Primary Central Nervous System Lymphoma

Lymphoma Tumor Board

May 19, 2017

Relative incidence of primary brain neoplasms

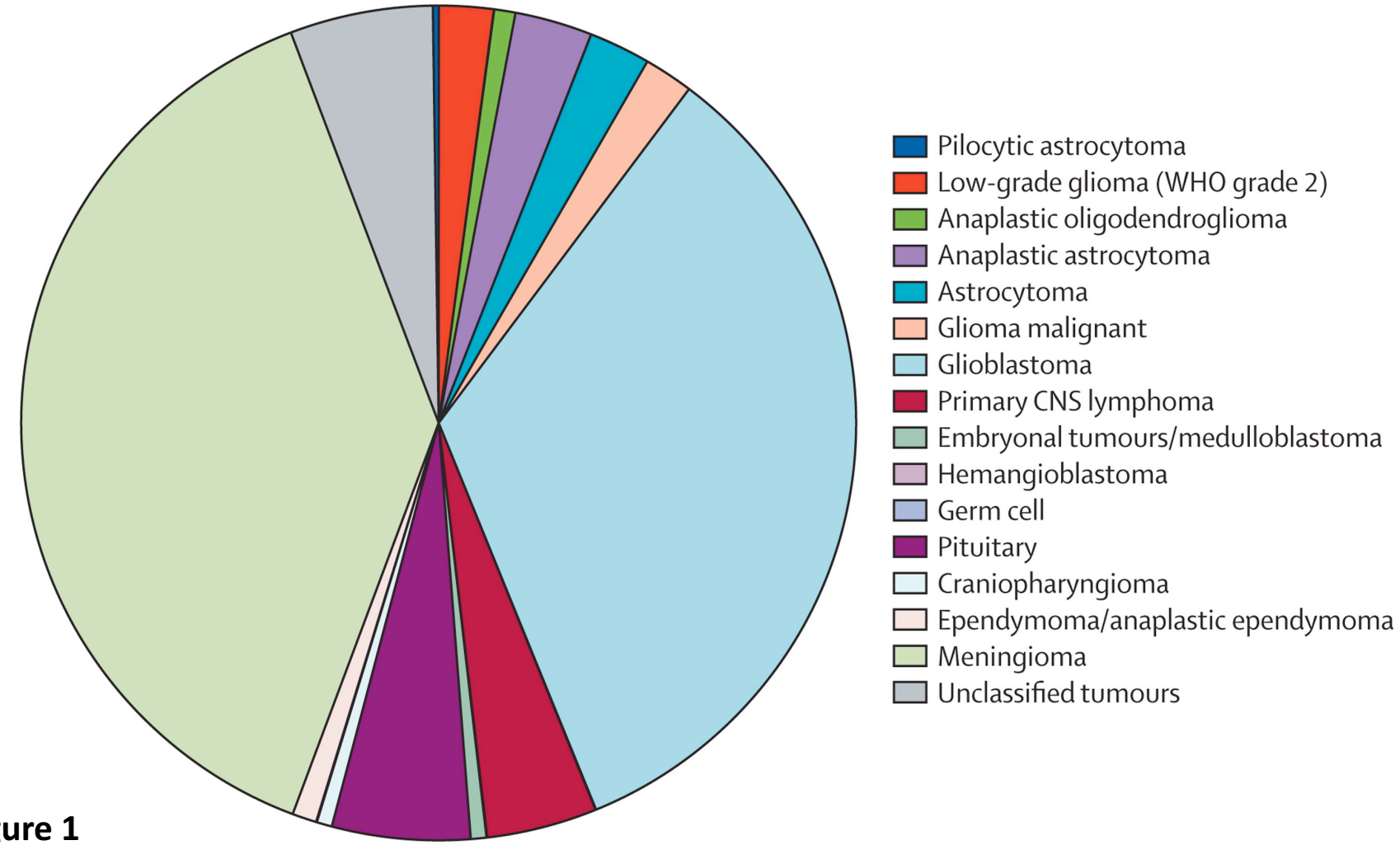


Figure 1

Respective yearly incidence of the different primary brain tumour types in *adults aged 65–74 years* between 1998 and 2002.

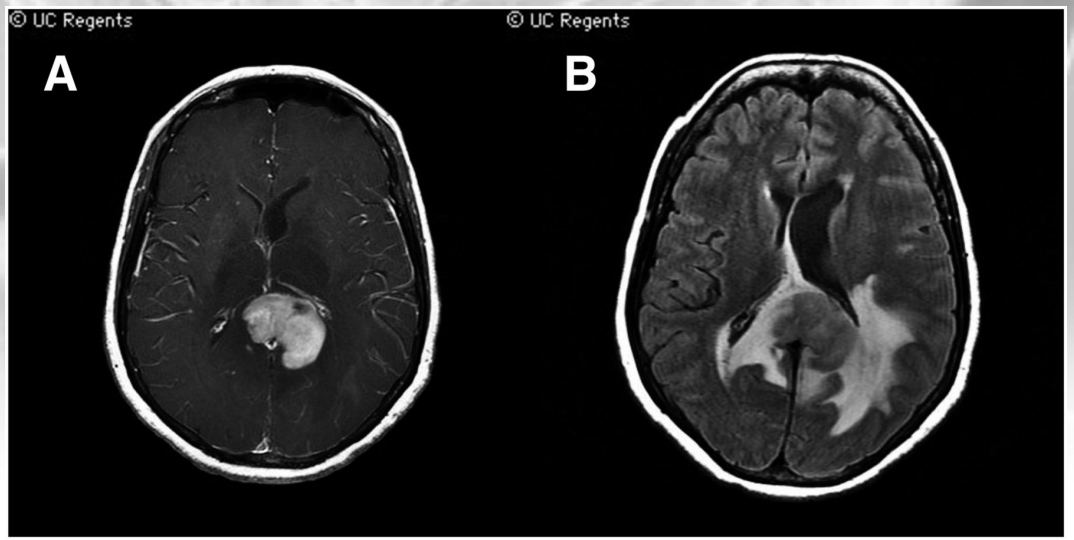
This distribution is representative of the distribution of primary brain tumours in adults aged 20–84 years. Data taken from the Central Brain Tumor Registry of the United States.[2]

Primary CNS Lymphoma (PCNSL)

- Aggressive malignancy that arises exclusively in the CNS
- Represents 4% of intracranial neoplasms and 4-6% of all extranodal lymphomas
- Represents around 20% of all cases of lymphoma in HIV-infected individuals
- Highly associated with EBV in immunodeficient patients
- Patients present with impaired general condition and poor performance status more often than other lymphomas
- Typically appears in 50-60 yr. olds
- Spinal cord lymphoma is the rarest manifestation of PCNSL
  - Often arises in the upper thoracic and lower cervical regions of the spinal cord
- Patients present with seizure, headache, cranial nerve findings, altered mental status, or other focal neurological deficits
- Symptoms at presentation may also include:
  - Fever
  - Night sweats
  - Weight loss
  - Diplopia
  - Dysphagia
  - Vertigo
  - Monocular vision loss

Diagnosis

- Brain biopsy
- MRI or contrast CT scan will show ring-enhancing lesions in the deep white matter
- 95% of cases will demonstrate homogenous enhancement localized to the tumor, with rare necrosis
  - This characteristic is useful in distinguishing PCNSL from glioblastoma
- Major differential diagnosis is cerebral toxoplasmosis
  - This is prevalent in AIDS patients and also presents with ring-enhanced lesions
- Lesions are solitary in 65% of patients and multifocal in 35%
- Cerebral hemisphere disease is most common (38%), followed by lesions within the thalamus/basal ganglia (16%), corpus callosum (14%), ventricular region (12%), and cerebellum (9%) (representative MR images below)



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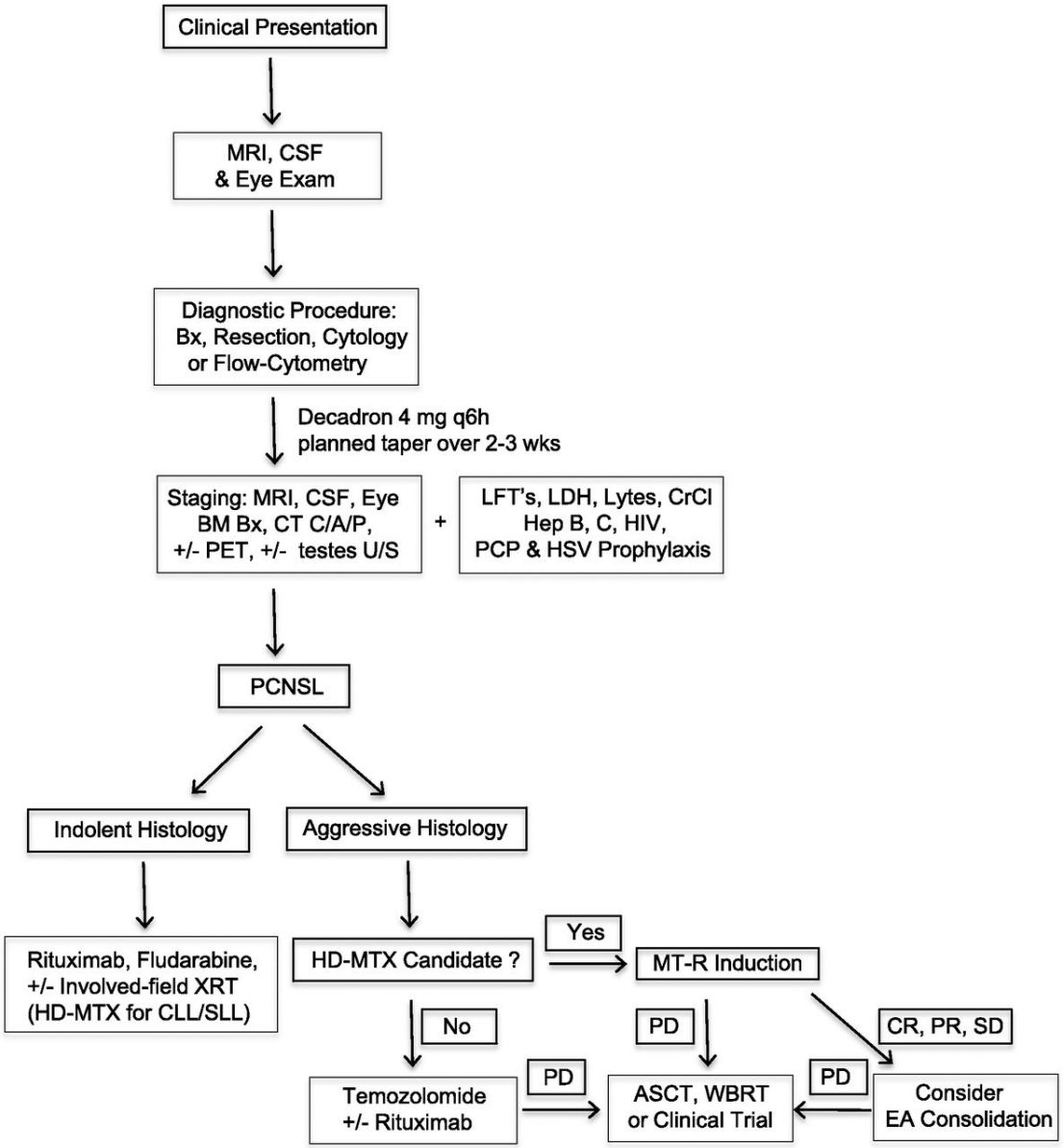
Diagnostic evaluation of suspected PCNSL



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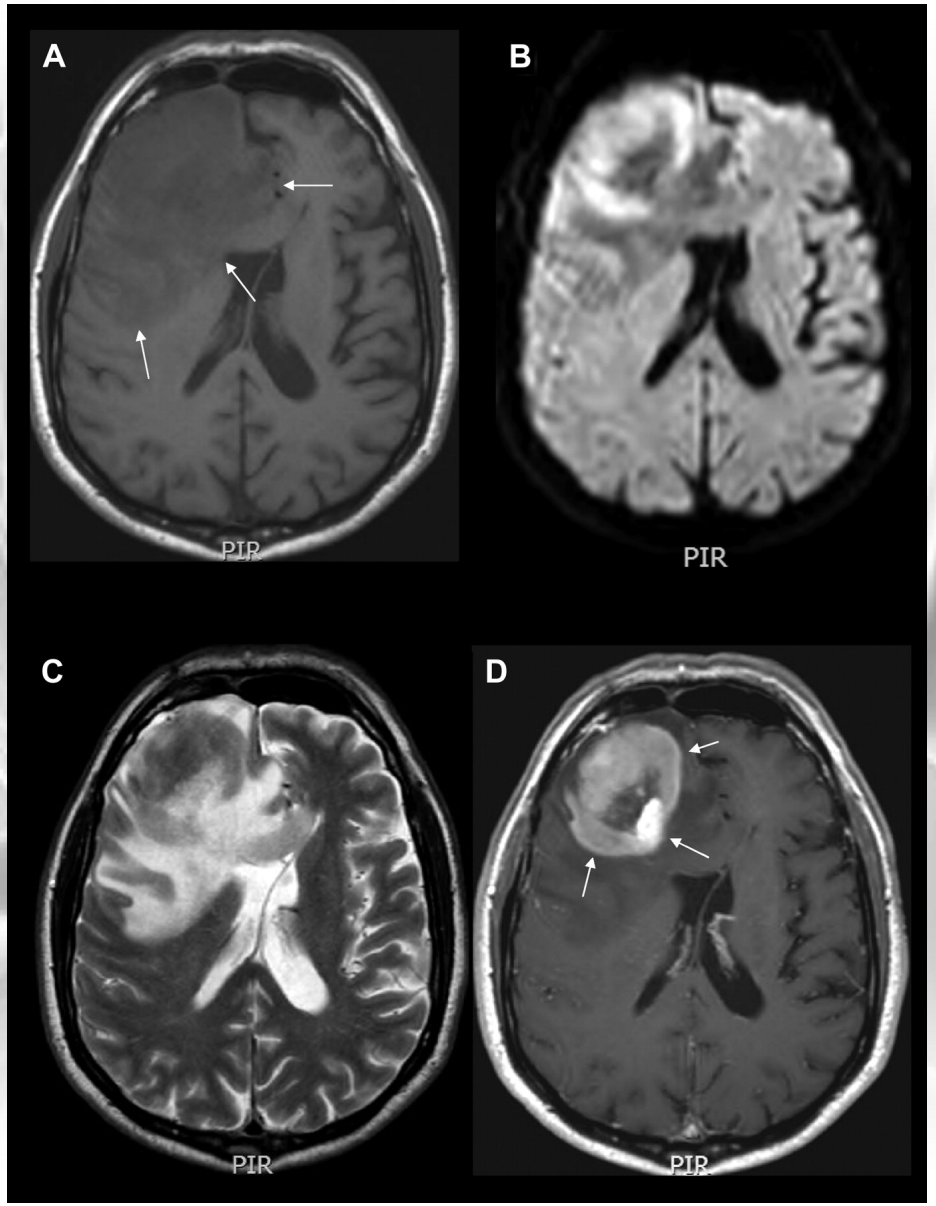
Magnetic resonance imaging of PCNSL



Andrés J. M. Ferreri Blood 2011;118:510-522

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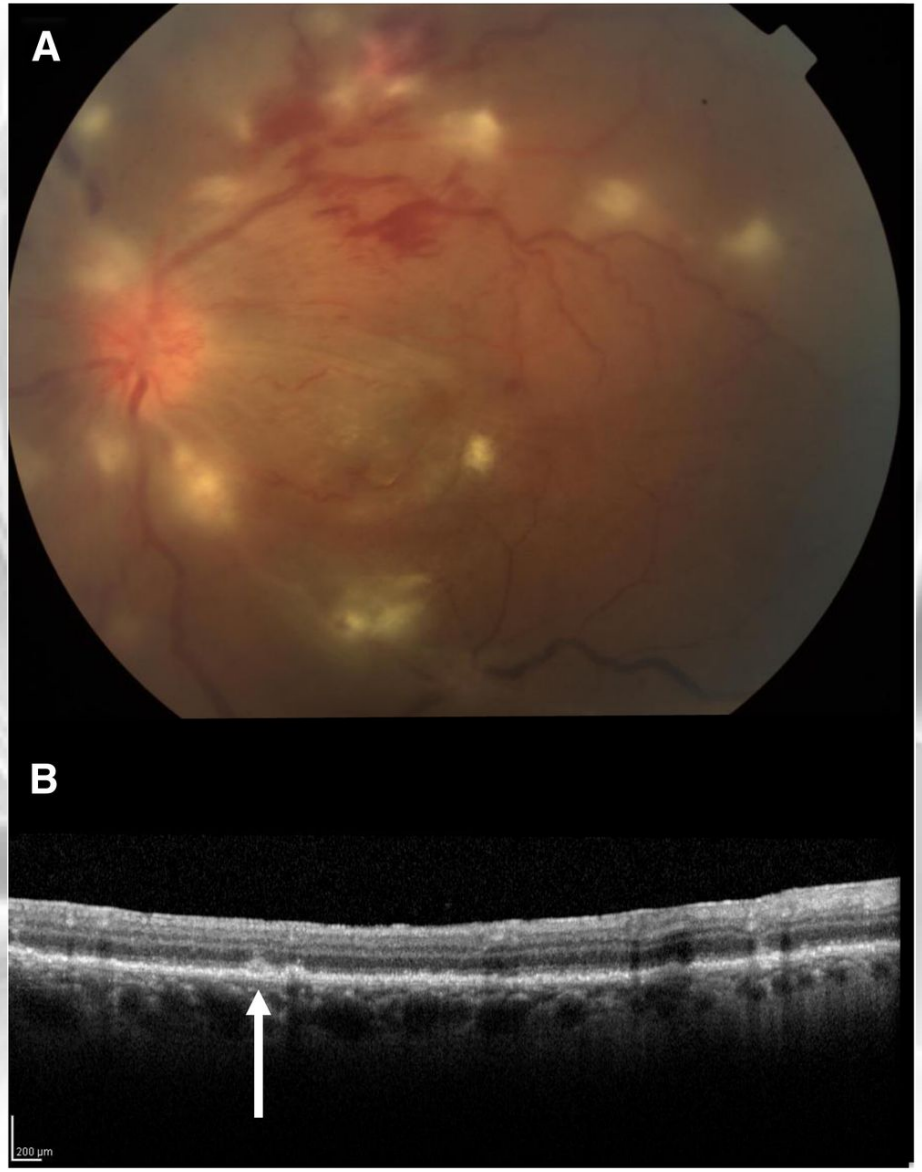
Intraocular lymphoma – a rare subtype of PCNSL



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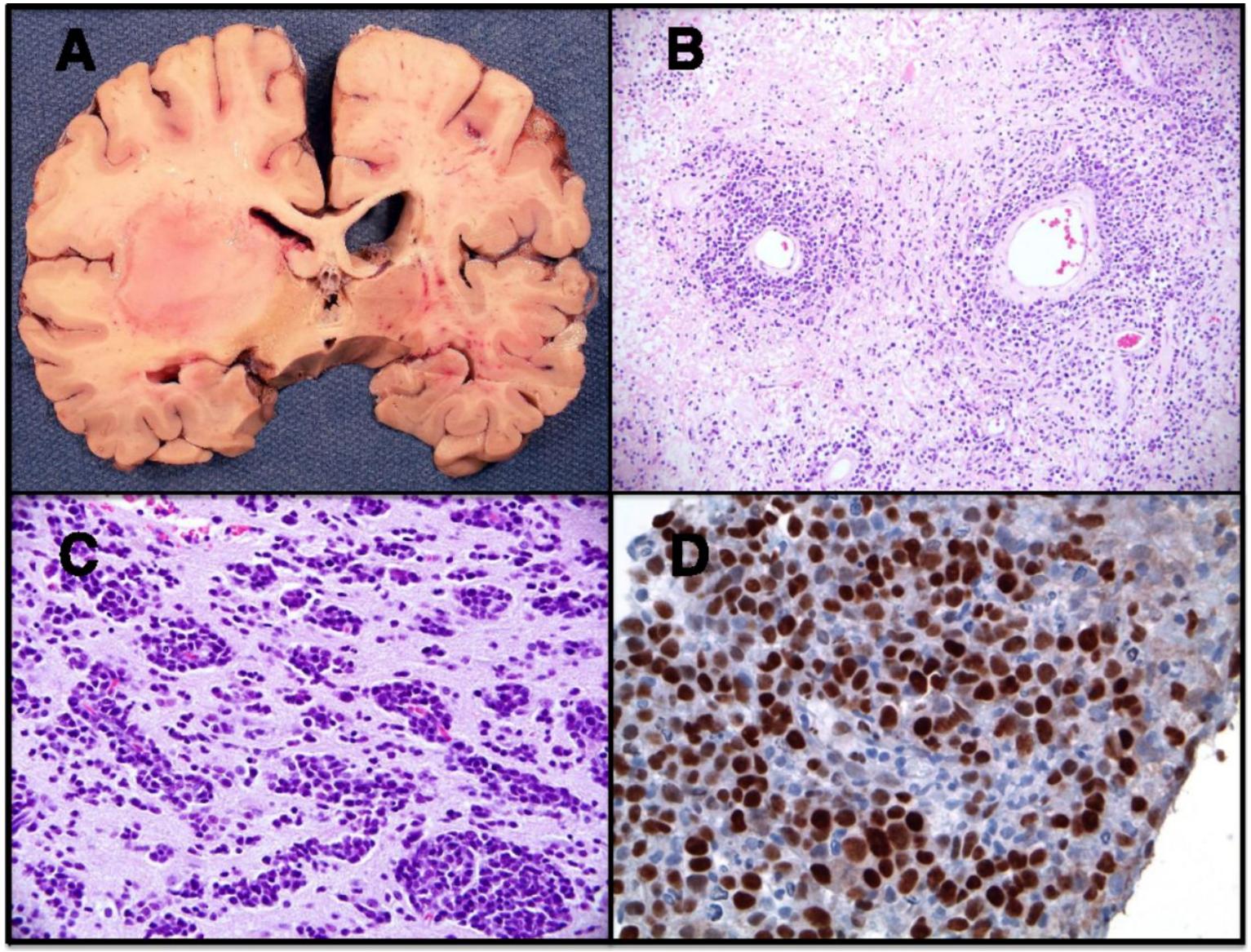
Pathologic features of PCNSL



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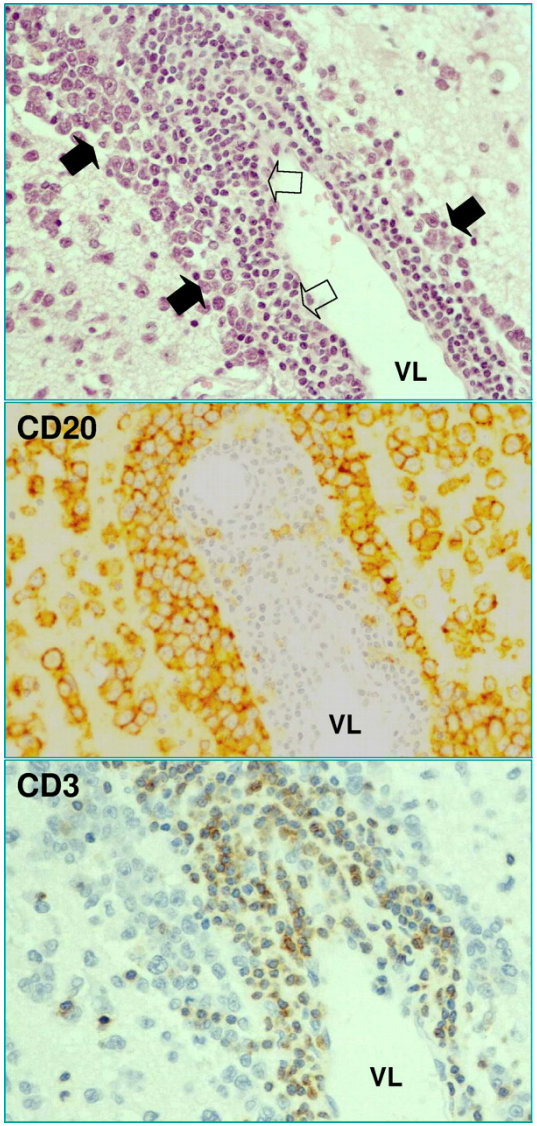
Classic histopathologic picture of PCNSL with diffuse large B-cell lymphoma morphology



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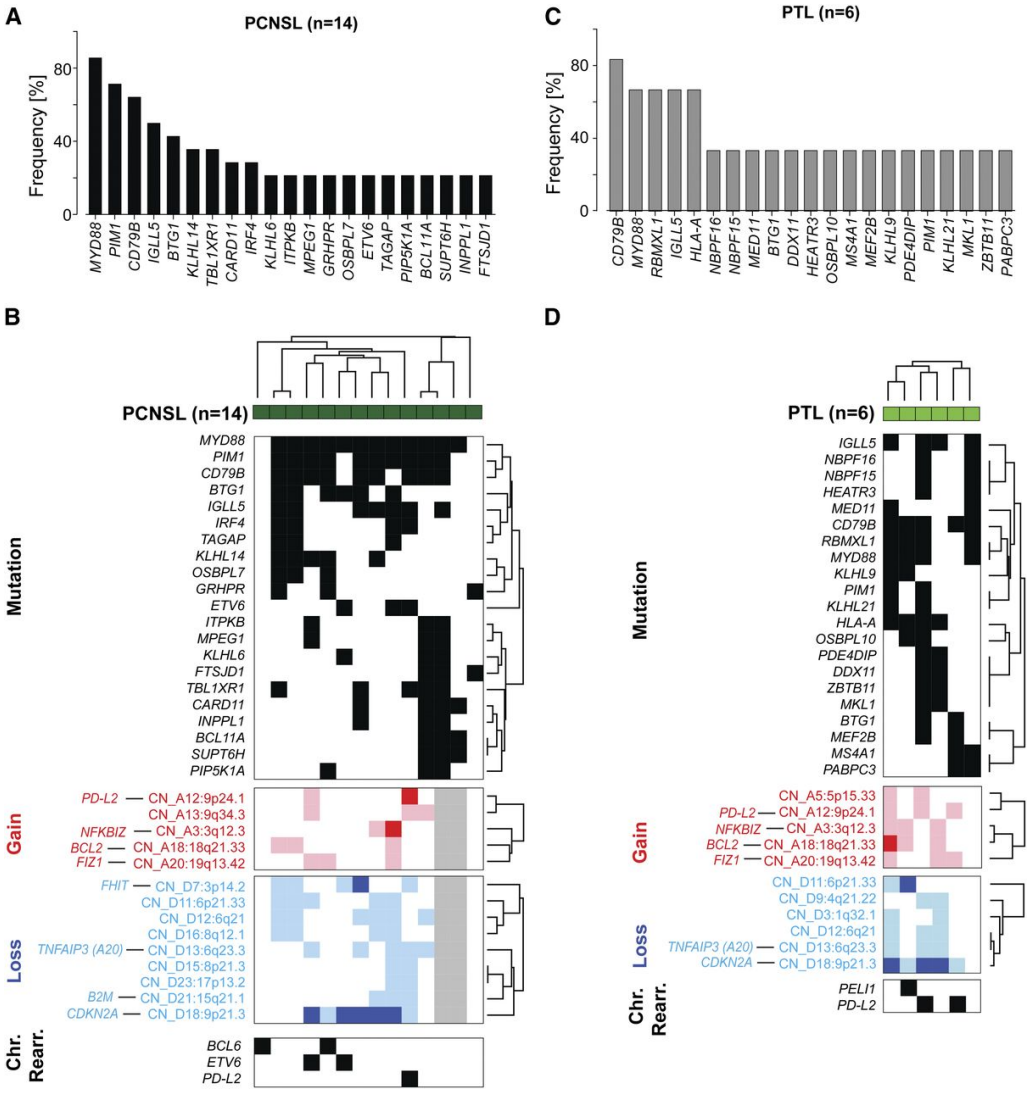
Somatic mutations and patterns of genetic alterations in PCNSL and PTL (primary testicular lymphoma)



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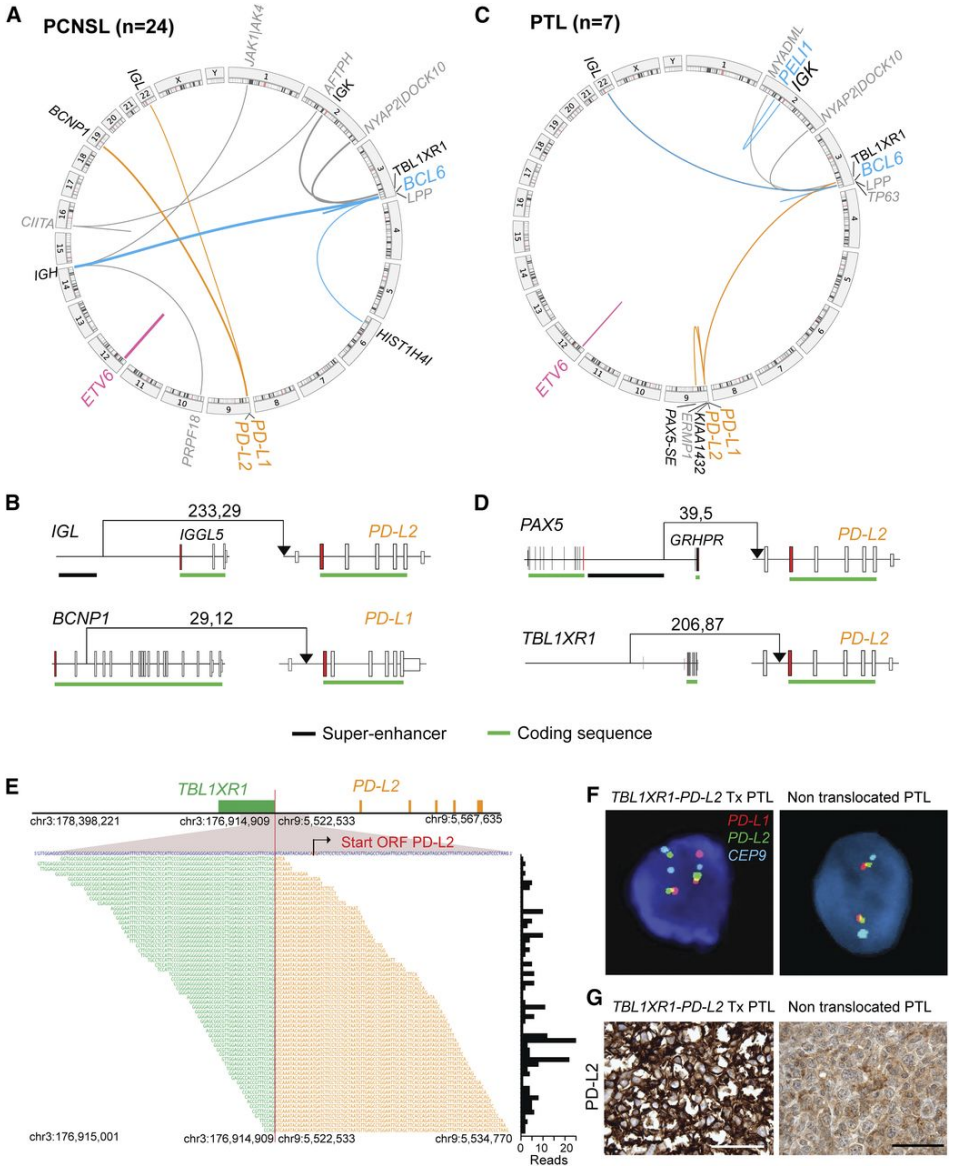
Chromosomal rearrangements in PCNSL and PTL



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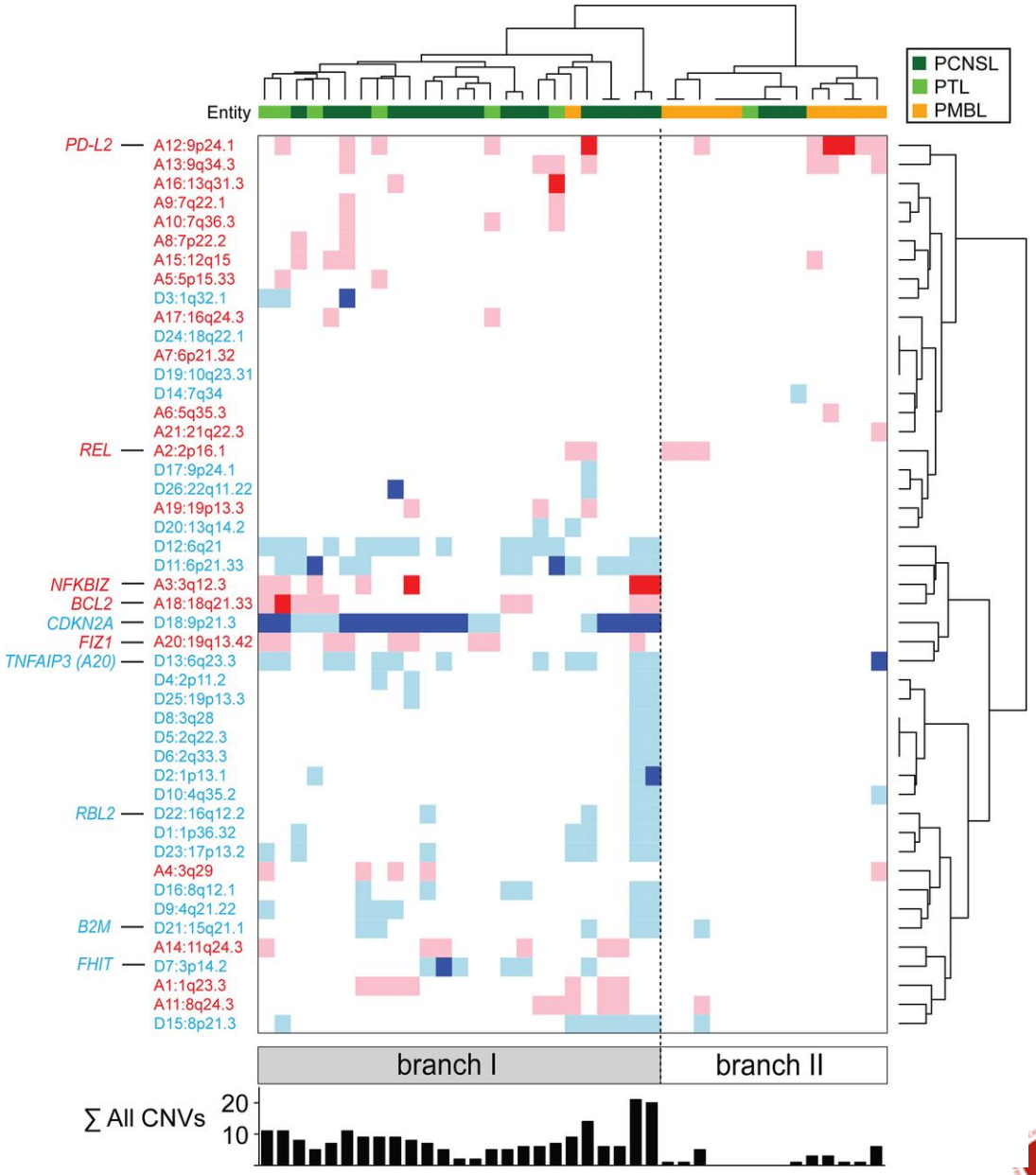
PCNSLs, PTLs, and PMBLs clustered by recurrent CNAs



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Unique combinations of structural alterations in discrete large B-cell lymphoma subtypes

	DLBCL		PTL	EBV⁻ PCNSL	PMBL
	All	ABC-type			
Genomic instability					
CDKN2A^{loss}	24% (43/180)[a]	35% (19/55)[a]	88% (44/50)[c]	71% (15/21)[k]	0% (0/11)
bi-alleic	19% (8/43)[a]	26% (5/19)[a]	77% (34/44)	73% (11/15)	0% (0/11)
CNAs of additional p53/cell cycle components	multiple[a,b]	multiple[a,b]	no	rare[d]	no
Total CNAs	high	high	high	high	low
Oncogenic TLR and BCR Signaling					
MYD88^{L265P}	12% (6/49)[e]	29% (45/155)[f]	78% (38/49)[g]	60% (33/55)[l]	NA
NFKBIZ^{gain}	9% (16/180)[a]	20% (11/55)[a]	42% (21/50)[h]	45% (28/62)[m]	0% (0/11)
NFKBIZ^{gain} and/or *MYD88*^{L265P}	NA	NA	92% (45/49)	83% (44/53)[n]	NA
CD79B^{Y196mut}					
Total	16% (8/49)[e]	23% (35/155)[f]	49% (22/45)[i]	38% (19/50)[o]	NA
Concurrent with *MYD88*^{L265P}	38% (3/8)[e]	43% (15/35)[f]	91% (20/22)	89% (17/19)	NA
PD-1 Ligand Deregulation					
9p24.1/*PD-L1*^{gain} and/or *PD-L2*^{gain}	6% (11/180)[a]	7% (4/55)[a]	54% (26/50)[h]	52% (33/63)[p]	55% (6/11)
PD-L1 or *PDL-2* translocation	NA	NA	4% (2/50)[j]	6% (4/66)[q]	20% (25/125)[r]

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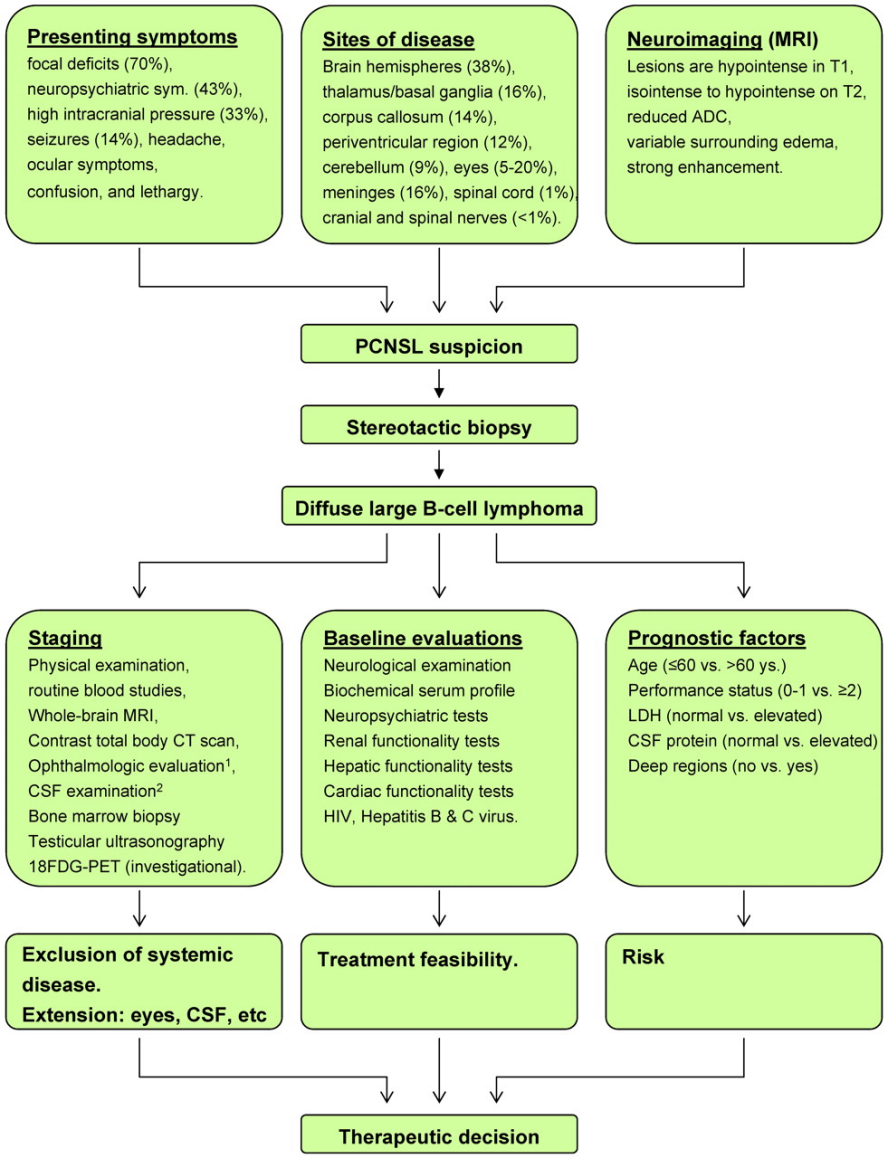
Treatment of PCNSL

- Surgical resection is usually ineffective because of the depth of the tumor
- Irradiation and corticosteroids can produce partial response
- Tumor recurs in more than 90% of patients
- Median survival is 10-18 months
- IV methotrexate (MTX) and folinic acid (leucovorin) may extend survival
- Radiation is not recommended to be used with methotrexate because of increased risk of leukoencephalopathy and dementia in older patients
- Standard CHOP therapies are ineffective in PCNSL due to poor penetration of the agents through the blood-brain barrier (BBB)
- Antimetabolites such as MTX and cytarabine (ara-C) – which cross BBB after IV administration – constitute the backbone of most anti-PCNSL regimens, with proven efficacy in prospective trials

Flow chart of management of PCNSL from presentation to therapeutic decision in ordinary clinical practice



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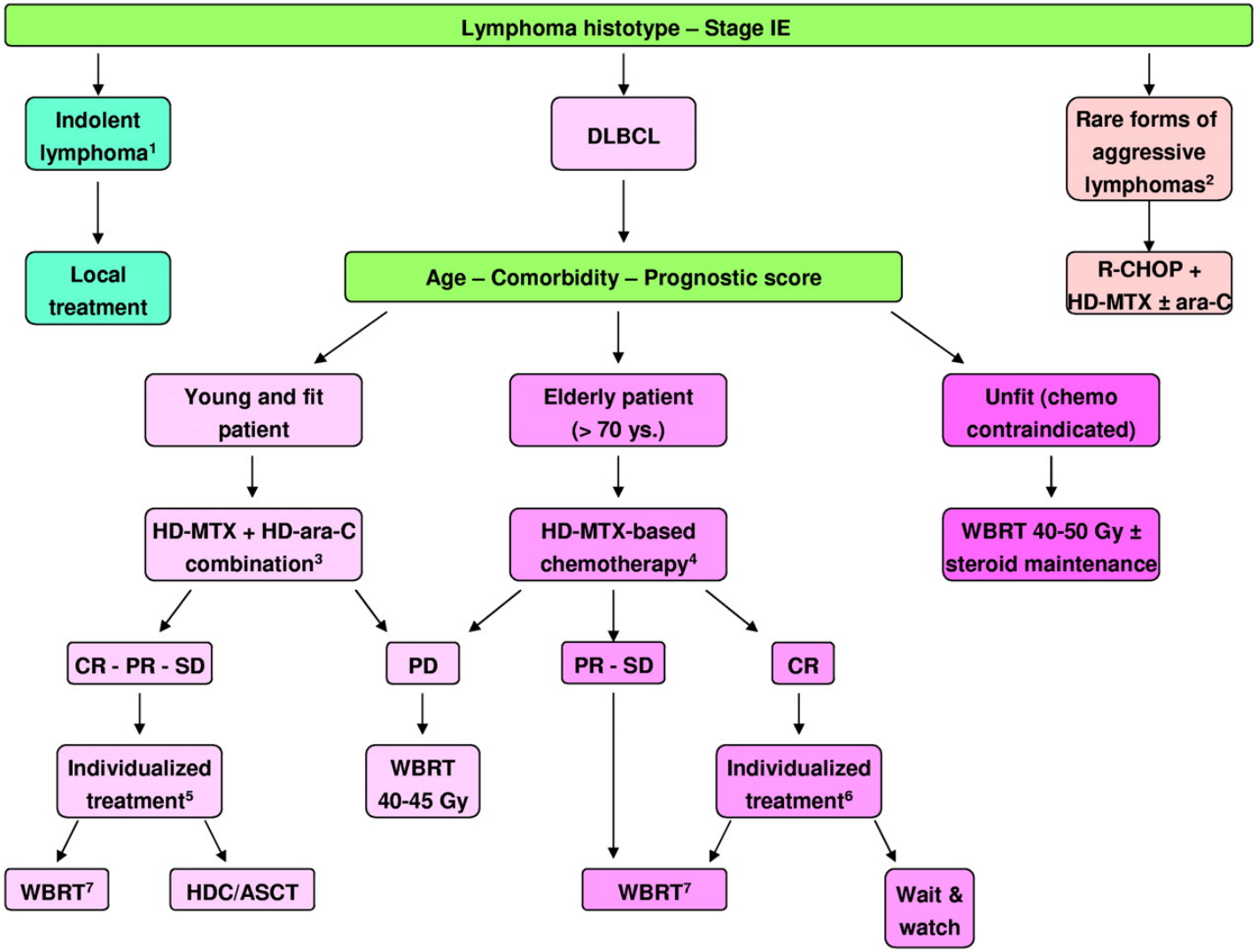
Flow chart of therapeutic management of PCNSL in everyday practice



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Salvage treatment for PCNSL

Table 4

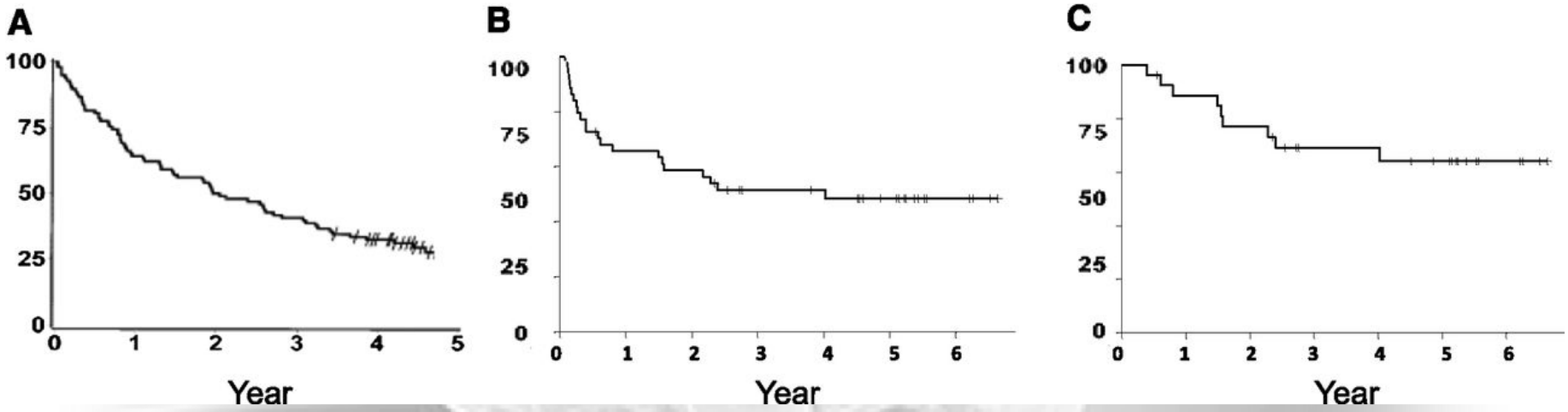
Salvage treatment for PCNSL

Treatment, Ref.	Study	No.	Median age, y	Prior RT, %	CR + PR, %	PFS	OS	1-y OS, %	Grade 3–4 neutropenia, %	Grade 3–4 thrombocytopenia, %	Other toxicities, %
VP16 + Ifosfamide + Ara-C[97]	R	16	54	100	37 + 0	4.5	6.0	41	69	50	37
i. a. Carboplatin ± VP16 ± CTX ± RT[98]	R	37	57	24	24 + 11	3.0	6.8	25	22	19	> 30
Methotrexate[85]	R	22	58	14	73 + 19	26	26	70	5	5	36
Temozolomide + rituximab[99]	R	15	69	13	40 + 13	2.2	10.5	58	7	27	7
Topotecan[45]	P	27	51	52	19 + 14	2.0	8.4	39	26	15	11
Temozolomide[42]	P	36	60	86	25 + 6	2.8	4.0	31	6	3	3
Rituximab[46]	P	9	NR	9	11 + 22	3.7	NR	NR	0	0	44*
Radiotherapy[68]	R	27	67	—	37 + 37	9.7	10.9	49	NR	NR	15†
Radiotherapy[100]	R	20	NR	—	60 + NR	NR	19.0	NR	NR	NR	58†

Progress in the treatment of PCNSL

RTOG 9310 (2002)

CALGB 50202 (2012)



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Long-term outcome in PCNSL patients treated with high-dose methotrexate and deferred radiation

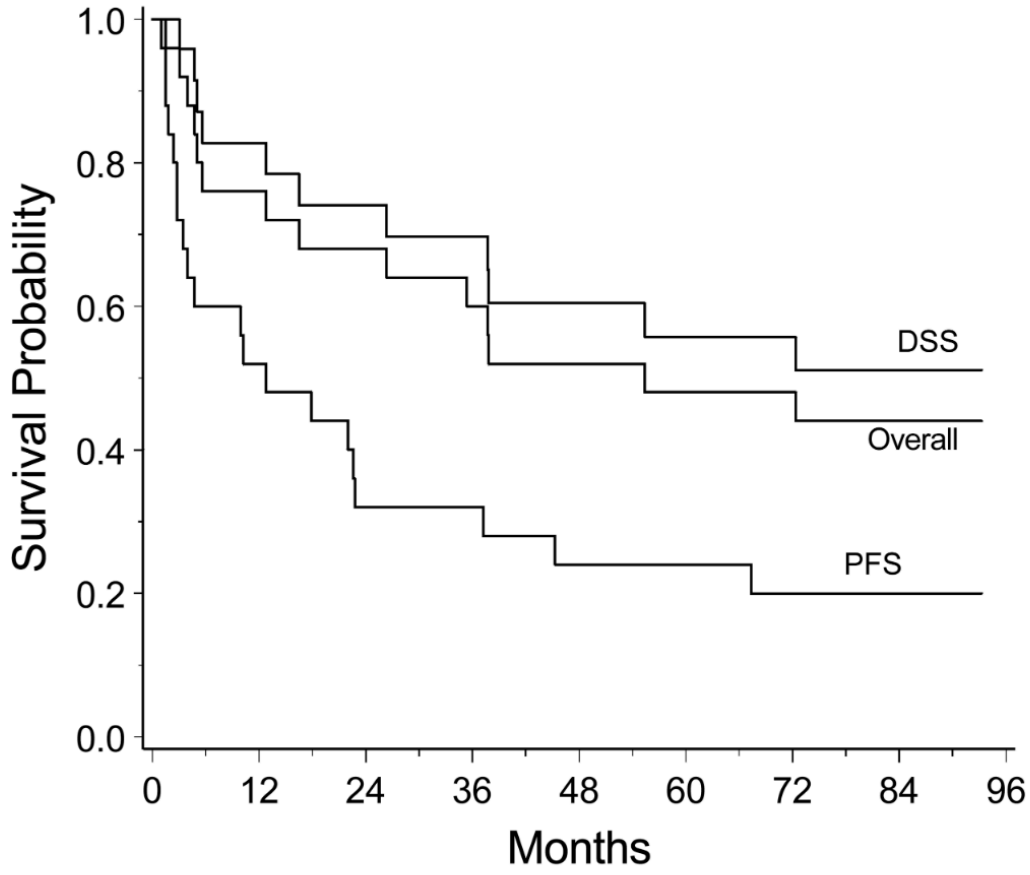

Figure 1.
Kaplan-Meier curves for overall survival (Overall), disease specific survival (DSS), and progression free survival (PFS) for the 25 patients treated with high dose methotrexate.

References

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