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Prognostic Factors and Treatment Outcomes in Primary CNS Lymphoma (PCNSL):

A Comprehensive Review with an Illustrative Case:

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Introduction

Primary Central Nervous System Lymphoma (PCNSL) is a rare and highly aggressive form of extranodal non-Hodgkin lymphoma that is confined to the brain, leptomeninges, eyes, or spinal cord without involving systemic sites. The prognosis of PCNSL remains worse compared to other extranodal diffuse large B-cell lymphomas, largely due to its aggressive behavior, the heterogeneity of the disease, and complexities in its management (Sopittapan, 2020). Despite these challenges, advancements in diagnosis, treatment methods, and prognostic assessments have gradually improved outcomes for patients over the past several decades.

This review offers a comprehensive synthesis of current research related to PCNSL prognosis. The review took place between September 2, 2023 to June 30, 2025. It focuses on identifying key prognostic factors, developing and validating predictive models, understanding the natural history of the disease, supporting clinical decision-making, optimizing patient care, and evaluating treatment efficacy, particularly the role of methotrexate-based chemotherapy. To illustrate these aspects, we include a representative clinical case on a real patient from the University of California, San Francisco Hospital, California (Martnez-Calle, 2018).

Life Cycle of PCNSL:

The following is an overview of the life cycle of non-Hodgkin CNS lymphoma (Central Nervous System lymphoma), focusing on its development, progression, and clinical course:

Life Cycle of Non-Hodgkin CNS Lymphoma

1. **Initiation:**
    - 1.1. Begins with genetic mutations in lymphocytes (a type of white blood cell).
    - 1.2. These mutations may be spontaneous or triggered by factors like immune suppression such as autoimmune diseases, congenital immunodeficiency disorders, and treatment with immunosuppressive drugs, HIV/AIDS, organ transplant, and mostly, in immunocompromised patients, PCNSL is strongly associated with the Epstein-Barr virus (EBV).
2. **Transformation:**
    - 2.1. At this point, the mutated lymphocytes become malignant (cancerous).
    - 2.2. These abnormal cells start to multiply uncontrollably.
3. **Localization in the Central Nervous System:**
    - 3.1. Unlike other lymphomas, these malignant cells primarily localize in the brain, spinal cord, or eyes.
    - 3.2. These malignant cells may originate in the CNS (primary CNS lymphoma) or spread from outside the CNS (secondary CNS lymphoma).
4. **Tumor Growth:**
    - 4.1. The lymphoma cells form tumors or infiltrate CNS tissues.
    - 4.2. Symptoms develop based on tumor location, for instance, headaches, confusion, vision changes, weakness.
5. **Clinical Presentation**

5.1. Patients often present with neurological symptoms.

5.2. Diagnosis is made through imaging (MRI/CT), lumbar puncture, and biopsy.

5.3. Furthermore, PET/CT images can be obtained to see how spread the PCNSL has gone through the body. PET/CT can be used to asses such parts of the body such as Oncological Index lesions, Lymph nodes, hypermetabolic lymphadenopathy, lungs and bones to see whether there is metastases, abdominal and pelvic organs to see whether there is metastases too.

6. **Progression:**

6.1. Without treatment, the disease can progress rapidly.

6.2. Tumors may grow, causing increased neurological impairment.

7. **Treatment:**

7.1. Common treatments include high-dose chemotherapy (often methotrexate-based), radiation therapy, and sometimes corticosteroids.

7.2. Response to treatment varies; some patients achieve remission, while others may relapse.

8. **Remission or Relapse:**

8.1. **Remission:** Cancer cells are no longer detectable; symptoms improve.

8.2. **Relapses:** Cancer returns, often requiring additional or alternative therapies.

9. **Long-term Outcomes**

9.1. Some patients achieve long-term remission.

9.2. Others may experience recurrent disease or complications from treatment.

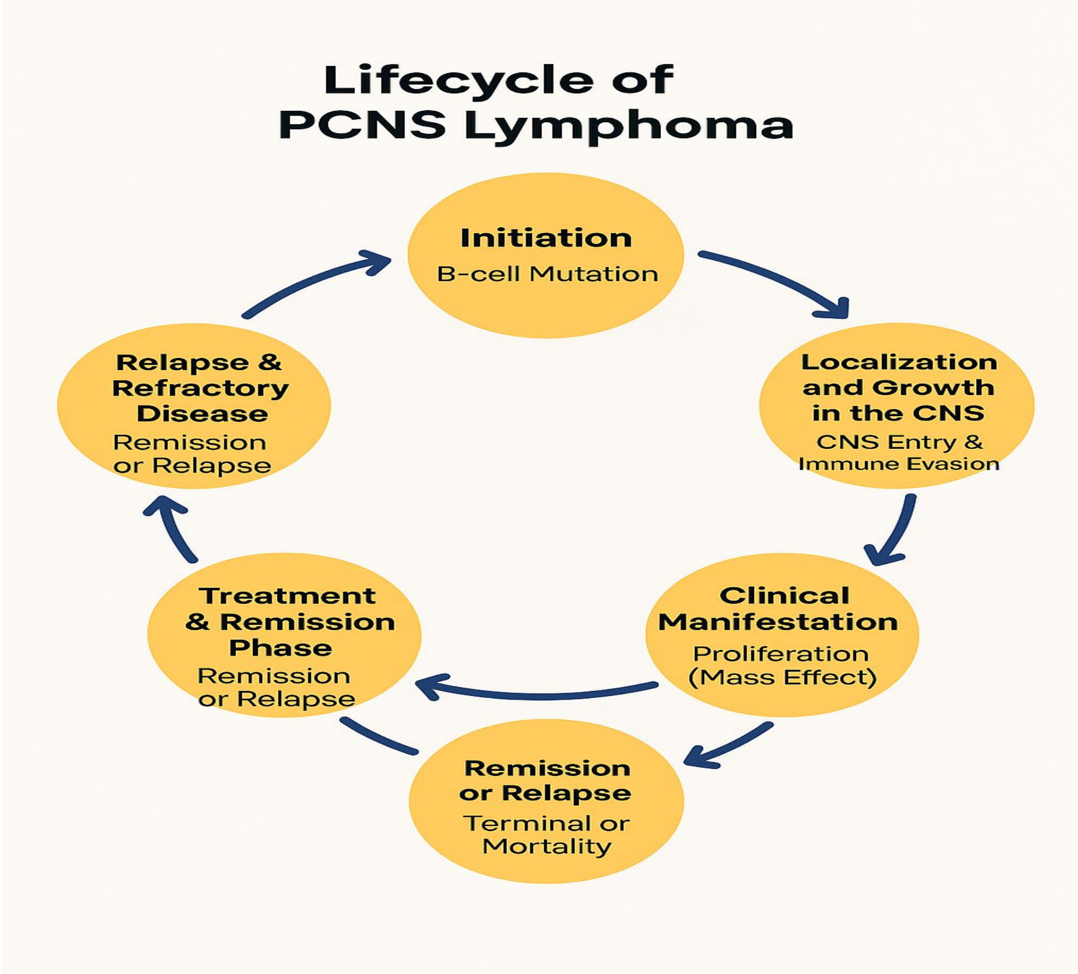


Figure 1. Lifecycle of primary central nervous system lymphoma (PCNSL). The diagram illustrates the sequential stages from initiation (B-cell mutation), through CNS localization and clinical manifestation, to remission/relapse, treatment phases, and eventual outcomes. **Image created by the authors**: Concept adapted from current literature on PCNSL pathophysiology (Liu et al., 2020; Yang et al., 2020).

This research began with the following Magnetic resonance imaging (MRI) brain report of a patient at UCSF Hospital. This report serves as a background and first report when the patient was diagnosed with PCNSL. The following is the report:

MRI BRAIN NAV WITH AND WITHOUT CONTRAST RESULTS:

UCSF RADIOLOGY PARNASSUS HOSPITAL MRI

DATE: SEPTEMBER 7, 2023, AT 7:00 PM

INDICATION (as provided by referring clinician): Presurgical Planning

ADDITIONAL HISTORY: 44-year-old male, with hypertension, food allergies on immunotherapy, and asthma with repeat presentation for positional dizziness and n/v that started 2 weeks prior (last seen in the Emergency Department for the same on (September 2, 2025). Productive bloody cough for 5 years and also being Lymphopenic.

COMPARISON: CT head dated Sept 7,2023 with concern for cellular or hemorrhagic right cerebellar mass.

TECHNIQUE: Multiple sequences through the brain were acquired at 3.0 tesla. Post-processing was done on an independent workstation.

MEDICATIONS:

Dotarem - 12.8 mL - Intravenous (accession 10023610768), None (accession 10023611038)

FINDINGS:

Centered within the dentate nucleus, or evidence extending into the right middle cerebellar peduncle is a homogeneously enhancing T2 hypointense lesion measuring approximately 19 x 9 x 12 mm. This is associated with extensive edema involving the entire right cerebellar hemisphere and brachium pontis, resulting in marked deformity of the fourth ventricle, partial effacement of the right cerebellopontine angle and of the superior cerebellar cistern.

Within the right superior frontal gyrus of the figure 1, there is an area of white matter hyperintensity with punctate area of postcontrast enhancement suggestive of a second site of abnormality. Adapted from Martínez-Calle et al., 2018.

In addition to these areas of abnormal enhancement, there is abnormal white matter FLAIR signal without enhancement particularly involving the bilateral putamen, caudate nuclei and thalami, best demonstrated in figure 4 image, hyperintensity is also demonstrated in the ventral and left pons and middle cerebellar peduncle, and diffusely around the lateral ventricles. These areas are not associated with significant mass effect, reduced diffusion or abnormal enhancement and may represent pre-existing small vessel disease, although unexpected in a patient of this age.

Cluster of punctate susceptibility in the left inferior temporal gyrus consistent with prior hemorrhage. This area is not associated with FLAIR abnormality, edema, enhancement or mass effect as seen in figure 3 earlier.

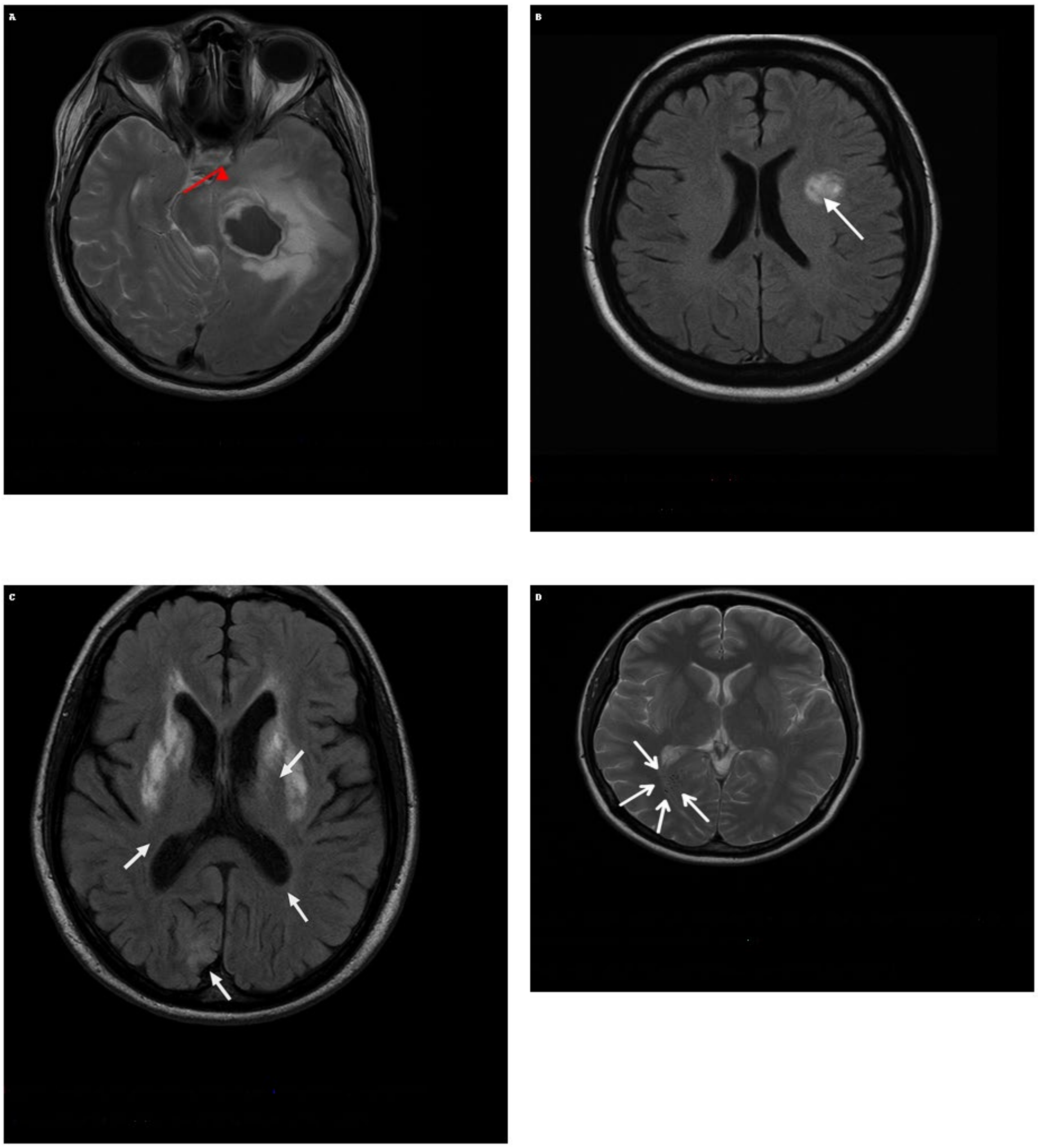


Figure 2. Representative MRI of the illustrative patient with PCNSL (MRI performed at UCSF Hospital, California). (A) T2-weighted axial MRI showing lesion with mass effect; (B) FLAIR sequence demonstrating hyperintense periventricular involvement; (C) multifocal periventricular lesions consistent with disease spread; (D) contrast-enhanced T1 MRI showing marked lesion uptake.

Image credit: Image credit: UCSF Radiology Parnassus Hospital MRI, Sept 7, 2023; June 30, 2025)

Pansinus inflammatory disease:

Markedly prominent nasopharyngeal soft tissues although the smooth contour favors this is reactive adenoid hypertrophy, also unexpected in a patient of this age.

There is, however, obstruction of the right eustachian tube with complete opacification of the right middle ear and mastoid.

IMPRESSION:

1. Intensely enhancing lesion with reduced diffusion within the right cerebellar hemisphere involving the right dentate nucleus with extensive associated edema and mass effect with fourth ventricular deformity and upward herniation, although no hydrocephalus at present.

2. Second more subtle lesion involving the right superior frontal gyrus white matter with punctate enhancement.

3. More subtle ill-defined diffuse white matter abnormality involving the periventricular white matter, basal ganglia, thalami and pons, without enhancement or mass effect may represent pre-existing chronic white matter disease.

4. The primary concern for cerebellar abnormality is lymphoma. Given the additional pansinus inflammatory disease and adenoidal hypertrophy which is resulting in right middle ear obstruction recommend evaluation of HIV status.

5. Extensive white matter abnormality without edema or enhancement suggests pre-existing abnormality which may be advanced small vessel disease given the history of hypertension.

MR BRAIN WITH AND WITHOUT CONTRAST: June 30, 2025, 7:57 PM

INDICATION (as provided by referring clinician): Primary CNS lymphoma in remission, attention to punctate focus of enhancement in the left cerebellum

ADDITIONAL HISTORY: None.

COMPARISON: MRI brain dated March 14, 2025..

TECHNIQUE: Multiple sequences through the brain were acquired at 1.5 tesla.

MEDICATIONS:

Dotarem - 15 mL - Intravenous

FINDINGS: (June 30, 2025):

Stable posttreatment changes of the right brachium pontis related to prior CNS lymphoma without residual enhancement. Previously seen punctate focus of susceptibility in the left cerebellum is unchanged. Associated punctate focus of enhancement is not clearly seen on the current study, although in part this may be due to differences in imaging technique.

Unchanged scattered foci of parenchymal susceptibility, likely posttreatment related. Status post right suboccipital burr hole craniotomy. Falcine calcifications.

No acute intracranial hemorrhage, hydrocephalus, herniation, or infarct. Similar minimal patchy periventricular and deep white matter as shown in figure 8 above which show FLAIR hyperintensities that are nonspecific but commonly seen in chronic small vessel ischemic disease. No abnormal dural or leptomeningeal enhancement.

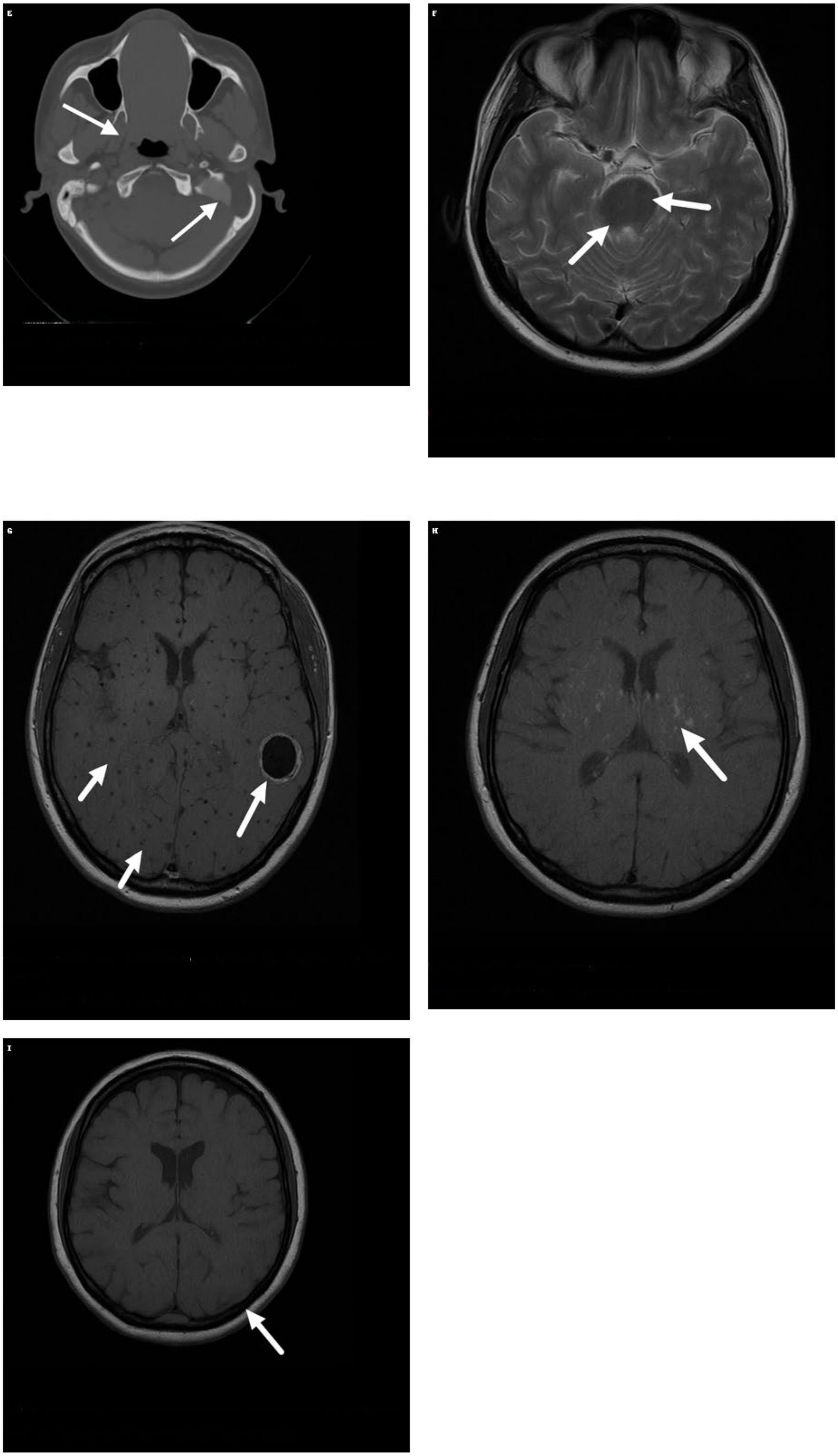
No extra-axial collection.

IMPRESSION:

1. Stable posttreatment changes in the right brachium pontis. No evidence for recurrent or progressive disease.

2. Previously seen focus of susceptibility in the left cerebellum is unchanged. Associated punctate focus of enhancement is not clearly seen on the current study, although in part this may be due to differences in imaging technique (1.5 vs 3T). Recommend that future follow-up studies be done on 3T.

Figure 3. Additional MRI and CT imaging of the illustrative patient with PCNSL (MRI performed at UCSF Hospital, California). (E) CT scan revealing a hypodense lesion; (F) MRI highlighting a posterior fossa lesion; (G) post-treatment MRI showing resection cavity changes; (H) FLAIR MRI with persistent periventricular hyperintensity; (I) follow-up MRI documenting interval response.
Image credit: UCSF Radiology Parnassus Hospital MRI, Sept 7, 2023; June 30, 2025).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1. Identifying Prognostic Factors in PCNSL:

Prognostic factors for primary central nervous system lymphoma (PCNSL) encompass a variety of clinical, biological, radiological, and molecular indicators that provide valuable insight into key outcomes such as overall survival (OS) and progression-free survival (PFS). Understanding and identifying these factors are crucial for accurately categorizing patients by risk level, which in turn informs personalized treatment planning and clinical decision-making (Sopittapan, 2020).

1.1 Clinical and Demographic Factors

1.1.1. Age:

Advanced age, typically defined as over 60 years, is consistently associated with poorer survival outcomes in patients with primary central nervous system lymphoma (PCNSL). This relationship likely reflects increased frailty and reduced tolerance to aggressive treatments in older individuals (Sopittapan, 2020). However, the specific age thresholds used to stratify risk vary across studies, with some prognostic models applying cutoffs at 50 years or even 80 years depending on the characteristics of the patient populations examined (Liu, 2020).

1.1.1.1. Assessment of patient functional ability using the Karnofsky Performance Status (KPS) or the Eastern Cooperative Oncology Group (ECOG) scale at diagnosis serves as a strong predictor of prognosis. Lower scores on these scales, indicating reduced functional capacity, are linked to poorer outcomes due to decreased ability to tolerate treatments and a higher likelihood of comorbid conditions. Therefore, a low KPS (≤70) or an ECOG score of ≥2 is considered abnormal and correlates with poorer prognosis. By contrast, a normal or favorable range is KPS ≥80 or ECOG 0–1, indicating better functional capacity and tolerance of methotrexate-based therapy (Ohanyan, 2024).

1.1.1.2. Neurocognitive function, as measured by the Mini-Mental State Examination (MMSE) score at baseline, independently predicts survival outcomes in patients with primary central nervous system lymphoma. This measure likely reflects the extent of brain involvement and tumor location, with lower MMSE scores indicating greater neurocognitive impairment and correlating with poorer prognosis. Baseline MMSE ≥24 is considered normal and correlates with favorable prognosis, while MMSE ≤23 indicates cognitive impairment and is associated with poorer survival outcomes in PCNSL (Meulen, 2021).

2. Scale	Normal / Good Prognosis	Low / Poor Prognosis	Clinical Interpretation
KPS (Karnofsky)	≥ 80–100 → Normal activity	≤ 70 → Requires assistance	High KPS = strong reserve, tolerates MTX
ECOG	0–1 → Fully active	≥ 2 → Significant limitations	ECOG 0–1 = favorable prognosis
MMSE	24–30 Normal cognition	≤ 23 → Cognitive impairment	Lower MMSE = poor survival, higher impairment

Table 1. Clinical and Functional Prognostic Scales in PCNSL.

Data source: Sopittapan (2020), Meulen (2021).

2.1.1.1. Patients with compromised immune systems, including those infected with HIV/AIDS, organ transplant, and mostly, in immunocompromised patients such as Epstein-Barr virus (EBV) tend to have worse outcomes in primary central nervous system lymphoma. This poorer prognosis is largely attributed to their diminished immune capability, which impairs the body's ability to control tumor growth and respond effectively to therapies (Yang, 2020).

1.2 Laboratory Biomarkers:

1.2.1. Inflammatory and nutritional markers have recently emerged as important independent predictors of prognosis in primary central nervous system lymphoma. Specifically, elevated levels of C-reactive protein (CRP) indicate systemic inflammation and correlate with poorer survival outcomes. Similarly, a low prognostic nutritional index (PNI), reflecting compromised nutritional and immune status, is associated with worse prognosis. Additionally, a high lactate dehydrogenase-to-lymphocyte ratio (LLR) serves as another marker tied to adverse survival, likely reflecting both tumor burden and immune system alterations (Zuo, 2023). The patient reviewed at UCS Hospital had normal C-Reactive Protein (C-RP) results. The C-Reactive Protein's normal range is <5.1 mg/L. The results for the patient were 0.2 mg/L on Sept 8, 2023, and 0.4 mg/L on March 26, 2024, thereby falling within the normal range.

1.2.2. Serum beta-2 microglobulin (B2MG) levels that increase during induction chemotherapy have been shown to predict poorer survival outcomes in patients with primary central nervous system lymphoma. Specifically, patients with elevated B2MG at diagnosis who experience a rise in serum B2MG levels three months after starting treatment have significantly shorter overall survival compared to those whose levels remain stable or decrease, reflecting greater disease burden and possible treatment resistance. Serum B2MG levels serve as a dynamic biomarker of prognosis in PCNSL. Normal levels (≤1.8 mg/L) or stable/decreasing values during induction chemotherapy are associated with favorable outcomes, whereas elevated baseline B2MG (>2.0 mg/L) and a subsequent rise at three months predict significantly shorter overall survival, reflecting higher tumor burden and potential treatment resistance (Hyung, 2018).

Biomarker	Normal Range	Prognostic Threshold	Clinical Impact
B2MG	0.7–1.8 mg/L	>2.0 mg/L or rising	Poor survival, higher tumor burden
LDH	140–280 U/L	Above ULN	High tumor turnover, aggressive disease
CSF Protein	<45 mg/dL	>45 mg/dL	Leptomeningeal involvement, worse survival
Albumin	3.5–5.0 g/dL	<3.5 g/dL	Frailty, inferior survival
Hemoglobin	13–17 g/dL (M) / 12–15 g/dL (F)	Pretreatment anemia	Independent poor survival factor
TMT	≥ 6–7 mm (M), ≥ 5–6 mm (F)	Below cutoff	Predicts frailty, toxicity, poor survival
L3-SMI	≥ 52–55 cm²/m² (M), ≥ 38–41 cm²/m² (F)	Below cutoff	Sarcopenia, poor outcome

Table 2. Laboratory and Biological Prognostic Biomarkers in PCNSL.
Data source: Hyung (2018), Zuo (2023), Leone (2021), Le (2019).

1.2.3. Pretreatment anemia has been identified as an independent predictor of poorer overall survival in patients with primary central nervous system lymphoma. Incorporating hemoglobin levels into prognostic assessments enhances the accuracy of survival predictions beyond that provided by existing clinical scoring systems alone (Le, 2019).

1.3 Radiological Factors:

1.3.1. The presence of lymphoma lesions in deep brain structures, such as the basal ganglia and brainstem, is associated with a poorer prognosis. This is likely due to the difficulty in delivering effective therapy to these critical and sensitive areas, as well as the potential for significant neurological impairment. Additionally, patients presenting with multiple brain lesions, or multifocal disease, tend to have worse outcomes, possibly reflecting a more aggressive disease course and increased tumor burden (Liu, 2020).

1.3.2. Diffusion-weighted imaging (DWI) provides valuable insights into tumor characteristics in primary central nervous system lymphoma by measuring the apparent diffusion coefficient (ADC). Lower ADC values reflect higher tumor cellularity, which is associated with more aggressive disease and correspondingly poorer progression-free and overall survival outcomes. This relationship demonstrates that ADC measurements from contrast-enhancing tumor regions can serve as a noninvasive prognostic biomarker for patient outcomes. Exact cutoffs vary between studies, but 0.7–0.9 is widely accepted as a prognostic threshold in PCNSL literature (Barajas, 2009).

1.3.3. Texture analysis of contrast-enhanced MRI identifies specific imaging features, such as gray-level co-occurrence matrix (GLCM) parameters including contrast, dissimilarity, and homogeneity, that are significantly associated with overall survival in patients with primary central nervous system lymphoma. These MRI-derived texture features can serve as valuable noninvasive biomarkers to predict patient prognosis and aid in clinical decision-making (Chen, 2019).

Biomarker	Reference / Range	Prognostic Threshold	Clinical Impact
ADC (DWI MRI)	0.7–0.9 $\times 10^{-3}$ mm^2/s	<0.9	Low ADC = high cellularity, poor survival
Texture Contrast	5–50	High contrast	Tumor heterogeneity, poor OS
Texture Dissimilarity	1–10	High dissimilarity	Aggressive tumor, poor survival
Texture Homogeneity	0–1	High homogeneity	Favorable prognosis

Table 3. Radiological Prognostic Imaging Biomarkers in PCNSL.
Data source: Barajas (2009), Chen (2019).

1.3.4. Evaluation of muscle mass using imaging biomarkers, specifically the skeletal muscle index measured at the third lumbar vertebra (L3-SMI) and the thickness of the temporal muscle (TMT), offers important information regarding a patient's biological frailty. These quantitative assessments have been independently linked to survival outcomes in patients with primary central nervous system lymphoma who are undergoing high-dose methotrexate-based chemotherapy (Leone, 2021).

1.3.5. Molecular and Tissue Biomarkers

1.3.5.1. Immunohistochemical subtypes of primary central nervous system lymphoma (PCNSL), specifically germinal center B-cell-like (GCB) and non-GCB phenotypes, show distinct clinical outcomes. Patients with the non-GCB subtype generally experience poorer treatment responses and reduced survival compared to those with the GCB subtype (Le, 2019).

Additionally, the presence of certain mismatch repair proteins, such as MSH2 and PMS2, is linked to improved progression-free and overall survival, indicating that DNA repair mechanisms play a significant role in influencing tumor behavior and patient prognosis (Lee, 2017).

Within the tumor microenvironment, elevated expression of programmed death-ligand 1 (PD-L1) on tumor cells, as well as increased levels of its soluble form (sPD-L1) in the serum, are associated with worse survival outcomes. This relationship underscores the importance of immune evasion pathways as both prognostic indicators and potential therapeutic targets in PCNSL (Cho, 2019).

Conversely, higher expression of Siglec-15 on peritumoral macrophages corresponds with better patient prognosis, suggesting that certain immune cell populations may exert protective effects in the disease context (Fudaba, 2021).

Gene Expression Signatures: Researchers have identified a set of 23 genes whose expression levels are strongly correlated with patient survival in primary central nervous system lymphoma. This gene classifier, which includes the BRCA1 protein, was developed using a random forests model and validated through immunohistochemical analysis, effectively stratifying patients based on their likely response to high-dose methotrexate chemotherapy. This gene classifier was developed in a pivotal study:

Kawaguchi et al., Clinical Cancer Research, 2012 developed and validated a 23-gene prognostic score for PCNSL using a random survival forests approach. It was further validated by immunohistochemical (IHC) scoring in independent datasets. Among the genes, BRCA1 protein expression emerged as strongly prognostic patients with high expression had significantly longer overall survival ($P < 0.0001$ in training, $P = 0.028$ in validation). For example, high BRCA1 $\log_2$ TPM expression (e.g., ≥7.0) within the 23-gene classifier is associated with favorable outcomes, likely due to enhanced DNA repair capacity. In contrast, patients classified into the poor-risk group by the gene-based prognostic score demonstrate significantly shorter overall survival when treated with high-dose methotrexate ($P < 0.0001$) (Kawaguchi, 2012).

Feature	Method	Threshold / Grouping	Interpretation
23-Gene Signature	RNA profiling + IHC	Favorable vs Poor risk groups	Stratifies survival on HD-MTX
BRCA1 Expression	IHC / $\log_2 \geq 7$	High vs Low	High = longer OS, better DNA repair
Nomogram Models	ECOG, Albumin, NLR, D-Dimer	Patient-specific predictions	Improved accuracy over traditional scores

Table 4. Molecular and Predictive Models for PCNSL Prognosis.
Data source: Kawaguchi (2012), Ling (2025).

Inflammation-Related Gene Models: Additionally, a newly developed prognostic model integrates clinical and biological variables such as lesion number, β2-microglobulin levels, systemic inflammation response index (SIRI), and Karnofsky Performance Status (KPS). This composite model has demonstrated improved accuracy in predicting overall and progression-free survival across different patient groups, including elderly patients and those receiving high-dose methotrexate or Bruton's tyrosine kinase inhibitors (Wu, 2023).

3. Building and Validating Prognostic Models

Multiple prognostic scoring systems have been created to categorize patients by risk and assist in guiding treatment decisions. However, due to variations in patient populations and differences in treatment approaches across studies, no single model has emerged as the definitive standard. This lack of consensus reflects the complexity and heterogeneity inherent in primary central nervous system lymphoma cases (Liu, 2020).

3.1 Existing Prognostic Scores

3.1.1. The Memorial Sloan Kettering Cancer Center (MSKCC) prognostic score categorizes patients with primary central nervous system lymphoma based on their age and functional status. It divides patients into three distinct groups, each associated with different survival outcomes. This model is widely recognized and validated due to its straightforward approach, focusing primarily on these two clinical factors (Abrey, 2006)

3.1.2. The International Extranodal Lymphoma Study Group (IELSG) score is a comprehensive prognostic tool that evaluates several clinical factors to predict outcomes in primary central nervous system lymphoma (PCNSL). It incorporates patient age, performance status, levels of serum lactate dehydrogenase (LDH), cerebrospinal fluid (CSF) protein concentration, and the presence of lymphoma involvement in deep brain structures. Compared to simpler models, this score provides a more detailed risk assessment but requires the collection of additional clinical and laboratory data for accurate calculation (Morales-Martinez, 2022).

3.1.3. The Nottingham/Barcelona prognostic model incorporates clinical variables such as the presence of multiple brain lesions (multifocality) and elevated cerebrospinal fluid (CSF) protein levels to stratify risk in patients with primary central nervous system lymphoma. This approach aids in identifying patients with more aggressive disease characteristics who may have poorer outcomes (Ahn, 2016).

4.1 Novel and Hybrid Models

4.1.1. The Taipei Score was developed using data from a cohort of newly diagnosed primary central nervous system lymphoma patients. It incorporates three key factors: age over 80 years, the presence of deep brain lesions, and an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or higher. By assigning one point to each factor, the model stratifies patients into four distinct risk groups, demonstrating strong discriminatory ability for predicting progression-free survival and overall survival. This scoring system has shown superior performance compared to older prognostic models (Liu, 2020).

4.1.2. The SII-MSKCC model combines the systemic immune-inflammation index (SII) with the Memorial Sloan Kettering Cancer Center (MSKCC) prognostic score to enhance the accuracy of predicting overall survival (OS) and progression-free survival (PFS) in patients with primary central nervous system lymphoma. This integrated model has demonstrated superior predictive performance compared to the MSKCC score alone, offering improved risk stratification for patient outcomes (Li, 2022).

4.1.3. The Xijing prognostic model integrates four key variables—lesion number, β2-microglobulin levels, systemic inflammation response index (SIRI), and Karnofsky Performance Status (KPS)—to stratify patients according to their risk. This model has demonstrated high predictive accuracy, effectively distinguishing outcomes even among elderly patients and those receiving targeted therapies (Wu, 2023).

4.1.2. Nomogram-based prognostic models incorporate variables such as the Eastern Cooperative Oncology Group (ECOG) performance status, serum albumin levels, D-Dimer, and the neutrophil-to-lymphocyte ratio (NLR) to provide individualized predictions of overall survival in patients with primary central nervous system lymphoma. These models have demonstrated superior accuracy and discrimination in survival prediction compared to traditional scoring systems, allowing for more precise risk stratification and personalized clinical decision-making (Ling, 2025).

Model	Factors	Risk Groups	Median OS / Outcome
MSKCC (2006)	Age, KPS	3 groups	Low risk ~8.5 yrs; High risk ~1.1 yrs
IELSG (2003)	Age>60, ECOG>1, LDH, CSF protein, deep lesion	Low–High risk	2-yr OS: 80% → 15%
Nottingham/Barcelona	Multifocality, CSF protein	2 groups	Poorer with multiple lesions
Taipei Score	Age>80, ECOG≥2, deep lesion	4 groups	Better stratification PFS/OS
SII-MSKCC	Systemic inflammation + MSKCC	Combined model	Higher predictive power
Xijing	Lesion number, B2MG, SIRI, KPS	Stratified risk	Strong accuracy in elderly/targeted therapy

Table 5. Comparative Prognostic Scoring Systems in PCNSL.

Data source: Abrey (2006), Ferreri (2003), Ahn (2016), Liu (2020), Li (2022), Wu (2023).

5.1. Validation and Limitations

Validating prognostic models in independent patient cohorts remains a significant hurdle. Variability in treatment approaches, such as the use of rituximab and differing consolidation therapies, as well as diverse patient demographics, can limit the general applicability of these models. Incorporating molecular markers and radiomic data holds considerable promise for enhancing the accuracy of prognosis predictions; however, this advancement depends on the availability of larger, well-characterized datasets and standardized methodologies (Morales-Martinez, 2022).

6. Understanding the Natural History of PCNSL

Primary central nervous system lymphoma (PCNSL) is characterized by an aggressive clinical course, frequently marked by early relapses and resistance to treatment. Before the introduction of modern therapies, patient survival was typically measured in months. However, advances in immunochemotherapy and consolidation strategies have significantly extended survival durations for many patients. These improvements reflect enhanced disease control and management options that have transformed the prognosis of PCNSL (Yang, 2020).

6.1.1. Median overall survival for unselected primary central nervous system lymphoma (PCNSL) patients generally remain under three years. Five-year survival rates vary between approximately 30% and 40%, influenced by factors such as treatment modalities and individual patient characteristics (Martnez-Calle, 2018).

6.1.2. Relapses in primary central nervous system lymphoma frequently occurs within the first five years following initial treatment and typically remains confined to the central nervous system. This pattern underscores the critical need for therapies that specifically target the CNS to achieve effective disease control and improve patient outcomes (Kim, 2011).

7. Cognitive decline and neurological impairments frequently occur in primary central nervous system lymphoma, largely due to the location of tumor lesions and the effects of surrounding brain edema. These neurological symptoms substantially impact patients' functional abilities and are closely linked to survival outcomes (Ohanyan, 2024).

8. Primary central nervous system lymphoma (PCNSL) displays a wide range of radiologic presentations, including rare diffuse infiltrative forms such as lymphomatosis cerebri. These atypical patterns often lead to delayed diagnosis and present significant challenges for effective treatment, contributing to poorer patient outcomes (Izquierdo, 2015).

9. Informing Clinical Decision-Making

Prognostic insights play a crucial role in determining the intensity of treatment, selection of consolidation strategies, and planning of supportive care for patients with primary central nervous system lymphoma. Patients with favorable prognostic factors, such as younger age and good performance status, are typically considered suitable candidates for aggressive high-dose methotrexate-based chemotherapy regimens, with or without consolidation therapies like autologous stem cell transplantation or reduced-dose whole-brain radiotherapy. Conversely, those with poorer prognostic indicators may benefit from individualized treatment approaches that balance efficacy with tolerability, including less intensive regimens or palliative care to preserve quality of life. Additionally, the presence of deep brain involvement, multifocal lesions, or adverse molecular markers often guides clinicians to escalate therapy or consider investigational protocols. Incorporating biomarkers and imaging findings further refines treatment decisions and monitoring, allowing early identification of treatment response or progression to optimize patient outcomes. This tailored approach helps maximize therapeutic benefit while minimizing toxicity, especially in vulnerable populations (Liu, 2020).

9.1. Treatment Decisions Based on Prognosis

9.1.1. Patients who are younger and maintain good functional status are generally considered appropriate candidates for treatment protocols centered on high-dose methotrexate. These therapeutic regimens can be delivered alone or combined with consolidation strategies such as whole-brain radiotherapy or autologous stem cell transplantation. The choice and intensity of consolidation depend on individual patient characteristics and specific treatment objectives (Martnez-Calle, 2018).

9.1.2. Patients with poorer prognosis may benefit from customized, less intensive treatment regimens or palliative care approaches that prioritize maintaining quality of life while minimizing treatment-related toxicity (Martnez-Calle, 2018).

The identification of deep brain lesions, the presence of multiple brain lesions, or unfavorable molecular characteristics often leads clinicians to consider more aggressive treatment approaches or to explore experimental therapies aimed at improving patient outcomes (Liu, 2020).

9.2. Monitoring and Biomarker-Guided Therapy

9.2.1. Assessment of early treatment response using magnetic resonance imaging (MRI), particularly diffusion-weighted imaging (DWI), plays an essential role in guiding decisions about whether to continue or adjust therapy in patients with primary central nervous system lymphoma. By measuring parameters such as the minimum apparent diffusion coefficient (ADC_min) in contrast-enhancing tumor regions, clinicians can noninvasively evaluate tumor cellularity and predict clinical outcomes. Lower ADC_min values have been linked to higher tumor cellular density and are associated with shorter progression-free survival and overall survival. Monitoring changes in ADC values after high-dose methotrexate-based chemotherapy can provide further insight into treatment effectiveness, supporting timely modifications in therapeutic strategies to optimize patient outcomes (Wieduwilt, 2012), (Barajas, 2009).

10. Changes in inflammatory markers, especially the neutrophil-to-lymphocyte ratio (NLR) measured after steroid treatment, can serve as early prognostic indicators in patients with primary central nervous system lymphoma, helping to predict progression-free survival and overall survival. Monitoring these shifts provides valuable insight into disease trajectory and treatment response. (Lo, 2022).

Markers detectable through liquid biopsy, such as serum soluble programmed death-ligand 1 (sPD-L1), offer a noninvasive approach for monitoring disease status and stratifying risk in patients with primary central nervous system lymphoma. Elevated serum sPD-L1 levels have been shown to reflect tumor PD-L1 expression and are correlated with poorer survival outcomes, indicating their potential utility in guiding risk-adapted treatment strategies. This biomarker could therefore serve as a practical tool to complement traditional tissue-based assessments and improve clinical management decisions. (Cho, 2019).

12. Improving Patient Care

Personalized prognostic assessments and tailored treatment strategies have led to improved survival rates and a reduction in neurotoxic side effects for patients with primary central nervous system lymphoma. Notably, certain treatment protocols now avoid whole-brain radiotherapy (WBRT) to minimize the risk of neurocognitive impairment commonly associated with this modality, especially in elderly patients (Sopittapan, 2020).

A multidisciplinary approach that includes expertise from hematology, neurology, radiology, and supportive care is essential for managing primary central nervous system lymphoma, particularly in elderly patients. This population often exhibits unique prognostic characteristics and varying tolerances to treatment, necessitating coordinated care to optimize outcomes and address their specific needs (Sopittapan, 2020).

Quantitative evaluation of muscle mass provides valuable insights into a patient’s biological frailty, offering an objective means to identify individuals at higher risk for poor outcomes in primary central nervous system lymphoma. Measurements such as the skeletal muscle index at the third lumbar vertebra (L3-SMI) and temporal muscle thickness (TMT) have shown significant associations with survival rates in patients undergoing high-dose methotrexate-based chemotherapy, suggesting their potential utility in guiding supportive care and therapeutic decision-making (Leone, 2021).

To summarize and understand the PCNSL history, a chart below was created to guide the healthcare providers and research a simplified clinical decision making regarding the PCNSL history:

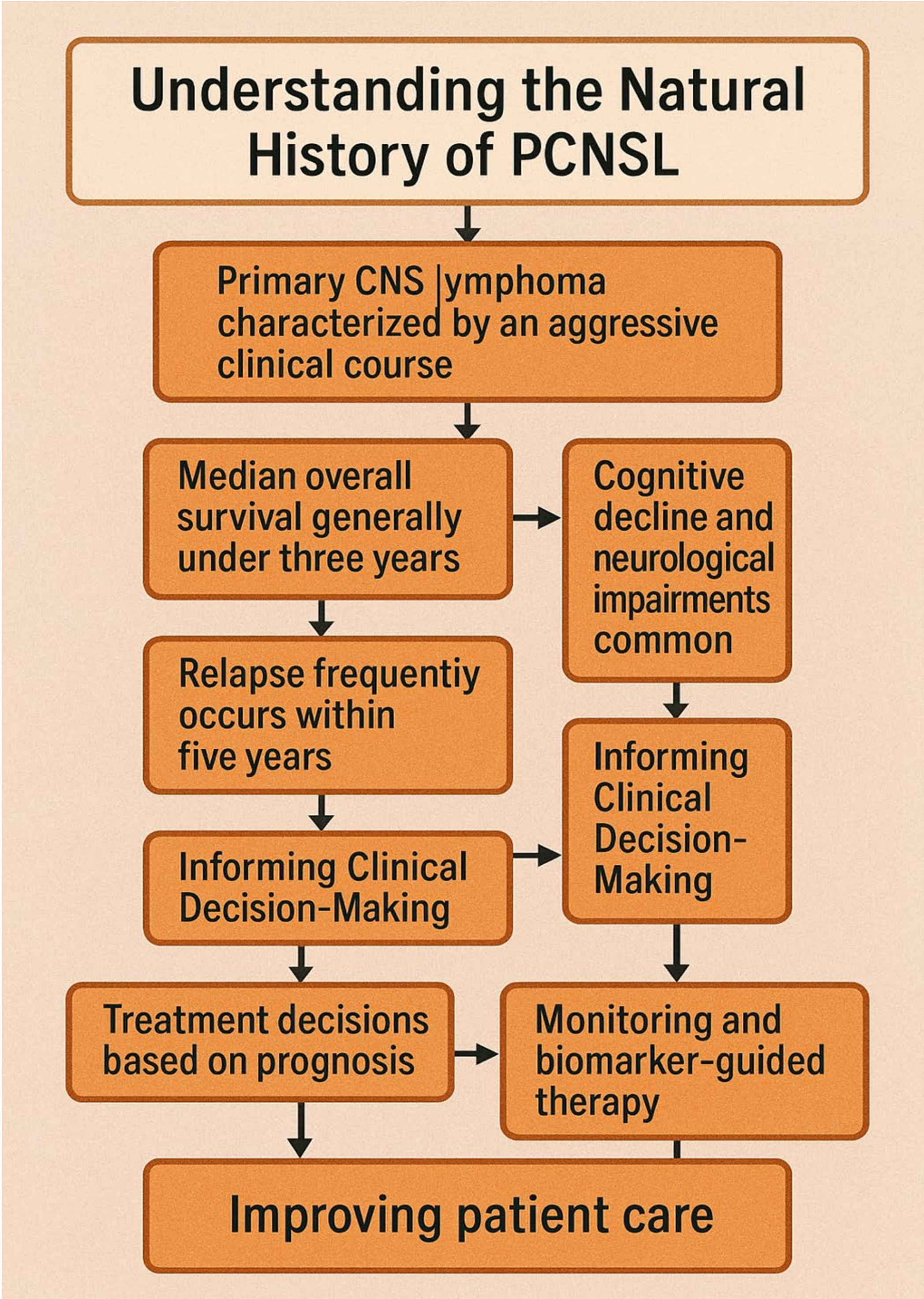


Figure 4. Understanding the natural history of primary central nervous system lymphoma (PCNSL).
A flowchart summarizing disease course, median survival, relapse, cognitive impairment, and the role of prognosis in clinical decision-making.
Image created by the authors: Concept adapted from Yang (2020), Martínez-Calle (2018).

11. Predicting Recovery and Effectiveness of Methotrexate Treatment

High-dose methotrexate (HD-MTX) remains the primary induction treatment for primary central nervous system lymphoma (PCNSL), demonstrating strong initial response rates. However, the durability of these responses varies widely among patients, with some experiencing long-term disease control while others face relapse or progression. Maintaining adequate dose intensity and completing multiple treatment cycles are critical factors associated with improved outcomes. Early discontinuation or dose reductions due to toxicity often correlate with poorer survival, highlighting the importance of balancing treatment efficacy and tolerability. Combining methotrexate with other agents, such as cytarabine, may enhance response rates, though further investigation is needed to confirm survival benefits in diverse patient populations (Martnez-Calle, 2018).

13. Methotrexate Efficacy:

13.1. High-dose methotrexate (HD-MTX) induces initial response rates of up to 75% in patients with primary central nervous system lymphoma. Among those who respond, the median progression-free survival ranges between two to three years (Martnez-Calle, 2018).

13.2. Combination treatment regimens that include high-dose methotrexate along with cytarabine have been shown to improve response rates in patients with primary central nervous system lymphoma. Likewise, adding rituximab to methotrexate-based therapy has demonstrated enhanced treatment responses. However, the effect of these combined therapies on long-term survival outcomes has yet to be definitively established and requires further clinical investigation (Martnez-Calle, 2018).

13.3. Maintaining the full dose of methotrexate during treatment, whenever patients can tolerate it, is strongly linked to improved survival outcomes. Both the intensity of the methotrexate dose and the total cumulative amount administered play critical roles in enhancing response rates and overall survival in primary central nervous system lymphoma patients (Martnez-Calle, 2018).

13.4. Discontinuing methotrexate treatment prematurely due to adverse side effects is associated with markedly worse outcomes, with survival rates similar to those observed in patients who receive only palliative care (Martnez-Calle, 2018).

14. Symptom Relief and Disease Reversibility

Patients typically exhibit clinical improvement, including the reduction of neurological symptoms and cerebral edema, within the initial cycles of high-dose methotrexate (HD-MTX) therapy. Serial imaging studies after treatment commonly demonstrate decreases in the size and contrast enhancement of tumor masses, along with diminished surrounding edema, reflecting effective tumor response and symptomatic relief. This pattern underscores the potential of HD-MTX regimens to achieve significant disease control early in the treatment course (Martnez-Calle, 2018).

15. Case Illustration

The UCSF patient initially presented with a right cerebellar lesion involving the dentate nucleus and extensive edema causing fourth ventricle deformity. Additional subtle enhancing lesions and diffuse white matter abnormalities suggested multifocal CNS involvement possibly compounded by small vessel disease and inflammation. After intensive IV methotrexate chemotherapy over ~18 months, post-treatment imaging demonstrated resolution of the major tumor mass, absence of acute hemorrhage or hydrocephalus, and only minimal residual or recurrent foci of enhancement without mass effect. These findings illustrate the potential for methotrexate-based regimens to induce significant tumor control and symptomatic relief within one year, though vigilance for recurrence via follow-up imaging is mandatory [case findings].

The normal, non-toxic Methotrexate blood level concentration after 72 hours following high-dose therapy is <0.1 umol/L. The patient’s result on Sept 26, 2023, was <0.05.

The following diagram shows the mechanism of Methotrexate therapy in its effort to treat the malignant B-cells:

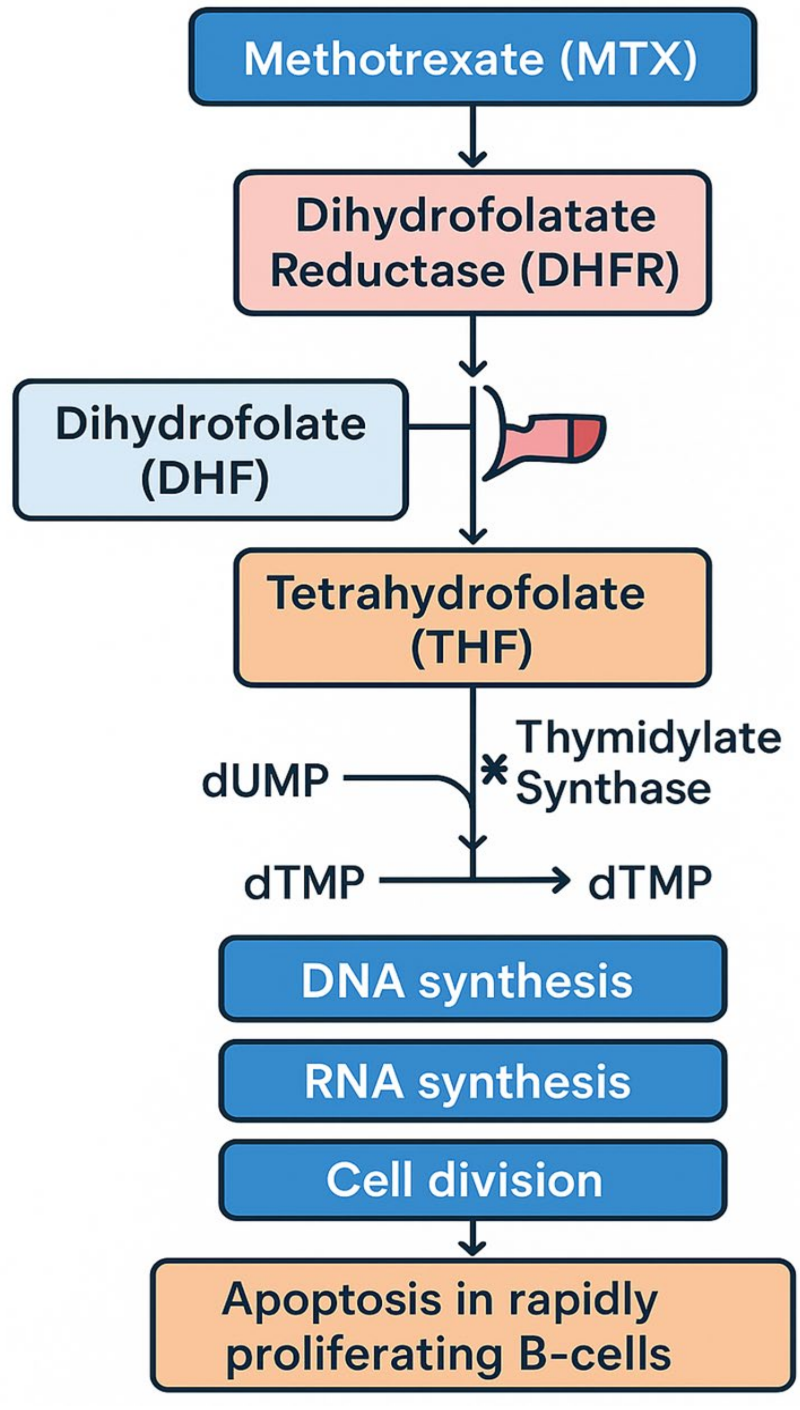


Figure 5. Mechanism of action of methotrexate (MTX) in PCNSL.

MTX inhibits dihydrofolate reductase (DHFR), blocking folate metabolism and DNA/RNA synthesis, leading to apoptosis of malignant B-cells.

Image created by the authors: Concept adapted from Barajas et al. (2009), Cho et al. (2019).

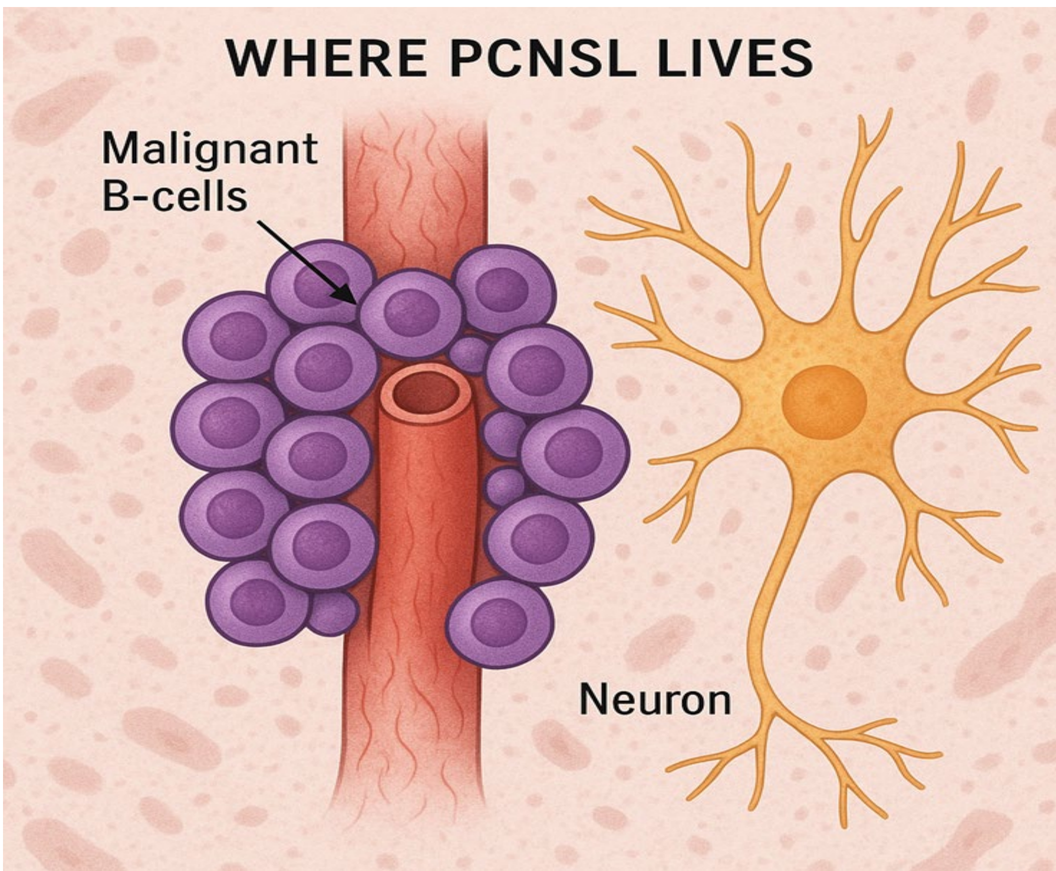
16. Where PCNSL lives:

The authors illustrated a zoom-in of the brain's perivascular region with malignant B-cells (PCNSL) cuffing a small vessel, next to a neuron. This can be demonstrated in the following diagram:

Zoomed-in Brain View:
Imagine a close-up of the brain's perivascular region (the area surrounding blood vessels).

16.1. Malignant B-Cells:
Primary Central Nervous System Lymphoma (PCNSL) cells—malignant B-cells—are shown clustering (cuffing) around a small blood vessel.

16.2. Neighboring Neuron:
A healthy neuron sits nearby, highlighting the proximity of the tumor cells to normal brain tissue.



17. **Figure 6.** Localization of PCNSL cells within the brain.
Illustration showing malignant B-cells cuffing around a cerebral vessel adjacent to a neuron.
Image created by the authors: Concept adapted from Fudaba et al. (2021).

How methotrexate travels:

The following diagram and its explanation will show how Methotrexate medication in a chemotherapy scenario travels to treat the malignant B-cells which cause PCNSL and eventually how Methotrexate can be distributed throughout the body system.

Thus, the pathway will be as follows:

How Methotrexate Travels

1. **Port-a-cath:**
   Methotrexate is injected into a port-a-cath (a device implanted under the skin for easy venous access).
2. **Superior Vena Cava (SVC):**
   The drug enters the SVC, the large vein carrying blood to the heart.
3. **Right Atrium:**
   It flows into the right atrium of the heart.
4. **Lungs:**
   Blood (and methotrexate) is pumped to the lungs for oxygenation.
5. **Left Heart:**
   Oxygenated blood returns to the left side of the heart.
6. **Aorta:**
   The left heart pumps it into the aorta, the body's main artery.
7. **Carotid Arteries:**
   Methotrexate travels up the carotid arteries toward the brain.
8. **Brain:**
   The drug reaches the brain, targeting PCNSL cells.
9. **Systemic Distribution:**
   Methotrexate also circulates throughout the rest of the body.

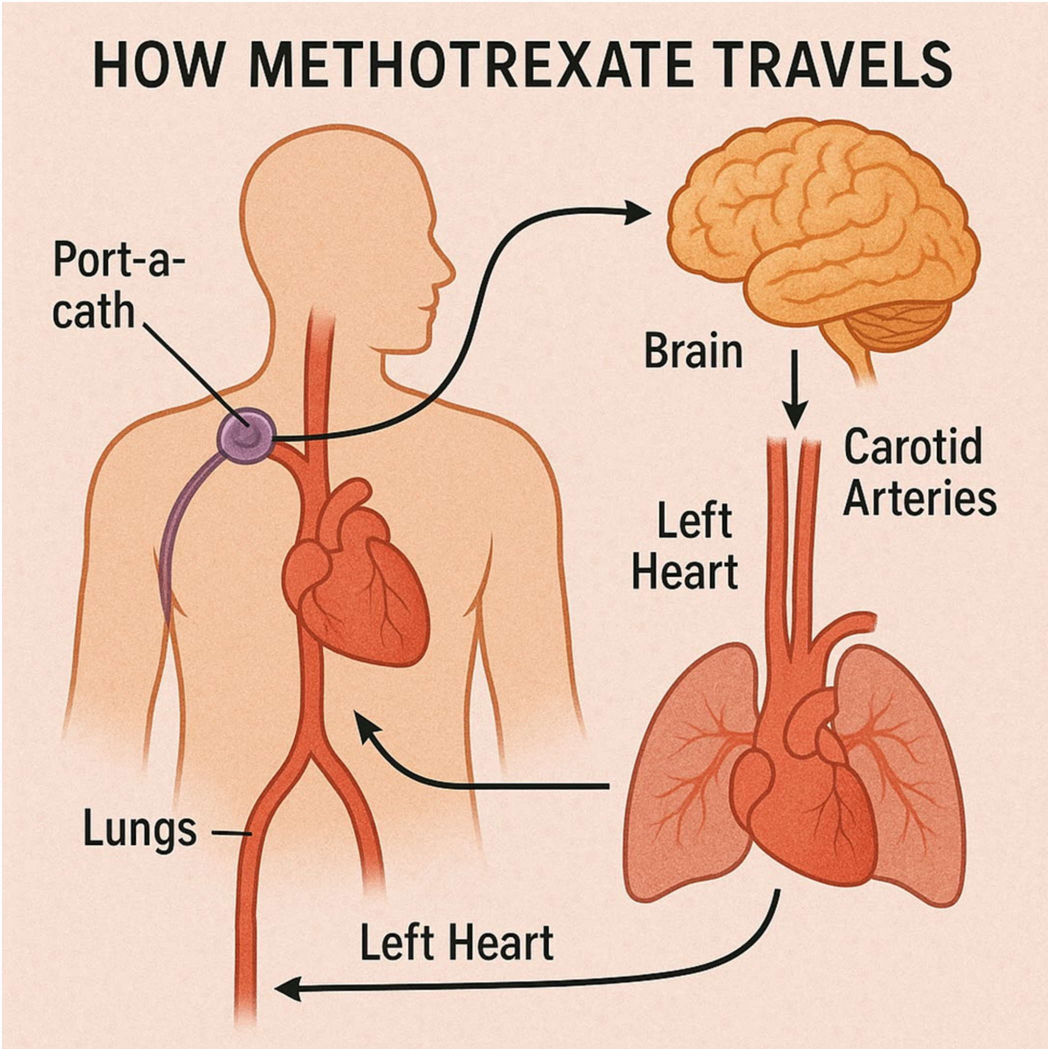


Figure 7. Distribution pathway of methotrexate (MTX) during chemotherapy.
Schematic showing MTX administration through a port-a-cath, circulation via the heart and lungs, and delivery to the brain through carotid arteries.
Image created by the authors: Adapted from Rubenstein et al. (2012).

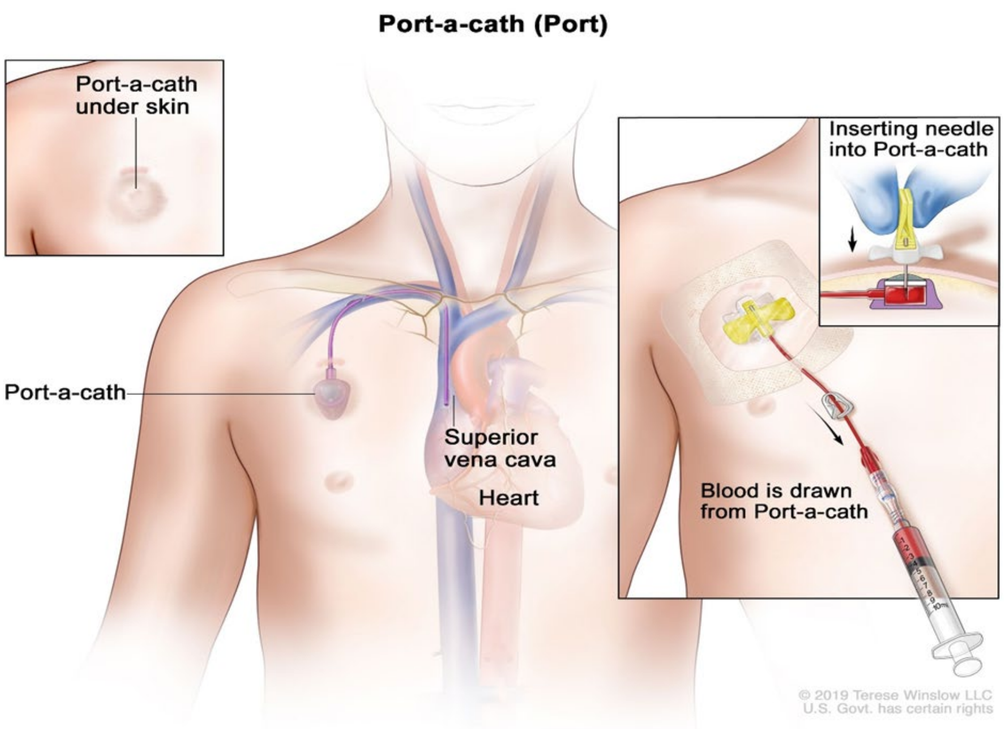


Figure 8. Port-a-cath system for methotrexate infusion.
Medical illustration showing the insertion, placement, and function of a port-a-cath for venous drug delivery.
Image Credit: Winslow, T. (2019). U.S. National Cancer Institute (Visuals Online).

Leucovorin Medication Therapy and its Mechanism:

Leucovorin (Wellcovorin, folinic acid) is commonly prescribed together with Methotrexate for a very specific reason:

Purpose of Leucovorin in Methotrexate Therapy:

Methotrexate works by blocking the enzyme dihydrofolate reductase (DHFR), which stops cells from making folate → halting DNA synthesis, and killing rapidly dividing cancer cells.

But Methotrexate also damages normal healthy cells (bone marrow, GI tract, and extra) because they also need folate.

It is important to know that Leucovorin is a reduced form of folic acid that can bypass DHFR inhibition.

It actually rescues normal cells by restoring their folate supply, without reducing Methotrexate's effect on cancer cells (since tumor cells usually retain more drug). This helps prevent or reduce toxic side effects like bone marrow suppression, mouth sores, and GI damage.bIn other words, Leucovorin is given after high-dose Methotrexate to protect normal tissues. Thus, this is called Leucovorin Rescue.

Important note:

The exact timing and dosing of Leucovorin after Methotrexate is crucial. Thus, too early can reduce anticancer effect, too late can lead to severe toxicity. That's why dosing schedules are closely monitored by doctors, often with blood methotrexate level checks.

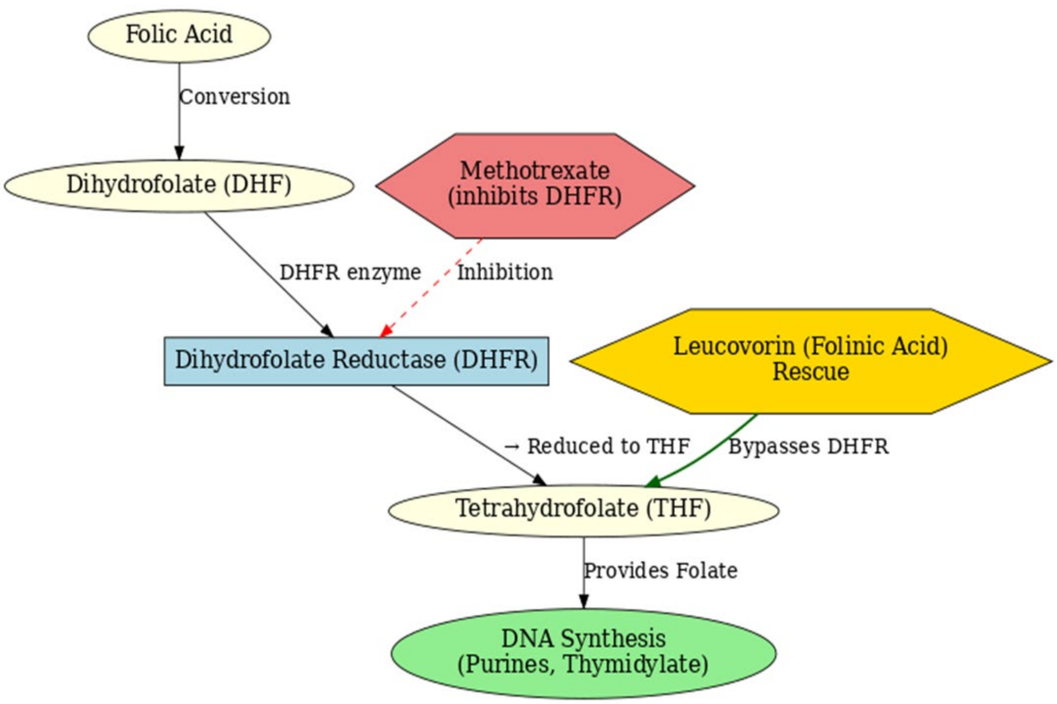


Figure 9. Mechanism of leucovorin (folinic acid) rescue following methotrexate treatment. Leucovorin bypasses DHFR inhibition, restoring THF production to protect normal cells while maintaining MTX antitumor activity.

Image created by the authors: Adapted from Lee (2017), Kawaguchi et al. (2012).

17. Research Gaps and Future Directions:

Despite significant advancements, prognostic research in primary central nervous system lymphoma (PCNSL) continues to face several challenges. One major difficulty is the considerable heterogeneity among patient populations, treatment protocols, and study designs, which complicates efforts to reach a consensus on prognostic factors and models. Moreover, many emerging molecular and inflammatory biomarkers have yet to be validated prospectively in larger, well-characterized cohorts, limiting their immediate clinical application. Integrating diverse data types—clinical, imaging, molecular, and systemic inflammatory markers—into comprehensive and reliable predictive models remains an ongoing task requiring further development. Additionally, optimizing treatment strategies specifically for elderly patients is an unmet need, as this population displays unique prognostic features and therapy tolerances that demand tailored approaches. Finally, the prognostic impact of novel therapeutics, such as Bruton's tyrosine kinase inhibitors and immune checkpoint inhibitors, is still under active investigation, necessitating continuous research to incorporate these agents into prognostic frameworks effectively (Ohanyan, 2024).

17.1. Considerable differences in patient demographics, treatment protocols, and research methodologies present significant obstacles to reaching a unified consensus on prognostic factors and models for primary central nervous system lymphoma. Variability in age distributions, therapeutic regimens, and outcome measurements across studies contribute to inconsistent and sometimes conflicting results, complicating the effort to establish prognostic criteria that are broadly applicable. This diversity highlights the critical need for standardized research approaches and well-characterized patient cohorts to enhance the reliability and generalizability of findings in prognostic research within this disease area (Ohanyan, 2024).

17.2. Many molecular and inflammatory biomarkers proposed for primary central nervous system lymphoma (PCNSL) require validation through prospective studies involving larger patient cohorts to reliably establish their prognostic significance and clinical utility. Until such validation is completed, their effectiveness in guiding treatment decisions and enhancing risk stratification remains limited (Morales-Martinez, 2022).

17.3. Integrating diverse types of data, including clinical information, imaging results, molecular markers, and systemic inflammation indicators—into cohesive predictive models remains an area requiring significant advancement. Developing such comprehensive models is essential to capture the complex interplay of factors influencing prognosis in primary central nervous system lymphoma and to improve the accuracy of patient outcome predictions (Morales-Martinez, 2022). This integration challenges researchers to combine heterogeneous datasets effectively while maintaining clinical relevance and facilitating practical application in diverse patient populations.

17.4. Treatment approaches for elderly patients with primary central nervous system lymphoma (PCNSL) require specialized prognostic models tailored to this age group, alongside therapeutic strategies that carefully balance treatment effectiveness with the risk of toxicity. Elderly patients often face challenges such as comorbidities, reduced baseline functional status, and increased vulnerability to treatment-related adverse effects, which can limit their ability to tolerate intensive regimens. Therefore, prognosis assessment tools specific to older populations are essential to guide clinicians in selecting appropriate therapies that optimize survival while minimizing harm (Martnez-Calle, 2018). Research indicates that delivering adequate methotrexate dose intensity and combining it with agents like cytarabine can improve response rates and survival outcomes in elderly PCNSL patients who are fit enough to receive such treatments. However, early treatment discontinuation is common in this group and is associated with poor prognosis comparable to palliative care (Martnez-Calle, 2018). These findings highlight the need for prognostic instruments that accurately identify candidates for intensive therapy and support the development of individualized treatment plans that balance efficacy and safety in the elderly (Martnez-Calle, 2018).

17.5. The prognostic significance of emerging therapies, including Bruton's tyrosine kinase inhibitors and immune checkpoint inhibitors, is currently under active investigation. These novel agents hold promises for improving outcomes in primary central nervous system lymphoma, but further research is necessary to fully understand their impact on patient prognosis (Cho, 2019).

Conclusion:

Prognosis research in primary central nervous system lymphoma (PCNSL) has identified a range of clinical, laboratory, imaging, and molecular factors that individually and collectively influence patient outcomes. These findings form the basis of prognostic models that support personalized clinical decision-making, allowing for more precise treatment planning and improved risk stratification. High-dose methotrexate-based chemotherapy continues to be the primary treatment modality for PCNSL, demonstrating significant effectiveness in controlling tumor growth and alleviating symptoms, often within the first year of therapy, as illustrated by detailed patient imaging and clinical follow-up. Ongoing research aimed at enhancing prognostic accuracy through the discovery of novel biomarkers, advanced radiomic techniques, and rigorous model validation is essential to advance patient management and enhance survival rates in this challenging disease (Martnez-Calle, 2018).

This review synthesizes current research and clinical insights to highlight the comprehensive and multifaceted strategies essential for advancing the understanding and management of primary central nervous system lymphoma (PCNSL). It emphasizes the integration of diverse prognostic factors, including clinical, biological, radiological, and molecular data, to enhance patient stratification and guide personalized treatment approaches. Continued progress depends on refining predictive models, validating emerging biomarkers, and incorporating novel imaging and molecular techniques to optimize outcomes in this complex disease (Ohanyan, 2024).

Declarations:

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Conflicts of Interest:

The authors declare that they have no conflicts of interest related to this work.

Ethical Approval and Consent:

This article is a literature review and does not involve new clinical research requiring institutional ethical approval. The illustrative patient case included in this review refers to one of the authors, who was treated at the University of California, San Francisco (UCSF) Hospital. The author has provided informed consent for the inclusion and publication of this case for scientific purposes.

Author Contributions:

Dr. Victor H. Mudenda conceived and drafted the review, performed the literature search, and contributed the illustrative patient case. Associate Professor Anastasiia Ihorivna Bezrodna, PhD, Professor James Rubenstein, MD, PhD, Professor Mykola Gavrylovich Shcherban, and Dr. Robert Marlin, MD critically reviewed the manuscript for accuracy and intellectual content. All authors approved the final version of the manuscript and agree to be accountable for its content.

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