European Journal of Physical and Rehabilitation Medicine 2025 Feb 17
DOI: 10.23736/S1973-9087.25.08573-9

ORIGINAL ARTICLE

Improved health-related quality of life after rehabilitation in patients with brain tumors is not affected by tumor type

Takahiro WATANABE [1, 2] *, Shinichi NOTO [3], Manabu NATSUMEDA [4], Shinji KIMURA [5], Fumie IKARASHI [1], Satoshi TABATA [1], Mayuko TAKANO [1], Yoshihiro TSUKAMOTO [4], Makoto OISHI [4]

[1]Department of Clinical Technology, University Medical and Dental Hospital of Niigata, Niigata, Japan; [2]Department of Rehabilitation Sciences, University of Health and Welfare Graduate School of Niigata, Niigata, Japan; [3]Department of Rehabilitation, University of Health and Welfare of Niigata, Niigata, Japan; [4]Department of Neurosurgery, Brain Research Institute, University of Niigata, Niigata, Japan; [5]Rehabilitation Center, University Medical and Dental Hospital of Niigata, Niigata, Japan

*Corresponding author: Takahiro Watanabe, [1]Department of Clinical Technology, University Medical and Dental Hospital of Niigata, 754 Ichibancho, Asahimachidori, Chuo-ku, Niigata-shi, Niigata, 951-8510, Japan. E-mail: tw112051@yahoo.co.jp

ABSTRACT

BACKGROUND: The effect of rehabilitation therapy on health-related quality of life (HRQOL) among patients with brain tumors has not been fully investigated.
AIM: This study aimed to evaluate the effect of rehabilitation therapy on HRQOL among patients with brain tumors using the HRQOL index. We also examined factors that influenced changes in HRQOL, including differences in brain tumor type.
DESIGN: Prospective cohort study.
SETTING: University Medical and Dental Hospital.
POPULATION: Patients with brain tumors aged 20 years or older undergoing rehabilitation therapy were included. Patients with cognitive decline, aphasia, or poor general condition who had difficulty answering HRQOL questions were excluded.
METHODS: The EuroQol-5 Dimension 5-Level (EQ-5D-5L), EORTC Quality of Life Questionnaire Core 30 (QLQ-C30), and EORTC Quality of Life Questionnaire Brain Cancer Module (BN20) were used to assess HRQOL before and after rehabilitation treatment. Brain tumor type was classified into five groups: World Health Organization (WHO) grade 1, WHO grade 2/3, WHO grade 4, primary central nervous system lymphoma, and metastatic brain tumor. We compared EQ-5D-5L index scores and QLQ-C30 and BN20 scores before and at the end of rehabilitation. Multiple regression analysis was used to examine factors affecting changes in EQ-5D-5L index score (EQ-5D-5L gain).
RESULTS: In total, 112 patients participated in this study. The median EQ-5D-5L index score significantly improved from 0.698 before rehabilitation to 0.772 at the end of rehabilitation ($P<0.001$, $r=0.46$). QLQ-C30 and BN20 scores showed significant improvement in physical functioning, global health status, pain, and motor dysfunction ($P<0.001$, $r>0.3$). Multiple regression analysis revealed that recurrence ($\beta=-0.191$, $P=0.037$) and baseline EQ-5D-5L index score ($\beta=-0.595$, $P<0.001$) affected EQ-5D-5L gain, whereas differences in brain tumor type did not.
CONCLUSIONS: HRQOL among patients with brain tumors improved at the end of rehabilitation therapy compared with before therapy. Furthermore, the EQ-5D-5L index score gain was not affected by brain tumor type.
CLINICAL REHABILITATION IMPACT: These results suggest rehabilitation therapy may contribute to improved HRQOL irrespective of brain tumor type.

(*Cite this article as:* Watanabe T, Noto S, Natsumeda M, Kimura S, Ikarashi F, Tabata S, *et al.* Improved health-related quality of life after rehabilitation in patients with brain tumors is not affected by tumor type. Eur J Phys Rehabil Med 2025 Feb 17. DOI: 10.23736/S1973-9087.25.08573-9)

KEY WORDS: Brain neoplasms; Rehabilitation; Quality of life.

Brain tumors are broadly classified into primary brain tumors and metastatic brain tumors (MBT), in which tumors from other organs metastasize to the brain. Worldwide, 296,851 new cases of cancer of the brain and nervous

system were diagnosed in 2018, with this number showing an increasing trend.[1] Treatment of brain tumors includes surgical resection, radiation therapy, and chemotherapy. The choice of treatment depends on the tumor type and location, and the patient's general condition. These treatment modalities have made significant progress in recent years and have extended the overall survival (OS) of patients with brain tumors. However, some malignant brain tumors have a poor prognosis, even when these standard therapies are used. In particular, the median OS for glioblastoma was reported as 16 months, and the 5-year survival rate as 16%.[2] Similarly, the median OS for MBT overall was 18 months with a 5-year survival rate of 24%, although the OS varied depending on the primary tumor.[2] Therefore, brain tumors can be characterized by different prognoses and courses as well as by treatment methods depending on their type.

Health-related quality of life (HRQOL) is a patient-reported outcome measure that has attracted increased attention as an indicator of the effectiveness of medical technology. It is considered important to maintain and improve patients' HRQOL as well as their OS, especially in cases with a poor prognosis. Therefore, it is necessary to evaluate HRQOL in patients with brain tumors, which is reflected in the increasing number of studies focused on HRQOL in this population.[3] HRQOL has also been used to investigate the effects of radiotherapy[4] and chemotherapy[5] on treatment efficacy and prognosis.

Patients with brain tumors can present with various central nervous system disorders, such as motor paralysis and higher brain dysfunction, even after standard treatment.[6] Rehabilitation therapy is particularly important for these patients and has been reported to be effective in improving activities of daily living (ADL), fatigue, and higher brain function.[7] Previous studies that compared patients with stroke[8] and brain injury[9] with similar neurological symptoms observed similar results in physical function, ADL, and home discharge rates in these diseases. Although there have been some reports on the effects of rehabilitation therapy on HRQOL among patients with brain tumors, there are fewer of these reports compared with other cancers.[10] Furthermore, limited reports have shown improvement in HRQOL with rehabilitation therapy,[11] and there is no consensus on its effectiveness.[12-14] Moreover, we could not find reports where HRQOL was examined before and after rehabilitation treatment using the EuroQol-5 Dimension 5-Level (EQ-5D-5L), which is a utility value scale.

Patients' HRQOL is a major concern in cases with highly malignant brain tumors, which have a poorer prognosis than other tumors. This means it is necessary to clarify the effects of rehabilitation treatment among these patients and examine the characteristics of HRQOL by different brain tumor types. In addition, understanding factors that influence changes in HRQOL may provide useful information for rehabilitation treatment. Therefore, this study aimed to examine the effect of rehabilitation treatment on HRQOL among patients with brain tumors using the HRQOL index. In addition, we examined factors that influenced changes in HRQOL, including differences by brain tumor type.

Materials and methods

Study design

This single-center prospective cohort study was performed in accordance with the principles of the Declaration of Helsinki. Approval for this study was granted by the Ethics Committee of Niigata University (Approval No. 2020-0380). The study was explained to participating patients both orally and in writing, and informed consent was obtained from all included patients.

Patients

This study included patients with brain tumors aged 20 years or older who were admitted to the Department of Neurosurgery, Niigata University Medical and Dental Hospital, for treatment of brain tumors from April 2016 to December 2023. Furthermore, these patients had been prescribed combinations of physical therapy (PT), occupational therapy (OT), and speech and language therapy (ST). Based on previous studies, patients were excluded if they had a Mini-Mental State Examination score ≤23 or had difficulty answering HRQOL questions because of aphasia, severe higher brain dysfunction, or poor general health.[15]

Patient assessments

The EQ-5D-5L, EORTC Quality of Life Questionnaire Core 30 (QLQ-C30), and the EORTC Quality of Life Questionnaire Brain Cancer Module (BN20) were used to assess HRQOL. In principle, patients were required to complete the HRQOL questions by themselves. However, in cases where patients had limitations that affected questionnaire completion or reading comprehension difficulties (*e.g.*, motor paralysis or visual field impairment due to central nervous system disorder), the therapist in

charge of the patient was able to assist them in answering the questions. The occupational therapist in charge used the Functional Independence Measure (FIM) to evaluate patients' ADL. Assessments were made at the beginning (baseline) and end of rehabilitation. At the beginning of rehabilitation, patients with brain tumors tend to be in poor general condition, including impaired consciousness, and it may be difficult for them to answer HRQOL questions. Therefore, this study defined the start of rehabilitation for HRQOL as the time when patients were able to use a wheelchair and could answer the HRQOL questions.

Assessment of general health

Information such as patients' age, sex, preadmission Karnofsky Performance Status (KPS), brain tumor classification, tumor location (right, left, brain stem/midline, cerebellum, bilateral/multiple tumors, or extra-axial tumor), presence of surgery, presence of radiotherapy, presence of chemotherapy, first occurrence or recurrence, length of hospital stay, and outcome destination were collected from medical records. The pathological diagnosis of brain tumors was based on the World Health Organization (WHO) 2016 Classification of Central Nervous System Tumors.[16] However, the WHO 2021 Classification of Central Nervous System Tumors was published during the study period.[17] Therefore, we classified anaplastic astrocytoma, IDH-wildtype and diffuse astrocytoma, and IDH-wildtype gliomas with TERT promoter mutations as grade 4 tumors. Based on previous studies,[18, 19] we classified patients into five groups: WHO grade 1 gliomas, WHO grade 2/3 gliomas, WHO grade 4 gliomas, primary central nervous system lymphomas (PCNSL), and MBTs. When assessing the presence or absence of surgery, biopsies were not regarded as surgery based on a previous study.[5]

EQ-5D-5L

The EQ-5D-5L is a generic preference-based measure developed by the EuroQol Group. This measure divides health status into five domains: mobility, self-care, common activities, pain/discomfort, and anxiety/depression. These health status domains are evaluated using five response options: no problems, slight problems, moderate problems, severe problems, and extreme problems. In Japan, the EQ-5D-5L conversion table was completed in 2015; therefore, an EQ-5D-5L index score reflecting the values of Japanese people can be calculated, with a range from −0.025 to 1.00 (perfect health).[20]

QLQ-C30 and BN20

In this study, the Japanese versions of the QLQ-C30 (version 3) and BN20 were used to evaluate HRQOL. These HRQOL questionnaires were developed by the European Organization for Research and Treatment of Cancer and have been reported to be valid and reliable measures.[21, 22]

The QLQ-C30 is a disease-specific HRQOL rating scale for patients with cancer. It comprises a functioning scale, a symptom scale, and an overall health scale. The functioning scale is further divided into physical functioning, role functioning, cognitive functioning, emotional functioning, and social functioning subscales. The symptom scale includes nausea and vomiting, fatigue, dyspnea, pain, insomnia, appetite loss, constipation, diarrhea, and financial difficulties.

The BN20 is a disease-specific measure of brain tumor symptoms and is divided into future uncertainty, visual disorder, motor dysfunction, communication deficit, headache, seizure, drowsiness, hair loss, itchy skin, weakness of legs, and loss of bladder control. We calculated the scores for each of the QLQ-C30 and BN20 subscales using a scale from 0 to 100, in accordance with the description in the Scoring Manual.

Rehabilitation programs

Rehabilitation was started within 3 days of admission or 5 days after surgery. PT, OT, and ST were provided 5 days per week. In principle, therapy sessions ranged from 20 minutes to 1 hour per day.

The PT and OT programs began with joint range of motion, muscle strengthening, and sitting exercises in bed. The PT program then introduced gait exercises, followed by a focus on applied movement exercises (*e.g.*, stair ascent and descent exercises). Upper-limb motor function, self-care, and household chores were practiced during OT. Exercises for cognitive dysfunction such as aphasia, attention, and naming were practiced during ST. The frequency of intervention and the program content were adapted to each patient's condition when early mobilization or active rehabilitation was difficult because of side effects from radiotherapy or chemotherapy.

Statistical analysis

The normality of the continuous variables used in the present analyses was checked using the Shapiro-Wilk Test, and all were non-normally distributed. Therefore, Kruskal-Wallis or χ^2 tests were used to compare patient characteristics by brain tumor type. Patients' HRQOL

and FIM at the beginning and end of rehabilitation treatment were compared using Wilcoxon signed-rank tests. Sub-analyses were performed using Wilcoxon signed-rank tests for within-group comparisons in each brain tumor category and Kruskal-Wallis tests for comparisons between brain tumor categories. Finally, multiple regression analysis was performed with EQ-5D-5L gain as the dependent variable and age, sex, pre-admission KPS, brain tumor type, presence of recurrence, length of hospital stay, and baseline EQ-5D-5L index score as independent variables. The forced entry method was used in this analysis to visually intercompare all independent variables. Categorical data were transformed into dummy variables. For brain tumor type, WHO grade 1 was used as the reference category based on a previous study.[15] P-P plots, Shapiro-Wilk tests, and Durbin-Watson ratios were used for residual analysis of multiple regression equations. SPSS for Windows version 27 was used for the statistical analyses, and the significance level was set at $P<0.05$ (two-sided). In the Wilcoxon signed-rank tests, the effect size (ES) was calculated using the point-biserial correlation coefficient, with $r \geq 0.1$ considered to indicate a small ES, $r \geq 0.3$ a medium ES, and $r \geq 0.5$ a large ES.

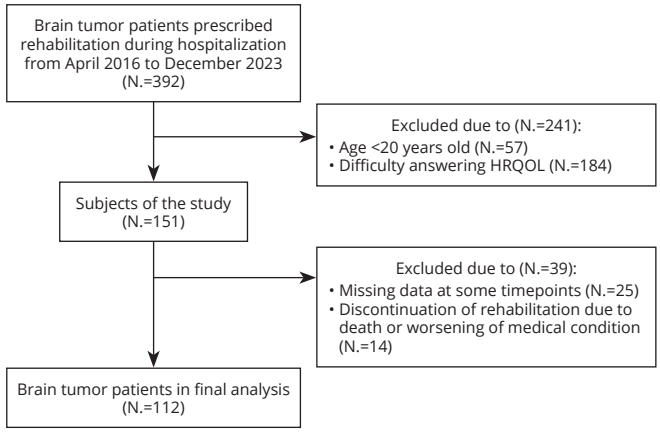

Figure 1.—Flow diagram for the study.

TABLE I.—*Patient's clinical and tumor characteristics.*

	All patients N.=112	WHO grade 1 N.=29	WHO grade 2/3 N.=15	WHO grade 4 N.=40	PCNSL N.=15	MBT N.=13	P value
Gender, N. (%)							0.003
Male	59 (53)	7 (24)	8 (53)	28 (70)	7 (47)	9 (69)	
Female	53 (47)	22 (76)	7 (47)	12 (30)	8 (53)	4 (31)	
Age, years	62 (50 - 69)	64 (54-71)	48 (41-65)	59 (51-68)	65 (57-74)	66 (55-71)	0.070
Pre-admission KPS, N. (%)							0.522
≥80	89 (79)	26 (90)	12 (80)	29 (73)	12 (80)	10 (77)	
<80	23 (21)	3 (10)	3 (20)	11 (27)	3 (20)	3 (23)	
Tumor histology or primary tumor location, N.		Meningioma 15 Schwannoma 10 Hemangioblastoma 2 Craniopharyngioma 1 Pituitary adenoma 1	Oligodendroglioma 6 Astrocytoma 4 Atypical meningioma 2 Pleomorphic xanthoastrocytoma 2 Ependymoma 1	Glioblastoma 33 Astrocytoma, IDH-wildtype 2 Diffuse midline glioma 1 High-grade glioma, NOS 4		Lung cancer 7 Gynecologic cancer 3 Breast cancer 1 Prostate cancer 1 Renal cell carcinoma 1	
Tumor location, N. (%)							<0.001
Right	36 (32)	0 (0)	8 (53)	18 (45)	7 (47)	3 (23)	
Left	27 (24)	0 (0)	6 (40)	15 (37)	2 (13)	4 (31)	
Brain stem/midline	3 (3)	0 (0)	0 (0)	3 (7)	0 (0)	0 (0)	
Cerebellum	11 (10)	2 (7)	0 (0)	2 (5)	3 (20)	4 (31)	
Both/multiple tumors	8 (7)	0 (0)	1 (7)	2 (5)	3 (20)	2 (15)	
Extra-axial tumor	27 (24)	27 (93)	0 (0)	0 (0)	0 (0)	0 (0)	
Treatment, N. (%)							<0.001
Surgical operation	83 (74)	29 (100)	13 (87)	28 (70)	2 (13)	11 (85)	<0.001
Radiation	58 (52)	0 (0)	7 (47)	35 (88)	5 (33)	11 (85)	<0.001
Chemotherapy	56 (50)	0 (0)	8 (53)	36 (90)	12 (80)	0 (0)	
Recurrence, N. (%)	27 (24)	4 (14)	10 (67)	10 (25)	2 (13)	1 (8)	0.001
Lengths of hospital stay, days	51 (23-70)	21 (18-30)	43 (18-72)	67 (52-70)	98 (51-114)	39 (27-57)	<0.001
Discharge disposition, N. (%)							0.799
Discharged home	93 (83)	24 (83)	14 (93)	32 (80)	13 (87)	10 (77)	
Transfer to a different hospital	19 (17)	5 (17)	1 (7)	8 (20)	2 (13)	3 (23)	

Values are median (IQR).
PCNSL: primary central nervous system lymphoma; MBT: metastatic brain tumor; KPS: Karnofsky Performance Status; NOS: not otherwise specified.

Results

Patient characteristics

The flow of this study is shown in Figure 1. The demographics of the included patients are shown in Table I. In total, 112 patients were included in this study. The median age was 62 years, 53% were male, 76% were first-onset, and 83% were discharged home. Patients were classified into five groups by brain tumor category: WHO grade 1 (N.=29), WHO grade 2/3 (N.=15), WHO grade 4 (N.=40), PCNSL (N.=15), and MBT (N.=13). There were no significant differences in age, pre-admission KPS, or home discharge rate among the five groups. However, there were differences in sex, brain tumor location, treatment, recurrence, and length of hospital stay between the groups. Total FIM scores improved significantly from 99.0 (79-115) at baseline to 120.0 (109-125) at the end of rehabilitation (P<0.001, r=0.74); mFIM and cFIM also showed significant improvements (P<0.001, r≥0.3) (Table II).

Comparison of HRQOL before and after rehabilitation treatment

The changes in HRQOL for all patients are shown in Table II. The EQ-5D-5L index score was 0.698 (0.540-0.795) at baseline and 0.772 (0.653-0.844) at the end of rehabilitation, showing significant improvement (P<0.001, r=0.46). The disease-specific measures showed significant improvements (*i.e.*, fewer appeals) in QLQ-C30 scores for physical functioning, role functioning, emotional functioning, global health status, fatigue, pain, and insomnia. The BN20 scores showed significant reductions (*i.e.*, fewer appeals) in future uncertainty, visual disorder, motor dysfunction, com-

TABLE II.—*Changes in HRQOL and FIM before and after rehabilitation treatment.*

	Baseline	Discharge	Change	P value	ES (r)
EQ-5D-5L index score	0.698 (0.540-0.795)	0.772 (0.653-0.844)	0.086 (-0.01-0.185)	< 0.001*	0.46**
Total FIM	99.0 (79-115)	120.0 (109-125)	12.0 (1-33)	<0.001*	0.74**
mFIM	65.5 (48-82)	87.5 (76-91)	10.5 (1-32)	<0.001*	0.74**
cFIM	34.0 (29-35)	35.0 (31-35)	0.0 (0-1)	<0.001*	0.37**
QLQ-C30 functional domains [a]					
Physical functioning	66.7 (47-87)	80.0 (67-87)	6.7 (0-27)	<0.001*	0.37**
Role functioning	66.7 (33-67)	66.7 (37-83)	0.0 (0-33)	0.007*	0.26
Cognitive functioning	66.7 (67-83)	83.3 (67-96)	0.0 (-17-17)	0.692	0.04
Emotional functioning	75.0 (67-92)	83.3 (67-92)	8.3 (-8-17)	0.024*	0.21
Social functioning	66.7 (50-83)	66.7 (50-100)	0.0 (0-17)	0.074	0.17
Global Health Status	50.0 (33-67)	58.3 (42-83)	8.3 (0-31)	0.001*	0.33**
QLQ-C30 symptom domains [a]					
Nausea and vomiting	0.0 (0-17)	0.0 (0-0)	0.0 (0-0)	0.067	0.17
Fatigue	33.3 (22-56)	33.3 (22-44)	0.0 (-19-11)	0.031*	0.20
Dyspnea	0.0 (0-33)	0.0 (0-33)	0.0 (0-0)	0.531	0.06
Pain	33.3 (0-33)	16.7 (0-33)	0.0 (-33-0)	<0.001*	0.37**
Insomnia	33.3 (0-67)	33.3 (0-33)	0.0 (-33-0)	0.003*	0.28
Appetite loss	0.0 (0-33)	0.0 (0-33)	0.0 (-25-0)	0.251	0.11
Constipation	33.3 (0-67)	33.3 (0-33)	0.0 (-33-0)	0.138	0.14
Diarrhea	0.0 (0-0)	0.0 (0-25)	0.0 (0-0)	0.434	0.07
Financial difficulties	33.3 (0-33)	33.3 (0-67)	0.0 (-33-0)	0.840	0.02
BN20 symptom domains [b]					
Future uncertainty	33.3 (17-50)	29.2 (17-42)	0.0 (-17-8)	0.030*	0.21
Visual disorder	0.0 (0-22)	0.0 (0-11)	0.0 (-11-0)	0.046*	0.19
Motor dysfunction	22.2 (11-33)	11.1 (0-33)	0.0 (-19-0)	<0.001*	0.35**
Communication deficit	11.1 (0-33)	11.1 (0-33)	0.0 (-11-0)	0.012*	0.24
Headache	33.3 (0-33)	33.3 (0-33)	0.0 (-33-0)	<0.001*	0.44
Seizure	0.0 (0-0)	0.0 (0-0)	0.0 (0-0)	0.008*	0.25
Drowsiness	33.3 (33-33)	33.3 (0-33)	0.0 (-33-0)	0.056	0.18
Hair loss	0.0 (0-33)	33.3 (0-33)	0.0 (0-33)	0.002*	0.29
Itchy skin	0.0 (0-33)	33.3 (0-33)	0.0 (0-33)	0.002*	0.29
Weakness of legs	33.3 (33-67)	33.3 (33-67)	0.0 (-33-0)	0.107	0.15
Loss of bladder control	0.0 (0-33)	0.0 (0-25)	0.0 (0-0)	0.012*	0.24

Values are median (IQR). *Analysis of the Wilcoxon signed-rank test (P<0.05); **ES(r)≥0.3.
ES: effect size; FIM: functional independence measure; mFIM: motor FIM; cFIM: cognitive FIM.
[a]In EORTC QLQ-C30, functional domains—higher scores are better; symptom domains—lower scores are better; [b]in EORTC BN20 symptom domains, lower scores are better.

TABLE III.— *EQ-5D-5L changes by brain tumor type.*

EQ-5D-5L Index Score	Baseline	Discharge	P value	ES (r)
Tumor type				
WHO grade 1	0.688 (0.541-0.769)	0.780 (0.695-0.875)	<0.001*	0.68**
WHO grade 2/3	0.772 (0.590-0.781)	0.737 (0.665-0.825)	0.972	0.01
WHO grade 4	0.632 (0.391-0.779)	0.699 (0.536-0.839)	0.014*	0.39**
PCNSL	0.736 (0.458-0.825)	0.781 (0.772-0.867)	0.003*	0.78**
MBT	0.780 (0.633-0.845)	0.780 (0.687-0.945)	0.075	0.49**

ES: Effect size, PCNSL: Primary central nervous system lymphoma, MBT: Metastatic brain tumor. Values are median (IQR).
*Analysis of the Wilcoxon Signed-Rank Test (P<0.05), **ES(r)>0.3.

munication deficit, headache, seizure, and loss of bladder control. Significant increases in scores (*i.e.*, increased complaints) were observed in two BN20 items (hair loss and itchy skin). However, only four items had an ES≥0.3: physical functioning (r=0.37), global health status (r=0.33), pain (r=0.37), and motor dysfunction (r=0.35). Table III shows the results of the comparison by brain tumor type. EQ-5D-5L index scores had improved significantly at the end of rehabilitation compared with baseline in the WHO grade 1, WHO grade 4, and PCNSL groups (P<0.05, r ≥ 0.3).

Characteristics of each dimension of EQ-5D-5L and related changes

The percentage of "no problems" (Level 1) responses increased in all dimensions between baseline and the end of rehabilitation treatment. However, more than 50% of patients still had problems with mobility, usual activities, and pain/discomfort dimensions at the time of discharge, with 74% of patients complaining of limitations in usual activities (Figure 2).

Factors affecting EQ-5D-5L gain

There were no significant differences in EQ-5D-5L index scores between the groups from baseline to the end of rehabilitation (Table IV). We performed multiple regression analysis to examine factors affecting EQ-5D-5L gain (Table V). Factors that independently influenced EQ-5D-5L gain were recurrence (B=−0.083, β=−0.191, P=0.037) and baseline EQ-5D-5L index score (B=−0.531, β=−0.595, P<0.001). Brain tumor type was not an influential factor.

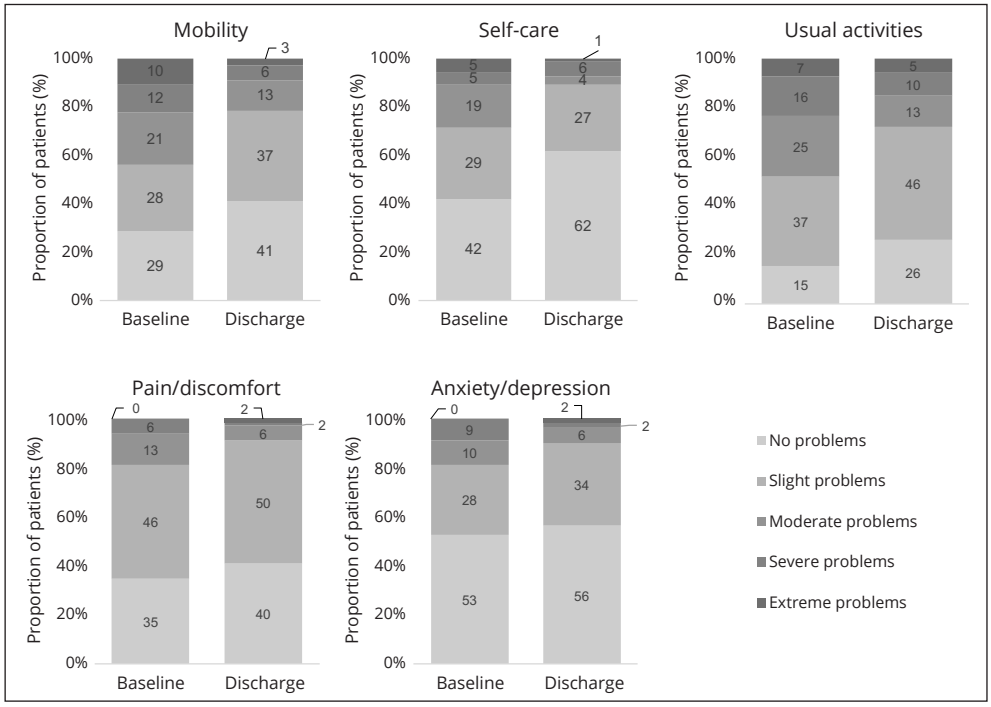

Figure 2.—Change in percentage of Levels in each dimension before and after rehabilitation.

TABLE IV.—*Comparison of EQ-5D-5L changes between brain tumor types.*

EQ-5D-5L Index Score	WHO grade 1	WHO grade 2/3	WHO grade 4	PCNSL	MBT	P value
Baseline	0.688 (0.541-0.769)	0.772 (0.590-0.781)	0.632 (0.391-0.779)	0.736 (0.458-0.825)	0.780 (0.633-0.845)	0.283
Discharge	0.780 (0.695-0.875)	0.737 (0.665-0.825)	0.699 (0.536-0.839)	0.781 (0.772-0.867)	0.780 (0.687-0.945)	0.159
Change	0.105 (0.000-0.193)	0.000 (−0.180-0.142)	0.070 (−0.049-0.186)	0.155 (0.022-0.367)	0.108 (−0.09-0.161)	0.158

Values are median (IQR).
PCNSL: primary central nervous system lymphoma; MBT: metastatic brain tumor.

TABLE V.—*Multiple regression analysis with EQ-5D-5L gain as dependent variable.*

	B	β	95% Confidence interval		P value
			Lower	Upper	
Intercept	0.454		0.264	0.644	< 0.001**
Age	-0.001	-0.006	-0.002	0.002	0.943
Gender					
Female (ref)					
Male	0.002	0.006	-0.057	0.062	0.944
Tumor type					
WHO grade 1 (ref)					0.305
WHO grade 2/3	-0.058	-1.07	-0.170	0.054	
WHO grade 4	-0.091	-0.236	-0.184	0.002	0.054
PCNSL	-0.013	-0.024	-0.138	0.111	0.834
MBT	-0.027	-0.047	-0.130	0.075	0.599
Lengths of hospital stay	0.001	0.180	-0.001	0.002	0.100
Recurrence					
No (ref)					
Yes	-0.083	-0.191	-0.160	-0.005	0.037*
Pre-admission KPS					
≥80 (ref)					
<80	-0.042	-0.092	-0.111	0.026	0.225
Baseline EQ-5D-5L index score	-0.531	-0.595	-0.669	-0.392	<0.001**

B: partial regression coefficient; β: standardized regression coefficient; PCNSL: primary central nervous system lymphoma; MBT: metastatic brain tumor; KPS: Karnofsky Performance Status.
Multiple R^2: 0.451, Adjusted R2: 0.396, Durbin-Watson statistic:1.48. **P<0.01, *P<0.05.

In the residual analysis of multiple regression equations, the P-P plot showed a straight line, with P>0.05 for the Shapiro-Wilk Test, and a Durbin-Watson statistic of 1.48.

Discussion

Characteristics of EQ-5D-5L Index Score in patients with brain tumors

Few studies have used the EQ-5D-5L in patients with brain tumors.[15, 23-26] This is the first study to investigate the EQ-5D-5L index score before and after rehabilitation treatment. The EQ-5D-5L index score for MBT was previously reported as 0.79,[26] which was consistent with the median value at the end of rehabilitation for MBT tumors in this study (0.780). However, simple comparisons could not be made because the purpose of the survey and the timing of the evaluation differed across studies and the EQ-5D-5L index score is calculated using a conversion table unique to each country. The mean EQ-5D-5L index score for the general population in Japan was reported as 0.936 for those in their 50s and 0.911 for those in their 60s,[27] 0.827 for outpatients with cancer,[28] and 0.52 for patients with stroke with similar functional impairment.[29] The median EQ-5D-5L index score at the end of rehabilitation for patients with brain tumors in this study was 0.772 (0.653-0.844). However, caution is needed in interpreting these results because of differences in assessment timing, patient age, and disease effects. These results suggest that the EQ-5D-5L index scores for patients in this study may be lower than those for the general population and other patients with cancer,[27, 28] but higher than those of patients with stroke showing similar symptoms.[29]

HRQOL characteristics by brain tumor type

A study that focused on HRQOL by brain tumor type reported that the EQ-5D-3L index score for high-grade glio-

ma (HGG) was 0.64 and that for low-grade glioma (LGG) was 0.79, showing a significant difference.[30] However, another study reported the EQ-5D-3L index score was 0.79 for grade 4 gliomas and 0.82 for grade 2/3 gliomas, with no significant difference between the two groups.[31] Another study used disease-specific measures (QLQ-C30 and BN20) to investigate HRQOL in patients with HGG, LGG, and benign tumors before the start of postoperative chemotherapy.[19] That study found the overall health of the HGG group was significantly lower than that of the LGG group.[19] It has also been reported that QLQ-C30 and BN20 scores for primary brain tumors and MBT were similar.[32] Therefore, the results may differ depending on the rating scale used and the brain tumor type being compared. We found that glioblastoma and recurrent cases were factors affecting the EQ-5D-5L Index Score at the end of rehabilitation.[15] In this study, the EQ-5D-5L index score for the grade 4 group was 0.699, which was lower than that for the other brain tumor types. However, the Kruskal-Wallis Test showed no difference between groups by brain tumor type. This may be because the patients analyzed in this study differed from those in previous studies, and the influence of other factors such as age, sex, and recurrence, was not fully examined.

Comparative results of HRQOL before and after rehabilitation treatment

Previous reports examining HRQOL before and after inpatient rehabilitation treatment reported improvements in FACT-Br[11] and some QLQ-C30 and BN20 items.[13] In the present study, we observed significant improvement in QLQ-C30 and some BN20 items at the end of rehabilitation treatment compared with baseline. The EQ-5D-5L index score also showed significant improvement. These results supported the possibility that inpatient rehabilitation treatment contributes to improved HRQOL, as noted in previous studies. Furthermore, we found that each EQ-5D-5L dimension showed a trend toward improvement at the end of rehabilitation treatment. In particular, 69% of patients indicated they had "no problems" in self-care at the end of rehabilitation, although 74% reported some limitations in their usual activities after rehabilitation treatment. However, this item covered work, study, and leisure activities, and it is possible that patients may not perceive improvement in these aspects during their hospitalization period. In addition, it is necessary to consider how the studied patient population tends to respond to such questionnaires. For example, Japanese patients tend to prefer ambiguous answers (*e.g.*, "slight problems") rather than absolute answers (*e.g.*, "no problems").[33] It may be that hesitation to give an absolute answer may have reduced the "no problems" response rate. Furthermore, the EQ-5D-5L item covering usual activities is likely to reflect the influence of specific activities that respondents engage in during their daily lives, and differences have also been noted depending on their disease.[34] In addition to experiencing motor paralysis and high levels of brain dysfunction, patients with brain tumors may require further treatment after hospital discharge, which may affect their usual activities. This could be a characteristic of HRQOL among this patient group. Interestingly, a similar QLQ-C30 item (social functioning) did not show any significant change. This suggested that rehabilitation therapy focused on usual activities may contribute to further improvement of HRQOL among patients with brain tumors. However, it has been noted that the EQ-5D-5L does not reflect specific clinical symptoms such as language function.[35] As the answers to the EQ-5D-5L questions are simple, we believe that this instrument offers a useful index for determining the effectiveness of rehabilitation treatment if the purpose is to measure comprehensive HRQOL.

We found that QLQ-C30 and BN20 scores showed statistically significant differences in several items at the end of rehabilitation treatment compared with baseline, but the ES was <0.3 for many items. In addition, ceiling and floor effects were observed for some items. Some QLQ-C30 and BN20 items consist of multiple questions, whereas others contain a single question. Therefore, each item is scored from 0 to 100 points, but the interval between the scores varies. In this study, there was an increase in complaints of hair loss and itchy skin items at the end of rehabilitation treatment compared with baseline. This may be attributable to the side effects of radiotherapy and chemotherapy. In other words, some QLQ-C30 and BN20 items may not easily reflect the effects of rehabilitation treatment. However, in the present study, items such as physical functioning, role functioning, motor dysfunction, and fatigue were improved, which may reflect the effect of rehabilitation treatment. Furthermore, although some symptoms are not directly related to rehabilitation treatment, they are still important for understanding a patient's general condition. Therefore, we believe that further investigation and analysis of the interpretation of QLQ-C30 and BN20 scores are needed.

Brain tumor treatment is multidisciplinary, and rehabilitation is an important part of treatment. In this study design, the improvement in HRQOL cannot be attributed to the effect of rehabilitation treatment alone, and this is con-

sidered a limitation of this study. However, as in previous reports,[7] this study also found improvements in ADL before and after rehabilitation treatment, and improvements were also seen in the HRQOL items related to this. From these results, we believe that it is suggested that rehabilitation therapy may be effective in improving the HRQOL of brain tumor patients.

Factors affecting EQ-5D-5L gain

To date, few reports have focused on the amount of change in HRQOL before and after rehabilitation therapy, and none have used the EQ-5D-5L Index Score. In this study, we focused on the EQ-5D-5L gain and examined influencing factors, including differences by brain tumor type. Multiple regression analysis with EQ-5D-5L gain as the dependent variable showed brain tumor type had no effect. This suggested that rehabilitation therapy may contribute to improved HRQOL among patients with brain tumors irrespective of brain tumor type. The baseline EQ-5D-5L gain was also an influential factor, which can be interpreted as indicating a ceiling effect of the EQ-5D-5L. Alternatively, it may indicate that a certain number of patients experienced a decline in HRQOL during rehabilitation treatment. We found that recurrent disease negatively affected EQ-5D-5L gain. In addition to functional decline over time and sequelae from the initial disease, recurrent cases are expected to experience new neurological symptoms because of the increase in tumor size caused by the recurrence.[36] Furthermore, patients with high-grade brain tumors may have poor life and functional outcomes because of limited treatment options at the time of recurrence.

Brain tumor recurrence has been reported to affect the association between EQ-5D-5L index score and total FIM score at the end of rehabilitation treatment, as well as psychological aspects of HRQOL.[15] Moreover, some reports indicated that the decline in physical function associated with recurrence leads to a decline in HRQOL. These results indicated that episodes of recurrence may hinder recovery of HRQOL in patients with brain tumors.[37] Therefore, support that more rigorously predicts improvement in HRQOL is needed for rehabilitation treatment for patients with recurrent brain tumors. Unfortunately, this study could not address the specific mechanisms by which recurrence affected HRQOL, and further detailed studies are needed.

Limitations of the study

The present study had several limitations. First, this study was conducted at a single institution, and patients with poor general health, cognitive decline, and aphasia were excluded. Therefore, the results do not reflect the entire population of patients with brain tumors who received rehabilitation therapy.

Second, the number of patients with brain tumors included in this study was relatively small, and the number of patients in each brain tumor type varied. Furthermore, various factors such as history of epilepsy and cognitive function,[38] tumor location and size,[39] and motor function[40] have previously been reported to affect HRQOL in patients with brain tumors. Moreover, the HRQOL of patients with MBT may also be affected by the time to resection and the number of brain metastases.[41] We were unable to examine these factors in this study. In addition, different brain tumor types require different treatments, and factors affecting HRQOL may differ by brain tumor type. We examined the possibility that tumor location and treatment method may affect HRQOL, but it was strongly associated with brain tumor type, and we were unable to construct an appropriate multiple regression model in this study. This is thought to be a characteristic of brain tumors and is thought to be a limitation of research targeting patients with brain tumors. On the other hand, by increasing the number of subjects and analyzing by brain tumor type, it is thought that the impact of the location of the brain tumor and the treatment method may become clear, and we recognize this as a future research topic.

Finally, late symptoms and recurrence due to radiotherapy and chemotherapy may have affected patients' HRQOL after discharge, which highlights that numerous factors are predicted to influence HRQOL in patients with brain tumors. However, we believe that these aspects are general limitations of analyses of diseases with a variety of conditions and symptoms and are not unique to this study. We note that it is necessary to analyze HRQOL by brain tumor type to examine the characteristics of HRQOL in patients with brain tumors in more detail. In addition, brain tumors are rare diseases, and there is a need to examine a larger number of cases in multicenter studies.

Conclusions

This study revealed that the EQ-5D-5L index score improved at the end of rehabilitation therapy during hospitalization for patients with brain tumors compared with at the beginning of rehabilitation. Furthermore, the EQ-5D-5L gain was not affected by brain tumor type. This indicates that rehabilitation therapy may improve HRQOL irrespective of patients' brain tumor type. However, patients with

brain tumors may still feel limited in their level of participation after rehabilitation treatment. Furthermore, recurrence may affect the improvement of HRQOL through rehabilitation.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.

2. [No authors listed]. Brain Tumor Registry of Japan. Neurol Med Chir (Tokyo) 2005-2008;2017:9–102.

3. Dirven L, Vos ME, Walbert T, Armstrong TS, Arons D, van den Bent MJ, *et al.* Systematic review on the use of patient-reported outcome measures in brain tumor studies: part of the Response Assessment in Neuro-Oncology Patient-Reported Outcome (RANO-PRO) initiative. Neurooncol Pract 2021;8:417–25.

4. Zhu JJ, Demireva P, Kanner AA, Pannullo S, Mehdorn M, Avgeropoulos N, *et al.*; Zvi Ram on behalf of the EF-14 Trial Investigators. Health-related quality of life, cognitive screening, and functional status in a randomized phase III trial (EF-14) of tumor treating fields with temozolomide compared to temozolomide alone in newly diagnosed glioblastoma. J Neurooncol 2017;135:545–52.

5. Coomans M, Dirven L, K Aaronson N, Baumert BG, van den Bent M, Bottomley A, *et al.*; EORTC Quality of Life Group and the EORTC Brain Tumor Group. The added value of health-related quality of life as a prognostic indicator of overall survival and progression-free survival in glioma patients: a meta-analysis based on individual patient data from randomised controlled trials. Eur J Cancer 2019;116:190–8.

6. Mukand JA, Blackinton DD, Crincoli MG, Lee JJ, Santos BB. Incidence of neurologic deficits and rehabilitation of patients with brain tumors. Am J Phys Med Rehabil 2001;80:346–50.

7. Pieczyńska A, Pilarska A, Hojan K. Predictors of functional outcomes in adults with brain tumor undergoing rehabilitation treatment: a systematic review. Eur J Phys Rehabil Med 2022;58:666–74.

8. Yu J, Jung Y, Park J, Kim JM, Suh M, Cho KG, *et al.* Intensive Rehabilitation Therapy Following Brain Tumor Surgery: A Pilot Study of Effectiveness and Long-Term Satisfaction. Ann Rehabil Med 2019;43:129–41.

9. Bilgin S, Kose N, Karakaya J, Mut M. Traumatic brain injury shows better functional recovery than brain tumor: a rehabilitative perspective. Eur J Phys Rehabil Med 2014;50:17–23.

10. Hansen A, Rosenbek Minet LK, Søgaard K, Jarden JO. The effect of an interdisciplinary rehabilitation intervention comparing HRQoL, symptom burden and physical function among patients with primary glioma: an RCT study protocol. BMJ Open 2014;4:e005490.

11. Hojan K, Gerreth K. Can Multidisciplinary Inpatient and Outpatient Rehabilitation Provide Sufficient Prevention of Disability in Patients with a Brain Tumor?-A Case-Series Report of Two Programs and A Prospective, Observational Clinical Trial. Int J Environ Res Public Health 2020;17:6488.

12. Huang ME, Wartella JE, Kreutzer JS. Functional outcomes and quality of life in patients with brain tumors: a preliminary report. Arch Phys Med Rehabil 2001;82:1540–6.

13. Hansen A, Pedersen CB, Jarden JO, Beier D, Minet LR, Søgaard K. Effectiveness of Physical Therapy- and Occupational Therapy-Based Rehabilitation in People Who Have Glioma and Are Undergoing Active Anticancer Treatment: Single-Blind, Randomized Controlled Trial. Phys Ther 2020;100:564–74.

14. McCarty S, Eickmeyer SM, Kocherginsky M, Keeshin S, Shahpar S, Semik P, *et al.* Health-Related Quality of Life and Cancer-Related Symptoms During Interdisciplinary Outpatient Rehabilitation for Malignant Brain Tumor. Am J Phys Med Rehabil 2017;96:852–60.

15. Watanabe T, Noto S, Natsumeda M, Kimura S, Tabata S, Ikarashi F, *et al.* Characteristics of health-related quality of life and related factors in patients with brain tumors treated with rehabilitation therapy. J Patient Rep Outcomes 2022;6:94.

16. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK. WHO classification of tumours of the central nervous system, revised 4th ed. WHO classification of tumours series. Lyon: International Agency for Research on Cancer; 2016

17. WHO Classification of Tumours Editorial. World Health Organization Classification of Tumours of the Central Nervous System. Fifth Edition. Lyon: International Agency for Research on Cancer; 2021

18. Tang V, Rathbone M, Park Dorsay J, Jiang S, Harvey D. Rehabilitation in primary and metastatic brain tumours: impact of functional outcomes on survival. J Neurol 2008;255:820–7.

19. Budrukkar A, Jalali R, Dutta D, Sarin R, Devlekar R, Parab S, *et al.* Prospective assessment of quality of life in adult patients with primary brain tumors in routine neurooncology practice. J Neurooncol 2009;95:413–9.

20. Ikeda S, Shiroiwa T, Igarashi A, Noto S, Fukuda A, Saito S, *et al.* Developing a Japanese version of the EQ-5D-5L value set. Hoken Iryou Kagaku 2015;64:47–55. [Japanese]

21. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, *et al.* The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365–76.

22. Taphoorn MJ, Claassens L, Aaronson NK, Coens C, Mauer M, Osoba D, *et al.*; EORTC Quality of Life Group, and Brain Cancer, NCIC and Radiotherapy Groups. An international validation study of the EORTC brain cancer module (EORTC QLQ-BN20) for assessing health-related quality of life and symptoms in brain cancer patients. Eur J Cancer 2010;46:1033–40.

23. Ellen JG, Boele FW, Hellman B, Duprey K, Nayak L, Morris J. Pilot study of smartphone-based health outcome tracking (OurBrainBank) for glioblastoma patients. Neurooncol Pract 2021;8:684–90.

24. Rahman MA, Brekke J, Arnesen V, Hannisdal MH, Navarro AG, Waha A, *et al.* Sequential bortezomib and temozolomide treatment promotes immunological responses in glioblastoma patients with positive clinical outcomes: A phase 1B study. Immun Inflamm Dis 2020;8:342–59.

25. Meunier A, Soare A, Chevrou-Severac H, Myren KJ, Murata T, Longworth L. Indirect and Direct Mapping of the Cancer-Specific EORTC QLQ-C30 onto EQ-5D-5L Utility Scores. Appl Health Econ Health Policy 2022;20:119–31.

26. Bjørnhart B, Hansen KH, Asmussen JT, Jørgensen TL, Herrstedt J, Schytte T. Effect and Tolerability of Immunotherapy in Patients with NSCLC with or without Brain Metastasis. Cancers (Basel) 2022;14:1682.

27. Shiroiwa T, Fukuda T, Ikeda S, Igarashi A, Noto S, Saito S, *et al.* Japanese population norms for preference-based measures: EQ-5D-3L, EQ-5D-5L, and SF-6D. Qual Life Res 2016;25:707–19.

28. Hirose C, Fujii H, Iihara H, Ishihara M, Nawa-Nishigaki M, Kato-Hayashi H, *et al.* Real-world data of the association between quality of life using the EuroQol 5 Dimension 5 Level utility value and adverse events for outpatient cancer chemotherapy. Support Care Cancer 2020;28:5943–52.

29. Izumi R, Noto S, Ikeda S, Fukuda T, Shiroiwa T, Igarashi A. Comparison of three utility measures in stroke patients using item response theory analysis. Niigata Journal of Health and Welfare 2013;13:1-12.

30. Jakola AS, Unsgård G, Solheim O. Quality of life in patients with intracranial gliomas: the impact of modern image-guided surgery. J Neurosurg 2011;114:1622–30.

31. Vera E, Acquaye AA, Mendoza TR, Gilbert MR, Armstrong TS. Relationship between symptom burden and health status: analysis of the MDASI-BT and EQ-5D. Neurooncol Pract 2018;5:56–63.

32. Chiu L, Chiu N, Zeng L, Zhang L, Popovic M, Chow R, *et al.* Quality

of life in patients with primary and metastatic brain cancer as reported in the literature using the EORTC QLQ-BN20 and QLQ-C30. Expert Rev Pharmacoecon Outcomes Res 2012;12:831–7.

33. Tasaki K, Shin J. [Japanese response bias: cross-level and cross-national comparisons on response styles]. Shinrigaku Kenkyu 2017;88:32–42.

34. Gamst-Klaussen T, Lamu AN. Does the EQ-5D usual activities dimension measure what it intends to measure? The relative importance of work, study, housework, family or leisure activities. Qual Life Res 2020;29:2553–62.

35. Drewes C, Sagberg LM, Jakola AS, Solheim O. Quality of life in patients with intracranial tumors: does tumor laterality matter? J Neurosurg 2016;125:1400–7.

36. Koh GC, Chen CH, Petrella R, Thind A. Rehabilitation impact indices and their independent predictors: a systematic review. BMJ Open 2013;3:e003483.

37. Boele FW, Douw L, Reijneveld JC, Robben R, Taphoorn MJ, Aaronson NK, *et al.* Health-related quality of life in stable, long-term survivors of low-grade glioma. J Clin Oncol 2015;33:1023–9.

38. Aaronson NK, Taphoorn MJ, Heimans JJ, Postma TJ, Gundy CM, Beute GN, *et al.* Compromised health-related quality of life in patients with low-grade glioma. J Clin Oncol 2011;29:4430–5.

39. Salo J, Niemelä A, Joukamaa M, Koivukangas J. Effect of brain tumour laterality on patients' perceived quality of life. J Neurol Neurosurg Psychiatry 2002;72:373–7.

40. Natsume K, Sakakima H, Kawamura K, Yoshida A, Akihiro S, Yonezawa H, *et al.* Factors Influencing the Improvement of Activities of Daily Living during Inpatient Rehabilitation in Newly Diagnosed Patients with Glioblastoma Multiforme. J Clin Med 2022;11:417.

41. Sheehan JP, Grills I, Chiang VL, Dong H, Berg A, Warnick RE, *et al.* Quality of life outcomes for brain metastasis patients treated with stereotactic radiosurgery: pre-procedural predictive factors from a prospective national registry. J Neurosurg 2018;131:1848–54.

Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions

Takahiro Watanabe, Shinichi Noto and Manabu Natsumeda made substantial contributions to the conception or design of the study; Shinji Kimura, Fumie Ikarashi, Satoshi Tabata, Mayuko Takano, Yoshihiro Tsukamoto, and Makoto Oishi contributed to the acquisition, analysis, and interpretation of the data. All authors participated in drafting the manuscript, and Takahiro Watanabe critically revised the draft. All authors read and approved the final version of the manuscript.

Acknowledgements

We would like to express our sincere gratitude to the patients who cooperated in this study, to the Department of Neurosurgery and Rehabilitation Medicine, and to the therapists at The Niigata University Medical and Dental Hospital. We also thank Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

History

Article first published online: February 17, 2025. - Manuscript accepted: January 17, 2025. - Manuscript revised: October 21, 2024. - Manuscript received: May 1, 2024.