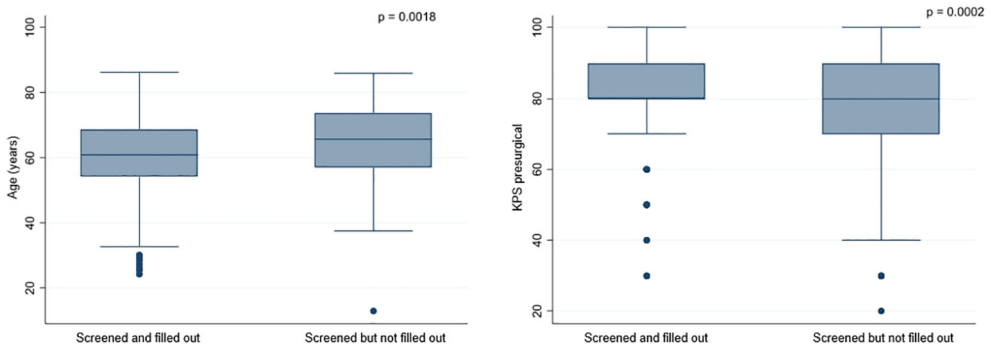

FIGURE 2
Graphs illustrating the significant influence of age and presurgical KPS on questionnaire completion.

4.2 Role of gender in psycho-oncological burden

Several studies have already identified female gender as a significant risk factor for higher psycho-oncological burden in cancer patients and have shown that this subpopulation experience more psychological distress than male patients (47, 48). Rapp et al. also identified female gender as a factor associated with a higher risk of pathological screening in both univariate and multivariate analyses (3). Some authors have indicated that even the gender of the caregivers predicted a higher burden (49, 50) and that the level of QoL in female patients was lower than that of male patients (50). These findings are in line with other studies analyzing QoL in different types of cancer: for example, female patients with chronic lymphocytic leukemia were found to have remarkably lower QoL scores in the areas of emotional and social functioning than male patients (51). Few studies have found no association between gender and the prevalence of depression, anxiety, or psycho-oncological needs (5, 37), while other authors suggest the opposite (52, 53), finding anxiety and depression more common in male patients (54). In a recent review, Zhou et al. (2023) stated that gender differences go beyond the simple masculine-feminine binary (55). According to other authors' findings, the impact of gender on distress, anxiety, and depression is still inconclusive when other factors, such as the primary tumor type and level of education, are considered (56). Other key factors also play a role in the development of psycho-oncological distress, for example, the presence of pre-existing mental health problems and their severity, healthcare costs, access to welfare support, as well as fewer educational qualifications and lack of social support (6).

An unambiguous, scientific explanation of why female patients tend to have a higher psycho-oncological burden is currently not possible. Considering the experience of our center, we can speculate that women tend to communicate their needs and problems more transparently than male patients, who often prefer not to show any signs of suffering. This possible interpretation is reflected in the

TABLE 3 Influence of various clinical parameters on psycho-oncological need.

	Psycho-oncological need		p-value
Parameter	Beyond threshold = 153 (59.3)	Below threshold = 105 (40.7)	
Tumor location			
Non – eloquent	96 (62.7)	86 (81.9)	**0.001**
Eloquent	57 (37.3)	19 (18.1)	
Aphasia			
No Aphasia	129 (84.3)	98 (93.3)	**0.042**
Aphasia	24 (15.7)	7 (6.7)	
Metastasis timing			
Metachronous	93 (60.8)	78 (74.3)	**0.034**
Synchronous	60 (39.2)	27 (25.7)	
Gender			
Male	68 (44.4)	64 (60.9)	**0.009**
Female	85 (55.6)	41 (39.1)	

Values are given as number of patients (%). P-values are highlighted in bold.

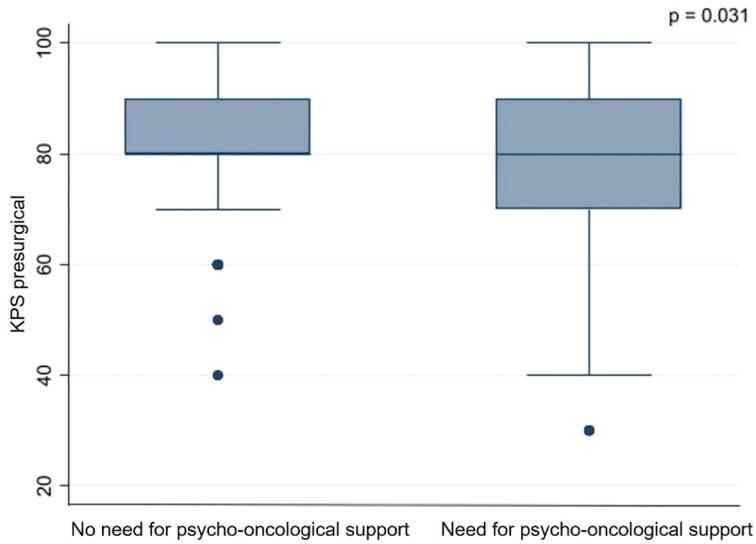

FIGURE 3
Influence of presurgical KPS on psycho-oncological burden.

TABLE 4 Multivariate analysis showing factors independently associated with a need for psycho-oncological intervention.

Parameter	Hazard Ratio	95% CI	p-value
Presurgical aphasia	2.325	2.703 1.948	0.317
Eloquent location	2.464	3.004 1.924	0.160
Female gender	2.668	3.173 2.163	**0.005**
Presurgical KPS	1.528	2.356 0.669	**0.028**
Synchronous metastasis	1.459	1.982 0.936	**0.045**

P-values less than or equal to 0.05 are highlighted in bold.

considerations by Northouse et al. (2000), who maintained that female patients are more comfortable disclosing their emotional distress and role problems. However, they are responsible for managing more roles inside and outside of the family and hence experience more role disruption and distress when illness occurs (49). This concept is reinforced by the fact that although female patients were more likely to experience depression, male patients were more likely to experience somatization (57).

In our opinion, these findings and considerations underscore two critical needs in the management of patients with brain metastasis. First, a gender-sensitive approach in psycho-oncological support, as already recommended by some authors

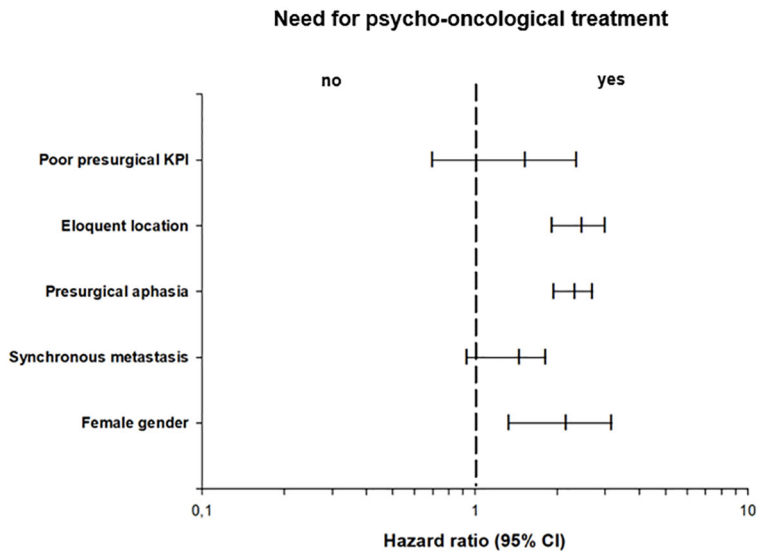

FIGURE 4
Multivariate binary logistic regression analysis of psycho-oncological need, showing the odds ratios of the impact of clinical characteristics in relation to psycho-oncological burden.

(49, 58), and second, to provide other psychological support strategies for male patients, considering that their psycho-oncological distress may be underestimated due to possible psychological embarrassment, reluctance to bother the physician, and higher barriers to help-seeking (59–62).

4.3 Possible supporting strategies to enhance quality of life

Once the causes of increased psycho-oncological needs have been identified, it would be appropriate to develop a strategy to reduce this burden (63). Notably, the use of psycho-oncological interventions in other oncological diseases can reduce psychological burden and improve QoL compared to patients receiving standard support alone (64). Effective psychotherapy for depression in patients with brain tumor is limited compared with cognitive behavioral therapy and participation in support groups (65). Therefore, an accurate identification of the categories of patients most in need of psycho-oncological support, who are carefully sensitized to targeted behavioral strategies, may lead to a breakthrough in the treatment of patients and improve a patient-centered healthcare service delivery model that helps individuals overcome barriers (66).

As more and more patients live with and beyond the diagnosis of BM, more research is needed to understand the potential impact of the long-term and late effects of cancer treatment on mental health and to prevent psycho-oncological burden. The treatment of co-morbid depression and anxiety in people with cancer requires higher clinical priority (6). A better understanding of the correlates of existential tension in patients with brain tumor is essential (65), and will ultimately improve patient-centered care (67) and address the quality of survival in addition to quantity (38).

As the prevalence of BM is steadily increasing and surgical success significantly affects prognosis by making adjuvant treatment more effective (68), neurosurgeons will be in contact with an increasing number of patients with brain metastases. Therefore, their respective departments should be prepared to recognize and adequately approach the essential psycho-oncological aspect as well.

4.4 Limitations

Our study has several limitations. The first limitation is the single-center, cross-sectional setting. Our data were, in fact, collected at a single point in time, so we cannot verify how the patients' needs evolved over time. This aspect will be analyzed by our group in a subsequent study. Moreover, due to the number of possible interactions, we did not investigate every single possible factor associated with mental health in general and in gender in particular. This problem is confirmed by other studies in the literature (69). In line with other authors (70), the level of psycho-oncological distress in each phase of care and the specific proposal for support and its effectiveness need to be clarified in further studies.

5 Conclusion

Our results show that the majority of BM patients experience a high level of psycho-oncological distress. In the multifactorial analysis, female gender, presurgical KPS, and synchronous BM presentation resulted as independent factors associated with a higher psycho-oncological burden and a major need for psycho-oncological intervention. The task of the treating physician should be to identify individuals with higher psycho-oncological needs in advance and to actively address their needs with a personalized, patient-centered approach to minimize the patients' psycho-oncological burden and to improve QoL.

Data availability statement

The raw data supporting the conclusions of this article will be made available on reasonable request via the corresponding authors.

Ethics statement

The studies involving humans were approved by Ethics committee, University Hospital Regensburg. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

TA: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. AF: Writing – review & editing. AMH: Validation, Writing – review & editing. CD: Validation, Writing – review & editing. E-MS: Data curation, Project administration, Writing – review & editing. ANH: Validation, Writing – review & editing. MV: Validation, Writing – review & editing. KR: Writing – review & editing. MJR: Writing – review & editing. PH: Validation, Writing – review & editing. RB: Writing – review & editing. TP: Writing – review & editing. EB: Validation, Writing – review & editing. NS: Project administration, Resources, Supervision, Validation, Writing – review & editing. MP: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2024.1463467/full#supplementary-material

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Determinants of quality of life following resection of skull base tumors: a systematic review

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Background: Skull base tumors represent a small subset of intracranial neoplasm. Due to their proximity to critical neurovascular structures, their resection often leads to morbidity. As a result, surgical interventions can exacerbate symptoms or cause new deficits, thereby impacting the patients' perceived quality of life (QoL). The factors influencing QoL in patients with skull base tumors remain underexplored. This systematic review aims to synthesize current research on QoL outcomes and identify potential factors influencing QoL in these patients.

Methods: A systematic literature review was conducted in PubMed using the keywords "Skull Base" AND "Quality of Life." A total of 815 studies published up to January 31, 2024, were screened. After abstract review, 656 studies were excluded, and 159 studies underwent full-text review. The wide variability in study methodologies and utilized QoL instruments made only a descriptive comparison possible.

Results: In total, 113 studies were systematically reviewed. Publications focusing on the same tumor type or localization were compared. The majority of studies addressed tumors of the anterior skull base, with pituitary adenomas, meningiomas and vestibular schwannomas being the most commonly represented. The impact of surgery on QoL is often underestimated by caregivers and has a more profound effect on patients than expected by surgeons. A transient decline in QoL after surgery was observed across almost all studies regardless of localization and entity. Factors influencing QoL included age, gender, tumor localization, surgical approach, tumor type, extent of resection, preoperative clinical status and neurological deficits. Radiotherapy and recurrent surgeries were predictors of poorer QoL. Early psychological intervention in complex tumors appears to enhance QoL. Some successful sealing techniques, such as nasoseptal flaps and lumbar drains, affected QoL. However, variability in study methodologies reduced the validity of the findings.

Conclusion: This review highlights the significant impact of skull base tumor surgery on patients' QoL. Given the major oncological and surgical challenges

presented by skull base tumors, their treatment significantly affects QoL, and gross total resection (GTR) should not always be the primary goal. Additionally, recognizing and addressing the modifiable and non-modifiable factors influencing QoL is crucial for improving patient outcomes and providing personalized care.

KEYWORDS

quality of life, skull base surgery, neurooncology, systematic review, patient-reported outcome measures

Introduction

Tumors at the skull base, while representing only a small subset of intracranial neoplasms, present considerable challenges in neurosurgery due to their proximity to critical neurovascular structures. This anatomical complexity necessitates highly specialized surgical approaches, often carrying a significant risk of morbidity (1).

Skull base tumors are a diverse group of adult and pediatric neoplasms and exhibit considerable heterogeneity in their originating tissue and dignity, encompassing a wide range of different histological tumor entities (2). These tumors typically arise outside the brain parenchyma and can develop in distinct anatomical compartments of the skull base such as the meninges (e.g. meningiomas), sellar region (e.g. pituitary adenomas or craniopharyngiomas), cranial nerves (e.g. schwannomas) or bone and cartilage tissue (e.g. chordomas or chondrosarcomas) (3). The estimated incidence of these tumors varies significantly depending on the tumor type, with pituitary adenomas being the most common, occurring at an incidence of approximately 2.7 per 100,000 individuals in the United States (4).

Most skull base tumors show limited responsiveness to chemotherapy. As a result, surgical resection and radiotherapy remain the primary therapeutic modalities (2). However, the proximity of these tumors to critical neurovascular structures, such as the cranial nerves, the brainstem and major blood vessels, poses a significant risk during surgical intervention, often making complete resection difficult or impossible (1). Consequently, surgery is typically the initial step in treatment, aimed at reducing tumor burden, followed by adjuvant radiotherapy to control residual tumor tissue.

Despite the benefits of surgery and radiotherapy, certain tumor types, such as sarcomas and chordomas, demonstrate resistance to conventional radiation therapy. In these cases, more advanced therapeutic techniques, such as particle beam therapy, have emerged as promising additional tools, offering enhanced precision and efficacy in targeting radioresistant tumors while sparing surrounding healthy tissue (5).

Historically, research on skull base tumors has concentrated on clinical endpoints such as mortality rates, surgical complications, the extent of tumor resection, responses to radiation therapy and overall survival rates (6–8). These factors are crucial for evaluating the efficacy of treatment modalities and for predicting long-term outcomes. However, they do not fully capture the comprehensive impact of the disease and its treatment on patients' daily lives.

Quality of life (QoL) has emerged as an equally important outcome measure. It is a multidimensional construct that encompasses physical, psychological and social aspects of health from the patient's perspective (9). These dimensions help understand the broader impacts of medical interventions, extending beyond immediate clinical outcomes. The diagnosis of a skull base tumor itself can carry a significant psychological burden, potentially leading to anxiety and depression (10, 11). Surgical interventions, while often necessary for managing or curing the disease, can exacerbate these issues, especially if they result in noticeable physical or functional deficits.

The recovery period for these patients can be demanding, involving rehabilitation, adjustment to new limitations, undergoing adjuvant therapy and coping with the fear of recurrence, all of which can further influence the patient's quality of life (12, 13).

Abbreviations: ASBQ, Anterior Skull Base Questionnaire; ALHR, Atkinson Life Happiness Rating; CES-D, Centre for Epidemiologic Studies Depression Scale; FACT-H&N, Functional Assessment of Cancer Therapy – Head and Neck; GTR, Gross Total Resection; KPS, Karnofsky Performance Scale; MDS, Midface Dysfunction Scale; STR, Subtotal Resection; SBI, Skull Base Inventory; QoL, Quality of Life; UPSIT, University of Pennsylvania Smell Identification Test; HUI, Health Utilities Index; SNOT, Sino Nasal Outcome Test; SF, Short-Form Health Survey; QoLI, Quality of Life Index; UoW QoL, University of Washington Quality of Life Questionnaire; HADS, Hospital Anxiety and Depression Scale; LMS, Lund-Mackay Score; ASK-12, Anterior Skull Base Nasal Inventory-12; EES-Q, Endoscopic Endonasal Sinus and Skull Base Surgery Questionnaire; ENS6Q, Empty Nose Syndrome 6 Item Questionnaires; CSS, Chronic Sinusitis Survey; GBI, Glasgow Benefit Inventory; RSOM-31, Rhinosinusitis Outcome Measure-31; BAST-24, Barcelona Smell Test 24; CSF, Cerebrospinal Fluid; EORTC QLQ C-30, EORTC of Cancer Quality of Life Core Questionnaire; SS-12, Sniffin' Sticks 12-item smell identification test; RNLI, Reintegration to Normal Living Index; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

In the last decades, there were no validated instruments available specifically designed to measure such complex outcomes. As a result, tools like custom questionnaires and the Karnofsky Performance Status Scale (KPS) were employed to indirectly assess QoL. Originally developed to evaluate the ability of cancer patients to perform ordinary tasks, the KPS primarily quantifies a patient's functional status and predicts their capacity to endure therapies. This scale is used predominantly by physicians to measure physical independence, rather than capturing the subjective well-being of the patient (14).

Over time, more advanced QoL assessment tools have been developed that directly measure the patient's experience, such as the 36-Item Short Form Survey (SF-36). The SF-36 is a reliable and validated instrument which consists of 36 questions split into eight categories that explore both the physical and psychological dimensions of health, including physical functioning, role limitations due to physical or emotional problems, vitality, emotional well-being, social functioning, pain and general health perception (15). This multifaceted approach to assess various health dimensions makes the SF-36 a widely used questionnaire across various fields of medicine, not just skull base oncology.

While general QoL instruments like the SF-36 cover a broad array of health aspects, certain anatomical locations require more specialized instruments. The Anterior Skull Base Questionnaire (ASBQ), for instance, is specifically designed to assess QoL facets relevant to anterior skull base pathologies. It provides a validated and comprehensive evaluation through 35 questions divided into six subdomains: performance, physical function, energy and vitality, pain, specific symptoms and emotional impact (16).

Other QoL instruments frequently utilized in skull base surgery, such as the Anterior Skull Base Nasal Inventory (ASK-12) and Sinonasal Outcome Test (SNOT-22), focus on sinonasal quality of life. These tools primarily assess nasal symptoms, neurological symptoms, emotional burden and quality of sleep, thus addressing only specific components of the overall QoL (17, 18).

While a wide variety of validated QoL instruments are available today, the ones mentioned above are the most frequently used to assess QoL in the studies we have reviewed.

This systematic review aims to investigate and mine current research focusing on QoL outcomes following the resection of skull base tumors. We will examine how these outcomes are assessed, the tools used to measure QoL, and the effect of various surgical approaches on patient-reported quality of life. By highlighting patient-centered measures, we aim to promote a more comprehensive understanding of treatment impacts, guiding both clinical decision-making and patient care strategies in skull base oncology.

Methods

To ensure a robust and transparent approach to our literature search and analysis, this systematic review is designed to comply with the PRISMA guidelines (19), as illustrated by the PRISMA flowchart (Figure 1).

We conducted the systematic literature review by searching PubMed using the keywords "Skull Base" AND "Quality of Life." This search included all studies published up to January 31, 2024. Our initial search yielded 815 publications. Following a screening of abstracts, 159 studies were selected for detailed evaluation. We excluded 656 studies based on the following criteria: lack of focus on quality of life, primary involvement with ENT pathologies, studies evaluating radiosurgery techniques, or those not centrally addressing skull base pathologies.

The selected 159 articles underwent full-text review by the first two authors. Further exclusions were applied for studies that did not employ a validated quality of life assessment tool.

In cases where certain tumor types were underrepresented, we performed additional, targeted literature searches and cross-referenced existing findings. This methodological step was crucial to ensure that no significant studies were overlooked, resulting in the inclusion of one more study.

The final collection comprised 113 studies and we systematically compared the outcomes across these studies to identify factors that significantly impact the quality of life following skull base tumor resection. Publications focusing on more than one tumor identity were discussed for every single tumor identity. In the corresponding tables, these studies have been marked with an asterisk (*). Additionally, our analysis assessed the variety and frequency of quality of life assessment tools used, and examined the distribution of studies by tumor type and location to identify any patterns or gaps in the research landscape. To determine the country of origin for each study, we recorded the country of the first author's affiliated institution.

Figures presented in this study were created using Microsoft PowerPoint for initial layouts and basic graphics and refined in Affinity Designer 2.5. The ggplot2 library in R was used for the visualization of bar charts.

Results

113 articles were included in this review, with the majority being published after 2010 (Figure 2A). The five most commonly utilized quality of life assessment tools included the SNOT-22 (n=44), the ASBQ (n=26), the SF-36 (n=24), the KPS (n=13) and the ASK-12 (n=6) (Figure 2B). The majority of the studies originated from the USA (n=34), United Kingdom (n=13), Australia (n=12), China (n=12), and Germany (n=11) (Figure 2C). Each study included in this review specifically targeted distinct tumor types or particular regions of the skull base (Figure 3).

Most publications focused on pituitary adenomas (n=44), different tumor identities located in the anterior skull base (n=23) and meningiomas (n=22).

Tumors of the anterior skull base

Tumors of the anterior skull base constitute a significant portion of skull base tumors, spanning a wide spectrum of

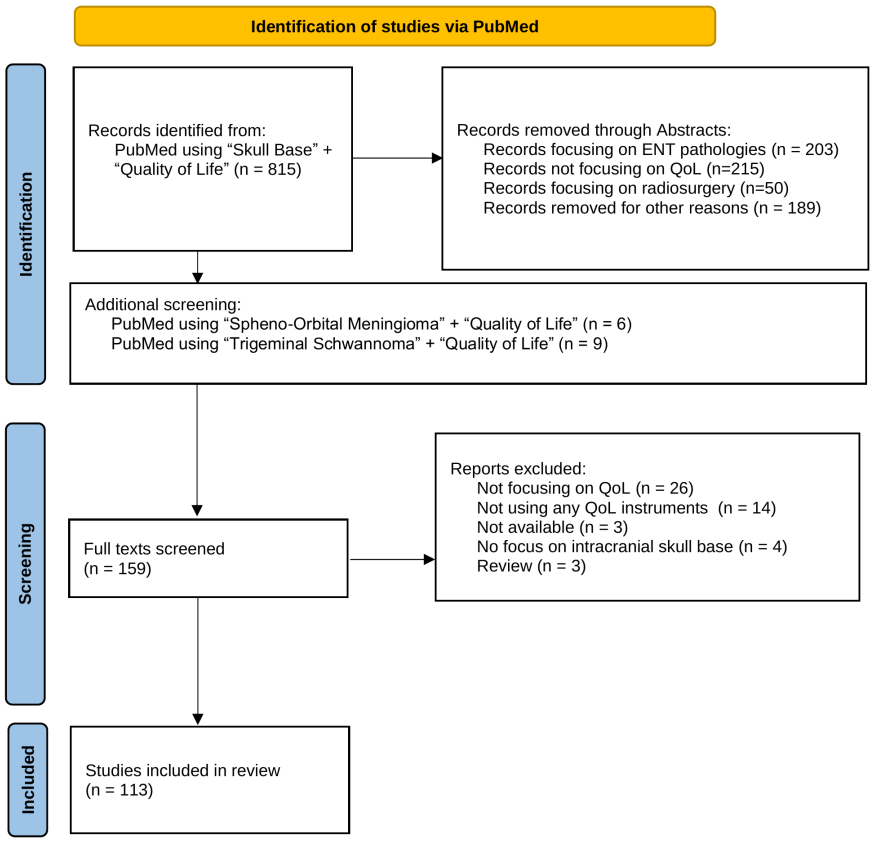

FIGURE 1
This flow chart outlines the systematic process of selecting studies for inclusion in the review, detailing the number of records identified, screened, and assessed for eligibility, as well as the reasons for exclusions at each stage.

different benign and malignant lesions. Historically, open surgical approaches were standard in the treatment of these lesions, including those that are highly invasive and often require extensive surgical intervention. Studies identified that focus on these tumors have been summarized in Table 1.

Recent advancements have increasingly supported the use of endoscopic endonasal approaches for treating anterior skull base lesions, where appropriate. While these techniques are not suitable for all tumors, they have been shown to improve QoL outcomes when compared to traditional open approaches like the subcranial approach, particularly as measured by the ASBQ (24). Furthermore, long-term QoL studies affirm the benefits of endoscopic methods for eligible lesions at the anterior skull base (26).

Earlier studies highlight the challenges associated with open surgery. High morbidity rates and significant disruptions in returning to work were noted among patients undergoing complex tumor resections (20). These issues are reflected in the diminished role function scores, indicating a negative impact on the patients perceived capacity to work (35, 36).

Studies suggests that QoL typically declines immediately following anterior skull base tumor resection, but generally returns to baseline within 6 to 12 months after surgery (24, 28, 37). Emotional and financial difficulties, as well as sleep disturbances, are common after surgery (35). Additionally, sinonasal QoL issues, such as nasal crusting or olfactory impairments, affect approximately two-thirds of patients (23). These conditions, as measured by the SNOT-22, often show improvement as early as 3 to 6 months following surgery (21, 27, 32, 39).

Some studies focusing specifically on meningiomas in the anterior skull base demonstrated significant improvement in QoL as early as one month after resection, with further improvements observed up to the six-month follow-up (42). However, more aggressive resections (Simpson Grade I) tend to result in higher rates of cranial nerve deficits (44). While visual improvement after surgery significantly impacts QoL, the loss of olfaction or taste is considered less critical (45). These neurological deficits were found to significantly decrease QoL (23, 39).

Significant disparities in QoL outcomes have been observed among patients with malignant and benign skull base pathologies (24). Patients with malignant pathologies experienced significantly lower QoL scores six months after surgery. However, there was a notable improvement in their QoL twelve months after surgery, as measured by the SNOT-22, HUI-2, and SF-36 (24, 31). In contrast, QoL scores for patients with benign tumors remained stable throughout the postoperative period (24).

Patients with malignant tumors of the anterior skull base often experience significant mental distress and psychiatric morbidity, necessitating the use of psychotropic medication in up to 80% of cases (35, 38, 41). Those undergoing extensive open cranial surgery may benefit from early psychiatric and psychological interventions,

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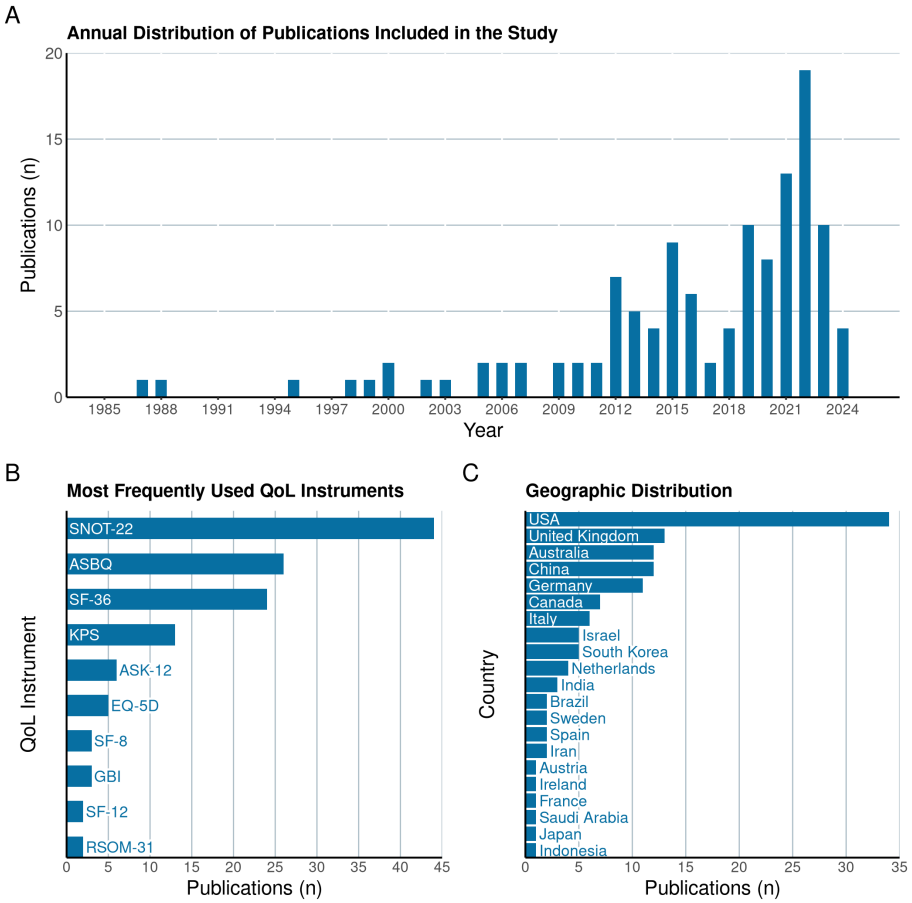

FIGURE 2
Illustration of the annual distribution of publications **(A)** included in the systematic review, highlighting trends in research volume over time. The figure also details the most frequently utilized Quality of Life (QoL) instruments in these studies **(B)** and the countries of origin of the included research **(C)**.

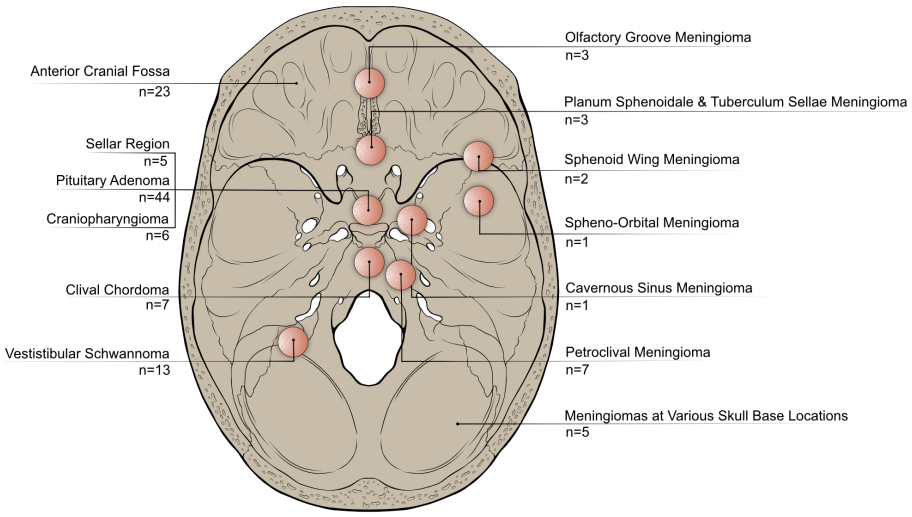

FIGURE 3
Categorization of publications included in this review based on the anatomical locations or tumor entities they focus on. This highlights variations in research focus across different anatomical regions or types of skull base tumors.

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TABLE 1 Studies investigating QoL in patients after resection of various tumors located in the anterior skull base.

First Author	Time of Surgery	Patients (n)	Surgical Approach	Follow-Up (months)	QoL Instruments	Factors Influencing QoL
(20)	1993-1997	18	Transbasal	Up to 60	SF-36	No significant factor.
(21)	2017-2018	46	Endoscopic endonasal	11,8 (mean)	SNOT-22	Temporary QoL impairments after surgery.
(22)	2010-2019	727	Various endoscopic endonasal approaches	Up to 24	SNOT-22	Mometasone irrigation after surgery improved sinonasal QoL.
(23)	Not specified	27	Various microsurgical approaches	At least 6	CES-D, ALHR, MDS	Recurrence, radiotherapy and MDS related to lower QoL.
(24)	2002-2007	48	Subcranial	28 (median)	ASBQ	Worse QoL in patients with malignant histopathology and adjuvant radiotherapy.
(25)	2008-2010	41	Expanded endonasal approach	At least 12	ASBQ	Female gender associated with poorer postsurgical QoL.
(26)	2014-2017	51	Various endoscopic endonasal approaches	At least 3	ASBQ, SBI, SNOT-22	Female gender, recurrent surgery and radiotherapy linked to poorer QoL.
(27)	2010-2013	250	Endoscopic endonasal	6	SNOT-22	Reconstruction with calcium hydroxyapatite and postoperative mucosal edema negatively impacted sinonasal QoL.
(28)	2010-2020	96	Endoscopic endonasal	6	SNOT-22	Short-term sleep impairment after surgery.
(29)	2014-2018	87	Endoscopic endonasal	6	UPSIT	Omega-3 supplementation linked to protective postoperative olfactory function.
(30)	2008-2010	36	Endoscopic endonasal	3	SNOT-20	Sinonasal QoL unaffected by surgery.
(31)	2009-2010	11	Endoscopic endonasal	> 5	SNOT-22, SF-12, HUI-2	QoL unaffected by surgery.
(32)	2012-2016	148	Endoscopic endonasal	>5	SNOT-22	Temporary QoL impairments after surgery.
(33)	2003-2010	78	Subcranial and endoscopic endonasal	Up to 12	ASBQ	Lower QoL in females in endoscopic group and adjuvant radiation therapy worsens QoL.
(34)	Not specified	38	Expanded endoscopic endonasal	60	ASBQ	Surgery-related lumbar drain insertion increases complications and reduces QoL.
(35)	1996-2004	19	Subcranial	44 (mean)	EORTC QLQ-30, EORTC QLQ-H&N35	Reduced QoL after surgery with no significant factors identified.
(36)	1995-2001	14	Not specified	40 (mean)	QoLI	Reduced QoL after surgery with no significant factors identified.
(37)	1994-2002	69	Subcranial	Up to 6	Custom Questionnaire	Old age, malignancy, comorbidity, radiotherapy and extensive surgery identified as negative QoL prognostic factors.
(38)	1992-2003	18	Various open and endoscopic approaches	30 (mean)	UoW QoL questionnaire, HADS	One-third of skull base malignancy patients exhibited significant mental distress and psychiatric morbidity.

(Continued)

TABLE 1 Continued

First Author	Time of Surgery	Patients (n)	Surgical Approach	Follow-Up (months)	QoL Instruments	Factors Influencing QoL
(39)	2021-2021	40	Endoscopic endonasal	Up to 24	ASBQ, SNOT-22	Temporary declines in olfactory, vision and taste function may lead to decreased short-term QoL.
(40)	1997-2010	153	Endoscopic endonasal	Up to 12	ASBQ	Age, expanded surgical approach and postoperative radiotherapy linked to worse QoL.
(41)	2005-2015	26	Anterolateral craniofacial resection with orbital exenteration	Up to 24	SF-8, HADS	80% of patients needed psychiatric intervention.
(11)*	2013-2017	23	Transnasal and transcranial	12	SF-36, EQ-5D various depression and anxiety scores	QoL improvement and psychological relief after surgery.
(42)	2007-2019	57	Endoscopic endonasal	Not specified	ASBQ	QoL improvement at 1 month postoperatively, with continued improvement stabilizing at 6 months after surgery.
(43)	2016-2022	50	Endoscopic endonasal	12	SNOT-22, ASBQ	Loss of olfaction reduces QoL, while visual improvement enhances QoL.

Publications focusing on more than one tumor identity have been marked with an asterisk (*). These publications were discussed for every single tumor identity.

which can help them return to normal psychological health approximately two years post-surgery (41). In contrast, patients with benign lesions often experience significant psychological relief following tumor resection, whether through open or endoscopic approaches (46).

Adjuvant radiotherapy significantly worsened physical functioning, role performance and vitality. Along with recurrent surgery, it was strongly linked to poorer quality of life outcomes, measured using the ASBQ, SBI, and SNOT-22 test (24, 26, 36, 47).

Several studies identified female gender as a predictor of poorer QoL outcomes following surgery, with significant reductions in all domains of the ASBQ. Female patients reported decreases in general performance, physical function, vitality, pain and emotional impact by 18 to 32%, whereas male patients noted improvements of up to 18% in these areas (24–26).

Other factors linked to poorer postoperative QoL include older age, comorbidities and more extensive surgeries (37). The use of a preventive lumbar drain for cerebrospinal fluid (CSF) leaks in transsphenoidal endoscopic tumor resection was associated with increased complications, longer hospital stays and overall decreased QoL (34).

Conversely, certain postoperative regimes, such as omega-3 supplementation after endoscopic transnasal surgery, might improve QoL due to its potential protective effects on olfactory function (29). Postoperative irrigation with mometasone twice a day significantly reduced postoperative SNOT-22 scores compared to budesonide and saline (22).

Tumors of the sellar region

The sellar region is the site of origin for various tumors arising from different tissue types, with adenomas and meningiomas being the most common. In recent years, the endoscopic transnasal approach has become a widely adopted surgical approach when suitable, leading to numerous studies that evaluate QoL using sinonasal QoL instruments such as the ASK-12 and SNOT-22 test Table 2.

While many studies report no significant change in the long-term ASK-12 and SNOT-22 scores before and after tumor resection in the sellar region, the SNOT-22 scores can deteriorate following surgery in the sellar region, typically worsening for a period of 3 to 12 weeks before returning to baseline levels within 3 to 6 months (49). In one study, tumors requiring an extended endoscopic endonasal approach were associated with worsened sinonasal QoL compared to those treated with a standard transsellar approach, measured by the SNOT-22 (50). However, other studies using the same measure reported no decline in sinonasal QoL in patients undergoing the extended approach (51). In contrast, QoL assessments using the SF-36 questionnaire generally show a significant improvement after surgery (48, 51). To address CSF leaks, a common complication of transnasal surgery, nasoseptal flaps are frequently used for reconstruction. However, these flaps seem to have little effect on the long-term quality of life outcomes (52).

Age significantly influences postoperative quality of life outcomes, with younger patients exhibiting a greater deterioration in quality of life following the resection of tumors in the sellar region compared to older individuals (49).

Pituitary adenomas

Table 3 provides a summary of the studies identified that predominantly focus on the quality of life in patients undergoing pituitary adenoma surgery. Studies encompassing multiple tumor

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TABLE 2 Studies investigating QoL in patients after surgery of various different tumors in the sellar region.

First Author	Time of Surgery	Patients (n)	Surgical Approach	Follow-Up (months)	QoL Instruments	Factors Influencing QoL
(48)	2016-2017	34	Endoscopic endonasal	6	SF-36, ASK-12, SNOT-22	Significant postoperative improvement in SF-36 scores.
(49)	2010-2014	46	Endoscopic endonasal	67 (mean)	SNOT-22, LMS	Younger patients experienced a higher rate of QoL deterioration.
(50)	2012-2017	767	Endoscopic endonasal	6	SNOT-20	The extended endonasal endoscopic approach resulted in worse QoL.
(51)	2014-2017	169	Endoscopic endonasal	6	SNOT-22	No difference in sinonasal QoL between baseline and 6 months after surgery.
(52)	Not specified	158	Endoscopic endonasal	12	ASBQ, SNOT-22	Reconstruction with a nasoseptal flap does not affect long-term QoL.

TABLE 3 Studies investigating QoL in patients after surgery of pituitary adenomas.

First Author	Time of Surgery	Patients (n)	Surgical Approach	Follow-Up (months)	QoL Instruments	Factors Influencing QoL
(53)	2018-2020	128	Endoscopic endonasal	14	ASK-12	Temporary decline in sinonasal QoL, recovered one month after surgery.
(43)	2016-20221	366	Endoscopic endonasal	Up to 12	ASBQ	Temporary decline in QoL, recovery 3 weeks after surgery with improvement above baseline afterwards.
(54)	2014-2016	101	Endoscopic endonasal	Up to 12	EES-Q	Time after intervention, male gender and older age positively influenced postoperative QoL.
(55)	Not specified	49	Endoscopic endonasal	At least 2	ENSQ6, SNOT-22	History of radiotherapy linked to impaired sinonasal QoL and sleep disturbances.
(56)	Not specified	20	Endoscopic endonasal	Up to 6	HADS, SNOT-20	Surgery had no influence on QoL.
(57)	2015-2018	62	Endoscopic endonasal	Up to 12	ASK-12, SF-12	Improvement in visual field deficits and time after intervention correlated with improved QoL after surgery.
(58)	2016-2017	60	Endoscopic endonasal	Up to 21	ASK-12	QoL unaffected by choice of endoscopic approach.
(59)	2019-2020	15	Endoscopic endonasal	Not specified	SNOT-22, Semi-structured interviews	Olfactory and breathing difficulties are major physical and psychological factors that reduce QoL.
(60)	2019-2021	58	Microscopic and endoscopic	Up to 3	SNOT-22, ASK-12, SF-36	QoL unaffected by surgical approach.
(61)	2019-2020	40	Endoscopic endonasal	Up to 6	SNOT-22, SF-36, CSS	Reduced sinus headaches with bilateral paraseptal approach.
(62)	2015-2019	109	Endoscopic endonasal	6	SNOT-22, EQ-5D	No previous sinonasal surgery associated with fewer nasal symptoms after surgery.
(63)	2016-2020	304	Endoscopic endonasal	Up to 12	ASBQ, SNOT-22	Frail patients experience the same QoL benefits from surgery as non-frail counterparts
(64)	2015-2018	42	Endoscopic endonasal	Up to 12	SF-36, SNOT-22	Improvements after surgery in physical, mental and nasal functionality as perceived by patients.

(Continued)

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TABLE 3 Continued

First Author	Time of Surgery	Patients (n)	Surgical Approach	Follow-Up (months)	QoL Instruments	Factors Influencing QoL
(65)	2010-2013	81	Endoscopic endonasal	16 (median)	ASBQ, SNOT-22	Total resection correlated with improved postoperative QoL.
(65)	2010-2012	40	Endoscopic endonasal	Up to 12	ASBQ, SNOT-22	Increased intranasal area after surgery had no effect on sinonasal QoL.
(66)	2014-2018	109	Endoscopic endonasal	Up to 4	SNOT-22	Nasoseptal flap usage and prior smoking may adversely impact postoperative QOL.
(47)	Not specified	82	Endoscopic endonasal	6	SNOT-22	Preserving the middle turbinate has no significant negative effects on sinonasal QoL.
(67)	Not specified	159	Endoscopic endonasal	36 (mean)	GBI	Cushing patients and those with preoperative visual impairments reported the greatest postoperative QoL improvements.
(68)	2016-2019	113	Endoscopic endonasal	3	SNOT-22, ASBQ	Postoperative prophylactic antibiotics showed no positive impact on sinonasal QoL.
(63)	2016-2020	304	Endoscopic endonasal	12	SNOT-22, ASBQ	Prolactinomas and non-functioning pituitary adenomas show QoL improvements as early as 3 months after surgery.
(69)	2016-2018	103	Endoscopic endonasal	6	SF-36	Problems with smell and taste significantly affect patient QoL.
(70)	2010-2012	85	Endoscopic endonasal	Up to 12	ASBQ	Recovery of smell, taste and visual impairments positively influenced patient QoL.
(71)	Not specified	38	Endoscopic endonasal	3	SF-36, RSOM-31	Reconstruction with a vascularized flap further decreased postoperative QoL.
(72)	2010-2011	39	Endoscopic endonasal	3	SNOT-22	Temporary decline in sinonasal QoL, recovered three months after surgery.
(73)	2014-2017	49	Endoscopic endonasal	6	SNOT-22, ASBQ	QoL improved 4 to 6 months after surgery, specifically in domains related to pain and vitality.
(74)	2013-2018	243	Endoscopic endonasal	3	SNOT-22	Early resolution of nasal crusting associated with better QoL.
(75)	Not specified	149	Endoscopic, Transnasal microscopic, sublabial	Not specified	SNOT-22, SF-36, CSS	Disease-specific QoL was superior with the endoscopic approach, resulting in reduced long-term sinonasal morbidity.
(46)*	2013-2017	17	Endoscopic endonasal	12	SF-36, EuroQoL, various anxiety and depression scales	Postoperative QoL improvement and psychological relief.
(76)	2012-2013	55	Endoscopic endonasal	3	SNOT-20, ASK-12	Endoscopic modified transseptal transsphenoidal approach showed better sinonasal QoL compared to endoscopic transnasal transsphenoidal approach.
(77)	2011-2013	100	Endoscopic endonasal	6	ASK-12, SF-8	Sinonasal QoL after endoscopic pituitary surgery hits a low at 2 weeks and recovers by 3 months after surgery.

(Continued)

TABLE 3 Continued

First Author	Time of Surgery	Patients (n)	Surgical Approach	Follow-Up (months)	QoL Instruments	Factors Influencing QoL
(78)	2011-2013	218	Endoscopic and microscopic endonasal	6	ASK-12, SF-8, EQ-5D	No difference in postoperative QoL between surgical techniques.
(79)	2012-2014	81	Endoscopic endonasal	3	SNOT-22	Better sinonasal QoL 3 months after surgery in the transseptal transsphenoidal approach group.
(80)	2011-2014	106	Endoscopic endonasal	At least 12	SNOT-22	ACTH-secreting adenomas associated with poorer sinonasal QoL.
(81)*	2009-2012	5/55	Endoscopic endonasal	12	SF-36, RSOM-31, BAST-24	Skull base surgery with an expanded endonasal approach had no negative long-term impact on QoL
(82)	2007-2016	18	Endoscopic endonasal	3 (mean)	SF-36	QoL improved 3 months after surgery compared to preoperative levels.
(83)	2018-2020	46	Endoscopic endonasal	3	ASK-12	Sinonasal QoL transiently declined, while olfaction and gustation showed long-lasting declines.
(84)*	2008-2011	47/85	Endoscopic endonasal	6	SNOT-22, ASBQ	Gross total resection increased postoperative QoL.
(85)	2014-2017	12/31	Endoscopic endonasal	12	SNOT-22	The use of a nasoseptal flap does not affect sinonasal QoL.
(86)*	2010-2011	38/66	Endoscopic endonasal	6	SNOT-22, ASBQ	Better short-term QoL in patients with gross total resection.
(87)	2014-2021	61/95	Endoscopic endonasal	34 (mean)	SNOT-22, ASBQ	Only one third of patients report negative sinonasal QoL.
(88)	2016-2020	451	Endoscopic endonasal	12	ASBQ	Deficient preoperative endocrine function associated with improved postsurgical QoL.
(89)	2017-2019	31/36	Endoscopic endonasal	6	SNOT-22, UPSIT	Sinonasal QoL unaffected by surgery.
(90)	2011-2012	22	Endoscopic endonasal	Up to 3	SNOT-22	Sinonasal QoL unaffected by surgery.
(91)	2000-2010	110	Endoscopic endonasal	Up to 12	RSOM-31	Hormone-secreting adenomas have the most adverse effect on QoL.

Publications focusing on more than one tumor identity have been marked with an asterisk (*). These publications were discussed for every single tumor identity.

types, including those involving patients with pituitary adenomas, are specifically annotated in the table.

Preoperative QoL, as measured by the ASBQ, was notably lower in female patients, those with diabetes, visual deficits, endocrinopathy, functioning adenomas, or headaches compared to patients with incidental adenomas (54, 88, 92). Additionally, QoL measured by the SF-36 questionnaire indicated decreased QoL in six of its eight domains preoperatively in patients with pituitary adenomas (82).

After surgery, QoL typically declined transiently in the first 2-4 weeks, particularly in sinonasal health and physical functioning, before improving to above baseline levels by 6-12 weeks and continuing to improve throughout the first postoperative year (43, 53, 74, 77, 82, 84, 92). Long-term improvements in QoL were observed following endoscopic surgery (65), exceeding preoperative levels (65), even among frail patients who experienced comparable visual and endocrine outcomes to their non-frail counterparts (63).

Postoperative nasal symptoms such as nasal discharge, pain and nasal whistling as well as issues with smell and taste significantly affected physical QoL (69, 87). These symptoms, peaking in the initial days after surgery (54), led to QoL impairments in domains such as sleep, mood, appetite, sexual desire, nutrition, health, hobbies and social interactions (59). However, these impairments typically resolved or significantly improved within three months after surgery, particularly in the domains of physical well-being, vitality and pain (11, 54, 57, 67, 73, 87). Several studies reported that olfactory and taste-specific QoL impairments, initially present after surgery, were no longer measurable 1 to 12 months later (53, 60, 70, 83, 89). Improvements in vision or visual field deficits were particularly associated with favorable QoL outcomes, which were measurable as early as three months after surgery (57, 67, 70).

In contrast to physical and social QoL, psychological QoL tended to improve directly postoperatively and three months after

surgery, psychological QoL returned to baseline (54), with some studies reporting normalization of mental functions only after one year (57). Significant improvements in overall postoperative QoL were driven by improved emotional states of the patients (11, 73).

Previous sinonasal surgery, smoking, and the use of a nasoseptal flap were linked to worse rhinologic symptoms and QoL (62, 66, 71). Although the nasoseptal flap could cause worse sinonasal morbidity and headache in the immediate postoperative period, it did not have a long-term negative impact on QoL, with patients typically returning to baseline by 3-6 months after surgery (66, 80, 84, 91). In contrast, other studies found no impairment in sinonasal QoL and olfactory function after surgery (93, 94), even when using a nasoseptal flap (85).

Several studies demonstrated that gross total resection (GTR) resulted in better postoperative QoL compared to subtotal resection, as measured by ASBQ and SNOT-22 (65, 84, 86). However, other studies showed no significant difference in QoL based on the extent of resection (73, 74). Female sex and older age were associated with worse postoperative QoL (43, 77), although age was not a consistent factor across all studies (92).

Functioning pituitary adenomas were associated with worse QoL, as measured by RSOM-31 and EES-Q QoL instruments (54, 91), although this was not universally observed across all studies (71, 73) and some authors report a preoperative endocrinopathy as a factor associated with better postoperative QoL measured by the ASBQ-35 (92). Patients with Cushing's disease reported significant QoL benefits from surgery, particularly in physical health domains. Prolactinoma and non-functioning pituitary adenoma patients also experienced significant QoL improvements three months after surgery (43). In contrast, ACTH-secreting adenomas were associated with worse sinonasal QoL after surgery. Tumor size did not significantly affect postoperative QoL (92).

Comparative studies of surgical approaches found that endoscopic techniques yielded better QoL outcomes measured by SF-36 and SNOT-22 compared to microscopic approaches (75). Conversely, other studies showed opposite results using the ASK, SF-8, and EQ-5D questionnaires (76, 78). Various endoscopic approaches have been explored in the literature, revealing only minor differences in QoL due to headache or olfactory function that were negligible in long-term follow-ups (47, 58, 60, 61, 79, 81, 90). Cerebrospinal fluid leaks during surgery did not significantly reduce QoL after surgery (73), although some studies noted slight negative associations (88).

Craniopharyngioma

Table 4 summarizes studies related to craniopharyngiomas, which frequently present surgical challenges due to their location and expansive growth. Studies involving multiple tumor types, including craniopharyngiomas, have been specifically annotated in the table.

A longitudinal study spanning over 20 years demonstrated that the overall QoL for patients, after resection of a craniopharyngioma, was relatively high, as measured by the SF-36 and KPS indices (95). Gross total resection is associated with a higher QoL (84, 96), while tumor recurrence or the need for additional resections tends to worsen QoL. Patients who experience visual improvement after surgery tend to report higher QoL scores, whereas persistent visual deficits lasting over a year, as well as hypopituitarism, have been shown to significantly worsen QoL (96).

Gender differences also appear to influence QoL outcomes, with female patients exhibiting lower QoL (96).

The studies we investigated found no significant differences in QoL outcomes among the various surgical techniques used for the resection of craniopharyngiomas. The primary methods fall into two main categories: endoscopic endonasal approaches and transcranial approaches (81, 96, 97). Typically, the endoscopic endonasal

TABLE 4 Studies investigating QoL in patients after craniopharyngioma surgery.

First Author	Time of Surgery	Patients (n)	Surgical Approach	Follow-Up (months)	QoL Instruments	Factors Influencing QoL
(95)	1996-2002	19	Various microsurgical approaches	Up to 280	SF-36, KPS	Overall high long-term QoL after surgery, with no associated factors.
(96)	2004-2013	31	Endoscopic endonasal	Up to 101	SNOT-22, ASBQ	Overall, postoperative QoL maintained at preoperative levels. Better QoL observed in patients with GTR and radiation therapy, while worse QoL was noted in patients with visual or endocrine deficits.
(97)	2001-2018	30	Transcranial and endoscopic endonasal	136 (mean)	SNOT-22, ASBQ	No difference in postoperative QoL between endonasal and transcranial approaches.
(81)*	2009-2012	3/55	Expanded endoscopic endonasal	12	SF-36, RSOM-31, BAST-24	Skull base surgery with an expanded endonasal approach had no negative long-term impact on QoL.
(86)*	2008-2011	4/85	Endoscopic endonasal	6	SNOT-22, ASBQ	Elapsed time after intervention and gross total resection increased QoL.
(84)*	2010-2011	2/66	Endoscopic endonasal	6	SNOT-22, ASBQ	Better short-term QoL in patients with gross total resection.

Publications focusing on more than one tumor identity have been marked with an asterisk (*). These publications were discussed for every single tumor identity.

approach may lead to short-term, self-limited impairments in sinonasal related QoL. Moreover, techniques such as the use of a nasoseptal flap or gasket seal reconstruction in an endoscopic approach do not result in a long-term decrease in sinonasal QoL (86).

Meningiomas

Meningiomas are among the most common types of skull base tumors and can develop in any part of the skull base, affecting various neurovascular structures and causing a wide range of symptoms. The choice of surgical approach for removing these tumors depends on their size and location, factors that can significantly influence patient QoL Table 5.

When the specific location of the meningioma at the skull base is not considered, resection commonly results in a temporary decline in QoL postoperatively. Typically, QoL returns to baseline levels about 12 months after surgery (99). Most studies report no significant long-term impairments in QoL following meningioma surgery (13, 99, 100). However, one study noted a decrease in QoL among patients over the age of 55 (98).

Surgical complications, including CSF leaks, wound infections and accidental cranial nerve injuries, can impact patients QoL following surgery (100). Conversely, other data indicates that surgical complications do not affect QoL (13). Severe complications such as postoperative hemorrhage and associated prolonged ICU stays can lead to functional deterioration after meningioma resection (101). Additionally, while one study observed improvements in neuropsychological functions after surgery (99), another reported no changes (13). However, neither study found these neuropsychological outcomes to influence the overall perceived QoL.

The anatomical location of meningiomas within the skull base plays a significant factor in postoperative QoL. Meningiomas situated in the posterior fossa are associated with poorer QoL outcomes compared to those located in the anterior or middle cranial fossa (13). This disparity may be attributed to the fact that the posterior fossa contains surgically highly demanding meningiomas, such as petroclival meningiomas, which present more complex challenges during resection.

Petroclival meningiomas

Petroclival meningiomas, despite their typically benign pathology, present significant surgical challenges due to their proximity to critical anatomical structures. The complex anatomy and difficult access of this region have driven the development of surgical techniques aimed at minimizing morbidity while achieving complete resection and maintaining the QoL for patients. However, the impact of surgery on QoL is often underestimated by caregivers and has a more profound effect on patients than expected by surgeons (102). The results of our findings are summarized in Table 6.

Postoperatively, patients typically experience a decline in QoL, which generally improves to preoperative levels within a year after surgery. Long-term follow-ups have shown that QoL even surpass preoperative levels, as measured by the KPS. However, it is important to note that severely disabled patients with a preoperative KPS score below 70 tend to have poorer outcomes one year after surgery (104).

Achieving a surgical cure often necessitates a gross total resection. However, studies have indicated that gross total resection of petroclival meningiomas can result in worse postoperative QoL compared to subtotal resection (105, 107). While aiming for gross total resection, careful attention must be paid to protecting anatomical structures, as lower cranial nerve palsies can prevent patients from returning to a normal life and significantly diminishing postoperative QoL (103). This is particularly crucial given the high risk of new postsurgical neurological deficits associated with petroclival meningioma surgery (108, 109).

TABLE 5 Studies investigating QoL in patients after skull base meningioma surgery.

First Author	Time of Surgery	Patients (n)	Surgical Approach	Follow-Up (months)	QoL Instruments	Factors Influencing QoL
(98)	2004-2015	56	Transcranial and endoscopic endonasal	Up to 106	SNOT-22, ASSBQ	QoL decreased postoperatively in patients aged over 55.
(99)	2009-2011	58	Not specified	58	EORTC QLQ-C30, HADS	The majority of patients showed stable or improved QoL after surgery, with only a minority deteriorating.
(100)	2012-2016	52	Predominantly frontotemporal approach	9 (mean)	EQ-5D	Better QoL linked to female sex, no proptosis, non-frontotemporal approaches, no optic nerve compression and no surgical complications.
(101)	2016-2020	165	Transcranial	Up to 60	KPS	Longer ICU stays and hemorrhagic complications result in worse functional outcomes.
(13)	2016-2019	89	Not specified	Up to 108	SF-36, EORTC QLQ-BN20	Surgical resection of posterior fossa meningiomas resulted in lower QoL.

TABLE 6 Studies investigating QoL in patients after petroclival meningioma surgery.

First Author	Time of Surgery	Patients (n)	Surgical Approach	Follow-Up (months)	QoL Instruments	Factors Influencing QoL
(102)	1992-1997	17	Transpetrosal	At least 12	SF-36	Postsurgical decrease in QoL. Majority with new or worsened neurological deficits.
(103)	1992-1999	19	Transpetrosal	Up to 12	SF-36, GOS	Postsurgical decrease in QoL. Majority with new or worsened neurological deficits.
(104)	1991-2004	150	Mixed; majority transpetrosal	102 (mean)	KPS	KPS decreased post-surgery, recovered after one year, and improved at long-term follow-up.
(105)	2008-2018	32	Mixed; majority retrosigmoid	35 (mean)	KPS, SF-36, GOS	GTR associated with worse postoperative QoL
(106)	1988-2012	64	Mixed; majority posterior petrosal	72 (mean)	KPS	Significant brainstem compression associated with better postoperative KPS.
(107)	1991-2010	71	Mixed; majority retrosigmoid	61 (mean)	KPS	QoL significantly correlated with extent of resection, preoperative brainstem edema, tumor-neurovascular relationships, and invasion depth into cavernous sinus.
(108)	2000-2020	25/60	Not specified	66 (mean)	Survey Battery	High overall postoperative QoL.

Additionally, patients with preoperative brainstem compression due to the tumor have been shown to experience significantly better QoL after surgery (102, 107). The impact of other anatomical factors, such as cavernous sinus infiltration, remains controversial, with some studies indicating no effect on QoL (102) and others suggesting an influence (107).

Sphenoid wing meningiomas

Sphenoid wing meningiomas can present a significant challenge for neurosurgeons aiming for complete and safe removal, particularly medial sphenoid wing meningiomas, which are associated with the poorest neurological functional outcomes, second only to petroclival meningiomas. These tumors negatively impact postoperative quality of life and have the highest recurrence rates among meningiomas (110–112). Two studies have investigated the quality of life in patients with sphenoid wing meningiomas, both specifically focusing on medial sphenoid wing meningiomas (Table 7).

Visual impairment has been identified as a significant factor contributing to both preoperative and postoperative reduced QoL in patients with medial sphenoid wing meningiomas that infiltrate the cavernous sinus (114).

Tumor recurrence and progression pose the major long-term risks following resection and the initial surgery is of crucial importance. It was observed that larger medial sphenoid wing meningiomas are associated with poorer immediate clinical outcomes, including less visual improvement and lower KPS scores and present greater challenges for complete removal. However, in the long-term, tumor size did not correlate with overall outcomes measured by KPS (113).

Spheno-orbital meningiomas

Spheno-orbital meningiomas are rare and our search identified only one study (Table 8) examining the QoL following their resection. This study reported a significant improvement in QoL, as measured by

TABLE 7 Studies investigating QoL in patients after sphenoid wing meningioma surgery.

First Author	Time of Surgery	Patients (n)	Surgical Approach	Follow-Up (months)	QoL Instruments	Factors Influencing QoL
(113)	1985-1999	127	Orbito-zygomatic frontotemporal, pterional and subfrontal approach	82 (mean)	KPS	Large tumors linked to poorer short-term outcomes, including visual improvement and KPS score. Long-term outcomes not correlated with tumor size.
(114)	2008-2021	36	Not specified	75 (mean)	KPS	Visual impairment found as the most significant factor reducing QoL

TABLE 8 Studies investigating QoL in patients after spheno-orbital meningioma surgery and cavernous sinus meningioma.

First Author	Time of Surgery	Patients (n)	Surgical Approach	Follow-Up (months)	QoL Instruments	Factors Influencing QoL
(115)	2016	40	Not specified	3	EORTC QLQ-C30	Postoperative significant improvement in QoL across all subcategories after spheno-orbital meningioma resection.
(116)	1996-2014	65	Mixed; Majority frontotemporal orbitozygomatic	Up to 199	KPS	Patients undergoing adjuvant stereotactic radiosurgery after cavernous sinus meningioma resection showed a tendency for improved KPS.

the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ). However, the analysis was limited to comparing preoperative QoL with assessments made three months after surgery and they identified no factors that significantly influenced the QoL outcomes (115).

Cavernous sinus meningiomas

Cavernous sinus meningiomas are the most prevalent primary tumors of the cavernous sinus, yet they comprise only about 1% of all intracranial meningiomas (117). A single study investigating the QoL of patients with cavernous sinus meningiomas was found (Table 8). This study indicated a tendency for improved KPS scores in patients who underwent adjuvant stereotactic radiosurgery compared to those who had only microsurgical resection, potentially due to better tumor control; however, the changes were not statistically significant (116).

Olfactory groove meningiomas

Olfactory groove meningiomas, which develop above the cribriform plate, can grow to substantial sizes before detection (118). The resection of these tumors can be achieved through various surgical approaches, depending on the surgeon's preference and the tumor size. We identified three studies examining the QoL in patients with olfactory groove meningioma (Table 9).

In selected cases, the endoscopic transnasal approach has demonstrated a good rate of smell preservation (119), while the supraorbital keyhole approach is associated with reduced postoperative edema and shorter hospital stays compared to traditional open approaches (120). However, the choice of surgical approach did not affect the overall QoL for these patients (120). One study using the Reintegration to Normal Living Index (RNLI) found that patients undergoing resection via the superior interhemispheric approach experienced a moderately reduced QoL, without identifying any specific factors influencing this outcome (121).

Tuberculum sellae and *planum sphenoidale meningiomas*

Tuberculum sellae and planum sphenoidale meningiomas originate in close proximity. Given that most studies we have reviewed involve cohorts with both types of meningiomas, we have combined them into a single section (Table 10). These studies primarily focus on evaluating the effectiveness of various surgical techniques and also assess quality of life outcomes.

QoL, as indirectly measured by the KPS, generally shows improvement after surgery, indicating an enhancement in patients' functional status (121, 122). Comparing different surgical approaches such as the supraorbital keyhole approach, the endoscopic endonasal approach and the unilateral subfrontal approach revealed no significant differences in QoL outcomes. Furthermore, the choice of surgical approach does not significantly impact the rates of gross total resection or postoperative vision outcomes, suggesting no indirect influence on QoL through these factors (122, 123).

TABLE 9 Studies investigating QoL in patients after olfactory groove meningioma surgery.

First Author	Time of Surgery	Patients (n)	Surgical Approach	Follow-Up (months)	QoL Instruments	Factors Influencing QoL
(119)	2009-2019	4	Endoscopic Transnasal	22 (mean)	SS-12	Endoscopic endonasal approach effectively preserved smell.
(120)	2005-2023	57	Supraorbital keyhole approach and traditional transcranial approaches	39 (mean)	ASBQ	No QoL difference among surgical approaches. Keyhole approach resulted in shorter hospital stays.
(121*)	1998-2008	34/52	Superior interhemispheric approach	57 (mean)	KPS, RNLI	No significant factors found.

Publications focusing on more than one tumor identity have been marked with an asterisk (*). These publications were discussed for every single tumor identity.

TABLE 10 Studies investigating QoL in patients after tuberculum sellae & planum sphenoidale meningioma surgery.

First Author	Time of Surgery	Patients (n)	Surgical Approach	Follow-Up (months)	QoL Instruments	Factors Influencing QoL
(122)	2012-2021	38	Unilateral subfrontal and endoscopic endonasal	66 (mean)	KPS	KPS increased by around 15 points after surgery. No significant factors identified.
(123)	2017-2020	20	Supraorbital keyhole approach and endoscopic endonasal	12	SF-36	No QoL difference between the two groups.
(121*)	1998-2008	18/52	Superior interhemispheric approach	57 (mean)	KPS, RNLI	No significant factors found.

Publications focusing on more than one tumor identity have been marked with an asterisk (*). These publications were discussed for every single tumor identity.

Vestibular schwannomas

Given the close proximity of vestibular schwannomas to critical structures such as the facial and vestibulocochlear nerves, surgical resection of these tumors can result in significant neurological deficits such as facial palsy, hearing loss or vertigo (124, 125). The results of our findings are summarized in Table 11.

Additionally, psychological factors such as depression, anxiety and sleep disorders further compound the challenges, negatively impacting the postoperative QoL in these patients (131).

Contrasting perspectives emerge regarding the overall post-surgical QoL in these patients. Some research suggests that quality of life remains stable postoperatively (126, 133). However, other studies (128, 131, 132, 136) indicate a post-surgical decline in QoL, which appears to normalize within six months post-surgery (132).

Smaller vestibular schwannomas with less than 1.5 cm in diameter have been associated with a more favorable postoperative quality of life (127). This finding is in contrast to other studies (128, 129) who report no significant impact of tumor size on postoperative QoL.

A particularly challenging complication is postoperative facial palsy, which significantly lowers QoL in social domains, notably among younger women under 40 years (125). Hearing preservation has been found critical for postoperative QoL with better preoperative hearing levels correlating with improved postoperative outcomes and QoL (124, 134).

Another aspect is the choice of surgical approach. Postoperative headaches have been linked to the retrosigmoid approach, showing a noticeable decrease in QoL, particularly among younger women, compared to the translabyrinthine or middle cranial fossa approaches (130). Otherwise, it was found that the surgical approach or even the treatment modality (Microsurgery, radiotherapy or combined therapy) generally does not affect postoperative QoL (129).

The economic impact on younger patients is also significant, with some studies noting a decrease in QoL due to financial stress, a factor less impactful on older patients who may possess greater financial reserves or be at a different career stage (128). However, such findings were not consistently reported across all studies (129).

Clival chordomas

Clival chordomas, although histologically classified as low-grade tumors, demonstrate clinically malignant behaviors due to their diffusely infiltrative growth patterns and high rates of recurrence and tumor-related mortality (137, 138). Given the aggressive nature of the disease and the necessity for comprehensive removal, the challenge of achieving a surgical outcome that effectively manages the disease while also preserving the patient's quality of life is crucial. The results of our findings are summarized in Table 12. The endoscopic endonasal approach has become a popular approach for resecting clival chordomas as it offers reduced morbidity compared to more extensive transcranial and transfacial approaches (141, 142).

Studies indicate that even extended endoscopic endonasal approaches do not negatively influence long-term QoL and only lead to temporary short-term impairments in general and sinonasal QoL (84, 86, 139). Comparisons with other treatment modalities, such as gamma knife surgery, also show no difference in QoL (139).

Gross total resection significantly improves the recovery of postoperative sinonasal QoL (84, 86). The use of a vascularized flap in endoscopic endonasal surgery is associated with more pronounced sinonasal symptoms compared to approaches that do not utilize the flap. Specifically, studies have indicated that such approaches can negatively affect physical and mental QoL at least up to three months post-surgery (71), highlighting the need for careful consideration of surgical techniques to minimize these effects. Additionally, the use of corticosteroids and pain medication correlates with reduced QoL after surgery (93).

Most studies utilize sinonasal QoL instruments. However, it should be noted that the resection of clival chordomas can lead to a variety of complications, such as neurological deficits or CSF leaks, which can increase the burden of the disease for the patient. Neurological deficits such as sensory deficits and bowel and

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TABLE 11 Studies investigating QoL in patients after vestibular schwannoma surgery.

First Author	Time of Surgery	Patients (n)	Surgical Approach	Follow-Up (months)	QoL Instruments	Factors Influencing QoL
(126)	2016-2017	7	Endoscopic transcranial transpromontorial	12,9 (median)	SF-36	No significant factor.
(127)	1981-1992	257	Not specified	51,6 (median)	Modified EORTC questionnaire	Improved postoperative QoL is associated with tumors smaller than 1.5 cm in size.
(128)	Not specified	53	Not specified	363	Modified GBI	Older patients experienced improved QoL.
(129)	Not specified	90	Translabyrinthine or retrosigmoid approach	> 18	SF-36	No significant factors; decreased postoperative QoL in 7/8 SF-36 items.
(130)	Not specified	1657	Translabyrinthine or retrosigmoid approach	96 (mean)	Custom Questionnaire	Young age, female sex, and retrosigmoid approach linked to increased postoperative headache.
(131)	1997-2001	42	Middle Cranial Fossa Approach	37 (median)	SF-36	No significant factors; decreased postoperative QoL in 8/8 SF-36 items.
(132)	2001-2003	33	Not specified	< 6	SF-36	No significant factors; postsurgical SF-36 scores normalized within 3 months.
(133)	1999-2007	121	Translabyrinthine or retrosigmoid approach	> 6	SF-36	No significant factors; postsurgical QoL nearly equivalent to healthy population.
(134)	2017-2020	63	Middle Cranial Fossa Approach	7 (mean)	WRS, PANQOL	Hearing preservation associated with higher QoL.
(124)	2005-2011	117	Middle Cranial Fossa Approach	> 6	SF-36	Postsurgical vertigo and impaired hearing status negatively impact QoL.
(125)	Not specified	398	Not specified	12 (median)	FaCE Scale	Facial palsy reduced QoL, particularly affecting social life in younger patients.
(135)	Not specified	397	Not specified	> 120	PANQOL	No difference in short-term (<6 years) or long-term (>10 years) QoL outcomes between radiotherapy, microsurgery, or combined therapies.
(136)	1996-1999	54/70	Not specified	38,4 (median)	SF-36	Surgical excision significantly reduced social functioning and role limitations due to physical functioning.

bladder dysfunction can significantly impact the QoL in these patients and diplopia has been linked to anxiety and depression and was often already present prior to surgery (93). While gross total resection should be attempted, avoiding neurological deficits is paramount to preserving the patient's QoL.

Discussion

This systematic review represents the first comprehensive evaluation of factors that influence QoL following the resection of skull base tumors across various anatomical locations. Whereas previous reviews have primarily focused on specific areas, such as the anterior skull base (143), or on particular approaches like the endoscopic endonasal approach (144), our extensive review covers a broad range of skull base locations and surgical techniques. This approach provides a more holistic perspective on postoperative QoL in patients with skull base tumors.

However, this literature review also demonstrates that most publications dealing with quality of life focus on the anterior skull base and the endoscopic endonasal approach. Hence, the most common used tools in this review were the SNOT -22 and the ASBQ, mainly evaluating the sinonasal outcome and quality of life. This leads to a potential bias, as other aspects of quality of life or other surgical approaches are less frequently discussed.

Our examination of the literature has revealed several key factors that may impact QoL following surgery.

Sociodemographic factors

We identified age and gender as two key sociodemographic factors that influence QoL after surgery.

Research has consistently shown that female gender is associated with poorer QoL outcomes in various skull base tumors (24–26, 37, 43, 96, 98, 100). The mechanism for this disparity is not clear and may

TABLE 12 Studies investigating QoL in patients after chordoma surgery.

First Author	Time of Surgery	Patients (n)	Surgical Approach	Follow-Up (months)	QoL Instruments	Factors Influencing QoL
(139)	2002-2010	40	Microsurgery vs. Gamma knife	Up to 60	KPS	No difference in KPS scores between groups at follow-up.
(86)*	2010-2011	6/66	Endoscopic endonasal	Up to 6	ASBQ, SNOT-22	Improved short-term QoL with gross total resection.
(84)*	2008-2011	8/85	Endoscopic endonasal	Up to 6	ASBQ, SNOT-22	Improved short-term QoL with gross total resection.
(71)	Not specified	38	Endoscopic endonasal	Up to 3	SF-36, RSOM-31	Vascularized flap reconstruction further decreased postoperative QoL.
(93)	Not specified	88	Not specified	Not specified	SF-36, KPS, PH-Q9	Neurological deficits, pain medication use, corticosteroid treatment, and depression levels impact QoL.
(81)*	2009-2012	3/55	Endoscopic endonasal transclival	Up to 12	ASBQ	No negative long-term QoL impact from skull base surgery via expanded endonasal approach.
(140)	1999-2018	167	Mainly endoscopic endonasal transclival	Up to 264	Katz-Index	No factors influencing postsurgical QoL.

Publications focusing on more than one tumor identity have been marked with an asterisk (*). These publications were discussed for every single tumor identity.

stem from a combination of biological, psychological and social factors. Biologically, hormonal differences could influence symptom severity and recovery trajectories (145). Psychologically, women may experience higher levels of distress or depression related to diagnosis and treatment, which can adversely affect QoL (146, 147). Socially, women often face greater challenges in balancing treatment with familial and caregiving responsibilities (148). This complex interplay highlights the need for gender-specific considerations in the management and support structures for tumor patients to optimize their QoL after surgery.

Age also appears to be a significant determinant of QoL. Numerous studies have demonstrated that older patients often experience a reduced QoL following the resection of skull base tumors (45, 98, 100). Conversely, research indicates that younger patients may suffer a more rapid deterioration in QoL compared to older individuals. This may be attributed to the greater economic impact experienced by younger patients, who often face substantial challenges in balancing recovery with employment and financial responsibilities (49, 128).

Tumor localization

Patients undergoing surgery for meningiomas in the anterior or middle cranial fossa generally report a higher postoperative QoL compared to those with tumors located in the posterior fossa (13). The proximity of posterior fossa tumors to critical brainstem and neurovascular structures means that more aggressive resections in this area tend to lead to neurological deficits, which are strongly correlated with reduced quality of life QoL for patients (103). However, in cases of petroclival meningiomas where the brainstem was compressed preoperatively, patients generally experience a significantly improved QoL after surgery (107).

Regardless of the tumor entity, QoL in patients with anterior skull base tumors typically declines immediately following resection. However, it generally returns to baseline levels within 6 to 12 months postoperatively (24, 28, 37). Endonasal approaches may initially disrupt nasal and sinus function, resulting in temporary discomfort and a reduced QoL, particularly in the sinonasal domain.

Tumor entity

Individuals with malignant pathologies, particularly in the anterior skull base, exhibited significantly lower QoL scores six months after surgery compared to patients with benign lesions. However, these patients demonstrated considerable improvements in QoL twelve months after surgery. In contrast, patients with benign tumors tended to experience a more stable QoL throughout their postoperative recovery period (24, 31).

The majority of studies examining meningioma resections at various skull base locations have shown a significant improvement in QoL after surgery (98, 100, 121, 122). Conversely, a smaller number of studies report no change in QoL following the surgical intervention (13, 99). Upon closer examination of meningioma location, petroclival meningiomas and medial sphenoid wing meningiomas are notably associated with a negative impact on QoL. This correlation might be attributed to poor neurological functional outcomes and the highest recurrence rates among meningiomas (110–112).

Patients undergoing resection of pituitary adenomas typically experience an improvement in QoL after surgery, following a transient decline primarily due to sinonasal symptoms related to the endonasal approach (43, 74, 82). These patients usually exhibit a good preoperative QoL, and the psychological relief experienced after surgery plays a crucial role in their overall QoL improvement (46). In contrast to tumor size (92), endocrinopathy negatively impacts the QoL for patients with pituitary adenomas (54, 91) and relief from these endocrine disorders has been linked to improved

QoL outcomes (43). Patients with prolactinomas may experience improvements in QoL as early as three months after surgery (43), whereas those with acromegaly or Cushing disease generally require significantly more time to recover their QoL (43, 149). This difference may be attributed to the residual effects on appearance, mood and metabolism that persist even after hormonal levels have normalized (150–152) However, it is important to note that examining QoL specifically related to endocrinopathy falls beyond the scope of this review and has been extensively discussed in previous reviews (153, 154).

Surgical approach

For most skull base tumors, a variety of surgical approaches are utilized for tumor resection. The choice of approach generally depends on the surgeon's experience and preference.

However, particularly for tumors located in the pituitary region and the anterior skull base, endoscopic approaches have been widely adopted due to their minimally invasive nature and the panoramic view they provide the surgeon. While endoscopic endonasal approaches are associated with a higher incidence of CSF leaks (24, 26, 73, 75, 121, 123), our findings indicate no significant impact on the QoL for patients from these leaks. However, the prophylactic insertion of a lumbar drain has been associated with poorer QoL after surgery, persisting as long as 12 months after the procedure. Patients who received lumbar drains experienced higher morbidity, longer hospital stays and a reduction in QoL potentially stemming from associated side effects such as discomfort, headaches or infections (34). In contrast, the use of nasoseptal flaps for reconstruction and prevention of CSF leaks is correlated with worsened rhinologic symptoms and headaches in the immediate postoperative period. However, these effects do not appear to impact long-term QoL (62, 66, 71, 80, 86, 91).

Few studies have compared different surgical approaches and their impact on QoL. Such comparisons were primarily limited to variations of the endonasal approach, which revealed only minor differences in long-term sinonasal QoL, particularly with expanded endoscopic approaches used for more complex tumors (50, 51, 61, 78, 79). However, most studies we have included lack comparisons of different open transcranial approaches or the comparison between open and endonasal approaches in terms of perceived QoL outcomes for patients.

Gross total resection and neurological deficits

Gross total resection (GTR) is the objective in most tumor surgeries, whenever feasible. This is particularly crucial in malignant tumors, where achieving complete resection is associated with longer survival and reduced recurrence rates. However, achieving GTR in skull base tumors often presents numerous challenges due to the proximity to critical neurovascular structures.

The studies included in this review indicate that the quality of life following GTR of skull base lesions generally improves or remains unchanged, irrespective of the surgical approach employed. The positive effect is particularly evident in cases of craniopharyngioma, where GTR is often linked to a significantly enhanced QoL. The correlation is likely due to the reduced likelihood of tumor recurrence, the decreased need for subsequent surgical interventions and the reduced necessity for adjuvant radiotherapy (96). Although pursuing GTR in cases of craniopharyngiomas may result in endocrinopathy, the overall benefits of GTR seem to outweigh the decrease in QoL caused by new endocrine disorders (96, 155).

In contrast, patients with petroclival meningiomas often experience a deterioration in QoL after gross total resection (105, 107). This decline may be attributed to the vastly different spectrum of complications associated with resecting petroclival meningiomas compared to craniopharyngiomas. The proximity of petroclival meningiomas to the lower cranial nerves and the brainstem significantly increases the likelihood of neurological deficits, which are associated with poor postoperative QoL (107). Therefore, it is necessary for the surgeon to balance the pursuit of gross total resection with the patient's QoL after surgery and tailor the surgical plan for each individual patient (109).

In meningioma patients, a more aggressive resection tend to lead to a greater incidence of cranial nerve deficits, which can significantly hinder a patient's ability to return to normal life and substantially diminish their QoL (44, 103). However, not all cranial nerve deficits uniformly impact QoL in the same way.

The severity and type of deficit play critical roles in determining the extent of impact. For example, cranial nerve deficits affecting motor function and thus enabling actions such as swallowing, may be more debilitating and disruptive compared to sensory deficits. Particularly, changes in vision significantly influence QoL both before and after surgery, with postoperative improvements in vision strongly correlating with enhanced QoL for the patient (23, 39, 57, 100, 156). While some publications consider the loss of olfaction or taste to be less impactful (45), the patient's occupation and leisure activities can significantly influence how anosmia affects their quality of life (157).

Furthermore, the individual's ability to adapt to these changes also varies, with some patients managing to find effective coping strategies that mitigate the impact on their daily lives. This complexity underscores the need for a personalized approach in postoperative care, aimed at addressing specific deficits and supporting overall well-being.

Vestibular schwannomas present significant challenges that can impact postoperative quality of life, with outcomes varying widely across different studies and neurosurgical centers. Due to the proximity to the facial and vestibulocochlear cranial nerves, complications typically result in neurological deficits related to their functions. Notably, younger women may experience drastic impairments in QoL due to postoperative facial palsy (125), whereas hearing loss affects QoL independently of gender (124, 134). Although the size of the tumor significantly influences the complexity of the surgery, its impact on QoL is less clear. Only one study has found a correlation between larger tumor size (> 1,5cm) and worse postoperative QoL (127), whereas two other studies reported no impact on QoL (128, 129).

Implications for clinical practice

The presented literature offers several key insights for clinicians. The evidence consistently shows a transient decline in QoL after surgery across almost all studies, regardless of the tumor's anatomical location or entity. Interestingly, this decline tends to recover to baseline levels postoperatively and in some cases, particularly with tumors treated at the anterior skull base, patient's quality of life surpasses preoperative levels. This could be attributed to the predominance of less invasive endoscopic surgeries in this region, which are associated with faster recoveries and less impactful long-term sinonasal outcomes compared to traditional open surgeries (158). However, we found no clear evidence demonstrating that endonasal approaches are superior to open approaches with regard to quality of life.

It is important to highlight that changes in QoL are significantly influenced by the patient's preoperative clinical status. Patients who were asymptomatic prior to surgery often experience a deterioration in QoL postoperatively (37). This observation brings to light the complexity of measuring QoL of patients who undergo surgery not because of current symptoms but to prevent future complications, a common scenario in skull base tumors. This preventative aspect of surgical intervention is often not captured in QoL assessments, emphasizing the need for developing more nuanced survey instruments that can capture the preventative necessity of skull base surgery.

However, our review of the current literature highlights the significant impact of non-modifiable factors such as age and sex on QoL outcomes, alongside modifiable factors like psychological support. Early psychological interventions, especially for patients undergoing treatment for complex tumors, appear to enhance QoL, suggesting the importance of integrated care models that address both physical and mental health after surgery (41).

Moreover, the severity of the tumor (malignant versus benign), the necessity of radiotherapy and recurrent surgeries are predictors of poorer QoL outcomes (31, 37, 96). This underscores the need for a tailored follow-up strategy that allocates more resources to high-risk patients to mitigate these effects.

Gross total resection, while often the primary goal in skull base surgery, should not always be considered, if followed by cranial nerve or other neurological deficits, diminishing the quality of life of patients. Surgical planning should include the patient's individual perception which neurological deficits they could endure. This often depends on the patient's occupation or leisure activities, making this decision highly individual.

The demographic characteristics of the skull base tumor population present additional challenges. Many patients are elderly with multiple comorbidities and depending on the tumor and treatment type, may have a shortened life expectancy. These factors complicate data collection and longitudinal study follow-ups, making large-scale, statistically significant conclusions difficult. Moreover, the histological variability of these tumors adds another layer of complexity in interpreting the impact on QoL.

It is crucial to recognize the multifaceted nature of QoL and the potential discrepancy between patient-reported outcomes and clinical assessments by healthcare providers (102). Regular collection of self-reported QoL data is vital, particularly given the improving survival rates for patients with skull base tumors. Such data not only provide insights into the patient's recovery trajectory but also help in adjusting care plans to enhance overall well-being of the patients.

Limitations

Our study has several limitations. This literature review was conducted using PubMed, other databases were not explored. Consequently, some studies addressing quality of life following skull base tumor resection may have been omitted. However, additional targeted literature searches were performed to address underrepresented tumor types. To our knowledge, this is the first review encompassing many different tumor types and anatomical localizations.

The variability in scores, tumor types, localizations and treatment modalities across the studies presented prevented direct comparisons. Therefore, this review cannot provide definitive conclusions regarding quality of life. Nevertheless, it offers insights into potential influential factors.

Most studies included in this review focus on anterior skull base tumors and the endoscopic endonasal approach. Consequently, the most frequently used assessment tools were the SNOT-22 and the ASBQ, which predominantly evaluate sinonasal quality of life. This focus may introduce bias, as other aspects of quality of life and different surgical approaches are less frequently discussed.

Additionally, this review only considered publications related to surgical treatment of skull base tumors and did not explicitly evaluate the impact of radiotherapy, conservative treatments, or other treatment modalities.

Conclusion

The transient decrease in QoL following skull base tumor resection is a commonly observed outcome across various anatomical locations and tumor entities. The recovery timelines and outcomes are influenced by a wide variety of factors such as tumor entity, anatomical localization, surgical techniques, patient demographics, and psychosocial considerations. Recognizing and addressing the factors influencing QoL is important for improving patient outcomes and emphasizing individualized care.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material Further inquiries can be directed to the corresponding author/s.

Author contributions

VS: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. TR: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. TK: Conceptualization, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Surgical treatment of rare peripheral nerve lesions: long-term outcomes and quality of life

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Introduction: Rare peripheral nerve lesions comprise a histologically diverse group of neoplastic and non-neoplastic entities, characterized by infrequent occurrence and variable clinical presentations, presenting significant diagnostic and therapeutic challenges. This study presents eight cases of surgically treated rare peripheral nerve lesions with previously unreported long-term outcomes involving quality of life (QOL) assessment.

Methods: A retrospective analysis was conducted on medical records from 2012 to 2022 to identify surgically treated cases of rare peripheral nerve lesions, selecting eight cases based on determined inclusion and exclusion criteria. Long-term outcomes and QOL were assessed 12 months post-surgery by patient examination, control imaging and self-reporting questionnaires.

Results: The study included 4 benign (hemangioblastoma, angiomatoid fibrous histiocytoma, endometriosis (n=2)) and 4 malignant lesions (NTRK-rearranged spindle cell neoplasm, lymphoma, metastatic breast carcinoma (n=2)). Even though benign lesions generally presented with better outcomes, this was more closely related with level of nerve invasion and postoperative sequele, rather than presence of malignancy.

Discussion: Because of a global lack of experience in handling such cases, this study aimed to present the cases we encountered in detail to serve as a basis for future literature reviews. The findings highlight the importance of individualized treatment strategies and long-term follow-up to optimize functional recovery and patient well-being.

KEYWORDS

rare diseases, peripheral nerves, peripheral nerve tumors, neurosurgery, patient outcome assessment, quality of life

1 Introduction

Rare medical diseases lack an internationally accepted consensus on their definition. They are usually defined by having a prevalence of less than 0.04%, with specific thresholds differing according to each country's standards (1–5). According to these criteria, diseases of the peripheral nervous system are relatively common, with prevalence estimates reaching up to 24%, depending on the study inclusion criteria (6–14).

However, no specific definitions or prevalence data exist to classify peripheral nerve diseases as rare. According to some authors, excluding the most common etiologies reveals a variety of histopathological entities that could be considered rare due to their low or unreported individual occurrence (15, 16). According to others, all infrequently encountered, rarely reported, and poorly studied peripheral nerve lesions could be considered rare. The surgically treated cases mostly include benign or malignant neoplastic (tumors), as well as non-neoplastic (tumor-like) lesions, which may originate from neural (primary/intrinsic/neurogenic) or surrounding (secondary/extrinsic/non-neurogenic) tissue (17–21).

Primary peripheral nerve tumors are not rare in surgical practice, accounting for up to 12% of all benign and 8% of all malignant soft-tissue tumors (22). They mostly include benign peripheral nerve sheath tumors (PNSTs), such as schwannomas and neurofibromas, which are not considered rare according to their prevalence rates (17–19, 23). All remaining benign PNTSs listed in the WHO classification list, such as peri-neurinoma, granular cell tumor, malignant peripheral nerve sheath tumor (MPNST), hybrid PNST, and unusual variants of schwannomas and neurofibromas are considered rare (20). Despite being considered rare, some of these lesions are sufficiently studied and reported in the literature, such as MPNST.

The MPNSTs are extremely rare, with an estimated prevalence of 0.001% within the general population (24). However, owing to their relatively higher occurrence within neurofibromatosis, they are not so rarely encountered, comprising up to 10% of all soft-tissue sarcomas and 10% of all surgically treated PNSTs (25–27). However, MPNST is a heterogeneous group of pathological entities, and some forms such as epithelioid are even rarer. In addition, regarding genomic heterogeneity in soft-tissue sarcomas, some genomic MPNST variants are also extremely rare or yet unreported in the literature (28).

Secondary peripheral nerve tumors comprise a group of various benign and malignant neoplasms with the potential to infiltrate neural tissue. Non-infiltrative compressive lesions should not be considered peripheral nerve tumors. All secondary peripheral nerve tumors are rare and, upon infiltration of neural tissue, become non-neural sheath tumors (18).

The malignant secondary nerve lesions usually affect the brachial and lumbal plexuses, with prevalence rates in cancer patients up to 0.43% and 0.71%, respectively (29). Because of anatomical proximity, up to 4.9% of breast carcinoma cases may infiltrate the brachial plexus, being the most reported and well-studied type of metastatic peripheral nerve disease. The lesser but significant amount includes brachial plexopathy induced by lung carcinoma. The remaining types of metastatic nerve involvement comprise a large group of individually rare presentations, mostly underreported and poorly studied in the literature (43).

Benign secondary peripheral nerve tumors are a large group of heterogeneous histological entities with low individual occurrence, often misconceived with tumor-like lesions. The tumor-like lesions are also a heterogeneous group of individually rare entities occurring due to various etiologies. Throughout the literature, some of these entities were transferred from one category to another, while others were continuously discussed in the same way. For example, ganglion nerve cysts are the most frequent tumor-like lesions, sometimes presented as neoplastic lesions in the literature. Nevertheless, they were considered rare in the past and are now being increasingly diagnosed and reported due to more frequent usage of nerve imaging modalities (17–20, 22).

Owing to their infrequent occurrence and diverse clinical presentation, rare peripheral nerve lesions present diagnostic and treatment challenges. The limited available literature often provides diverse and incomparable study results, leaving surgeons to rely heavily on personal experience in managing these cases. This paper aims to evaluate long-term outcomes and quality of life (QOL) in eight patients who underwent surgical treatment for rare peripheral nerve lesions. By providing new insights, this study seeks to enrich the existing literature and offer a reference point for future research (20, 40, 44, 50).

2 Materials and methods

A retrospective analysis of patients' medical records was performed at the author's department for 10 years (1 January 2012 to 31 December 2022) to select the surgically treated cases of rare peripheral nerve lesions. The eight selected cases were included in the study according to the following inclusion and exclusion criteria.

2.1 Inclusion criteria

- Surgically treated patients for rare peripheral nerve lesions during the selected period
- Electromyoneurography (EMNG), ultrasound (US), and magnetic resonance imaging (MRI) verified nerve lesion
- Intraoperatively verified infiltration of the nerve
- Performed biopsy and histopathological analysis
- The pathohistological diagnosis is
    - noted in less than five cases during the selected period or
    - not findable as a case report in the literature or
    - already described in the literature as a rare peripheral nerve lesion or
    - with unreported incidence and prevalence rates, or
    - mostly reported through individual case reports

- Regular follow-up minimum 1 year after the surgery
- Signed patient approval to participate in the study

2.2 Exclusion criteria

- Surgically treated patients for cranial or spinal nerve pathology
- Preoperative disability due to other nerve injury
- The pathohistological diagnosis is
    - noted in more than five cases for a selected period (ganglion nerve cyst and MPNST)
    - intraoperatively excluded infiltration of the nerve (epithelioid sarcoma)
    - already described in the literature as a non-rare lesion (ganglion nerve cyst)

2.3 Outcome assessment

The postoperative evaluation was performed 1 day, 14 days, and 12 months after surgery. The outcome after 12 months was considered as long-term. On the first day, the patient examination included an assessment of pain and a Color Doppler Scan to exclude vein thrombosis. On the 14th day after surgery, the examination included pain and motor strength assessment and stitch removal. QOL was assessed 12 months after surgery.

- Pain was assessed using Visual Analog Scale (VAS) for pain.
- Motor strength was examined by the Medical Research Council (MRC) Manual Muscle Testing (MMT).
- QOL was assessed using SF-36 (Short form 36) and PNSQOL (Peripheral Nerve Surgery Quality of Life) questionnaires (Supplementary Material 1).

2.4 Data description and writing

The manuscript was prepared based on a thorough analysis of the collected data. The manuscript was drafted and refined with the assistance of ChatGPT (version January 2025, GPT-4-turbo, OpenAI) to improve clarity and coherence. The final manuscript was critically reviewed and edited by the author to ensure accuracy, scientific integrity, and compliance with journal guidelines.

3 Results

Our case series included two primary lesions, originating from the neural tissue, and six secondary lesions, originating from surrounding tissue (Figure 1). There was an equal amount of benign and malignant lesions (4:4). Two cases—ulnar nerve hemangioblastoma and isolated sciatic nerve endometriosis—have already been reported in the literature by some of the authors from our team but without long-term outcomes and QOL assessment (30, 31).

3.1 NTRK rearranged spindle cell neoplasm of the tibial nerve

A 51-year-old man presented with an expansive mass in the right popliteal fossa. He initially noticed the mass 2 years earlier, with gradual enlargement, which became more pronounced over the last 6 months. Prior to admission, he had undergone two unsuccessful needle aspirations of the popliteal mass, because a regional medical center doctor had mistakenly identified it as a Becker's cyst.

3.1.1 Clinical evaluation

Physical examination revealed a demarcated expansive mass approximately 3 cm in diameter palpable in the medial part of the right popliteal fossa. Neurologic examination excluded motor deficits, while the patient reported cyclic occurrence of pain radiating from the knee to the lower back (VAS = 3). Both USG and MRI of the right knee confirmed the presence of a tumor in the popliteal fossa, clearly demarcated from surrounding structures and morphologically suggestive of a tibial nerve schwannoma (Figure 2).

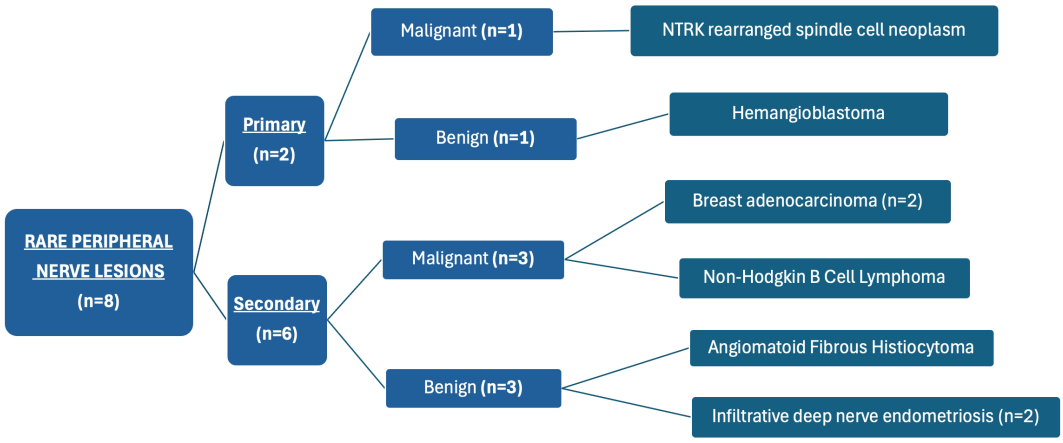

FIGURE 1
Distribution of the study cases according to their characteristics.

3.1.2 Surgical procedure

The patient was placed in a prone position, and the right tibial nerve was explored using a medial popliteal approach. The encapsulated tumor, sized up to 5 cm, originated from the tibial nerve. The tumor capsule was promptly vascularized and adherent with the vessels from the surrounding tissues. Upon dissection of the tumor capsule, identification, and transection of the originating fascicles, the sole tumor removal was not possible due to its fibrotic adherence to a large popliteal blood vessel. An attempt to separate the tumor from the underlying large vein resulted in vein rupture, requiring immediate vascular repair.

The tumor was covered with a grayish-white membrane, measuring 53 × 44 × 43 mm. On cross-section, the tissue had a soft-elastic to tough consistency, heterogeneous appearance, grayish-white, and light brown color, structureless, fibrous, and partly nodular, with irregular yellowish reticular zones and solid, compact areas of firmer consistency, with no clear signs of necrosis or bleeding.

3.1.3 Short-term follow-up

On the first day after surgery, there were no changes in the overall status of the patient. Considering performed vascular repair, the patient was hospitalized for a few days longer than planned and daily checked for deep vein thrombosis using CDS. On the fifth day after surgery, the thrombosis was verified and the patient was examined by a vascular surgeon and then discharged with appropriate advice and medicamentous therapy. Two weeks after surgery, there were no changes in the patient's general and neurologic status. He was examined by a vascular surgeon and radiologist and advised for further self-management.

Histopathological, immunohistochemical, and FISH analyses proved the diagnosis of NTRK rearranged spindle cell neoplasm, with an NTRK1 gene present in approximately 20% of analyzed nuclei. According to established regulations, the patient was admitted to the Council for Soft-Tissue Tumors of Extremities, which serves as a referral body in our country. The Council indicated a CT scan of the body to exclude metastatic dissemination. Upon exclusion, he was advised to be actively involved in regular imaging controls to prevent potential progressive tumor recurrence.

3.1.4 Long-term follow-up

There were no significant changes in the long-term functionality of this patient. Twelve months after our surgery, he still receives

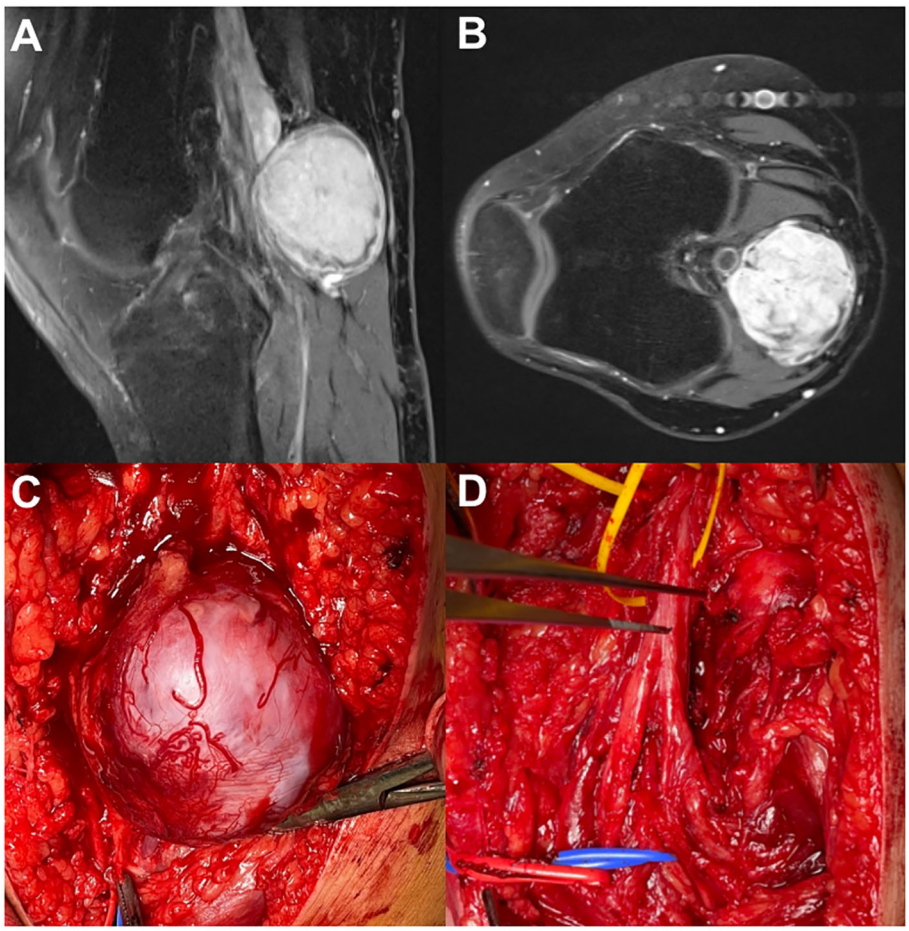

FIGURE 2
NTRK rearranged spindle cell neoplasm. **(A)** MRI—sagittal view. **(B)** MRI—axial view. **(C)** Open exploration (popliteal approach) of the tumor and tibial nerve. **(D)** Tibial nerve after tumor removal.

therapy for deep vein thrombosis and lives satisfied, knowing that there are no signs of tumor dissemination or local recurrence, relying on regular CT and MRI controls. At examination, the patient presented with local pain in the right knee (VAS = 3), which was not associated with the tumor surgery, but rather a recent injury considering MRI findings of a bone bruise in the medial tibial condyle, post-traumatic changes in the posterior medial collateral ligament, and swelling of the medial collateral ligament. Despite that, his SF-36 scores indicate strong physical functioning at 0.85, with no significant limitations in physical or emotional roles, both scoring 1.0. Energy is high at 0.8, and emotional wellbeing and social functioning are positive at 0.8 and 1.0, respectively. The PNSQOL score was almost maximal (77/80). The patient has only mild difficulties in recreational activities and no challenges with work tasks. There are minimal issues with pain and sleep, showing that discomfort may be well-managed. Socially and emotionally, experiences of pity are rare, with no reported discrimination, and the tumor has not impacted social life or daily activities. Satisfaction is very high in all areas, including the condition of the extremity, social life, and professional life, indicating that the patient experiences minimal limitations and maintains wellbeing across physical, social, and emotional domains.

3.2 Ulnar nerve hemangioblastoma

A 70-year-old man presented with a slow-growing, palpable mass on his right upper arm, present for 2 years. His main complaint was discomfort during palpation and consequential propagation of paresthesia into the right hand.

3.2.1 Clinical evaluation

Physical examination located the palpable Tinel-positive mass at the anterior side of the right upper arm. Neurologic examination excluded motor weakness. An EMNG test was conducted, revealing an ulnar nerve lesion in the right upper arm associated with bilateral median nerve entrapment at the level of carpal tunnel.

3.2.2 Surgical procedure

The patient was placed in a supine position with an abducted upper arm and an extended forearm. The tumor was round, encapsulated, reddish-orange, well-vascularized, up to 2.5 cm in diameter, with one nerve fascicle entering its tissue (Figure 3). All fascicles were carefully dissected and remained intact.

3.2.3 Short-term follow-up

On the first day after surgery, there were no changes in the neurological findings compared to before surgery. After 2 weeks, the patient reported a reduction in paresthesia intensity and occurrence. Histopathological and immunohistochemical analysis verified a peripheral nerve hemangioblastoma, WHO grade I. The patient was referred for physical therapy.

3.2.4 Long-term follow-up

Twelve months after surgery, the patient presented with a complete absence of paresthesia radiating from the upper arm to the hand. The only impairment that remained was hypoesthesia of the fourth and fifth fingers. However, his QOL data show generally positive outcomes. Physical functioning is high at 0.85, indicating minimal limitations and role limitations are moderate, with scores of 0.75 for physical and 0.78 for emotional aspects. Energy is robust at 0.9, while emotional wellbeing at 0.64 and social functioning at 0.75 suggest stable emotional health and good social interactions. According to PNS QOL scores (76/80), the patient experiences mild difficulties in recreational and work activities, reports no sleep issues, and has not experienced feelings of pity or discrimination. Satisfaction levels are high, as well as social and professional life, reflecting well-maintained QOL across all areas.

3.3 Brachial plexus neurolymphomatosis

A 14-year-old female patient presented with right shoulder pain and progressive weakness of the right arm during the last 7 months. Because of the patient's claims that the onset of symptomatology was associated with a quick, inappropriate shoulder move that she made, most physicians considered it traumatic and referred her to physical therapy. There were no signs of recovery after 6 months of physical therapy.

3.3.1 Clinical evaluation

On admission, a neurologic examination revealed complete right brachial plexus palsy (MRC 0). EMNG indicated a suspectable lesion of posterior and lateral brachial plexus fascicles, with possible involvement of superior and middle trunks. MRI indicated an increased T2 signal of the C5, C6, and C7 roots and their distal branching with suspectable chronic epi- and intraneural hematomas.

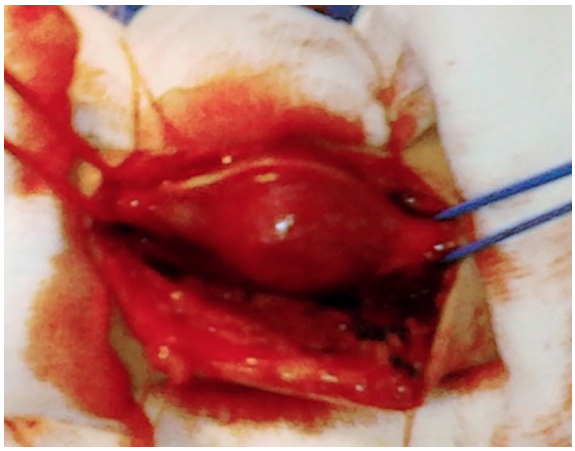

FIGURE 3
Ulnar nerve hemangioblastoma. Reposted courtesy of Prof. Lukas Rasulić.

3.3.2 Surgical intervention

The patient was placed supine, and supraclavicular brachial plexus exploration was performed. During the surgery, superior and middle brachial plexus trunks were sclerotic and neoplastically altered, fused, and compressed by the surrounding tissue (Figure 4). Surgical decompression and external neurolysis were performed, followed by electrodiagnostic testing. Since there was no signal conduction during direct nerve stimulation, an incision biopsy of the altered nerve elements was performed.

3.3.3 Short-term follow-up

There were no signs of recovery up to 1 month after surgery. Histopathological and immunohistochemical findings indicated a large B-cell non-Hodgkin lymphoma. The FISH analysis showed the C-MYC and BCL-2 gene rearrangement, indicating a definitive diagnosis of a "double-hit" high-grade B cell lymphoma (centroblast, non-GCB type). The patient was referred to a pediatric hematologist for evaluation and further management.

Six months after surgery, a progression of disease was noted, presented by the development of left leg weakness (MRC 3). An MRI indicated an extensive neoplastic dissemination affecting most body parts. The patient was then subjected to various combinations of chemotherapeutic agents, complicated by allergic reactions to many of them (rituximab, methotrexate, bactrim, and pentamidine). After three cycles of therapy, leg strength started to recover, and after six cycles, the arm started to recover. After the seventh cycle, MR findings indicated regression of disseminated disease.

3.3.4 Long-term follow-up

Twelve months after surgery, the patient achieved significant functional recovery in terms of regaining muscle strength of the leg (MRC 5), elbow flexion (MRC 5), and shoulder abduction (MRC 3). The PET/CT finding verified that there are no active focuses of the disease.

In this case, the SF-36 scores reveal an excellent QOL with minimal limitations. Physical functioning is nearly optimal at 0.95, and there are no physical or emotional role limitations, both scoring 1.0. High energy (0.9), strong emotional wellbeing (0.92), and no pain (1.0) indicate physical comfort and stable mental health. Social functioning is unaffected (1.0), with the patient experiencing no sleep issues, pity, or discrimination.

PNSQOL scores (53/80) confirm full independence in daily and professional activities, and satisfaction levels are very high across all areas, including social and professional life. Overall, the patient experiences minimal impact from the lymphoma, maintaining an active, independent life with strong wellbeing across physical, social, and emotional dimensions.

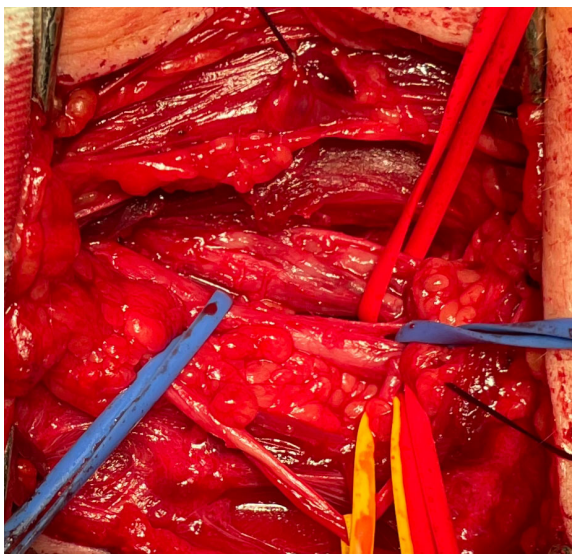

FIGURE 4
Brachial plexus neurolymphomatosis (supraclavicular exploration).

3.4 Infraclavicular neoplastic brachial plexopathy due to breast carcinoma

A 46-year-old woman with a history of right mastectomy (6 years earlier) and chemotherapy due to breast carcinoma presented with pain and progressive weakness of the right arm during the last 2 years. Neurologic examination showed a painful (VAS = 10) extended right upper brachial plexus palsy (MRC 1-2). EMNG and MRI evaluation indicated an infiltrative lesion affecting the infraclavicular portions of the medial and posterior fascicles.

The patient was placed in a supine position, and an infraclavicular approach was used to explore the plexus. Intraoperative findings included scarring tissue compressing the brachial plexus elements, with an expansive infiltrative lesion of the medial and posterior fascicles (Figure 5). Decompression and external neurolysis were performed, followed by incision biopsy.

The patient was satisfied with the surgery after the first day due to significant pain relief (VAS = 5). Two weeks after surgery, the pain almost completely diminished (VAS = 2), but there was no improvement in the arm strength. The histomorphological analysis showed the recurrence of the previously treated breast carcinoma. The patient was referred to an oncologist and biological therapy was started.

Twelve months after surgery, the patient reports improvement in QOL in terms of the absence of pain, while there was no functional recovery. However, her SF-36 and PNSQOL results indicate a reduced QOL across multiple domains.

The SF-36 scores show moderate physical functioning at 0.5, with severe limitations in both physical and emotional roles, each scoring 0, suggesting significant challenges in daily responsibilities and emotional strain due to physical limitations. Energy is low at 0.3, reflecting persistent fatigue, while emotional wellbeing is also low at 0.32, indicating a considerable impact on mental health. Social functioning is minimal at 0.125, possibly related to physical discomfort as indicated by a pain score of 0.525, and the overall perception of general health is poor at 0.2.

PNSQOL (47/100) results further highlight challenges with independence and social interactions, with moderate difficulty reported for personal hygiene and severe limitations in household tasks and recreational activities, indicating significant restrictions in daily life. The patient often experiences pity and occasional humiliation, which may exacerbate emotional challenges and contribute to social isolation. Despite these difficulties, the patient reports moderate satisfaction with social life and high satisfaction in their professional life, possibly reflecting coping mechanisms or support in structured environments. The combined SF-36 and PNSQOL results suggest that while the patient faces considerable physical and social limitations, they show resilience in maintaining aspects of social and professional satisfaction.

3.5 Supra-infraclavicular neoplastic brachial plexopathy due to breast carcinoma

A 57-year-old woman with a history of partial resection of breast carcinoma presented with right cervico-brachial syndrome and arm weakness. She complained of pain (VAS = 10) for the last 3 years, and multiple attempts of physical therapy modalities were attempted without signs of improvement. After some time, the patient experiences almost complete paresis of the right arm.

MRI of the cervical spine showed a massive expansive formation in close relation with adjacent blood vessels, bone, and nerves on the right side. Neurological examination revealed complete brachial plexus palsy with hypotrophy of all muscles. The tumor was palpable in both the supraclavicular and infraclavicular regions.

An infraclavicular decompression with biopsy was performed. There was immediate pain relief (VAS = 4) following surgery. Post-operative histopathological findings showed a morphological finding that corresponds to adenocarcinoma metastasis.

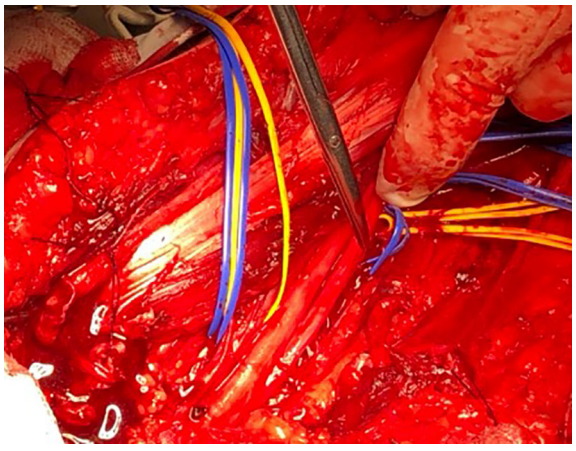

FIGURE 5
Infraclavicular neoplastic brachial plexopathy due to breast carcinoma (infraclavicular exploration).

The SF-36 scores of this patient indicated substantial physical limitations (0.4) and severe restrictions in both physical and emotional roles, scoring 0 for each. This patient faces chronic fatigue (energy score of 0.3) and lower emotional wellbeing (0.36), reflecting both physical and mental challenges. Social functioning is low (0.125), and general health is also poor (0.2). PNSQOL (44/80) scores reveal severe difficulty with personal care and household tasks, hindering independence. The patient experiences occasional pity and rare discrimination, indicating moderate resilience. However, professional satisfaction is low, in contrast to moderate satisfaction in social life, reflecting the strain on regular functioning due to physical limitations.

3.6 Isolated sciatic nerve endometriosis

A 45-year-old woman presented with cyclic occurrence of sciatica in the right leg for the last 3 years with a progression during the last year. Before our examination, the patient was conservatively managed in other institutions and considered a case of degenerative lumbosacral disease.

3.6.1 Clinical evaluation

Upon admission, refractory sciatic pain (VAS = 9) was the patient's main complaint, associated with reduced motor strength of all muscle groups of the right leg (MRC grade 4). EMNG was used to confirm sciatic nerve injury. An MRI showed a non-demarcated expansive lesion, up to 4 cm in diameter, located in the piriformis muscle lodge, infiltrating the muscle and sciatic nerve (Figure 4).

3.6.2 Surgical procedure

The patient was placed in a prone position and the sciatic nerve was explored through an open transgluteal approach (Figure 6). A macroscopic finding included a diffusely altered sciatic nerve in the piriform canal, compressed by calcified fibrous tissue. Microscopic findings revealed a diffusely changed and thickened sciatic nerve, filled with dark liquid cysts. Surgical decompression, release, and external neurolysis were performed, followed by an incision biopsy of a cyst and surrounding altered nerve tissue.

3.6.3 Short-term follow-up

On the first postoperative day, the patient was satisfied and reported pain relief (VAS = 6) while muscle weakness of the left leg progressed [foot flexion (MRC grade 3) and extension (MRC grade 2)].

Histomorphological findings indicated a deep infiltrative sciatic nerve endometriosis. The patient was referred to physical therapy and a gynecologist for evaluation and further management, who prescribed triptorelin therapy for 6 months. During the therapy, the patient experienced significant pain relief (VAS = 3) and recovery of leg strength [foot flexion (MRC grade 5) and extension (MRC grade 3)]. She was able to walk independently without supporting devices.

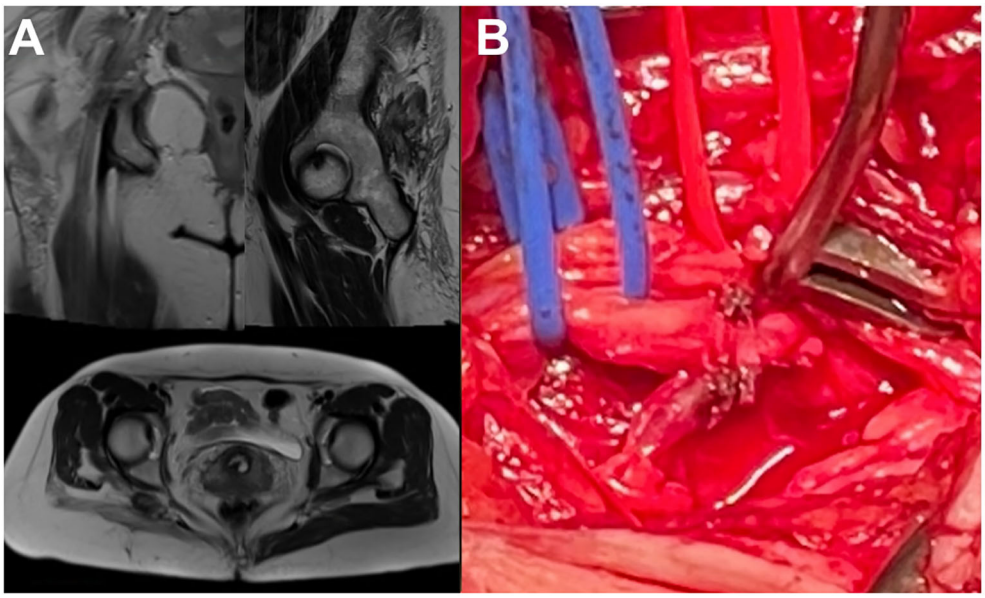

FIGURE 6
Isolated sciatic nerve endometriosis. **(A)** MRI finding. **(B)** Intraoperative finding (transgluteal approach).

Triptorelin was excluded from the therapy after 6 months, followed by progression of pain and gait disturbances. The patient was referred to a neurosurgeon for an opinion on the necessity of repeating the therapy concerning the patient's QOL. The neurologic exam revealed the weakness of the foot flexion (MRC grade 3) and extension (MRC grade 1), associated with intensive sciatic pain (VAS = 8) and being unable to walk without supporting devices. The patient was referred back to the gynecologist with advice to repeat triptorelin therapy.

3.6.4 Long-term follow-up

Upon continuation of the gynecologic medical treatment, the patient recovered in terms of pain reduction (VAS = 2) but maintained weakness of foot extension (MRC grade 2). SF-36 scores show moderate physical limitations (0.4) but strong emotional resilience, with an emotional role score of 1.0. The patient experiences some fatigue (energy score of 0.3) but maintains stable emotional wellbeing (0.64) and excellent social functioning (1.0). Minimal pain (0.9) suggests physical discomfort is limited, allowing independence in daily tasks per PNSQOL (68/80) findings. Social and professional satisfaction is moderate, indicating a balanced QOL.

3.7 Associated sciatic nerve endometriosis

A 40-year-old woman presented with pain and paresthesia in the lower back during the last 2 years, being more severe during the menstrual cycle. The last 5 months were characterized by progression in terms of paresthesia propagation into all fingers of the right foot, altering her gait performance. Three years earlier, the patient was subjected to intrapelvic endometriosis surgery.

3.7.1 Clinical evaluation

Upon admission, the patient's main complaint was propagating right leg paresthesia ending with foot hypoesthesia and consequential disbalance-associated difficulties in walking. The motor strength of all muscle groups of the right leg was reduced (MRC grade 3), while the foot exhibited deformities with contractures. The lower back pain (VAS = 6) that occasionally accompanied the paresthesias was not significant, according to the patient's claims. Upon EMNG verification of the sciatic nerve lesion, the USG indicated a preserved nerve continuity associated with piriform and gemellus muscle tendinitis. An MRI revealed a non-homogeneous thickening of the right sciatic nerve at the level of the ischio-femoral space (Figure 7).

3.7.2 Surgical procedure

The patient was placed in a prone position, and the right sciatic nerve was explored through an open transgluteal approach. In both macroscopic and microscopic findings, the sciatic nerve was sclerotic and adherent to surrounding tissue. A careful decompression and external neurolysis were performed, followed by an incision biopsy of epineurium infiltrated by adherent sclerotic tissue.

3.7.3 Short-term follow-up

The first day after surgery, the patient reported a slight reduction of paresthesia without evident improvement in gait performance. Two weeks after surgery, the muscle strength of the right leg improved (MRC 4) with evident progress in walking

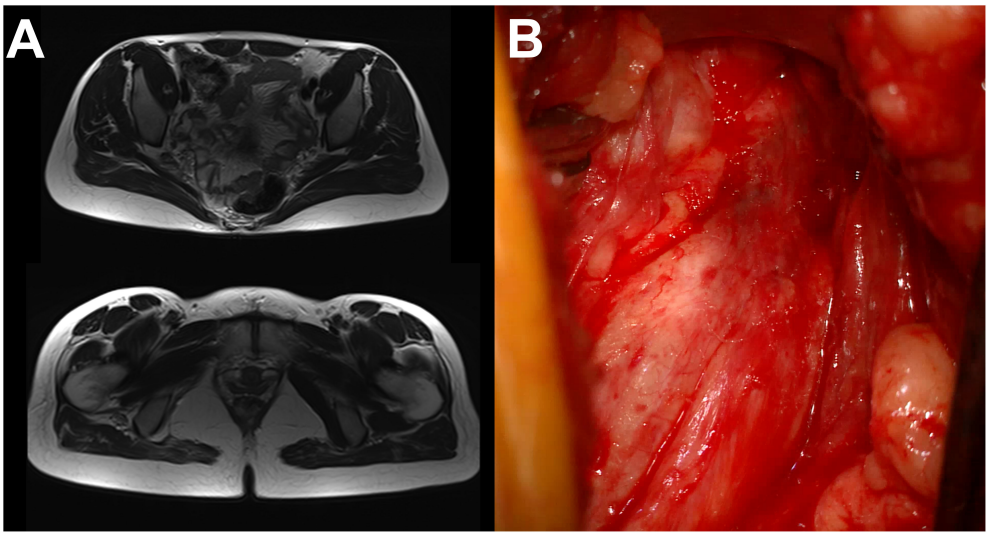

FIGURE 7
Sciatic nerve endometriosis. **(A)** MRI finding. **(B)** Intraoperative microscopic finding (transgluteal approach).

function. One month after surgery, the patient presented with complete muscle strength recovery (MRC 5), absence of pain, and paresthesias while only complaining about the foot deformity.

Histomorphological and immunohistochemical findings revealed micro-focuses of endometriotic tissue infiltrating the epineurium. The patient was referred to a gynecologist for further management. However, the gynecologist assumed that the endometriotic tissue was removed from the sciatic nerve and, upon USG exclusion of intrapelvic endometriotic involvement, decided not to prescribe hormonal therapy.

Six months after surgery, the patient experienced symptom exacerbation, presented as intermittent leg pain (VAS = 9), muscle weakness (MRC 3), and walking inability. An MRI revealed progression in size of the endometriotic tissue affecting the right sciatic nerve. The patient was readmitted to a gynecologist to reconsider hormonal therapy. One month later, upon the patient's request, she was subjected to a bilateral oophorectomy.

3.7.4 Long-term follow-up

Twelve months after our surgery and 5 months after the bilateral oophorectomy, the patient experienced incomplete muscle strength recovery (MRC grade 4), reduction of pain (VAS = 3), and paresthesia while lacking improvement in foot deformity. SF-36 scores reveal moderate physical functioning (0.65) and balanced scores in energy (0.6) and emotional wellbeing (0.72), indicating overall resilience. Social functioning and general health are moderately high (0.75), pointing to a positive outlook. PNSQOL results (68/80) indicate mostly independent daily functioning, with occasional difficulty in specific tasks. Experiences of pity are infrequent and do not appear to affect the patient significantly. Satisfaction scores are moderate across social and professional domains, suggesting that the patient has adapted well to the condition despite some physical restrictions. During examination, she stated that she is satisfied with her current QOL and is looking forward to achieving a complete functional recovery.

3.8 Angiomatoid fibrous histiocytoma of the saphenous nerve

A 33-year-old woman presented with pain and paresthesias in the left popliteal fossa propagating through the anterior side of the lower leg during the last 3 years. The patient's main complaint was extremely intense, sharp, propagating pain (VAS = 10) initiated by even the slightest touch.

3.8.1 Clinical evaluation

Muscle strength was preserved in all muscle groups. There were no gait disturbances. There was no pain in the resting state. EMNG findings confirmed a saphenous nerve lesion, while USG revealed a hypoechogenic expansive lesion involving the nerve. The MRI finding characteristics of the lesion suspected a neurofibroma. The lesion was below skin level and was not visible by inspection, and palpation revealed its location by inducing the pain with minimal pressure.

3.8.2 Surgical procedure

The patient was placed in the lateral position, providing a medial approach to the popliteal fossa. The intraoperative finding revealed a tumor of fibrous consistency and very adherent to surrounding tissues involving the entire diameter of the saphenous nerve (Figure 8). The tumor was dissected from surrounding tissues and removed by transecting the proximal and distal parts of the saphenous nerve. The following act included debridement of the surrounding soft tissues covered with adhesive neoplastic tissue.

3.8.3 Short-term follow-up

On the first postoperative day, the muscle motor strength was preserved, while intensive preoperative pain could not be induced by palpating the skin over the triggering projection. The patient only complained about the pain around the operative wound (VAS = 2), which was limiting her walking.

Two weeks after surgery, there was no pain (VAS = 0) and paresthesia, leading to complete functional recovery. Histomorphological, immunohistochemical, and FISH analyses indicated a mesenchymal tumor with the characteristics of angiomatoid fibrous histiocytoma (AFH). According to established regulations, the patient was admitted to the Council for Soft-Tissue Tumors of Extremities, which serves as a referral body in our country.

Two months after surgery, the patient remained asymptomatic. The CT scan of the body was used to exclude malignant dissemination. However, a follow-up MRI revealed a local tumor recurrence without involving the transected nerve stumps. Despite the patient having no complaints, she was submitted to an indicated revision surgery performed by an orthopedic surgeon. Such revision surgery aims to prevent another local recurrence by providing gross total tumor resection and more radical debridement of surrounding tissues.

3.8.4 Long-term follow-up

Twelve months after our surgery, the patient presented with loco-regional knee pain (VAS = 4) and lower leg lymphedema, persisting for the past 10 months as a consequence of revision surgery. In addition, the most recent MRI finding indicated a local re-recurrence of the tumor.

The SF-36 scores revealed moderate physical functioning (0.5) and severe role limitations in both physical and emotional aspects, each scoring 0. Energy and emotional wellbeing scores are moderate at 0.65 and 0.68, respectively, reflecting some resilience despite fatigue. Social functioning and pain are also moderate (0.5 and 0.45), suggesting occasional discomfort that might affect social interactions. PNSQOL (52/80) findings indicate that the patient is independent in most daily activities but struggles with household chores. Occasional pity and rare humiliation suggest mild emotional challenges, though satisfaction remains moderate in social and professional life.

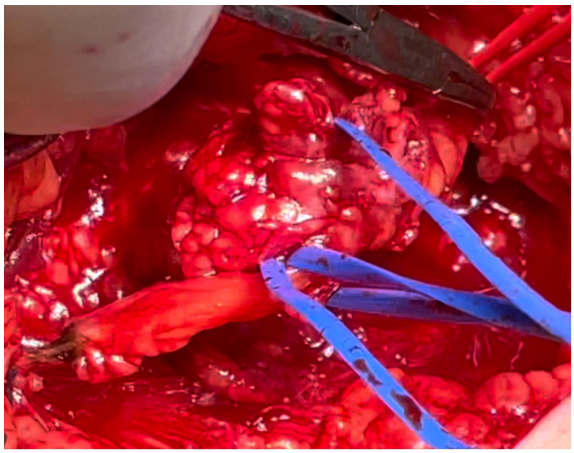

FIGURE 8
Intraoperative macroscopic finding of saphenous nerve AFG (popliteal approach).

4 Discussion

Rare peripheral nerve lesions individually represent an extremely small portion of all nerve cases but display various presentations and, collectively, become more impactful. Because of a global lack of experience in handling such cases, this study aimed to present the cases we encountered in detail to serve as a basis for future literature reviews. The following text discusses each study case individually, as well as within its histological category, and in comparison with all other cases, focusing on factors that reduce or enhance QOL.

4.1 Peripheral nerve NTRK rearranged spindle cell neoplasm

Neurotrophic tyrosine receptor kinase (NTRK) neoplasms are a rare subset of soft-tissue tumors characterized by gene fusions involving NTRK1, NTRK2, or NTRK3. These fusions lead to constitutive activation of TRK proteins, driving oncogenesis. While NTRK fusions are documented across various tumors, their occurrence in spindle cell neoplasms, particularly those originating from nerve tissues, is uncommon. NTRK rearranged spindle cell neoplasms (NTRK-RSCNs) are a rare type of NTRK fusion-positive sarcomas that share some diagnostic and treatment challenges with other soft-tissue sarcomas while differing in the need for specialized molecular testing, as well as variable clinical presentation and nature of surgical complications (32–34).

NTRK-RSCNs can present as a slow-growing mass and therefore be misdiagnosed as benign tumors, which initially occurred in our patient. Their expansive growth is usually characterized by adhesive attachment to surrounding structures, which occurred in our patient, and led to a vascular nerve lesion requiring immediate surgical repair. On the other side, these NTRK-RSCNs can present as a fast-growing mass, which can be misdiagnosed with MPNSTs.

Timely recognition of NTRK-RSCNs is crucial to avoid misdiagnosis as benign lesions, given their potential for recurrence and dissemination. Conversely, they should not be mistaken for MPNST, as NTRK-RSCNs have a lower recurrence rate and very rarely disseminate. This distinction typically means that surgery alone is sufficient without adjuvant therapy, though regular imaging follow-ups are necessary with a potential for targeted immunotherapy.

To our knowledge, there are no reports on long-term outcomes and QOL in patients treated for nerve NTRK-RSCNs. We consider that QOL in these patients, as in patients with soft-tissue sarcomas in general, will primarily depend on the extent of nerve and surrounding tissue invasion, the severity of postoperative sequelae, and the recurrence rate. A study on QOL in high-grade

soft-tissue sarcomas found that while patients recover well physically from surgery, the mental component showed no improvement, regardless of age, highlighting the need for comprehensive care that addresses both physical and mental health. Since the recurrence and dissemination rates are low in patients with NTRK-RSCNs, mental support may be out of greatest significance. The long-term outcome in our case showed a high QOL with strong physical and social functioning, minimal pain, and high emotional wellbeing—outcomes that align with literature findings on the benefits of proactive care and psychosocial support in maintaining QOL for similar cases.

4.2 Peripheral nerve hemangioblastoma

Hemangioblastomas are rare benign vascular tumors that mostly occur in the CNS, with an incidence rate of 0.141 per 100,000 person-years according to one study (35). There are only a few cases in the literature arising from the peripheral nerves usually presented as pain in the innervation field of the affected nerve (18, 30, 36–39). Surgical resection is a primary option, which may require nerve resection and repair depending on the severity of intraneural infiltration.

Based on our knowledge, there is a lack of papers in the literature concerning QOL following peripheral nerve hemangioblastoma surgery. The patient presented in our study had no significant deficits before surgery and the treatment was indicated for diagnostic purposes. His long-term outcomes were characterized by reduced severity of preoperative symptoms and no tumor recurrence. Therefore, we consider that in such cases, long-term outcomes and QOL after surgery mostly depend on the severity of nerve infiltration and outcomes of nerve recovery rather than the tumor's pathological characteristics.

4.3 Neurolymphomatosis

Neurolymphomatosis (NL) is a rare manifestation of non-Hodgkin's lymphoma (NHL), presented as the involvement of peripheral nerves, occurring in approximately 3% of the cases with NHL. Contrary to the categorization of other peripheral nerve lesions, where NL is always considered secondary, NL itself can be either primary, originating within peripheral nerve tissue, though less common, or secondary, invading from surrounding tissues, which is more typical. In most cases, NL involves diffuse large B-cell NHL, affecting the brachial plexus; however, it remains poorly studied in the literature, especially in pediatric cases (40).

A recent meta-analysis aimed to analyze long-term outcomes and prognostic factors in patients with NL, revealing their shorter median survival compared to cases affecting the central nervous system or vascular elements. Furthermore, it emphasized that NL diagnosis is challenging and that the patient's age and time elapsed from symptom onset to the treatment are the main prognostic factors (41).

The histomorphological features and location of NL in our case align with the most frequent instances reported in the literature, while remaining extremely rare considering the age group. The initial misdiagnosis as a traumatic injury, leading to delayed appropriate treatment, reflects the diagnostic challenges in patients with NL. Even though the time from symptom onset to diagnosis and treatment was longer in our case, compared to the median in the general NL population, the survival time was longer. This may be attributed to the patient's age, contributing to its impact as a prognostic factor.

There are reports on QOL following brachial plexus lymphomatosis to be compared. The high QOL scores in our case indicate minimal limitations and strong wellbeing, suggesting that with timely and appropriate treatment, patients can achieve favorable outcomes, as highlighted in the literature.

4.4 Neoplastic peripheral neuropathy

Peripheral nerve lesions in patients with malignancy occur in 1.7% to 16% of cases, mostly affecting the cervical, brachial, or lumbar plexus (42). Brachial plexus lesions associated with malignancy mostly result from metastatic infiltration [neoplastic brachial plexopathy (NBP)] or radiation therapy [radiation-induced brachial plexopathy (RBP)]. The literature does not provide a calculated incidence of NBP and RBP among patients with malignancy. Some studies report the prevalence of NBP among cancer patients to be 0.43%, while RBP occurs in 1% of patients who have undergone radiation therapy.

Lung or breast carcinoma metastases are the most common causes of NBP (43, 44). Breast-originating NBP is mostly caused by metastatic spreading through the axillary lymph nodes, infiltrating the infraclavicular nerve elements, while direct invasion or vascular spreading is less common. Progressive pain is usually the first symptom, followed by progressive arm weakness distributed within the C8 and T1 root innervation field. Tumor expansion and invasion of the retroclavicular and supraclavicular nerve elements may involve all brachial plexus roots. The onset of symptoms may be delayed, starting many years after diagnosing the primary tumor site. In our study, both cases followed this pattern, with symptom onset delayed by a few years, starting with progressive pain and followed by arm weakness. In both cases, the infiltration involved infraclavicular nerve elements, with one case showing expansion into the retroclavicular space.

Breast-originating NBP is commonly associated with RBP due to the proximity of the radiation target area to brachial plexus elements. Differential diagnosis can be confirmed through neurologic examination, EMNG, USG, or MRI findings. NBP is usually characterized by severe pain as the predominant complaint, along with USG and MRI confirmation of an expansive lesion. In contrast, RBP is characterized by less severe pain, lymphedema, and involvement of the supraclavicular plexus elements, along with EMNG signs of myokymia and MRI evidence of nerve thickening without any focal mass. Both of our patients had a positive history of radiotherapy but presented with pain as the most significant complaint, and USG and MRI verified the presence of the focal mass lesion. It is worth mentioning that it is not unusual to delay the diagnosis due to the similarity of the symptoms with cervical spine pathology, which was seen in one of our patients (45).

The clinical presentation of our patients is comparable with the literature data. The primary indication for surgery in both cases was pain relief, and postoperatively, both patients reported satisfaction with their treatment outcome, as it provided substantial pain relief. However, both patients presented with lower QOL compared to the population with breast carcinoma in general, most likely due to nerve involvement, resulting in pain and functional deficits (46).

The differences in motor deficits most likely contributed to variations in QOL outcomes between the two cases. The infraclavicular case showed moderate physical functioning with some social interaction challenges and moderate satisfaction across social and professional domains. Despite persistent fatigue and moderate difficulties in daily activities, her satisfaction was relatively high in professional life, likely supported by a structured environment that accommodated her limitations. In contrast, the supra-infraclavicular case presented with lower physical functioning and more significant dependency in daily tasks. This greater physical limitation affected her professional satisfaction, which was very low, while she maintained only moderate satisfaction in her social life.

4.5 Peripheral nerve endometriosis

Endometriosis is a benign chronic inflammatory disease in which endometrium-like tissue infiltrates the structures outside the uterus, affecting up to 10%–15% of female patients in the reproductive period, with a prevalence rate of up to 2% and annual incidence rates of up to 0.3%, respectively (47, 48). The endometriosis may significantly alter QOL presenting as dysmenorrhea, chronic pelvic pain, right iliac fossa pain, dysuria, dyspareunia, or infertility (49).

In cases affecting the sciatic nerve, the symptoms include cyclic sciatica usually misleading the diagnostic process toward degenerative spine diseases (50). The cases of intrapelvic sciatic nerve involvement that require surgery are usually managed using the laparoscopic approach by the gynecologists (51, 52). In cases of extrapelvic endometriosis with the involvement of the sciatic nerve, an open transgluteal approach may be necessary to diagnose or relieve the symptoms (53). Based on our knowledge, there were no reports on QOL following sciatic nerve endometriosis cases that were treated by an open transgluteal approach (54).

Our study included two cases of extrapelvic sciatic nerve endometriosis, one of which was isolated and the second was associated with intrapelvic involvement. Both cases presented with sciatica and cyclical progression of symptoms, which were reduced immediately following the surgical decompression.

The case with isolated sciatic nerve involvement presented a diagnostic challenge due to the isolated extrapelvic involvement of the sciatic nerve, which was rarely reported in the literature (55). The intraoperative finding was unspecific and unfamiliar with the previous experience, and an attempt to widely explore the nerve and provide a proper biopsy resulted in sciatic nerve injury and consequential leg weakness. In the other case, a positive history of endometriosis treatment and MRI-verified presence of intrapelvic endometriotic tissue played a great role in planning the surgery. A careful non-extensive decompression and biopsy were performed, without postoperative complications and significant improvement of the patient's functionality.

Comparing QOL between these two cases, notable differences appear in physical functioning, energy, and satisfaction levels. The isolated case has lower physical functioning and energy compared to the extended pelvic case, suggesting greater limitations in daily activities. Despite these physical constraints, the first case reports strong social functioning and moderate satisfaction, reflecting good emotional resilience and social support, though frequent experiences of pity from others may impact overall satisfaction. In contrast, the second case experiences slightly better emotional wellbeing and fewer perceived social barriers, and expresses higher satisfaction across life domains, likely due to improved physical capacity and energy.

When compared with general endometriosis populations (56), both patients' scores in physical, social, and emotional functioning are notably higher than reported medians. This difference may stem from the isolated nature of the sciatic nerve lesion, as opposed to the more extensive intrapelvic endometriosis often seen in other cases, which tends to more broadly reduce overall QOL. The isolated

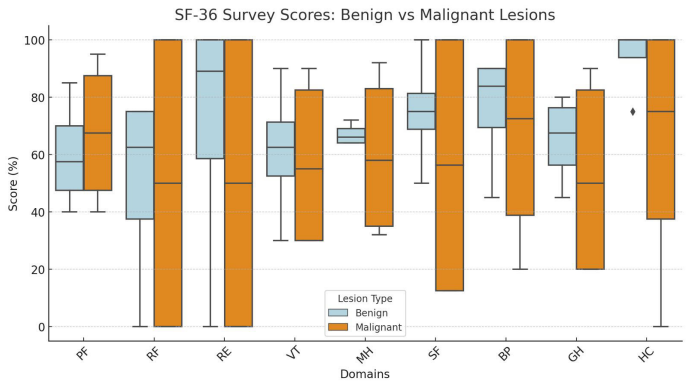

FIGURE 9
SF-36 scores with reference to the presence of malignancy: PF, physical functioning; RF, role limitations due to physical health; RE, role limitations due to emotional problems; VT, vitality (energy); MH, mental health (emotional well-being); SF, social functioning; BP, body pain; GH, general health; HC, health change.

localization likely limits some of the systemic effects common in widespread endometriosis, preserving certain aspects of QOL.

4.6 Peripheral nerve angiomatoid fibrous histiocytoma

AFHs are rare and low-grade soft-tissue lesions that typically arise from subcutaneous and deep dermal tissue of extremities. In rare cases, recurrence or tumor metastasis was noted (57). Based on our knowledge, there are no reports on AFH affecting a peripheral nerve and QOL following its surgical management. In our case, radical nerve resection with surrounding tissue debridement did not alter the patient's postoperative functionality. However, because of the recurrence of the tumor and the need for more radical tissue debridement, the 1-year QOL was significantly reduced. The low QOL scores across multiple domains demonstrate the profound impact postoperative sequelae have on QOL despite the fact that the lesion is benign.

5 Study limitations

The limitations of this study include several key factors. First, the small sample size of only eight cases limits the generalizability of the findings, as rare peripheral nerve lesions have inherently low prevalence, making it difficult to draw broad conclusions applicable to a wider population. The retrospective nature of the study relies on existing medical records, which may lack detailed information on certain patient experiences or outcomes, potentially affecting the accuracy of the data. Furthermore, variations in lesion type, location, and individual patient characteristics introduce heterogeneity, which complicates comparisons and may influence QOL outcomes independently of the lesion type.

Another limitation is the lack of a control group, which makes it challenging to assess the relative impact of surgery on QOL compared to other treatment modalities. Since QOL assessments, including SF-36 and PNSQOL, were conducted only at specific intervals, they may not fully capture fluctuations in the patients' QOL over time, particularly between the immediate postoperative period and the long-term follow-up.

Finally, the study's reliance on self-reported measures of satisfaction and QOL may introduce bias, as patients' subjective experiences can be influenced by factors beyond the clinical outcomes, such as support systems or personal expectations. These limitations highlight the need for future studies with larger sample sizes, prospective designs, and more standardized follow-up intervals to validate and expand upon the findings in this study.

6 Summary

This study presents long-term outcomes and QOL for eight patients who underwent surgical treatment for rare peripheral nerve lesions, highlighting the diversity in clinical presentation and the complexities of treatment. These lesions, including both primary and secondary origins, as well as benign and malignant types, underscore the challenges in diagnosis and management due to their rarity and varied characteristics. Surgical intervention was often complicated by adherence to surrounding structures, as seen in cases of NTRK-RSCN and endometriosis, leading to postoperative complications.

Although benign lesions generally showed better overall QOL (Figure 9), this was more closely related to the level of nerve invasion and postoperative sequelae, such as pain or motor deficits, rather than the benign or malignant nature of the lesion itself. For instance, the benign saphenous nerve AFH case resulted in very low QOL due to significant postoperative complications, while the malignant tibial nerve NTRK-RSCN and brachial plexus lymphoma case had a high QOL, as there were minimal functional deficits and effective pain management. This suggests that postoperative outcomes, particularly regarding nerve function preservation and pain control, play a critical role in determining QOL, often more so than the lesion's benign or malignant classification.

Psychological support is of great importance in managing malignant lesions, as it significantly contributes to maintaining and improving QOL. Even when physical and functional outcomes are favorable, the emotional and psychological challenges associated with a malignant diagnosis can impact wellbeing. Providing comprehensive psychological support helps patients cope with fears of recurrence, treatment side effects, and social or professional limitations, ultimately enhancing their overall resilience and QOL.

In conclusion, this study emphasizes the importance of an individualized approach in managing rare peripheral nerve lesions. Long-term outcomes were rather associated with the severity of nerve invasion and persistent symptomatology, rather than the involvement of malignancy. Despite a lack of standardized protocols, early intervention, targeted treatment strategies, and psychosocial support contributed positively to functionality and QOL in most cases.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving humans were approved by Ethic committee of Medical Faculty, University of Belgrade. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

ASa: Writing – original draft, Writing – review & editing. ML: Writing – original draft, Writing – review & editing. JG: Writing – original draft, Writing – review & editing. AM: Writing – original draft, Writing – review & editing. ASt: Data curation, Writing – original draft. GP: Writing – original draft, Writing – review & editing. AT: Data curation, Writing – original draft. LV: Data curation, Writing – original draft. LR: Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2024.1476019/full#supplementary-material

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