

# Primary CNS Lymphoma Multimodality Management

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# Definition of PCNSL

- Primary Central Nervous System Lymphoma  
(PRY-mayr-ee SEN-trul NER-vus SIS-tem lim-FOH-muh)

Cancer that forms in the lymph tissue of the brain, spinal cord, meninges (outer covering of the brain), or eye (called ocular lymphoma). Also called PCNSL and primary CNS lymphoma.

<http://www.cancer.gov/dictionary/?CdrID=45345>

# Epidemiology

- PCNSL - Accounts for <1- 2% of all NHLs and 3% to 6% of all primary brain tumors
- Annual incidence rate of PCNSL in the United States is approximately 0.04 to 0.06 per 100,000 person-years
- Incidence has increased 10-fold in past 30 years, and the increase cannot be totally explained by the advent of HIV.
- Impacts two distinct populations:
  - Immunocompromised (HIV, organ transplantation, immunodeficiency syndromes) - arise from EBV infection of B-cell lymphocytes
  - Immunocompetent - no known etiology. B-cells have no normal role in the brain

## Epidemiology....

- Age at Presentation:
  - Non-HIV related primary CNS lymphoma is 6th decade and the peak incidence is at the 8<sup>th</sup> decade
  - HIV related presentation is related to stage of HIV and average age at presentation is 35 yrs
- Male – Female Ratio
  - Immunocompetent PCNSL - Approximately 2:1.
  - HIV–related PCNSL – 90% are male, the majority of whom have used i.v. drugs.

# Predisposing factors

- HIV Infection
- Iatrogenic immune suppression
- Congenital immune deficiency
- Autoimmune disorders
- Sporadic PCNSL – in immunocompetent persons; Flu like or GI illness have been seen in 15 % of patients with PCNSL.

# Risk Factors for development of PCNSL

- 2 - 6% Risk in patients with AIDS
  - This risk may increase as the length of survival is extended in AIDS patients with the use of highly active antiretroviral therapy (HAART).
- 1 - 5% Risk in Solid organ transplant patients
  - 1-2 % for Renal Transplant
  - 2-7 % for heart, lung, or liver transplant recipients.
- 4% risk in patients with congenital immune deficiency

# Pathogenesis

- The cellular and molecular events leading to neoplastic lymphocytic infiltration of the central nervous system (CNS) seen in PCL remain to be clarified .
- The CNS normally lacks lymphoid aggregates and it remains speculative whether malignant transformation develops locally within normally trafficking CNS lymphocytes, or systemically in a sub-population of lymphocytes with specific tropism for the CNS

## Pathogenesis....

- Such tropism may be facilitated through the expression of specific cell-surface adhesion molecules, such as CD44 and CD18, and various chemokine receptors. Spreading of malignant lymphoid cells within the CNS is believed to involve a complex interaction of selectin and adherin molecules, such as adhesion molecule CD44 and transmembrane protein receptor Fas(CD95)



## Pathogenesis....

- PCL may be a consequence of EBV-mediated clonal expansion and malignant transformation of B-lymphocytes, a process that may be regulated by immune mechanisms
- Immunoglobulin variable heavy gene (IgHV) analysis
  - Almost all PCL cells demonstrate IgHV genes that have high levels of somatic mutations and show intracлонаl heterogeneity pointing towards their derivation from mutated germinal center B cells
- IHC evaluation suggests that PCL are derived from post-germinal center B cells

# Pathology

- Usually B-cell histology
- T-cell variants account for <5% of PCNSL in developed countries; their behavior is very similar to B-cells
- 85% are either aggressive or highly aggressive variants of NHL
- These are CD 20 and CD 45 positive
- Most common abnormality reported in downregulation of p16 and more rarely the methylation of CDKN2A gene.

# Clinical Presentation

- PCL can manifest in the brain, its coverings, the eye, or spinal cord.
- Five distinct clinicopathological entities have been described
  - Intracranial lesion (solitary or multiple)
  - Diffuse leptomeningeal or periventricular lesions
  - Vitreous/uveal deposits
  - Intradural spinal cord lesion
  - Nerve seeking lymphoma (Neurolymphomatosis)

# Primary Cerebral Lymphoma

- Most cases of PCL present as symptoms related to periventricular lesions in the brain
- Presenting symptoms
  - Headaches, blurred vision, motor difficulties, CN Palsies
  - Personality changes
    - Depression, apathy, psychosis, confusion, memory impairment, slowness of thought, or visual hallucinations
    - Personality changes are most often associated with lesions of the frontal lobes, periventricular white matter, or corpus callosum.
    - These changes tend to develop slowly and remain unnoticed for long periods.

# Primary leptomeningeal lymphoma

- 10-25% PCL will develop meningeal involvement.
- It is extremely rare for patients without brain involvement to present with primary meningeal involvement.
- Symptomatic leptomeningeal involvement at presentation should prompt serious consideration of an underlying systemic lymphoma.
- Leptomeningeal disease can manifest with worsening headaches, cranial nerve palsies, meningismus, cervical/lumbar radiculopathies, and hydrocephalus.

# Primary intraocular lymphoma

- Primary intraocular lymphoma (PIOL) refers to a PCNSL which initially presents in the eye with or without concurrent central nervous system (CNS) involvement.
- 15 to 25 percent of patients with PCNSL will have involvement of the eye.
- 38 percent of patients with ocular involvement will not have ocular symptoms
- Diagnosis can be made by biopsy of the involved vitreous, choroid, or retina
- Primary ocular lymphoma should be differentiated from retro-orbital lymphoma, which is frequently associated with systemic extranodal disease.

# Primary intraocular lymphoma

- It usually involves the posterior segment of the eye, including the vitreous, choroid, or retina, with subsequent development of uveitis (usually chronic and bilateral and occasionally atypical), exudative retinal detachment, and retinal/vitreous hemorrhages
- Occasionally, visual symptoms may follow occlusion of the retinal artery as a result of lymphomatous infiltration.
- Fluorescein angiography may help to confirm retinal involvement. If ocular involvement is noted, color photography of the posterior pole of the eye should be obtained.
- Diagnosis, therefore, requires a high degree of suspicion



# Primary spinal lymphoma

- Primary spinal involvement - <1 % patients with PCL.
- Spinal Nodules – Discrete , Intramedullary location.
- Secondary spinal involvement - Diffuse leptomeningeal involvement or extradural nodules.
- Spinal cord involvement manifests as a myelopathy.
  - The pattern of weakness and sensory level (if present) will depend on the localization and extent of the lesion.
  - The majority of reported cases have involvement of lower cervical or upper thoracic regions.



# Nerve-seeking lymphoma (neurolymphomatosis)

- Neurolymphomatosis refers to the lymphomatous invasion of nerve roots of the cranial or spinal nerves.
- Symptoms include loss of facial sensation or motor function, such as asymmetric weakness of the extremities
- The hallmark of neurolymphomatosis is poorly localized severe pain in the absence of parenchymal lesions of the brain or spinal cord.
- The process frequently spares the meninges; thus CSF cytologic studies may not be revealing

# Anatomy

- Restricted to brain, CFS, eyes, or rarely spinal cord
- 75 % are generally supratentorial and 25% infratentorial.
- Multifocal in 50% of AIDS-related variants, and multifocal in 25% of immunocompetent variants.
- MRI significantly underestimates extent of involvement; PCNSL is considered to be a diffuse infiltrating disease
- Classified as Stage IE NHL, because they are typically restricted to a single extranodal site

# Diagnostic Workup

As Recommended by the  
International PCNSL Collaborative Group

# The International PCNSL Collaborative Group (IPCG)

IPCG guidelines for baseline evaluation

Pathology	Clinical	Laboratory	Imaging
Centralised review of pathology	Complete medical and neurological examination	HIV serology	Contrast-enhanced cranial MRI scan (CT if MRI contraindicated)
Immunophenotyping	Dilated eye examination, including slit lamp examination and fundoscopy	Vitreous biopsy +/- chorioretinal biopsy, immunohistochemistry, IgH-PCR <sup>1</sup> , serum LDH level	CT of chest, abdomen and pelvis
	Record prognostic factors (age, performance status)	CSF cytology, flow cytometry, IgH-PCR	Bone marrow aspirate and trephine biopsy
	Serial evaluation of cognitive function	24-hour urine collection for creatinine clearance if HD-MTX planned	Testicular ultrasound in elderly males

<sup>1</sup> Polymerase chain reaction for detection of immunoglobulin heavy chain rearrangements.

# Clinical Evaluation

- Comprehensive Physical Examination emphasizing peripheral Lymph nodes, Liver , Spleen and Testis (for male patients)
- Comprehensive neuropsychologic examination including assessment of cognitive function
- Record the following
  - Age
  - Performance Status
  - Corticosteroid dose
  - MMSE

# Clinical Evaluation

**Table 1. International PCNSL Collaborative Group Guidelines for Baseline Evaluation for Clinical Trials<sup>a</sup>**

Pathology	Clinical	Laboratory	Imaging
Centralized review of pathological findings Immunophenotyping	Complete medical and neurological examination	HIV serology	Contrast-enhanced cranial MRI <sup>b</sup>
	Dilated eye examination, including slitlamp evaluation	Serum LDH level	CT of chest, abdomen, and pelvis
	Recording of prognostic factors (age, performance status)	CSF cytology, flow cytometry, immunoglobulin heavy-chain PCR	Bone marrow biopsy with aspirate
	Serial evaluation of cognitive function <sup>c</sup>	24-h urine collection for creatinine clearance <sup>d</sup>	Testicular ultrasonography in elderly men

Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; HIV, human immunodeficiency virus; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PCNSL, primary central nervous system lymphoma; PCR, polymerase chain reaction.

<sup>a</sup>Adapted from the article by Abrey et al.<sup>6</sup>

<sup>b</sup>Contrast-enhanced cranial CT should be obtained in patients who have a contraindication for MRI (eg, those with a pacemaker) or who cannot tolerate MRI (eg, those with claustrophobia).

<sup>c</sup>The Mini-Mental State Examination is used commonly, although improved instruments are being developed.

<sup>d</sup>For patients who will receive high-dose methotrexate.

# Laboratory Evaluation

- Liver Function tests
- Renal function tests
  - Creatinine
  - Blood Urea Nitrogen
  - Creatinine Clearance
- Hematology function tests
  - Complete Blood counts with differentials
  - Platelet counts
  - LDH\*
- HIV Infection testing

\* LDH is an independent prognostic marker



# Evaluation of Extent of disease

- CT Scans of Chest / Abdomen and Pelvis
- PET scan if CT imaging negative
- Bone marrow biopsy (12.5% have systemic disease)
- Testicular USG (Testicular lymphoma spread to CNS easily)
- Ophthalmological Evaluation
  - Dilated fundoscopic examination
  - Slit lamp examination – to assess vitreous, retina and optic nerves
  - Fluorescein angiography - to assess retina



# CNS Evaluation

- MRI Brain with Gadolinium Contrast
- MRI Spine if spinal symptoms are present
- To do CT Brain / Spine with contrast for patients in whom MRI is contraindicated eg Cardiac pacemaker

# CSF Examination

- To be obtained preoperatively or 1 week postoperatively
- Via lumbar puncture or via Ommaya reservoir
- Tests to be done in CSF
  - Cytology
  - Cell count , Glucose and Protein
  - Flow Cytometry for EBV DNA
  - Beta 2 microglobulin
  - Immunoglobulin gene rearrangement
- Clonal B cell lymphocytosis in conjunction with typical radiological features is strongly suggestive of PCNSL

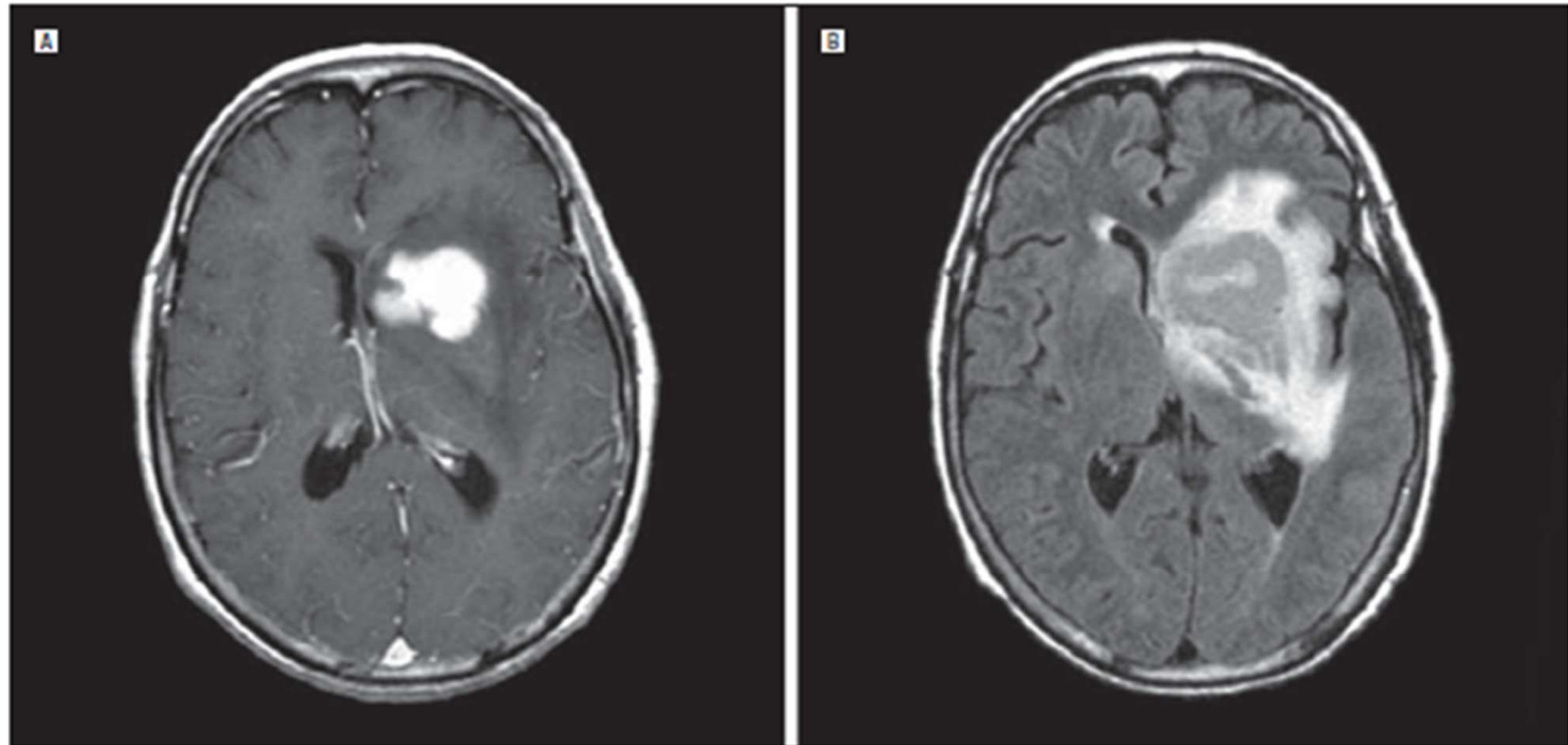
# CT Scan

- Whole-body computed tomography (CT) should be obtained to exclude the presence of systemic lymphoma.
- To be done only in the setting of medical contraindication to the use of MRI.
- If CT imaging is obtained,
  - PCNSL lesions are typically hyperdense or isodense.
  - All lesions enhance after administration of contrast.
  - Calcification and hemorrhage are rarely seen in immunocompetent patients [\(13\)](#).
  - In HIV-positive patients a wider spectrum CT imaging characteristics can be seen, including a greater likelihood of detecting nonenhancing or ring-enhancing lesions.
  - Hemorrhage and necrosis is also more common in HIV-associated PCNSL

# MRI Scan

- Characteristic pretreatment MRI findings
- Contrast enhancement,
- Tumor diameter of at least 15 mm
- Contact with the subarachnoid space
- Hypointense or isointense on T1-weighted MRI images
- 50% are hyperintense on T2-weighted images.
- Uniform enhancement is common
- Modest edema and mass effect are present.
- Calcification, hemorrhage, or necroses are scarcely seen

# MRI Findings



**Figure.** Magnetic resonance imaging. A, Postcontrast T1-weighted magnetic resonance image from a patient with primary central nervous system lymphoma. Note the homogeneous enhancement and periventricular location. B, Fluid-attenuated inversion recovery sequence demonstrating extensive peritumoral edema with mass effect on the lateral ventricle.

# MRS

- MRS Findings
  - Loss of N-acetylaspartate (NAA)
  - Decrease in creatine (Cr)
  - Dramatic increase in choline (Cho), lactate (Lac)
  - Increase in Lipids/macromolecules (Lip/MM)
- HIV-related PCNSL
  - Nonenhancing lesions
  - Irregular enhancement patterns
  - Haemorrhage and necrosis are more common

# F18-FDG PET Scan

- To distinguish MRI lesions that are suspicious for PCNSL from inflammatory and infectious processes.
- In HIV-positive patients, the standard uptake value ratio (SUV) for subjects found to have cerebral infections was significantly lower than the SUV for PCNSL patients.
- FDG-PET is also useful in monitoring therapeutic response, especially in patients with persistent equivocal post treatment MRI findings.

# Prognostic Factors



# Prognosis

- Pts with AIDS and Without AIDS
- Both groups do equally poorly without therapy (1–3 month mean survival), but the overall survival for treated patients is much better for patients without AIDS (18.9 months) than for those with AIDS (2.6 months).

Fine HA, Mayer RJ: Ann Intern Med 119 (11): 1093-104, 1993.  
Nasir S, DeAngelis LM: Oncology (Huntingt) 14 (2): 228-34;  
discussion 237-42, 244, 2000.

# Patient Related Prognostic Factors

- Multiple factors for poor prognosis:
  - Age >60
  - ECOG PS >1
  - Elevated LDH
  - Elevated CSF protein
  - Deep regions of the brain
- European Stratification: 5 variables above. Risk groups: 0-1 factors, 2-3 factors, 4-5 factors
- MSKCC Stratification: 2 variables, age and KPS

# MSKCC RPA Classification

- 2 variables - Age and KPS

RPA Class I	Age $\leq$ 50	8.5 yrs
RPA Class II	Age $\geq$ 50 , KPS $\geq$ 70	3.2 yrs
RPA Class III	Age $\geq$ 50 , KPS $<$ 70	1.1 yrs

- 38 patients analyzed. RPA analysis.
- External validation from 3 RTOG prospective trials
- MSKCC data: median OS 8.5 yrs vs. 3.2 yrs vs. 1.1 yrs
- Validation with RTOG data: median OS 5.2 yrs vs. 2.1 yrs vs. 0.8 yrs
- Conclusion: Simple, universally applicable

Abrey LE, Ben-Porat L, Panageas KS, Yahalom J, Berkey B, Curran W, Primary central nervous system lymphoma: The MSKCC prognostic model.

Journal of Clinical Oncology. 2006 Dec 20;24(36):5711–571

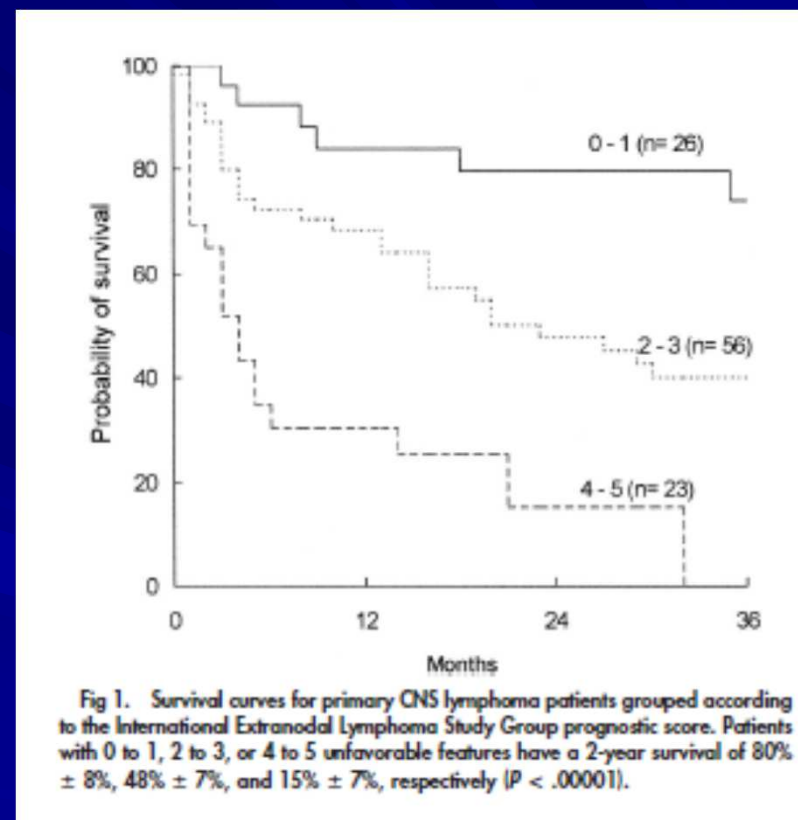
# Nottingham/Barcelona prognostic score

- Based on age  $>60$  , performance status  $>2$ , and Extent of disease (multifocal / unifocal )
- The power of this scheme to detect important prognostic factors is questioned as it is based on a rather small cohort of 77 patients.
- Poor survival correlated with a higher score, median survivals being 55, 41, 32 and 1month for scores of 0, 1, 2, and 3 respectively.

Bessell EM, Graus F, Lopez-Guillermo A, Lewis SA, Villa S, Verger E, et al. Primary non-hodgkin's lymphoma of the CNS treated with CHOD/BVAM or BVAM chemotherapy before radiotherapy: Long-term survival and prognostic factors. Int J Radiat Oncol Biol Phys. 2004 6/1;59(2):501–508.

# International Extra-nodal Lymphoma Study Group Score

- Five point Scoring System
  - Age
  - ECOG performance status,
  - LDH
  - CSF total protein concentration,
  - Involvement of deep structures
- The IELSG identifies three separate risk groups based on the presence of no to one, two to three, or four to five of the factors.
- 2-year OS:
  - Score 0-1: 80%;
  - Score 2-3: 48%;
  - Score 4-5: 15%



Prognostic scoring system for primary CNS lymphomas: the International Extranodal Lymphoma Study Group experience." (Ferrerri AJ, JCO. 2003 Jan 15;21(2):266-72)

# Blay's Score

- Multivariate predictors:
  - CSF protein >0.6 g/l
  - ECOG >2
  - Age >60
- Prognostic risk groups: median OS:
  - Good 54 months,
  - Intermediate 20 months,
  - Poor 4 months

Multivariate analysis of prognostic factors in patients with non HIV-related primary cerebral lymphoma. A proposal for a prognostic scoring." (Blay JY, Br J Cancer. 1993 May;67(5):1136-41.)

# Tumor related prognostic factors

- Bcl-6 as a potentially promising prognostic marker for PCNSL
- Patients treated with high-dose i.v. methotrexate who expressed Bcl-6 had a median survival of 101 months as compared with 14.7 months for those not expressing Bcl-6.
- Importantly, this finding held up in statistical analysis controlling for age, a powerful clinical prognostic factor as previously noted.

Braaten KM, Betensky RA, de Leval L, Okada Y, Hochberg FH, Louis DN, et al. BCL-6 expression predicts improved survival in patients with primary central nervous system lymphoma.

Clin Cancer Res. 2003 March 1;9(3):1063–1069.



# Response Criteria

Table 3. IPCG response criteria

Response	Brain imaging	Glucocorticoid dose	Eye examination	CSF cytology
CR	No enhancing disease	None	Normal	Negative
uCR	No enhancing disease	Any	Normal	Negative
	Minimal enhancing disease	Any	Minor RPE <sup>1</sup> abnormality	Negative
PR	50% decrease in enhancement	NA	Minor RPE abnormality or normal	Negative
	No enhancing disease	NA	Decrease in vitreous cells or retinal infiltrate	Persistent or suggestive of disease
PD	25% increase in enhancement Any new site of disease	NA	Recurrent or new disease	Recurrent or positive
SD	All scenarios not covered by responses above			

<sup>1</sup> Retinal pigment epithelium



# Treatment modalities



# Surgery

# Role of Surgery

- The role of surgical management on PCNSL is to establish a tissue diagnosis.
- Given the multifocality and propensity for subarachnoid space involvement, aggressive resections are rarely indicated.
- If PNCSL is suspected on clinical and radiographic grounds, a stereotactic biopsy is sufficient.
- CSF analysis, including immunoglobulin gene rearrangement studies using polymerase chain reaction (PCR) can identify clonal lymphocytic populations, which may be sufficient to establish a diagnosis of PCNSL.

# Role of Surgery

- The role of surgery is restricted to stereotactic biopsy of a lesion suggestive of PCNSL in order to gain material for histopathological diagnosis [Batchelor and Loeffler, 2006].
- Every attempt to completely resect this diffusely infiltrating lesion is contraindicated.
- Surgical removal as a part of multimodal therapy has been shown to be associated with a worse prognosis [Bellinzona et al. 2005].

# Radiotherapy

# WBRT

- Treatment of PCNSL with WBRT
  - Responses in more than 90% of cases
  - Responses are not long-lasting
  - Patients relapse, in almost all cases in the radiation field.
- A review of 92 patients treated with WBRT revealed that 68% experienced recurrent disease; local failure accounted for 93% of the recurrences.
- Investigators have suggested that some relapses represent reseeding from the CSF rather than true recurrence.

Loeffler et al . *J Clin Oncol* 1985; **3**: 490–94.

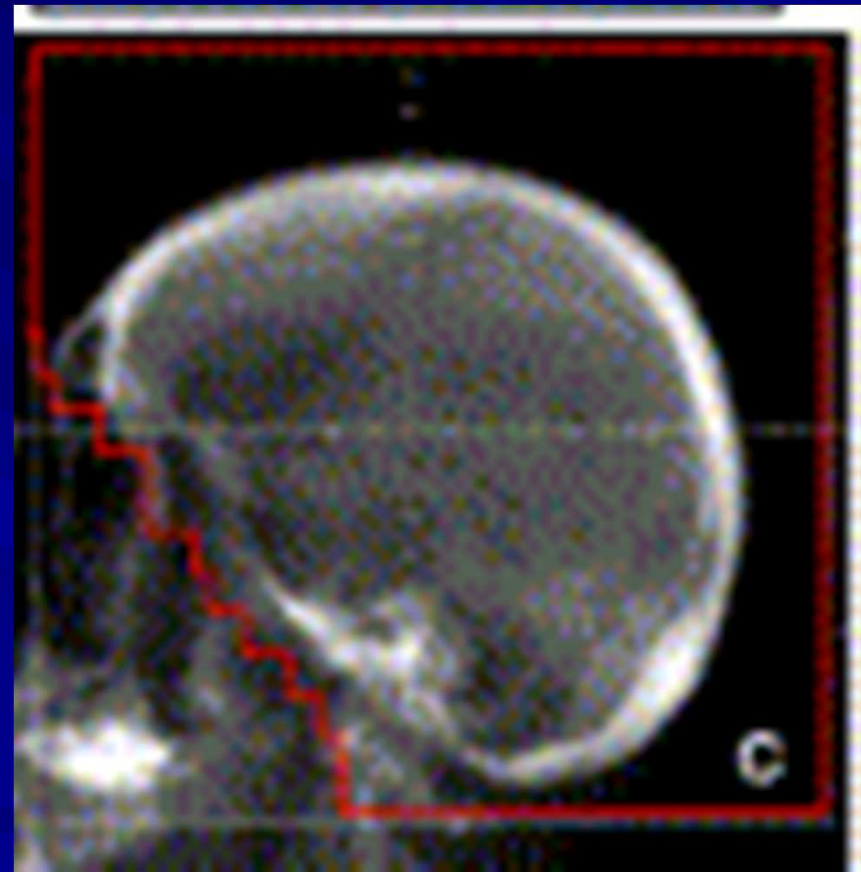
Uematsu M, et al *Acta Oncol* 1992; **31**: 551–54.

# Treatment Volume

- Whole-brain field - empirically chosen to address the multifocal nature of PCNSL.
- A left and right lateral equally weighted, opposed-field arrangement using 6- to 10-Mv photon is most often used.
- Custom cerrobend blocks or multileaf collimation is used to shape the fields.
- The field shaping at the skull base must be carefully considered to avoid inadvertent shielding of the meninges / subarachnoid space in the region of the anterior temporal lobes and the cribriform plate.
- Most often the posterior third of the orbits are included in the treatment volume.

# Treatment Volume

- The anterior edge of the field is typically made coplanar via a gantry rotation so as to avoid exposure of the contralateral eye because of anterior divergence of the lateral beam.
- The anterior, posterior, and superior field borders include 1 to 2 cm of “fall-off” to ensure adequate dosimetric coverage of the meninges/subarachnoid space.
- The inferior border is usually the C1 to C2 or C2 to C3 vertebral body interspace.





# Treatment Volume

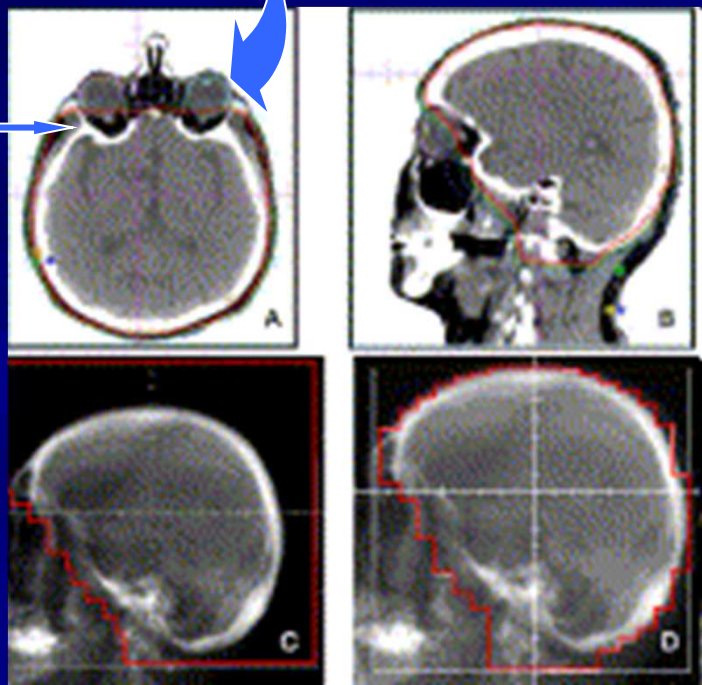
- When ocular involvement is evident and WBRT alone is to be given or when there is a desire to boost the eyes after initial response to “up front” chemotherapy, the entirety of both eyes are included for a portion of the treatment up to a dose of 20 to 30 Gy.
- The use of AP electron fields together with shaped whole-brain fields that shield the anterior orbits is an alternative treatment approach to address eye involvement.
- For some patients, a scalp block may be added after 18 to 20 Gy to minimize the likelihood of developing permanent convexity alopecia.

# PCNSL

100% isodose line shown in red

Adequate coverage of the subarachnoid space

Coplanar anterior field edge in region of the posterior orbit, thereby avoiding divergence into contralateral orbit.

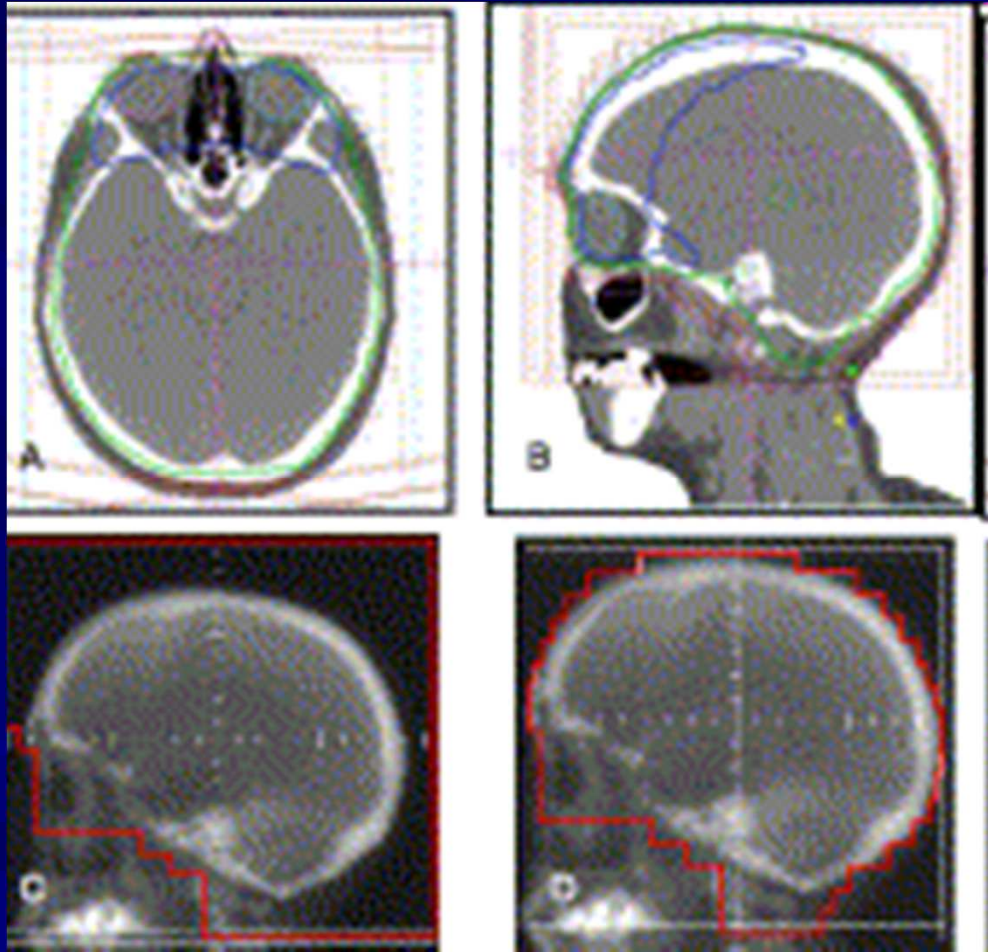


Typical WBRT multi-leaf collimation

Scalp Blocks

- To consider after 18 to 20 Gy has been delivered to the initial WBRT fields.
- Use of such a scalp block allows adequate dose to subarachnoid space while lowering the probability of permanent convexity alopecia.

# PCNSL with Orbit involvement



110% isodose – blue  
100% isodose - green

Compensating filters or “wedges”  
– To improve dose homogeneity

The total dose and fractionation scheme can be modified to lessen the risk of acute and late toxicity associated such dosimetric inhomogeneity.

# Radiation Dose

- Murray *et al.* reported a dose response for PCNSL patients treated with WBRT alone
- Overall survival at 5 years
  - Patients > 50Gy - 42.3%
  - Patients < 50 Gy - 12.8%
- Based on this review, a minimum of 50 Gy radiation to the primary tumor is recommended.
- This trial was the basis for RTOG 83-15

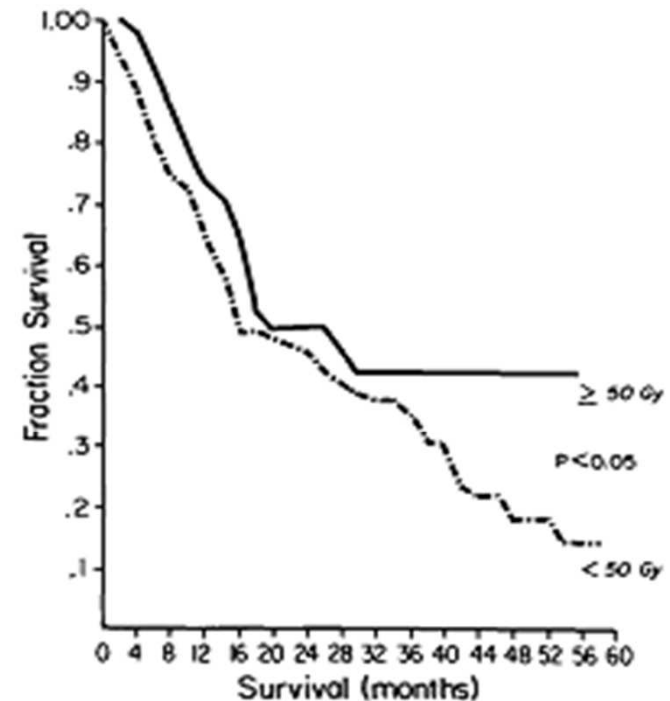
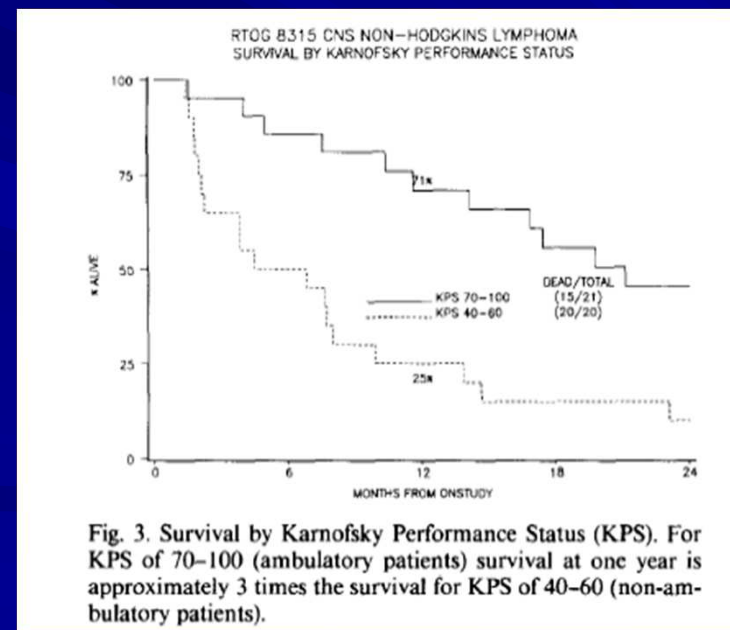
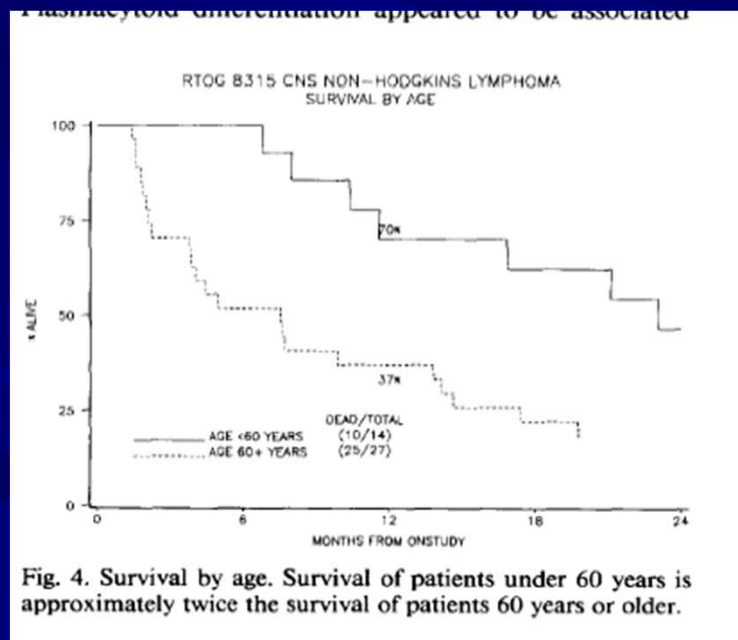


FIG. 2. Graph showing survival times in 188 cases collected from the literature and 10 cases in the present series in which irradiation dosage is available. *Solid line* indicates those patients receiving a dosage of 50 Gy or above; *broken line* represents those receiving a dosage of less than 50 Gy. The difference was statistically significant ( $p < 0.05$ ).



# RTOG 83-15

- Fractionated WBRT to 40 Gy followed by a boost to the initial tumor site(s) of 20 Gy. The treatment was delivered using 2-Gy fractions
- No survival Advantage with escalation of WBRT
- Prognostic Factors – Age and Performance status



# RTOG 88-06

## RTOG 83-15

40.00 Gy whole brain and meninges

+

20.00 Gy boost

60.00 Gy (2.0 Gy/fraction) = Total Dose

## RTOG 88-06

CHOD 2 cycles

CT scan brain

No progression

CHOD 1 cycle

RT

Progression

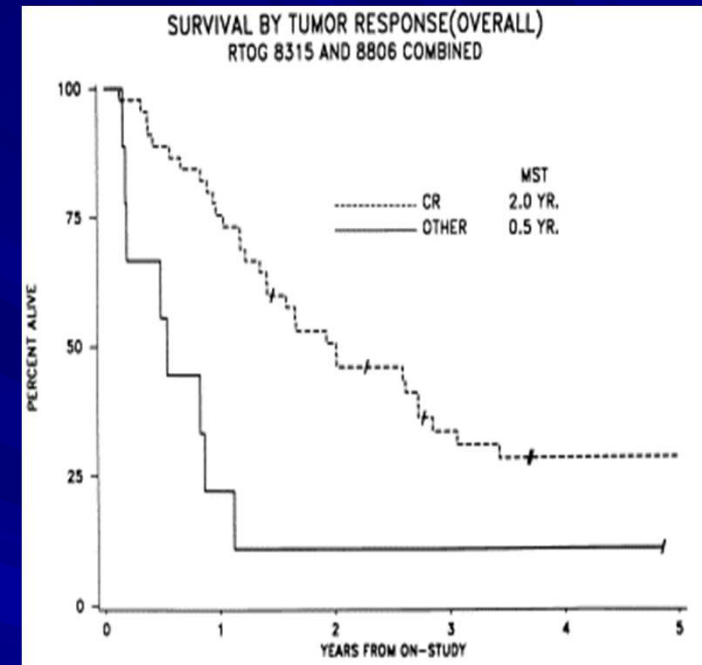
RT

### CHOD regimen

Cyclophosphamide 750 mg/m<sup>2</sup> IV day 1  
Adriamycin 50 mg/m<sup>2</sup> IV day 1  
Vincristine 1.4 mg/m<sup>2</sup> IV day 1 (Maximum dose 2.0 mg)  
Dexamethasone 6 mg/m<sup>2</sup> PO days 1-5  
IT Methotrexate 12 mg/dose via LP or Ommaya reservoir  
twice weekly x 3 weeks, then once weekly x 3 weeks  
Chemotherapy cycles repeated every 21 days

### Radiation Therapy

Whole brain 41.40 Gy  
Boost 18.00 Gy  
Total dose 59.40 Gy (1.8 Gy/fraction)



Schultz et al J Clin Oncol.  
Corn et al IJROBP 2000

Complete tumor response - 80% of treated patients.

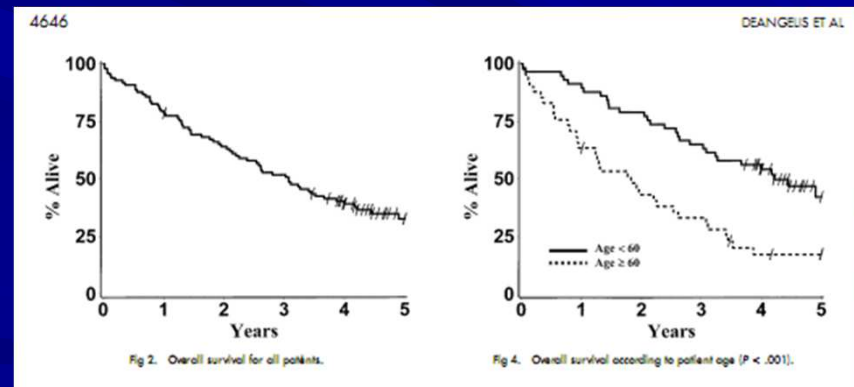
Complete response was associated with statistically improved median survival, 2 years vs. 0.5 years

# RTOG 93-10

- Patients first received five cycles of methotrexate 2.5 g/m<sup>2</sup>, vincristine, procarbazine, and intraventricular methotrexate (12 mg).
- Whole-brain radiotherapy (RT) was administered to a total dose of 45 Gy and all patients received high-dose cytarabine after RT
- If ocular lymphoma was present, both eyes were included in the RT field to a total dose of 36 Gy in 20 fractions

**Median PFS – 24 months**  
**Median OS - 36.9 months**

**Earlier RTOG trials**  
**Median survivals of 11 to 12 months**





# RTOG 93 15

- Subset of patients from RTOG 93 10 who had CR to pre WBRT chemotherapy
- HFRT regimen of 36 Gy delivered at 1.2 Gy b.i.d..
- To test whether Smaller doses/ # and a lower total dose in a sequential chemotherapy and WBRT regimen reduces treatment-related neurotoxicity.
- Results
  - No statistical difference in progression-free survival or overall survival for the patients
  - Delayed but did not eliminate the development of severe neurotoxicity associated with combined chemoradiation

# RTOG-9310

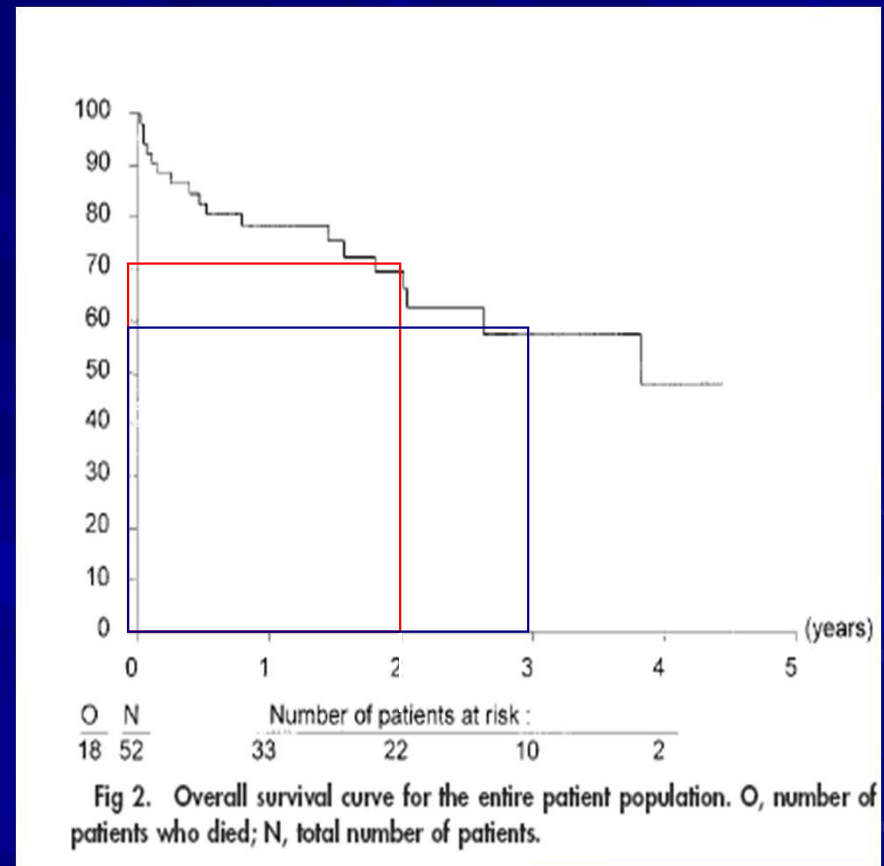
- A multicenter trial of 102 patients used high-dose methotrexate (2.5 g/m<sup>2</sup>) for five cycles, intravenous vincristine, oral procarbazine, intraventricular methotrexate, and either 45 Gy of WBRT or 36 Gy in a hyperfractionated schedule
- Median progression-free survival (PFS) was 24 months, and median overall survival (OS) was 37 months.
- Severe delayed neurologic toxic effects were seen in 15% of patients.

# RTOG 02-27

- RTOG 02-27 is ongoing Phase I/II trial
- Tests the efficacy of pre-WBRT chemotherapy that includes high-dose i.v. methotrexate, rituximab, and temozolamide and post-WBRT maintenance temozolamide.
- The WBRT hyperfractionated regimen piloted in RTOG 93-10 is being used in this trial with the goal of further defining the role of dose reduced WBRT.

# EORTC 20962

- Patients younger than 66 years used high-dose methotrexate, teniposide, carmustine, methylprednisolone, intrathecal methotrexate, cytarabine, and hydrocortisone followed by 40 Gy of radiation therapy;
- Median survival was 46 months,
- 2yr SR 68% ; 3yr SR 59%
- 10% toxic death rate
- Follow-up was too short (median 27 months) to fully assess severe delayed neurologic toxic effects.



# Neurotoxicity due to Chemoradiation

- Combined chemoradiotherapy is associated with severe neurologic impairment in 40% of patients and a neurotoxicity related mortality of 30%, especially in patients older than 60 years of age.
- In fact, a direct relationship between age and risk of neurotoxicity has been reported and female sex, MTX dose more than 3 g/m<sup>2</sup>, intrathecal chemotherapy, and higher tumor radiation dose have also been proposed as risk factors for this complication.
- Avoiding radiotherapy in patients older than 60 years of age in complete remission after primary chemotherapy has been proposed as a strategy to minimize neurotoxicity (see Chemotherapy as Exclusive Treatment).

# High Dose Methotrexate Alone

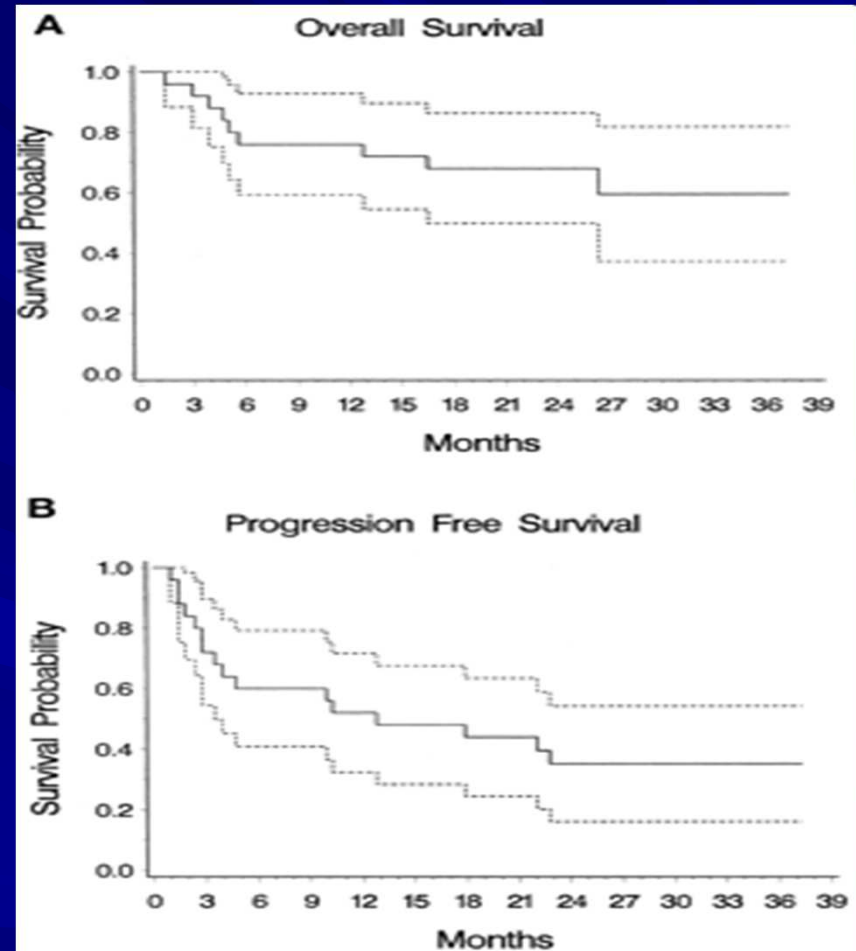
# NOA - 03

- German Trial
- MTX was administered at a dosage of 8 g/m<sup>2</sup> as a 4-hour infusion every 14 days for six cycles
- WBRT given only for salvage / disease progression
- The study was terminated after including 37 of 105 projected patients, since the overall response rate was only 35%.
- Even with the application of salvage WBRT in 20 out of these 37 patients either for progressive disease (PD) or for relapse, median survival did not exceed 25 months



# NABTT 9607

- Same protocol
- It achieved a 74% overall response rate (52% CR and 22% PR)
- Median PFS - only 12.8 months [Batchelor et al. 2003]
- Median overall survival of 55 months the result of efficient salvage therapy at progression or relapse [Gerstner et al. 2008].



Batchelor T, et al.: Treatment of primary CNS lymphoma with methotrexate and deferred radiotherapy: a report of NABTT 96-07. J Clin Oncol 21 (6): 1044-9, 2003

# Reduced dose WBRT

- Bessel et al
- Chemotherapy
  - CHOD / BVAM

## Radiotherapy

Whole-brain irradiation (to C2/C3 interspace):

CHOD/BVAM I: 45 Gy in 25 fractions during a 5-week period plus boost to site of single lesion (10 Gy in five fractions in 1 week)

CHOD/BVAM II: 30.6 Gy in 17 fractions during a 5-week period; if no CR after chemotherapy: 45 Gy plus boost to site of single lesion

Addition of spinal irradiation (35 Gy in 25 fractions in 5 weeks) if CSF cytology positive

	CHOD BVAM i	CHOD BVAM ii
Radiotherapy Dose	45 Gy / 25 #	30.6 Gy / 17 #
CR Rate	68%	77%
3yr Relapse Risk	29%	70%
Age<60, CR 3yr SR	92%	60%

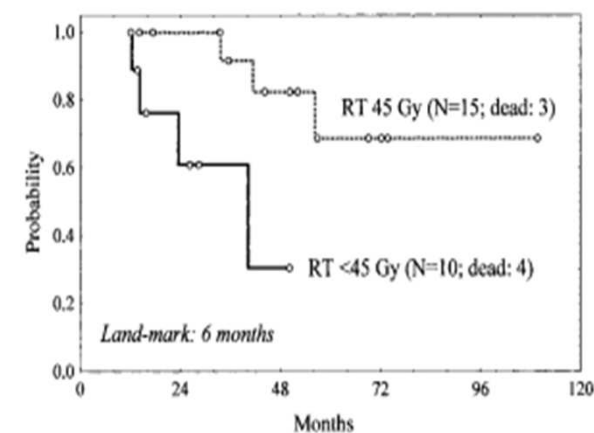


Fig 3. OS of 25 patients reaching CR after chemotherapy according to the RT dose administered (45 Gy v 30.6 Gy) ( $P = .04$ ).

Message: Do not reduce WBRT dose to < 45 Gy in young patients

Bessel et al Journal of Clinical Oncology. 2002 Jan 1;20(1):231–236.

# Combined Radioimmunotherapy

Rituximab,  
Methotrexate,  
Procarbazine,  
Vincristine

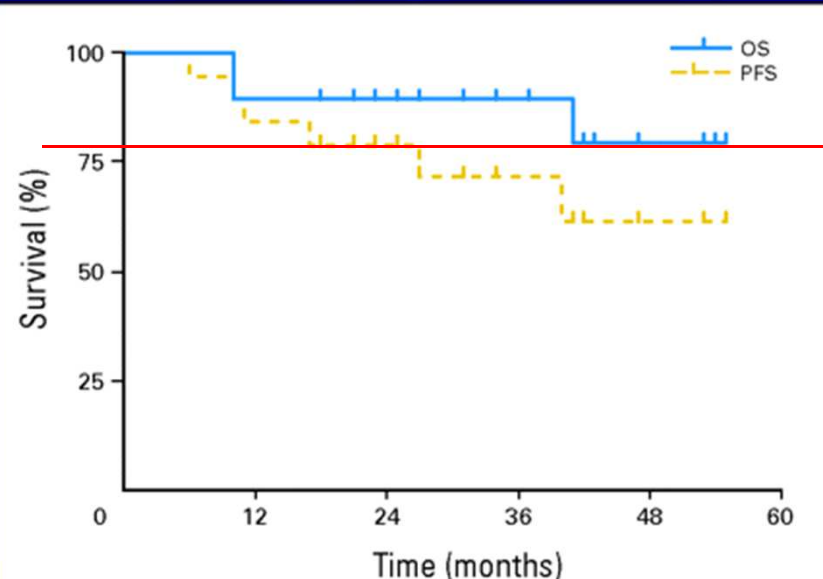
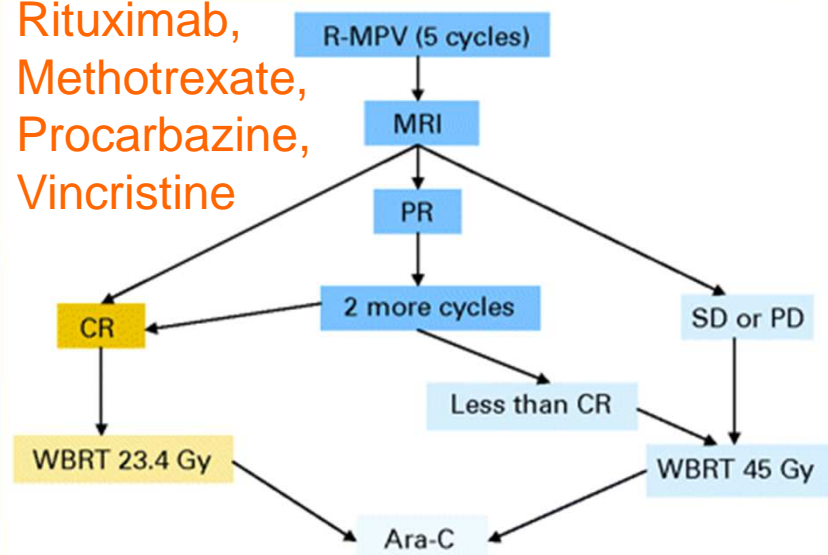


Table 3. Outcome by RPA class

RPA Class	No. of Patients	Median Age (years)	Median KPS	CR Rate (%)	Months			
					Median OS	Median PFS	Published OS	Published PFS
1*	7	47	80	57	NR	NR	102	24
2†	14	58.5	80	71	41	28.5	38	22
3‡	9	63	60	89	NR	41	13	7

Abbreviations: RPA, recursive positioning analysis; KPS, Karnofsky performance score; CR, complete response; OS, overall survival; PFS, progression-free survival; NR, not reached.

\*Age ≤ 50 years.

†Age > 50 years, KPS ≥ 70.

‡Age > 50 years, KPS ≤ 70.

# Randomised trials in PCNSL

# MRC –(1988-95)

- First of the only two randomised trials in PCNSL
- 53 pts, treated with surgery, then randomized 2:1 to RT►CHOP vs RT alone.
- RT dose 40/20 WBRT +14 Gy boost to 2cm margin.
- In RT-CHOP arm, RT was followed by CHOPx6.
- Outcome: No difference in OS adjusted for age/KPS
- Conclusion: inconclusive study due to poor accrual, but CHOP no clear role

# International Extranodal Lymphoma Study Group (IELSG), 2009

- High-dose cytarabine plus high-dose methotrexate versus high-dose methotrexate alone in patients with primary CNS lymphoma: a randomised phase 2 trial
- Multicenter phase 2, randomized. 79 pts, age  $\leq 75$ . Randomized to 4 courses of MTX vs MTX + cytarabine.
- Following chemo, whole brain RT was given.
  - RT – 36 Gy / 20 # ; Shield orbits at 30 Gy
  - Age < 60, CR , RT – 36 Gy WBRT
  - PR , RT – 36 Gy WBRT + 9 Gy Boost
  - Stable / Progression , RT – 40 Gy WBRT + 9 Gy Boost

# Results

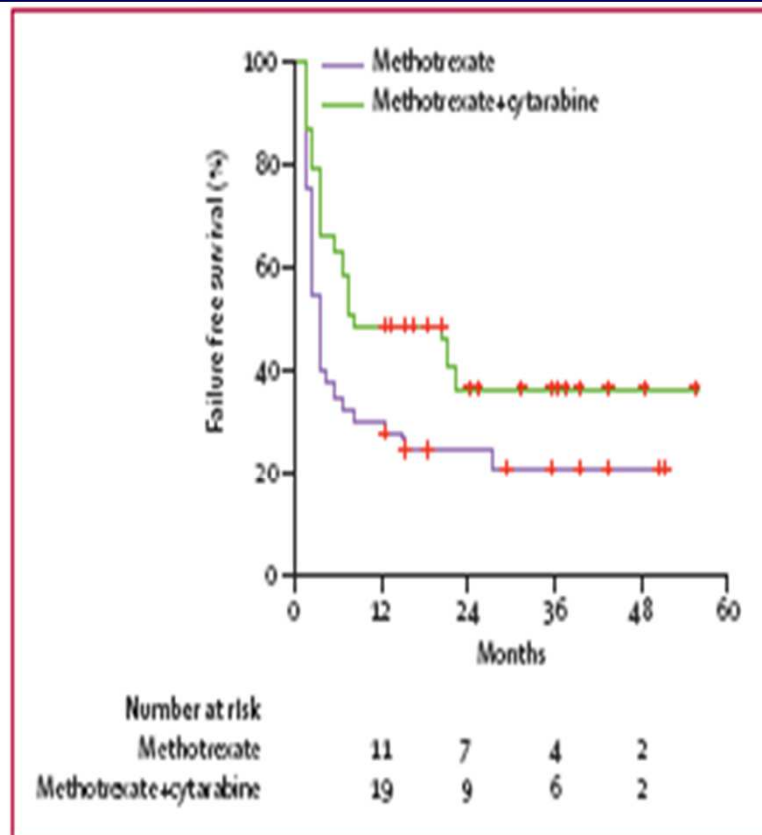


Figure 2: Failure-free survival curves

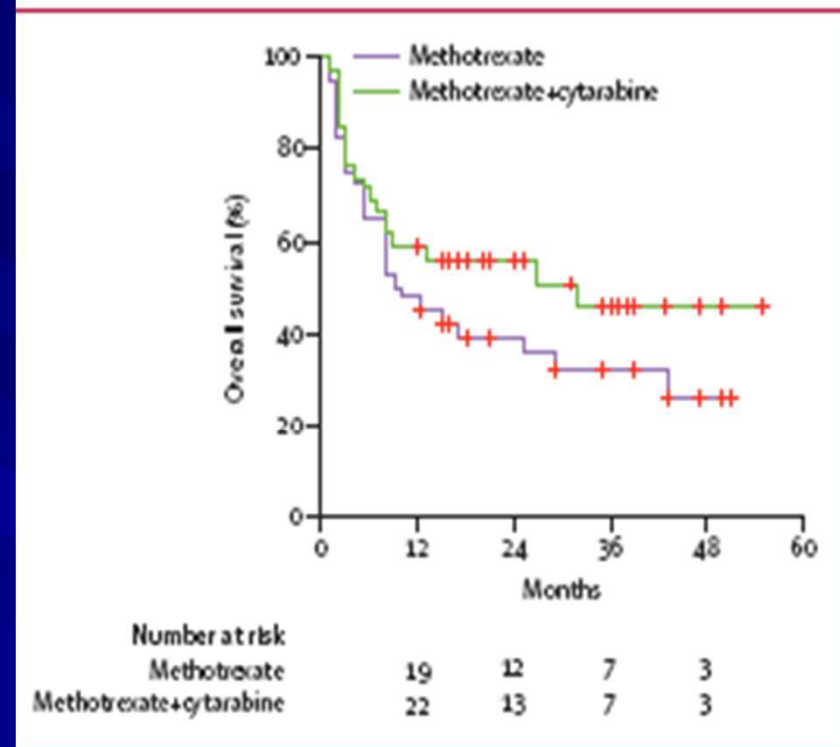


Figure 3: Overall survival curves



	N	TS*	Primary chemotherapy†			ORR‡	CRR§	Median FU (months)	OS	NT	
			Drugs	M dose	it CHT				2 year	5 year	
Series treated with chemotherapy alone											
Guha-Thakurta <sup>1</sup>	31	C	M	8 g/m <sup>2</sup> /14 d	..	100%		31	63%	NR	0%
Hoang-Xuan <sup>6</sup>	50	C	M, L, P, N	1 g/m <sup>2</sup> /10 d	M	48%	42%	36	45%	NR	8%
Batchelor <sup>7</sup>	25	C	M	8 g/m <sup>2</sup> /14 d	-	74%	52%	23	70%	NR	5%
Pels <sup>8</sup>	65	C	M, V, L, C, A, O	5 g/m <sup>2</sup> /28 d	ivM/a	71%	61%	26	69%	43%	3%
Herrlinger <sup>9</sup>	37	C	M	8 g/m <sup>2</sup> /14 d	..	35%	30%	56	51%	25%	20%
Series treated with high-dose M plus radiotherapy											
Glass <sup>10</sup>	25	CR	M	3.5 g/m <sup>2</sup> /21 d	..	88-92%	56-88%	60	58%	38%	8%
O'Brien <sup>11</sup>	46	CR	M	1 g/m <sup>2</sup> /7 d	a¶	NR-95%	NR-82%	36	62%	37%	22%
Abrey <sup>12</sup>	31	CRC	M	1 g/m <sup>2</sup> /7 d	M	64-87%	NR-87%	97	72%	22%	32%
Series treated with high-dose-M-containing chemotherapy plus radiotherapy											
Blay <sup>13</sup>	25	CR	A, a, C, M, O, P	3 g/m <sup>2</sup> /21 d	M/a/P	72-72%	67-78%	24	70%	56%	0%
Bessell <sup>14</sup>	34	CRC	a, Bn, M, O, ±CHOP	1.5-3 g/m <sup>2</sup> /14 d	..	68-71%	62-77%	16	43%	33%	NS
Korfel <sup>15</sup>	56	CR	Bn, M, N, P	1.5 g/m <sup>2</sup> /28 d	M	71-100%	54-61%	8	86%	NS	29%
Brada <sup>16</sup>	31	CR	A, B, C, M, O, P	2 g/m <sup>2</sup> /15 d	M/a/P¶	67-89%	..	24	48%	36%	7%
Abrey <sup>17</sup>	52	CRC	M, N, O	3.5 g/m <sup>2</sup> /7 d	M	90-94%	56-87%	60	75%	40%	25%
DeAngelis <sup>18</sup>	102	CR	M, N, O	2.5 g/m <sup>2</sup> /14 d	M	94%-NR	58-NR	56	64%	32%	15%
Poortmans <sup>19</sup>	52	CR	Bn, M, O, P	3 g/m <sup>2</sup> /14 d	M	NR-81%	33-69%	27	69%	NR	12%
Ferreri <sup>20</sup>	41	CR	A, Z, M, T	3.5 g/m <sup>2</sup> /21 d	..	76-83%	44-56%	49	50%	41%	NR
Shah <sup>21</sup>	30	CRC	M, N, O, R	3.5 g/m <sup>2</sup> /14 d	M¶	93%-NR	44-77%	37	67%	NR	NR

The Lancet 2009, 374 , 1512-20

# Results

- CR in 18% (MTX) vs 46% (MTX+C);
- Overall response rate 40% and 69%.
- Increased Gr 3-4 hemato toxicity, 15% vs 92%;
- Treatment-related death in 1 pt vs 3 pts.
- Conclusion: The addition of high-dose cytarabine to high-dose methotrexate improved outcome with acceptable toxicity in pts 75 yrs and younger.

# Chemotherapy

- Lack of long-term efficacy of WBRT alone has prompted the investigation of combined chemotherapy and radiation therapy approaches.
- Non Penetrating Chemotherapy Trials
  - Phase II, prospective, combined modality, intergroup trial, tested agents commonly used for systemic lymphoma, such as cyclophosphamide, adriamycin, vincristine, and prednisone.
  - Nonpenetrating chemotherapy were subsequently tried
  - These trials collectively have failed to identify any improvement in survival over the use of WBRT alone.
  - Failed due to non penetration through the BBB

# BBB Penetrating Chemotherapy

- Penetrating Chemotherapy regimens
  - High-dose methotrexate and cytosine arabinoside
- Hybrid regimens
  - Has both penetrating and nonpenetrating chemotherapy
  - Substantial improvement in survival
  - Particularly for patients less than 50 to 60 years of age
- High rates of initial response in these trials have also prompted treatment strategies that defer WBRT, with the hope that the delayed neurotoxicity largely attributed to WBRT can be avoided.

- In most trials, when WBRT is used, radiation doses are similar to the doses when radiation therapy alone is used.
- A significant number of patients treated with up-front chemotherapy will require deferred or salvage WBRT

	First author (Ref)	Median age	Chemotherapy	<u>Penetrating</u>		IT/IO therapy	Radiation WBRT (boost)	XRT at relapse	PFS	OS	Neurotoxicity
				Yes	No						
XRT alone	Nelson (23)	66	None			None	40 Gy (20 Gy)		NS	1 y 48% 2 y 28%	None

# Chemotherapy Alone

Source	Chemotherapy Regimen	Patients, No.	Intrathecal Chemotherapy	WBRT	CR, % (No./Total No.)	PR, % (No./Total No.)	OS, mo <sup>a</sup>	PFS, mo <sup>a</sup>
Chemotherapy Without RT								
Pels et al, <sup>20</sup> 2003	MTX (5 g/m <sup>2</sup> ), vincristine, ifosfamide, dexamethasone, cyclophosphamide, cytarabine, vindesine	65	Prednisolone, MTX, cytarabine	None	61 (37/61)	10 (6/65)	50	21
Hoang-Xuan et al, <sup>21</sup> 2003	MTX (1 g/m <sup>2</sup> ), lomustine, procarbazine, methylprednisolone	50	Cytarabine, MTX	None	42 (21/50)	6 (3/50)	14.3	10.6
Gerstner et al, <sup>22</sup> 2008; Batchelor et al, <sup>23</sup> 2003	MTX (8 g/m <sup>2</sup> )	25	None	None	52 (12/25)	NA	55.4	12.8



# Chemoradiotherapy

Source	Chemotherapy Regimen	Patients, No.	Intrathecal Chemotherapy	WBRT	CR, % (No./Total No.)	PR, % (No./Total No.)	OS, mo <sup>a</sup>	PFS, mo <sup>a</sup>
Chemotherapy With RT								
Poortmans et al, <sup>16</sup> 2003	MTX (3 g/m <sup>2</sup> ), teniposide, carmustine	52	Cytarabine, MTX	30 Gy with 10-Gy boost	69 (36/52)	12 (6/52)	46	NA
Gavrilovic et al, <sup>17</sup> 2006; Abrey et al, <sup>18</sup> 2000	MTX (3.5 g/m <sup>2</sup> ), procarbazine, vincristine, cytarabine	57	MTX	45 Gy in those aged <60 y	56 (27/48)	33 (16/48)	51	129
Shah et al, <sup>15</sup> 2007	MTX (3.5 g/m <sup>2</sup> ), rituximab, procarbazine, vincristine, cytarabine	30	None	23.4 Gy if CR; 45 Gy if not CR	77 (23/30)	NA	2-y OS, 67% <sup>b</sup>	40 <sup>b</sup>
Ferreri et al, <sup>19</sup> 2009	MTX (3.5 g/m <sup>2</sup> ) with or without cytarabine	MTX alone, 40; MTX plus cytarabine, 39	None	Added based on response and age	MTX alone, 18; MTX plus cytarabine, 46	MTX alone, 23; MTX plus cytarabine, 23	3-y survival: MTX alone, 32%; MTX plus cytarabine, 46%	3-y survival: MTX alone, 21%; MTX plus cytarabine, 38%

# Intrathecal chemotherapy

- PCNSL – tends to involve the subarachnoid space,
- Intrathecal chemotherapy, most often methotrexate, is often prophylactically administered together with high-dose intravenous methotrexate or multiagent chemotherapy to ensure adequate CSF drug levels.
- A recent case matched retrospective comparison of high-dose intravenous methotrexate with or without intrathecal methotrexate failed to demonstrate a difference in survival, disease control, or neurotoxicity . The authors contend that adequate CSF methotrexate levels can be achieved when adequate doses and infusion rates are used with intravenous methotrexate alone.
- Other intrathecal agents used in PCNSL regimens include Ara-C and hydrocortisone.

# Intrarterial chemotherapy

- Intrarterial chemotherapy delivered with mannitol blood–brain barrier disruption has been used in the treatment of PCNSL.
- This technique allows enhanced delivery of chemotherapeutic agents that do not readily cross the blood–brain barrier when administered intravenously.
- Neuwelt *et al.* reported
  - Prolonged survival with preservation of cognitive function
  - complete tumor clearance and had stable or improved neurocognitive function 1 to 7 years posttreatment.
  - more aggressive, costly, and requires considerable experience to administer safely than standard intravenous chemotherapy.
- This approach is currently be explored further in the Blood Brain Barrier Consortium.

Neuwelt et al J Clin Oncol. 1991 September 1;9(9):1580–1590.

Source	Chemotherapy Regimen	Patients, No.	Intrathecal Chemotherapy	WBRT	CR, % (No./Total No.)	PR, % (No./Total No.)	OS, mo <sup>a</sup>	PFS, mo <sup>a</sup>
Intra-arterial Chemotherapy								
Angelov et al, <sup>24</sup> 2009	Intra-arterial MTX	149	None	None	57.8	24.2	3.1 y; 8.5-y OS, 25%	1.8 y; 5-y PFS, 31%

# High-dose chemotherapy with stem cell support

- High-dose chemotherapy supported with autologous peripheral blood stem cell transfusion is another strategy
- This approach
  - Allows drug dose escalation that would overcome the blood–brain barrier constraints for drugs that do not penetrate the blood–brain barrier in sufficient concentrations when given at conventional lower doses.
  - Allows dose intensification of penetrating chemotherapy agents, thereby eliminating the need for WBRT.

# High-dose chemotherapy with stem cell support

- Two recent Phase II multi-institutional trials have tested this approach and have established its feasibility
- Although the treatment was feasible, the event-free survival for both trials was not superior to that achieved with conventional chemotherapy and WBRT.
- A complete response rate of 44% (OSHO-Ostdeutsche Studiengruppe Hamato-Onkologie) and 70% (GOELAMS- Groupe Ouest Est des Leucemies et des Autres Maladies du Sang) for the two trials was similar to that achieved with conventional chemotherapy.
- Despite the intent to defer or eliminate the need for WBRT with this approach, all patients in the GOELAMS trial and 9 of 23 patients who failed to achieve a complete response in the OSHO trial received WBRT.
- Induction regimen toxicity remains a potential pitfall of this approach, as one death occurred during induction in the GOELAMS trial and three deaths occurred in the OSHO trial.
- The authors conclude that this approach is best considered for patients with refractory disease, those in relapse, or those partially responding to conventional chemotherapy.

Annals of Oncology. 2007 Apr;18(4):665–671

Bone Marrow Transplant. 2006 Sep;38(6):417–420.



# Acute Radiation Effects

- All Patients : Total scalp alopecia, erythema, and dry desquamation of the scalp within the treatment portal.
- Some patients: Fatigue, anorexia, mild nausea, or headache. Inflammation of the external auditory canal (rarely progressing to external otitis media)
- Uncommon : accumulation of middle ear fluid associated with eustation tube dysfunction is not uncommon.
- Patients requiring treatment to the entire eye are likely to experience conjunctival irritation and may note dry eyes.
- All acute effects are typically reversible with resolution 4 to 6 weeks from completion of WBRT.
- Patients with persistent serous otitis media who fail to respond to oral decongestants may require myringotomy tube placement.



# Late Radiation Effects

- WBRT to doses >30 Gy delivered in conventional fractions of 1.8 to 2 Gy will likely experience permanent, total or partial, scalp alopecia.
- Sensory neural hearing loss  $\geq 45$  Gy to inner ear .
- All patients are at a high risk of developing cataracts that may or may not require treatment.
- Patient receiving steroids, chemotherapy, and or WBRT that includes the entire eye are at the highest risk for developing cataracts.
- All patients receiving WBRT are at risk for developing neurocognitive dysfunction

# Neurotoxicity

- The main disadvantage of WBRT is its neurotoxicity.
- Presents as dementia, ataxia and urinary incontinence, and is associated with MRI evidence of leucoencephalopathy, which tend to develop after a delay of several years
- Neurotoxicity is more common after WBRT than after high-dose systemic MTX, and the risk is particularly high in patients who receive combined modality therapy, especially if the radiotherapy is given after MTX (Correa et al, 2004).
- Hence WBRT alone cannot be recommended as first-line treatment of CNS DLBCL except as palliation in patients unfit to receive chemotherapy.

○DeAngelis et al, 2001; Fitzsimmons et al, 2005; Batchelor & Loeffler, 2006).

- The risk of developing neurocognitive decline after WBRT
  - Increases with age (particularly age >60 years)
  - Total WBRT dose,
  - Co-administration of chemotherapy, and
  - Sequence of chemotherapy delivery (highest risk with concurrent or post-WBRT chemotherapy administration).
- Post-WBRT cognitive decline may be accompanied by symptoms similar to that seen with normal pressure hydrocephalus including urinary incontinence and gait abnormalities.

# Recurrent / Progressive PCNSL

Table 4. Treatment for recurrent/progressive PNSL

Chemotherapy	N	Response to salvage therapy	Median overall survival (months)	Median survival after salvage chemotherapy (months)	Reference
PCV (range, 1–9 cycles)	7	CR: 4/7 PR: 2/7 PD: 1/7	16+	12+	69
Topotecan 1.5 mg/m <sup>2</sup> /day × 5 days	9	CR: 4/9 PR: 2/9 SD: 2/9 PD: 1/9	NA	10+ in complete responders	70
Carboplatin (ia; n = 2) plus etoposide (iv; n = 10) plus cyclophosphamide (iv; n = 12)	24	CR: 5/17 PR: 2/17 SD: 7/17 PD: 3/17 NA: 7/24	NA	6.7	71
Rituximab (monoclonal antibody to CD-20) 375–500 mg/m <sup>2</sup> weekly × 4	3	PR: 1/3 (33%) SD: 2/3 (66%)	Not calculated	Not calculated	72
Thiotepa 750 mg/m <sup>2</sup> , misulben 10 mg/kg, cyclophosphamide 120 mg/kg, +/- Ara-C and etoposide	10	CR: 6/10 (60%) PR: 4/10 (40%)	NA	Not reached after 24 months	73

Also see Table 1 legend. Chemotherapy regimens: PCV: procarbazine 60 mg/m<sup>2</sup> (day 8 to 21), CCNU 100 mg/m<sup>2</sup> (day 1), vincristine 2 mg (day 8 and 29). CR, complete response; PR, partial response; PD, progressive disease; SD, stable disease; N, intravenous; ia, intra-arterial

Table 3. Several fundamental challenges yet to be addressed in future PCNSL trials

- 
1. What is the best MTX-based chemotherapy for PCNSL?
  2. What is the best administration schedule for high dose MTX?
  3. Is combined chemotherapy superior to high dose MTX regimens?
  4. Is intra-thecal chemotherapy necessary for all patients with PCNSL?
  5. What is the role for blood brain barrier disruption, what agents?
  6. What is the role for high dose chemotherapy with autologous stem cell transplant
  7. Is WBRT necessary for all patients with PCNSL
  8. Has the optimal total dose and fractionation scheme for WBRT
  9. What is the best treatment for ocular involvement in patients with PCNSL?
  10. What is the best treatment for meningeal lymphoma?
  11. What is the optimal salvage therapy for progressive or relapsed PCNSL patients?
- 

Adapted from Ferreri(62)

MTX-methotrexate

PCNSL- primary central nervous system lymphoma

# Take home message

- Optimal therapy for PCNSL remains to be defined.
- Initial treatment needs to include penetrating chemotherapy including methotrexate.
- In patients with a complete response, 45 Gy (1.8 Gy/d) of radiation therapy should be delivered as WBRT, that is, to a volume encompassing the whole brain. Alternately, a hyperfractionated dose of 36 Gy, given 1.2 Gy twice daily to the whole brain, could be considered
- In patients experiencing a partial response to penetrating chemotherapy, a salvage chemotherapy regimen could be considered or WBRT to the doses and volumes described above.



# Take home message

- Care needs to be exercised in treating patients >60 years of age, secondary to concerns for neurocognitive toxicity
- In this cohort of patients, it is reasonable to consider penetrating chemotherapy including methotrexate and, upon complete response, deferral of WBRT.
- If the patient has a partial response to chemotherapy, salvage chemotherapy or WBRT can be considered.
- In the event of recurrence, salvage chemotherapy or WBRT to the doses and volumes described above can be delivered.



