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The Innovation Medicine

Evidence-based guidelines for the diagnosis and management of primary central nervous system B-cell lymphoma

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Received: September 29, 2025; Accepted: March 3, 2026; Published Online: March 4, 2026; https://doi.org/10.59717/j.xinn-med.2026.100201

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Citation: Yang H., Xun Y., Ke C., et al. (2026). Evidence-based guidelines for the diagnosis and management of primary central nervous system B-cell lymphoma. *The Innovation Medicine* **4**:100201.

INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is a rare and aggressive lymphoma restricted to the CNS, predominantly recognized in the 2022 WHO classification as a subtype of diffuse large B-cell lymphoma (DLBCL) arising in immune-privileged sites.[1] It accounts for approximately 2-3% of all primary CNS tumors and 4-6% of all extranodal lymphomas. Despite advances in diagnostic and therapeutic approaches, management remains challenging, relapse is frequent, and prognosis remains unsatisfactory. Rapid therapeutic advances and inconsistent recommendations necessitate updated, harmonized guidelines.

Building on the latest clinical experience, these guidelines synthesize recommendations from the European Hematology Association-European Society for Medical Oncology (EHA-ESMO, 2024), the European Association of Neuro-Oncology (EANO, 2023), and the Chinese expert consensus (2024 version).[2] Given that >95% of cases are DLBCL, these guidelines are restricted to B-cell lymphomas, excluding rare subtypes requiring distinct strategies. These guidelines provide updated and clinically meaningful recommendations for standardized diagnosis, treatment, and long-term management, excluding exploratory approaches to ensure applicability. The evidence grading follows each original source (EHA-ESMO: Oxford I-V; EANO: Level A-C/Good Practice Point [GPP]; Chinese expert consensus: CN-consensus).

DIAGNOSIS AND ASSESSMENT

PCNSL is strongly suspected when characteristic clinical or radiological features are present, and patients should promptly follow the "imaging first, biopsy priority, and minimize steroid use before biopsy" protocol. Typical features include: ① CNS space-occupying lesions associated with progressive neurological deficits or rapidly progressive cognitive/behavioral decline, particularly in elderly patients; ② Typically multiple, homogeneously enhancing lesions in deep brain structures (basal ganglia, thalamus, corpus callosum, periventricular regions), but solitary lesions may also occur; ③ Unexplained ocular involvement or cerebrospinal fluid (CSF) abnormalities (protein elevation, monoclonal B-cell populations, MYD88 mutation); ④ Intracranial lesions in immunodeficiency (HIV, post-transplantation, long-term immunosuppression).

For suspected PCNSL, contrast-enhanced MRI is the preferred initial modality (LoE Oxford Level II, EANO Level A, CN-consensus). Standardized protocols should include diffusion-weighted imaging (DWI) showing restricted diffusion, perfusion-weighted imaging (PWI) with low relative cerebral blood volume to exclude glioblastoma, and MR spectroscopy (MRS) demonstrating a lipid peak. If imaging findings support PCNSL, a prompt stereotactic biopsy is mandatory, avoiding corticosteroids. If administered, corticosteroids must be discontinued and biopsy performed only after typical lesion reappearance on repeat MRI.

Management requires early coordination by a multidisciplinary team (MDT) integrating neurosurgery, neuroradiology, neuropathology, radiation oncology, hematology, ophthalmology, and rehabilitation (LoE Oxford Level V, EANO GPP, CN-consensus). Before therapy begins, baseline assessments should include CSF analysis, ophthalmologic examination, and neurocognitive assessment, providing reference values for subsequent efficacy and toxicity monitoring (LoE Oxford Level IV, EANO Level B-C/GPP, CN-consensus). Baseline risk stratification using the International Extranodal Lymphoma Study Group (IELSG) or Memorial Sloan Kettering Cancer Center (MSKCC) scores (see Figure 1 for details) aids in prognostication, follow-up planning, and trial eligibility. However, these scores have limitations, as neurological symptoms are strongly influenced by tumor location and mass effect, which can confound scoring and may not accurately reflect true disease severity. Looking ahead, incorporating additional biomarkers may refine risk stratification and improve treatment guidance. Importantly, risk scoring should not delay the "imaging-biopsy" diagnostic process but should calibrate subsequent treatment and surveillance strategies. PET-CT is strongly recommended for systemic staging to confirm the diagnosis (LoE Oxford Level II-III, EANO Level A, CN-consensus).

INDUCTION THERAPEUTIC STRATEGIES

Induction therapeutic management of PCNSL is centered on high-dose methotrexate (HD-MTX, ≥3 g/m^2)-based combination therapy, consistently recognized as the first-line standard (LoE Oxford Level I, EANO Level A, CN-consensus). This backbone is preferably combined with other blood-brain barrier (BBB)-penetrating agents such as cytarabine, temozolomide, or alkylators, with thiotepa recommended based on prospective trial data (LoE Oxford Level I-II; EANO Level B; CN-consensus). Rituximab addition may be considered, although evidence for a survival benefit is inconsistent (NCT00098774, NCT00147953, ACTRN12610000908033, NTR2427), and its use should be guided by MDTs based on patient characteristics and drug accessibility. Common protocols include R-MPV (rituximab, methotrexate, procarbazine, vincristine), MATRix (methotrexate, cytarabine, thiotepa, rituximab), MA ± R (methotrexate, cytarabine ± rituximab), and MT-R (methotrexate, temozolomide, rituximab). The IELSG32 trial confirmed that MATRix significantly improves response rates, progression-free survival, and overall survival (NCT01011920). Preliminary evidence supports incorporating BTK inhibitors in combination with HD-MTX-based regimens for first-line therapy. Ibrutinib (ChiCTR1900027811, NCT04514393, NCT05600660, NCT04446962), orelabrutinib (ChiCTR2100049483), and zanubrutinib (ChiCTR2000039485) have reported encouraging efficacy in early-phase studies. Notably, second-generation BTK inhibitors demonstrate superior response depth; for instance, zanubrutinib has achieved a complete remission (CR) rate of up to 93% and overall response rate (ORR) 91.7% in selected cohorts (CN-consensus).

Supportive management is essential, including standardized hydration and urine alkalinization, leucovorin rescue, serum MTX monitoring, and vigilant control of renal function and drug interactions (e.g., proton pump inhibitors, NSAIDs, trimethoprim-sulfamethoxazole) (LoE Oxford IV-V, EANO GPP, CN-consensus).

For elderly or frail patients, dose adjustment or interval extension is advised according to performance status and organ function (LoE Oxford Level II, EANO Level A, CN-consensus). A comprehensive geriatric assessment (CGA) is useful when applicable. Split dosing and intensified supportive care may be considered to balance efficacy with toxicity.

Patients unable to tolerate HD-MTX-based induction may receive reduced-

Diagnosis and Assessment

Fast-track pathway: imaging first, biopsy priority, minimizing steroid exposure before biopsy

Suspicious features

- Neurological deficits or cognitive decline in elderly
- Solitary or multiple enhancing lesions in deep brain
- Ocular or CSF changes
- Lesions in immunodeficiency

Baseline assessment

- CSF: cytology, flow cytometry, protein, MYD88
- Ophthalmology: comprehensive eye exam
- Cognition: MMSE or other validated test

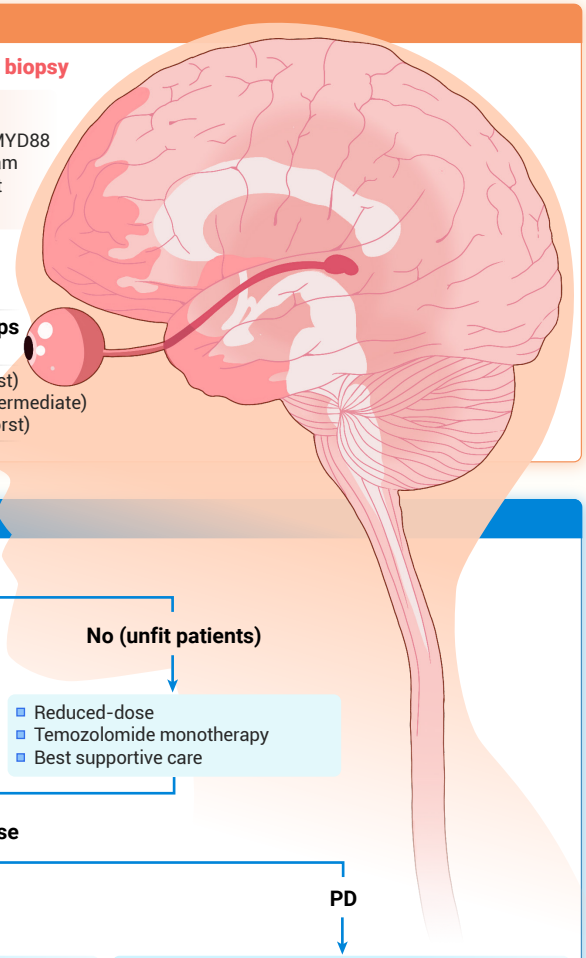
Risk stratification and staging

IELSG

Classification factors (1 point each)	Risk groups (points)
Age>60 years, ECOG≥2, LDH ↑, CSF protein ↑, deep brain involvement	Low (0–1) Intermediate (2–3) High (4–5)

MSKCC

Classification factors	Risk groups
Age<50 years	Class 1 (Best)
Age≥50 years and KPS≥70	Class 2 (Intermediate)
Age≥50 years and KPS<70	Class 3 (Worst)



Induction and Consolidation Strategies

HD-MTX based chemotherapy suitability

Yes (fit patients)

- HD-MTX (≥3g/m²) ± BBB agents ± Rituximab
- Common protocols: R-MPV, MATRix, MA±R, MT-R

Yes (elderly/frail populations)

- Adjusted HD-MTX regimens (dose reduction, interval extension, split dosing)
- CGA-guided adjustment

No (unfit patients)

- Reduced-dose
- Temozolomide monotherapy
- Best supportive care

Consolidation According to Induction Response

CR/CRu/PR

Fit for ASCT

- Thiotepa-based conditioning
- Eligibility by PS or organ function, not age alone

ASCT-ineligible

- Reduced-dose WBRT
- Non myeloablative chemotherapy

PD

Switch to

Relapse/Refractory management

Relapse/Refractory and Follow-up

Relapse/Refractory management

- Salvage therapy
- Common options: HD-MTX rechallenge ± BBB agents; alternative chemotherapy; WBRT 36Gy ± boost/SRS (if no prior WBRT); ASCT if sensitive; clinical trials (BTKi, lenalidomide, PD-1, CAR-T)
- Elderly/frail: low-toxicity regimens, MDT-guided

Follow-up

- MRI: q3mo (year 2), then q6–12mo
- CSF, ophthalmology, cognition (MMSE) as needed
- IELSG reassessment
- PET-CT for relapse/atypical lesions
- Risk-adapted, MDT-led, expert centers

Abbreviations: HD-MTX, high-dose methotrexate; ASCT, autologous stem cell transplantation; WBRT, whole-brain radiotherapy; IELSG, International Extranodal Lymphoma Study Group; MSKCC, Memorial Sloan Kettering Cancer Center; ECOG, Eastern Cooperative Oncology Group; KPS, Karnofsky Performance Status; CSF, cerebrospinal fluid; MMSE, Mini-Mental State Examination; CGA, comprehensive geriatric assessment; MDT, multidisciplinary team; BBB, blood–brain barrier; SRS, stereotactic radiosurgery; PD, progressive disease; CR/CRu/PR, complete response/unconfirmed complete response/partial response; mo, month.

Figure 1. Diagnosis and management of primary central nervous system lymphoma.

dose WBRT (23-30 Gy), temozolomide monotherapy, or best supportive care, tailored through MDT evaluation (LoE: Oxford Level II-III, EANO Level B-C, CN-consensus).

CONSOLIDATION AND MAINTENANCE

For patients achieving chemosensitivity (CR, unconfirmed CR [CRu], or partial response [PR]) after induction, intensive chemotherapy with autologous stem cell transplantation (ASCT) is the preferred consolidation approach, with thiotepa recommended as the conditioning agent of choice (LoE Oxford Level I-II, EANO Level A-B, CN-consensus). Given the risk of delayed neurotoxicity and the availability of ASCT, conventional-dose whole-brain radiotherapy (WBRT) is not recommended as the preferred consolidation for these patients (LoE Oxford Level I-II, EANO Level A-B, CN-consensus).

Older age alone is not an absolute contraindication to transplantation. Eligibility for ASCT is determined by performance status, key organ function, and, where appropriate, CGA. Elderly patients meeting these criteria may still be considered for ASCT (LoE Oxford Level II-IV, EANO Level B-C/GPP, CN-consensus). Patients with progressive disease (PD) after induction should not proceed to consolidation but instead transition to re-induction or salvage therapy (see "Relapse/Refractory Management") (LoE Oxford Level IV-V, EANO Level C/GPP, CN-consensus).

For patients unfit for ASCT, most often due to older age, comorbidities, or impaired functional status, alternatives include reduced-dose WBRT (approximately 23-30 Gy), non-myeloablative chemotherapy, or myeloablative

chemotherapy, selected through MDT evaluation (NCT01511562). The intensity of these strategies should balance tumor control against the risk of long-term neurotoxicity, with particular attention to cognitive outcomes in patients older than 60 years (LoE Oxford Level IV-V, EANO Level C/GPP, CN-consensus).

RELAPSE/REFRACTORY MANAGEMENT AND FOLLOW-UP

Management of relapse or refractory (R/R) PCNSL remains challenging. For relapses after initial chemosensitivity, HD-MTX rechallenge ± BBB-penetrating agents is preferred (LoE Oxford Level IV, EANO Level B, CN-consensus). In patients without prior WBRT, salvage treatment with WBRT at 36 Gy/18-20 fractions, with optional boost or stereotactic radiosurgery, can be considered. Patients who regain chemosensitivity after re-induction and are otherwise eligible may proceed to ASCT as consolidation. For those with SD/PD or intolerance to further intensive therapy, alternative induction regimens or short-course/local radiotherapy may be employed for cytoreduction and symptom relief (LoE Oxford Level II-III, EANO Level B-C, CN-consensus). In elderly/frail patients, a low-toxicity principle is advised, prioritizing short-course or focal radiotherapy to minimize delayed neurotoxicity.

BTK inhibitors have established efficacy in R/R PCNSL. Ibrutinib remains a standard reference with an ORR of 50-60%. However, second-generation agents are advancing rapidly; Tirabrutinib has received approval in Japan for R/R PCNSL due to its proven efficacy, Zanubrutinib is being actively explored, leveraging its superior BBB penetration (higher CSF/IC50 ratio) to potentially deepen CNS responses (CN-consensus). Other strategies including lenalidomide and PD-1 inhibitors have also yielded positive signals in small prospective studies and case series.[3] Notably, novel immunotherapy has evolved towards T-cell engaging (TCE) strategies, encompassing both bispecific T-cell engagers and CAR-T cell therapy. Emerging bispecific T-cell engagers, particularly CD3xCD20 bispecific antibodies, show promising CNS activity with a manageable safety profile. In parallel, CAR-T cell therapy (CD19/CD20) serves as a potent salvage modality for eligible patients with refractory disease. All treatment decisions should be made within an MDT framework to balance functional status with therapeutic goals.

Follow-up should be structured around MRI: every 3 months (Year 2), then every 6-12 months. CSF and ophthalmologic evaluations are considered as clinically indicated (LoE EANO GPP, CN-consensus). Dynamic prognostic reassessment (e.g., IELSG) is encouraged. Long-term cognitive monitoring, commonly performed with MMSE, should be incorporated into routine toxicity assessment (LoE Oxford Level V, LoE EANO GPP, CN-consensus). PET-CT may be considered for staging, suspected relapse, or atypical imaging findings to improve diagnostic accuracy (LoE Oxford Level III, EANO Level A, CN-consensus). Surveillance schedules can be adapted according to baseline risk stratification and patient characteristics, often with more intensive monitoring early after therapy and reduced frequency later, particularly in elderly or frail populations. Monitoring renal function, drug interactions, and infection prophylaxis is also recommended for long-term management (LoE EANO GPP, CN-consensus).

CONCLUSION AND OUTLOOK

As a rare disease, PCNSL continues to lack robust randomized trials, and current evidence remains limited. Currently, consensus has been established regarding risk stratification, HD-MTX-based induction, ASCT consolidation, and contrast-enhanced MRI-driven surveillance.[3] Key uncertainties persist around the routine use of rituximab or temozolomide, the role of reduced-dose WBRT, treatment strategies for elderly and frail patients, and the management of immunocompromised and ocular PCNSL, underscoring the need for prospective trials, real-world data, and international collaboration.[4] Future advances, including the use of BTK inhibitors in induction and relapse/refractory management,[2] TCE strategies, gut microbiome modulation,[5] cfDNA-based MRD[2] for relapse prediction, and biologic stratification based on MYD88/CD79B mutations, may transform clinical pathways. However, these strategies remain investigational and require further validation before routine adoption.

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FUNDING AND ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (82203844, 82203213, 81911530169), Basic and Applied Basic Research Project of Guangdong Province (2024A1515140151), the Innovation Support Program for Chongqing Overseas Returnees (cx2025115), Chongqing medical scientific research project (Joint project of Chongqing Health Commission and Science and Technology Bureau) (2025ZDXM005 and 2026MSXM022), Chongqing Science and Technology Bureau (CSTB2025NSCQ-GPX0396), the Science and Technology Research Program of Chongqing Municipal Education Commission (KJZD-K202300408), and CQMU Program for Youth Innovation in Future Medicine (Grant No. W0202). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript

AUTHOR CONTRIBUTIONS

H.Y[1]: Conceptualization, Methodology, Investigation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing, Funding acquisition. Y.X.: Conceptualization, Methodology, Investigation, Formal analysis, Writing – review & editing, Funding acquisition. C.K.: Investigation, Writing – review & editing. L.W.: Formal analysis, Writing – review & editing. H.Y[4]: Conceptualization, Supervision, Writing – review & editing, Funding acquisition.

DECLARATION OF INTERESTS

The authors declare no competing interests.