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ORIGINAL ARTICLE

The Real-World status and risk factors for a poor prognosis in elderly patients with primary central nervous system malignant lymphomas: a multicenter, retrospective cohort study of the Tohoku Brain Tumor Study Group

Kenichiro Asano[1] · Yoji Yamashita[2] · Takahiro Ono[3] · Manabu Natsumeda[4] · Takaaki Beppu[5] · Kenichiro Matsuda[6] · Masahiro Ichikawa[7] · Masayuki Kanamori[8] · Masashi Matsuzaka[9] · Akira Kurose[10] · Kiyoshi Saito[7] · Yukihiko Sonoda[6] · Kuniaki Ogasawara[5] · Yukihiko Fujii[4] · Hiroaki Shimizu[3] · Hiroki Ohkuma[1] · Chifumi Kitanaka[11] · Takamasa Kayama[12] · Teiji Tominaga[8]

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Abstract

Background Elderly patients with primary central nervous system malignant lymphoma (EL-PCNSL) may not be given sufficient treatment due to their poor pre-treatment Karnofsky Performance Status (KPS) and comorbidities. Therefore, a retrospective, cohort study was performed to evaluate risk factors associated with a poor prognosis of EL-PCNSL in the Tohoku Brain Tumor Study Group.

Methods Patients aged ≥ 71 years with PCNSL were enrolled from eight centers. Univariate analysis was performed with the log-rank test. A Cox proportional hazards model was used for multivariate analysis.

Results Three of the total 142 cases received best supportive care (BSC). Treatment was given to 30 cases without a pathological diagnosis, 3 cases with cerebrospinal fluid (CSF) cytology, and 100 cases with a pathological diagnosis. After confirmation of no differences in progression-free survival (PFS) and overall survival (OS) between the group treated without pathology and the groups diagnosed by pathology or CSF cytology and between median age ≥ 76 years and < 76 years, a total of 133 patients were studied. The median pre-treatment KPS was 50%. Median PFS and median OS were 16 and 24 months, respectively. Risk factors associated with poor prognosis on Cox proportional hazards model analysis were pre-treatment cardiovascular disease and central nervous system disease comorbidities, post-treatment pneumonia and other infections, and the absence of radiotherapy or chemotherapy.

Conclusions Pre-treatment comorbidities and post-treatment complications would affect the prognosis. Radiation and chemotherapy were found to be effective, but no conclusions could be drawn regarding the appropriate content of chemotherapy and whether additional radiotherapy should be used.

Keywords Elderly patient · PCNSL · Risk factor

Introduction

Primary central nervous system malignant lymphoma (PCNSL) is a rare disease, and usually more than half of the patients are over 60 years of age [1]; however, the percentage of PCNSL among all brain tumors has been increasing in recent years. In the Report of the Brain Tumor Registry of Japan, the percentage of all-age PCNSLs among all brain tumors increased from 3.2% in 2004 to 4.5% in 2008. The proportion of PCNSL occurring in patients aged 70 years or older (elderly patients with PCNSL (EL-PCNSL)) has also increased, from 28.1 to 35.9% [2, 3]. However, this applies not only to Japan, but also to other countries [2–4].

The Eastern Cooperative Oncology Group Performance Status (ECOG-PS) and Karnofsky Performance Status (KPS) before treatment are worse in EL-PCNSL than in younger patients, as reported by Zeremiski et al. [5], and more pre-treatment comorbidities have been

✉ Kenichiro Asano
asanoken@hirosaki-u.ac.jp

Extended author information available on the last page of the article

Table 1 Patients' clinical characteristics

Characteristic		Median (IQR), Range, *N*. (%)*
Age (y)		
Median		76 (73–80), 71–92
Sex		
Male		65 (48.9)
Female		68 (51.1)
Time until diagnosis (months)		
Median		1 (1–2), 0.5–12
Pre-treatment KPS (%)		
Median		50 (40–60), 30–90
Tumor location		
Cortical location		
Frontal	89 (66.9)	43 (32.3)
Temporal		19 (14.3)
Parietal		10 (7.5)
Occipital		8 (6.0)
Cerebellum		9 (6.8)
Deep location		
Corpus callosum	44 (33.1)	13 (9.8)
Basal ganglia		8 (6.0)
Thalamus		9 (6.8)
Corona radiata		5 (3.8)
Ventricle		4 (3.0)
Hypothalamus		3 (2.3)
Others		2 (1.5)
Maximum tumor diameter (mm)		
Median		36.3 (25.6–46.7), 3.5–75.3
Multicentric lesion		
No		66 (49.6)
Yes		67 (50.4)
Bilateral and unilateral disease		
Bilateral		20 (15.1)
Right		49 (36.8)
Left		64 (48.1)
Dissemination		
Yes		29 (21.8)
No		104 (78.2)
Pre-treatment comorbidity		
Hypertension		56 (26.3)
Diabetes Mellitus		17 (8.0)
Hyperlipidemia		13 (6.1)
Hyperuricemia		3 (1.4)
Systematic cancer		20 (9.4)
Cardiovascular disease		21 (9.9)
Central nervous system disease		24 (11.3)
Orthopedics disease		15 (7.0)
Gastric ulcer		5 (2.3)
Prostatic hypertrophy		5 (2.3)
Hearing disturbance		4 (1.9)
Respiratory disease		3 (1.4)
Others		27 (12.7)
Chemotherapy		

Table 1 (continued)

Characteristic	Median (IQR), Range, *N*. (%)*
No	36 (27.1)
Yes	97 (72.9)
HD-MTX, the number of cycles**	73 (54.9), 3 (2–3), 1–5
MPV, R-MPV, or R-MPV-A the number of cycles**	19 (14.3), 4 (1–5), 1–5
CHOP, etc., the number of cycles**	5 (3.8), 3 (3–5), 3–5
Radiotherapy	
No	23 (17.3)
Yes	110 (82.7)
LBRT, the total dose (Gy)**	11 (8.3), 30 (24–40),20–56
WBRT, the total dose (Gy)**	47 (35.3), 30 (23.4–30), 20–50.4
WBRT + LBRT, the total dose (Gy)**	52 (39.0), 42 (40–50.3), 34–60
Post-treatment KPS (%)	
Median	60 (40–75), 0–100
Post-treatment complications	
Pneumonia and other infections	28 (33.3)
Gastro-intestinal bleeding	3 (3.6)
DIC	2 (2.4)
Cardiovascular complications	12 (14.3)
Symptomatic epilepsy	1 (1.2)
Postoperative bleeding	2 (2.4)
Renal function damage	11 (13.1)
Others	25 (29.8)
Second-line therapy	
Subtotal	61 (100)
BSC	32 (52,5)
Radiotherapy	8 (13.1)
Radiotherapy + chemotherapy	8 (13.1)
Chemotherapy	13 (21.3)
Outcome	
Alive	39 (29.3)
Dead	76 (57.1)
Impossible to follow-up cases	18 (13.5)

KPS Karnofsky Performance Status, *HD-MTX* High dose methotrexate therapy, *MPV* HD-MTX + Procarbazine + Vincristine therapy, *R-MPV* Rituximab + MPV therapy, *R-MPV-A* R-MPV-AraC therapy, *CHOP* cyclophosphamide + Hydroxydaunorubicin + Vincristine + Prednisolone therapy, *LBRT* Local boost radiation therapy, *WBRT* whole-brain radiation therapy, *DIC* disseminated intravascular coagulation; *BSC* best supportive care

*Values are medians (interquartile range), ranges, or *N* (%)

**Values are *N* (%), medians (interquartile range), and ranges

reported [6]. Therefore, it is expected that EL-PCNSL would show the same tendency in Japan, which may lead to unavoidable best supportive care (BSC), omitted biopsies, and unsatisfactory treatment due to various pre-treatment comorbidities. In addition, EL-PCNSL are rarely included in prospective clinical trials [7, 8] making it difficult to determine their actual treatment status precisely [5, 9].

Therefore, how many patients are actually diagnosed and treated is not known. To answer this question, the incidence, treatment, and final outcome of PCNSL in elderly patients in the Tohoku and Niigata regions in the Tohoku Brain Tumor Study Group were examined to identify factors associated with a poor prognosis, and the Real-World status of PCNSL in elderly patients was examined.

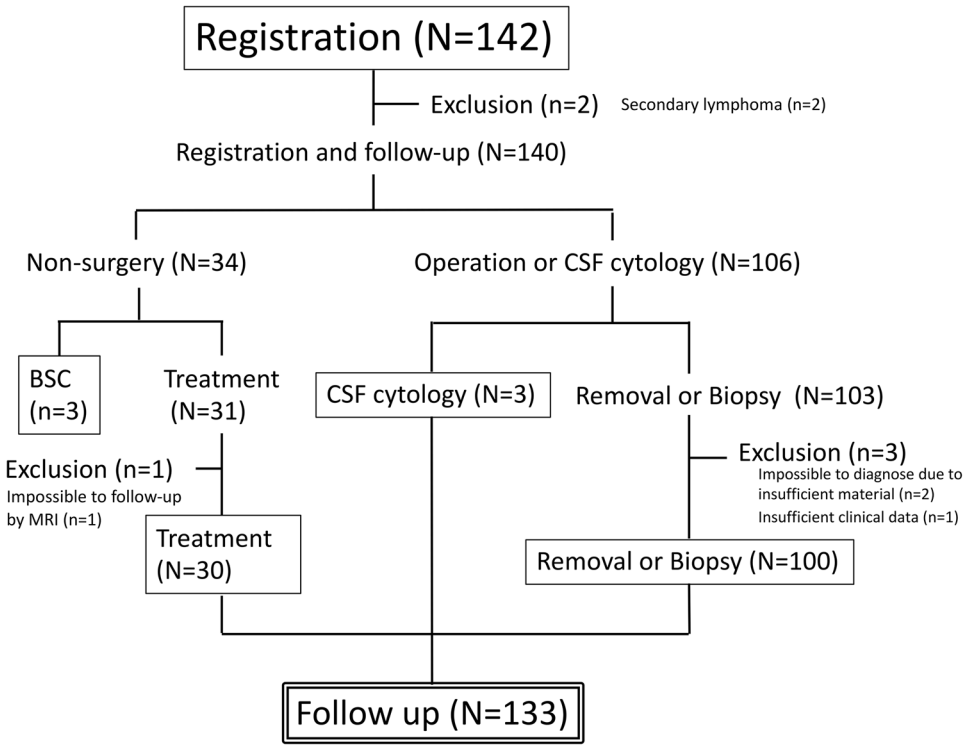


Fig. 1 CONSORT-style flow diagram of the study. The study involved 133 of 142 consecutive elderly patients with primary central nervous system malignant lymphoma in three groups. The first group was three patients in the best supportive care group of treatment without biopsy. The second group included 30 patients in the treatment group without biopsy. The third group included three patients in the cerebrospinal fluid cytology group and 100 patients in the biopsy and central pathological confirmation group

Materials and methods

A Real-World study of all patients with immunocompetent EL-PCNSL aged 71 years or older who were treated or not treated including BSC at 8 centers participating in the Tohoku Brain Tumor Study Group from January 2011 to the end of December 2018 was performed. Cases diagnosed as PCNSL without biopsy or resection, cases treated based on cerebrospinal fluid (CSF) cytology, and cases treated based on biopsy or resection were included. To exclude secondary malignant lymphoma, pre-treatment CT, MRI, perfusion MRI, 8F-fluorodeoxyglucose (FDG) positron emission tomography (PET), blood sampling, and whole-body CT were performed in patients treated with or without biopsy. In patients who were treated without biopsy or resection, the response rate on MRI after treatment, and the overall course of the disease were reviewed to exclude other possible enhancing malignant tumors, and it was confirmed that they did not deviate from the clinical characteristics of lymphoma. Finally, the patients were enrolled at the discretion of the attending physician [10, 11]. Patients who underwent biopsy or resection were diagnosed as having CD-20-positive PCNSL by central pathological diagnosis.

An Excel questionnaire was sent to each institution, and the survey was conducted by linkable anonymizing from each patient's medical record and image server. The survey items included basic patient information, time from initial symptom to diagnosis, pre-treatment KPS, pre-treatment comorbidities, target lesion location, maximum tumor diameter, multiple lesions or no, presence of dissemination on MRI or clinical symptoms, surgery, radiotherapy (RT), dose and technique of RT, presence of chemotherapy and number of cycles, presence of new post-treatment complications, and best MRI response at the end of treatment (within 3 months). KPS at 3 months, progression-free survival (PFS), treatment at recurrence, overall survival (OS), and cause of death were also investigated.

The start date of treatment was defined as the start date of chemotherapy or RT. For patients who could not receive chemotherapy or radiation for various reasons after biopsy or resection, the date of surgery was defined as the date of treatment initiation. PFS was defined as the date of confirmation of tumor growth or until the date of death. OS was defined as the date of final confirmation of survival or until the date of death. The last follow-up was December 31, 2018. Tumor size was determined using the Macdonald Criteria [12], and the response rate was determined according to the International Primary CNS Lymphoma Collaborative Group (IPCNSLCG) [13]. For the determination of the MRI best response rate within 3 months after treatment, the complete response rate (CRR) was defined as CR + CRu/CR + CRu + PR + SD + PD + NA (not determined). Pre-treatment comorbidity was defined as disease under treatment or follow-up at the time of initiation of treatment, and included previous treatment in the case of cancer.

Table 2 Univariate analysis of the no-surgery or biopsy group and the surgery or CSF cytology group

Characteristic	Surgery	Characteristic category	*N*. (%)	Median (IQR), Range	Method of statistical analysis	*p* value
Age (y)	No		30 (22.6)	78 (72.8–81.3), 71–92	Mann–Whitney *U* test	0.85
	Yes		103 (77.4)	75 (73–79), 71–88		
Sex	No	Male	15 (11.3)		Fisher's exact test	1.00
		Female	15 (11.3)			
	Yes	Male	50 (37.6)			
		Female	53 (39.8)			
Time until diagnosis (months)	No		30 (22.6)	1.25 (1–2), 0.5–5	Mann–Whitney *U* test	0.28
	Yes		103 (77.4)	1 (1, 2), 0.5–12		
Pre-treatment KPS (%)	No		30 (22.6)	50 (30–62.5), 30–90	Mann–Whitney *U* test	0.05
	Yes		103 (77.4)	50 (40–60), 30–90		
Tumor location	No	Cortical location*	10 (7.5)		Fisher's exact test	0.001
		Deep location**	20 (15.0)			
	Yes	Cortical location	74 (55.6)			
		Deep location	29 (21.8)			
Maximum tumor diameter (mm)	No		30 (22.6)	30 (21.3–41.4), 11.2–73	Mann–Whitney *U* test	0.015
	Yes		103 (77.4)	38.4 (26.7–49.1), 3.5–75.3		
Multicentric lesion	No	No	12 (9.0)		Fisher's exact test	1.00
		Yes	12 (9.0)			
	Yes	No	54 (40.6)			
		Yes	55 (41.4)			
Bilateral disease	No	No	23 (17.3)		Fisher's exact test	0.16
		Yes	7 (5.3)			
	Yes	No	90 (67.7)			
		Yes	13 (9.8)			
Dissemination	No	No	15 (11.3)		Fisher's exact test	< 0.001
		Yes	15 (11.3)			
	Yes	No	89 (66.9)			
		Yes	14 (10.5)			
Pre-treatment comorbidity	No	No	3 (2.3)		Fisher's exact test	1.00
		Yes	27 (20.3)			
	Yes	No	12 (9.0)			
		Yes	91 (68.4)			
Chemotherapy (CT)	No	No	6 (4.5)		Fisher's exact test	0.36
		Yes	24 (18.0)			
	Yes	No	30 (22,6)			
		Yes	73 (54.9)			
Radiotherapy (RT)	No	No	4 (3.0)		Fisher's exact test	0.60
		Yes	26 (19.5)			
	Yes	No	19 (14.3)			
		Yes	84 (63.2)			
Pattern of treatment combination	No	CT or RT or Nothing	10 (7.5)		Fisher's exact test	0.40
		Combination(CT + RT)	20 (15.0)			
	Yes	CT or RT or Nothing	45 (33.8)			
		Combination(CT + RT)	58 (43.6)			
Complete response rate of CR and CRu after treatment (operation) within 3 months	No	CR + CRu	20 (15.0)		Fisher's exact test	1.00
		PR + SD + PD + NE	10 (7.5)			
	Yes	CR + CRu	67 (50.4)			
		PR + SD + PD + NE	36 (27.1)			

Table 2 (continued)

Characteristic	Surgery	Characteristic category	*N*. (%)	Median (IQR), Range	Method of statistical analysis	*p* value
Post-treatment KPS (%)	No		30 (22.6)	50 (30–82.5), 0–100	Mann–Whitney *U* test	0.26
	Yes		103 (77.4)	60 (50–70), 0–100		
Second-line therapy	Subtotal		61 (45.9)		NA	NA
	No	BSC	8 (13.1)		Fisher's exact test	0.55
		CT or RT or combination	6 (9.8)			
	Yes	BSC	21 (34.4)			
		CT or RT or combination	26 (42.6)			
Outcome	No	Alive	8 (6.0)		Chi-squared test	0.93
		Dead	18 (13.5)			
		Impossible to follow-up	4 (3.0)			
	Yes	Alive	31 (23.3)			
		Dead	58 (43.6)			
		Impossible to follow-up	14 (10.5)			

IQR interquartile range, *NA* not applicable, *BSC* best supportive care, *KPS* Karnofsky Performance Status, *CR* complete response, *CRu* CR/unconfirmed, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluable

*Cortical locations are frontal lobe, temporal lobe, parietal lobe, occipital lobe, and cerebellum

**Deep locations are corpus callosum, basal ganglia, thalamus, corona radiata, ventricle, hypothalamus, and others

In the statistical analysis, Mann–Whitney's *U* test, Fisher's exact test, and the chi-squared test were used for comparisons between groups. For pre-treatment comorbidities and new post-treatment complications, only items with more than 10 comorbidities and complications were subjected to statistical analysis. Univariate analysis was performed by the log-rank test using the Kaplan–Meier method. A Cox proportional hazards model was used for multivariate analysis of risk factors. The entire statistical analysis was performed on a Mac OSX 10.15.7 operating system, using the JMP®14 (SAS Institute, Cary, NC, USA) statistical software.

Results

Patients' background characteristics

A total of 142 patients were enrolled. Of these, two patients were excluded due to secondary central nervous system lymphoma. There were 3 cases of BSC without aggressive treatment based on imaging diagnosis alone. Thirty-one patients were treated with radiation or chemotherapy without surgery. Of these, 1 case was excluded due to difficulty in MRI follow-up, and only 3 cases were treated as PCNSL based on imaging diagnosis, cytological diagnosis by lumbar puncture, and abnormally high levels of IL-2R in CSF. A total of 103 patients underwent surgical removal or biopsy for tissue confirmation, and they were treated at each institution. These specimens were reviewed, but two cases had very little tumor cell component and could not be diagnosed by central pathological review, and one case had no tumor cell component and could not be diagnosed. All of the 100 cases with tissue confirmation were CD-20-positive, diffuse large B cell malignant lymphoma (DLBCL). A total of 133 cases, including 30 cases without tissue confirmation, 3 cases diagnosed by CSF examination, and 100 cases with tissue confirmation, were examined (Table 1 and Fig. 1).

Table 2 shows the results for the no-surgery or biopsy group and the surgery or CSF cytology group. There was no significant difference between the two groups. However, the no-surgery and biopsy group had significantly more patients with a small tumor, CSF seeding, or a deep tumor (corpus callosum, basal ganglia, thalamus, corona radiata, ventricle, hypothalamus, and others). The median (m)PFS of the no-surgery and biopsy group and the surgery or CSF cytology group was 16 months (95% confidence interval (CI), 11–21 months) and 15 months (95% CI 11–21 months), respectively, with no significant difference ($p = 0.79$). The median (m)OS was 27 months (95% CI 12–52 months) and 21 months (95% CI 15–32 months), respectively, with no significant difference ($p = 0.91$) between the two groups (Fig. 2a, b).

Table 3 shows the comparison between the age groups using a cut-off of the median age of 76 years. There was no significant difference in mPFS between patients aged 76 years or older and patients younger than 76 years, except for the significant difference in bilateral disease in patients younger than 76 years; mPFS for patients aged

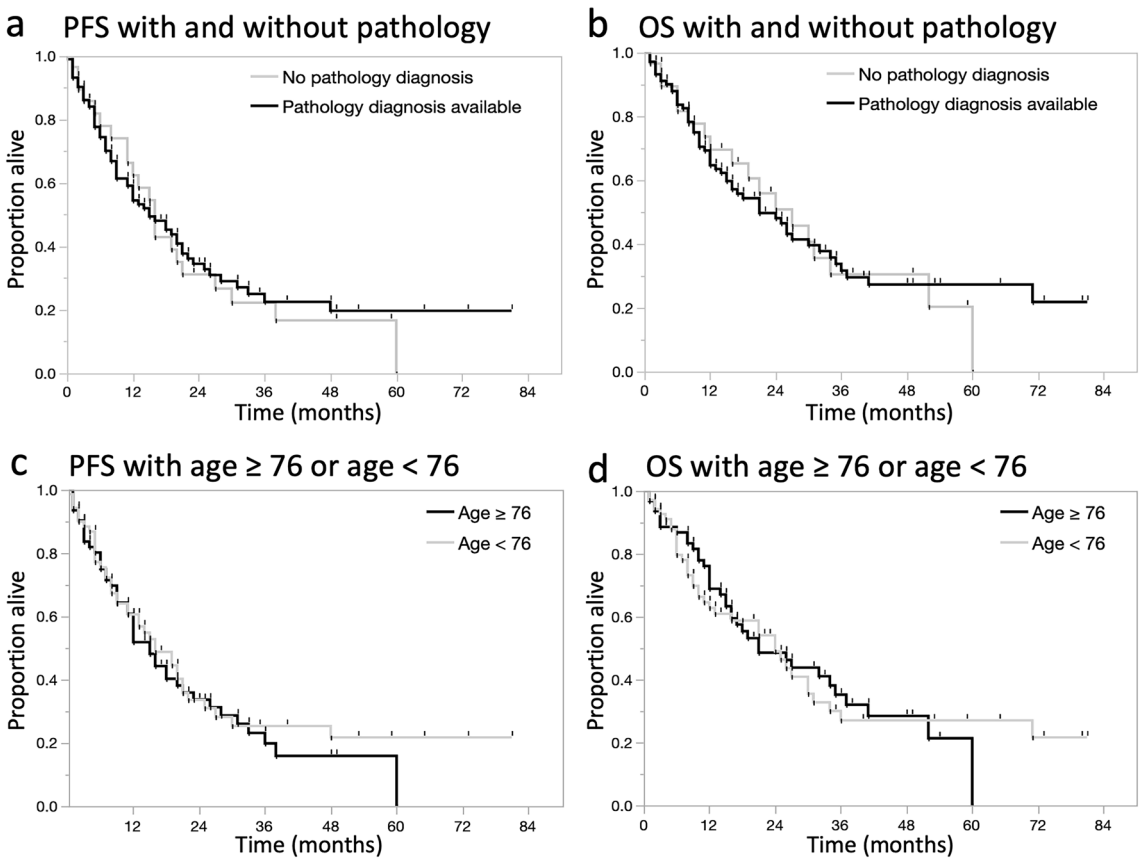


Fig. 2 Kaplan–Meier survival curves of progression-free survival (PFS) and overall survival (OS). **a** Kaplan–Meier survival curves of PFS comparing the no-surgery or biopsy group (gray line) and the surgery or CSF cytology group (black line). The median (m)PFS of the no-surgery and biopsy group and that of the surgery or CSF cytology group are not significantly different ($p=0.79$). **b** Kaplan–Meier survival curves of OS comparing the no-surgery or biopsy group (gray line) and the surgery or CSF cytology group (black line). The mOS of the no-surgery and biopsy group and that of the surgery or CSF cytology group are not significantly different ($p=0.91$). **c** Kaplan–Meier survival curves of PFS comparing the younger than 76 years group (gray line) and the group aged 76 years or older (black line). mPFS of the younger than 76 years group (gray line) and that of the group aged 76 years or older (black line) are not significantly different ($p=0.56$). **d** Kaplan–Meier survival curves of OS comparing the younger than 76 years group (gray line) and the group aged 76 years or older (black line). mOS of the younger than 76 years group (gray line) and that of the group aged 76 years or older (black line) are not significantly different ($p=0.92$)

76 years or older and for those younger than 76 years was 16 months (95% CI 11–21 months) and 15 months (95% CI 11–21 months), respectively, with no significant difference ($p=0.56$); mOS was 24 months (95% CI 12–30 months) and 21 months (95% CI 15–35 months; $p=0.92$), respectively, with no significant difference between the two groups (Fig. 2c, d).

After these investigations, it was determined that there was little variation between the groups and ages, and a total of 133 patients were studied (Fig. 1). The characteristics of the 133 cases (65 males and 68 females; median age 76 years) are shown in Table 4. The pre-treatment KPS ranged from 30 to 90% (median 50%). As initial treatment, 110 patients (82.7%) received RT, and 97 patients (72.9%) received chemotherapy. RT alone was used in 32 patients (24.1%), with high-dose methotrexate (HD-MTX) + RT in 59 patients (44.4%), R-MPV (rituximab, MTX, procarbazine, and vincristine) (including MPV or R-MPV-A (rituximab, MTX, procarbazine, vincristine. and Ara-C)) + RT

Table 3 Univariate analysis by age group

Characteristic	Age (y)	Characteristic category	*N*. (%)	Median (IQR), Range	Method of statistical analysis	*p* value
Age (y)	≥ 76		71 (53.4)	80 (77–83), 76–92	Mann–Whitney *U* test	< 0.001
	< 76		62 (46.6)	73 (72–74), 71–75		
Sex	≥ 76	Male	31 (23.3)		Fisher's exact test	0.86
		Female	31 (23.3)			
	≥ 76	Male	34 (25.6)			
		Female	37 (27.8)			
Time until diagnosis (months)	≥ 76		71 (53.4)	1 (1–2), 0.5–8	Mann–Whitney *U* test	0.42
	< 76		62 (46.6)	1 (0.875, 2), 0.5–12		
Pre-treatment KPS (%)	≥ 76		71 (53.4)	50 (40–60), 30–90	Mann–Whitney *U* test	0.35
	< 76		62 (46.6)	50 (40, 70), 30–90		
Tumor location	≥ 76	Cortical location*	44 (33.1)		Fisher's exact test	0.86
		Deep location**	27 (20.3)			
	< 76	Cortical location	40 (30.0)			
		Deep location	22 (16.5)			
Maximum tumor diameter (mm)	≥ 76		71 (53.4)	32.5 (25–44), 13.6–69.8	Mann–Whitney *U* test	0.13
	< 76		62 (46.6)	40.0 (27–50), 3.5–75.3		
Multicentric lesion	≥ 76	No	41 (30.8)		Fisher's exact test	0.06
		Yes	30 (22.6)			
	< 76	No	25 (18.8)			
		Yes	37 (27.8)			
Bilateral disease	≥ 76	No	65 (48.9)		Fisher's exact test	0.029
		Yes	6 (4.5)			
	< 76	No	48 (36.1)			
		Yes	14 (10.5)			
Dissemination	≥ 76	No	56 (42.1)		Fisher's exact test	1.00
		Yes	15 (11.3)			
	< 76	No	48 (36.1)			
		Yes	14 (10.5)			
Pre-treatment comorbidity	≥ 76	No	43 (32.3)		Fisher's exact test	1.00
		Yes	28 (21.1)			
	< 76	No	37 (27.8)			
		Yes	25 (18.8)			
Chemotherapy (CT)	≥ 76	No	24 (18.0)		Fisher's exact test	0.08
		Yes	47 (35.3)			
	< 76	No	12 (9.0)			
		Yes	50 (37.6)			
Radiotherapy (RT)	≥ 76	No	12 (9.0)		Fisher's exact test	1.00
		Yes	59 (44.4)			
	< 76	No	11 (8.3)			
		Yes	51 (38.3)			
Pattern of treatment combination	≥ 76	CT or RT or Nothing	34 (25.6)		Fisher's exact test	0.12
		Combination(CT + RT)	37 (27.8)			
	< 76	CT or RT or Nothing	21 (15.8)			
		Combination(CT + RT)	41 (30.8)			
Complete response rate of CR and CRu after treatment (operation) within 3 months	≥ 76	CR + CRu	41 (30.8)		Fisher's exact test	0.15
		PR + SD + PD + NE	30 (22.6)			
	< 76	CR + CRu	44 (33.1)			
		PR + SD + PD + NE	18 (13.5)			

Table 3 (continued)

Characteristic	Age (y)	Characteristic category	*N*. (%)	Median (IQR), Range	Method of statistical analysis	*p* value
Post-treatment KPS (%)	≥ 76		71 (53.4)	50 (40–70), 0–100	Mann–Whitney *U* test	0.44
	< 76		62 (46.6)	60 (40–82.5), 0–90		
Second-line therapy	Subtotal		61 (45.9)		NA	NA
	≥ 76	BSC	15 (24.6)		Fisher's exact test	1.00
		CT or RT or combination	13 (21.3)			
	< 76	BSC	17 (27.9)			
		CT or RT or combination	16 (26.2)			
Outcome	≥ 76	Alive	23 (17.3)		Chi-squared test	0.65
		Dead	38 (28.6)			
		Impossible to follow-up	10 (7.5)			
	< 76	Alive	16 (12.0)			
		Dead	38 (28.6)			
		Impossible to follow-up	8 (6.0)			

IQR interquartile range, *NA* not applicable, *BSC* best supportive care, *KPS* Karnofsky Performance Status, *CR* complete response, *CRu* CR/unconfirmed, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluable, *BSC* best supportive care

*Cortical locations are frontal lobe, temporal lobe, parietal lobe, occipital lobe, and cerebellum

**Deep locations are corpus callosum, basal ganglia, thalamus, corona radiata, ventricle, hypothalamus, and others

in 14 patients (10.5%); chemotherapy alone was used in only 14 patients (10.5%), and R-MPV (including MPV or R-MPV-A) was used in four patients (3.6%). In addition, four patients (3.0%) who were dropout cases in the early treatment phase failed to receive treatment in the initial phase (details below).

There were 61 cases of relapse during the follow-up period. Of these, 32 (52.5%) were given BSC as second-line therapy, accounting for about half of the cases. Salvage RT was added in 8 cases (13.1%), salvage RT and chemotherapy were added in 8 cases (13.1%), and salvage chemotherapy alone was added in 13 cases (21.3%). The final outcome at the end of follow-up was survival in 39 patients (29.3%) and death in 76 patients (57.1%), and no outcome information was available in 18 patients (13.5%) (Table 1).

Treatment and response rate

The overall m PFS was 16 months (95% CI 12–20 months) and m OS was 24 months (95% CI 16–30 months), despite the variety of treatments, RT, chemotherapy, and number of cycles. In addition, there was a significant difference in mOS between the 32 patients treated with RT alone and the 59 patients treated with HD-MTX + RT (12 months and 32 months, respectively; $p < 0.001$). A comparison of 32 patients in the RT alone group and 14 patients in the R-MPV + RT (including MPV or R-MPV-A) group also showed a significant difference ($p = 0.036$), although the R-MPV group had not yet reached mOS. There was no significant difference between the HD-MTX + RT treatment group and the R-MPV + RT (or MPV or R-MPV-A) group ($p = 0.79$). R-MPV or R-MPV therapy is a recently introduced therapy, with a maximum follow-up of 48 months.

The best response within the first 3 months of treatment was interpreted as CR in 35 (26.3%), CRu in 52 (39.1%), PR in 40 (30.1%), SD in 0 (0.0%), and PD in 3 (2.3%) cases. Thus, the CRR was 65.4% (87/133 cases) (Table 4 and Fig. 3).

Pre-treatment comorbidities

There were 117 patients (88.0%) with pre-treatment comorbidities and 16 patients (12.0%) with no comorbidities. The total number of comorbidities was 213, or 1.8 comorbidities per patient. The most common pre-treatment comorbidity was hypertension, with 56 cases (26.3%). This was followed by central nervous system diseases such as post-stroke syndrome and dementia, with 24 cases (11.3%). Cardiovascular diseases such as arrhythmia, heart failure, angina pectoris, and myocardial infarction accounted for 21 cases (9.9%), comorbidities of systemic cancer other than brain tumor accounted for 20 cases (9.4%), and diabetes mellitus accounted for 17 cases (8.0%) (Tables 1 and 4).

Surgical complications within 1 month postoperatively and early treatment dropouts within 3 months

There were a total of 10 surgical complications within 1 month after surgery (9.7% of surgical cases). These

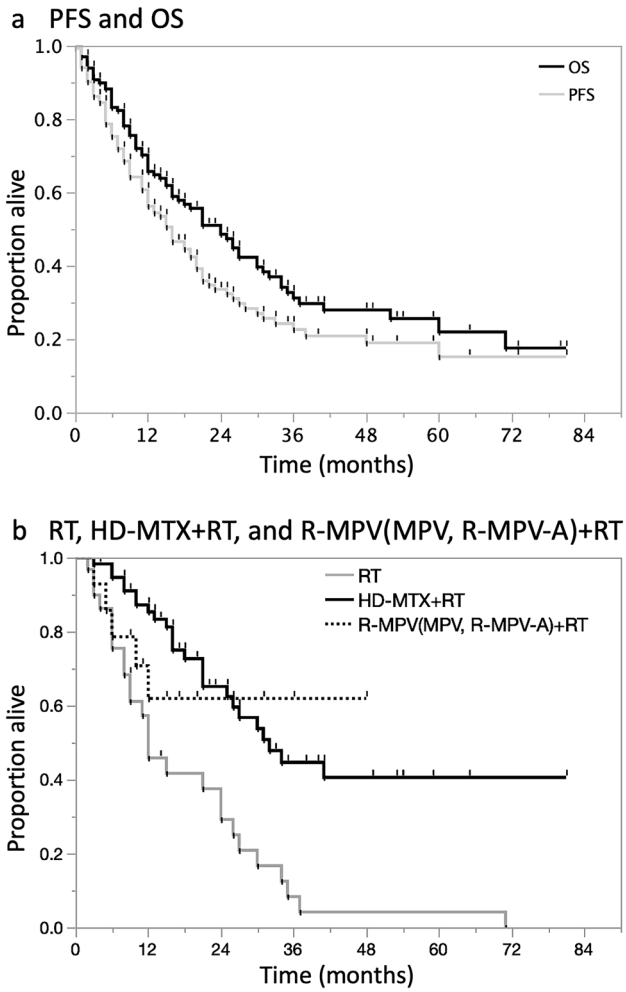


Fig. 3 Kaplan–Meier survival curves of progression-free survival (PFS) and overall survival (OS), and OS according to treatments. **a** PFS (gray line) and OS (black line) as a whole. **b** OS in patients who received radiotherapy (RT) (gray line) alone and high-dose methotrexate (HD-MTX) + RT (black line) ($p < 0.001$). OS in patients who received RT (gray line) alone and R-MPV (or MPV, or R-MPV-A) + RT (gray dot line) ($p = 0.036$). OS in patients who received HD-MTX (black line) + RT and R-MPV (or MPV, or R-MPV-A) + RT (gray dot line) ($p = 0.36$)

included 2 cases of postoperative bleeding, 3 cases of deep vein thrombosis (DVT), 2 cases of pneumonia (1 case of *Pneumocystis carinii* pneumonia), and 1 case each of spontaneous pneumothorax, upper gastrointestinal bleeding, and urinary tract infection. A total of 15 (11.3%) patients dropped out within 3 months after the start of treatment, including those with complications from the above surgery, all of which occurred within 2 months. The breakdown was as follows: four patients died of complications including operation-related complications (26.7%), four patients died of tumors (26.7%), one patient refused treatment (6.7%), and six patients were lost to follow-up due to hospital transfer (40.0%). The breakdown of the four deaths due to complications was: one patient died of *Pneumocystis carinii* pneumonia, one patient died of pulmonary embolism (PE) due to upper gastrointestinal bleeding and deep venous thrombosis (DVT), one patient died of myelosuppression, cholecystitis, and pseudoenteritis, and one patient died of postoperative biopsy hemorrhage.

Post-treatment complications and causes of death

Tables 1 and 4 show the post-treatment complications (complications during the course of treatment), including the above early dropout cases. Fifty-four patients (40.6%) had some complications during the course of treatment, and 79 patients (59.4%) had no complications. The total number of complications was 84 in 54 patients, or a rate of 1.6 per patient. The most common complication was pneumonia and other infections in 28 patients (33.3%), followed by DVT, PE, and cardiac disease in 12 patients (14.3%), and renal dysfunction including delayed MTX excretion in 11 patients (13.1%). There were two cases of postoperative hemorrhage, including the above-mentioned fatal case.

The number of deaths at the last follow-up was 76 (57.1%), of which 38 (50.0%) were apparent tumor deaths, 33 (43.4%) were complication deaths, and 5 (6.6%) were deaths of unknown cause, accounting for about half of the deaths and about one-quarter of the total population. The breakdown of deaths due to complications was pneumonia and other infections in 15 patients (45.5%), accounting for about half of the deaths due to complications.

Risk factors associated with a poor prognosis

Univariate analysis

Significant differences in mPFS and mOS were observed for cardiovascular disease (PFS: + 8 months vs − 18 months, $p = 0.004$; OS: + 11 months vs. 27 months, $p = 0.001$), central nervous system disease (PFS: + 6 months vs − 18 months, $p = 0.033$; OS: + 9 months vs. − 26 months, $p = 0.038$), post-treatment KPS (PFS: < 60 11 months vs ≥ 60 19 months, $p = 0.005$; OS: < 60% 12 months vs. ≥ 60% 34 months, $p < 0.001$), presence of chemotherapy (PFS: + 7 months vs − 19 months, $p < 0.001$; OS: + 30 months vs. − 12 months, $p < 0.001$), presence of radiotherapy (PFS: + 7 months vs − 16 months, $p = 0.029$; OS: + 25 months vs. − 9 months, $p = 0.045$), best response of CRR within 3 months (PFS: CRR 20 months vs non-CRR 9 months, $p = 0.032$; OS: CRR 30 months vs. non-CRR 12 months, $p = 0.013$), post-treatment pneumonia and other infections (PFS: + 11 months vs − 19 months, $p = 0.003$; OS: + 16 months vs. 27 months, $p < 0.001$),

Table 4 Results of univariate analysis of progression-free survival and overall survival using log-rank test

Characteristic	*N*. (%)	Median PFS (95%CI)	*p* value (log-rank test)	Median OS (95%CI)	*p* value (log-rank test)
Age (y)					
≥ 76	71(53.4)	16 (11–21)	0.56	24 (12–30)	0.68
< 76	62(44.6)	15 (11–21)		21 (16–37)	
Sex					
Male	65 (48.9)	19 (12–21)	0.61	21 (15–27)	0.09
Female	68 (51.1)	13 (9–21)		31 (15–41)	
Time until diagnosis (months)					
≥ 1	24 (18.0)	21 (6–28)	0.80	26 (16–32)	0.90
< 1	109 (82.0)	16 (12–20)		21 (11–31)	
Pre-treatment KPS (%)					
≥ 50	86 (64.7)	16 (12–22)	0.50	25 (16–34)	0.54
< 50	47 (35.3)	13 (8–21)		21 (12–31)	
Maximum tumor diameter (mm)					
≥ 36.3	67 (50.4)	15 (12–23)	0.25	24 (15–41)	0.27
< 36.3	66 (49.6)	16 (9–21)		24 (12–30)	
Multicentric lesion					
No	66 (49.6)	19 (11–22)	0.61	25 (16–34)	0.58
Yes	67 (50.4)	14 (9–20)		21 (12–30)	
Dissemination					
Yes	29 (21.8)	13 (11–20)	0.39	17 (11–30)	0.15
No	104 (78.2)	18 (11–21)		26 (16–34)	
Pre-treatment comorbidity*					
Hypertension (+)	56 (42.1)	15 (11–23)	0.41	21 (12–30)	0.27
Hypertension (−)	77 (57.9)	16 (11–21)		26 (16–37)	
Diabetes Mellitus (+)	17 (12.8)	12 (3–31)	0.42	24 (16–30)	0.53
Diabetes Mellitus (−)	116 (87.2)	16 (12–20)		28 (8–37)	
Hyperlipidemia (+)	13 (9.8)	16 (5-.)	0.91	36 (6-.)	0.54
Hyperlipidemia (−)	120 (90.2)	16 (12–20)		24 (16–30)	
Systematic cancer (+)	20 (15.0)	19 (7–28)	0.83	24 (9–71)	0.99
Systematic cancer (−)	113 (85.0)	15 (12–20)		24 (16–31)	
Cardiovascular disease (+)	21 (15.8)	8 (2–13)	0.004	11 (6–16)	0.001
Cardiovascular disease (−)	112 (84.2)	18 (12–21)		27 (21–34)	
Central nervous system disease (+)	24 (18.0)	6 (3–15)	0.033	9 (5-.)	0.038
Central nervous system disease (−)	109 (82.0)	18 (13–21)		26 (19–32)	
Orthopedics disease (+)	15 (11.3)	20 (5–23)	0.93	31 (15–37)	0.71
Orthopedics disease (−)	118 (88.7)	15 (11–19)		21 (15–30)	
Chemotherapy					
No	36 (27.1)	7 (4–13)	< 0.001	12 (8–24)	< 0.001
Yes	97 (72.9)	19 (15–31)		30 (21–52)	
Radiotherapy					
No	23 (17.3)	7 (2–48)	0.029	9 (2–36)	0.045
Yes	110 (82.7)	16 (13–21)		25 (19–31)	
Pattern of treatment combination					
RT only	32 (24.1)	7 (5–14)	< 0.001	12 (8–24))	< 0.001
HD-MTX + RT	59 (44.4)	26 (18–36)		32 (21-.)	
R-MVP(or MPV or R-MPV-A) + RT	14 (10.5)	. (5–.)		. (6–.)	
CHOP + RT	5 (3.8)	–	–	–	–
HD-MTX	14 (10.5)	–	–	–	–

Table 4 (continued)

Characteristic	*N*. (%)	Median PFS (95%CI)	*p* value (log-rank test)	Median OS (95%CI)	*p* value (log-rank test)
R-MPV(or MPV or R-MPV-A)	5 (3.6)	–	–	–	–
Nothing	4 (3.0)	–	–	–	–
Complete response rate of CR and CRu after treatment (operation) within 3 months					
CR	35 (26.3)	20 (15–23)	0.032	30 (19–35)	0.013
CRu	52 (39.1)				
Subtotal (%) 87 (65.4)					
PR	40 (30.1)	9 (6–16)		12 (6–24)	
SD	0 (0.0)				
PD	3 (2.3)				
NE	3 (2.3)				
Subtotal (%) 46 (34.6)					
Post-treatment KPS (%)					
≥ 60	63 (47.4)	19 (16–30)	0.005	34 (21–52)	< 0.001
< 60	70 (52.6)	11 (6–14)		12 (8–21)	
Post-treatment complications*					
Pneumonia and other infections (+)	28 (21.1)	11 (7–15)	0.003	16 (8–21)	< 0.001
Pneumonia and other infections (−)	105 (78.9)	19 (14–23)		27 (21–41)	
Cardiovascular complications (+)	12 (9.0)	8 (3–13)	0.001	12 (3–24)	0.001
Cardiovascular complications (−)	121 (91.0)	16 (12–21)		26 (19–34)	
Renal function damage (+)	11 (8.3)	31 (2–.)	0.98	32 (2–.)	0.41
Renal function damage (−)	122 (91.7)	16 (12–20)		24 (16–30)	

PFS progression-free survival, *OS* overall survival, *KPS* Karnofsky Performance Status, *RT* radiotherapy; *HD-MTX* high-dose methotrexate therapy, *MPV* HD-MTX + procarbazine + vincristine therapy, *R-MPV* Rituximab + MPV therapy, *R-MPV-A* R-MPV-AraC therapy, *CHOP* cyclophosphamide + hydroxydaunorubicin + vincristine + prednisolone therapy, *CR* complete response, *CRu* CR/unconfirmed, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluable

*Picked up more than ten items

and post-treatment DVT, PE, and cardiac complications (PFS: + 8 months vs − 16 months, $p = 0.001$; OS: + 11.5 months vs. 26 months, $p = 0.001$) (Table 4 and Fig. 4).

Cox proportional hazards model

Multivariate analysis was performed using a Cox proportional hazards model for PFS. The results showed that there were significant associations with age (HR 1.993; 95%CI 1.1186–3.358; $p = 0.009$), pre-treatment cardiovascular disease (HR 3.008; 95%CI 1.508–5.803; $p = 0.002$), pre-treatment central nervous system disease (HR 2.686; 95%CI 1.318–5.233; $p = 0.007$), radiotherapy (− / + HR 3.064; 95% CI 1.573–5.965; $p = 0.001$), chemotherapy (− / + HR 4.615; 95% CI 2.563–8.274; $p < 0.001$), best response rate of CRR within 3 months (HR 1.863; 95% CI 1.090–3.137; $p = 0.023$), and post-treatment pneumonia and other infections (HR 2.936; 95% CI 1.586–5.352; $p < 0.001$). Multivariate analysis was performed using a Cox proportional hazards model for OS. The results showed that there were significant associations of OS with pre-treatment cardiovascular disease (HR 3.432; 95% CI 1.612–7.065; $p = 0.002$), pre-treatment central nervous system disease (HR 2.869; 95% CI 1.280–6.126; $p = 0.012$), radiotherapy(− / +) (HR 3.536; 95% CI 1.748–6. 854; $p = 0.001$), chemotherapy(− / +) (HR 3.733; 95%CI 1.994–6.959; $p < 0.001$), and post-treatment pneumonia and other infections (HR 3.505; 95% CI 1.827–6.665; $p < 0.001$); these were all determined to be independent prognostic factors (Table 5).

Discussion

The increase in the number of elderly patients with malignant lymphoma with a high rate of pre-treatment comorbidities and treatment-related complications is a common problem worldwide [6]. In the case of patients

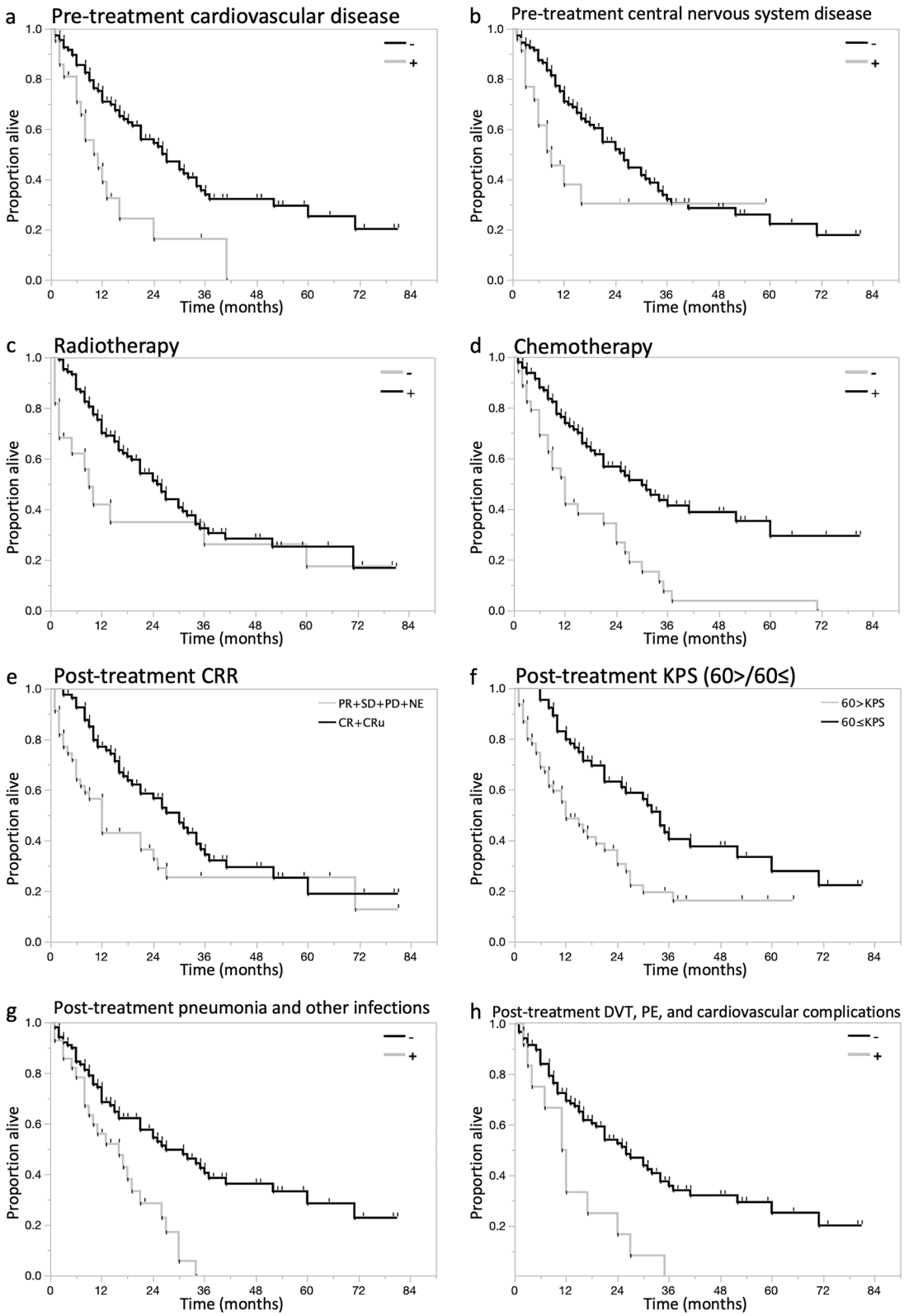
Table 5 Cox proportional hazard model of factors associated with progression-free survival and overall survival

Characteristic	Progression-free survival			Overall survival		
	p value	Hazard ratio	95% CI	*p* value	Hazard ratio	95% CI
Age (≥ 76/ < 76 y)	0.009	1.993	1.186–3.358	0.06	1.739	0.994–3.046
Sex (male/female)	0.95	1.015	0.629–1.650	0.20	1.434	0.824–2.488
Pre-treatment KPS (< 50/ ≥ 50%)	0.16	1.488	0.859–2.635	0.33	1.337	0.749–2.436
Pre-treatment comorbidity						
HT (±)	0.85	1.059	0.573–1.913	0.93	1.030	0.507–2.008
DM (±)	0.91	1.046	0.445–2.314	0.43	0.701	0.276–1.688
HL (±)	0.46	1.412	0.539–3.280	0.72	1.212	0.393–3.270
Systemic cancer (±)	0.38	0.742	0.360–1.426	0.44	0.753	0.349–1.507
Cardiovascular disease (±)	0.002	3.008	1.508–5.803	0.002	3.432	1.612–7.065
Central nervous system disease (±)	0.007	2.686	1.318–5.233	0.012	2.869	1.280–6.126
Chemotherapy (−/+)	< 0.001	4.615	2.563–8.274	< 0.001	3.733	1.994–6.959
Radiotherapy (−/+)	0.001	3.064	1.573–5.965	0.001	3.536	1.748–6.854
Post-treatment CRR (−/+)	0.023	1.863	1.090–3.137	0.08	1.677	0.949–2.922
Post-treatment KPS (< 60/ ≥ 60%)	0.82	1.066	0.624–1.812	0.32	1.352	0.749–2.439
Post-treatment complications						
Pneumonia and other infections (±)	< 0.001	2.936	1.586–5.352	< 0.001	3.505	1.827–6.665
Cardiovascular complications (±)	0.55	1.260	0.578–2.593	0.43	1.380	0.609–2.948
Renal dysfunction (±)	0.47	1.525	0.447–4.321	0.08	3.091	0.884–9.123

CI confidence interval, *KPS* Karnofsky Performance Status, *HT* hypertension, *DM* diabetes mellitus, *HL* hyperlipidemia, *CRR* complete response rate (CR+CRu/CR+CRu+PR+SD+PD+NA), *CR* complete response, *CRu* CR/unconfirmed, *PR* Partial response, *SD* Stable disease, *PD* progressive disease, *NE* not evaluable, *DVT* deep venous thrombosis, *PE* pulmonary embolism.

aged 70 years or older, PFS was 16.1 months in the elderly group compared to 35 months in the young group, even in CR cases, and there are reports that salvage therapy at the time of recurrence, including chemotherapy, was not performed[14], indicating that patients may not be treated satisfactorily. Previously, there was no definition of elderly and younger age groups using a cut-off value [15]. There are many reports that elderly patients have a worse prognosis, but the cut-off age ranged from 60 to 80 years [16–19], and a systematic review defined it as 75 years [20]. However, few cohorts have been directly compared. Zeremski et al. [5] retrospectively compared 20 consecutive cases in German Primary Central Nervous System Lymphoma Study Group-1 (G-PCNSL-SG-1). A comparative study was conducted between the HD-MTX basic therapy with whole-brain irradiation group as initial treatment and the irradiation avoidance group in which whole-brain irradiation was replaced with HD-AraC therapy, with 66 consecutive cases in the 'real-life group' treated otherwise. The median age was 62 and 70 years, with the real-life group being older, median KPS was 80% vs 70%, which also shows the poor condition of the real-life group, mOS was 33.4 months and 9.3 months, and mPFS was 24.8 months and 3.4 months, indicating that the elderly population was clearly in worse condition. Thus, there are very few studies of EL-PCNSL that are based on actual clinical practice, and in fact, there are probably quite a few cases that are not treated BSC cases. In the present study, only 3 of 142 enrolled patients had BSC, and it was shown that EL-PCNSL was treated fairly actively. Compared with the 'real-life group' of Zeremski et al. [5], the present cases had a higher median age of 76 years (vs. 70 years) and a lower pre-treatment KPS of 50% (vs. 70%). However, the treatment outcome was good, with PFS of 16 months (vs 3.4 months) and OS of 24 months (vs 9.3 months). The results of the present study are highly reliable because they are based on Real-World data collected from all patients in a regional center hospital, and one can assume that the data are almost complete.

In addition, although some cases of PCNSL are difficult to image, Japanese patients usually have non-germinal center type DLBCL(non-GCB) [21], and if PCNSL is immunocompetent, specific imaging findings such as CT, MRI, and FDG-PET, as well as clinical and spinal fluid examination findings, can be evaluated [22]. The risk of postoperative hemorrhage is also observed in a certain percentage of biopsy procedures [23]. In fact, in the present study, two cases of postoperative hemorrhage were observed, and one was a case of early death and dropout. Therefore, before treatment, the patient should be checked by CSF cytology if possible, whole-body


a
Pre-treatment cardiovascular disease
b
Pre-treatment central nervous system disease
c
Radiotherapy
d
Chemotherapy
e
Post-treatment CRR
PR+SD+PD+NE
CR+CRu
f
Post-treatment KPS (60>/60≤)
60>KPS
60≤KPS
g
Post-treatment pneumonia and other infections
h
Post-treatment DVT, PE, and cardiovascular complications
Proportion alive
Time (months)
0.0
0.2
0.4
0.6
0.8
1.0
0
12
24
36
48
60
72
84
-
+

◂**Fig. 4** Kaplan–Meier survival curves of independent variables. **a** OS in patients with pre-operative cardiovascular disease (gray line) and without pre-operative cardiovascular disease (black line) ($p=0.001$). **b** OS in patients with pre-operative central nervous disease (gray line) and without pre-operative central nervous disease (black line) ($p=0.038$). **c** OS in patients who received radiotherapy (black line) and who did not receive radiotherapy (gray line) ($p=0.045$). **d** OS in patients who received chemotherapy (black line) and who did not receive chemotherapy (gray line) ($p<0.001$). **e** OS in patients who achieved post-treatment he complete response rate (CRR) (black line) and who did not achieve CRR (gray line) ($p=0.013$). **f:** OS in patients with a post-treatment KPS score ≥ 60 (black line) and < 60 (gray line) ($p<0.001$). **g** OS in patients with post-treatment pneumonia or other infections (gray line) and without post-treatment pneumonia and other infections (black line) ($p<0.001$). **h** OS in patients with post-treatment deep venous thrombosis (DVT), pulmonary embolism (PE), or cardiovascular complications (gray line) and without post-treatment DVT, PE, and cardiovascular complications (black line) ($p=0.001$)

FDG-PET CT, enhanced dynamic susceptibility weighted magnetic resonance (DSC-MR) perfusion imaging MRI, testicular ultrasound if possible, liquid biopsy for *MYD88* mutation, and so on [10, 11, 24–27]. A liquid biopsy for *MYD88* mutation to differentiate from glioblastoma or metastatic brain tumor, followed by a skip biopsy, may be one option for EL-PCNSL. In view of the potential complications of biopsy and the time required for diagnosis, the usefulness of liquid biopsy is also important [24, 27]. Although biopsy is the gold standard, it is useful to note that there were 30/142 (21.1%) such cases. In fact, in the comparison of differences between the biopsy group and the non-biopsy group, most of the patients with small deep dissemination were in the non-biopsy group, which clearly shows selection bias (Table 2). However, there was no significant difference in PFS or OS between the biopsy and non-biopsy groups (Fig. 2a, b). In fact, the Japanese Brain Tumor Society guidelines (JSNO) also mention that surgery is difficult for elderly and at-risk patients, which might be the Real-World situation in Japan [28]. In addition, the percentage of bilateral disease was higher in younger patients and lower in elderly patients when comparing patients aged 76 years or older and those younger (Table 3). One possible reason for this is that if PCNSL is generally divided into germinal center type (GCB) and non-GCB, GCB is more common in the middle line, whereas non-GCB is more likely to occur laterally [29]. Hans et al. reported that there is no difference between GCB and non-GCB depending on age [30], but there are many differences between GCB and non-GCB depending on race, with Japanese and other Asian people having more non-CGB [21] and non-GCB being more common in older age groups [31, 32]. Therefore, it is possible that bilateral disease is more common in patients under 76 years of age because of the high incidence of middle line disease, and less common in the elderly. In addition, although there were no significant differences in PFS and OS, elderly patients over 76 years of age tended not to receive chemotherapy (Tables 3 and 4). This includes old cases from around 2011, when MTX-based chemotherapy with high nephrotoxicity was avoided in the elderly and RT was used instead. As a result, no significant differences in PFS and OS were observed. In the present study as well, treatment mainly by HD-MTX has been performed for the past 10 years, but it is thought that treatment has been performed for each case according to the patient's condition, and the number of treatment cycles and radiation methods varied. Under such circumstances, on both univariate and multivariate analyses of the presence or absence of RT and the presence or absence of chemotherapy, the prognosis of patients treated with RT and chemotherapy was significantly different from that of those treated without RT and chemotherapy. These results are noteworthy. The disadvantages of HD-MTX-based chemotherapy for EL-PCNSL are low rates of CR and PR and the short mPFS and mOS. A sub-analysis of the elderly patients in the G-PCMD-SG-1 trial also showed that the CR + PR rate was 44%, mPFS 4.0 was months, and mOS was 12.5 months, which was significantly worse than in the younger patients [14]. Furthermore, in the present study, 3 months CRR was 65.4% (87/133). Therefore, since Morris et al. [33] reported R-MPV therapy in 2013, R-MPV therapy has been introduced, but not all centers are on the same start, and the maximum follow-up period is 48 months, so the comparison with HD-MTX is short. In fact, this is the limitation of a retrospective study (Fig. 3).

Some reports have shown that pre-treatment low PS or KPS is associated with a poor prognosis in EL-PCNSL [16, 18–20, 34]. The report by Kasenda et al. [20] showing that pre-operative KPS ≥ 70% is the strongest prognostic factor for mortality in their large systematic review of 783 elderly PCNSL is particularly compelling. In the present cases, however, univariate analysis showed that pre-treatment KPS was irrelevant, but that there was a significant difference in KPS improvement after treatment. The reason for this might be that KPS would improve and the prognosis would improve if a therapeutic response were seen by aggressive intervention for EL-PCNSL patients. However, we believe that the cause of it not being identified as related to prognosis in the Cox proportional hazards model is stronger factor of systemic pre-treatment comorbidities and after treatment complications. In the analysis of factors associated with a poor prognosis, the results for OS were close to those for PFS, which may be attributed to the fact that 52.5% of patients (about half) received BSC as second-line treatment after relapse (Tables 4 and 5, Fig. 3). The significance of this suggestion that

pre-treatment comorbidities, especially cardiac and central nervous system comorbidities, and post-treatment new infectious complications affect prognosis is great, and this is a point of focus that has not received much attention. In other words, if we pay attention to patients with pre-treatment comorbidities, minimize new post-treatment complications, and aggressively intervene in the treatment of patients with low PS, long-term survival could be expected even in EL-PCNSL patients.

This study has several inherent limitations, which has potential implications for its interpretation. First, this was a retrospective study, the data were provided by eight centers, and all patients with low KPS and various comorbidities were included. In addition, because the data were obtained from various centers, the treatment strategy was not uniform, and the overall PFS and OS may be biased. Second, it is difficult to make comparisons according to the type of chemotherapy because of the variety of treatments. Similarly, it is difficult to compare treatment outcomes due to the variety of radiotherapy techniques. Third, non-surgical cases were also included. Before and after treatment, fairly strict patient selection criteria were required, and the final decision was made by the attending physician. Although the possibility of misdiagnosis seems small, it cannot be ruled out that cases with misdiagnosis may be included. Fourth, the no-surgery cases showed selection bias for small, deep-seated, and disseminated tumors. Fifth, 6 (40%) of the patients who dropped out of treatment within 3 months included patients who were missing, which is a slightly high percentage and may potentially affect PFS and OS. Therefore, prospective studies with appropriately designed allocation factors including all elderly patients and patients with low PS are needed in the future. Subanalyses of biological factors, MRI, cognitive function, and changes in PS are also necessary.

In conclusion, we have presented the Real-World status of EL-PCNSL. Patients were treated actively even at an advanced age, but further prospective studies are needed to determine the appropriate treatment. Factors associated with a poor prognosis included lack of radiation or chemotherapy, pre-treatment cardiovascular complications, history of brain disease, and new post-treatment infections.

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Author contributions KA and HO contributed to the concept and design of the study. KA and MM contributed to the acquisition and analysis of the data. AK contributed to central pathological diagnosis. All authors contributed to drafting the text and preparing the figure. KA, YY, TO, MN, TB, KM, MI, and MK contributed to acquisition of the data in individual institutions. KS, YS, KO, YF, HS, HO, and TT contributed to supervision in individual institutions. YS, CK, TK, and TT contributed to supervision and advising on the whole project.

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Availability of data and material The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability Not applicable.

Declarations

Conflict of interest M. Natsumeda has received honoraria from Novocure; Y. Sonoda has received honoraria from Eisai, Dai-ichi Sankyo, and Chugai and research grants from Astellas, Eisai, Otsuka, Dai-ichi Sankyo, Chugai, Tsumura, Bayer, Pfizer, Fuji-film, and HOYA PENTAX; K. Asano, Y. Yamashita, T. Ono, T. Beppu, K. Matsuda, M. Ichikawa, M. Kanamori, M. Matsuzaka, A. Kurose, K. Saito, K. Ogasawara, Y. Fujii, H. Shimizu, H. Ohkuma, C. Kitanaka, T. Kayama, and T. Tominaga have no conflict of interest to declare.

Ethical approval This study was conducted with the approval of the ethics committees of Hirosaki University Graduate School of Medicine (2018-118) and individual institutions. In addition, since this was a retrospective study, notifications to patients to opt-out were given on the homepage of each hospital.

Consent to participate The institutional review board waived the requirement for informed consent, owing to the retrospective nature of the study. However, the details of the study are posted on the hospital's homepage (http://www.med.hirosaki-u.ac.jp/~neuros/).

Consent for publication Not applicable.

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Authors and Affiliations

Kenichiro Asano[1] · Yoji Yamashita[2] · Takahiro Ono[3] · Manabu Natsumeda[4] · Takaaki Beppu[5] · Kenichiro Matsuda[6] · Masahiro Ichikawa[7] · Masayuki Kanamori[8] · Masashi Matsuzaka[9] · Akira Kurose[10] · Kiyoshi Saito[7] · Yukihiko Sonoda[6] · Kuniaki Ogasawara[5] · Yukihiko Fujii[4] · Hiroaki Shimizu[3] · Hiroki Ohkuma[1] · Chifumi Kitanaka[11] · Takamasa Kayama[12] · Teiji Tominaga[8]

1 Department of Neurosurgery, Hirosaki University Graduate School of Medicine, 5 Zaifu-cho, Hirosaki 036-8562, Japan

2 Department of Neurosurgery, Miyagi Cancer Center, Natori, Japan

3 Department of Neurosurgery, Akita University Graduate School of Medicine, Akita, Japan

4 Department of Neurosurgery, Brain Research Institute, University of Niigata, Niigata, Japan

5 Department of Neurosurgery, Iwate Medical University, Morioka, Japan

6 Department of Neurosurgery, Faculty of Medicine, Yamagata University, Yamagata, Japan

7 Department of Neurosurgery, Fukushima Medical University, Fukushima, Japan

8 Department of Neurosurgery, Tohoku University Graduate School of Medicine, Sendai, Japan

9 Department of Medical Informatics, Hirosaki University Hospital, Hirosaki, Japan

10 Department of Anatomic Pathology, Hirosaki University Graduate School of Medicine, Hirosaki, Japan

11 Department of Molecular Cancer Science, Faculty of Medicine, Yamagata University, Yamagata, Japan

12 Department of Advanced Cancer Medicine, Yamagata University Graduate School of Medical Science, Yamagata, Japan