



# Prognostic Factors of the Primary Central Nervous System Lymphoma: Clinical Experience from a Tertiary Care Center in the Middle East

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## Abstract

**Aim** Primary central nervous system lymphoma (PCNSL) is a rare extra nodal non-Hodgkin's lymphoma. The optimal treatment for PCNSL is still unclear. In this study, we present our experience with management of PCNSL in a tertiary care center in Iran.

**Methods** In this retrospective study, 58 patients with tissue diagnosis of PCNSL were studied. All patients were treated with chemotherapy including intravenous high-dose methotrexate, rituximab and temozolomide and radiotherapy by the same oncologist. Statistical analysis was performed using SPSS.

**Results** The mean overall survival (OS) in this study was  $37.4 \pm 13.6$  months and the mean progression free survival (PFS) was  $35.1 \pm 9.8$  months. The mean time to progression was  $15.2 \pm 8.79$  months among 8 patients who experienced progression in this series. Finding of a positive CSF cytology was not linked with disease progression, while HIV infection and multifocal involvement at initial presentation were strongly linked to a lower PFS. The single most important factor affecting the OS was the histopathologic type of the PCNSL; two of the three patients who died from their disease in this series had non-B cell PCNSL, whereas only one patient with DLBCL died because of brainstem involvement.

**Conclusion** The results of this study show a lower rate of HIV-infection in patients with PCNSL as compared to the series from the western countries. Non-B cell histopathology and HIV-infection were found to be associated with the dismal prognosis.

## Keywords

- brain tumor
- HIV
- lymphoma
- primary CNS lymphoma

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## Introduction

Primary central nervous system lymphoma (PCNSL) is a rare and aggressive extra nodal non-Hodgkin's lymphoma (NHL).<sup>1,2</sup> PCNSL most commonly presents as an intracerebral mass; however, it may involve the brain, spinal cord, leptomeninges, or eyes without evidence of systemic involvement at the time of diagnosis.<sup>2,3</sup> With an overall incidence rate of 0.44 per 100,000 populations, it accounts for 2% of all primary CNS tumors.<sup>4</sup> The optimal treatment for PCNSL is still unclear.<sup>5</sup> New therapeutic approaches have markedly improved the survival; however, the optimal management of this disease still poses a challenge in neuro-oncology.<sup>6</sup>

To date, an increasing number of cases have been reported from Western countries. However, we did not find any report about PCNSL from middle east countries in our review of the literature. In this study, we present our experience with management of PCNSL in a tertiary care center in Iran and compare the clinical and paraclinical features of our patients with those of the others.

## Methods

In this retrospective study, patients with tissue diagnosis of PCNSL between January 2011 and December 2018 were studied. All patients were examined both by the neurosurgeons and oncologist of our center. Patients underwent a complete evaluation for evidence of extra-CNS disease including ophthalmological evaluation, serum and urine protein electrophoresis, lumbar puncture, positron emission tomography (PET) scan, testicular ultrasound in male patients, bone marrow biopsy, as well as thoraco-abdomino-pelvis computed tomography (CT) imaging. Inclusion criteria were a diagnosis of PCNSL, confirmed by histopathological evaluation and consistent longitudinal follow-up at our institution for a minimum of 1 year.

All patients were treated with chemotherapy including intravenous high-dose methotrexate, rituximab, and temozolomide and radiotherapy by the same oncologist (ME).

Medical records included age, sex, Karnofsky performance score (KPS), sign and symptoms, ocular involvement, leptomeningeal involvement (on imaging and/or CSF cytology), laboratory data (HIV tests, CSF cytology), findings of whole CNS CT scan and Magnetic resonance imaging (MRI), and follow-up data (progression and survival). This study was conducted in accordance with the Declaration of Helsinki and the ethics committee of our institution approved the study.

Statistical analysis was performed using SPSS (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp; 2016). Descriptive statistics were mean and standard deviation (SD) for the quantitative variables and frequencies for the qualitative variables. Comparisons between the categorical variables were performed by Pearson's chi-square test and Fisher exact test. Mann-Whitney was applied for inter-group comparison of continuous variables between the two groups.

## Results

Fifty-eight patients with mean age of 48 years (range of 24 to 78 years) were enrolled including 32 females (55.1%) and 26 males (44.9%). The mean follow-up period was 40.2 months (ranging from 12 to 66 months).

The most common locations were frontal lobe (16, 27.6%) and periventricular area (15, 25.8%). The histologic diagnosis of lymphoma was confirmed in all cases via stereotactic biopsy (55, 94.8%) or open surgery (3 [5.2%]: two with the impression of glioma and one with uncus herniation needing emergent decompression). The most common histological finding was diffuse large B-cell lymphoma (DLBCL), which was found in 56 patients (96.5%), the two others had Burkitt's and T cell lymphoma. Contrast-enhanced brain MRI was done in all patients that revealed multiple lesions in 7 patients (12%) and one lesion in the remaining 51 (88%). Systemic evaluations did not reveal any additional abnormality except positive HIV antibody detected in three patients (5.1%). All patients underwent ophthalmologic examination for chorio-retinal involvement, which was observed in three patients (5.1%). Six (10.3%) patients had positive CSF cytology for lymphoma cells, 3 of them had also evidence of leptomeningeal enhancement over cerebral hemispheres. Two of the 6 patients (33.3%) with positive CSF cytology had HIV infection and 4 cases (66.6%) had multiple lesions in brain. Eight patients (13.7%) needed at least another admission for disease progression: three of them died from disease progression; two patients with Burkitt's (after 13 months) and T cell lymphoma (after 18 months) and one with brain stem involvement (after 12 months), in the other five patients, the disease progression was controlled after treatment. In comparison to the other patients, the 8 patients who experienced progression had no significant difference in the rate of positive CSF cytology (1 patient, 12.5%, vs. 5, 10%,  $p=0.72$ ) but had higher rate of HIV infection (2, 25%, vs. 1, 2%,  $p=0.000$ ) and multiple lesions on their initial MRI (3, 37.5% vs. 4, 8%,  $p=0.001$ ). The mean age of patients who had a progression was  $60.8 \pm 5.3$  years as compared to the others ( $45.9 \pm 14.1$  years) ( $p=0.003$ ).

The mean overall survival in this study was  $37.4 \pm 13.6$  months and the mean progression-free survival (PFS) was  $35.1 \pm 9.8$  months. The mean time to progression was  $15.2 \pm 8.79$  months (range: 8–26 months) among 8 patients who experienced progression in this series.

There was no mortality related to the surgical procedure (biopsy or craniotomy) in this series. ▶**Table 1** summarizes the clinical features and the patient outcomes in this study.

## Discussion

The overall prognosis for PCNSL remains poor for the majority of cases despite remarkable medical progression and less than 30% of patients can be cured successfully.<sup>1,7</sup> This is the first report of patients with PCNSL in the middle east according to our review of literature.

The majorities (~ 95%) of PCNSLs are classified as DLBCL, and the remaining cases are low-grade B cell lymphoma, or

**Table 1** Characteristic features of the patients

Variables		Number (%)
Age	< 50	38
	50–70	17
	> 70	3
Sex	Male	26 (44.9)
	female	32 (55.1)
Karnofsky performance score (KPS)	< 70	3 (5.1)
	> 70	55 (94.9)
Signs and symptoms	FND*	10 (17.2)
	Seizure	19 (32.7)
	RICP*	41 (70.7)
	Others	23 (39.6)
Location of tumor	Lobar	28 (48.2)
	Bi-hemispheric	7 (12.0)
	Peri-ventricular	15 (25.8)
	Brain stem	1 (1.7)
	Multiple lesion	7 (12.0)
Multifocal	Yes	14 (24.1)
	No	44 (75.9)
Ocular involvement	Yes	3 (5.1)
	No	55 (94.9)
Leptomeningeal involvement	Yes	6 (10.3)
	No	52 (89.7)
HIV positive	Yes	3 (5.1)
	No	55 (94.9)

\*FND: focal neurological deficit, RICP: raised intracranial pressure.

rarely, T cell or Burkitt's lymphoma.<sup>1</sup> In a study on 167 patients with PCNSLs, Yuan et al reported the histological type as DLBCL in 150 cases (89.8%).<sup>1</sup> In the study of Yadav et al, all 32 patients with PCNSL were reported to have DLBCL.<sup>8</sup> In our study, the most common histological type was DLBCL which was found in 56 patients (96.5%).

Although most patients are immunocompetent, human immunodeficiency virus (HIV) infection and organ transplantation are considered as the predisposing factors for PCNSL. Epstein-Barr virus (EBV) infection is also suggested to play a role in the oncogenesis among the immunocompromised patients.<sup>1,2</sup> Dandachi et al in a retrospective study on 144 patients with PCNSL in 2019, reported the HIV infection to be positive in 19% of the cases. Patients with HIV were more likely to have multiple lesions, hemorrhage, and peripheral rim enhancement on imaging; to receive palliative care or whole brain radiation; and less likely to receive chemotherapy.<sup>5</sup> In our study, HIV infection was detected in three patients (5.1%) and all the three survived until the end of the study and experienced no progression. In our study, two of the three patients with HIV infection experienced disease progression, but none of them died

from disease progression. It seems that HIV infection is associated with higher rate of progression/recurrence but does not affect the overall survival.

In our study, 10.3% of patients had positive CSF cytology for lymphoma cells, three of them had also evidence of leptomeningeal enhancement over cerebral hemispheres. Kiewe et al in 2010 reported 92 patients with PCNSL; median event-free survival (EFS) of patients with meningeal dissemination (MD) was 26 months, of those without MD 34.1 months; median OS of these two patients' groups was 45.5 and 42.5 months, respectively.<sup>9</sup> In a study by Ghesquière et al, CSF cytology was not identified as a prognostic factor for OS and they suggest that the evaluation of CSF provides no additional information for survival although this test should be necessary to diagnose leptomeningeal involvement.<sup>10</sup> In our study, finding of a positive CSF cytology was more probable among HIV-infected patients (2 out of 3) and those with multiple involvement site on brain MRI (4 out of 7). Nevertheless, based on our results, only one of the six patients with positive CSF cytology had a progressive disease, who had the features of HIV infection and multiple brain lesions as well.

According to the review of literature, high-dose methotrexate (MTX)-based polychemotherapy regimen prolongs the survival and is currently considered the most effective treatment and the standard of care for patients with PCNSL.<sup>5,11</sup> The role of intrathecal chemotherapy and whole brain radiation therapy is controversy.<sup>5</sup> A population-based cohort of 189 patients with PCNSL in 2019, variable patterns of first-line treatments with increasing use of rituximab and high-dose MTX-based poly-chemotherapy after 2007, were shown to be associated with an increase in median OS restricted to patients aged below 70 years.<sup>12</sup> Dalia et al reported that patients treated initially with high-dose MTX-based therapy had improved overall and progression-free survival, with no improvement shown with added radiation or intrathecal therapy.<sup>3</sup> In our study, all patients were treated with rituximab and high-dose MTX and the mean overall survival and PFS in this study were  $37.4 \pm 13.6$  and  $35.1 \pm 9.8$  months, respectively. The mean time to progression was  $15.2 \pm 8.79$  months among eight patients who experienced progression in this series. Yuan et al showed the median OS and PFS were 37 months and 17 months, respectively, with a median follow-up of 25 months.<sup>1</sup> In a study on 89 Chinese patients with PCNSL, Liu et al reported a median OS of 45.3 months and median progression-free survival of 30.0 months.<sup>13</sup>

In a study by Ney et al, a retrospective review of 174 PCNSL patients aged older than 65 years was done; age and performance status were identified as the most important predictors of survival.<sup>14</sup> Lin et al investigated the risk factors of early mortality (death within 60 days after diagnosis) in 133 patients with PCNSL: approximately 9.8% had early mortality; and in multivariate analysis, age 80 years or more and involvement of the basal ganglia were identified as independent risk factors of early mortality, and MTX-based chemotherapy served as an independent protective factor.<sup>15</sup> Yuan et al reported that residual tumor after operation,

chemotherapy without HD-MTX, and palliative treatment were independent prognostic markers and Eastern Cooperative Oncology Group (ECOG) Performance Status more than 3, multifocal lesions, and palliative treatment were revealed as unfavorable independent prognostic markers for PFS.<sup>1</sup> Ghesquière et al evaluated 132 patients with PCNSL with a median follow-up of 102 months and reported that the time-dependent effect of age, performance status and tumor site lost their prognostic value after 6 months from diagnosis.<sup>10</sup> In our study, patients who experienced disease progression had statistically significant older ages in comparison to the other patients (60.8 vs. 45.9 years).

Our study is limited by being retrospective and the number of the patients. In particular, the number of the patients with HIV infection, positive CSF cytology and multifocal lesions was not large enough and thus the comparisons made in this article need to be proved in larger studies from similar populations.

## Conclusion

Our study shows that HIV infection is less common among PCNSL patients in comparison to the series coming from the western countries. Finding of a positive CSF cytology was not linked to disease progression, while HIV infection and multifocal involvement at initial presentation were strongly linked to a lower progression-free survival. The single most important factor affecting the OS was the histopathologic type of the PCNSL; two of the three patients who died from their disease in this series had non-B cell PCNSL, whereas only one patient with DLBCL died because of brainstem involvement.

### Funding

None.

### Conflict of Interest

None declared.

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