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Health-related quality of life in outpatients with primary central nervous system lymphoma after radiotherapy and high-dose methotrexate chemotherapy

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Abstract. Chemoradiotherapy for primary central nervous system lymphoma (PCNSL) is associated with a considerable risk of long-term neurotoxicity. The present study aimed to assess the health-related quality of life (HRQOL) of outpatients with PCNSL who have received radiotherapy and high-dose methotrexate (HDMTX) chemotherapy, and to determine the factors that cause a decline in HRQOL and interfere with home living. A total of 37 patients were surveyed 0.9-14.2 years after their initial diagnosis and treatment. Each patient completed a multi-part HRQOL questionnaire that was used to examine the associations of HRQOL scores with leukoencephalopathy, Karnofsky performance status (KPS) scores, age, history of recurrence and HDMTX-based chemoradiotherapy. The results demonstrated that the history of recurrence, number of cycles of MTX chemotherapy and age affected the development of leukoencephalopathy. Reductions in KPS score were associated with a history of recurrence (P=0.03), but not with leukoencephalopathy (P=0.8). KPS score, leukoencephalopathy and age were significantly associated with a decline in HRQOL score. A decline in the HRQOL associated with a reduction in KPS score was also observed by multivariate analyses. Deterioration of the HRQOL among outpatients with PCNSL post-chemoradiotherapy was significantly associated with older age (≥66 years) and decreased KPS score. Older patients with a history of recurrence had a higher risk for deteriorated QOL due to development of leukoencephalopathy. Therefore, it is recommended that clinicians monitor the KPS score among outpatients with PCNSL. QOL examination for older patients with a lower KPS score was found to be particularly important for identifying any obstacles for home living.

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Key words: health-related quality of life, outpatients, primary central nervous system lymphoma, Karnofsky performance status score, leukoencephalopathy

Introduction

Whole-brain radiotherapy in combination with high-dose methotrexate (HDMTX)-based chemotherapy has resulted in long-term remissions and improved survival rates in patients with primary central nervous system lymphoma (PCNSL) (1). However, leukoencephalopathy is associated with a risk of neurotoxicity and may severely interfere with cognitive function (2,3). Progressive leukoencephalopathy with cognitive deterioration is associated with a significant decrease in the quality of life (QOL) (4).

Health-related quality of life (HRQOL) has been recognized as an important measure in patients with primary brain tumors (5). Beyond the goal of prolonging survival, the treatment of patients with PCNSL aims to maintain or improve their well-being and HRQOL. HRQOL surveys have the potential to become a relevant method for evaluating the functional impairments resulting from the tumor as well as its treatment, as well as for obtaining information regarding the social and medical requirements of PCNSL patients. Previous studies demonstrated that lifestyle interventions have improved the HRQOL in cancer survivors (6,7). While this type of assessment may be helpful to hospitalized patients, HRQOL surveys may be more important for improving the QOL of outpatients with PCNSL living at home.

The present study focused on determining the factors that contribute to a decline in QOL for outpatients with PCNSL, and elucidated the association of the Karnofsky performance status (KPS) score, leukoencephalopathy, disease recurrence, age and treatment with HRQOL.

This retrospective study was approved by the Institutional Review Board of the National Cancer Center and the Osaka

National Hospital, National Hospital Organization. QOL evaluation was performed using medical interview sheets during routine care at our hospitals. All the patients whose QOL data were included in the study provided prior inclusive informed consent regarding medical research.

Materials and methods

Patients. Between April 2011 and April 2015, 37 patients with a history of PCNSL visited the visited the outpatient clinics of the National Cancer Center Hospital and the Osaka or Tokyo National Hospital, National Hospital Organization. Each patient completed the European Organization for Research and Treatment of Cancer (EORTC) Core 30 Questionnaire (QLQ-C30) and Brain Neoplasm Questionnaire (BN20). These patients were first diagnosed with PCNSL in Japan between December 2000 and November 2013 at the National Cancer Center Hospital (Tokyo, Japan) or at the Osaka National Hospital, National Hospital Organization (Osaka, Japan). The patients received high-dose methotrexate (HDMTX) chemotherapy (3-5 g/m^2), which was repeated every 2 weeks for a maximum of 5 cycles. After chemotherapy, patients received whole-brain radiotherapy. In case of relapse, the patients received 3-5 cycles of rituximab and HDMTX chemotherapy. Detailed information on all the patients is listed in Table I.

Questionnaires and data collection. Prior to data collection, the Institutional Review Board of each participating center approved the study protocol. The EORTC QLQ-C30 is an internationally validated instrument commonly used to assess the QOL in patients with cancer (8), whereas the EORTC QLQ-BN20 is a validated questionnaire for patients with primary brain tumors (9). HRQOL was assessed using the Japanese version of QLQ-C30 (version 3.0) (8) and QLQ-BN20 (9). These questionnaires were previously described by our group (10). We also evaluated KPS. KPS is a clinical score obtained from a numerical scale from 0 to 100 representing a patient's ability to perform daily and working activities, self-care, and the need for assistance (11).

Magnetic resonance imaging (MRI). Each patient underwent MRI every 2-3 months for the first 5 years from the timepoint of the patient's initial treatment, and every 6 months thereafter. The scale reported by Monaco *et al* (12) was used to evaluate white matter changes on MRI at the QOL survey. A grading scale was devised to assess imaging changes using T2 or fluid-attenuated image recovery sequences as follows: Grade 1, little or no white matter hyperintensity; grade 2, limited periventricular hyperintensity; and grade 3, diffuse white matter hyperintensity. Local white matter changes from specific tumors were not included (12).

Statistical analysis. A cross-sectional design was applied and the results were analyzed using JMP software, version 8 (SAS Institute Inc., Cary, NC, USA). The analysis was performed on all 37 cases. $P<0.05$ was considered to indicate statistically significant differences. Multiple regression analysis was performed to evaluate the extent to which age, KPS, leukoencephalopathy and history of recurrence were independent risk factors for HRQOL.

Results

Patient characteristics. A total of 37 outpatients completed the questionnaires. The median age at the time of initial treatment was 63.0 years and the median age at the time of the QOL survey was 65.0 years (Table I). The median interval between initial diagnosis and QOL evaluation was 3.3 years (range, 0.9-14.2 years). Of all the patients, 59.4% had a KPS score of ≥80 at the time of diagnosis and 56.8% had a KPS score of ≥80 at the time of the QOL evaluation. A total of 17 patients (46%) had a higher KPS score at the time of the QOL evaluation compared with that at the time of initial diagnosis. Of the patients with improved KPS scores, 14 (82%) had a KPS score of ≥80 at the time of the QOL survey. Of the patients with improved KPS scores, 5 had a KPS <80 at initial diagnosis and their KPS score improved to ≥80 during the subsequent QOL evaluation. In 13 patients (35%), the KPS scores remained unchanged between the timepoint of diagnosis and their QOL evaluation, whereas 7 patients (19%) exhibited a decline in their KPS score at the timepoint of QOL evaluation compared with that at diagnosis, and all these patients had a KPS score <80 at the time of the QOL survey. A total of 6 patients had a KPS score <80 at the time of the QOL evaluation, while having had a KPS score ≥80 at initial diagnosis. A change in KPS score from diagnosis to QOL survey was associated with a history of recurrence (P=0.03) (Table II). The KPS at the time of the QOL survey was associated with the KPS at diagnosis (P=0.02) and with age at the time of the QOL survey (P=0.007) (Table II). A change in KPS score from diagnosis to the timepoint of the QOL survey was not correlated with leukoencephalopathy. Similarly, KPS at QOL was not correlated with leukoencephalopathy. With regard to leukoencephalopathy, 7 patients had grade 1, 21 had grade 2 and 9 had grade 3 disease at the time of the QOL survey. According to the univariate analysis, patients aged ≥65 years developed significantly more severe white matter changes compared with those aged <65 years (P=0.03) (Table III). Furthermore, patients with a history of recurrence developed more white matter changes compared with those without recurrence (P=0.003) (Table III). Patients treated with ≥8 cycles of MTX chemotherapy developed more white matter changes compared with those treated with <8 cycles (P=0.02) (Table III). However, according to the multivariate analysis, age, history of recurrence and the number of chemotherapy cycles did not affect the white matter changes.

QLQ-C30 and QLQ-BN20 scores compared with KPS scores, leukoencephalopathy and age at the time of QOL survey. As shown in Table IV, various QLQ-C30 functional status scores and symptom scores were significantly associated with the KPS scores at the time of the QOL survey, namely physical functioning (P<0.0001), role functioning (P<0.0001), cognitive functioning (P=0.01), social functioning (P=0.0005) and fatigue (P=0.003). In addition, the following key QLQ-BN20 symptoms were also associated with the KPS score: Visual disorder (P=0.04), motor dysfunction (P=0.03), communication deficit (P=0.0002), drowsiness (P=0.0001), leg weakness (P=0.004) and bladder control (P=0.005).

Various QLQ-C30 functional status scores were significantly associated with leukoencephalopathy (grade 1 vs. grade 2-3), namely physical functioning (P=0.009), role functioning (P=0.03), emotional functioning (P=0.01)

Table I. Characteristics of patients with primary central nervous lymphoma.

Characteristics	Number of patients	Years	Percentage
Gender			
Male	25		67.6
Female	12		32.4
Age at diagnosis (years)			
Median		63	
Range		33-77	
≥60	21		56.8
Age at timepoint of QOL survey (years)			
Median		65	
Range		39-81	
≥60	26		70.3
KPS at diagnosis			
≥80	22		59.5
<80	15		40.5
KPS at timepoint of QOL survey			
≥80	21		56.8
<80	16		43.2
Leukoencephalopathy			
Grade 1	7		18.9
Grade 2	21		56.8
Grade 3	9		24.3
History of recurrence at timepoint of QOL survey			
+	16		43.2
-	21		56.8
Additional chemotherapy at recurrence prior to QOL survey			
+	12		75.0
-	4		25.0
Time since diagnosis at timepoint of QOL survey (months)			
Median		39.3	
Range		11.3-170.0	
≥5 years	10		27.0

QOL, quality of life; KPS, Karnofsky performance status.

and cognitive functioning (P=0.004). Similarly, several symptom scores were associated with leukoencephalopathy (grade 1 vs. grade 2-3): Fatigue (P=0.002), constipation (P=0.03) and financial difficulties (P=0.04). In addition, several key QLQ-BN20 characteristics were also associated with leukoencephalopathy (grade 1 vs. grade 2-3), such as future uncertainty (P=0.04), visual disorder (P=0.04) and leg weakness (P=0.04).

Various QLQ-C30 functional status scores and symptom scores were significantly associated with age at QOL survey (Table IV): Physical functioning (P=0.002), role functioning (P=0.006), cognitive functioning (P=0.002), social functioning (P=0.03) and fatigue (P=0.03). The following key QLQ-BN20 symptoms were also associated with the age at the time of QOL survey: Visual disorder (P=0.02), drowsiness (P=0.001) and leg weakness (P=0.02).

The time from initial diagnosis did not affect the decline in QOL. History of recurrence (P=0.048) and chemotherapy (P=0.049) were only associated with fatigue and no other correlations were observed (Table IV).

Multivariate analysis. The multivariate analysis indicated that KPS scores were predictive of the QOL in terms of physical functioning (P<0.0001), role functioning (P=0.006), social functioning (P=0.009), fatigue (P=0.02), drowsiness (P=0.02) and leg weakness (P=0.02) (Table V). The age at the time of the QOL survey was predictive of the QLQ-C30 symptom scores for drowsiness (P=0.04). Leukoencephalopathy was predictive of the QLQ-C30 symptom scores for fatigue (P=0.008). Unlike age, leukoencephalopathy, history of recurrence and KPS score at the time of the QOL survey were predictive of various QOL-associated EORTC QLQ-C30 and BN20 scores.

Leukoencephalopathy. The multivariate analysis demonstrated that leukoencephalopathy rather than chemotherapy (P=0.3) or KPS score (P=0.8) was correlated with age at the time of the

Table II. Correlation between changes in KPS score, KPS at diagnosis, KPS at QOL survey, age, leukoencephalopathy, history of recurrence and time from the treatment in patient with primary central nervous system lymphoma.

	Change in KPS score from diagnosis to timepoint of QOL survey				KPS at timepoint of QOL survey		
Variables	Improvement	No change	Decline	P-value	<80	≥80	P-value
KPS at diagnosis				0.3			0.02
<80	8	6	1		10	5	
≥80	9	7	6		6	16	
Age at QOL survey (years)				0.3			0.007
<65	10	4	3		3	14	
≥65	7	9	4		13	7	
History of recurrence at QOL survey				0.03			0.05
+	6	4	6		10	6	
-	11	9	1		6	15	
Leukoencephalopathy				0.8			0.1
Grade 1	4	2	1		1	6	
Grade 2-3	13	11	6		15	15	
Time since diagnosis at QOL survey (years)				0.9			0.7
<5	13	9	5		11	16	
≥5	4	4	2		5	5	

QOL, quality of life; KPS, Karnofsky performance status.

Table III. Correlation between leukoencephalopathy and patient age, history of recurrence, chemotherapy and KPS in patients with primary central nervous system lymphoma.

	Leukoencephalopathy			Univariate	Multivariate
	Grade 1	Grade 2	Grade 3	P-value	P-value
Age at QOL survey (years)				0.03	0.09
<65	6	9	2		
≥65	1	12	7		
History of recurrence at QOL survey				0.003	0.07
+	1	7	8		
-	6	14	1		
Chemotherapy prior to QOL survey				0.02	0.3
MTX <8 cycles	7	16	4		
MTX ≥8 cycles	0	5	5		
KPS at QOL survey				0.09	0.8
<80	1	9	6		
≥80	6	12	3		

QOL, quality of life; KPS, Karnofsky performance status; MTX, methotrexate.

QOL survey (P=0.09) and a history of recurrence (P=0.07), but the association was not significant (Table III).

Discussion

The present study suggested that a decline in HRQOL among outpatients with PCNSL is mainly associated with a decline in KPS score, leukoencephalopathy and older age (≥65 years). Leukoencephalopathy was associated with recurrence, additional chemotherapy and older age. A reduction in KPS scores was associated with recurrence in the outpatients.

In previous studies, KPS scores have been generally correlated with overall QOL in patients with brain tumors (11,13-15). KPS is an easy to assess and a reliable measure of functional status in cancer patients (16); however, it does not assess patients' difficulties with performing everyday activities when living at home. Furthermore, older patients tend to have lower KPS scores (14). In the present

Table IV. European Organization for Research and Treatment of Cancer QLQ-C30 and BN20 scores according to time from initial treatment, age, KPS, history of recurrence, chemotherapy and leukoencephalopathy in patients with primary central nervous system lymphoma.

	Time since diagnosis			Age at QOL survey			KPS at QOL survey			History of recurrence			Chemotherapy			Leukoencephalopathy		
Variables	<5 years	≥5 years	P-value (t-test)	<65 years	≥65 years	P-value (t-test)	<80	≥80	P-value (t-test)	+	-	P-value (t-test)	<8 cycles	≥8 cycles	P-value (t-test)	Grade 1	Grade 2-3	P-value
Number of cases	27	10		17	20		16	21		16	21		27	10		7	30	
Gender																		
Male	19	6		13	12		9	16		12	13		16	9		6	19	
Female	8	4		4	8		7	5		4	8		11	1		1	11	
Age at QOL survey, yrs																		
Median	67	58		57	69		69	60		66	63		65	66		59	67.5	
Range	39-81	43-79		39-63	65-81		48-81	39-79		48-81	39-79		39-79	48-81		39-65	48-81	
QLQ C-30 funct.																		
1) Global health	61.1±25.0	67.5±29.8	0.5	68.6±30.3	57.9±21.5	0.2	53.6±25.1	69.8±25.2	0.06	66.7±25.5	59.9±26.8	0.4	61.7±26.6	65.8±25.9	0.7	73.8±31.7	60.3±24.5	0.2
2) Physical funct.	66.2±33.0	71.3±35.4	0.7	85.1±19.4	52.7±35.6	0.002	39.2±31.1	89.2±11.2	<0.0001	56.3±38.6	76.2±26.2	0.07	71.9±32.3	56.0±34.6	0.2	96.2±7.6	60.9±33.4	0.009
3) Role funct.	64.8±34.1	76.7±35.3	0.4	84.3±24.6	54.2±35.8	0.006	44.8±34.8	85.7±21.3	<0.0001	59.4±39.9	74.6±28.7	0.2	71.6±33.6	58.3±36.2	0.3	92.9±18.9	62.2±34.7	0.03
4) Emotional funct.	82.4±19.0	84.2±14.9	0.8	86.3±19.8	80.0±15.9	0.3	82.8±15.7	82.9±19.6	0.98	83.9±13.4	82.1±20.8	0.8	82.7±19.6	83.3±12.4	0.9	97.6±4.1	79.4±18.0	0.01
5) Cognitive funct.	64.8±27.9	83.3±20.8	0.06	84.3±21.6	57.5±25.6	0.002	57.3±30.4	79.4±20.3	0.01	66.7±25.1	72.2±29.0	0.5	69.8±30.3	70.0±17.2	0.98	95.2±8.1	63.9±26.7	0.004
6) Social funct.	68.5±34.1	81.7±26.6	0.3	84.3±23.9	61.7±35.5	0.03	52.1±34.9	87.3±20.3	0.0005	65.6±28.8	77.0±34.8	0.3	74.1±35.3	66.7±23.6	0.5	92.9±13.1	67.2±33.8	0.06
QLQ C-30 symptoms																		
7) Fatigue	35.0±27.9	18.9±20.3	0.1	20.3±22.6	39.4±27.3	0.03	45.1±27.1	19.6±21.1	0.003	32.6±25.8	29.1±28.0	0.7	30.0±29.5	32.2±18.5	0.8	3.2±5.4	37.0±25.7	0.002
8) N/V	3.7±13.3	0.0±0.0	0.4	4.9±16.4	0.8±3.7	0.3	1.0±4.2	4.0±14.8	0.4	5.2±16.9	0.8±3.6	0.3	1.2±4.4	6.7±21.1	0.2	2.4±6.3	2.8±12.4	0.9
9) Pain	11.1±14.6	5.0±11.2	0.2	8.8±15.7	10.0±12.6	0.8	11.5±13.2	7.9±14.5	0.5	7.3±12.1	11.1±15.2	0.4	9.9±14.1	8.3±14.2	0.8	2.4±6.3	11.1±14.7	0.1
10) Dyspnea	11.1±24.5	3.3±10.5	0.3	7.8±14.6	10.0±26.7	0.8	14.6±29.7	4.8±12.0	0.2	10.4±26.4	7.9±18.0	0.7	9.9±24.1	6.7±14.1	0.7	4.8±12.6	10.0±23.4	0.6
11) Insomnia	21.0±29.5	13.3±23.3	0.5	19.6±26.5	18.3±29.6	0.9	20.8±31.9	17.5±25.0	0.7	16.7±24.3	20.6±30.7	0.7	18.5±29.7	20.0±23.3	0.9	4.8±12.6	22.2±29.5	0.1
12) Appetite loss	8.6±14.9	3.3±10.5	0.3	3.9±11.1	10.0±15.7	0.2	10.4±16.0	4.8±12.0	0.2	8.3±14.9	6.3±13.4	0.7	6.2±13.2	10.0±16.1	0.5	0.0±0.0	8.9±15.0	0.1
13) Constipation	21.0±28.0	16.7±23.6	0.7	17.6±26.7	21.7±27.1	0.7	22.9±29.1	17.5±25.0	0.5	18.8±24.2	20.6±28.8	0.8	19.8±28.1	20.0±23.3	0.98	0.0±0.0	24.4±27.6	0.03
14) Diarrhea	3.7±10.7	3.3±10.5	0.9	3.9±11.1	3.3±10.3	0.9	4.2±11.4	3.2±10.0	0.8	4.2±11.4	3.2±10.0	0.8	2.5±8.9	6.7±14.1	0.3	0.0±0.0	4.4±11.5	0.3
15) Financial issues	17.3±23.3	10.0±16.1	0.4	15.7±26.7	15.0±17.0	0.9	20.8±16.7	11.1±24.3	0.2	20.8±16.7	11.1±24.3	0.2	12.3±22.9	23.3±16.1	0.2	0.0±0.0	18.9±22.6	0.04
BN20																		
1) Future uncertainty	25.3±25.1	12.5±14.3	0.1	17.2±22.5	25.8±23.6	0.3	26.6±25.5	18.3±21.2	0.3	24.5±23.1	19.8±23.6	0.6	21.0±23.7	24.2±22.7	0.7	6.0±7.9	25.6±24.1	0.04
2) Visual disorder	16.0±21.4	6.7±9.4	0.2	5.9±16.7	20.0±19.3	0.02	20.8±19.8	7.9±17.3	0.04	12.5±17.2	14.3±21.1	0.8	14.0±19.9	12.2±18.5	0.8	0.0±0.0	16.7±20.2	0.04
3) Motor dysfunction	21.8±22.7	16.7±21.1	0.5	15.7±22.6	24.4±21.5	0.2	29.2±21.4	13.8±20.8	0.03	20.8±24.3	20.1±21.0	0.9	21.8±23.0	16.7±20.5	0.5	9.5±17.5	23.0±22.6	0.2
4) Comm. deficit	28.0±29.3	18.9±22.9	0.4	16.3±22.9	33.3±29.5	0.06	43.8±27.7	11.6±18.4	0.0002	30.6±30.8	21.7±25.2	0.3	21.0±25.1	37.8±31.9	0.1	12.7±25.2	28.5±27.8	0.2
5) Headache	9.9±15.5	16.7±17.6	0.3	11.8±16.4	11.7±16.3	0.99	12.5±16.7	11.1±16.1	0.8	8.3±14.9	14.3±16.9	0.3	12.3±16.4	10.0±16.1	0.7	9.5±16.3	12.2±16.3	0.7
6) Seizure	3.7±10.7	6.7±21.1	0.6	5.9±17.6	3.3±10.3	0.6	6.3±18.1	3.2±10.0	0.5	4.2±11.4	4.8±15.9	0.9	3.7±14.1	6.7±14.1	0.6	9.5±25.2	3.3±10.2	0.3
7) Drowsiness	40.7±26.7	43.3±35.3	0.8	25.5±18.7	55.0±29.2	0.001	60.4±30.4	27.0±17.1	0.0001	52.1±29.7	33.3±25.8	0.048	35.8±27.6	56.7±27.4	0.049	28.6±23.0	44.4±29.5	0.2
8) Itchy skin	21.0±21.0	26.7±21.1	0.5	21.6±20.2	23.3±21.9	0.8	25.0±25.8	20.6±16.6	0.5	16.7±21.1	27.0±20.1	0.1	27.2±20.7	10.0±16.1	0.02	28.6±23.0	21.1±20.5	0.4
9) Hair loss	12.3±22.9	10.0±22.5	0.8	7.8±18.7	15.0±25.3	0.3	14.6±21.0	9.5±23.9	0.5	16.7±27.2	7.9±18.0	0.2	11.1±24.5	13.3±17.2	0.8	23.8±41.8	8.9±15.0	0.1
10) Leg weakness	40.7±32.5	23.3±22.5	0.1	23.5±22.9	46.7±33.2	0.02	52.1±32.1	23.8±23.9	0.004	35.4±33.3	36.5±29.6	0.9	37.0±31.1	33.3±31.4	0.8	14.3±26.2	41.1±29.9	0.04
11) Bladder control	22.2±27.7	26.7±41.0	0.7	17.6±29.1	28.3±32.9	0.3	39.6±37.0	11.1±19.2	0.005	22.9±29.1	23.8±33.6	0.9	24.7±34.1	20.0±23.3	0.7	19.0±37.8	24.4±30.2	0.7

Values are expressed as the mean ± standard deviation. QOL, quality of life; KPS, Karnofsky performance status; funct., functioning; N/V, nausea and vomiting; comm., communication.

Table V. Multivariate and univariate analyses of European Organization for Research and Treatment of Cancer QLQ-C30 and BN20 score in patients with primary central nervous system lymphoma.

		Univariate	Multivariate (multi regression analysis)	
Variables	Associated factors	P-value (t-test)	t	P-value
QLQ C-30 functioning				
2) Physical functioning	Age at QOL survey	0.002	-0.84	0.4
	KPS at QOL survey	<0.0001	5.00	<0.0001
	Leukoencephalopathy	0.009	1.61	0.1
	History of recurrence	0.07	-0.10	0.9
3) Role functioning	Age at QOL survey	0.006	-0.94	0.4
	KPS at QOL survey	<0.0001	2.98	0.006
	Leukoencephalopathy	0.03	1.07	0.3
	History of recurrence	0.2	0.06	0.9
5) Cognitive functioning	Age at QOL survey	0.002	-1.72	0.09
	KPS at QOL survey	0.01	1.28	0.2
	Leukoencephalopathy	0.004	1.99	0.05
	History of recurrence	0.5	0.67	0.5
6) Social functioning	Age at QOL survey	0.03	-0.38	0.7
	KPS at QOL survey	0.0005	2.79	0.009
	Leukoencephalopathy	0.06	1.02	0.3
	History of recurrence	0.3	0.28	0.8
QLQ C-30 symptoms				
7) Fatigue	Age at QOL survey	0.03	0.18	0.9
	KPS at QOL survey	0.003	-2.54	0.02
	Leukoencephalopathy	0.002	-2.84	0.008
	History of recurrence	0.7	-1.35	0.2
BN20				
2) Visual disorder	Age at QOL survey	0.02	0.99	0.3
	KPS at QOL survey	0.04	-1.39	0.2
	Leukoencephalopathy	0.04	-1.57	0.1
	History of recurrence	0.8	-1.41	0.2
7) Drowsiness	Age at QOL survey	0.001	2.12	0.04
	KPS at QOL survey	0.0001	-2.44	0.02
	Leukoencephalopathy	0.2	0.44	0.7
	History of recurrence	0.048	1.14	0.3
10) Leg weakness	Age at QOL survey	0.02	0.70	0.5
	KPS at QOL survey	0.004	-2.40	0.02
	Leukoencephalopathy	0.04	-1.55	0.1
	History of recurrence	0.9	-1.57	0.1

QOL, quality of life; KPS, Karnofsky performance status.

study, the KPS scores of patients aged <65 years were significantly higher compared with those of patients aged ≥65 at the time of the QOL survey. Low KPS score appear to indicative of a deterioration in the QOL of the outpatients with PCNSL. QOL assessment is therefore recommended for older patients with lower KPS scores, as it is crucial to identify any obstacles for home living.

Hoang-Xuan *et al* (17) assessed the efficacy and toxicity of chemotherapy alone in patients with PCNSL aged >60 years. Their aim was to avoid or at least delay radiotherapy. They reported that 12% of patients with PCNSL aged >60 years had decreased KPS scores, 52% had stable scores and 36% exhibited an increase in their score. Treatment-related cognitive decline occurred in 8% of patients and a performance status decline occurred in 12% of the patients; however, in the majority of the patients, cognitive function and performance status were maintained or improved until disease progression (17). In the present study, all the patients had received radiotherapy and HDMTX chemotherapy prior to the QOL survey. In the majority of the patients, the KPS score was maintained (35%) or improved (46%) between the time of diagnosis and QOL evaluation. Of the 21 patients who had no recurrence, 14 had a KPS score of ≥80 at initial diagnosis, and only 1 (7.1%) of the 14 patients exhibited a decrease in the KPS score. Of 16 patients who had recurrence, 8 had a KPS score ≥80 at the time of initial diagnosis and relapsed prior to the QOL survey; 5 of them exhibited a decline in the KPS score. A reduction in KPS scores was correlated with a history of recurrence at the time of the QOL

survey. According to the results of the present study, the QOL of outpatients with a stable KPS score appeared to deteriorate whenever a recurrence occurred. Furthermore, Abray *et al* (18) reported that patients aged >60 years who received radiotherapy were at a significantly higher risk of delayed neurotoxicity (83%) and a reduction of the KPS score. In the present study, KPS scores were associated with age at the time of the QOL survey. KPS score at the time of the QOL survey declined in older patients who survived after chemoradiotherapy.

Omuro *et al* (4) reported that age ≥60 years was a statistically significant risk factor for developing neurotoxicity. Kiewe *et al* (19) evaluated surviving patients without evidence of lymphoma or late neurotoxicity, and reported a positive correlation between radiological and clinical abnormalities. White matter abnormalities on MRI were associated with whole-brain radiotherapy and corresponded with poorer performance in attention/executive function, verbal memory, motor skills and poorer self-perceived QOL (20). By contrast, Fliessbach *et al* (21) reported that neurological symptoms were not associated with leukoencephalopathy. In the present study, leukoencephalopathy was not found to be significantly associated with a reduction in KPS scores, but was significantly asociated with various QLQ-C30 functional status scores. Furthermore, leukoencephalopathy was significantly correlated with older age, a history of recurrence and chemotherapy.

The limitations of the present study included a small sample size of outpatients with stable KPS scores. A decrease in the KPS score was a key indicator for the decline in QOL of the outpatients. QOL assessment in older patients with lower KPS score is crucial for identifying any obstacles for home living.

In conclusion, the present results suggest that a decline in the HRQOL among outpatients with PCNSL is mainly associated with a reduction in KPS scores as well as leukoenchephalopathy and older age (≥65 years). A decline in KPS scores was associated with recurrence in the outpatients. Older patients with a history of recurrence are at the highest risk for a decline in QOL due to development of leukoencephalopathy.

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