^{18}F-FDG PET/CT and clinicopathological characteristics of neurolymphomatosis in lymphoma patients

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Abstract

Objective: Neurolymphomatosis (NL) is a rare but serious manifestation defined as invasion of peripheral nervous system by malignant lymphocytes. Thus, this study investigated fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) and clinicopathological characteristics of NL in lymphoma patients. **Subjects and Methods:** Clinicopathological and ^{18}F-FDG PET/CT findings and treatment regimens were retrospectively investigated in 20 lymphoma patients with NL, and analyzed their correlation with progression-free survival (PFS) and overall survival (OS). **Results:** These 20 lymphoma patients (11 males, 9 females; median age, 49 years) included 10 primary and 10 secondary NL patients. Non-Hodgkin's lymphoma (NHL) was noted in 19 patients, B-cell NHL was associated with 18 cases, and diffuse large B-cell lymphoma was the most common. Notably, 18 patients were aggressive lymphoma while 2 were indolent lymphoma. The affected neural structures included nerve roots (n=17), peripheral nerves (n=3), cranial nerves (n=3), and neural plexus (n=2). Fluorine-18-FDG was avid in all cases, and the median maximum standardized uptake value (SUVmax) of neural and all lesions was 12.2 (range, 3.3-25.6) and 15.0 (range, 4.4-34.2), respectively. The median PFS and OS of all patients were 9.3 and 14.3 months. The 12-month OS rate of 18 patients with aggressive lymphoma receiving intrathecal chemotherapy/autologous stem cell transplants (IT chem/ASCT) was significantly higher than who did not (64.8% vs 15.9%). **Conclusion:** The majority of NL occurred in patients with aggressive lymphoma, of which B-cell NHL were the predominant subtypes. Fluorine-18-FDG PET/CT imaging of NL was mainly characterized by intense glucose accumulation alongside peripheral nerves, and IT chem/ASCT was suggested to improve the outcomes of NL.

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Introduction

Neurolymphomatosis (NL) is a rare but serious clinical entity defined as invasion of the peripheral nervous system (PNS) (peripheral nerves, nerve roots, plexus, and cranial nerves) by hematological malignancies, generally non-Hodgkin lymphoma (NHL) [1, 2]. Primary NL is defined as neural involvement present at the time of diagnosis of a hematological malignancy, while secondary NL is characterized as a site of progression or relapse of a previously diagnosed hematological malignancy [1, 2]. Neurolymphomatosis can often be concomitant with lymphomatous infiltration of the central nervous system (CNS) or disseminate into the brain and spinal cord [3, 4]. Central nervous system involvement is a seriously fatal event, such as a median survival of only 3 to 7 months reported in diffuse large B-cell lymphoma (DLBCL) [5 ,6]. Therefore, early and accurate diagnosis of NL is of pivotal importance in the clinical management of such cases.

Nerve biopsy is the gold standard for the diagnosis of NL; however, in routine clinical practice, the biopsy of the involved nerves is challenging to perform and prone to increase the risk of permanent nerve injury [3, 7, 8]. Magnetic resonance imaging (MRI) is the first-choice imaging modality for the CNS, but it is less sensitive and accurate in assessing the PNS [2, 9-11]. Moreover, other diagnostic modalities, such as contrast-enhanced computed tomography (CECT), cerebrospinal fluid (CSF) cytology and bone marrow (BM) examination, always have false negative findings in most NL cases [9-13]. Therefore, a clinically feasible non-invasive method is critical to facilitate the diagnosis of NL.

Fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)/CT is an imaging technology that can provide a whole-body evaluation, which has been effectively used to make the diagnosis, assess the staging, and predict the outcomes of the patients with lymphoma. However, due to the rarity of NL, the recognition of ^{18}F-FDG PET/CT in lymphoma patients with NL is mainly reported in sporadic cases or small se-

ries [4, 9, 10, 12-18], and its role in the clinical management of NL remains undefined. Therefore, this study aimed to collect the clinicopathological characteristics, ^{18}F-FDG PET/CT findings, treatment regimens, and outcomes of NL in lymphoma patients, and investigate their roles in such cases.

Subjects and Methods

Patients

From March 2012 to January 2022, 20 lymphoma patients with NL who underwent ^{18}F-FDG PET/CT examination in our hospitals were retrospectively included in the present study. The confirmation of NL was based on a composite of clinical nerve symptoms, other diagnostic modalities, including MRI, CECT, CSF cytology, BM examination, and nerve biopsy, and clinical follow-up. The patients with the known toxic, compressive, inflammatory, or paraneoplastic neuropathies were excluded. The clinical data of the enrolled patients were collected, including sex, age, lymphoma type, stage, primary or secondary, neurological symptom, affected neural site and structure, CNS involvement, and treatment regimens. This retrospective study was approved by the institutional ethics committee of our hospitals and the informed consent was waived.

^{18}F-FDG PET/CT

Positron emission tomography/CT scans were performed using a Biograph 16 (Siemens Healthineers, Erlangen, Germany), or uEXPLORER (United Imaging Healthcare, Shanghai, China). All patients were inquired to fast and avoid strenuous exercise at least 6h before ^{18}F-FDG injection, and the level of fasting blood glucose was no more than 11.0 mmol/L. Images were captured approximately 60±5min after intravenous injection of 3.7MBq of ^{18}F-FDG per kilogram of body weight. For Biograph 16 PET/CT scanner, six or seven-bed positions were imaged from the base of the skull to the mid-thigh, and PET images were obtained for 2-3min per bed position. For uEXPLORER, a total-body PET imaging was performed using a list-mode PET acquisition with a 5 min duration. All image reconstructions were performed with the ordered-subset expectation maximization algorithm, incorporating a CT-based transmission map.

Positron emission tomography metabolic parameters were analyzed through syngo station (Siemens Healthineers, Erlangen, Germany). Volume of interest (VOI) was manually drawn on the lesion. VOI of the mediastinal blood pool was drawn in thoracic aorta, and VOI of the liver was drawn in the lesion-free region of the right liver lobe. The maximum value of a VOI was defined as the maximum standardized uptake value (SUVmax). Metabolic tumor volume of all lesions (TMTV) was computed with 40% of SUVmax as the threshold, and total lesion glycolysis of all lesions (TLG) was calculated according to the following formula: TLG= SUVmean×MTV. Positron emission tomography/CT imaging results were independently analyzed and interpreted by two experienced nuclear medicine physicians who were blinded to the patients' clinical and pathological information.

Follow-up

The median duration of follow-up was 11.6 months, ranging from 0.3 to 38.2 months. Progression-free survival (PFS) was defined as the time interval from the diagnosis of NL to the date of the finding of post-treatment tumor progression or death of any cause. Overall survival (OS) was defined as the time interval from the diagnosis of NL to the date of death of any cause or until the end of Feb 2022.

Statistical analysis

SPSS 25.0 software (IBM Corp., Armonk, NY, USA) was used for statistical analysis in the current study. Pearson's Chi-square (χ^2 test) or Fisher's exact tests were carried out to evaluate differences in distribution of categorical variables, while the independent t-test or Mann-Whitney U test was performed for continuous variables. Continuous variables were expressed as the median (range minimum-maximum). Kaplan-Meier survival analysis was performed to predict the PFS and OS. The predictive value of ^{18}F-FDG PET/CT parameters and clinical factors was analyzed via univariate and multivariate Cox proportional hazards regression. $P<0.05$ was considered to be statistically significant.

Results

Patients' characteristics

As showed in Table 1, a total of 20 lymphoma patients with NL (11 males, 9 females, with a median age of 49 years old) were enrolled in this study. Among these 20 patients, 19 patients were pathologically confirmed with NHL, and the remaining one had Hodgkin's lymphoma (HD). B-cell NHL was associated with 18 NL cases, of which DLBCL was the most common (n=13). Indolent lymphoma (follicular lymphoma grade 2, n=1; lymphoplasmacytoid lymphoma, n=1) was in 2 patients while aggressive lymphoma was in 18 patients. Except for one case with stage IE, the rest 19 patients were stage IV.

The neurological symptoms were present in 13 patients, including pure sensory (n=7), pure motor (n=2), and mixed sensorimotor (n=4). Pain, numbness, and weakness were the predominant clinical manifestations. A single neural site involved by NL was found in 12 patients and multiple affected neural sites were present in 8 patients. The affected neural structures consisted of nerve roots (n=17), peripheral nerves (n=3), cranial nerves (n=3) and neural plexus (n=2). In addition, 3 out of 20 patients had the coexistent CNS involvement at the diagnosis of NL.

Multiple diagnostic modalities were performed in the enrolled patients for the diagnosis of NL, including MRI (n=13), CECT (n=16), CSF cytology (n=9), BM examination (n=15), and nerve biopsy (n=1). Magnetic resonance imaging was positive in 38.5% (5/13) cases, CECT was positive in 100% (16/16) cases, CSF cytology was positive in 11.1% (1/9) cases, and BM examination was positive in 40.0% (6/15) cases. Besides, the positive result was also found in only one case with nerve biopsy.

Table 1. *Patient demographics, diagnostic modalities, and treatment.*

No	Sex	Age (yr)	Lymphoma type	Pri./Sec.	Nerve symptom	Stage	PET/CT		MRI	CECT	CSF cytology	BM examination	Nerve biopsy	Treatment
							NL site (SUVmax)	Non-NL lesion (SUVmax)						
1	M	73	DLBCL	Pri.	P	IVA	right brachial plexus, left sacral nerve-sacral plexus-sciatic nerve (24.1)	mediastinum, right perinephric fat (30.5)	N	P	/	/	/	R-miniCHOP
2	M	15	ALCL	Pri.	N	IVA	left sacral nerve (5.2)	mediastinum, muscle (9.4)	/	P	N	N	/	NHL-BFM-90, IT chemotherapy (MTX+DXM)
3	F	43	FL	Pri.	N	IVA	right sacral nerve (7.0)	LNs, humerus, femur (9.1)	/	P	/	P	/	R2
4	F	57	DLBCL	Pri.	P	IVA	bilateral lumbosacral nerve (11.8)	LNs, liver, spleen, muscle, bone (17.0)	N	P	/	/	/	R-CHOP
5	M	54	DLBCL	Pri.	N	IE	left sacral nerve (5.6)	/	/	P	N	N	/	R-CHOEP, RT, IT chemotherapy (MTX+Ara-C)
6	F	65	DLBCL	Pri.	P	IVA	bilateral cervical nerve (4.4)	/	N	P	/	P	/	GDP, HD-MTX
7	M	50	LPL	Pri.	P	IVA	right sacral nerve (3.3)	bone (5.2)	N	P	/	N	/	GB

(continued)

8	F	67	DLBCL	Pri.	P	IVB	bilateral cervical and right lumbosacral nerve (5.0)	CNS (brain), pericardium, spleen, kidney, perinephric fat, bone (10.8)	/	P	N	P	/	R-miniCDOP
9	M	47	DLBCL	Pri.	N	IVA	left thoracic nerve (15.7)	LNs, mediastinum, pericardium, intestine (34.2)	N	P	N	N	/	R-CHOP, IT chemotherapy (MTX+Ara-C)
10	M	17	BL	Pri.	N	IVA	right lumbar nerve (13.6)	pericardium, breast, stomach, kidney, intestine, peritoneum, testis, penis, bone (16.7)	/	P	/	P	/	R-Hyper-CVAD, IT chemotherapy (MTX+Ara-C)
11	F	37	DLBCL	Sec	P	IVA	left thoracic nerve (13.1)	/	P	/	N	P	/	R-Hyper-CVAD, R-EPOCH, IT chemotherapy (MTX+Ara-C)
12	M	61	DLBCL	Sec.	P	IVB	left sacral plexus-sciatic nerve (12.5)	/	N	P	/	N	P	R-CHOP
13	M	60	DLBCL	Sec.	P	IVA	right jugular foramen area nerve, and bilateral cervical, thoracic and lumbosacral nerve (16.4)	CNS (spinal cord) (4.8)	P	P	/	/	/	R2, Ibrutinib, consolidative ASCT
14	F	52	BCL	Sec.	P	IVA	left jugular foramen area nerve, and bilateral sacral nerve (17.2)	LNs, pleura, ileocecal junction (24.5)	P	P	N	N	/	BR, R2, HD-MTX, PD-1

(continued)

15	M	46	DLBCL	Sec.	N	IVA	cauda equina (12.9)	CNS (brain), stomach (23.3)	/	P	N	N	/	R-CDOP
16	M	84	DLBCL	Sec.	P	IVA	right lumbar nerve (8.5)	LNs, pleura, stomach, duodenum, kidney, gallbladder, prostate, penis, muscle (14.3)	N	P	/	/	/	BR+DMX
17	M	41	BCL	Sec.	P	IVB	left trigeminal nerve (25.6)	/	P	/	/	P	/	R-MED, RT
18	F	33	DLBCL	Sec	P	IVA	left sacral nerve (8.4)	LNs (19.4)	N	/	P	N	/	R-CHOP, IT chemotherapy (MTX+Ara-C)
19	F	46	DLBCL	Sec.	N	IVA	left sciatic nerve (7.7)	bilateral lungs (10.4)	P	/	N	/	/	R2-CHOP R-GOD+orelabrutinib, IT chemotherapy (MTX+Ara-C)
20	F	48	HD	Sec.	P	IVB	right sacral nerve (15.6)	LNs, bone (13.6)	/	P	/	N	/	ABVD, IGEV, PD-1, consolidative ASCT

DLBCL: diffuse large B-cell lymphoma, ALCL: anaplastic large cell lymphoma, FL: follicular lymphoma, LPL: lymphoplasmacytoid lymphoma, BCL: B-cell lymphoma (unclassified), BL: Burkitt's lymphoma, HD: Hodgkin's lymphoma, NL: neurolymphomatosis, LNs: lymph nodes, CNS: central nerve system, CSF: cerebronspinal fluid, BM: bone marrow, M: male, F: female, yr: year; Pri.: primary, Sec.: secondary, P: positive, N: negative, and "/": no; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-miniCHOP: rituximab, low-dose CHOP; NHL-BFM-90: non-Hodgkin lymphoma Berlin-Frankfurt-Münster-90; IT: intrathecal; MTX: methotrexate; DXM: dexamethasone; R2: rituximab, lenalidomide; R-CHOEP: rituximab, cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone; RT: radiotherapy; Ara-C: cytarabine; GDP: gemcitabine, dexamethasone, cisplatin; HD-MTX: high-dose methotrexate; GB: obinutuzumab, bendamustine; R-CDOP: rituximab, cyclophosphamide, vindesine, doxorubicin liposome, prednisone; R-miniCDOP: rituximab, low-dose CDOP; R-Hyper-CVAD: rituximab, cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, cytarabine; R-EPOCH: rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; ASCT: autologous stem cell transplant; BR: Bendamustine, rituximab; R-MED: rituximab, methotrexate, etoposide, dexamethasone; R2-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, lenalidomide; R-GOD: rituximab, gemcitabine, vincristine, dexamethasone; ABVD: doxorubicin, bleomycin, vinblastin, dacarbazine; IGEV: ifosfamide, gemcitabine, vinorelbine, steroids.

^{18}F-FDG PET/CT

Among these 20 patients, all NL lesions were FDG-avid and mainly characterized by intense glucose accumulation alongside peripheral nerves. The median SUVmax of neural lesions and all lesions was 12.2 (range, 3.3-25.6) and 15.0 (range, 4.4-34.2), respectively (Table 1).

Primary and Secondary NL

Of these 20 patients, 10 patients presented with primary NL (Figure 1) and 10 patients with secondary NL (Figure 2). Clinicopathological characteristics and PET/CT metabolic parameters of the two groups were shown in Table 2. No significant differences in sex, age, lymphoma type, stage, neurological symptoms, affected neural site and structure, CNS involvement, and PET/CT metabolic parameters (SUVmax of all lesions, SUVmax of neural lesions, SUVmax of mediastinal blood pool, SUVmax of liver, TMTV, and TLG) were found between the two groups (P>0.05).

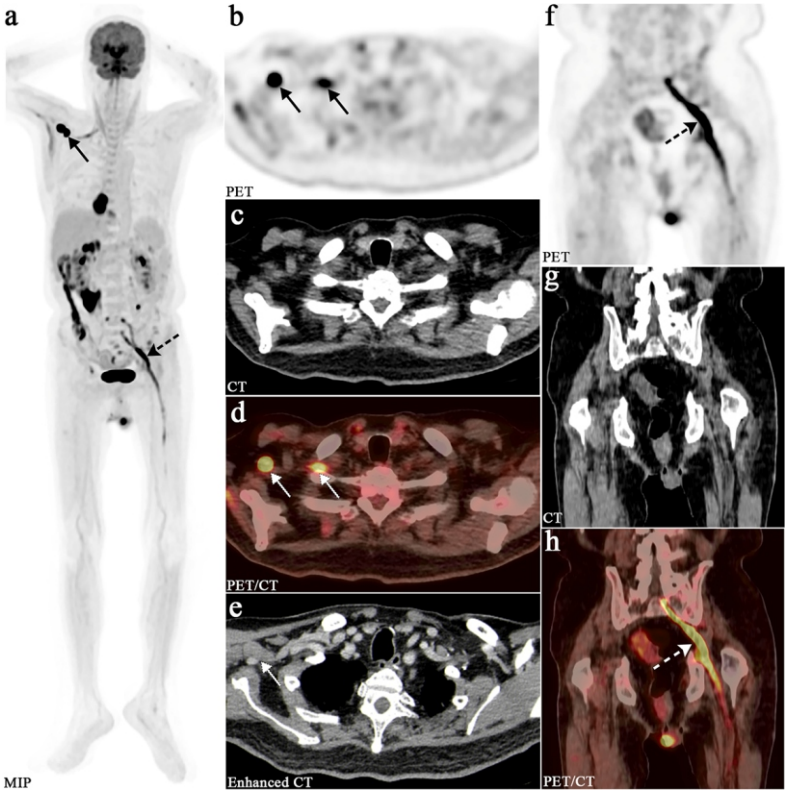

Figure 1. Primary NL was detected in a 73-year-old man at the diagnosis of DLBCL, involving right brachial plexus (solid arrows) on the MIP (a), axial PET (b), CT (c), fused PET/CT (d), and contrast-enhanced CT (e) images, and left sacral nerve-sacral plexus-sciatic nerve (dotted arrows) on the MIP (a), coronal PET (f), CT (g), and fused PET/CT (h) images.

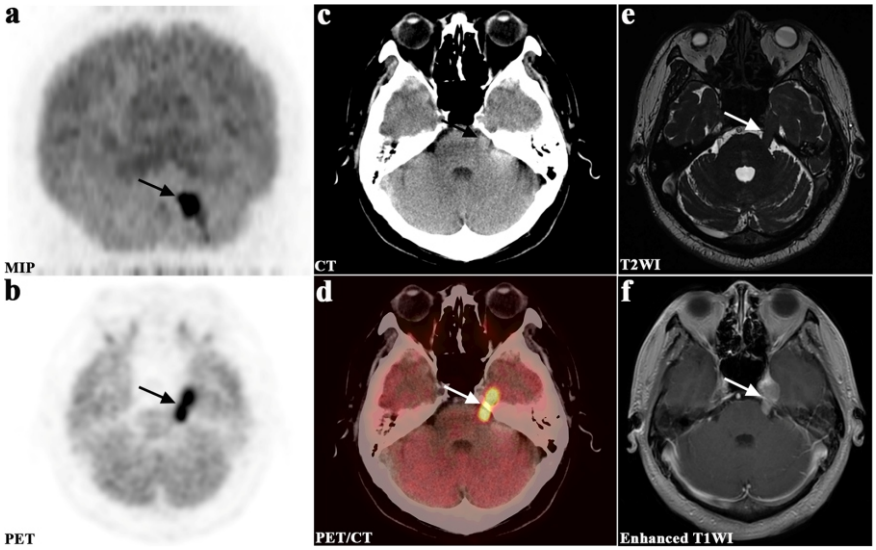

Figure 2. Secondary NL was detected in a 41-year-old man with a previously diagnosed BCL (unclassified), involving left trigeminal nerve (solid arrows) on the MIP (a), axial PET (b), CT (c), fused PET/CT (d), T2WI (e), and enhanced T1W1 (f) images.

Table 2. *Clinicopathological, PET/CT, survival data of primary NL and secondary NL.*

Characteristics	Total NL	Primary NL	Secondary NL	P value
Sex, n				
Male	11	6	5	1.000
Female	9	4	5	
Age/years old, median (range)	49 (15-84)	52 (15-73)	47 (33-84)	0.799
Lymphoma type, n				
B cells	18	9	9	1.000
Non-B cells	2	1	1	
Lymphoma type, n				
Indolent	2	2	0	0.474
Aggressive	18	8	10	
Stage, n				
Limited (I-II)	1	1	0	1.000
Advanced (III-IV)	19	9	10	
Neurological symptom, n				
Positive	13	5	8	0.350
Negative	7	5	2	
Type of neurological symptom, n				
Pure sensory	7	2	5	0.782
Pure motor	2	1	1	
Sensorimotor	4	2	2	
Affected neural site, n				
Single	12	6	6	1.000
Multiple	8	4	4	
Affected neural structure, n				
Peripheral nerves	3	1	2	NA
Nerve roots	17	10	7	
Neural plexus	2	1	1	
Cranial nerves	3	0	3	

(continued)

CNS involvement, n				
Yes	3	1	2	1.000
No	17	9	8	
PET parameters, median (range)				
SUVmax of all lesions	15.0 (4.4-34.2)	10.1 (4.4-34.2)	16.0 (10.4-25.6)	0.399
SUVmax of neural lesions	12.2 (3.3-25.6)	6.3 (3.3-24.1)	13.0 (7.7-25.6)	0.136
SUVmax of mediastinal blood pool	1.6 (1.0-2.7)	1.5 (1.2-2.1)	1.9 (1.0-2.7)	0.263
SUVmax of liver	2.8 (1.7-4.3)	2.8 (1.7-4.0)	2.9 (2.1-4.3)	0.605
TMTV	39.8 (2.8-899.4)	134.8 (7.4-899.4)	31.0 (2.8-267.4)	0.065
TLG	345.5 (18.5-4047.1)	986.0 (18.5-4047.1)	148.2 (20.8-1476.1)	0.133

NL: neurolymphomatosis, CNS: central nervous system, and NA: not applicable. *Indicated statistically significant.

Treatment

All patients (n=20) received varying regimens of frontline intravenous chemotherapy after being diagnosed with NL, as detailed in Table 1. In addition, intrathecal (IT) chemotherapy was administered to seven patients on the foundation of systematic chemotherapy to control and treat NL. Two patients received consolidative autologous stem cell transplants (ASCT) after remission of lymphoma from high-dose systematic chemotherapy. Local radiotherapy was delive-red to the involved sites of NL comb

Follow-up and prognosis

During the follow-up period of the 20 patients, remission was achieved in 9 patients, while disease progression was observed in 11 patients, including 10 deaths. The median PFS and OS of the 20 patients was 9.3 months and 14.3 months, respectively; and the 12-month and 24-month PFS and OS rates were 48.8% and 35.6%, as well as 52.7% and 34.6%, respectively. Univariate and multivariate Cox regression analysis of the 20 patients showed that clinicopathological features, PET/CT metabolic parameters, and treatment regimens had no significant association with PFS or OS (P>0.05, Table 3).

With the exclusion of two cases of indolent lymphoma (patient No. 3 and 7 in Table 1), the remaining 18 NL patients with aggressive lymphoma were further incorporated into the prognosis analysis. The median PFS of the 18 patients was 9.3 months, and 12-month and 24-month PFS rates were 45.6% and 31.3%, respectively (Figure 3a). The median OS of the 18 patients was 9.3 months, and 12-month and 24-month OS rates were 49.6% and 28.3%, respectively (Figure 3b). Univariate Cox regression analysis showed that no variable had significant association with PFS (P>0.05). However, Kaplan-Meier survival analysis presented that the PFS rate of patients treated with IT chemotherapy or ASCT (IT chem/ASCT) after frontline systemic chemotherapy was significantly higher than those who did not (P=0.036, Figure 3c). In terms of OS, univariate Cox regression analysis and Kaplan-Meier survival analysis consistently showed that the use of IT chem/ASCT was associated with significant improvement in OS compared with regimens without IT chem/ASCT (HR=0.023, 95%CI: 0.06-0.95, P=0.042, Table 4; 12-month OS: 64.8% vs 15.9%, P=0.027, Figure 3d). How-ever, multivariate Cox regression analysis showed that no variable was significantly associated with OS (P>0.05).

Discussion

Traditionally, NL was regarded as an extremely rare clinical entity; however, the reported incidence of NL seemed to be increasing [1, 9, 19-21]. Due to the lack of familiarity with NL, the diagnosis of this disease was often delayed. Clinically, NL was more common in men than women, and the patient age at the time of diagnosis ranged from 8 to 84 years old [1-3, 22]. Similar to the literatures reported previously, our study had a 55% male population, and the median age was 49 years old. Furthermore, this study showed that most NL was associated with B-cell NHL and DLBCL was the most common subtype, and neurological symptoms such as pain, numbness, and weakness were presented in more than half of cases, which were also in line with the previous studies [2, 11, 23]. Notably, except for two cases with indolent lymphoma, the majority of NL cases were aggressive lymphoma [9, 12, 23]. Combining these clinical features of sex, age, lymphoma type, and neurological symptoms, it is necessary to raise the clinician's suspicion of NL.

Diagnostic modalities of NL mainly included ^{18}F-FDG PET/CT, MRI, CECT, CSF cytology, BM examination, and nerve

Table 3. *Univariate Cox proportional hazards regression for OS and PFS of all patients (n=20).*

	PFS			OS		
	P value	HR	95% CI	P value	HR	95% CI
Age	0.137	1.02	0.99-1.06	0.097	1.03	1.00-1.06
Sex (male)	0.731	0.81	0.25-2.67	0.518	0.66	0.19-2.31
Neurological symptom	0.405	1.76	0.46-6.70	0.449	1.72	0.42-6.99
Secondary vs. primary	0.490	1.54	0.45-5.30	0.495	1.57	0.43-5.67
CNS involvement	0.858	0.83	0.11-6.55	0.855	1.22	0.15-9.87
Multiple affected neural sites	0.128	2.61	0.76-8.94	0.146	2.77	0.70-10.91
SUVmax of all lesions	0.531	0.97	0.88-1.07	0.719	0.98	0.90-1.08
SUVmax of neural lesions	0.399	1.05	0.94-1.17	0.382	1.05	0.94-1.17
TMTV	0.185	1.00	0.99-1.00	0.185	1.00	0.99-1.00
TLG	0.163	1.00	0.99-1.00	0.167	1.00	0.99-1.00
IT chemotherapy/ASCT	0.133	0.39	0.11-1.34	0.106	0.32	0.08-1.27

CNS: central nerve system, IT: intrathecal, ASCT: autologous stem cell transplant. * Statistically significant.

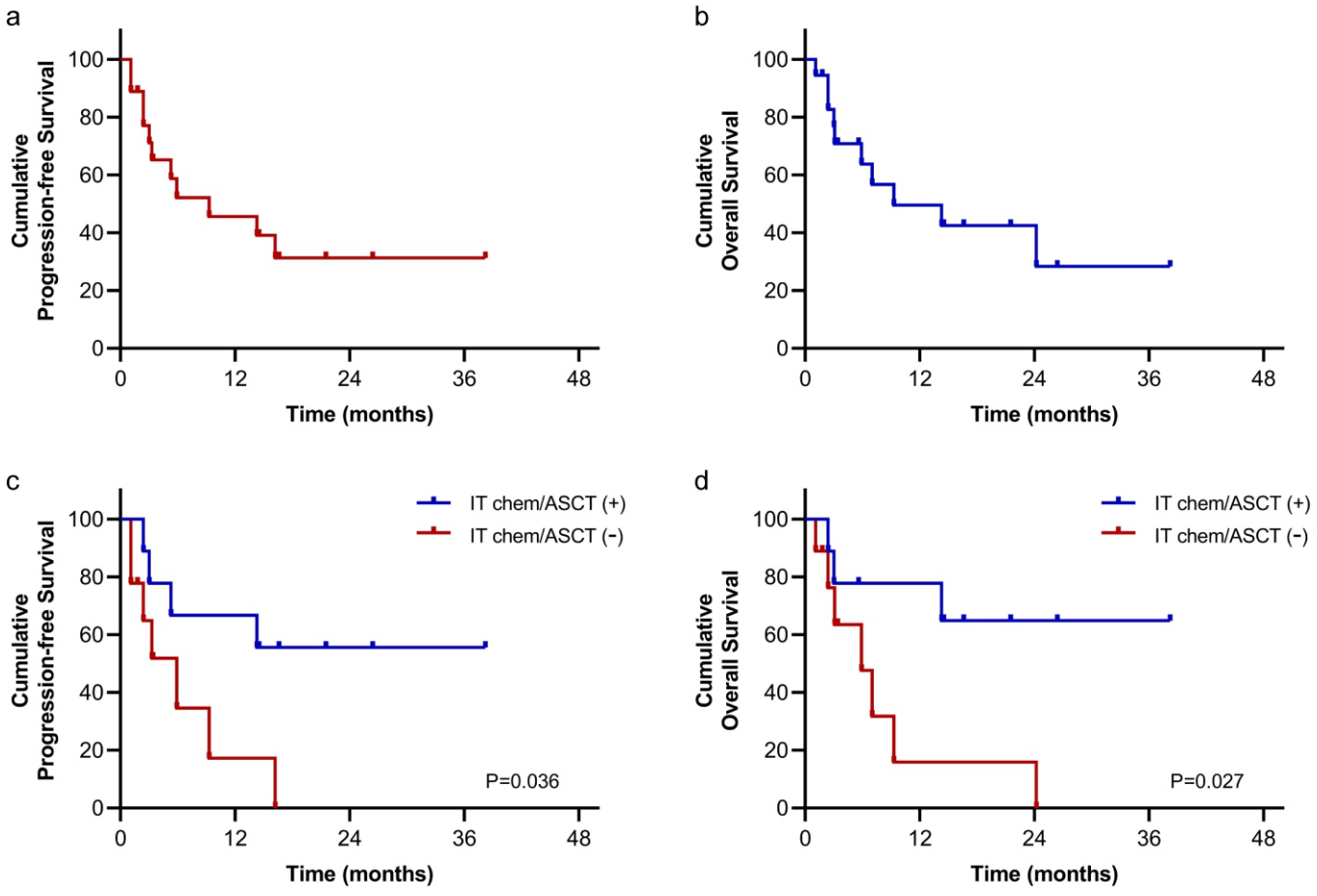

Figure 3. The Kaplan-Meier curve of PFS (a) and OS (b) in patients with aggressive lymphoma (n=18); and the Kaplan-Meier curve of PFS (c) and OS (d) in patients receiving IT chem/ASCT vs. those who did not.

Table 4. *Univariate and multivariate Cox proportional hazards regression for OS of aggressive lymphoma patients (n=18).*

	Univariate			Multivariate		
	P value	HR	95% CI	P value	HR	95% CI
Age	0.127	1.02	0.99-1.06	0.588	1.01	0.97-1.06
Sex (male)	0.243	0.46	0.12-1.70	-	-	-
Neurological symptom	0.695	1.32	0.33-5.32	-	-	-
Secondary vs. primary	0.714	1.27	0.35-4.57	0.817	1.19	0.28-5.07
CNS involvement	0.928	1.10	0.14-8.94	0.723	1.54	0.14-16.74
Multiple affected neural sites	0.202	2.44	0.62-9.58	-	-	-
SUVmax of all lesions	0.483	0.97	0.87-1.07	-	-	-
SUVmax of neural lesions	0.553	1.04	0.92-1.16	-	-	-
TMTV	0.363	1.00	0.99-1.00	-	-	-
TLG	0.333	1.00	0.99-1.00	-	-	-
IT chemotherapy/ASCT	0.042*	0.23	0.06-0.95	0.324	0.40	0.06-2.49

*CNS: central nerve system, IT: intrathecal, ASCT: autologous stem cell transplant. * Statistically significant.*

biopsy. Specially, imaging modalities may more easily be accepted by the patients because of their non-invasiveness. Magnetic resonance imaging is the most commonly used imaging modality for diagnosing nerve system diseases. Different from the high sensitivity in detection of CNS lymphoma, the efficacy of MRI is limited by the patchy distribution or small size of the lesion of NL [13, 19, 24]. On the contrary, the vast majority of lymphoma involving the nerve system was aggressive in nature, and always displayed high glucose accumulation on ^{18}F-FDG PET/CT imaging. For example, Grisariu et al. (2010) reported that ^{18}F-FDG PET/CT was positive in 87.5% of NL cases and MRI was positive in 80% cases [2]. Salm et al. (2012) showed positive PET results in 91% of NL patients and MRI in 59% of patients [11]. Byun et al. (2017) displayed that the diagnostic yield was 100.0% for 18F-FDG PET/CT and 75.0% for MRI in NL patients [9]. Moreover, Zhou et al. (2014) revealed that the positive rates for ^{18}F-FDG PET and syn-modality CT were 100% and 36.8%, respectively [13]. Overall, ^{18}F-FDG PET/CT was superior to other imaging modalities in detecting NL with high sensitivity.

Moreover, ^{18}F-FDG PET/CT provides the whole-body evaluation, which is superior to other imaging modalities in accurately identifying the extent of the nervous system and systemic lesions. As part of systemic lesions involved by hematological malignancies, especially aggressive malignancies, the glucometabolism level of NL was basically consistent with systemic lesions and always displayed intense glucose uptake. For example, Zhou et al. (2014) revealed that the average SUVmax of NL was 6.4±3.0 (range, 3.3-13.7) in 8 patients [13]. DeVries et al. (2019) reported that the average SUVmax of B-cell NL was 7.1±4.5 (range, 1.5-17.0) in 25 patients [22]. Similar to the previous studies, the median SUVmax of NL in our study was 12.2 with the range from 3.1 to 25.6.

Neurolymphomatosis can present as the primary manifestation of a hematological malignancy at the diagnosis with or without the coexistence of nodal and / or other extranodal involvement, and can also be secondary that occurs as a site of progression or relapse of a previously diagnosed hematological malignancy [23]. In most literatures, secondary NL was more common than primary NL in hematological malignancies [2, 3, 12, 22]. Conversely, Khurana et al. (2021) reported that primary NL was noted in 52% of cases of lymphoma and leukemia [23], which was similar to our findings that primary NL and secondary NL accounted for half of the cases, respectively. The diagnosis of secondary NL suggested that ^{18}F-FDG PET/CT also played an essential role in monitoring progression and detecting relapse of lymphoma. Furthermore, ^{18}F-FDG PET/CT metabolic parameters and clinicopathological features of primary NL and secondary NL were compared in the current study, and no significant differences were found between the two groups. It has been shown that primary NL has better survival than secondary NL [2, 23]. However, in our cohort, we didn't find significant difference in their survival, which may be attribu-

ted to the small sample and different therapeutic interventions. This suggests that primary or secondary NL is a serious disease with a poor prognosis, despite its different stages (initial, progressive and recurrent) [19, 21].

Due to the rarity and lack of clinical experience, there are no clear standard regimens for NL. Previously, the majority of NL patients underwent systemic chemotherapy alone or combined with radiotherapy [2, 21]. However, NL can often be concomitant with lymphomatous infiltration of CNS or disseminate into brain and spinal cord [3, 4], which prompts the use of CNS prophylaxis with frontline therapy [25]. At present, the application of CNS prophylaxis in NL patients was generally reserved, and the benefit on survival of NL remains not yet conclusive. We found that the use of IT chem/ASCT was associated with significant improvement in PFS and OS of patients with aggressive lymphoma compared with regimens not containing IT chem/ASCT. Notably, ASCT effectively improved the outcome of one case with CNS involvement (patient No. 13 in Table 1) in our study, which had been proven to be associated with OS of NL patients [23, 26].

In addition to IT chemotherapy and ASCT, high-dose methotrexate (HD-MTX) is also an important regimen used for CNS prophylaxis [23, 25, 27]. It was reported that no significant difference in affecting CNS relapse between the two routes of HD-MTX and IT chemotherapy [25]. However, the OS of two cases receiving HD-MTX in this study was only 3.1 and 5.9 months (patient No. 8 and 15 in Table 1), respectively. Kobayashi et al. (2019) also found that HD-MTX-based chemotherapy had insufficient efficacy against NL [28]. It may be attributable to the limited penetrability of HD-MTX in the blood-nerve barrier [28]. Moreover, differences between the two routes include greater parenchymal penetration with HD-MTX at the cost of greater hematologic, renal, and other toxicities, vs. more restricted distribution with IT administration but generally fewer toxicities [25]. Thus, we suggested that the clinicians should promptly carry out IT chem/ASCT with frontline chemotherapy to improve the outcomes.

There are some limitations to this study. Firstly, the relatively small number of patients and the retrospective nature of the study may cause statistical bias. Secondly, the nerve biopsy ratio in our study was low, which may be elevated under the guide of ^{18}F-FDG PET/CT examination in future clinical practice. Finally, the follow-up period was variable and relatively short in some patients to evaluate progression or relapse of NL.

In conclusion, the majority of NL occurred in patients with aggressive lymphoma, of which B-cell NHL were the predominant subtypes. Fluorine-18-FDG PET/CT imaging of NL was mainly characterized by intense glucose accumulation alongside peripheral nerves, and subsequent IT chem/ASCT was suggested to improve the outcomes of NL.

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Bibliography

1. Baehring JM, Damek D, Martin EC et al . Neurolymphomatosis. *Neuro Oncol* 2003; 5(2): 104-15.
2. Grisariu S, Avni B, Batchelor TT et al. Neurolymphomatosis: an International Primary CNS Lymphoma Collaborative Group report. *Blood* 2010; 115 (24): 5005-11.
3. Baehring JM, Batchelor TT. Diagnosis and management of neurolymphomatosis. *Cancer J* 2012; 18(5): 463-8.
4. Singh SS, Mittal BR, Kumar R et al. Primary Central Nervous System Lymphoma With Diffuse Neurolymphomatosis Involving Multiple Cranial and Spinal Nerve Roots. *Clin Nucl Med* 2020; 45(6): e285-e287.
5. Ghose A, Elias HK, Guha G et al. Influence of Rituximab on Central Nervous System Relapse in Diffuse Large B-Cell Lymphoma and Role of Prophylaxis--A Systematic Review of Prospective Studies. *Clin Lymphoma Myeloma Leuk* 2015; 15(8): 451-7.
6. El-Galaly TC, Cheah CY, Bendtsen MD et al. Treatment strategies, outcomes and prognostic factors in 291 patients with secondary CNS involvement by diffuse large B-cell lymphoma. *Eur J Cancer* 2018; 93: 57-68.
7. van den Bent MJ, de Bruin HG, Bos GM, Brutel de la Riviere G, Sillevis Smitt PA. Negative sural nerve biopsy in neurolymphomatosis. *J Neurol* 1999; 246(12): 1159-63.
8. Kamiya-Matsuoka C, Shroff S, Gildersleeve K et al. Neurolymphomatosis: a case series of clinical manifestations, treatments, and outcomes. *J Neurol Sci* 2014; 343(1-2): 144-8.
9. Byun JM, Kim KH, Kim M et al. Diagnosis of secondary peripheral neurolymphomatosis: a multi-center experience. *Leuk Lymphoma* 2017; 58(11): 2624-32.
10. Bronstein Y, Tummala S, Rohren E. F-18 FDG PET/CT for detection of malignant involvement of peripheral nerves: case series and literature review. *Clin Nucl Med* 2011; 36(2): 96-100.
11. Salm LP, Van der Hiel B, Stokkel MP. Increasing importance of ^{18}F-FDG PET in the diagnosis of neurolymphomatosis. *Nucl Med Commun* 2012; 33(9): 907-16.
12. Kinoshita H, Yamakado H, Kitano T et al. Diagnostic utility of ^{18}F-FDG-PET in neurolymphomatosis: report of five cases. *J Neurol* 2016; 263(9): 1719-26.
13. Zhou WL, Wu HB, Weng CS et al. Usefulness of ^{18}F-FDG PET/CT in the detection of neurolymphomatosis. *Nucl Med Commun* 2014; 35(11): 1107-11.
14. Tsang HH, Lee EY, Anthony MP, Khong PL. ^{18}F-FDG PET/CT diagnosis of vagus nerve neurolymphomatosis. *Clin Nucl Med* 2012; 37(9): 897-8.
15. Guo H, Mosci C, Iagaru A. Demonstration of peripheral nerve root involvement by non-Hodgkin's lymphoma on ^{18}F-FDG PET/CT. *Eur J Nucl Med Mol Imaging* 2012; 39(4): 729-30.
16. Ganeshalingam R, Roach P, Schembri GP. Diffuse Large B-Cell Lymphoma Recurring as Neurolymphomatosis on ^{18}F-FDG PET/CT. *Clin Nucl Med* 2019; 44(2): 145-7.
17. Salm LP, Van der Hiel B, Stokkel MP. Neurolymphomatosis diagnosed by ^{18}F-FDG PET-CT. *Clin Nucl Med* 2013; 38(6): e261-262.
18. Araz M, Soydal C, Ozturk C et al. An uncommon presentation of diffuse large B cell lymphoma with multiple peripheral nerve involvement demonstrated BY ^{18}F-FDG PET/CT. *Eur J Nucl Med Mol Imaging* 2020; 47(1): 218-9.
19. Shree R, Goyal MK, Modi M et al. The Diagnostic Dilemma of Neurolymphomatosis. *J Clin Neurol* 2016; 12(3): 274-81.
20. Jellinger K, Radiaszkiewicz T. Involvement of the central nervous system in malignant lymphomas. *Virchows Arch A Pathol Anat Histol* 1976; 370(4): 345-62.

21. Gan HK, Azad A, Cher L, Mitchell PL. Neurolymphomatosis: diagnosis, management, and outcomes in patients treated with rituximab. Neuro Oncol 2010; 12(2): 212-5.
22. DeVries AH, Howe BM, Spinner RJ, Broski SM. B-cell peripheral neurolymphomatosis: MRI and 18F-FDG PET/CT imaging characteristics. Skeletal Radiol 2019; 48(7): 1043-50.
23. Khurana A, Novo M, Nowakowski GS et al. Clinical manifestations of, diagnostic approach to, and treatment of neurolymphomatosis in the rituximab era. Blood Adv 2021; 5(5): 1379-87.
24. Albano D, La Grutta L, Grassedonio E et al. Pitfalls in whole body MRI with diffusion weighted imaging performed on patients with lymphoma: What radiologists should know. Magn Reson Imaging 2016; 34(7): 922-31.
25. Orellana-Noia VM, Reed DR, McCook AA et al. Single-route CNS prophylaxis for aggressive non-Hodgkin lymphomas: real-world outcomes from 21 US academic institutions. Blood 2022; 139(3): 413-23.
26. Ghobrial IM, Buadi F, Spinner RJ et al. High-dose intravenous methotrexate followed by autologous stem cell transplantation as a potentially effective therapy for neurolymphomatosis. Cancer 2004; 100(11): 2403-7.
27. Illerhaus G, Kasenda B, Ihorst G et al. High-dose chemotherapy with autologous haemopoietic stem cell transplantation for newly diagnosed primary CNS lymphoma: a prospective, single-arm, phase 2 trial. Lancet Haematol 2016; 3(8): e388-397.
28. Kobayashi H, Abe Y, Miura D et al. Limited efficacy of high-dose methotrexate in patients with neurolymphomatosis. Int J Hematol 2019; 109(3): 286-91.