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REGION

CNS Lymphoma

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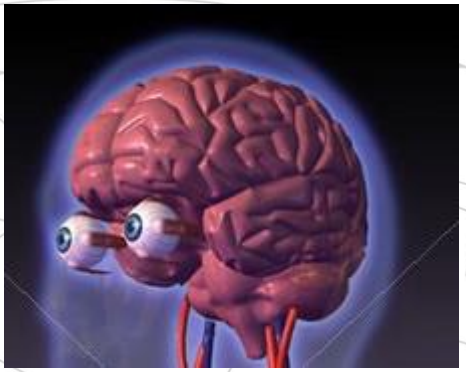
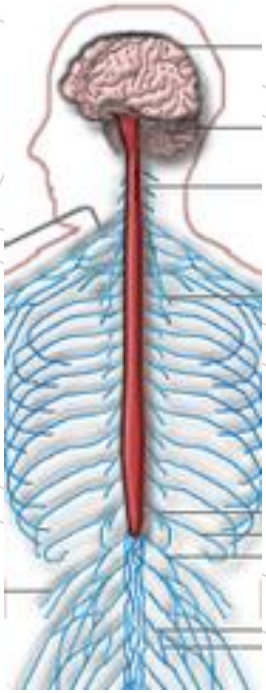
GLOBAL EXCELLENCE IN HEALTH

Primary CNS lymphoma



- Primary intracerebral or intraocular lymphomas
- Excluded:
  - Lymphomas of the dura
  - Intravascular lymphoma
  - Lymphomas with evidence of systemic disease or secondary lymphomas
  - Immunodeficiency-associated lymphoma

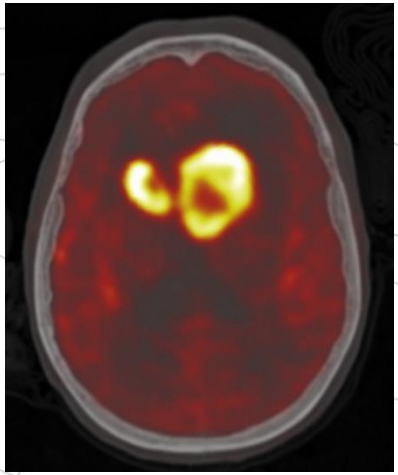


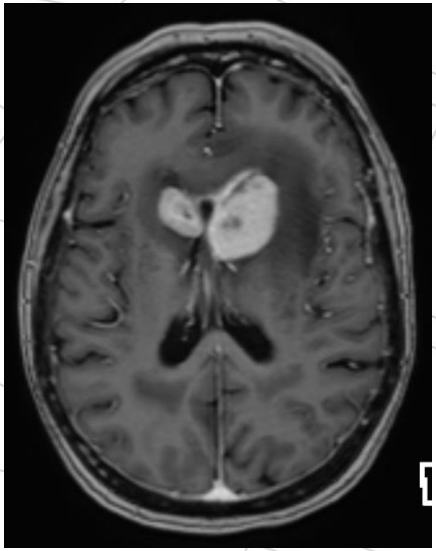
Epidemiology and clinical presentation

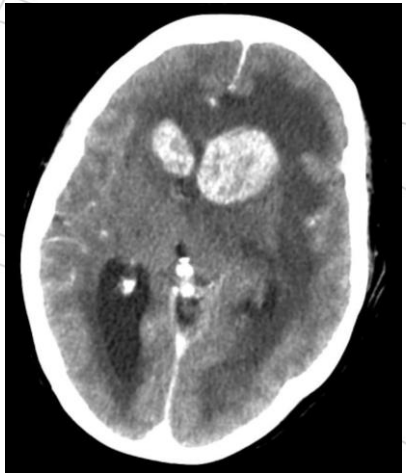
- Rare, < 1 % of NHL, 2-3 % of primary brain tumours
- Median age 60
- Increasing incidence in > 65 year old
- Location:
  - Supratentorial brain 60 %
  - Thalamus and basal ganglia 25 %
  - Intraocular 15 %
  - Corpus callosum 10 %
  - Meninges 10 %
  - Cerebellum 6-9 %
  - Spinal cord 1 %

Symptoms and diagnosis

- Symptoms
  - Focal neurological symptoms 50-70 %
  - Changes of personality 40-70 %
  - Symptoms of increased intracranial pressure 33 %
  - Convulsions 14 %
- Diagnosis (avoid steroids before if possible)
  - CT: hyperdense lesion
  - MR:
    - hyperintense on T2
    - hypointense on T1
    - homogenous contrast enhancement
    - surrounding oedema
    - haemorrhage, calcification and necrosis rare
    - multifocal in 40-50 %
    - periventricular location 60 %
    - leptomeningeal involvement up to 40 %
  - Whole body PET/CT
  - Biopsy (stereotactic)
  - CSF cytology, flow cytometry, PCR
  - Slit lamp examination
- Differential diagnosis:
  - High grade gliomas, metastases, demyelinisation, infections (toxoplasmosis, fungi)

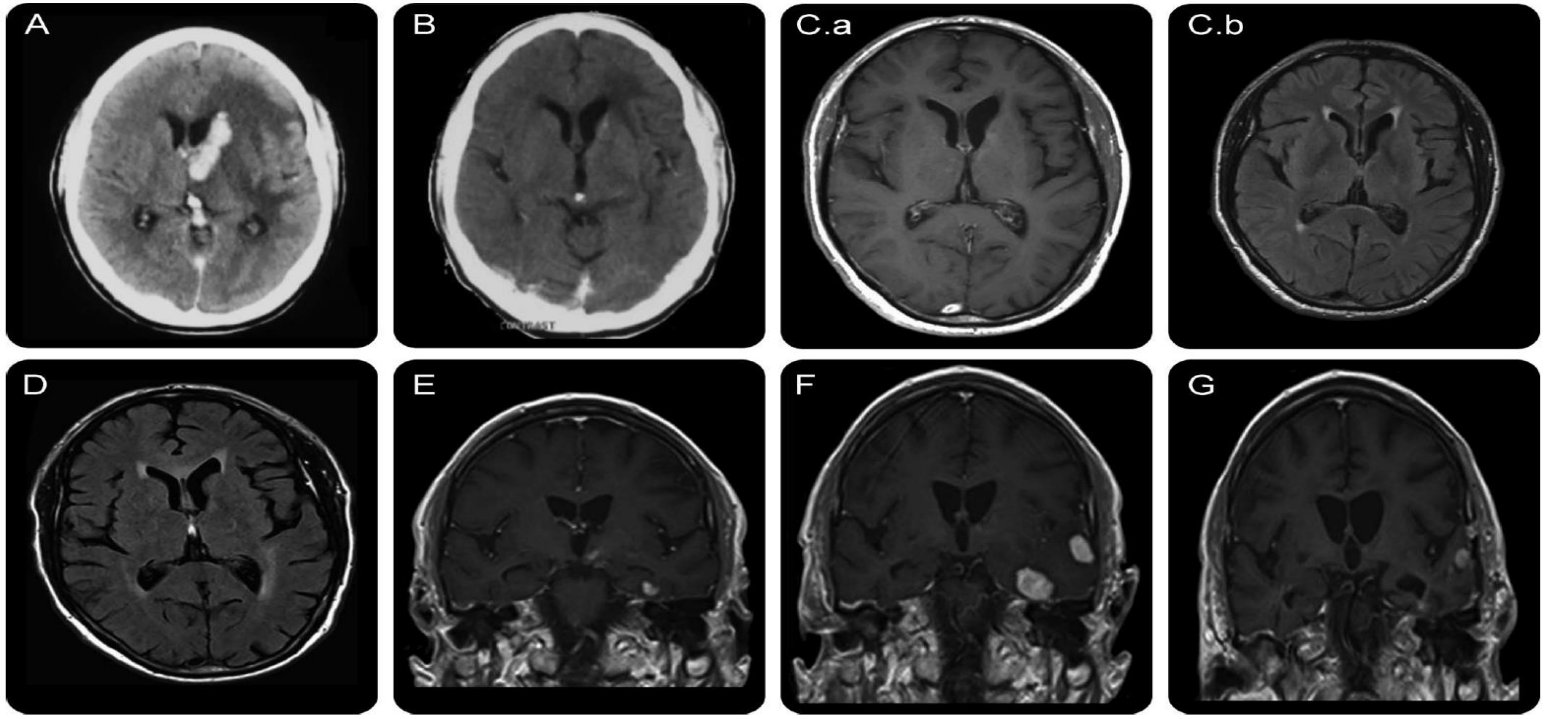






Avoid steroids before biopsy: ”Vanishing tumour”

Figure Neuroimaging series highlighting the initial radiologic abnormality that vanished and the recurrence 7 years later that led to the diagnosis of primary CNS lymphoma



(A) CT highlights a large, enhancing, space-occupying lesion in the left basal ganglia with associated edema and mass effect. (B) Image confirms a reduction in size of the caudate mass 1 week after initiation of steroid therapy. A complete radiologic response was observed on follow-up MRI brain (C.a [contrast] and C.b [fluid-attenuated inversion recovery]). (D) MRI brain performed following re-presentation with confusion and hallucinations was normal. (E) T1-weighted image postgadolinium confirms numerous foci of enhancement in the left temporal lobe. (F) Repeat MRI brain confirms progression of the left temporal lobe lesions suspicious for malignancy. (G) Following completion of 4 cycles of chemotherapy, a good radiologic response to treatment is evident on MRI brain.

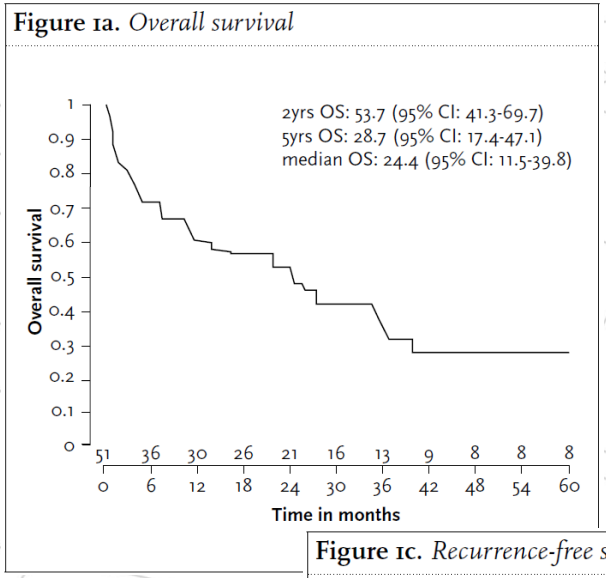
Kelly CM, Neurology 2015; 85: e69-73

Histopathology

- 98 % B-cell lymphomas
- 95 % of these DLBCL
  - Gene expression signatures as for DLBCL in general (GCB, ABC, type 3 large BCL)
  - Unique molecular features:
    - B-cell receptors recognize CNS proteins
    - Different microRNA expression patterns
    - Extracellulær matrix-related genes are upregulated
- Remaining cases (very rare):
  - Lymphoplasmacytic lymphoma
  - Lymphoblastic lymphoma
  - SLL
  - Plasmablastic lymphoma
  - T-cell lymphomas (often ALCL)

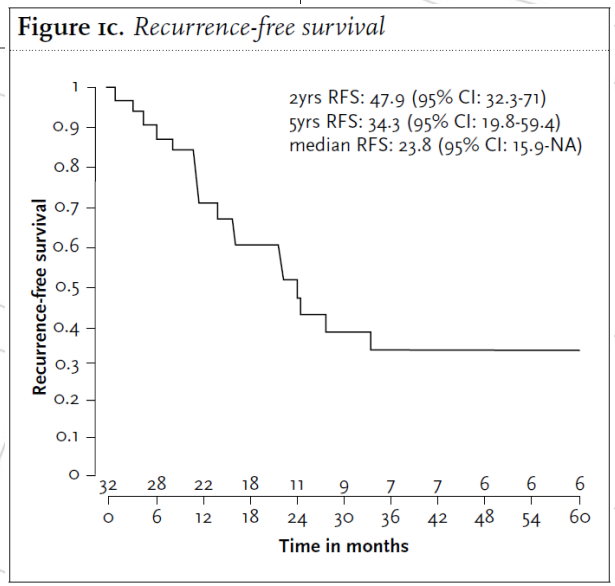
Challenges to treatment

- Despite high chemo- and radiosensitivity:
  - Remissions are frequently short
  - BBB limits the access of many drugs
  - High risk of severe neurotoxic effects of treatment, especially in elderly patients



52 pts treated outside protocols in Amsterdam 2000-2010.

Hart A et al., Netherlands J Med 2014; 72: 218-23

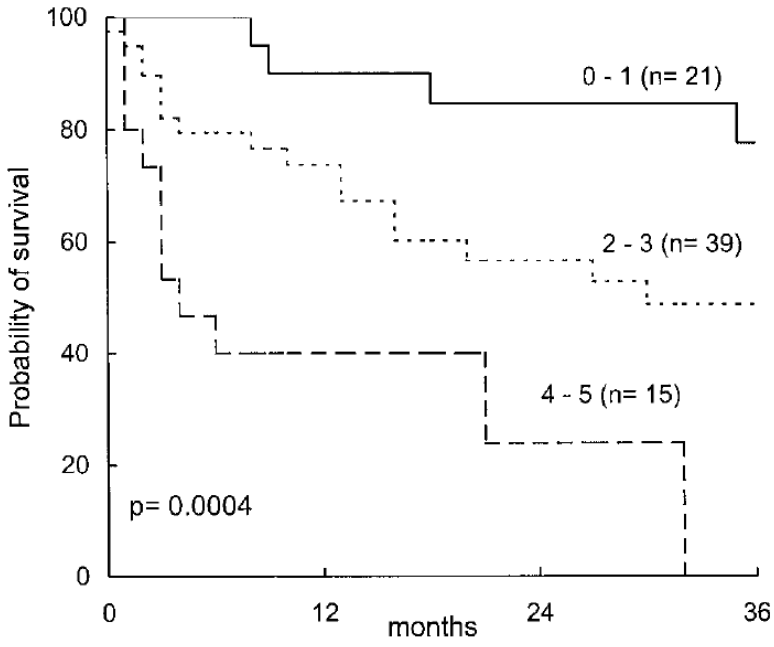


Prognostic scores

- IELSG score: Age > 60, PS >1, LDH ↑, CSF protein ↑, Involvement of deep structures (periventricular regions, basal ganglia, brainstem, cerebellum) (Ferreri A et al. JCO 2003; 21: 266-72)

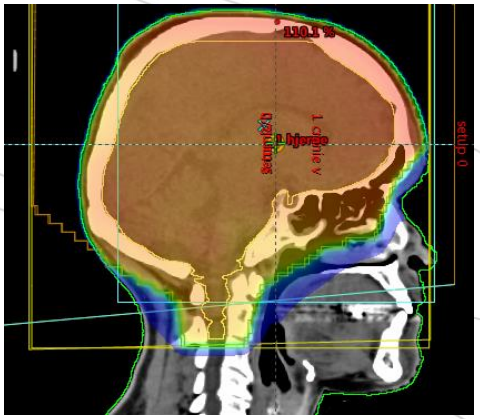
- MSKCC groups: ≤ 50 years, > 50 years and KPS ≥ 70 (PS 0-1), > 50 years and KPS < 70 (PS 2-4)
(Abrey L et al. JCO 2006; 24: 5711-5)

- Nottingham/Barcelona score: Age > 60, PS > 2, multifocal tumours or meningeal disease
(Bessell E et al. IJROBP 2004; 59: 501-8)



Treatment: single modality

- Resection: Not a recommended treatment
  - Tumour is infiltrative, may be multifocal involving leptomeninges or deep brain regions
  - Median survival after surgery alone: 1-4 months
- Corticosteroids:
  - Cause regression in up to 40 %
  - Patients usually relapse quickly
  - Response to steroids is a favourable prognostic marker (survival 117 months vs. 5.5 months)
- Radiation:
  - Tumour is multifocal and infiltrative, so WBRT is used
  - Initial radiographic response in 90 %
  - Relapse usually occurs within a few months
  - Median survival 12-18 months
- Chemotherapy:
  - CHOP does not work

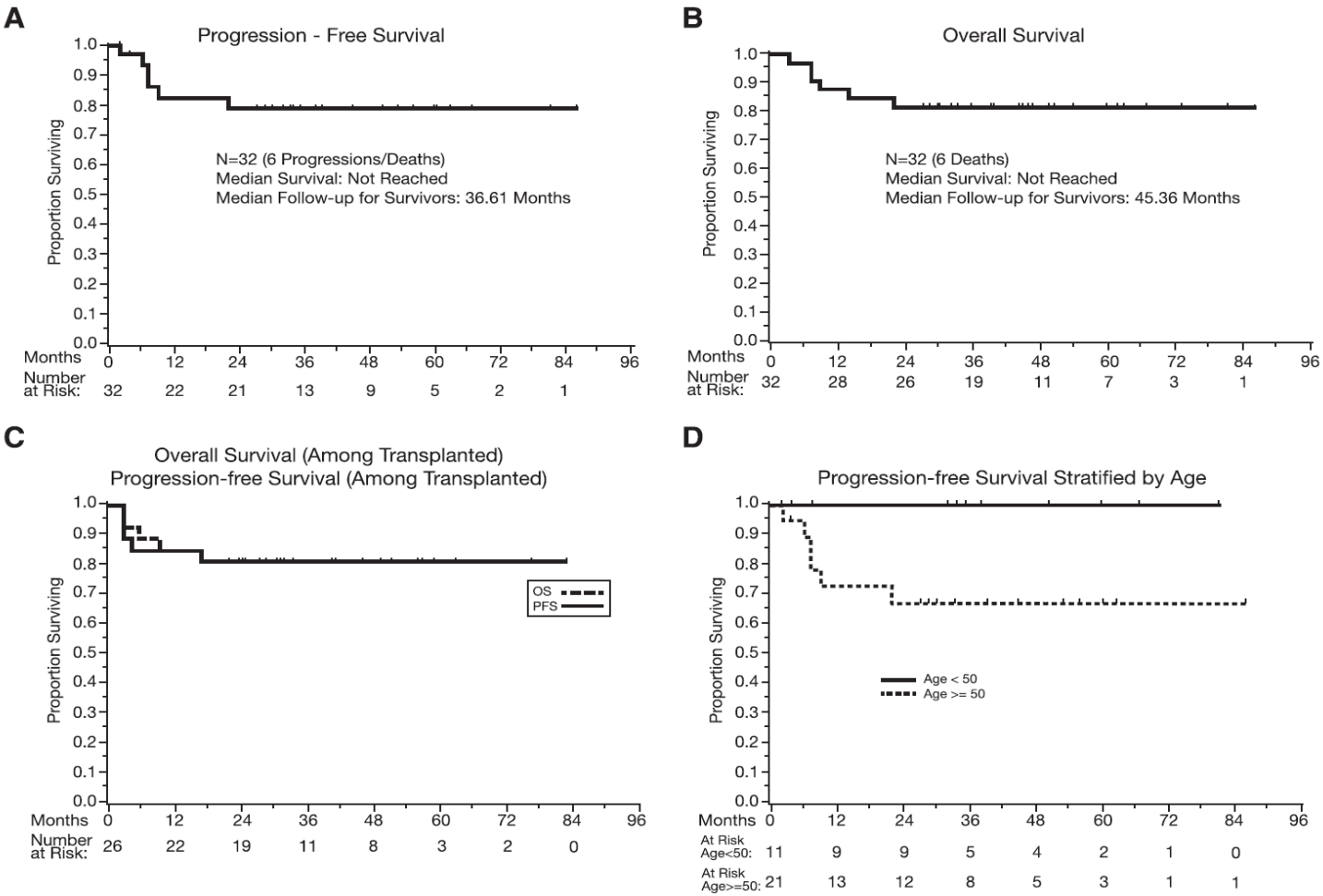


Treatment, pts. ≤ 65 years

- HD-MTX (1.5-8 g/m^2) improved OS (31-79 months)
- HD-MTX combined with HD Ara-C superior in randomized study (IELSG 20)
- Combination with drugs that penetrate into the CNS, e.g., Thiotepa, Procarbazine, Vincristine
- Rituximab penetrates into CNS in PCNSL patients (not in healthy individuals), IELSG32 trial 1st randomization showed R-arms to be superior
- High-dose chemotherapy and ASCT:
  - BEAM proved suboptimal
  - Thiotepa, Busulfan, and Cyclophosphamide penetrate CNS better
- Intrathecal/intraventricular chemotherapy: no clear evidence, associated with infections in Ommaya reservoir

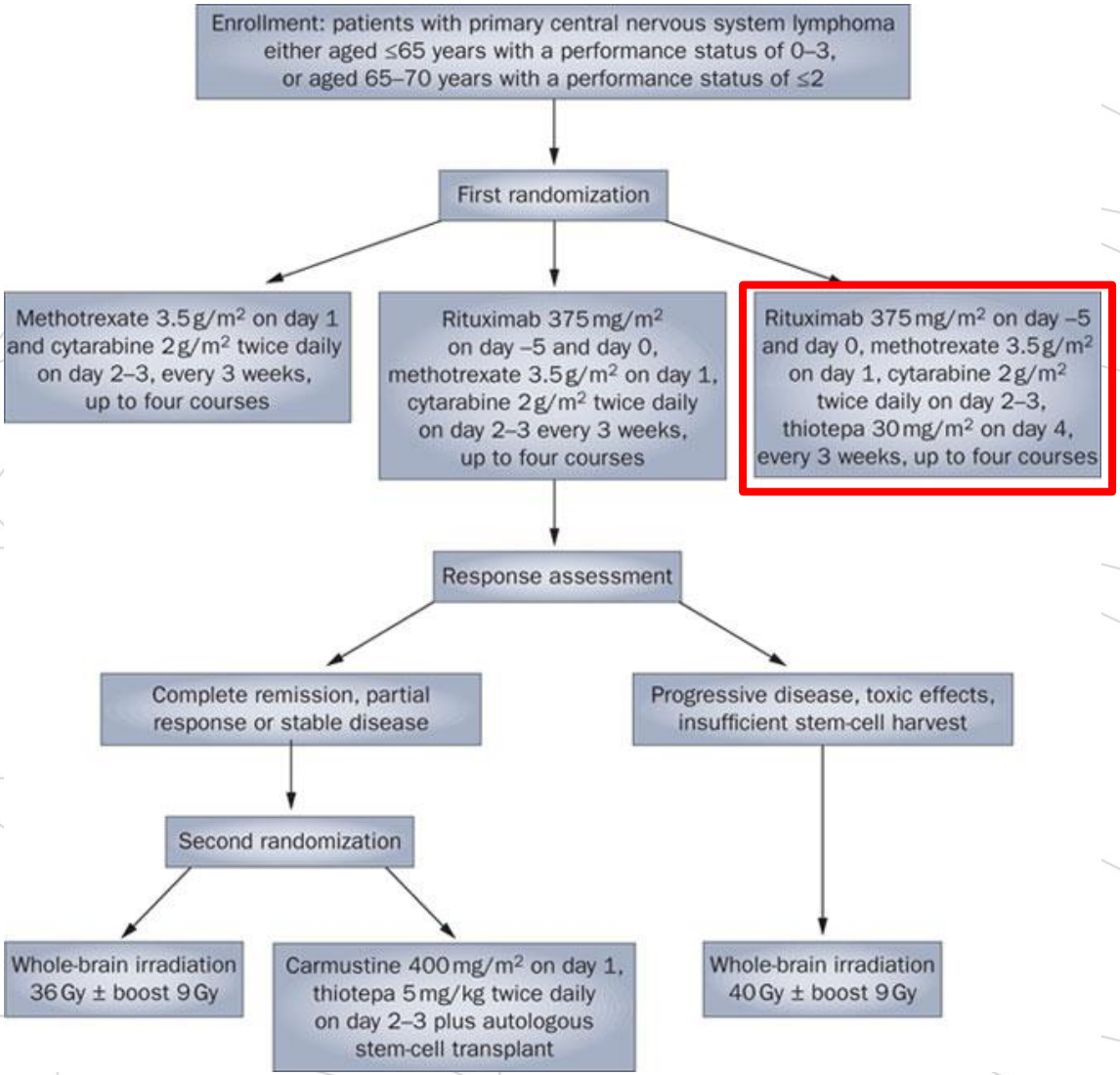
R-MVP followed by HDC with TBC and ASCT

Omuro A et al, Blood 2015; 125: 1403-10

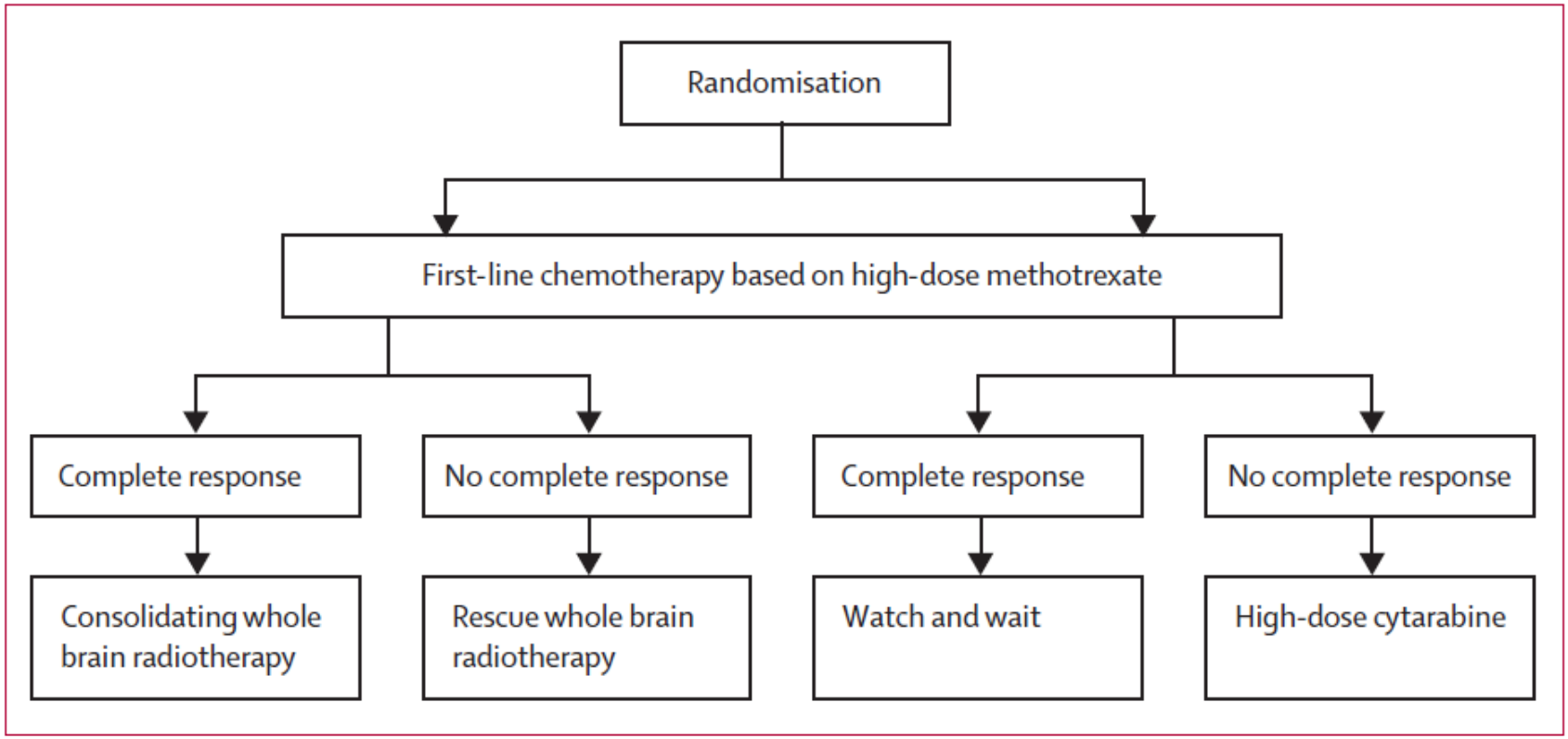


Is HDCT and ASCT as consolidation indicated?

- Awaiting results of 2nd randomization in IELSG32 trial
- Ferreri AJ et al, Abstract 009, 13th ICML

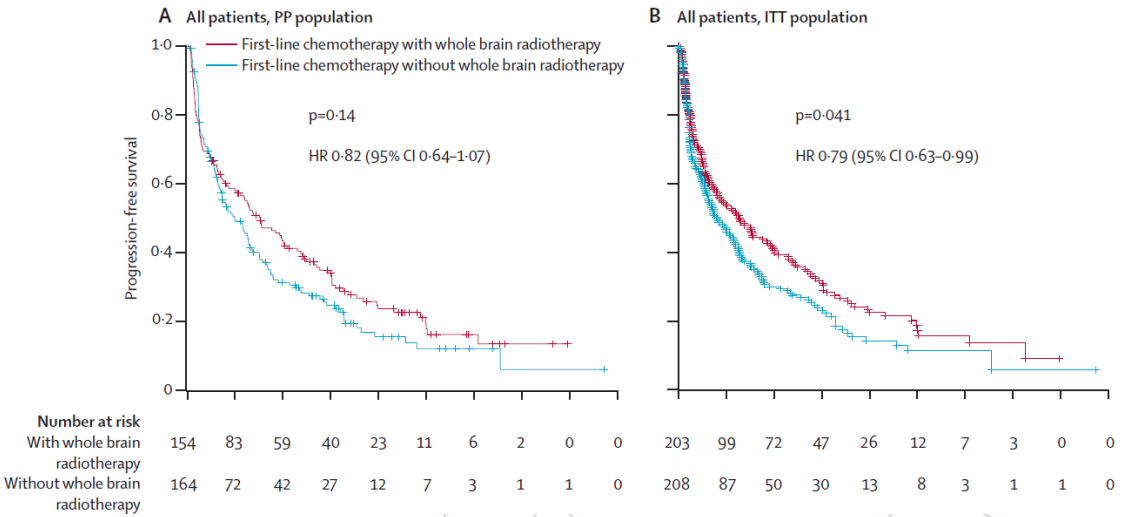


Is additional radiotherapy indicated?



One published randomized trial with many flaws (protocol violations) G-PCNSL-SG-1, 551 pts randomized

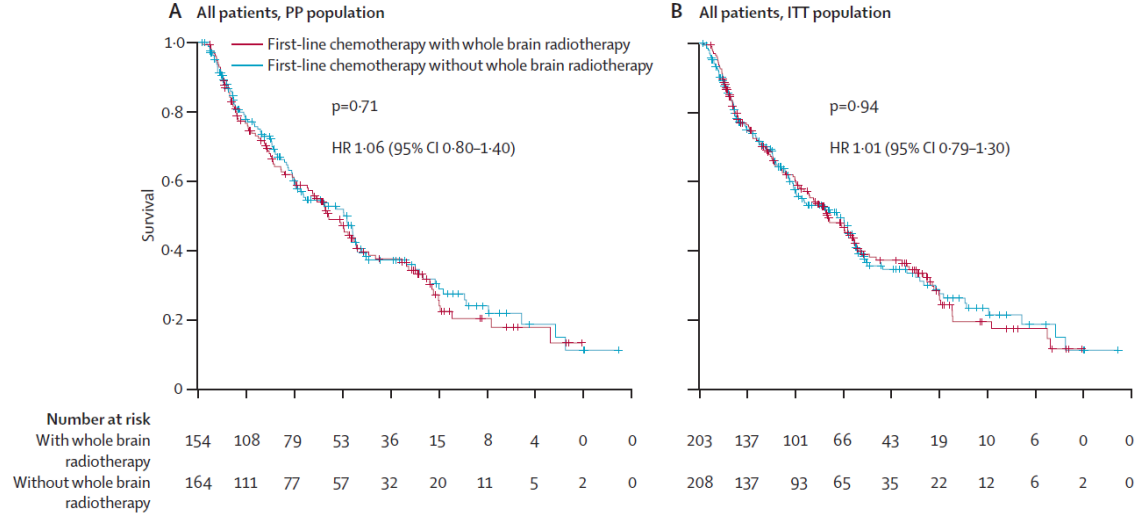
Thiel E et al. Lancet Oncol 2010; 11: 1036-47



G-PCNSL-SG-1

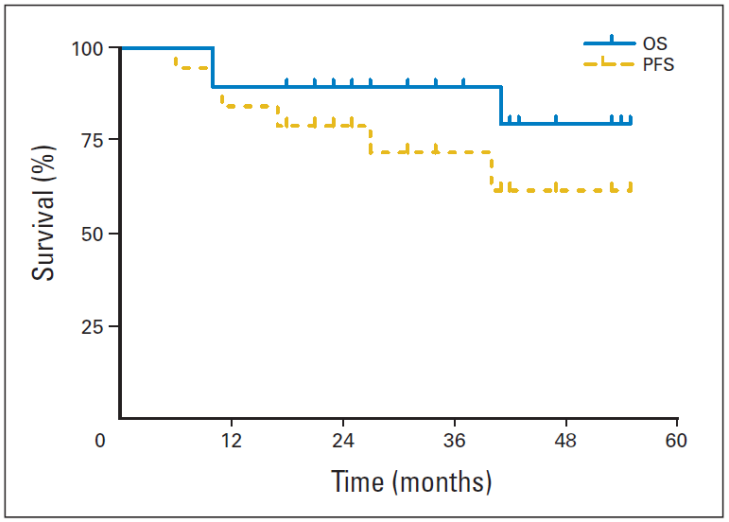
WBRT 45 Gy

Neurotoxicity:
49 % with WBRT,
26 % without WBRT



WBRT

- Awaiting results of 2nd randomization in IELSG32
- WBRT to 23.4 Gy in CR patients



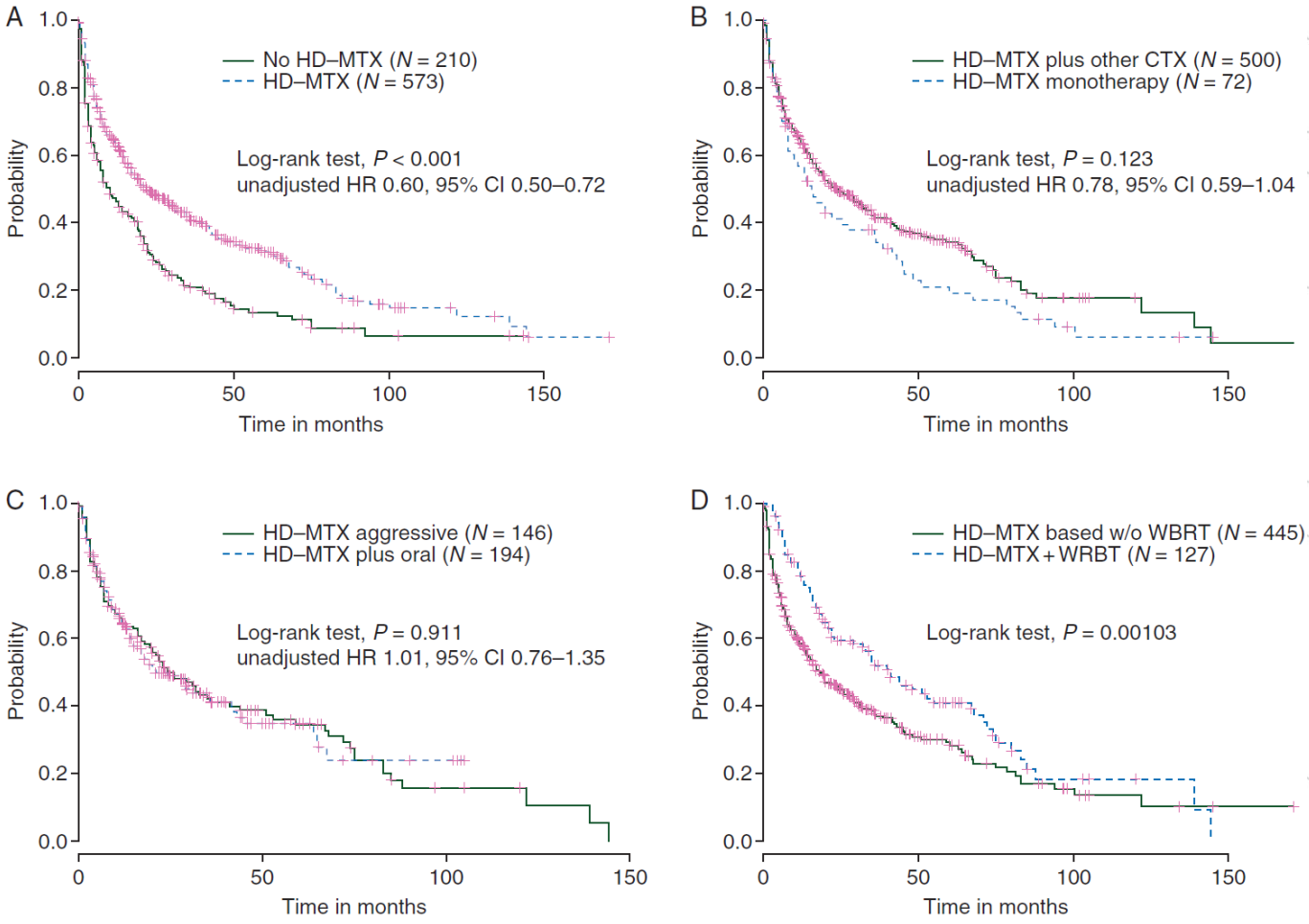
Shah GD et al, JCO 2007; 25: 4730-5

  - Not associated with cognitive decline up to 2 years post-treatment even in older pts
  - Awaiting results for RTOG-1114

Treatment, pts. > 65 years

- Age and PS should determine treatment
- HD-MTX should be used if possible
- Combined with e.g. R-MPV
- WBRT should not be used due to neurotoxicity

Kasenda B et al, Ann Oncol 2015; 26: 1305-13



Report of an International Workshop to Standardize Baseline Evaluation and Response Criteria for Primary CNS Lymphoma

Lauren E. Abrey, Tracy T. Batchelor, Andrés J.M. Ferreri, Mary Gospodarowicz, Elisa J. Pulczynski, Emanuele Zucca, Justine R. Smith, Agnieszka Korfel, Carole Soussain, Lisa M. DeAngelis, Edward A. Neuwelt, Brian Patrick O'Neill, Eckhard Thiel, Tamara Shenkier, Fransesc Graus, Martin van den Bent, John F. Seymour, Philip Poortmans, James O. Armitage, and Franco Cavalli

JCO 2005; 23: 5034-43

Table 4. Response Criteria for Primary Central Nervous System Lymphoma

Response	Brain Imaging	Corticosteroid Dose	Eye Examination	CSF Cytology
CR	No contrast enhancement	None	Normal	Negative
CRu	No contrast enhancement	Any	Normal	Negative
	Minimal abnormality	Any	Minor RPE abnormality	Negative
PR	50% decrease in enhancing tumor	Irrelevant	Minor RPE abnormality or normal	Negative
	No contrast enhancement	Irrelevant	Decrease in vitreous cells or retinal infiltrate	Persistent or suspicious
PD	25% increase in lesion	Irrelevant	Recurrent or new ocular disease	Recurrent or positive
	Any new site of disease: CNS or systemic			

Abbreviations: CR, complete response; CRu, unconfirmed complete response; RPE, retinal pigment epithelium; PR, partial response; PD, progressive disease.

Treatment of recurrent disease

- ≤ 65 years, good PS: Intensive induction chemotherapy (e.g., HD-MTX/HD-Ara-C re-induction, Carmustine, Thiotepa, Cyclophosphamide, Busulfan, Ifosfamide, Carboplatin, Etoposide) and HD-CT and ASCT
- > 65 years and/or significant co-morbidity: R-Temozolomide
- Poor performance status (also as primary treatment): WBRT as palliative treatment, dose and fractionation depending on expected survival

Primary intraocular lymphoma (PIOL)

- Presents with blurred vision and/or floaters
- Mimics chronic posterior uveitis and responds to steroid
- Bilateral in 64-83 % although it may seem unilateral at first
- Diagnosis: vitreous aspiration or vitrectomy
- 16-34 % have CNS involvement at presentation

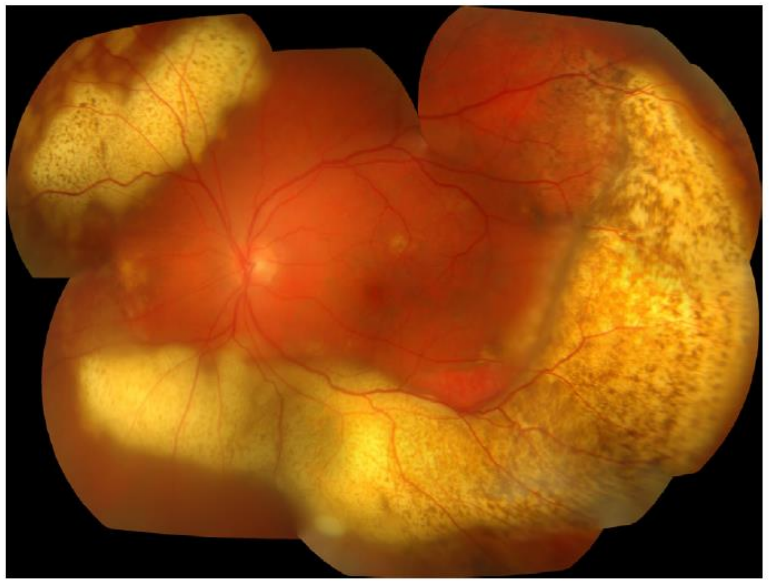


Fig. 1 – Composite color fundus photograph of the left eye of a patient with PIOL. Note the hazy appearance of the fundus due to the presence of vitreous cells, marked yellow subretinal infiltrates with overlying retinal pigment epithelial changes ("leopard spotting") and accumulation of subretinal fluid. Vitreous tap failed to provide sufficient cells for diagnosis, so a vitrectomy with retinotomy and subretinal aspirate was required to diagnose PIOL.

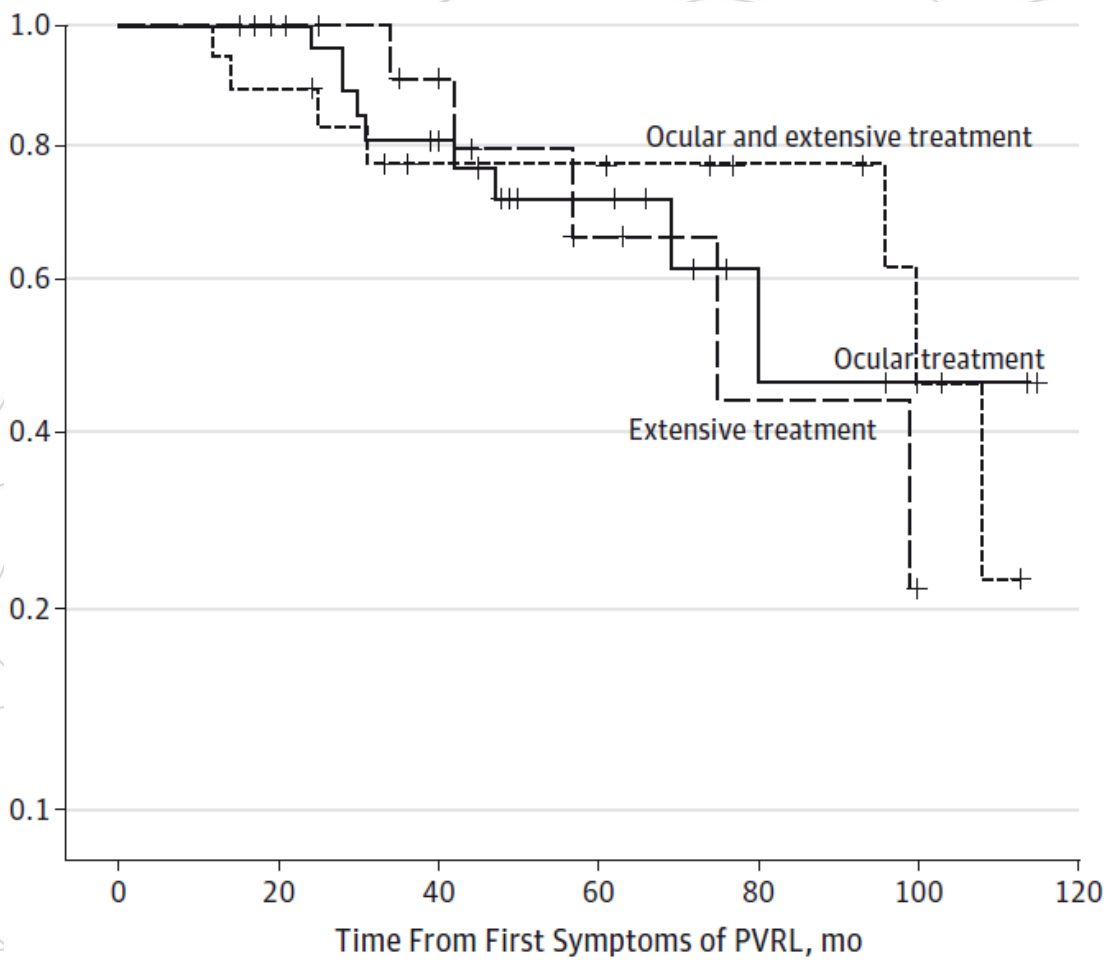
Isolated PIOL

- Recent 17-centre European study of 78 cases (Riemens A et al. JAMA Ophthalmol 2015; 133: 191-7)
- Median duration from symptom to diagnosis 10 months
- 36 % subsequently developed CNSL
- Ocular treatment:
  - Local radiotherapy
  - Intravitreal Methotrexate
  - Intravitreal Rituximab

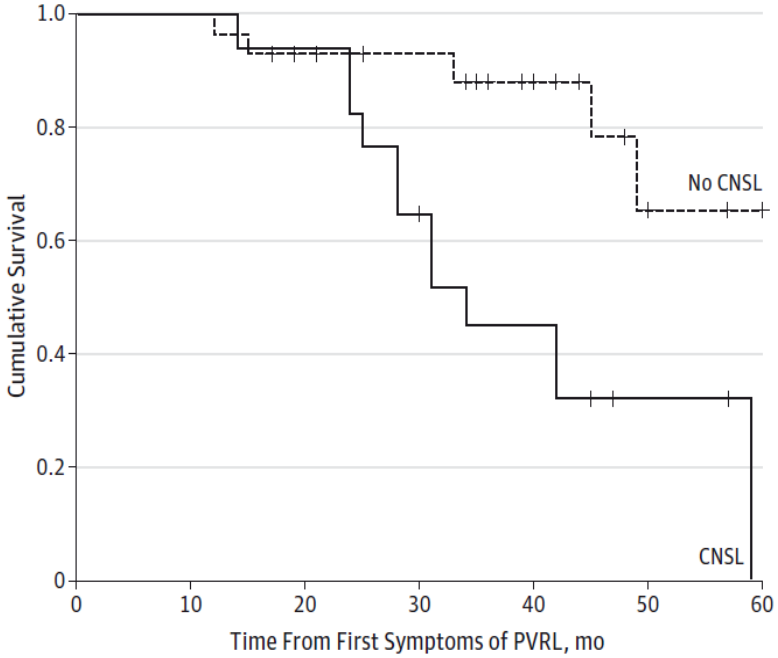
Isolated PIOL

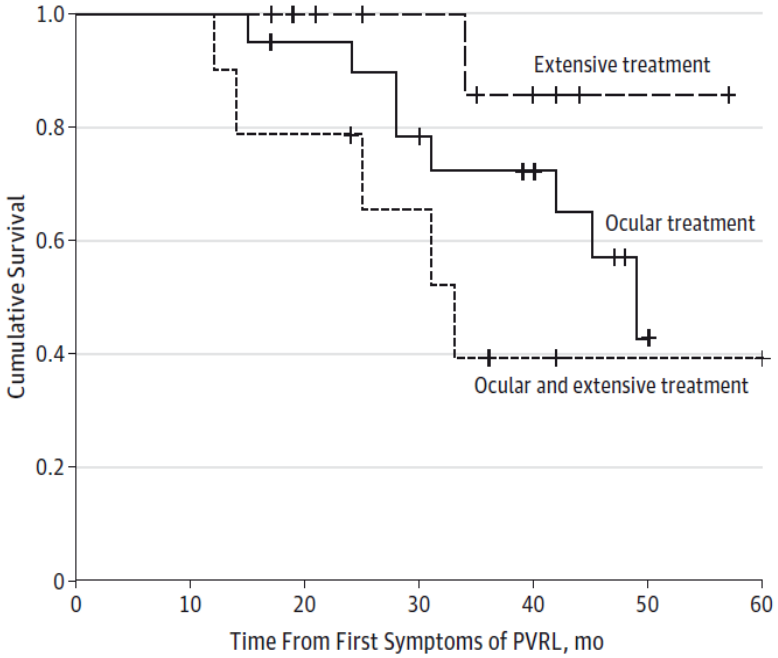
Time to development of CNSL

Riemens A et al. JAMA Ophthalmol 2015; 133: 191-7



Isolated PIOL





Riemens A et al. JAMA Ophthalmol 2015; 133: 191-7

Thank you for your attention