Original Article

Outcome and Prognostic Factors of Primary Central Nervous System Lymphoma in Southern Thailand

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Abstract

Context: Primary central nervous system lymphoma (PCNSL) is an uncommon type of brain tumor that has an aggressive disease course. Its outcomes, including factor-related outcomes, are therefore not well established in our country. **Aims:** This study aims to investigate the outcome and prognostic factors in PCNSL patients at our institute. **Settings and Design:** Retrospective study in a single university hospital. **Subjects and Methods:** We reviewed consecutive cases of newly diagnosed PCNSL at Prince of Songkla University from 2005 to 2018. The data were collected to evaluate the treatment outcomes and prognostic factors. **Statistical Analysis Used:** The Kaplan–Meier method for survival analysis, and Cox regression for variable analysis. **Results:** Eighty-seven patients met the inclusion criteria. Patients were predominantly male, and their mean age was 58.8 ± 11.2 years. Only four patients were infected with HIV. Motor weakness was the most common presentation, and neuroimaging revealed multiple lesions in 56.3% of patients. The patients were divided into four groups according to treatment modality: palliative treatment, whole-brain radiotherapy (WBRT) alone, chemotherapy (CMT) alone, and combined WBRT and CMT groups. The median overall survival was 7 months. The 1-, 2-, and 5-year survival rates were 29%, 21.5%, and 4.6%, respectively. The age of >60 years was a significant poor prognostic factor. In addition, patients who received combined treatment exhibited the highest survival rate. **Conclusions:** PCNSL has a low survival rate, even in the present era. Older age is the most substantial factor associated with unfavorable outcomes. The most effective treatment is combined with WBRT and CMT.

Keywords: *Brain tumor, chemotherapy, overall survival, primary central nervous system lymphoma, whole-brain radiotherapy*

Introduction

Primary central nervous system lymphoma (PCNSL) is a rare cancer that has an aggressive course. PCNSL is a type of extranodal non-Hodgkin's lymphoma (NHL) located along the craniospinal axis. More than 95% of cases are diffuse large B-cell lymphoma (DLBCL).[1] The disease incidence is more common in immunocompromised patients.[2,3] However, this rate has increased in healthy elderly within the current decade.[4]

In general, the outcomes of PCNSL patients are worse than those with extranodal NHL in other organs, for which the median survival rate ranges from 9 to 35 months.[2,3,5-7] Unfortunately, certain standard therapy components are still controversial including the extent of surgical resection[8] and the appropriate postoperative treatments (chemotherapy [CMT], whole-brain radiotherapy [WBRT], immunotherapy, or combined therapy).[7]

Patient prognosis depends on various patient factors, PCNSL factors itself, and whether or not a patient has received treatment.[9,10] The prognostic models for predicting patient outcomes, such as the International Extranodal Lymphoma Study Group score,[6] Memorial Sloan Kettering Cancer Center score,[5] and the Nottingham-Barcelona score,[11] are well established.

In Thailand, the outcome of PCNSL patients is not well defined, especially in the era of CMT.[12] Accordingly, this study aims to evaluate the treatment result in terms of survival rate and prognostic factors in PCNSL patients at our institute.

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Subjects and Methods

Patients

After approval from the relevant Ethics Committees (REC 62-051-10-4), a retrospective review of consecutive cases of newly diagnosed PCNSL between January 2005 and June 2018 at a single institution was performed. Our institute, Prince of Songkla University, is a university hospital that serves as a referral neuro-oncologic center in the south of Thailand. We included patients aged 15 years and older. Every patient received a histopathologic diagnosis after stereotactic brain biopsy or tumor resection. The selection of cranial surgery depended on clinical conditions such as mass effect, neurological deficit, and the attending neurosurgeon's decision.

We critically reviewed relevant data from the institute's database, which included the patient characteristics (sex, age, and performance status with Eastern Cooperative Oncology Group [ECOG] score at the time of diagnosis), preoperative laboratory test results (HIV status, serum lactic acid dehydrogenase [LDH], and cerebrospinal fluid [CSF] protein), preoperative neuroimaging (computed tomography [CT] or magnetic resonance imaging [MRI] of the brain, size, location, and the number of lesions), type of surgery (biopsy, gross total resection, and subtotal resection), pathology report (DLBCL or another type), postoperative treatment (palliative, CMT, and WBRT), and status of the patient (deceased or alive). Experienced pathologists also reviewed all tissue pathologies. The selection of postoperative treatment depended on the patient's performance status, and the consulting hematologist and radiologist's opinion. A combined treatment group means patients receiving CMT and radiotherapy, which may or may not be accepted at the same time. Furthermore, we excluded patients with systemic lymphoma involvement diagnosed by CT scan of the chest, whole abdomen, and pelvis or bone marrow analysis.

The upper limit of normal serum LDH was 140 U/L.[13] The cut off level for normal CSF protein was <60 mg/dL in patients older than 60 years of age and <45 mg/dL in patients younger than 61 years.[6] Biopsy referred to when stereotactic surgery was performed or when <25% of the preoperative tumor volume was resected. Gross total resection was defined as craniotomy, complete tumor resection, and when the tumor was not detected on postoperative imaging. The remaining patients were classified into subtotal resection group. To determine their current status, we followed up all patients in February 2019 by telephone and reviewed the institute data and/or the civilian registration database.

Statistical analysis

The R Statistical Software version 3.5.0 (R Foundation, Vienna, Austria) was used for the statistical analysis. For descriptive purposes, the patient demographic data and clinical characteristics, total number, percent, and means with standard deviations were calculated. We used the Kaplan–Meier method for survival analysis. Cox regression was performed for univariable analysis, whereas backward stepwise analysis was used for multivariable analysis. In this study, a $P < 0.05$ represented a statistically significant difference.

Results

Patient characteristics

At our center, 92 patients were diagnosed with lymphoma of the brain, of which five patients with secondary CNS lymphoma were excluded. Finally, this study enrolled the data of 87 patients. Patients were predominantly male (45 patients, 51.7%), and the average patient age was 58.8 years (range, 30–80 years). There were four HIV-positive patients (4.8%) and no other immunodeficiency diseases. The most prevalent underlying condition was hypertension (35.6%). Accordingly, most of the patients had ECOG scores >1.

Weakness was the most common presenting symptom (66.7%), followed by increased intracranial pressure-related symptoms such as headache (44.1%) and altered consciousness (37.9%). Most patients had multiple (56.3%), unilateral (52.9%), and cortical lesions (55.2%). More than 60% of patients had not undergone lumbar puncture to obtain CSF; thus, CSF protein level information was missing. In all patients, 2.3% of data on the LDH level were missing. Approximately 70% of the group had normal serum LDH levels. The clinical characteristics of the patients are shown in Table 1.

More than 80% of patients were diagnosed by stereotactic brain biopsy [Figure 1a]. Thirteen patients underwent craniotomy for tumor removal [Figure 1b,c]. Most patients (8 out of 13) had a single infiltrative lesion with marked perilesional brain edema. Preoperative MRI and intraoperative frozen sections could not distinguish PCNSL from other malignant brain tumors such as brain metastasis or high-grade glioma. Three patients in the craniotomy group had an intraventricular tumor. One patient had a single lesion in the cerebellum. Furthermore, another patient had a lesion in the sellar region. The pathological diagnosis was DLBCL in 96.6% of cases. The other three patients were diagnosed with peripheral T-cell lymphoma.

Most patients (77%) received at least one treatment, either CMT alone, brain radiation alone, or both. The remaining patients were classified into the palliative group and received the best supportive treatment. After 2013, the number of patients who received CMT was increased. The average time until therapy initiation was 27 days after surgery (range, 6–161 days). In the radiation (as a first treatment or single treatment in 32 patients) and

Table 1: Characteristics of primary central nervous system lymphoma patients (*n*=87)

Factor	*n* (%)
Gender	
Male	45 (51.7)
Female	42 (48.3)
Mean of age-year (SD)	58.8 (11.2)
Presenting signs or symptoms	
Weakness	58 (66.7)
Headache	41 (47.1)
Alteration of consciousness	33 (37.9)
Seizure	5 (5.7)
ECOG	
1	22 (25.3)
2	35 (40.2)
3	24 (27.6)
4	6 (6.9)
HIV reactive status	4 (4.8)
Number of lesion	
Single	38 (43.7)
Multiple	49 (56.3)
Location(s)	
Cortical	48 (55.2)
Basal ganglion	33 (37.9)
Corpus callosum	26 (29.9)
Periventricular	25 (28.7)
Cerebellum	14 (16.1)
Brainstem	4 (4.6)
Lateralization	
Unilateral	46 (52.9)
Bilateral	41 (47.1)
LDH level (U/L)	
Normal	62 (71.3)
High	23 (26.4)
No data	2 (2.3)
CSF Protein (mg/dL)	
Normal	15 (17.2)
High	15 (17.2)
No data	57 (65.6)
Extend of tumor resection	
Biopsy	74 (85.1)
Subtotal resection	12 (13.8)
Gross total resection	1 (1.1)
Pathology	
Diffuse large B-cell	84 (96.6)
Peripheral T-cell	3 (3.4)

CSF – Cerebrospinal fluid; ECOG – Eastern Cooperate Oncology Group performance status; HIV – Human immunodeficiency virus; LDH – Lactate dehydrogenase; SD – Standard deviation

CMT groups (as a primary treatment or only treatment in 35 patients), the average time to treatment initiation was 22 days after surgery (range, 6–161 days) and 30 days after surgery (range, 6–120 days), which was slower, respectively. The postoperative treatment details are shown in Table 2.

Survival outcome and prognostic factors

There were no missing data in this part of the study. The average follow-up time was 18.3 months (range, 0–109 months). At the end of February 2019, 23% of the patients were alive, and the median overall survival was 7 months. The 1-, 2-, and 5-year overall survival rates were 29%, 21.5%, and 4.6%, respectively [Figure 2]. The median overall survival of patients in the palliative group was only 1 month. However, the median overall survival of patients in the CMT only group, brain radiation alone group, and the combined treatment group was 2, 7, and 15 months, respectively [Figure 3].

In the univariate analysis, the age of >60 years and palliative treatment were significant prognostic factors for death [Table 3]. Nevertheless, the only treatment modalities that were significant in the multivariable analysis treatment. Those who received CMT combined with radiotherapy exhibited the best survival (hazard ratio [HR], 0.18, $P < 0.001$).

We also evaluated the univariable analysis by excluding the palliative group and using the radiotherapy group as the reference. The significant factors were the same as those mentioned above. Age and treatment were significant prognostic factors for death in the univariable analysis. Correspondingly, the treatment factor of combined CMT and WBRT was substantial (HR, 0.47, $P = 0.03$).

Discussion

Our study reported the experiences of a single institute over 14 years and evaluated the outcomes of PCNSL patients who were treated with limited available resources. Unfortunately, this study found that patients had a short survival time with a median overall survival of 7 months compared with previous studies that found that the median overall survival of PCNSL patients was higher and ranged from 9 to 100 months.[3,5,7,10,12,14-16] Based on our knowledge, the different survival rates were primarily influenced by the patient's status and treatment options.

A patient's preoperative status plays a significant role in determining treatment outcomes. Currently, age, pretreatment PS, location, tumor number, absolute lymphocyte count, serum LDH, and CSF protein concentration are all generally accepted prognostic factors from four prognostic models.[5,6,11,14] These models may help clinicians identify higher-risk patients and select proper treatment strategies. However, our result reveals that the only significant prognostic factor is postoperative treatment. Patients who received both CMT and brain radiation had better survival outcomes. In contrast, previous studies found that older age and pretreatment PS are significant prognostic factors.[2,3,5,6,10,11,13,14] Most previous studies defined older age as >60 years,[3,6,13,16-18] whereas others used >50 years as the cut off.[2,5,11,14] In our study, older age was a significant predictor of poor outcomes in

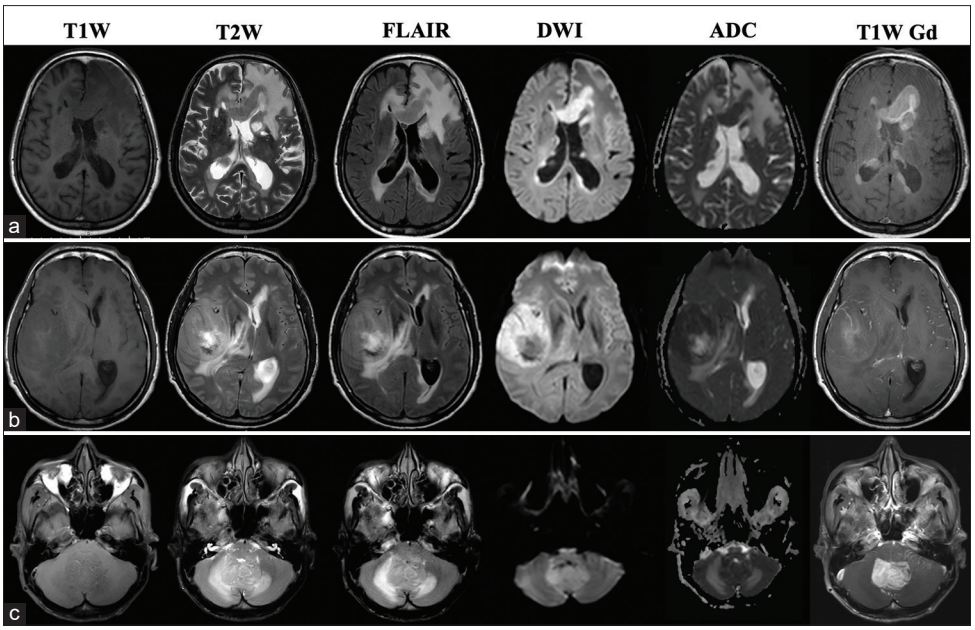

Figure 1: Demonstration of three primary central nervous system lymphoma patients. (a) The MRI finding of typical primary central nervous system lymphoma. Tumors located at corpus callosal, periventricular, and subependymal. On T1W found hypointense, T2W and FLAIR are iso- to hyperintense, DWI is restricted, ADC is hypointense, and T1W gadolinium-enhanced image are homogeneous. This patient underwent a stereotactic biopsy for tissue diagnosis. (b and c). The MRI of non-typical cases of primary central nervous system lymphoma who received craniotomy for tumor removal. (b) They demonstrate a right temporal mass with central Gd enhancement. (c) They show posterior fossa tumor with heterogeneous enhanced

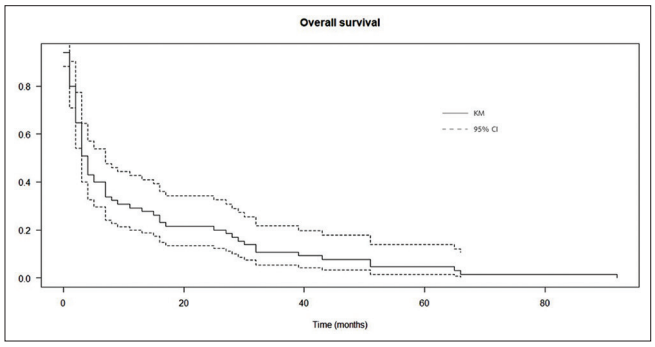

Figure 2: Kaplan–Meier survival analysis with 95% confidence interval of overall survival duration in 87 primary central nervous system lymphoma patients

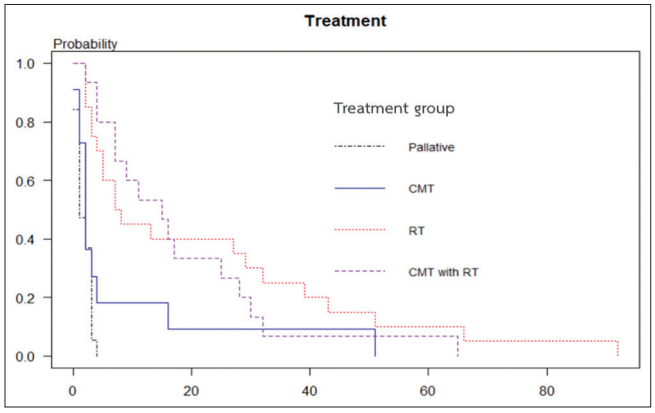

Figure 3: Survival of primary central nervous system lymphoma patients by postsurgical treatment subgroups. The log-rank test shows a statistically significant difference in survival by treatment subgroups (*P* < 0.001)

Table 2: Postoperative treatment of primary nervous system lymphoma patients and time to treatment among treatment modalities

Postoperative treatment	*n* (%)	Time to treatment (days)*
Palliative	20 (23.0)	-
CMT	19 (21.8)	36.5 (9-120)
WBRT	21 (24.1)	29.3 (6-161)
WBRT + CMT	27 (31.1)	24.4 (7-60)

*Range of time to treatment (minimum-maximum).
CMT – Chemotherapy; WBRT – Whole brain radiotherapy; WBRT + CMT – Combined treatment with whole-brain radiotherapy and chemotherapy

the univariable analysis, and age was a poor prognostic factor, but not significant, in the multivariable analysis. It should be caused by the majority of the patients in this study being elderly.

The standard treatment protocol for PCNSL has been widely adopted. However, the protocol differs among the many current guidelines[19,20] and depends on existing evidence and resource availability. In the first half of this study, newly diagnosed PCNSL patients were treated with radiotherapy. Then, in 2011, the Thai Society of Hematology launched practical guidelines for PCNSL (http://tsh.or.th). From that time, CMT consisting of high-dose methotrexate became the mainstay of treatment. It provided more prolonged survival when combined with whole-brain radiotherapy as our demonstrated result (CMT alone vs. CMT + WBRT, median overall survival of 7 months vs. 15 months).

Table 3: Factors associated with death in primary central nervous system patients by Cox regression analysis

Factor	Univariate analysis HR (95% CI)	*P*	Multivariable analysis† HR (95% CI)	*P*
Gender				
Male	Reference value			
Female	1.16 (0.71-1.89)	0.54		
Age				
<60	Reference value		Reference value	
≥60	1.78 (1.08-2.93)	0.02	1.18 (0.66-2.09)	0.57
Preoperative ECOG				
≤ 2	Reference value			
>2	0.66 (0.34-1.28)	0.22		
Hypertension*	0.89 (0.53-1.48)	0.65		
Dyslipidemia*	1.17 (0.59-2.13)	0.64		
Diabetes mellitus*	1.64 (0.84-3.19)	0.14		
Heart disease*	0.64 (0.09-4.69)	0.66		
Presenting signs or symptoms				
Headache*	0.79 (0.48-1.31)	0.36		
Seizure*	0.57 (0.17-1.85)	0.35		
Weakness*	1.25 (0.74-2.10)	0.39		
Alteration of consciousness*	1.28 (0.77-2.11)	0.32		
HIV reactive status*	0.49 (0.12-2.07)	0.33		
Tumor location(s)				
Cortical*	0.97 (0.59-1.59)	0.91		
Periventricular*	1.01 (0.60-1.70)	0.96		
Basal ganglion*	1.49 (0.90-2.45)	0.11		
Corpus callosum*	0.92 (0.55-1.56)	0.77		
Brainstem*	1.83 (0.56-5.90)	0.31		
Cerebellar tumor*	1.30 (0.67-2.50)	0.42		
Bilateral tumor*	1.03 (0.63-1.68)	0.89		
Number of tumor(s)				
Single	Reference value			
Multiple	1.21 (0.73-1.99)	0.45		
LDH level				
<500	Reference value			
≥500	1.37 (0.79-2.37)	0.25		
CSF protein level				
<150	Reference value			
≥150	0.75 (0.22-2.58)	0.65		
Extend of resection				
Biopsy	Reference			
Tumor resection	1.59 (0.08-3.16)	0.18		
Postoperative treatment				
Palliative treatment	Reference value		Reference value	
RT	0.14 (0.06-0.31)	<0.001	0.15 (0.06-0.33)	<0.001
CMT	0.37 (0.16-0.85)	0.02	0.42 (0.17-1.04)	0.06
CMT with RT	0.16 (0.07-0.37)	<0.001	0.18 (0.07-0.41)	<0.001

*Data show only "yes group" while reference groups (no group) are hidden; †Backward stepwise method. CMT – Chemotherapy; CSF – Cerebrospinal fluid; ECOG – Eastern Cooperate Oncology Group performance status; HIV – Human immunodeficiency virus; LDH – Lactate dehydrogenase; RT — Whole-brain radiotherapy; HR – Hazard ratio

Some studies have noted that the choice of surgery might influence the treatment outcome. The extent of resection provides a theoretical benefit of decreased mass effect, cytoreduction, and improved tumor response to concurrent chemoradiotherapy in glioblastoma patients.[21] However, this strategy was found to be inconsistent with PCNSL patients.[8,16,22,23] Similar to our results, surgical factors were previously not found to be related to survival benefits. In

this study, the role of the neurosurgical intervention was limited to biopsy for tissue diagnosis. Tumor removal or debulking is not recommended.

This study has many limitations. First, the study design has a selection bias, given that it is a retrospective study that did not have specified patient selection criteria for any treatments. Second, this study was conducted at a single institute; therefore, the sample size is too small. Third, the treatment regimen changed over time, which may have contributed to chronological bias. Finally, we did not explore the molecular profiles (e.g., gene expression profiles and immunohistochemistry) of the PCNSL patients. These data are important prognostic factors in recent studies.[24] A future prognostic study should be included in this issue.

Conclusions

According to the advance in CMT for PCNSL patients, the survival rate was improved. The most extended survival was found in combined therapy with WBRT and MTX-based CMT. However, the best regimen was still ongoing to study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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