



# Management of Primary CNS Lymphomas

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# PCNSL - Talk Tour



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- **Treatment**
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  - ✓ **Combined modality approach**
  - ✓ **Role of Chemotherapy**
  - ✓ **Role of Surgery**
  - ✓ **Role of High dose chemotherapy and SCT**
  
- **Management of primary Intra-ocular Lymphoma**



## Definitions – PCNSL

**Primary central nervous system lymphoma (PCNSL)** is a NHL confined to the cranio-spinal axis (brain, leptomeninges, spinal cord or eyes) **without** evidence of systemic spread.

**Primary Intra-ocular lymphoma (PIOL)** –  
PCNSL primarily involving the eye initially

NHL sometimes spares the brain entirely and involves cranial nerves, nerve roots, or cauda equina owing to primary infiltration of the leptomeninges. On rare occasions there may be predominant infiltration of nerve roots, nerve plexus, or peripheral nerves only - a condition referred to as **Neurolymphomatosis** (NL).

## PCNSL - Epidemiology



- PCNSL is rare.
- Less than 5% of primary brain tumors (2.7% of all primary brain tumors diagnosed in the US from 1995 to 1999).
- Risk is more in patients who have congenital or AIDS, (3600 times risk) including organ transplant recipients
- Diagnosed in at least 2% of HIV-infected individuals
- Is an AIDS-defining illness.
- Incidence has decreased with availability of HAART



# Aetiopathogenesis

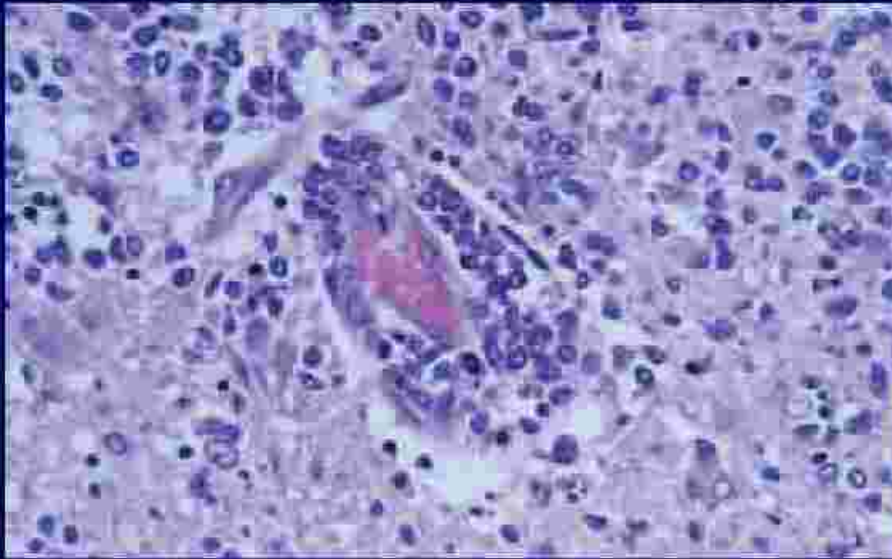


## Role of Epstein-Barr virus (EBV) genome

Detected in 0% to 20% of PCNSLs patients who do not have immunocompromise.

Nearly 100% in AIDS PCNSL

Latent membrane protein-1 IHC is positive in AIDS PCNSL compared with AIDS-related systemic non-Hodgkin's lymphomas suggesting a potentially different pathogenesis.



## Pathology

**90% are DLBCL**

**10% are poorly characterized low-grade lymphomas, Burkitt's lymphomas, and T-cell lymphomas.**



The DLBCL type of PCNSL is composed of immunoblasts or centroblasts

Have a predilection for blood vessels, resulting in lymphoid clustering around small cerebral vessels

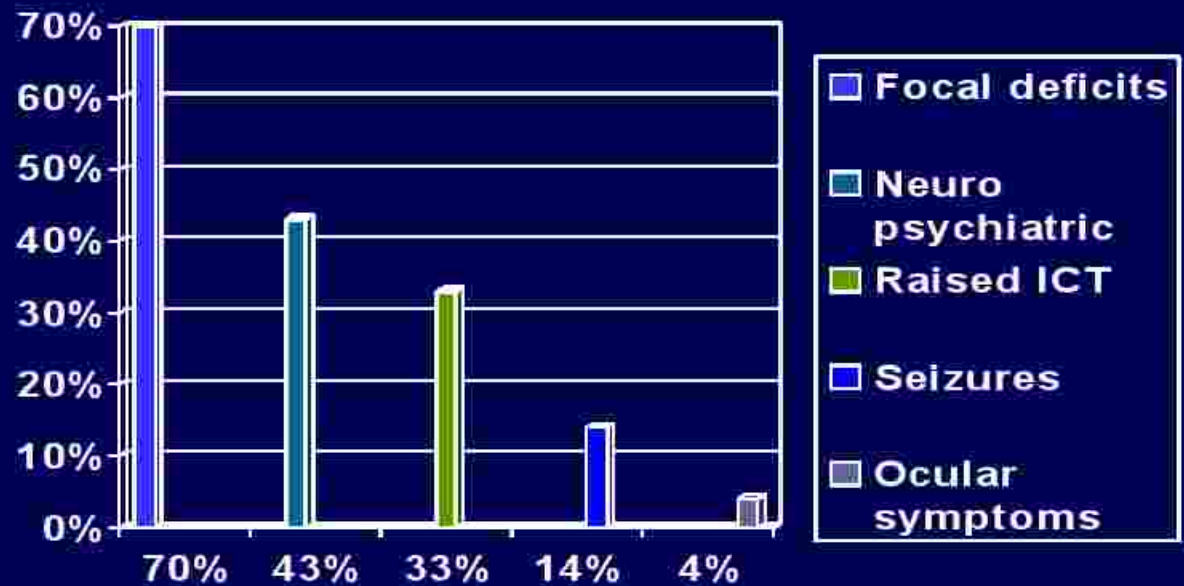
PCNSL is a late germinal center or post-germinal center lymphoid neoplasm.

The tumor arises in an **Extraneural** environment with subsequent localization to the CNS, possibly by virtue of a specific **Neurotropism**.

# Presentation - PCNSL



Typically present with neurologic symptoms and signs rather than systemic “B” symptoms



Bataille B, et al: Primary intracerebral malignant lymphoma: A report of 248 cases. J Neurosurg 92:261-266, 2000



## Presentation - PCNSL



- PCNSL involving the leptomeninges show no clinical signs of leptomeningeal disease usually (only 16-41%).
- Approximately 20% of patients will have ocular involvement at the time of PCNSL diagnosis. Both eyes affected in most patients.
- Patients with intraocular lymphoma generally complain of floaters, blurred vision, diminished visual acuity, and painful red eyes.



# Diagnostic evaluation



**Clinical Evaluation**

**Imaging**

**Pathology**

**Laboratory evaluation**



# Diagnostic Evaluation

## International PCNSL Collaborative group Guidelines for baseline evaluation

Pathology	Clinical	Laboratory	Imaging
Central review of Pathology	Complete medical and neurological examination	HIV Serology	Contrast enhanced cranial MRI
	Dilated eye examination including slit lamp examination	CSF cytology, Flow cytometry, IgH PCR	CT scan – Chest, abdomen and Pelvis
Immuno - phenotyping	Record prognostic factors (Age, PS)	24 hour urine collection for Creatinine clearance	Bone marrow aspiration and Biopsy
	Serial evaluation of cognitive function		Testicular USG in elderly

Abrey LE, et al: Report of an international workshop to standardize baseline evaluation and response criteria for primary central nervous system lymphoma. J Clin Oncol 23:5034-5043, 2005

# Neuro-imaging in PCNSL - Characteristics

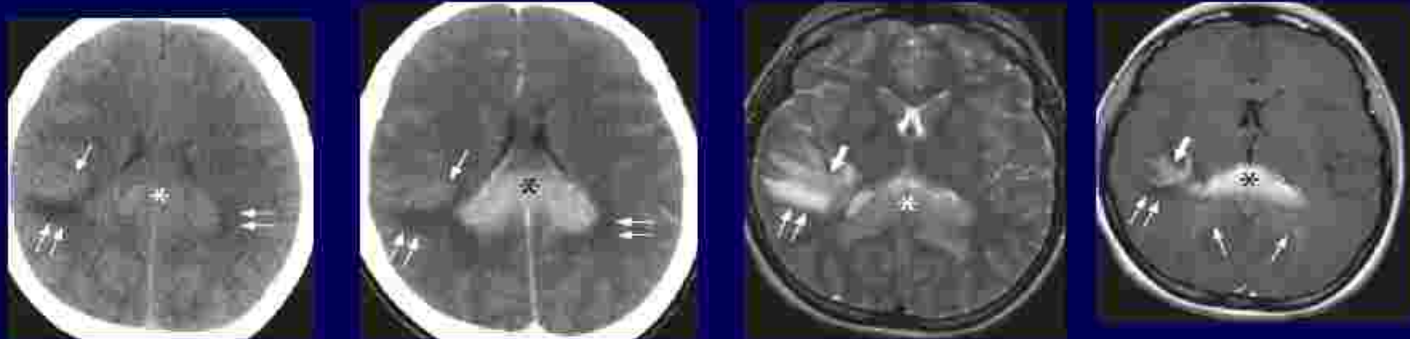


**Contrast-enhanced cranial MRI** is the optimal imaging modality for assessing patients with PCNSL unless contra-indicated.

PCNSL is often **isodense to hyperdense on CT images** and isointense to hypointense on T2-weighted MRI images, a finding that is attributed to its high cell density and scant cytoplasm

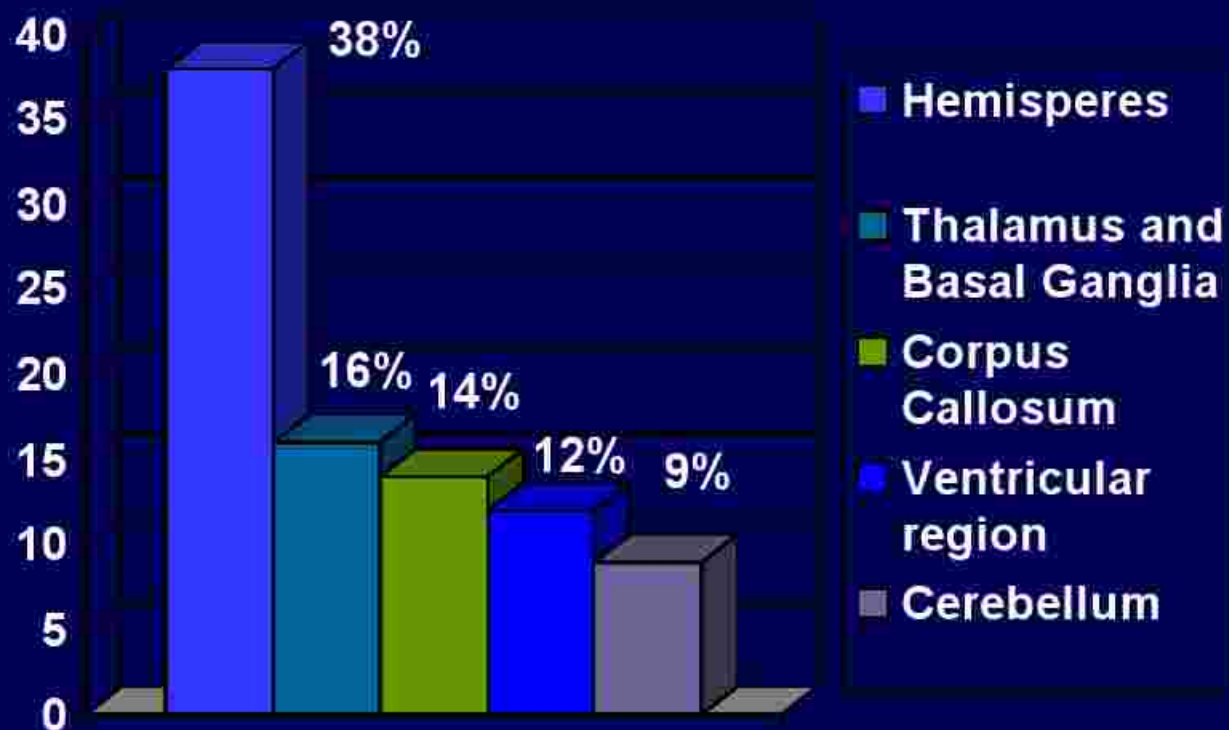
Post-contrast CT or MR images, typically reveal a homogeneous pattern of enhancement.

**Enhancement along the Virchow-Robin spaces**, although not constant, is a **highly specific** feature.





## Neuro-imaging in PCNSL Pattern of involvement



Kuker W, et al: Primary central nervous system lymphomas (PCNSL): MRI features at presentation in 100 patients. *J Neurooncol* 72:169-177, 2005



# Prognostication- PCNSL



**Ann Arbor Staging does not apply in PCNSL**

## **International Extranodal Lymphoma Study Group – Parameters associated with poor prognosis:**

- Age older than 60 years (most powerful prognostic factor)
- ECOG performance status greater than 1
- Elevated serum LDH
- High CSF protein concentration
- Tumor location within the deep regions of the brain (periventricular regions, basal ganglia, brainstem, and/or cerebellum).

### **Biochemical markers –**

BCL-6 over-expression – associated with longer survival (101 months versus 14.7 months in those in whom it is not expressed)

P53 and c-Myc expression associated with worse prognosis



## Prognostication- PCNSL

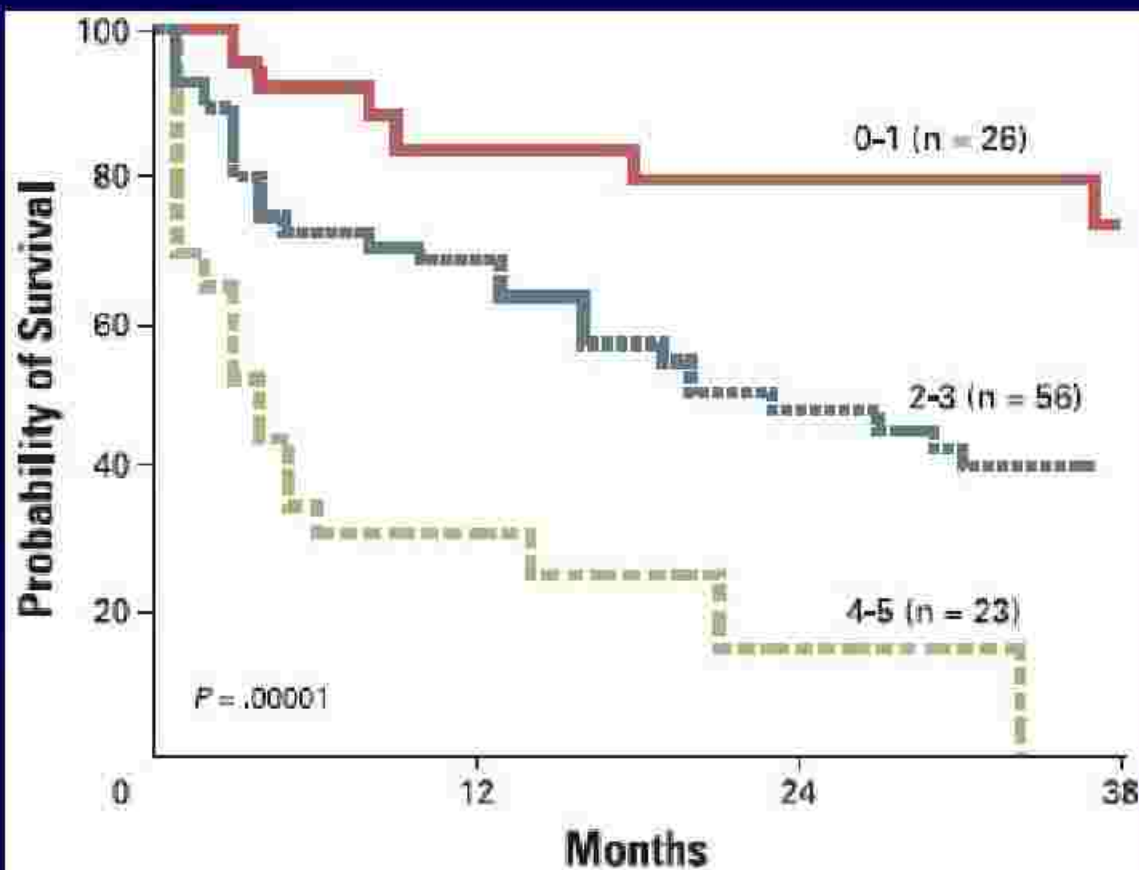
Age older than 60 years

ECOG PS greater than 1

Elevated serum LDH

High CSF protein conc

Tumor location within the deep regions of brain



Score	OS at 2 years
0 or 1	80%
2 or 3	48%
4 or 5	15%

Ferreri AJ et al: Prognostic scoring system for primary CNS lymphomas: The International Extranodal Lymphoma Study Group experience. *J Clin Oncol* 21:266-272, 2003



## PCNSL – Treatment aspects

- Extremely radiosensitive and chemo-sensitive tumor
- Relapses are common
- Current trials seek to identify the most appropriate combined modality treatment
- Minimizing the permanent treatment induced neurological deficits is a significant consideration in treating PCNSL





## Role of steroids in the management of PCNSL

- **Exert apoptotic effect** on lymphoid cells through cytoplasmic steroid receptors.
- Dexamethasone has been associated with initial CR (15%) and PR (25%)
- **Remission is only temporary** although it can outlast the steroid administration.
- **Resistance** is common on re-exposure.
- **Should be avoided during evaluation of patient** and before biopsy and CSF examination – False negative results
- May be started after Bx is done to control vasogenic edema and resultant mass effect.
- Unclear whether steroids need to be an integral part of any regimen as is true for systemic lymphomas





## Radiotherapy alone in PCNSL

- PCNSL – **Multifocal** in brain
- Historically RT involves whole brain RT
- **RT in PCNSL does not achieve comparable disease control or overall survival as compared to systemic NHL (IE disease)**
- **5 year survival is 4%**

Dose	36 to 40Gy
ORR	90%
Median OS	11.6 mo
Relapses within irradiated field	61%

**Increasing dose to 60Gy does not decrease local relapses**

**Increased likelihood of treatment related neurotoxicity especially in patients above 60 years**

**Nelson DF et al:** NHL of the brain: Can high dose, large volume radiation therapy improve survival? Report on a prospective trial by the RTOG: RTOG 8315. *Int J Radiat Oncol Biol Phys* 23:9-17, 1992

## Reasons for failure of RT as a single modality of treatment in PCNSL



- ✓ **PCNSL may be confined to the nervous system but it is potentially disseminated within it at diagnosis.**
- ✓ **Ocular or CSF involvement may be present, even if not identified on a staging evaluation. These areas could be potential reservoirs of untreated disease if the patient receives only WBRT.**
- ✓ **PCNSL may have a unique biology that accounts for its worse outcome despite its comparable histological appearance to most systemic diffuse large B-cell lymphoma,**

# Chemotherapy in PCNSL



Standard use of systemic NHL treatment regimens in PCNSL –

- Associated with transient responses of brain lesions,
- Frequent recurrences
- Florid leptomeningeal involvement at relapse.

**Four prospective trials (one randomized)**

All failed to show an advantage of CHOP/CHOD plus WBRT over WBRT alone.

**CHOP has no role in the treatment of PCNSL**



# Chemotherapy in PCNSL

## The role of Methotrexate



- First recognized when it was discovered that patients who had systemic NHL that relapsed in the CNS responded to high-dose MTX
- The ability of **high-dose MTX to penetrate the CNS** makes it an attractive agent for the treatment of PCNSL
- Rapid infusion of high-dose MTX over three hours greatly **raises the drug level in the CSF** (maximum therapeutic concentration in 4-6 hours after the start of an infusion), and **remains above the minimum therapeutic concentration in the CSF for up to 24 hours** (blood to CSF ratio of 30:1).
- **Methotrexate (MTX)-based regimens are the only regimens with a significant advantage over RT alone.**



## Chemotherapy in PCNSL

### The role of Methotrexate



**Cytotoxic CSF levels of methotrexate achieved is sufficient to treat microscopic or macroscopic tumor in the leptomeninges is avoided in most PCNSL patients.**

**Commonly used methotrexate-based, combined-modality regimen consists of five cycles (10 weeks) of pre-irradiation**

- **IV MTX 2.5 g/m<sup>2</sup>**
- **IV Vincristine 1.4 mg/m<sup>2</sup>**
- **Oral Procarbazine 100 mg/m<sup>2</sup>/d for 7 days,**
- **IT Methotrexate 12 mg,**
- **Dexamethasone taper**

**Followed by WBRT 45 Gy and post-WBRT high-dose Cytarabine 3 g/m<sup>2</sup>/d for two doses.**

# Chemotherapy in PCNSL

## The role of Chemotherapy Plus WBRT - Studies



Study	No. of pts	Regimen	Radiotherapy (Gy)	RR (%)	OS (Median)
Gabbai et al, 1989	13	IV MTX (3.5 g/m <sup>2</sup> )	30-44	92	9.5
DeAngelis et al, 1992	31	IV MTX (1 g/m <sup>2</sup> ) + IT MTX (12 mg × 6) IV MTX (3.5 g/m <sup>2</sup> )	40 + 4.4 boost	64	41
Glass et al, 1994	25	MPV (IV MTX 3.5 g/m <sup>2</sup> ) + IV ara-C + IT MTX (12 mg × 3)	30-44	88	33
Abrey et al, 2000	52	MPV (IV MTX 3 g/m <sup>2</sup> ) MPV (IV MTX 2.5 g/m <sup>2</sup> ) + IT MTX (12 mg × 5)	45 in 35/52 pts	90	60
Ferreri et al, 2001	13	MBVP (IV MTX 3 g/m <sup>2</sup> ) + IT	39.6	92	25+
DeAngelis et al, 2002	102	MTX (15 mg) +	45	94	30+
Poortmans et al, 2003	52	IT ara-C (40 mg) + hydrocortisone (25 mg × 2)	30 + 10 boost	81	46

# Chemotherapy in PCNSL

## The role of Chemotherapy alone - Studies



Study	pts	Regimen	RR (%)	OS (Median)
Freilich et al, 1996	13	IV MTX (1 g/m <sup>2</sup> or 3.5 g/m <sup>2</sup> ) + IT MTX (12 mg) + VCR (1.4 mg/m <sup>2</sup> ) + PO procarbazine (100 mg/m <sup>2</sup> ) + IV ara-C (3 g/m <sup>2</sup> ); 5 pts with IV thiotepa (40 mg) in place of VCR	52	30.5
Cheng et al 1998	13	60MES IV Mtx (8gms/m <sup>2</sup> ) plus IT Mtx (12mg/m <sup>2</sup> x 4 if positive CSF)	84	6 PFS
Sandor et al 1998	14	MTV (IV Mtx 8gms/m <sup>2</sup> plus IT Arac (15mg/day x 3 days x2doses	100	16.5 PFS
Guha	31	IV MTX (8 g/m <sup>2</sup> ) + consolidation with 3.5 g/m <sup>2</sup> every 3 <sup>rd</sup> month	100	30+
McAllister et al, 2000	74	IA MTX (2.5 g) + CTX + etoposide	65	40.7
Batchelor et al, 2003	25	25/IV MTX (8 g/m <sup>2</sup> )	74	22.8+
Pels et al, 2003	65	IV MTX (5 g/m <sup>2</sup> ) + IV ara-C (3 g/m <sup>2</sup> ) + ifosfamide/vincristine/cyclophosphamide/dexamethasone + IT MTX (3 mg) + IT ara-C30 mg) + prednisone (2.5 mg x 3)	71	

Hematol Oncol Clin N Am 19 (2005) 611–627



# Chemotherapy alone in PCNSL

## Current status



Considered in PCNSL patients older than age 60 a group at highest risk for radiation-related neurotoxicity.

Durable responses are possible, although most patients eventually experience relapse.

One multicenter phase II study –

Single-agent therapy with high-dose  
Mtx 8 g/m<sup>2</sup>

CR rate of 52%,  
PFS of 12.8 months,  
OS of 55.4 months, with only minimal  
toxicity

Multi-agent CT without RT – 65 pts

ORR -71%  
CRs – 61%  
PRs 10%  
Median TTP 21 months  
Median OS -50 months

Pels H, J Clin Oncol 21:4489-4495, 2003

Batchelor TT, J Clin Oncol 21:1044-1049, 2003



## The role of surgery in PCNSL

- To **removal of all gross tumor or debulking tumor** confers **no survival benefit** over biopsy alone
- Survival after surgery alone is 1 to 4 months.
- The multifocal pattern of growth and the deep location of many PCNSL brain masses make complete surgical removal difficult in most patients, if not impossible.
- **Role of surgery is confined to establishment of diagnosis only** and a stereotactic biopsy is indicated for all patients with symptoms suggestive of PCNSL.



## Role of HDCT and ASCT in PCNSL

Very few studies giving credibility to this strategy.

A single study of 28 patients newly diagnosed with PCNSL

Used high-dose MTX (3.5 g/m<sup>2</sup>) and high-dose cytarabine as induction treatment, followed by transplantation in 14 responders

- EFS was only 5.6 months for partial responders
- Complete responders - 9.3 months
- Median overall survival was not reached with a median follow-up of 28 months

Cheng et al - 7 patients – relapse free survival 5-42 months

Stem cell rescue may have a role in recurrent PCNSL

Soussain and colleagues – 20 patients

Three-year OS was 60% and three-year EFS rate was 53%.





## PCNSL recurrence Salvage Chemotherapy Studies

Treatment	No. of Pts	ORR	OS (months)
WBRT	21	20-27	10.9
Methotrexate	22	29-22	61.9
PCV	7	6-7	16
Temozolamide (TMZ)	23	6-23	3.5
TMZ plus Rituximab	15	8-15	14
Topotecan	15	6-15	32
HDCT plus ASCT	10	10 of 10	24+

## Conclusion - PCNSL



- Rare form of extra-nodal NHL and is typically a DLBCL that is confined to the nervous system and eyes.
- The diagnosis of PCNSL is supported by CT and MRI studies as well as CSF testing, but is ultimately confirmed on the basis of stereotactic biopsy
- Current treatment regimens are achieving long-term remissions though in only a small fraction of patients
- Methotrexate-based, multiagent chemotherapy currently is the treatment of choice, especially in the elderly patient population
- The optimal role and timing of WBRT in the management of newly diagnosed PCNSL patients has yet to be established.
- Minimizing the risk of neurotoxicity by deferring WBRT in patients older than age 60 is an important objective.

# Primary Intra-Ocular Lymphoma - PIOL



Typically affects an older population (50-60yrs)

Two distinct forms of intraocular lymphoma.

- **Arises outside the central nervous system (CNS) and metastasizes to the eye.**
- **The second type arises from within the CNS and eye and usually is referred to as primary CNS lymphoma (PCNSL)**

**Approximately 15% to 25% of PCNSL patients will have ocular involvement at the time of diagnosis**



# Primary Intra-Ocular Lymphoma – PIOL

## Presentation



**Intermediate or posterior uveitis (inflammatory process affecting the posterior segment of the eye)**

**Bilateral in at least 80% of cases**

**Affects vitreous, retina, subretinal pigment epithelium (RPE), and the optic nerve head, or any combination of these sites**

**Patients usually will complain of floaters and a mild decrease in vision**

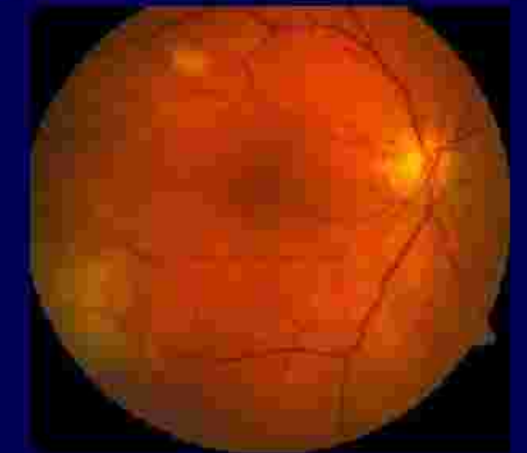
# PIOL – Ophthalmic evaluation



Keratic precipitates



Slit lamp bio-microscopy  
Showing sheets of vitreous cells



Fundus – Subretinal creamy infiltrates



Fluorescein angio  
Perturbation of RPE

## Diagnostic work-up

**Neuroimaging  
Cytologic analyses CSF**

**If the above are non-diagnostic a Vitrectomy usually is performed, with cytologic analysis of the vitreous biopsy**



## Primary Intra-Ocular Lymphoma – PIOL Therapy

Therapy for this disorder is still problematic.

Radiotherapy, - minimal effect on extending survival, radiation retinopathy

Chemotherapy, with an emphasis on a therapeutic schedule that includes both systemic and intrathecal (using an Ommaya implant) agents

### **Intraocular injections of methotrexate**

**PROBLEMS** - Retinal detachment, cataract, maculopathy, vitreous hemorrhage, optic atrophy, and sterile endophthalmitis and damage to the limbal stem cells



## Summary of treatment and prognosis of primary intraocular lymphoma patients published from 1989–2004



Study [reference]	Treatment options	Regimen	Response (n/N)	Disposition
Batchelor et al, 2003 [42]	Systemic chemo	Hi-dose MTX	7/9 responded 2/9 refractory	2 deaths (intracranial progression)
Batchelor et al, 2003 [43]	Systemic chemo	Hi-dose MTX	4/5 responded	
Valluri et al, 1995 [44]	Systemic chemo (adjunct to intrathecal + RT)	MTX + ara-C	3/3 responded	
Strauchen et al, 1989 [45]	Systemic chemo	ara-C	1/6 CR 4/6 PR	
Ferreri et al, 2001 [46]	Systemic chemo + RT	Hi-dose MTX + RT	½ temozolamide for relapse	Death due to neurotoxicity
Ferreri et al, 2002 [47]	chemo ± RT <sup>a</sup>	chemo + RT: 11, RT: 3 chemo: 3 chemo + RT: 5	Combination had best control	Ocular relapse associated with shorter survival
Hormigo et al, 2004 [12]	chemo +ORT +WBRT	chemo: 4 chemo + ORT: 8 chemo + ORT + WBRT: 2		3/4 ocular relapse 0/8 ocular relapse 1/2 ocular relapse
Mason et al, 2003 [48]	Intrathecal	MTX + ara-C	2/2 responded	
Sandor et al, 1998 [39]	Intrathecal + chemo	MTX + ara-C MTX + ara-C + thiopeta + vincristine + dexamethasone	3/5 complete 2/5 partial	
Smith et al, 2002 [41]	Adjunctive intravitreal chemo	MTX	22/22 responded 6/22 recurrence (retreatment with response)	6/16 deaths (intracranial progression)

# Primary Intra-Ocular Lymphoma – PIOL Summary



**PIOL is a rare subset of PCNSL.**

**It typically masks as a chronic ocular inflammatory disease that is resistant to corticosteroid therapy.**

**The diagnosis can be challenging, and it requires the immediate processing of ocular biopsy specimens**

**Treatment is still a dilemma, and future studies are aimed at delineating the underlying tumor biology and thus developing better-targeted therapies.**



**Thank You**