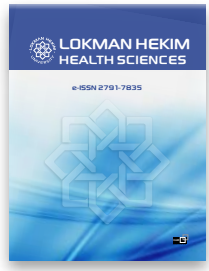
LOKMAN HEKIM HEALTH SCIENCES

DOI: 10.14744/lhhs.2026.70744
Lokman Hekim Health Sci 2026;6(3):431–437



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ORIGINAL ARTICLE

Primary Central Nervous System Lymphomas: A Descriptive Study

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Abstract

Introduction: Primary central nervous system lymphomas (PCNSL) are relatively uncommon, aggressive tumors of B-cells localized within the central nervous system and eye, without systemic involvement. In this study, we present the clinical characteristics, treatments, pathological and immunohistochemical features of PCNSL patients treated in a single center over a period of 6 years.

Methods: This study included patients diagnosed with PCNSL between January 2013 and December 2019. Clinical-pathological and immunohistochemical characteristics were recorded. 1-year overall survival and 1-year progression-free survival rates were analyzed. The International Extranodal Lymphoma Study Group (IELSG) score was used to predict prognosis.

Results: A total of 18 patients were included in the study: 11 women (61.1%) and 7 men (38.9%). The median age was 54 years (range 22–81). Multifocal involvement was detected in 8 patients (44.4%), deep involvement in 6 patients (33.3%), and deep plus multifocal involvement in 4 patients (22.2%). Age (<60 years) (p=0.017), low IELSG score (p=0.011), and autologous hematopoietic stem cell transplantation (aHSCT) (p=0.049) were associated with 1-year overall survival. Surgical resection (p=0.038) and radiotherapy (p=0.045) were factors associated with 1-year progression-free survival.

Discussion and Conclusion: PCNSL is characterized by its aggressive nature and extranodal involvement. The effectiveness of current treatment options for this disease is limited, and clinical outcomes are generally poor. While age (<60 years), low IELSG scores, and the use of aHSCT therapy have been shown to be associated with improved 1-year overall survival outcomes, conversely, surgical treatment was negatively associated with progression-free survival.

Keywords: Hematopoietic stem cells; Lymphoma; Nervous system

Primary central nervous system lymphoma (PCNSL) is an aggressive B-cell malignancy. It is localized to leptomeninges, brain, eyes, and spinal cord without systemic involvement at the time of diagnosis. PCNSL accounts for around 2–5% of all brain tumors and 4–6% of extranodal lymphomas. Its annual incidence is estimated at 0.4–0.7 cases/100,000 people. It generally appears at an advanced age (average of 60 years). Symptom manifestation varies according to the specific region of the nervous system affected. The most prevalent presentations include cognitive and behavioral changes, indications of elevated intracranial pressure, and focal neurological deficits. In

Cite this article as: *Eren D, Çetin M. Primary Central Nervous System Lymphomas: A Descriptive Study. Lokman Hekim Health Sci 2026;6(3):431–437.*

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E-mail: dr.davuteren@gmail.com **Submitted:** 15.10.2025 **Revised:** 06.01.2026 **Accepted:** 12.01.2026 **Available Online:** 06.08.2026

contrast, patients with leptomeningeal involvement may be asymptomatic. Diagnosis involves the use of stereotactic biopsy along with neuroimaging, while cerebrospinal fluid (CSF) analysis may be useful in some patients. Histologically, PCNSL is identified as a highly cellular tumor with a diffuse growth pattern that infiltrates cerebral blood vessels, disrupting reticulin fiber structure. This characteristic vessel wall change and perivascular space infiltration usually occur at the periphery of the tumor.[1]

Treatment advancements over the last two decades, particularly with high-dose methotrexate (HD-MTX)-based chemotherapy, have improved outcomes, with survival rates reaching 60–70% among younger patients with good performance status. There are debates about the most appropriate treatment method despite all these developments. There are opposing views on surgery, radiotherapy, additional chemotherapy, and chemotherapy to be applied directly to the CSF.[2]

This study aims to compare the demographic characteristics, clinical features, staining characteristics of pathology specimens, treatments received, and treatment responses of patients diagnosed with PCNSL in Erciyes University between 2013 and 2019.

Materials and Methods

This study included 18 adult patients diagnosed with PCNSL at Erciyes University between January 2013 and December 2019. However, two patients died due to rapid disease progression before any treatment could be initiated. Therefore, while demographic and clinical characteristics at admission are reported for all 18 patients, the analyses for treatment response, 1-year overall survival, and progression-free survival were conducted on the remaining 16 patients who received treatment. The study protocol was designed to collect demographic information, clinical and laboratory findings, pathological staining characteristics, treatment regimens, complications, and survival criteria. The International Extranodal Lymphoma Study Group (IELSG) score was used to determine prognosis in patients. The components of this scoring system are: Eastern Cooperative Oncology Group (ECOG) performance status >1, age >60, high blood lactate dehydrogenase (LDH) levels, high CSF protein levels, and deep-seated tumors (involving the brainstem, corpus callosum, cerebellum, or basal ganglia). In this system, each positive finding is assigned 1 point. Low risk is defined as 0–1 points, intermediate risk as 2–3 points, and high risk as 4–5 points.

Patients received chemotherapy according to the MATRix or MPV regimens. MATRix Protocol: Methotrexate (3500 mg/m^2) on day 1, followed by folinic acid every 6 h between days 2 and 4, cytarabine (ARA-C, 2×2000 mg/m^2) on days 2 and 3, tiotepa (30 mg/m^2) on day 4, and rituximab (375 mg/m^2) on day 0. MPV Protocol: Methotrexate (3500 mg/m^2), followed by folinic acid every 6 h on days 2 and 4, vincristine (1.4 mg/m^2) on day 1, procarbazine (100 mg/m^2 orally) on days 1–7, intrathecal methotrexate (12 mg on day 1), and dexamethasone (16 mg/day). As consolidation therapy, patients underwent whole brain radiotherapy (WBRT) and/or autologous hematopoietic stem cell transplantation (aHSCT). In addition, aHSCT was used as a rescue regimen in patients with recurrent disease.

Remission was defined as the absence of contrast-enhancing lesions or a >50% reduction in tumor size on imaging. Refractory disease was defined as a <50% reduction or a <25% increase in tumor size. Relapse was defined as the detection of new foci during follow-up in patients considered to be in remission. Survival time and progression-free survival time were measured based on a 1-year period from the date of diagnosis. The concept of deep involvement was defined as involvement of the brainstem, basal ganglia, cerebellum, and corpus callosum. The term multifocal involvement was used to indicate involvement in more than one focus detected on radiological imaging.

Ethical Approval

The current study received approval from the Erciyes University Ethics Committee (approval date: January 29, 2020, protocol number 2020/49) and was carried out in compliance with the principles outlined in the Declaration of Helsinki.

Statistical Analysis

In this study, statistical analyses were conducted with the Statistical Package for the Social Sciences 22.0 program (International Business Machines Corp.; Armonk, New York, USA). Continuous variables were expressed as mean±standard deviation or median (minimum-maximum) after evaluating for normality using the Shapiro-Wilk test. Categorical variables were presented as frequencies and percentages. Since the sample size was small and several cells in the contingency tables had expected counts <5, Fisher's exact test was used for all categorical comparisons. The Student's t-test was used for variables showing a normal distribution, whereas the Mann–Whitney U test was applied to variables that were not normally distributed. A

p<0.05 was considered statistically significant. Multiple comparisons were performed without formal adjustment; thus, these results should be interpreted as exploratory.

Results

This study included 18 adult patients diagnosed with PCNSL. Eleven (61.1%) of the patients were female, and seven (38.9%) were male. The median age of the patients was 54 years (range 22–81). Causes for hospital admission were focal neurological deficit symptoms in nine patients, symptoms related to increased intracranial pressure (headache, dizziness, nausea-vomiting, etc.) in six patients, and vision loss in one patient. The mean time from symptom onset to diagnosis was 3.5 (1–15) months. At the time of diagnosis, 15 patients had an ECOG status below 2, while three patients had a status of 2 or higher. The demographic and clinical characteristics of the patients are presented in Table 1.

Deep located lesions were detected in six patients (33.3%), while multifocal involvement was present in eight patients (44.4%). The most common site of involvement was the cerebral hemispheres (13 patients, 66%); in the remaining patients, involvement was detected in the pituitary gland, putamen, cerebellopontine junction, retro cerebellar region, and fourth ventricle. At the time of diagnosis, LDH levels were above 215 (our laboratory cutoff value) in 8 patients and below 215 in 10 patients. At the time of diagnosis, the absolute lymphocyte count was above 0.9*103/µL (our laboratory cutoff value) in 14 patients.

According to the IELSG scoring system, eight patients were in the intermediate risk category, and 10 were in the low-risk category.

It revealed that subtotal or total resection surgery was performed in 14 patients, while surgery was performed in four patients for stereotactic biopsy. The pathology results of 17 patients were diffuse large B-cell lymphoma, while the pathology of one patient was consistent with Burkitt lymphoma.

A total of 16 patients received induction chemotherapy, 13 of whom were treated with the MPV protocol and 3 with the MATRix protocol. The MATRix regimen was used in a total of 7 patients, while in six patients it was administered as consolidation therapy or rescue therapy in cases of relapse. Seven patients received radiotherapy in addition to chemotherapy.

Sixteen patients who received treatment after diagnosis were evaluated for 1-year overall survival (Table 2). Total mortality during the follow-up period was observed in 11 patients (including two patients who died before treatment).

Table 1. Characteristics of all patients

Variable	Statistics*
Age (years), Median (min-max)	54 (22–81)
	n (%)
Sex	
Male	7 (38.9)
Female	11 (61.1)
Symptoms at admission**	
Focal neurological deficit	9 (56.3)
Signs of ıncreased ıntracranial pressure	6 (37.5)
Loss of vision	1 (6.3)
Tumor localization	
Deep	6 (33.3)
Multifocal	8 (44.4)
Deep+Multifocal	4 (22.2)
Laboratory findings	
Creatinine (mg/dL) (mean±SD)	0.67±0.16
ALT (IU/L) (mean±SD)	27.8±23.6
LDH> 215 (IU/L)	8 (44.4)
Lymphocyte count <900/µL	4 (22.2)
IELSG score	
Low risk (0–1)	10 (55.6)
Intermediate risk (2–3)	8 (44.4)
High risk (4–5)	0 (0.0)
Surgical procedure	
Resection (Total/Subtotal)	14 (77.8)
Biopsy	4 (22.2)

*: p<0.05 was considered statistically significant; **: Symptom data were available for 16 patients. Statistical analyses were performed using Student's t-test or Mann–Whitney U test for continuous variables, and Fisher's exact test for categorical variables. SD: Standard deviation; ALT: Alanine aminotransferase; LDH: Lactate dehydrogenase; IELSG: International Extranodal Lymphoma Study Group.

Among the 16 patients evaluated for 1-year overall survival, six deaths occurred within the 1st year. The 1-year overall survival rate was 62.5%, and the longest survival time was determined to be 50 months. In addition, the 1-year progression-free survival rate was calculated as 43.8%.

Factors associated with 1-year overall survival included being under 60 years of age (p=0.017), low IELSG score (p=0.011), and aHSCT (p=0.049). Surgical treatment (p=0.038) was negatively associated with 1-year progression-free survival, while radiotherapy (p=0.045) was associated with improved progression-free survival. Factors associated with 1-year progression-free survival are shown in Table 3.

Among the seven patients who developed relapse after treatment, the median survival time was 4 months (range

Table 2. Factors associated with 1-year overall survival (n=16)

Variable	Survivor (n=10) n (%)	Non-survivor (n=6) n (%)	p*
Age			0.017
<60 years	9 (90.0)	2 (33.3)	
≥60 years	1 (10.0)	4 (66.7)	
Sex (Male)	5 (50.0)	2 (33.3)	0.635
ECOG score ≥ 2	1 (10.0)	2 (33.3)	0.531
Comorbidities	2 (20.0)	4 (66.7)	0.119
Lesion location			1
Deep	3 (30.0)	3 (50.0)	
Multifocal	5 (50.0)	3 (50.0)	
IELSG risk score			0.011
Low risk	8 (80.0)	1 (16.7)	
Intermediate risk	2 (20.0)	5 (83.3)	
LDH> 215 IU/L	3 (30.0)	4 (66.7)	0.301
Lymphocyte <900/µL	1 (10.0)	3 (50.0)	0.098
Surgery	7 (70.0)	6 (100.0)	0.25
Chemotherapy regimen			
MPV	7 (70.0)	5 (83.3)	1
MATRix	8 (80.0)	2 (33.3)	0.118
Rituximab	8 (80.0)	3 (50.0)	0.299
aHSCT (Consolidation)	6 (60.0)	0 (0.0)	0.049
Radiotherapy	6 (60.0)	1 (16.7)	0.145
Immunophenotype			
Bcl-2 positive	7 (70.0)	3 (50.0)	0.604
Bcl-6 positive	8 (80.0)	6 (100.0)	0.5
Mum-1 positive	6 (60.0)	2 (33.3)	0.608
CD-10 positive	3 (30.0)	0 (0.0)	0.25
Ki67 ≥50%	9 (90.0)	6 (100.0)	1

*: p<0.05 was considered statistically significant. All categorical comparisons were analyzed using Fisher's Exact Test. LDH: Lactate dehydrogenase; aHSCT: Autologous hematopoietic stem cell transplantation; ECOG: Eastern Cooperative Oncology Group.

Table 3. Factors Associated with 1-year progression-free survival (n=16)

Variable	Survivor (n=7) n (%)	Non-survivor (n=9) n (%)	p*
Age			0.615
<60 years	5 (71.4)	5 (55.6)	
≥60 years	2 (28.6)	4 (44.4)	
Sex (Male)	3 (42.9)	4 (44.4)	1
ECOG Score ≥ 2	1 (14.3)	2 (22.2)	1
Comorbidities	2 (28.6)	4 (44.4)	0.635
Lesion location			
Deep	2 (28.6)	4 (44.4)	0.635
Multifocal	2 (28.6)	6 (66.7)	0.165
IELSG risk score			0.344
Low risk	5 (71.4)	4 (44.4)	
Moderate risk	2 (28.6)	5 (55.6)	
LDH> 215 IU/L	3 (42.9)	4 (44.4)	1
Lymphocyte <900/µL	1 (14.3)	3 (33.3)	0.588
Surgery	4 (57.1)	9 (100.0)	0.038
Chemotherapy			
MPV	5 (71.4)	7 (77.8)	1
MATRix	5 (71.4)	5 (55.6)	0.635
Rituximab	5 (71.4)	6 (66.7)	1
Radiotherapy	5 (71.4)	2 (22.2)	0.045
Immunophenotype			
Bcl-2 positive	4 (57.1)	6 (66.7)	1
Bcl-6 positive	5 (71.4)	9 (100.0)	0.165
Mum-1 positive	4 (57.1)	4 (44.4)	1
CD-10 positive	2 (28.6)	1 (11.1)	0.544
Ki67 ≥50%	6 (85.7)	9 (100.0)	0.438

*: p<0.05 was considered statistically significant. All categorical comparisons were analyzed using Fisher's Exact Test. LDH: Lactate dehydrogenase; IELSG: International Extranodal Lymphoma Study Group; ECOG: Eastern Cooperative Oncology Group.

1–6 months). The median survival time in the four patients who experienced refractory disease was also found to be 4 months (1–8 months). Pneumonia (56.3%) was identified as the most common chemoradiotherapy-related complication among treatment-related complications. Table 4 presents details regarding treatment-related complications.

Discussion

This study highlights the aggressive course and poor prognosis of PCNSL. Our findings show that advanced age, high IELSG score, and the absence of aHSCT were associated with poorer 1-year overall survival. Surgical excision was negatively associated with progression-free survival, while radiotherapy was associated with improved outcomes.

We observed that being under 60 years of age at diagnosis was associated with better 1-year overall survival. Literature review reveals conflicting information regarding the effect of advanced age on survival. Although most studies indicate advanced age as a negative factor in survival, there are also studies that present conflicting findings.[3,4] Increase in comorbidities with age, decrease in organ function, and decrease in treatment tolerability may affect this situation. The fact that the patient with the longest survival time (50 months) in our study was 81 years old suggests that the

Table 4. Complications related with treatment

Category and complication	n	%
Infectious complications (n=16)*		
Pneumonia	9	56.3
Febrile neutropenia	7	43.8
Bacteremia	7	43.8
Invasive fungal infection	4	25.0
Urinary tract infection	3	18.8
Neutropenic colitis	2	12.5
Surgery-related complications (n=14)		
Neurological deficit	4	28.6
Surgical site infection	2	14.3
Central hypothyroidism	1	7.1
Diabetes insipidus	1	7.1
Thromboembolic events (n=16)*		
Deep vein thrombosis	2	12.5
Pulmonary thromboembolism	1	6.3
Ischemic cerebrovascular events	1	6.3

*: Percentages were calculated based on the 16 patients who received chemoradiotherapy. p<0.05 was considered statistically significant.

negative effects of advanced age on survival may stem from increasing organ dysfunction, chronic diseases, and low performance status rather than chronological age. The fact that this patient had no organ dysfunction or chronic disease at the time of diagnosis and tolerated all treatments well supports this hypothesis. Among ten patients without comorbidities at diagnosis, the 1-year overall survival rate was 80%, while among the six patients with comorbidities, this rate was 33%. Although this finding is not statistically significant, it shows that current health conditions may negatively affect the course of the disease. When classifying patients into risk groups, considering performance status, underlying health conditions, and organ dysfunction may be more useful than chronological age.

In our study, there was no significant difference in 1-year overall survival or 1-year progression-free survival between patients with an ECOG performance score below 2 and those with a score of 2 or above. In contrast, when patients were classified according to the IELSG scoring system, the 1-year overall survival rate was higher in the low-risk group compared with the intermediate-risk group (88.9% vs. 28.6%). There are studies in the literature showing that a low performance score has negative effects on survival. [5] High LDH and deep involvement were not associated with 1-year overall survival. At this point, it was thought that the age and CSF protein levels in scoring system were more dominant. PCNSL's low annual incidence and the similarity of its presenting symptoms (increased intracranial pressure symptoms, focal neurological deficits, etc.) with many other common neurological diseases can delay the diagnostic process. The fact that patients' initial presentations are usually to neurology clinics and that various treatments (especially steroids) are administered during the period before a PCNSL diagnosis is made may lead to changes in CSF protein and serum LDH levels. Therefore, when creating risk scoring systems for PCNSL, it may be a more accurate approach to use patient-specific and disease-specific factors rather than biochemical parameters that may change with treatment. Recent studies comparing scoring systems and radiology-supported models support our findings.[6,7]

The role of surgery in PCNSL treatment is a controversial topic in the literature. Most studies have shown that total or subtotal resection does not contribute to survival and may have negative effects due to post-operative complications.[8] A smaller number of studies have reported that gross surgery in selected patients has a positive effect on survival.[9] The presence of tumor infiltrates even in areas without radiological involvement in autopsy series of PCNSL patients indicates that total resection is not possible in most patients, even if surgical margins are wide. [10] In our study, the 1-year overall survival rate was 100% in three patients diagnosed with stereotactic biopsy and who did not undergo total or subtotal surgical resection, while this rate was 53.8% in 13 patients who underwent surgery. However, this result is not statistically significant. Progression-free survival was 100% in the group that did not undergo surgery, while it was 30.8% in those who underwent surgery, and this difference was found to be statistically significant. In addition, four patients developed neurological deficits, two patients developed wound site infections, and one patient each developed diabetes insipidus and central hypothyroidism as a result of surgery.

Although there is no standard chemotherapy regimen for PCNSL treatment, evidence-based guidelines are primarily based on regimens containing HD-MTX.[11] In our study, all patients receiving chemotherapy were administered regimens containing HD-MTX. Thirteen patients received MPV chemotherapy, and three patients received MATRix chemotherapy as induction chemotherapy. Seven patients received the MATRix regimen, and six patients received aHSCT as rescue or consolidation therapy. The 1-year overall survival rate was 80% in patients treated with the MATRix regimen and 58.3% in those receiving the MPV regimen. However, these results are not statistically

significant. The absence of a group of patients treated with regimens not containing HD-MTX in our study prevented us from performing a reliable analysis.

The modern PCNSL treatment approach involves administering consolidation therapy to reduce the risk of relapse after achieving a complete or partial response to HD-MTX-based induction.[12] In our study, aHSCT administered as consolidation therapy was found to be associated with improved 1-year overall survival. The 1-year overall survival rate was 100% in the 6 patients who received aHSCT, while it was 40% in the 10 patients who did not receive it. This finding is consistent with studies showing that aHSCT has curative potential in the treatment of PCNSL, especially in young and suitable patients.[13] The latest European Hematology Association-European Society for Medical Oncology (2024) guidelines recommend consolidation strategies, including aHSCT, for eligible patients. Overall, these data further support the view that aHSCT may offer curative potential in selected patients with PCNSL.[1]

In our study, progression-free survival was found to be statistically significantly longer in the group of patients who had radiotherapy. In PCNSL treatment, WBRT is considered an effective treatment method that provides high local control rates. However, complications such as persistent neurocognitive disorders, which are observed particularly in patients over 60 years of age and significantly reduce quality of life, limit the use of this treatment.[14]

Among the limitations of the study, its retrospective design may lead to natural biases in the data collection process. Second, the small sample size reduces statistical power and complicates subgroup analyses; in addition, survival was assessed as a categorical outcome rather than a time-to-event measure, which may not fully capture disease dynamics. In particular, the limited number of events precluded the use of multivariate analysis to identify independent prognostic factors, and multiple comparisons were performed without adjustment, increasing the risk of spurious findings. The main reason for failing to reach meaningful results in the comparison of treatment regimens is this. Finally, the single-center nature of the study limits the generalizability of the results, and the findings should therefore be interpreted as exploratory and hypothesis-generating.

Conclusion

PCNSL's are aggressive tumors with a poor prognosis. Advanced age has been considered a risk factor for poor prognosis in studies, but the absence of comorbidities may be an indicator of good prognosis regardless of age. aHSCT treatment has been shown to improve survival outcomes. Patients receiving radiotherapy had a higher 1-year progression-free survival rate. However, due to the complications, its use in elderly patients should be approached with caution. Surgical resection is mentioned in the literature as a treatment option, but its place in PCNSL treatment is controversial due to post-operative complications, and it has been found to have no significant association with survival.

Patient symptoms at presentation, ECOG performance score, deep or multifocal tumor involvement, gender, presence of comorbidities, absolute lymphocyte count, high serum LDH levels, tumor phenotypic characteristics, and chemotherapy regimens administered were not significantly associated with 1-year overall survival and 1-year progression-free survival.

Ethics Committee Approval: The Erciyes University Ethics Committee granted approval for this study (date: 29.01.2020, number: 2020/49).

Informed Consent: Written informed consent was obtained.

Conflict of Interest: The authors affirm that they have no competing interests in relation to this study.

Financial Disclosure: The authors declared that this study has received no financial support.

Use of AI for Writing Assistance: Not declared.

Authorship Contributions: Concept: DE, MÇ; Design: DE; Supervision: MÇ; Data Collection or Processing: DE; Analysis or Interpretation: DE; Literature Search: MÇ; Writing: DE; Critical Review: DE, MÇ.

Peer-review: Double blind peer-reviewed.

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