

## NARRATIVE REVIEW

## Consensus guidelines for the management of primary central nervous system lymphoma for low and middle-income countries

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### Abstract

Primary lymphoma of the central nervous system (PCNSL) is a rare and aggressive form of extranodal non-Hodgkin lymphoma primarily involving the brain, spinal cord, cerebrospinal fluid, and eyes. The role of surgical intervention in PCNSL is currently limited to biopsy and decompression of critical structures if needed – extended resection is debated. Chemotherapy is the mainstay of treatment. In lower and middle-income countries (LMICs), issues like delayed diagnosis and resource constraints are widespread. These guidelines provide a framework for addressing PCNSL in LMICs, emphasizing the importance of early diagnosis, tailored treatment approaches, and ongoing patient monitoring to improve outcomes for this rare and aggressive disease.

**Keywords:** Lymphoma, non-Hodgkin, biopsy, nervous system, physiologic decompression, spinal cord, brain tumours

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### Introduction

Primary lymphoma of the central nervous system (PCNSL) is an aggressive form of extranodal non-Hodgkin lymphoma (NHL) that is primarily limited to the involvement of brain parenchyma, spinal cord, cerebrospinal fluid (CSF), and the eyes. The disease is more commonly seen in individuals who are immunocompromised in comparison to immunocompetent individuals. This is particularly true for individuals with solid organ transplantation and those affected with the Human immunodeficiency virus.

Primary CNS lymphoma is a rare disease with an incidence of 0.4 to 0.5 per 100,000 persons per year, accounting for

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approximately 4 to 5 percent of all primary brain tumors.<sup>1,2</sup> It has a higher incidence in males, with a mean age at diagnosis of 65 years.<sup>3</sup> Rarely individuals with primary CNS involvement can have a systemic relapse that carries a poor prognosis.

Secondary CNS lymphoma is a part of systemic disease, which is more common in relapse cases. The median time from systemic diagnosis to CNS disease is one year, but it can also present within six months.<sup>4</sup> The factors associated with increased risk of CNS involvement include aggressive subtypes of NHL, older age at diagnosis, advanced stage, and involvement of testis, orbit, and paranasal sinuses.<sup>5,6</sup>

### Methodology

The literature search of the high-quality data on lymphomas was done in June 2022 on different databases including PubMed, Google Scholar, Scopus, and Embase. The most relevant and high-quality studies were analyzed to develop the evidence-based recommendations. An expert panel was convened consisting of specialists and leading experts within the field of neuro-oncology to identify the gaps in diagnosis and management of primary CNS lymphoma within Pakistan. Experts from neurosurgery, oncology, neuro-radiology, radiation oncology, and neuro-pathology were tasked with identifying best-practice recommendations and their application within the context of Pakistan as an LMIC. Members of the panel collected and analysed published evidence within their specialties for the management of CNS lymphoma. Often there was consideration given to the availability of infrastructure and resources within the region.

These recommendations were thus collated and discussed among senior members of the panel. They were reviewed and debated regarding utility and evidence-based practices. Recommendations once drafted were once again reviewed by the experts for any disagreements or further required points. Based on this second review process as well as insight from senior panel members, a finalized set of recommendations culminated

in a consensus draft that was then agreed upon by the panel at large. This draft paper was edited for clarity and brevity, for the purposes of dissemination and publication.<sup>7</sup>

## Initial evaluation

### Clinical presentation and evaluation

The clinical presentation of CNS lymphomas is highly variable depending upon the anatomical location of the lesion. The signs and symptoms range from focal neurological deficits (50-70%), altered mentation, behavioural changes (32-43%), and manifestations related to raised intracranial pressure (headache, nausea, vomiting, and papilloedema; 32-33%) and seizures (11-14%).<sup>8</sup> Rare symptomatology includes isolated visual symptoms (4%) ranging from pain, redness, blurry vision, decreased visual acuity, and visual floaters.<sup>9</sup>

Neurolymphomatosis may be seen as the only clinical presentation of lymphoma resulting from infiltration of the peripheral nervous system that manifests differently. This can include plexopathy, mononeuritis multiplex, foot drop, radiculopathy, and cranial nerve palsies. Symptoms of nerve involvement can result in extreme pain not amenable to neuropathic pain medications.<sup>10</sup>

The diagnosis of CNS lymphoma can be delayed in low- and middle-income countries (LMICs) because of delayed health-seeking behaviour combined with a high misdiagnosis rate. This can result in a high disease burden at presentation. According to one study, the median time from the onset of symptoms to diagnosis is reported to be around 3.5 – 5 months in the Indian subcontinent compared to the Western population, which is about 2.5 – 3 months.<sup>11, 12</sup> Individuals in LMIC commonly present with headaches due to raised intracranial pressure as the index presentation compared to focal neurological deficits in the Western population.<sup>13, 14</sup> The Eastern Cooperative Oncology group (ECOG) performance status is  $\geq 3$  in individuals residing in LMIC in comparison to higher-income countries.<sup>15, 16</sup>

### Diagnostic workup

Lymphoma is fundamentally a multisystem disease. A systemic approach is needed to investigate the patient considering a wide array of differentials. Primary CNS lymphoma typically appears as a solitary (60%) parenchymal mass involving the supratentorial compartment with a greater predilection for the periventricular region.<sup>17</sup> It can be multifocal in 20-40 % of cases with up to 8 lesions.<sup>18, 19</sup> Frontal and parietal lobes are involved more commonly in the supratentorial compartment. Lymphomatous lesions involve deep

periventricular structures in the brain, including the corpus callosum and basal ganglia.<sup>20</sup>

MRI with and without contrast is the modality of choice. The lesion appears hypo to isointense on the T1 weighted image while hypointense on T2 and FLAIR sequences. Lymphomas show diffusion restriction owing to high cellular content, appearing hyperintense on diffusion-weighted imaging (DWI) with corresponding low ADC (apparent diffusion coefficient) values. MR spectroscopy shows an elevated choline peak with reduced N-acetyl aspartate (NAA) and Cr levels. Leptomeningeal enhancement can also be present in some cases. There is mild peritumoral oedema compared to gliomas and metastasis.<sup>20</sup> The low cost and wide availability of CT scan make it a valuable alternative to MRI in resource-limited settings in LMICs. On CT, lymphoma characteristically appears hyperdense with homogeneously contrast enhancement.<sup>21</sup>

It's essential to differentiate CNS lymphoma from other pathologies that closely mimic on MRI. Glioblastoma is one of the closest differentials of lymphoma on imaging. High-grade gliomas usually elicit heterogeneous contrast enhancement with central necrosis compared to more homogeneously enhancing lymphomas. Unlike glioblastomas, lymphomas manifest restricted diffusion. Metastasis is also a common differential to lymphoma, usually showing central necrosis, peripheral enhancement, and extensive peritumoral oedema. Other differentials may include tumefactive demyelination and infectious etiologies such as an abscess.<sup>21</sup>

A complete staging workup is required once the diagnosis is confirmed. This includes MRI whole spine with and without contrast, lumbar puncture, systemic imaging with and without bone marrow biopsy, and ophthalmology evaluation. In addition, baseline blood workup should include complete blood count, liver and kidney function tests, serum lactate dehydrogenase (LDH), and HIV and Hepatitis serology.

Lumbar puncture if safe, should be performed for all patients with suspected or confirmed PCNS lymphoma. It is indicated in cases where biopsy isn't available and/or to rule out leptomeningeal involvement.<sup>22</sup> CSF (3-10 ml) should be sent for detailed report (DR) and cytology. Immunohistochemistry analysis of sample tissue is often sufficient and practical for most resource-limited settings, however, if facilities are available beta-2 microglobulin levels, IgH gene rearrangement, and flow cytometry may be considered for CSF analysis. A detailed report reveals elevated white cell count and protein. Glucose is usually

normal.

18 Fluorodeoxyglucose PET scan is recommended to rule out systemic disease; if not available, it can be replaced with CT scan of the neck, chest, abdomen, and pelvis with and without contrast. It is particularly useful in patients with renal dysfunction or contrast allergies. In addition, PET has high sensitivity in detecting systemic lymphoma compared to CT scans.<sup>23</sup> It is also superior to MRI in determining the therapeutic response to chemotherapy. However, its cost and availability limit practicality in LMICs.

For individuals aged over 60 with CNS lymphoma, it is essential to undergo an evaluation to exclude the possibility of a primary testicular neoplasm, which accounts for 15% of cases.<sup>24</sup> A thorough testicular examination, complemented by ultrasound, offers substantial diagnostic advantages, especially since PET scans and CT scans have limited efficacy in detecting testicular diseases.

Ophthalmology evaluation is mandated in all patients suspected of CNS lymphoma, as 5-20 % of these tumours present with intraocular involvement only. Most patients present with floaters and blurry vision with intact visual acuity, unless direct central macular involvement. Approximately 50% of patients are asymptomatic at presentation, underlying the need for examination. A slit lamp examination should be done, followed by fluorescein angiography and colour photography if an abnormality is detected. Confirmatory tests may include flow cytometry of vitreous fluid and tissue biopsy from the vitreous, retina, and choroid tissue. Primary vitreoretinal lymphoma (PVRL) is a subset where lymphoma arises in the eyes first without brain involvement. Though this is initially a limited disease, 60-90% of patients develop CNS relapse.

### **Surgical management**

The role of surgery for Primary CNS lymphoma (PCNSL) is focussed on tissue biopsy for histopathological confirmation before starting chemotherapy. Solitary lesions can be elected for either standard biopsy or stereotactic sampling if such capabilities are available, resulting in lower surgical morbidity and hospital stay. The tissue sample can be obtained via stereotactic biopsy with a greater than 80% diagnostic yield.<sup>25</sup> Surgical biopsy is not indicated when the tumour is located deep within the brain parenchyma or multifocal, as it may increase the morbidity of patients. For multicentric lesions, the most accessible and safest lesion is biopsied, ensuring the adequacy of samples obtained. The intraoperative frozen section may help confirm the preliminary diagnosis; if the

lesion is shown to be glial or metastatic neoplasm, then the procedure may need to be converted to maximum safe resection.

Debulking of the lesion is usually not recommended, due to the disease's excellent response to chemotherapy obviating any need for debulking. However, large lesions compressive adjacent critical structures or resulting in obstructive hydrocephalus would benefit from maximum safe resection. The objective is then to improve the patient's functional status and allow early initiation of chemotherapy. Recent evidence from meta-analysis suggests that overall survival and progression free survival are higher in PCNSL patients who undergo resection compared to biopsy only.<sup>26</sup> However, this remains to be further validated in other trials.

The use of corticosteroids before biopsy should be avoided as it leads to lysis of tumour cells, decreasing the diagnostic yield of biopsy. Non-diagnostic rates range from 37% after a short period of steroid use (less than one week) to 57 % after a long course of steroid (greater than one week). Therefore, steroid use should be discontinued before biopsy in patients with suspected lymphoma.<sup>27, 28</sup> Re-imaging is advised after 2-4 weeks in cases of suspected CNS lymphoma that usually disappears after steroid use.

The rates of complications associated with surgical resection and biopsy are similar. These complications encompass the risks of surgical site infection, bleeding, meningitis, cerebrospinal fluid leakage, intracranial haemorrhage, seizures, focal deficits, brain infarction, as well as systemic complications.<sup>29, 30</sup>

### **Pathological assessment histopathology**

The characteristic histology is a diffuse large B cell lymphoma (DLBCL), which belongs to the family of non-Hodgkin B cell lymphoma, in more than 90 percent of the cases. Uncommon causes include Burkitt lymphoma and low-grade B-cell lymphomas including MALT lymphoma and T-cell lymphoma.<sup>31</sup> Immunodeficiency-associated CNS lymphoma and intravascular large B cell lymphoma are now considered unique types, of CNS lymphoma distinct from primary diffuse, large B, cell lymphoma of the CNS.

Characteristic histological features of primary CNS lymphoma include malignant cells with minimal cytoplasm, angiocentric growth pattern, and frequent mitotic activity. A background of reactive inflammatory cells may also accompany these features. Haematolymphoid nature should be confirmed by

immunohistochemical staining.

The malignant tumour cells show a mature, late germinal-center exit B cells phenotype. The tumour expresses mature B-cell markers including PAX5, CD20, CD19, and CD79a. Immunohistochemical stains such as CD10, Bcl6, and MUM1 are frequently used to sub-classify the tumour into germinal center type and non-germinal center type tumours. CD10 expression is less common (less than 10% of all CNS B cell lymphoma) and should prompt a search for an extracranial source of lymphoma. In cases where diagnostic tumour cells are not seen, the pathologist should elicit the history of steroid use which leads to apoptosis of tumour cells.

### Molecular pathology

Three distinct molecular subgroups of primary CNS lymphoma have been categorised according to gene expression. These different subgroups include germinal center B-cell like, activated B-cell like/non germinal centers, and type 3 subgroups. Most of these tumours have overlapping features of germinal center and activated B cell differentiation subtypes as immunohistochemical analysis has revealed expression of the MUM-1 gene (activated B cell marker) and BCL-6 (a marker of germinal center). The BCR signalling pathway may be affected by recurrent mutations, especially MYD88 and CD79B, that activate nuclear factor  $\kappa$ B (NF- $\kappa$ B). Other alterations may also be seen, including gain at chromosome 9p24.1, which suggests that evasion of immune responses and modulation of pathways contribute to the pathogenesis of CNS lymphomas.<sup>32</sup>

### Chemotherapy

The first-line lymphoma treatment, both primary CNS and systemic, is chemotherapy. However, the chemotherapy regimens for systemic lymphoma differ from primary CNS lymphoma as many of these therapeutic agents do not cross the blood-brain barrier.

A modern treatment approach to primary CNS lymphoma includes two phases: induction and consolidation phase.

### Induction phase

Combination chemotherapy regimens are used during the induction phase. The treatment protocol incorporates high-dose Methotrexate (MTX), which has high initial response rates in combination with other agents.

According to several studies, the dose of MTX employed is between 3 and 8 g/m<sup>2</sup>, although the optimal dose has yet to be established. It's essential to administer MTX as a rapid infusion over 2- hours at a dose of at least 3 g/m<sup>2</sup> to achieve maximum therapeutic concentration in CNS at

intervals of 10-21 days.<sup>33</sup>

The International Extranodal Lymphoma Study Group (IELSG) study has demonstrated the value of combining HD-MTX with other cytotoxic agents. Adding cytarabine in combination with HD-MTX improves complete response rate and progression free survival compared to methotrexate alone. Adding Rituximab to a combination of MTX/cytarabine further improves the response rate.

Within resource-limited centers, the modified DeAngelis Protocol is a viable option, consisting of five to seven cycles of MVP (Methotrexate, Vincristine, and Procarbazine) followed by radiation and consolidation with two cycles of high-dose Cytarabine considering the challenges faced by the high cost of drugs such as rituximab which doesn't impact overall outcome.<sup>34</sup> Repeat hospital admissions for infusions and toxicity management underlie the need for practicable application of such protocols. Specific methotrexate serum levels may not be available in many centres; our institutional experience has been to universally admit patients to the hospital for HD-MTX to maintain adequate hydration and urine alkalinization for timely methotrexate clearance, with renal function monitoring. With timely intervention, HD-MTX can be delivered effectively.<sup>35</sup> Due to the toxicity of HD-MTX, only centres with the capability for monitoring, typically tertiary care centres, should manage these patients.

The poor CNS penetration indicates the use of high-dose MTX in addition to R-CHOP regimen (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone) in individuals with secondary CNS involvement.<sup>36</sup>

Elderly and frail patients are less tolerant of the adverse effects of intensive induction chemotherapy regimens. In these individuals, less intensive treatment options can be considered. According to the PRIMAIN protocol for elderly patients, a combination of Methotrexate with Rituximab and Procarbazine can be used for six cycles every 28 days, followed by a maintenance dose of Procarbazine for another six cycles.<sup>37</sup>

Palliative treatment can be considered in patients deemed unfit for methotrexate-based chemotherapy. This includes whole brain radiotherapy and oral chemotherapeutic agents like Temozolomide or corticosteroids. A small retrospective study of single agent temozolomide in elderly patients with comorbidities showed a prolonged response (>12 months), progression free survival of 5 months, and overall survival of 21 months.<sup>38</sup>

Frequently observed adverse effects of Methotrexate-based chemotherapy encompass renal failure, atypical blood cell counts, disruptions in liver function, pneumonitis, mucositis, and leukoencephalopathy. Other serious effects may include the reactivation of latent viruses, particularly hepatitis, and the activation of latent tuberculosis.

### Consolidation phase

Patients responding to initial induction and with non-progressive disease should be considered for consolidation therapy to improve overall outcomes. According to the recommendations, this phase of treatment should be commenced within 6-8 weeks of the first day of the final induction chemotherapy cycle.<sup>39</sup>

High-dose Thiotepa (HDT) based chemotherapy with Autologous Stem Cell Transplantation (ASCT) is considered first-line consolidation therapy. Based on the findings from the International Extra-nodal Lymphoma Study Group 32 (IELSG32), 24 out of 28 patients who initially had a partial response following induction therapy were able to attain a complete response after undergoing HDT-ASCT.<sup>40</sup>

Patients, not eligible for HDT-ASCT and those with residual disease following induction chemotherapy should receive whole brain radiotherapy (WBRT) as part of consolidation treatment.<sup>41</sup> The cost and availability of Thiotepa are concerning in LMICs. As per NCCN guidelines, alternative options may include a high-dose Cytarabine with or without Etoposide or continuing high dose Methotrexate/Rituximab-based regimen for 1 year.

### Radiotherapy

Radiotherapy had previously been the mainstay in treating PCNSL. It is currently used in the consolidative phase of management in combination with the chemotherapeutic agent to maintain remission. Isolated whole brain radiotherapy can achieve rapid remission; however, recurrences are particularly common. The median survival is 12-18 months with radiation alone, but when combined with chemotherapy, the median survival can be increased to 31-90 months.<sup>42,43</sup>

Isolated whole brain radiation therapy can be used in individuals unfit for methotrexate-based regimens, particularly elderly individuals with comorbidities. It is indicated for induction of remission and in the consolidation phase to maintain remission.<sup>44</sup>

Neurotoxicity is a major complication associated with whole brain radiotherapy. Patients may show marked leukoencephalopathy, which leads to cortical and

subcortical atrophy resulting in gait abnormalities, incontinence, and cognitive deficits.<sup>45</sup>

### Disease relapse

Managing patients who experience disease relapse is a daunting task, characterized by a grim prognosis and a median overall survival ranging from 3 to 5 months.<sup>46</sup> It's recommended that all relapses should be discussed in multidisciplinary meetings involving neurosurgeons, neuro-oncologists, and radiation oncologists. Individualised salvage treatment should be considered in cases of relapse and recurrence.

All patients with relapses occurring more than two years after initial diagnosis should undergo repeat biopsy and re-staging to plan further treatment. Intensive treatment options may include high-dose methotrexate when the first remission to HD-MTX is over two years. Other options include Ifosfamide-based immunochemotherapy if there's an early relapse with MTX-based treatment.<sup>47</sup>

Patients ineligible for intensive treatment should be considered for whole brain radiotherapy, corticosteroids, or oral Temozolomide.

A recent systematic review highlighted promising evidence for the use of the irreversible Bruton tyrosine kinase inhibitor, ibrutinib, for the treatment of recurrent/relapsing PCNSL, especially in combination therapy.<sup>48</sup> However further trials are needed to establish its efficacy.

### Follow up

All patients diagnosed with lymphoma of CNS should remain under continuous follow-up as there's a high risk of recurrence. It's observed that recurrences may be seen more than ten years after treatment, and about 6-25 percent of recurrences are asymptomatic.<sup>49</sup> The requirement of complete remission includes the disappearance of contrast-enhancing lesions, the absence of malignant cells in CSF, and the complete disappearance of previous ocular involvement.

All patients should undergo routine clinical examination and imaging at follow-up. The guidelines from the National Comprehensive Cancer Network (NCCN) suggest undergoing brain imaging every three months during the initial two years, followed by imaging every six months for the subsequent three years, and then yearly for the subsequent five years.<sup>50</sup>

Routine evaluation of CSF and spine imaging is not indicated unless an abnormality is suspected. Similarly, patients with intraocular involvement previously should undergo ophthalmologic examination routinely.

**Table-1:** Summary of Recommendations for Primary CNS Lymphoma.

<b>Radiology</b>	<ul style="list-style-type: none"> <li>• MRI brain with and without contrast.</li> <li>• 'Minimum required' MRI protocol:               <ul style="list-style-type: none"> <li>o Imaging on at least 0.5T.</li> <li>o Sequences: Axial T2 and coronal or axial FLAIR sequence; pre-contrast T1 and contrast-enhanced T1.</li> </ul> </li> <li>• Tumour location, tumour margins, enhancement pattern, tumour size and presence of haemorrhage/mineralisation must be included.</li> <li>• Systemic imaging (CT chest, abdomen, and pelvis with contrast) and blood workup to differentiate between primary and secondary disease lymphoma and ophthalmological assessment.</li> </ul>
<b>Neurosurgery</b>	<ul style="list-style-type: none"> <li>• Surgery is usually indicated to obtain tissue for histopathology.</li> </ul>
<b>Neuropathology</b>	<ul style="list-style-type: none"> <li>• Haematoxylin and eosin (H&amp;E) preparation for histological typing.</li> <li>• Intraoperative consultation to rule out gliomas and metastatic tumours is crucial.</li> <li>• Immunohistochemical stain panel including CD20, CD3, CD30, Ki-67 etc, for definite characterisation.</li> </ul>
<b>Medical and Radiation Oncology</b>	<ul style="list-style-type: none"> <li>• Mainstay in the treatment of both primary and secondary CNS lymphoma.</li> <li>• Multiple chemotherapeutic regimens are available depending on patient factors – we recommend a modified DeAngelis protocol with active renal and systemic toxicity monitoring.</li> <li>• Radiotherapy is a part of PCNSL management as an adjunct to chemotherapy according to the modified DeAngelis protocol.</li> <li>• Patients who are not a candidate for chemotherapy radiation therapy can be considered alone.</li> <li>• WBRT with advanced techniques such as 3DCRT/IMRT/VMAT with a conventional fractionation schedule is recommended.</li> <li>• For patients with complete response after chemotherapy WBRT dose should be limited to 23.4 Gy in 13 fractions at 1.8 Gy fraction.</li> <li>• For patients with partial response to chemotherapy or who are not candidates for chemotherapy WBRT dose is 36 Gy in 1.8-2 fraction followed by a boost to gross disease for a total dose of 45 Gy.</li> </ul>
<b>Follow-up</b>	<ul style="list-style-type: none"> <li>• First follow-up at post-op day 10 for wound assessment, stitch removal, discussion related to histopathology and NOTB recommendations.</li> <li>• Serial follow-up with an MRI brain is recommended every three months for the first two years, six monthly imaging for the next three years, and then annually</li> </ul>

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for five years.

MRI: Magnetic resonance imaging, FLAIR: Fluid-attenuated inversion recovery, CT: Computed tomography, CNS: Central nervous system, PCNSL: Primary central nervous system lymphoma, WBRT: Whole brain radiotherapy, 3DCRT: Three-dimensional conformal radiotherapy, IMRT: Intensity-modulated radiation therapy, VMAT: Volumetric modulated arc therapy, Gy: Gray, NOTB: Neuro-Oncology tumour board.

### Steroids and decision-making

If workup shows a lesion with homogeneous contrast-enhancement, CNS lymphoma should be suspected. Steroids therapy should be deferred initially for surgical biopsy as soon as possible for the patient. After an adequate sample, confirmed on frozen section if available, has been obtained, clinicians can empirically initiate steroids treatment. In some circumstances, patients present to clinics having already started steroids to treat mass-effect symptoms. In such a case, a new MRI scan should be obtained where possible – if involution of the lesion is seen, steroids should be withheld and repeat MRI done after 2-3 weeks, or if symptoms recur.

### Miscellaneous/Prognosis/Quality of life

The overall outcome and prognosis of a patient with CNS lymphoma are highly variable. Age is an independent factor of the prognosis, with the elderly population having poor outcomes, a high risk of early death, and being frequently disabled. In contrast, younger individuals have higher long-term survival and cure rates.<sup>51</sup>

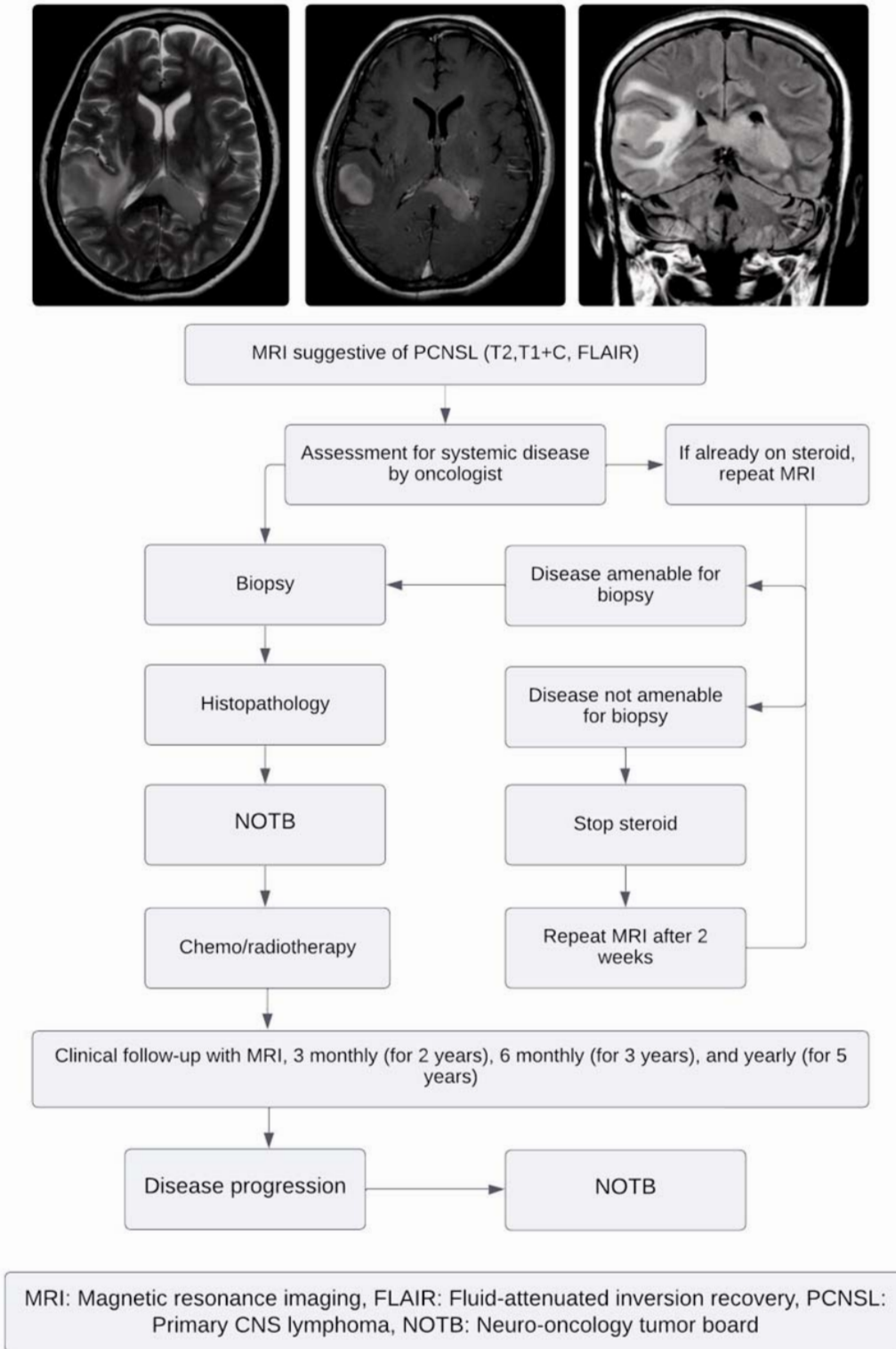
Functional performance status is one of the strongest predictors of survival in PCNSL – Karnofsky Performance Status is a useful determinant of pre-treatment function and survival likelihood.<sup>52</sup>

According to a study, the quality of life was good in about 72% of the patients.<sup>53</sup> However, in some patients, the quality of life had declined, mainly due to loss of social functioning. Most patients suffer from cognitive impairment at presentation. Individuals who experience subnormal performance at long-term follow-up primarily affect attention and executive functions.

Younger patients treated with MTX based systemic polychemotherapy have an acceptable quality of life without significantly deteriorating cognitive deficits.

### Conclusion

These guidelines set a practical framework to support healthcare professionals working in limited resource settings, (see Table 1 and Figure 1). By implementing these guidelines, we can significantly improve outcomes



**Figure-1:** Management of PCNSL algorithm.

while effectively providing multi-disciplinary neuro-oncology care in resource-constrained countries, like Pakistan.

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## References

- Villano JL, Koshy M, Shaikh H, Dolecek TA, McCarthy BJ. Age, gender, and racial differences in incidence and survival in primary CNS lymphoma. *Br J Cancer* 2011;105:1414-8. doi: 10.1038/bjc.2011.357.
- Mendez JS, Ostrom QT, Gittleman H, Kruchko C, DeAngelis LM, Barnholtz-Sloan JS, et al. The elderly left behind-changes in survival trends of primary central nervous system lymphoma over the past 4 decades. *Neuro Oncol* 2018;20:687-94. doi: 10.1093/neuonc/nox187.
- O'Neill BP, Decker PA, Tieu C, Cerhan JR. The changing incidence of primary central nervous system lymphoma is driven primarily by the changing incidence in young and middle-aged men and differs from time trends in systemic diffuse large B-cell non-Hodgkin's lymphoma. *Am J Hematol* 2013;88:997-100. doi: 10.1002/ajh.23551.
- Bernstein SH, Unger JM, Leblanc M, Friedberg J, Miller TP, Fisher RI. Natural history of CNS relapse in patients with aggressive non-Hodgkin's lymphoma: a 20-year follow-up analysis of SWOG 8516 -- the Southwest Oncology Group. *J Clin Oncol* 2009;27:114-9. doi: 10.1200/JCO.2008.16.8021.
- Hollender A, Kvaloy S, Nome O, Skovlund E, Lote K, Holte H. Central nervous system involvement following diagnosis of non-Hodgkin's lymphoma: a risk model. *Ann Oncol* 2002;13:1099-107. doi: 10.1093/annonc/mdf175.
- van Besien K, Ha CS, Murphy S, McLaughlin P, Rodriguez A, Amin K, et al. Risk factors, treatment, and outcome of central nervous system recurrence in adults with intermediate-grade and immunoblastic lymphoma. *Blood* 1998;91:1178-84.
- Bajwa MH, Shah MM, Mustansir F, Gauhar F, Baig E, Zafar SN, et al. A Guideline On Guidelines – Neuro-Oncology Guideline Standards For Low And Middle-Income Countries. *J Pak Med Assoc* 2024;74(Suppl 3):s87-92. Doi: 10.47391/JPMA.S3.GNO-10.
- Bataille B, Delwail V, Menet E, Vandermarcq P, Ingrand P, Wager M, et al. Primary intracerebral malignant lymphoma: report of 248 cases. *J Neurosurg* 2000;92:261-6. doi: 10.3171/jns.2000.92.2.0261.
- Hong JT, Chae JB, Lee JY, Kim JG, Yoon YH. Ocular involvement in patients with primary CNS lymphoma. *J Neurooncol* 2011;102:139-45. doi: 10.1007/s11060-010-0303-9.
- Grisariu S, Avni B, Batchelor TT, van den Bent MJ, Bokstein F, Schiff D, et al. Neurolymphomatosis: an International Primary CNS Lymphoma Collaborative Group report. *Blood* 2010;115:5005-11. doi: 10.1182/blood-2009-12-258210.
- van der Meulen M, Dirven L, Habets EJJ, van den Bent MJ, Taphoorn MJB, Bromberg JEC. Cognitive functioning and health-related quality of life in patients with newly diagnosed primary CNS lymphoma: a systematic review. *Lancet Oncol* 2018;19:e407-18. doi: 10.1016/S1470-2045(18)30356-5.
- Haldorsen IS, Espeland A, Larsen JL, Mella O. Diagnostic delay in primary central nervous system lymphoma. *Acta Oncol* 2005;44:728-34. doi: 10.1080/02841860500256272.
- Patekar M, Adhikari N, Biswas A, Raina V, Kumar L, Mohanti BK, et al. Primary CNS Lymphoma in India: A 17-Year Experience From the All India Institute of Medical Sciences. *J Glob Oncol* 2019;5:1-9. doi: 10.1200/JGO.18.00124.
- Tun HW, Personett D, Baskerville KA, Menke DM, Jaeckle KA, Kreinest P, et al. Pathway analysis of primary central nervous system lymphoma. *Blood* 2008;111:3200-1. doi: 10.1182/blood-2007-10-119099.
- Bataille B, Delwail V, Menet E, Vandermarcq P, Ingrand P, Wager M, et al. Primary intracerebral malignant lymphoma: report of 248 cases. *J Neurosurg* 2000;92:261-6. doi: 10.3171/jns.2000.92.2.0261.
- Mahadevan A, Rao CR, Shanmugham M, Shankar SK. Primary central nervous system diffuse large B-cell lymphoma in the immunocompetent: Immunophenotypic subtypes and Epstein-Barr virus association. *J Neurosci Rural Pract* 2015;6:8-1. doi: 10.4103/0976-3147.143171.
- Zucca E, Conconi A, Mughal TI, Sarris AH, Seymour JF, Vitolo U, et al. Patterns of outcome and prognostic factors in primary large-cell lymphoma of the testis in a survey by the International Extranodal Lymphoma Study Group. *J Clin Oncol* 2003;21:20-7. doi: 10.1200/JCO.2003.11.141.
- Mohile NA, Abrey LE. Primary central nervous system lymphoma. *Neurol Clin* 2007;25:1193-207. doi: 10.1016/j.ncl.2007.07.001.
- Coulon A, Lafitte F, Hoang-Xuan K, Martin-Duverneuil N, Mokhtari K, Blustajn J, et al. Radiographic findings in 37 cases of primary CNS lymphoma in immunocompetent patients. *Eur Radiol* 2002;12:329-40. doi: 10.1007/s003300101037.
- Mansour A, Qandeel M, Abdel-Razeq H, Abu Ali HA. MR imaging features of intracranial primary CNS lymphoma in immune competent patients. *Cancer Imaging* 2014;14:22. doi: 10.1186/1470-7330-14-22.
- Joshi A, Deshpande S, Bayaskar M. Primary CNS lymphoma in Immunocompetent patients: Appearances on Conventional and Advanced Imaging with Review of literature. *J Radiol Case Rep* 2022;16:1-17. doi: 10.3941/jrcr.v16i7.4562.
- Schroers R, Baraniskin A, Heute C, Vorgerd M, Brunn A, Kuhnhen J, et al. Diagnosis of leptomeningeal disease in diffuse large B-cell lymphomas of the central nervous system by flow cytometry and cytopathology. *Eur J Haematol* 2010;85:520-8. doi: 10.1111/j.1600-0609.2010.01516.x.
- Fox CP, Phillips EH, Smith J, Linton K, Gallop-Evans E, Hemmaway C, et al. Guidelines for the diagnosis and management of primary central nervous system diffuse large B-cell lymphoma. *Br J Haematol* 2019;184:348-63. doi: 10.1111/bjh.15661.
- Zucca E, Conconi A, Mughal TI, Sarris AH, Seymour JF, Vitolo U, et al. Patterns of outcome and prognostic factors in primary large-cell lymphoma of the testis in a survey by the International Extranodal Lymphoma Study Group. *J Clin Oncol* 2003;21:20-7. doi: 10.1200/JCO.2003.11.141.
- von Baumgarten L, Illerhaus G, Korfel A, Schlegel U, Deckert M, Dreyling M. The Diagnosis and Treatment of Primary CNS Lymphoma. *Dtsch Arztebl Int* 2018;115:419-26. doi: 10.3238/arztebl.2018.0419.
- Chojak R, Koźba-Gosztyła M, Polańska K, Rojek M, Chojko A, Bogacz R, et al. Surgical resection versus biopsy in the treatment of primary central nervous system lymphoma: a systematic review and meta-analysis. *J Neurooncol* 2022;160:753-61. doi: 10.1007/s11060-022-04200-7.
- Gametchu B. Glucocorticoid receptor-like antigen in lymphoma cell membranes: correlation to cell lysis. *Science* 1987;236:456-61. doi: 10.1126/science.3563523.
- Weller M. Glucocorticoid treatment of primary CNS lymphoma. *J Neurooncol* 1999;43:237-9. doi: 10.1023/a:1006254518848.
- Schellekes N, Barbotti A, Abramov Y, Sitt R, Di Meo F, Ram Z, et al. Resection of primary central nervous system lymphoma: impact of patient selection on overall survival. *J Neurosurg* 2021;135:1016-25. doi: 10.3171/2020.9.JNS201980.

30. Wu S, Wang J, Liu W, Hu F, Zhao K, Jiang W, et al. The role of surgical resection in primary central nervous system lymphoma: a single-center retrospective analysis of 70 patients. *BMC Neurol* 2021;21:190. doi: 10.1186/s12883-021-02227-3.
31. Camilleri-Broët S, Martin A, Moreau A, Angonin R, Hénin D, Gontier MF, et al. Primary central nervous system lymphomas in 72 immunocompetent patients: pathologic findings and clinical correlations. *Groupe Ouest Est d'étude des Leucémies et Autres Maladies du Sang (GOELAMS)*. *Am J Clin Pathol* 1998;110:607-12. doi: 10.1093/ajcp/110.5.607.
32. Chapuy B, Roemer MG, Stewart C, Tan Y, Abo RP, Zhang L, et al. Targetable genetic features of primary testicular and primary central nervous system lymphomas. *Blood* 2016;127:869-81. doi: 10.1182/blood-2015-10-673236.
33. Fox CP, Phillips EH, Smith J, Linton K, Gallop-Evans E, Hemmaway C, et al. Guidelines for the diagnosis and management of primary central nervous system diffuse large B-cell lymphoma. *Br J Haematol* 2019;184:348-63. doi: 10.1111/bjh.15661.
34. Houillier C, Soussain C, Ghesquières H, Soubeyran P, Chinot O, Taillandier L, et al. Management and outcome of primary CNS lymphoma in the modern era: An LOC network study. *Neurology* 2020;94:e1027-39. doi: 10.1212/WNL.0000000000008900.
35. Shahzadi M, Ahmed D, Sawani S, Moosajee M. Outcome of Primary CNS Lymphoma; A Retrospective Analysis. *Asian Pac J Cancer Care* 2022;7:41-6. DOI 10.31557/apjcc.2022.7.1.41-46.
36. Kim SJ, Oh SY, Kim JS, Kim H, Lee GW, Won JH, et al. Secondary central nervous system (CNS) involvement in patients with diffuse large B-cell lymphoma: a therapeutic dilemma. *Ann Hematol* 2011;90:539-46. doi: 10.1007/s00277-010-1104-0.
37. Fritsch K, Kasenda B, Schorb E, Hau P, Bloehdorn J, Möhle R, et al. High-dose methotrexate-based immuno-chemotherapy for elderly primary CNS lymphoma patients (PRIMAIN study). *Leukemia* 2017;31:846-52. doi: 10.1038/leu.2016.334.
38. Kurzweily D, Glas M, Roth P, Weimann E, Lohner H, Waha A, et al. Primary CNS lymphoma in the elderly: temozolomide therapy and MGMT status. *J Neurooncol* 2010;97:389-92. doi: 10.1007/s11060-009-0032-0.
39. Ferreri AJM, Cwynarski K, Pulczynski E, Fox CP, Schorb E, La Rosée P, et al. Whole-brain radiotherapy or autologous stem-cell transplantation as consolidation strategies after high-dose methotrexate-based chemoimmunotherapy in patients with primary CNS lymphoma: results of the second randomisation of the International Extranodal Lymphoma Study Group-32 phase 2 trial. *Lancet Haematol* 2017;4:e510-23. doi: 10.1016/S2352-3026(17)30174-6.
40. Nelson DF. Radiotherapy in the treatment of primary central nervous system lymphoma (PCNSL). *J Neurooncol* 1999;43:241-7. doi: 10.1023/a:1006206602918.
41. Morris PG, Correa DD, Yahalom J, Raizer JJ, Schiff D, Grant B, et al. Rituximab, methotrexate, procarbazine, and vincristine followed by consolidation reduced-dose whole-brain radiotherapy and cytarabine in newly diagnosed primary CNS lymphoma: final results and long-term outcome. *J Clin Oncol* 2013;31:3971-9. doi: 10.1200/JCO.2013.50.4910.
42. Abrey LE, Ben-Porat L, Panageas KS, Yahalom J, Berkey B, Curran W, et al. Primary central nervous system lymphoma: the Memorial Sloan-Kettering Cancer Center prognostic model. *J Clin Oncol* 2006;24:5711-5. doi: 10.1200/JCO.2006.08.2941.
43. Bellinzona M, Roser F, Ostertag H, Gaab RM, Saini M. Surgical removal of primary central nervous system lymphomas (PCNSL) presenting as space occupying lesions: a series of 33 cases. *Eur J Surg Oncol* 2005;31:100-5. doi: 10.1016/j.ejso.2004.10.002.
44. Langner-Lemercier S, Houillier C, Soussain C, Ghesquières H, Chinot O, Taillandier L, et al. Primary CNS lymphoma at first relapse/progression: characteristics, management, and outcome of 256 patients from the French LOC network. *Neuro Oncol* 2016;18:1297-303. doi: 10.1093/neuonc/nov033.
45. Nepal G, Khurana M, Bucheli DH, Bhandari S, Joshi U, Bhagat R, et al. Ibrutinib in Refractory or Relapsing Primary Central Nervous System Lymphoma: A Systematic Review. *Neurol Int* 2022;14:99-10. doi: 10.3390/neurolint14010009.
46. Hoang-Xuan K, Bessell E, Bromberg J, Hottinger AF, Preusser M, Rudà R, et al. Diagnosis and treatment of primary CNS lymphoma in immunocompetent patients: guidelines from the European Association for Neuro-Oncology. *Lancet Oncol* 2015;16:e322-3. doi: 10.1016/S1470-2045(15)00076-5.
47. van der Meulen M, Dirven L, Habets EJJ, van den Bent MJ, Taphoorn MJB, Bromberg JEC. Cognitive functioning and health-related quality of life in patients with newly diagnosed primary CNS lymphoma: a systematic review. *Lancet Oncol* 2018;19:e407-18. doi: 10.1016/S1470-2045(18)30356-5.

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