NEURO-ONCOLOGY

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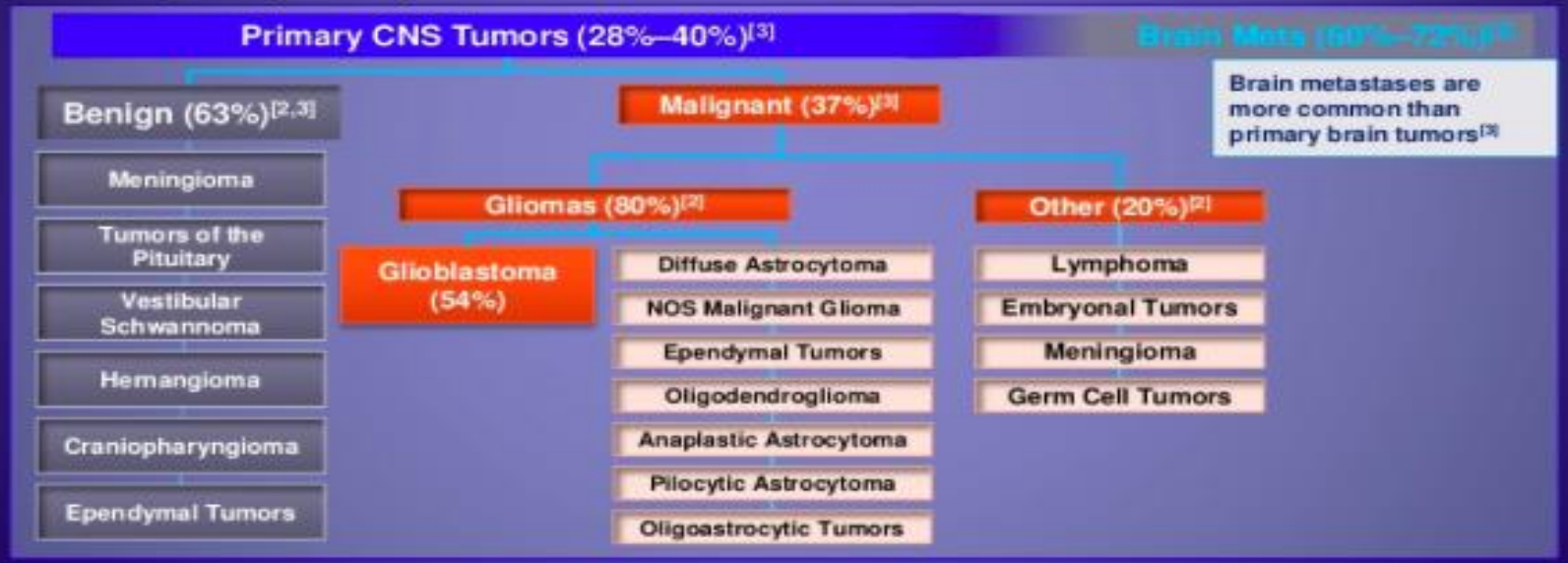
12/10/2019

PRIMARY CNS TUMORS

- Heterogeneous group of tumor
- Distributed throughout the brain/spine
- Multiple cell origin
- --Glial cells, Arachnoidal fibroblasts, nerve cells, endothelial cells, Germ cell, Pineal cell

Primary CNS Tumors

- CNS tumors arise from CNS cells and are categorized according to the cell type/tissue from which they originate[1]
- Gliomas arise from glial cells and neuronal precursors, and constitute 80% of all malignant primary brain and CNS tumors[2]

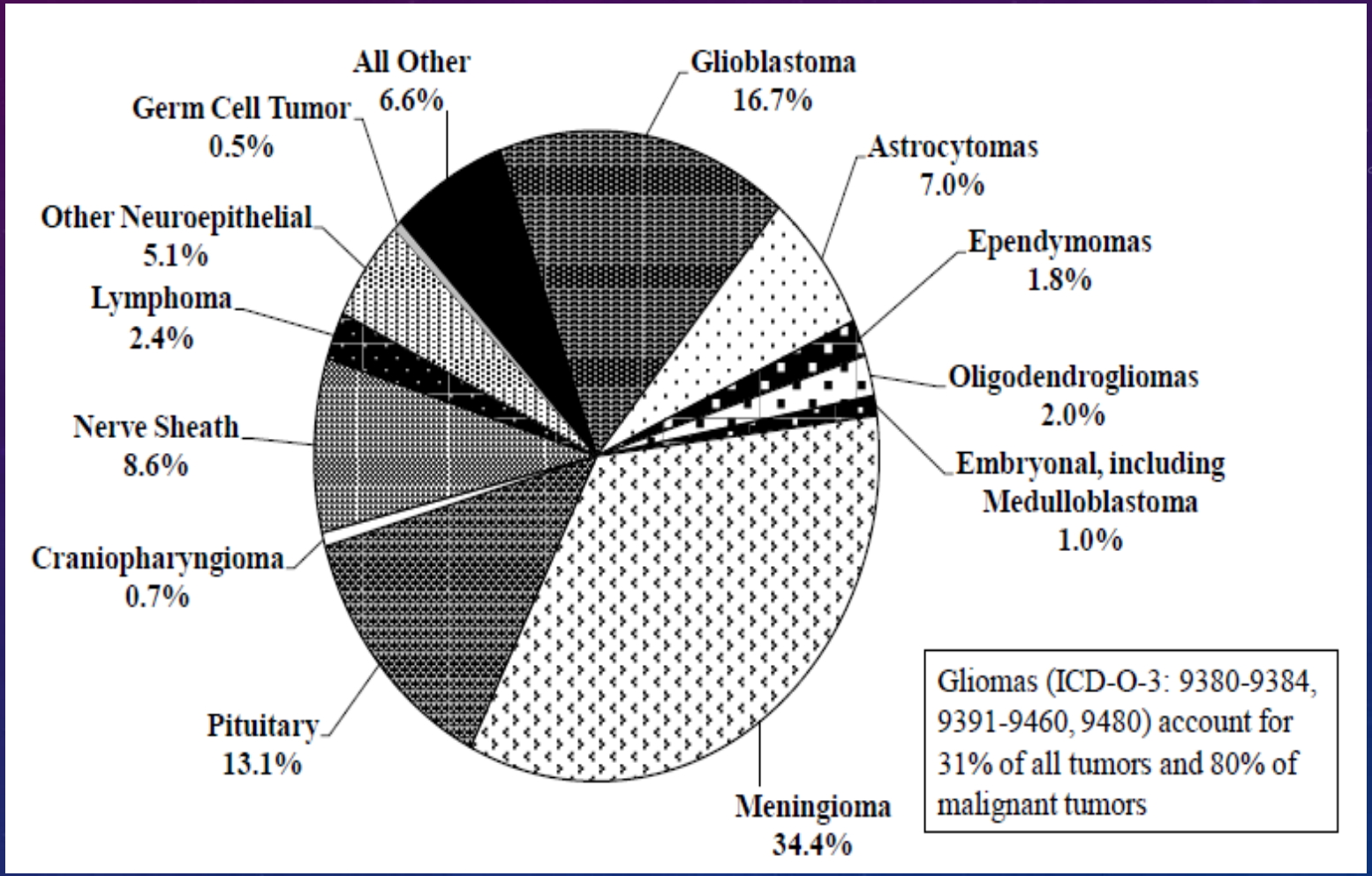


CNS, central nervous system; NOS, Not Otherwise Specificed

1. DeAngelis LM. *N Engl J Med*. 2001;344(2):114-123.
2. Ostrom QT et al. *Neuro Oncol*. 2013;15(Suppl 2):ii1-ii56.
3. Brain Tumor Information. Available at http://www.braintumor.org/brain-tumor-information/. Accessed December 17, 2015.

EPIDEMIOLOGY

CBTRUS REPORT



COMMON GLIOMAS

- Glioblastoma and high Grade Gliomas:
- -Anaplastic Gliomas
- Anaplastic Oligodendroglioma

- Low Grade Glioma
- Astrocytoma
- Oligodendroglioma

World Health Organization (WHO) Grades of CNS Tumors

- Brain tumors are typically graded according to cellular origin and aggressiveness[1]
- WHO classification combines tumor type with degree of malignancy[1-3]

			mOS (yrs)
Low-grade	Grade I[3]	• Low proliferative potential • Potentially curable with surgical resection alone	>10[4]
Low-grade	Grade II[3]	• Infiltrative properties • Tendency to recur and progress to malignancy despite low-level proliferation	>5[3]
High-grade	Grade III[3,5,6]	Includes malignant astrocytomas • Histological evidence of malignancy • Often recur as higher grade tumors	3[3]
High-grade	Grade IV[3]	Includes glioblastoma and variants* • Cytologically malignant • Rapid pre- and postoperative disease evolution	1[1]

* Gliosarcoma, giant cell glioblastoma, and small cell glioblastoma.[1]

CNS, central nervous system; mOS, median Overall Survival

1. Wen PY, Kesari S. *N Engl J Med.* 2008;359(5):492-507.
2. DeAngelis LM. *N Engl J Med.* 2001;344(2):114-123.
3. Louis DN et al. *Acta Neuropathol.* 2007;114(2):97-109.
4. Burkhard C et al. *J Neurosurg.* 2003;98(6):1170-1174.
5. NCCN Guidelines®. Central Nervous System Cancers. V1.2015.
6. Kleihues P, Ohgaki H. *Neuro Oncol.* 1999;1(1):44-51.

HISTOLOGICAL CLASSIFICATION OF TUMORS

- Based on predominant cell type
- Presence or absence of standard pathological features
- Degree of anaplasia
- Used to predict biological behavior
- Grading

HISTOLOGICAL CLASSIFICATION

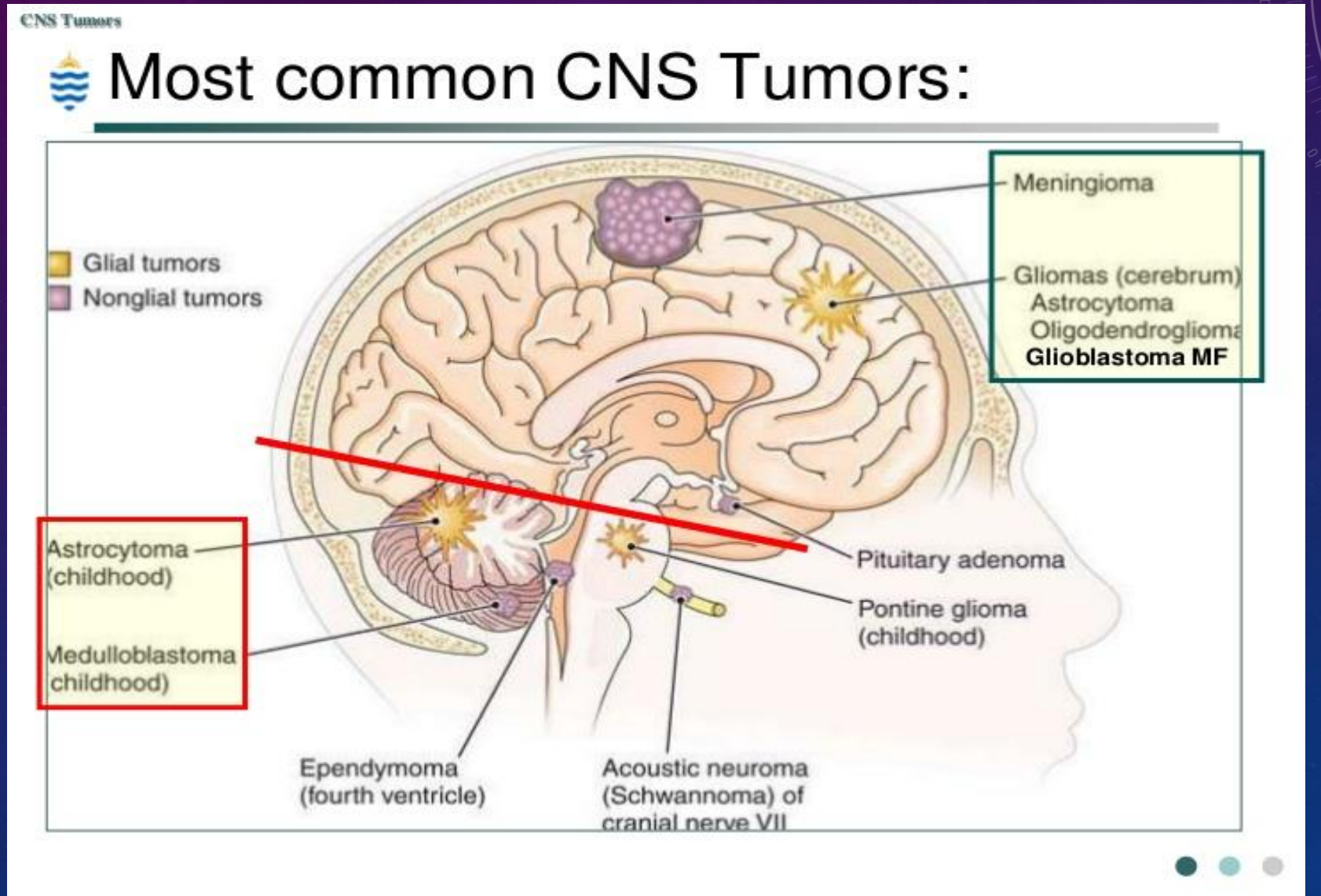
- Kernohan 1949
- Ringertz 1950
- St. Anne-Mayo 1981
- World Health Organization (WHO) 1979, 1999, 2007, 2016

WHO classification of tumours of the central nervous system

Diffuse astrocytic and oligodendroglial tumours	
Diffuse astrocytoma, IDH-mutant	9400/3
Gemistocytic astrocytoma, IDH-mutant	9411/3
Diffuse astrocytoma, IDH-wildtype	*9400/3*
Diffuse astrocytoma, NOS	9400/3
Anaplastic astrocytoma, IDH-mutant	9401/3
Anaplastic astrocytoma, IDH-wildtype	*9401/3*
Anaplastic astrocytoma, NOS	9401/3
Glioblastoma, IDH-wildtype	9440/3
Giant cell glioblastoma	9441/3
Gliosarcoma	9442/3
Epithelioid glioblastoma	*9440/3*
Glioblastoma, IDH-mutant	9445/3*
Glioblastoma, NOS	9440/3
Diffuse midline glioma, H3 K27M–mutant	9385/3*
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9450/3
Oligodendroglioma, NOS	9450/3
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9451/3
Anaplastic oligodendroglioma, NOS	*9451/3*
Oligoastrocytoma, NOS	*9382/3*
Anaplastic oligoastrocytoma, NOS	*9382/3*
Other astrocytic tumours	
Pilocytic astrocytoma	9421/1
Pilomyxoid astrocytoma	9425/3
Subependymal giant cell astrocytoma	9384/1
Pleomorphic xanthoastrocytoma	9424/3
Anaplastic pleomorphic xanthoastrocytoma	9424/3
Ependymal tumours	
Subependymoma	9383/1
Myxopapillary ependymoma	9394/1
Ependymoma	9391/3
Papillary ependymoma	9393/3
Clear cell ependymoma	9391/3
Tanycytic ependymoma	9391/3
Ependymoma, *RELA* fusion-positive	9396/3*
Anaplastic ependymoma	9392/3
Other gliomas	
Chordoid glioma of the third ventricle	9444/1
Angiocentric glioma	9431/1
Astroblastoma	9430/3
Choroid plexus tumours	
Choroid plexus papilloma	9390/0
Atypical choroid plexus papilloma	9390/1
Choroid plexus carcinoma	9390/3

Neuronal and mixed neuronal-glial tumours	
Dysembryoplastic neuroepithelial tumour	9413/0
Gangliocytoma	9492/0
Ganglioglioma	9505/1
Anaplastic ganglioglioma	9505/3
Dysplastic cerebellar gangliocytoma (Lhermitte–Duclos disease)	9493/0
Desmoplastic infantile astrocytoma and ganglioglioma	9412/1
Papillary glioneuronal tumour	9509/1
Rosette-forming glioneuronal tumour	9509/1
Diffuse leptomeningeal glioneuronal tumour	
Central neurocytoma	9506/1
Extraventricular neurocytoma	9506/1
Cerebellar liponeurocytoma	9506/1
Paraganglioma	8693/1
Tumours of the pineal region	
Pineocytoma	9361/1
Pineal parenchymal tumour of intermediate differentiation	9362/3
Pineoblastoma	9362/3
Papillary tumour of the pineal region	9395/3
Embryonal tumours	
Medulloblastomas, genetically defined	
Medulloblastoma, WNT-activated	9475/3*
Medulloblastoma, SHH-activated and *TP53*-mutant	9476/3*
Medulloblastoma, SHH-activated and *TP53*-wildtype	9471/3
Medulloblastoma, non-WNT/non-SHH	9477/3*
Medulloblastoma, group 3	
Medulloblastoma, group 4	
Medulloblastomas, histologically defined	
Medulloblastoma, classic	9470/3
Medulloblastoma, desmoplastic/nodular	9471/3
Medulloblastoma with extensive nodularity	9471/3
Medulloblastoma, large cell / anaplastic	9474/3
Medulloblastoma, NOS	9470/3
Embryonal tumour with multilayered rosettes, C19MC-altered	9478/3*
Embryonal tumour with multilayered rosettes, NOS	*9478/3*
Medulloepithelioma	9501/3
CNS neuroblastoma	9500/3
CNS ganglioneuroblastoma	9490/3
CNS embryonal tumour, NOS	9473/3
Atypical teratoid/rhabdoid tumour	9508/3
CNS embryonal tumour with rhabdoid features	*9508/3*
Tumours of the cranial and paraspinal nerves	
Schwannoma	9560/0
Cellular schwannoma	9560/0
Plexiform schwannoma	9560/0

CNS TUMOR LOCATION



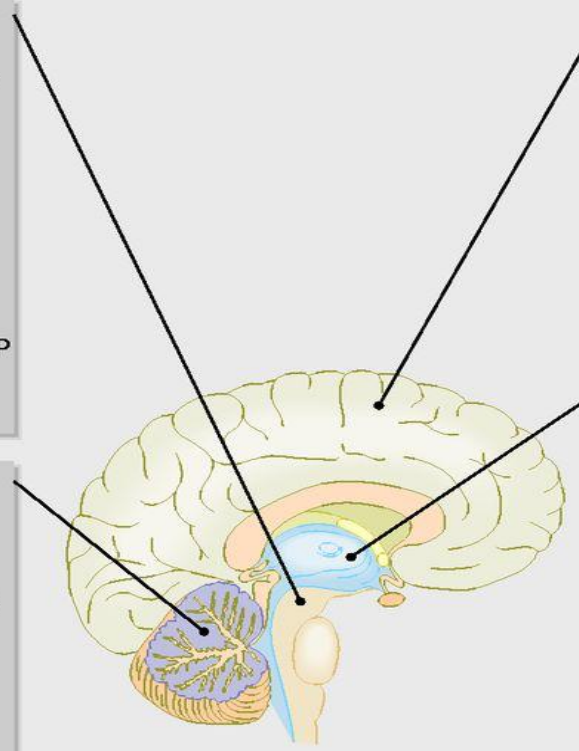
ANATOMIC LOCATION AND CLINICAL CONSIDERATION

Brain stem tumours
Occur in at least 10% of patients:
- Abnormal gait and coordination difficulties
- Cranial nerve palsies (unspecified)
- Pyramidal signs (unspecified)
- Headache*
- Squint
- Focal motor weakness
- Facial palsy
- Papilloedema*

Occur in 5-10% of patients:
- Unspecified symptoms and signs of raised ICP
- Abnormal eye movements
- Behavioural change or school difficulties

Cerebellar tumours
Occur in at least 10% of patients:
- Nausea and vomiting*
- Headache*
- Abnormal gait and coordination difficulties
- Papilloedema*
- Abnormal eye movements
- Lethargy*
- Nausea without vomiting*

Occur in 5-10% of patients:
- Unspecified symptoms and signs of raised ICP*
- Weight loss
- Focal motor weakness
- Macrocephaly*
- Impaired consciousness*
- Vertigo or auditory symptoms
- Squint
- Stiff neck
- Head tilt
- Accidental head injury



Cerebral hemisphere tumours
Occur in at least 10% of patients:
- Unspecified symptoms of raised ICP*
- Seizures
- Papilloedema*
- Focal neurological signs
- Headache*
- Hemiplegia

Occur in 5-10% of patients:
- Nausea and vomiting*
- Macrocephaly *

Central tumours
Occur in at least 10% of patients:
- Headache*
- Abnormal eye movements and squint
- Nausea and vomiting*
- Papilloedema*
- Reduced visual acuity
- Unspecified symptoms and signs of raised ICP*
- Diabetes insipidus
- Abnormal gait and coordination difficulties

Occur in 5-10% of patients:
- Optic atrophy
- Behavioural change or school difficulties
- Altered level of consciousness*
- Reduced visual fields
- Seizures
- Hemiplegia
- Focal motor deficit
- Developmental delay
- Short stature
- Weight loss
- Vertigo or auditory symptoms
- Visual or eye abnormalities (unspecified)

GENERAL SIGNS AND SYMPTOMS

- Signs and symptoms of Intracranial pressure
- - Headaches , Nausea and vomiting
- - Change in personality, mood, Mental capacity and concentration
- - Psychomotor slowing

SEIZURE

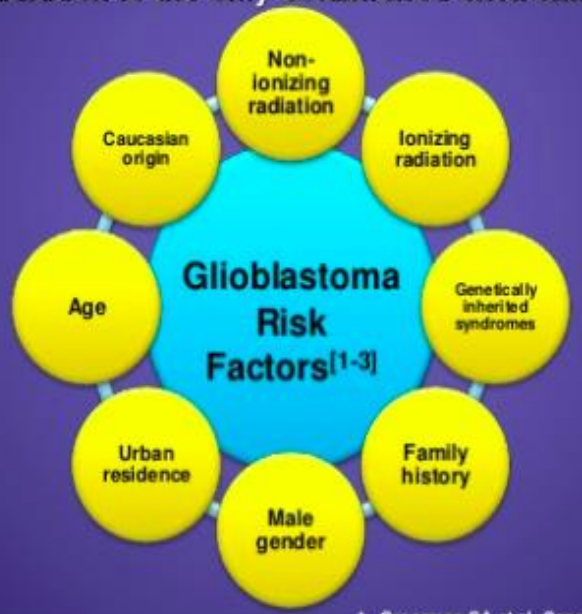
- Seizure are a presenting symptom in 20% of patient with a brain tumor
- <10% OF PATIENTS WITH A SEIZURE HAVE BRAIN TUMOR
- More Common in Low grade tumors compared to high grade

GLIOBLASTOMA MULTIFORME

- The most common malignant primary brain tumor
- Biologically aggressive
- Mean presentation 56-64 year
- Median survival 12-15 months

Risk Factors for Glioblastoma

- Etiology of brain tumors is not well understood[1]
  - Ionizing radiation is the only established environmental risk factor[1,2]



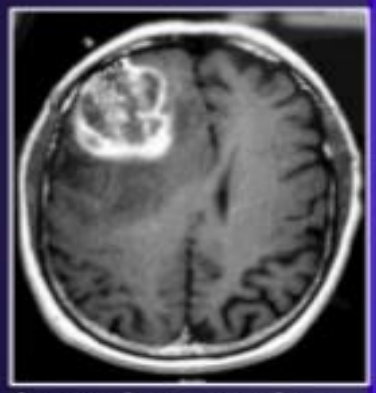
1. Grossman SA et al. *Cancer Invest.* 1999;17(5):299-306.
2. Neglia JP et al. *J Natl Cancer Inst.* 2006;98(21):1528-1537.
3. Deorah S et al. *Neurosurg Focus* 2006;20(4):E1.

CELLPHONE AND BRAIN TUMOR !

- Two NCI-sponsored case–control studies, each conducted in multiple U.S. academic medical centers or hospitals between 1994 and 1998 that used data from questionnaires or computer-assisted personal interviews . Neither study showed a relationship between cell phone use and the risk of glioma, meningioma, or acoustic neuroma.
- The CERENAT study, another case–control study conducted in multiple areas in France from 2004 to 2006 : This study found no association for either gliomas or meningiomas
- A pooled analysis of two case–control studies conducted in Sweden that reported statistically significant trends of increasing brain cancer risk for the total amount of cell phone use and the years of use among people who began using cell phones before age 20 .
- Another case–control study in Sweden, part of the Interphone pooled studies, did not find an increased risk of brain cancer among long-term cell phone users between the ages of 20 and 69 .
- The CEFALO study, an international case–control study of children diagnosed with brain cancer between ages 7 and 19, which found no relationship between their cell phone use and risk for brain cancer .

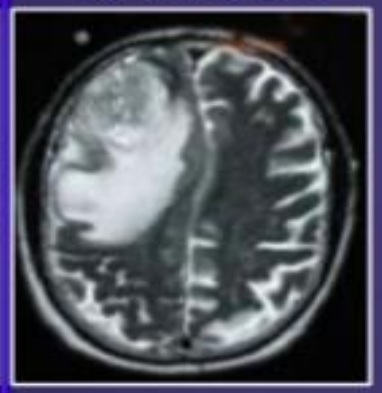
Glioblastoma Workup and Diagnosis

T1-weighted MRI*
Contrast-enhanced[1]



Irregular margins may make defining exact tumor size challenging[2]

T2-weighted/ FLAIR MRI*†
Not contrast-enhanced[1,2]

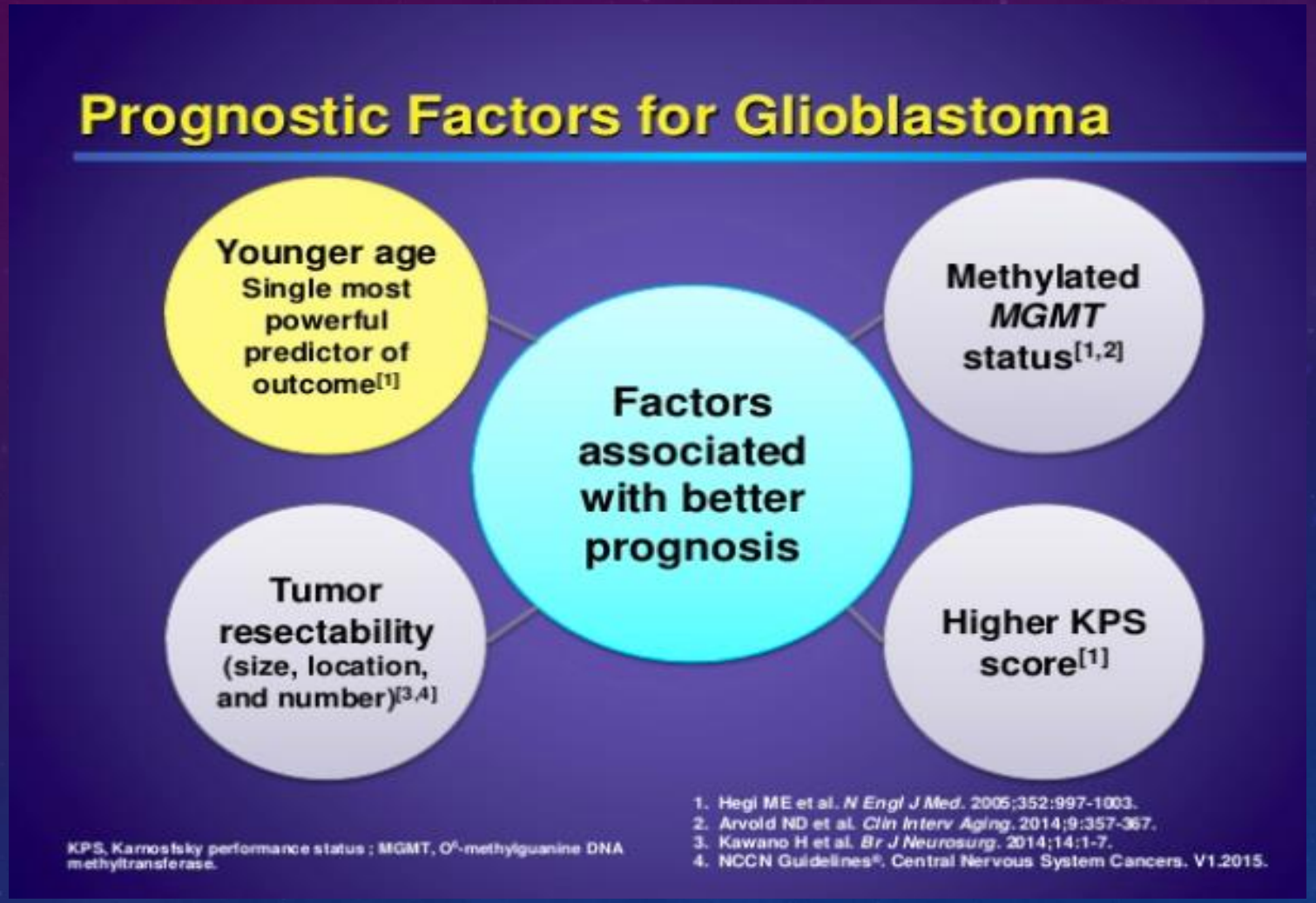


May result in improved definition of tumor volume[5]

* MRI images of same glioblastoma tumor.[1]
† Image shows T2 MRI.
BBB, blood-brain barrier; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging.

- **MRI:** Preferred imaging modality for high-grade glioma diagnosis and treatment-planning[3]
  - BBB disruption results in enhancement on contrast MRI[4]
    - Challenging to distinguish between grade III and IV glioma by MRI
- No lab studies can currently suggest or confirm diagnosis of glioblastoma[2]
  - Tissue diagnosis is mandatory[6]

1. Uddin ABMS. Medscape, Neurologic manifestations of glioblastoma multiforme workup. Available at: http://emedicine.medscape.com/article/1156220-workup#showall. Accessed December 17, 2015.
2. Bruce JN. Medscape. Glioblastoma multiforme workup. Available at http://emedicine.medscape.com/article/283252-workup#showall. Accessed December 17, 2015.
3. Omuro A, DeAngelis LM. *JAMA*. 2013;310(17):1842-1850.
4. DiStefano AL et al. *Biomed Res Int*. 2014;2014:154350.
5. Pope WB, Hessel C. *AJNR Am J Neuroradiol*. 2011;32(5)794-797.
6. Stupp R et al. *Ann Oncol*. 2014;25(Suppl 3):iii93-iii101.


Prognostic Factors for Glioblastoma
Younger age
Single most powerful predictor of outcome[1]
Methylated MGMT status[1,2]
Factors associated with better prognosis
Tumor resectability (size, location, and number)[3,4]
Higher KPS score[1]
KPS, Karnofsky performance status ; MGMT, O6-methylguanine DNA methyltransferase.
1. Hegi ME et al. N Engl J Med. 2005;352:997-1003.
2. Arvold ND et al. Clin Interv Aging. 2014;9:357-367.
3. Kawano H et al. Br J Neurosurg. 2014;14:1-7.
4. NCCN Guidelines®, Central Nervous System Cancers. V1.2015.

Prognostic Factors for Glioblastoma: Age

- Elderly* patients represent ~50% of newly diagnosed glioblastoma[1]
  - Virtually all elderly glioblastoma tumors are primary and characterized by genetic differences[1]

Survival Rates by Age Group[2]		
Age Group (yrs)	1-Year Survival, %	5-Year Survival, %
0-19	57.2	19.2
20-44	66.5	16.9
45-54	52.7	5.9
55-64	40.7	3.8
65-74	23.7	1.7
75+	9.2	0.8

- Glioblastoma incidence: increases with age[1,2]
- Glioblastoma survival rates: decrease with age[1,2]

* Definition of "elderly" varies, with most randomized trials including patients aged 60, 65, or 70 years and older.[1]

1. Arvold ND et al. *Clin Interv Aging*. 2014;9:357-367.
2. Ostrom QT. *Neuro Oncology*. 2013;15(Suppl 2):ii1-ii56.

Select Biomarkers in Glioblastoma

Biomarker	Prognostic Indication	Prognostic Association: Favorable	Prognostic Association: Poor
MGMT methylation[1]	• Methylated in 30%–60% of cases • Methylated *MGMT* increases response to chemotherapy • Unmethylated *MGMT* decreases response to chemotherapy	✓	
IDH1/2 mutations[2,3]	• More common in lower grade glial tumors • IDH1/2 mutation occurs in approximately 3.7% of primary GBMs versus 73.3% in secondary GBM	✓	
EGFR amplification[4,5]	Observed in ~50% of primary glioblastomas		✓
EGFRvIII mutation[4]	• *EGFR*-amplified cells often contain *EGFRvIII* mutation, which confers constitutive activity • 30% glioblastoma tumors express *EGFRvIII*		✓

- Potential of prognostic biomarkers in identifying specific patient populations has not yet been fully realized[6]
- ***MGMT* methylation status** is the only biomarker with predictive implications on treatment outcomes identified to date[6]

EGFR, epidermal growth factor receptor; IDH1/2, isocitrate dehydrogenase 1/2; MGMT, O^6-methylguanine DNA methyltransferase.

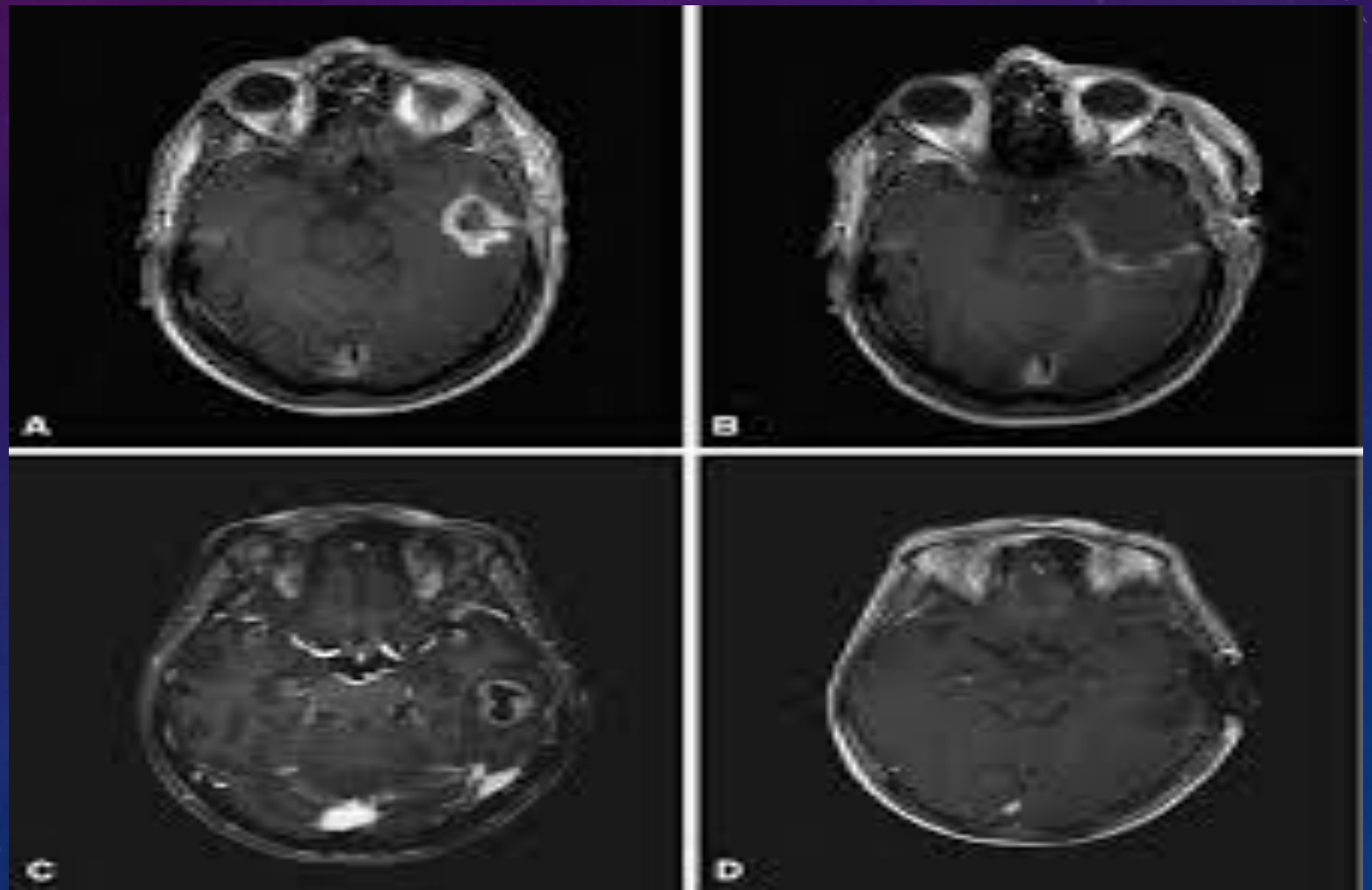
1. Preusser M et al. *Ann Neurol*. 2011;70(1):9-21.
2. Nobusawa S et al. *Clin Cancer Res*. 2009;15(19):6002-6007.
3. Yan H et al. *N Engl J Med*. 2009;360(8):765-773.
4. Johnson H et al. *Mol Cell Proteomics*. 2012;11(12):1724-1740.
5. Stupp R et al. *Ann Oncol*. 2014;25(Suppl 3):iii93-iii101.
6. McNamara MG et al. *Cancers*. 2013;5(3):1103-1119.

GOAL OF THERAPY FOR GLIOBLASTOMA

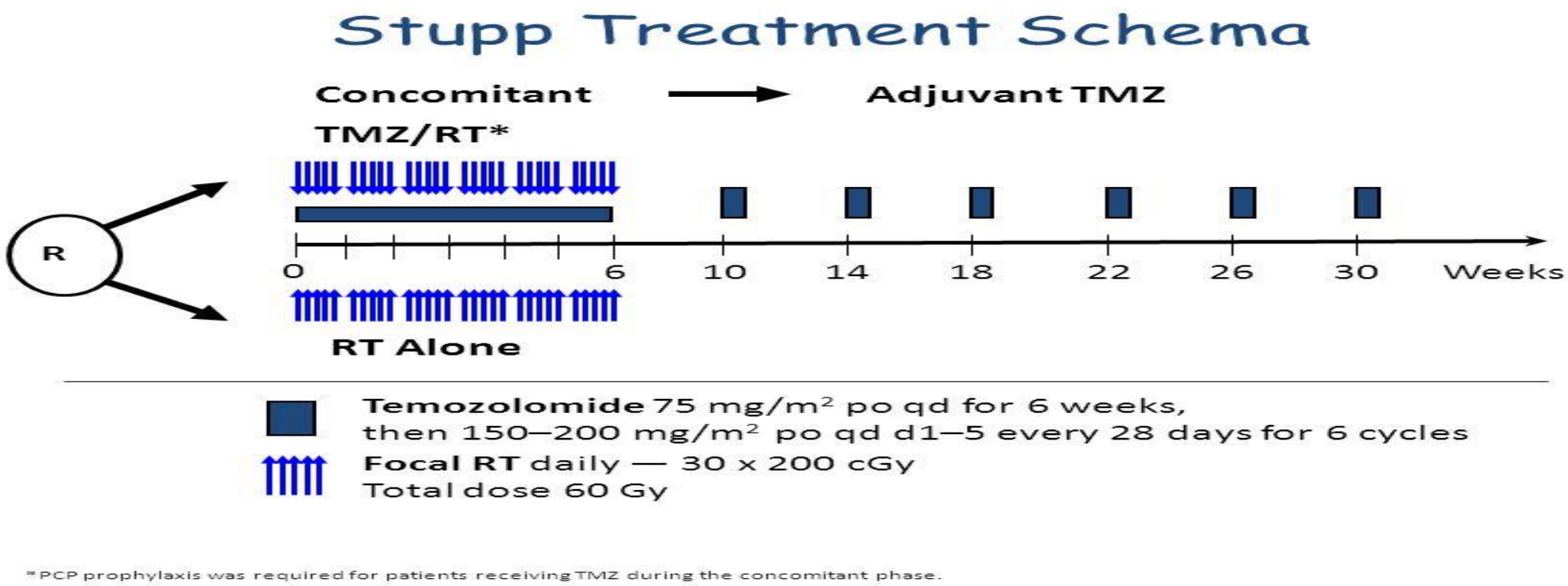
- There are no curative therapies for glioblastoma
- Glioblastoma recurrence rate is nearly 100%
- Treatment goals are focused on preserving PS/QoL and extending survival

Surgery :	Radiotherapy :	Chemotherapy:
. Pathological diagnosis **. Relieve mass effects** **. Increase survival** **. Decrease corticosteroid need**	**. Increase survival**	**. Extend survival** **. Potentially increase therapeutic effect of RT**

SURGERY GOAL :
MAXIMAL SAFE RESECTION



ADJUVANT TREATMENT



The widespread use of TMZ in glioblastoma is based on the EORTC/NCIC trial

Key Inclusion Criteria[1]

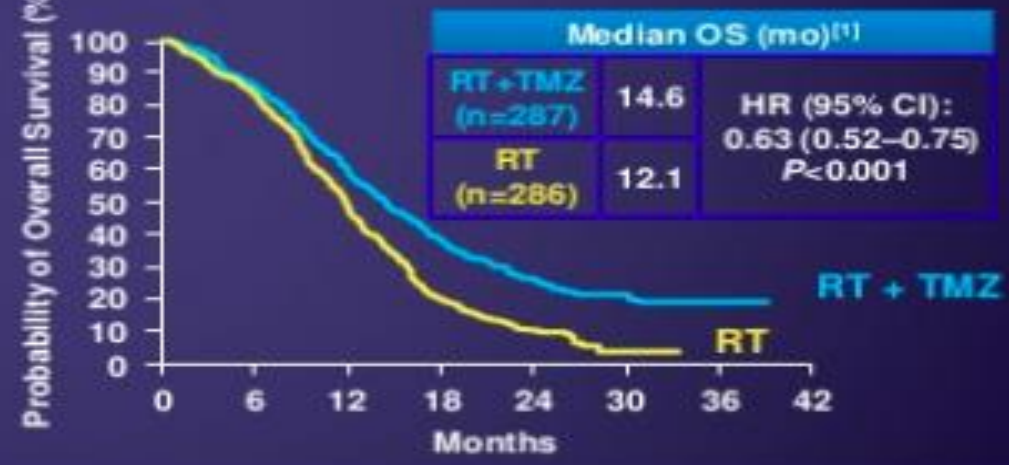
- 18–70 years old
- Newly diagnosed glioblastoma
- WHO PS≤2

N=573

R

- Daily TMZ + RT → 6 cycles TMZ
- RT alone

- ~2 month increase in mOS[1]
- 2-yr survival: 26.5% vs 10.4%[1]
- 5-yr survival: 10% vs 2%[2]



Median OS (mo)[1]		
RT+TMZ (n=287)	14.6	HR (95% CI): 0.63 (0.52–0.75) *P*<0.001
RT (n=286)	12.1	

CI, confidence interval; EORTC, European Organization for Research and Treatment of Cancer; HR, hazard ratio; mOS, median OS; NCIC, National Cancer Institute of Canada; OS, overall survival; PS, performance status; R, randomization; RT, radiotherapy; TMZ, temozolomide; WHO, World Health Organization.

1. Stupp R et al. *N Engl Med.* 2005;352(10):987-996.
2. Stupp R et al. *Lancet Oncol.* 2009;10(5):459-466.

NOVO-TTF

- Non-invasive medical device that applies tumor-treating fields (TTF) via electrodes placed on the scalp, shown to have antimitotic activity[1,2]
- Phase III trial in newly diagnosed glioblastoma was terminated at interim analysis due to early success[3]
  - Control arm pts are now crossing over to receive SOC + TTF[3]

Trial[4]	Study Arms	N	mPFS[3]	mOS[3]	2-yr Survival[3]
EF-14 NCT00916409 Phase III	SOC + TTF* vs SOC	315[3] (interim analysis)	7.1 vs 4 mo HR=0.63; *P*=0.001	19.6 vs 16.6 mo HR=0.75; *P*=0.034	43% vs 29%

* Administered as 4 insulated electrode arrays placed on scalp.[4]

1. Vymazal J, Wong ET. *Semin Oncol*. 2014;41(Suppl6):
2. Stupp R et al. *Eur J Cancer*. 2012;48(14):2192-2202.
3. PR Newswire. Novocure EF-14 PhIII. www.prnewswir
news-releases/novocure-announces-the-ef-14-phase-
trial-of-tumor-treating-fields-in-patients-with-newly-d
glioblastoma-has-been-terminated-at-the-interim-ana
to-early-success-282808841.html. Accessed Decemb

HR, hazard ratio; mOS, median overall survival; mPFS, median progression-free survival; SOC, standard of care; TTF, tumor-treating fields.

- Virtually all patients eventually relapse[1]
- There is no standard of care for relapsed patients[2]

Recurrent Disease[3,4]

- Chemotherapy
  - Temozolomide
  - Nitrosoureas
  - PCV
  - Cyclophosphamide
  - Cisplatin/Carboplatin
- Targeted therapies
  - Bevacizumab* ± chemotherapy
  - Erlotinib/Imatinib†
- Re-resection ± carmustine wafer
- Alternating electric field therapy
- Re-irradiation‡
- Clinical trials (NCCN and ESMO/EANO)

* Currently approved by FDA but not EMA. BEV + chemo considered if BEV monotherapy fails (NCCN); BEV ± irinotecan is Category 3C in ESMO.

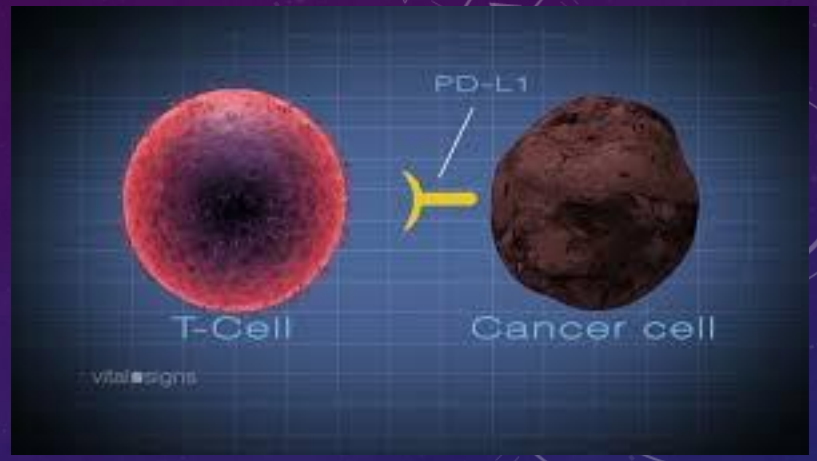
† Recommended in ESMO guidelines (Category 2C) but not in NCCN guidelines.

‡ Data are lacking on re-irradiation of recurrent glioblastomas, and its use is controversial.

BEV, Bevacizumab; EANO, European Association for Neuro-Oncology; ESMO, European Society for Medical Oncology; EMA, European Medicines Agency; FDA, Food and Drug Administration; NCCN, National Comprehensive Cancer Network; PCV, procarbazine/lomustine/vincristine.

1. Felsberg J et al. *Int J Cancer*. 2011;129(3):659-670.
2. Gil-Gil MJ et al. *Clin Med Insights Oncol*. 2013;7:123-135.
3. NCCN Guidelines. Central Nervous System Cancers. V1. 2015
4. Stupp R et al. *Ann Oncol*. 2014;25(Suppl3):iii93-iii101.

TARGETED THERAPY AND IMMUNOTHERAPY



BMS'S IMMUNOTHERAPY DRUG OPDIVO FAILS IN PHASE III BRAIN CANCER STUDY

THE DRUG WAS BEING TESTED IN COMBINATION WITH RADIATION THERAPY AMONG NEWLY DIAGNOSED PATIENTS WITH GLIOBLASTOMA, A NOTORIOUSLY DIFFICULT-TO-TREAT AND INVARIABLY FATAL DISEASE.

VACCINE THERAPY

Cell-based vaccines[1,2]:
DCs pulsed with tumor cells or TAAs, or tumor cell–derived vaccines transferred back to body to induce immune response

Peptide-based vaccine[1,2]:
Mimic TAAs or tumor-targeting peptides to induce immune response (± adjuvant)

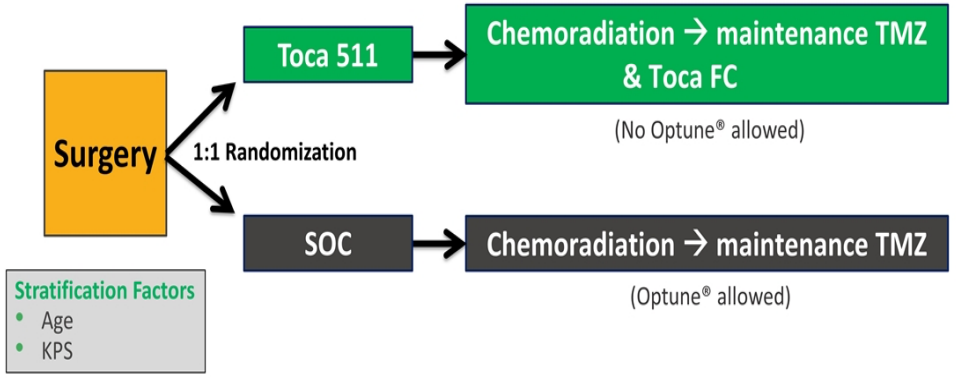
DC, dendritic cell; TAAs, tumor-associated antigens.

1. Reardon DA et al. *Expert Rev Vaccines*. 2013;12(6):597-615.
2. Hegde M et al. *Discov Med*. 2014;17(93):145-154.
3. Mohme M et al. *Cancer Treat Rev*. 2014;40(2):248-258.

NRG-BN006: Trial of Toca 511 & Toca FC in ndGBM

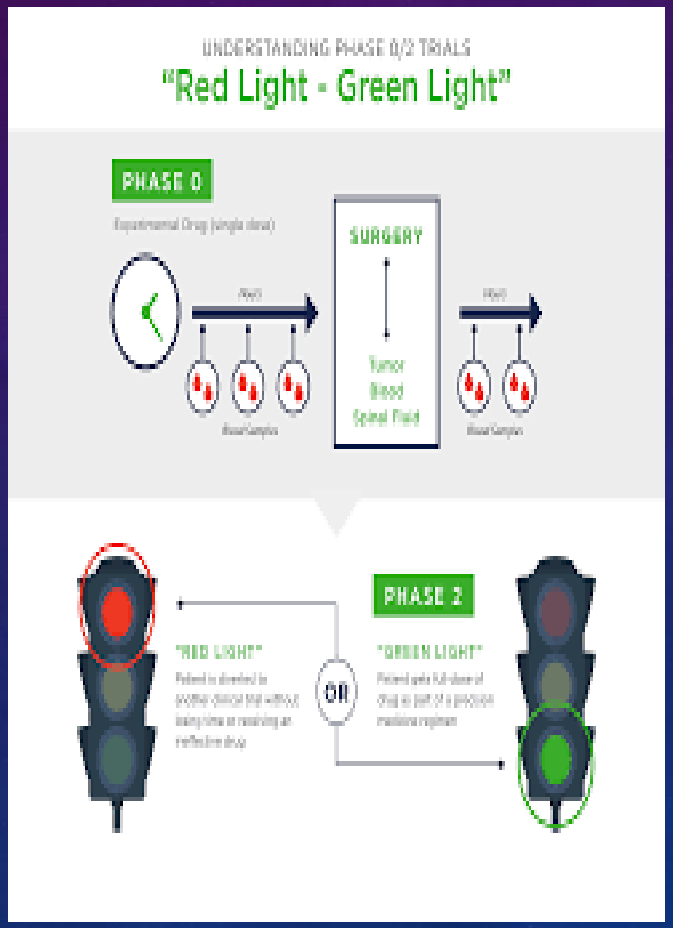
Toca 511 & Toca FC + Standard of Care vs Standard of Care Alone in Newly Diagnosed GBM (ndGBM)

NRG-BN006 was evaluated by the NCI Cancer Therapy and Evaluation Program (CTEP) Brain Malignancies Steering Committee



Tocagen

PHASE 0/2 TRIAL GLIOBLASTOMA



Ivy Brain Tumor Center

at the BARROW NEUROLOGICAL INSTITUTE

QUESTION :

- A 72-year-old man is evaluated 4 weeks after resection of a right parietal glioblastoma multiforme that was confirmed to be grade IV by analysis of a biopsy specimen. A postoperative MRI showed an area of cavitation where the previously necrotic contrast-enhancing mass lesion had been, with faint contrast enhancement at the edges consistent with postoperative changes. His exercise tolerance was excellent before the surgical resection, and he now is ambulatory with a cane and needs no assistance with activities of daily living.
- On physical examination, vital signs are normal. The patient exhibits minor inattention to the left side, a left visual field deficit, left arm and leg drift, an overall muscle strength of 4/5, a 3+ biceps reflex, and an extensor plantar response on the left.

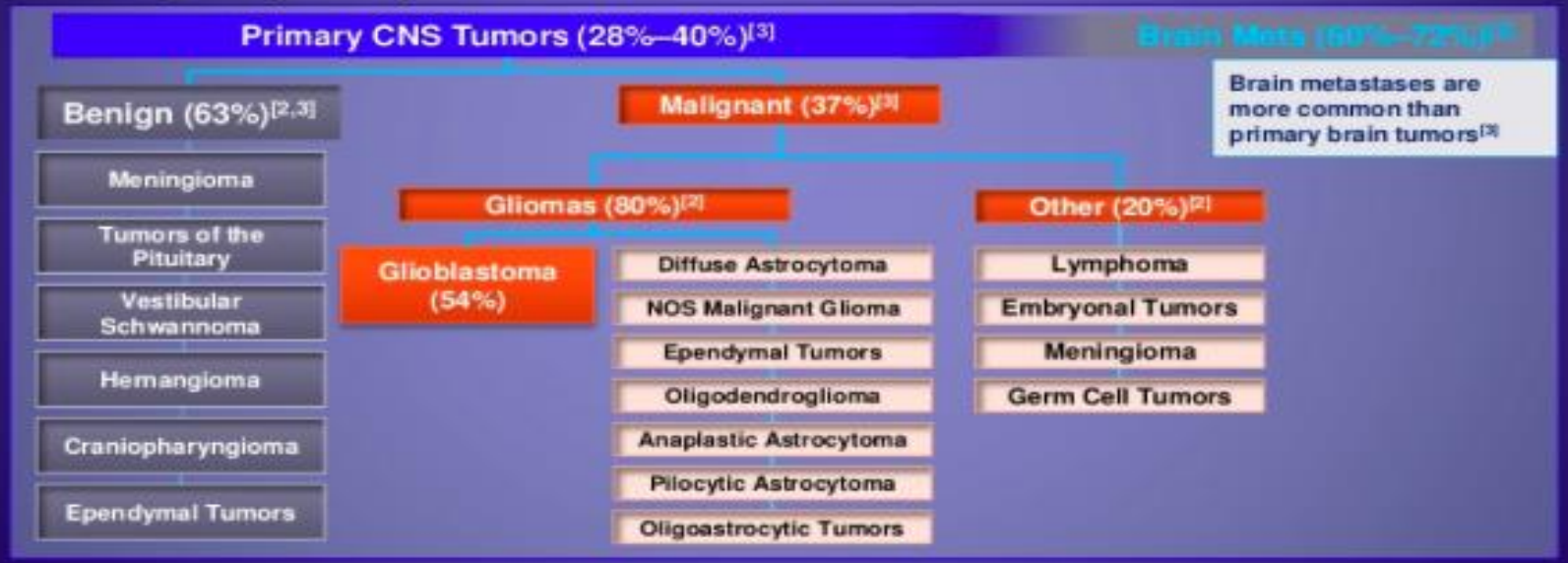
- which of the following is the most appropriate next step in treatment?

- A: Radiation Therapy
- B: Temozolomide
- C: Radiation+Temozolomide
- D: No further Treatment

- **Combined-Modality Therapy With Radiation and Chemotherapy for Elderly Patients With Glioblastoma in the Temozolomide Era: A National Cancer Database Analysis.**
- Rusthoven CG[1], Koshy M[2], Sher DJ[3], Ney DE[4], Gaspar LE[1], Jones BL[1], Karam SD[1], Amini A[1], Ormond DR[5], Youssef AS[5], Kavanagh BD[1].
- The optimal management for elderly patients with glioblastoma (GBM) is controversial. Following maximal safe resection or biopsy, accepted treatment paradigms for elderly patients with GBM include combined-modality therapy (CMT) with both radiotherapy (RT) and chemotherapy (CT), RT alone, and CT alone.
- **OBJECTIVE:** To evaluate the overall survival (OS) outcomes associated with RT, CT, and CMT for elderly patients with GBM in the modern temozolomide era.
- **RESULTS:**
- A total of 16 717 patients (median [range] age, 73 [65-≥90 y]; 8870 [53%] male) were identified. The median OS by treatment was 9.0 (95% CI, 8.8-9.3) months with CMT (8435 patients), 4.7 (95% CI, 4.5-5.0) months with RT alone (1693 patients), 4.3 (95% CI, 4.0-4.7) months with CT alone (1018 patients), and 2.8 (95% CI, 2.8-2.9) months with no therapy (5571 patients) ($P < .001$). On multivariate analysis, CMT was superior to both CT alone (hazard ratio, 1.50 [95% CI, 1.40-1.60]; $P < .001$) and RT alone (hazard ratio, 1.47 [95% CI, 1.39-1.55]; $P < .001$), whereas no differences were observed between CT alone vs RT alone ($P = .60$). Propensity score-matched analyses redemonstrated improved OS with CMT over CT alone ($P = .002$) and RT alone ($P < .001$); no differences were observed between CT alone vs RT alone ($P = .44$).

Primary CNS Tumors

- CNS tumors arise from CNS cells and are categorized according to the cell type/tissue from which they originate[1]
- Gliomas arise from glial cells and neuronal precursors, and constitute 80% of all malignant primary brain and CNS tumors[2]



CNS, central nervous system; NOS, Not Otherwise Specificed

1. DeAngelis LM. *N Engl J Med*. 2001;344(2):114-123.
2. Ostrom QT et al. *Neuro Oncol*. 2013;15(Suppl 2):ii1-ii56.
3. Brain Tumor Information. Available at http://www.braintumor.org/brain-tumor-information/. Accessed December 17, 2015.

PCNSL

- Relatively rare tumor
- extranodal non-Hodgkin lymphoma (NHL) confined to the brain, leptomeninges, eyes, or spinal cord
- 1-2% of primary CNS tumors
- median age of 65 years at diagnosis
- increasing frequency in immunocompetent patients.

EPIDEMIOLOGY

- Central Brain Tumor Registry of the United States (CBTRUS)
- Brain Lymphoma
  - 2.7% of all primary CNS tumors
  - 0.43/100000 person per year
  - 1000-1500 cases per year
  - Peak incidence in 75-84 years old

EOIDEMIOLOGY

- Incidence in AIDS patients 1.9 to 6%
  - Peak incidence 3rd decade
  - Decreased after HART therapy

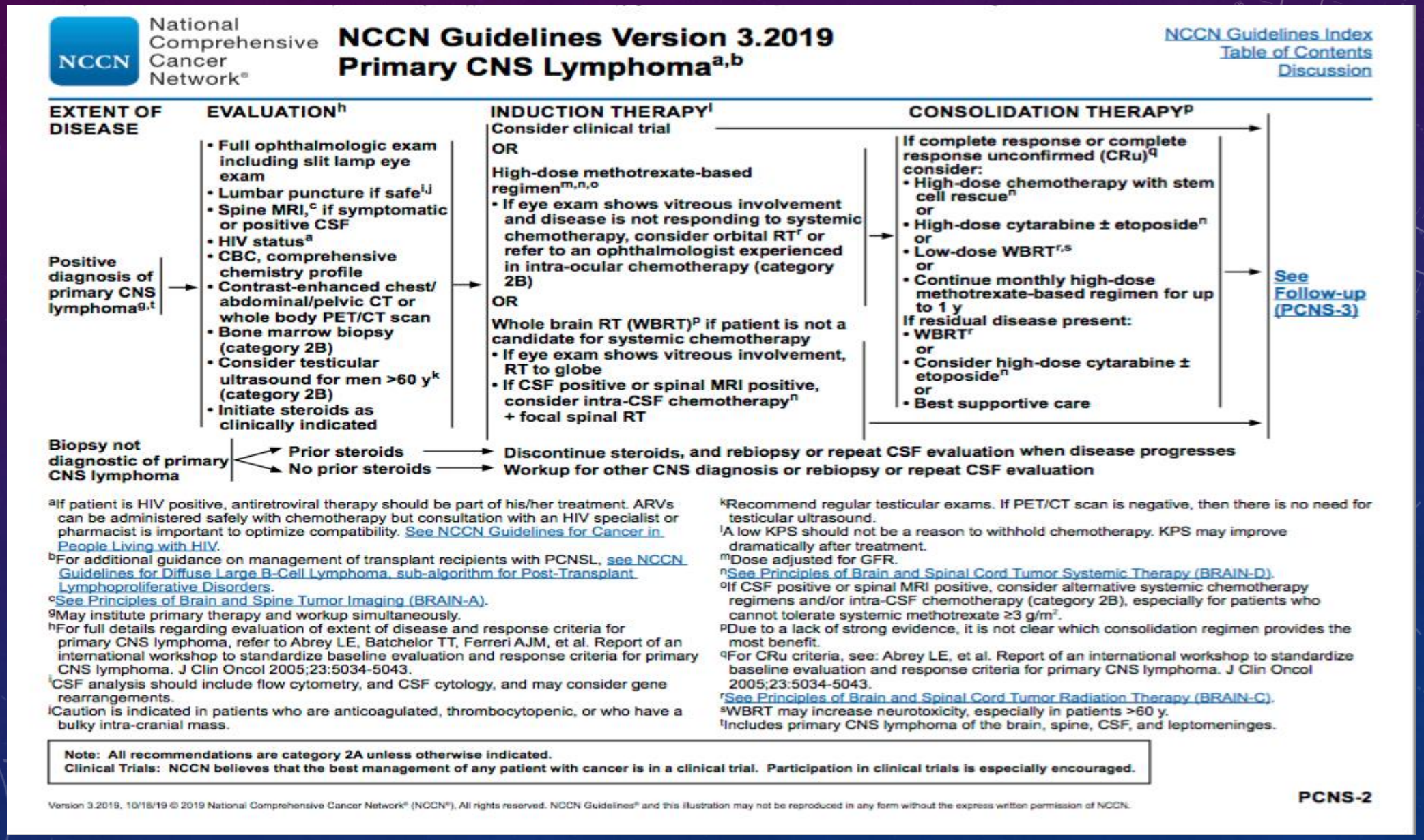
PATHOLOGY

- DLBCL is the most common (90%) Mostly activated B cell–like (ABC) subtype.
- MIB-1 50-90%
- CD 20 positive, chromosomal translocations of the *BCL6* gene, deletions 6q, hypermutation in proto-oncogenes including *MYC* and *PAX5*.
- Low grade Lymphoma, Burkitt, T-cell Lymphoma (10%)
- Although the incidence of EBV is high in immunocompromised Pts, virtually all tumor specimens from immunocompetent hosts are EBV-negative

SYMPTOMS

- Primary symptoms may result from local mass effect, Increased ICP , from ocular involvement, or from focal deposits on cranial or spinal nerve roots.
- Neurocognitive symptoms are the most common presenting clinical features of PCNSL
- B symptoms such as weight loss, fevers, and night sweats are infrequent in PCNSL.

PCNSL WORK UP



National Comprehensive Cancer Network

NCCN Guidelines Version 3.2019
Primary CNS Lymphoma[a,b]

NCCN Guidelines Index
Table of Contents
Discussion

EXTENT OF DISEASE

Positive diagnosis of primary CNS lymphoma[g,t]

EVALUATION[h]

- Full ophthalmologic exam including slit lamp eye exam
- Lumbar puncture if safe[i,j]
- Spine MRI,[c] if symptomatic or positive CSF
- HIV status[a]
- CBC, comprehensive chemistry profile
- Contrast-enhanced chest/abdominal/pelvic CT or whole body PET/CT scan
- Bone marrow biopsy (category 2B)
- Consider testicular ultrasound for men >60 y[k] (category 2B)
- Initiate steroids as clinically indicated

INDUCTION THERAPY[l]

Consider clinical trial

OR

High-dose methotrexate-based regimen[m,n,o]

- If eye exam shows vitreous involvement and disease is not responding to systemic chemotherapy, consider orbital RT[r] or refer to an ophthalmologist experienced in intra-ocular chemotherapy (category 2B)

OR

Whole brain RT (WBRT)[p] if patient is not a candidate for systemic chemotherapy

- If eye exam shows vitreous involvement, RT to globe
- If CSF positive or spinal MRI positive, consider intra-CSF chemotherapy[n] + focal spinal RT

CONSOLIDATION THERAPY[p]

If complete response or complete response unconfirmed (CRu)[q] consider:

- High-dose chemotherapy with stem cell rescue[n]

or

- High-dose cytarabine ± etoposide[n]

or

- Low-dose WBRT[r,s]

or

- Continue monthly high-dose methotrexate-based regimen for up to 1 y

If residual disease present:

- WBRT[r]

or

- Consider high-dose cytarabine ± etoposide[n]

or

- Best supportive care

See Follow-up (PCNS-3)

Biopsy not diagnostic of primary CNS lymphoma

- Prior steroids → Discontinue steroids, and rebiopsy or repeat CSF evaluation when disease progresses
- No prior steroids → Workup for other CNS diagnosis or rebiopsy or repeat CSF evaluation

[a] If patient is HIV positive, antiretroviral therapy should be part of his/her treatment. ARVs can be administered safely with chemotherapy but consultation with an HIV specialist or pharmacist is important to optimize compatibility. See NCCN Guidelines for Cancer in People Living with HIV.

[b] For additional guidance on management of transplant recipients with PCNSL, see NCCN Guidelines for Diffuse Large B-Cell Lymphoma, sub-algorithm for Post-Transplant Lymphoproliferative Disorders.

[c] See Principles of Brain and Spine Tumor Imaging (BRAIN-A).

[g] May institute primary therapy and workup simultaneously.

[h] For full details regarding evaluation of extent of disease and response criteria for primary CNS lymphoma, refer to Abrey LE, Batchelor TT, Ferreri AJM, et al. Report of an international workshop to standardize baseline evaluation and response criteria for primary CNS lymphoma. J Clin Oncol 2005;23:5034-5043.

[i] CSF analysis should include flow cytometry, and CSF cytology, and may consider gene rearrangements.

[j] Caution is indicated in patients who are anticoagulated, thrombocytopenic, or who have a bulky intra-cranial mass.

[k] Recommend regular testicular exams. If PET/CT scan is negative, then there is no need for testicular ultrasound.

[l] A low KPS should not be a reason to withhold chemotherapy. KPS may improve dramatically after treatment.

[m] Dose adjusted for GFR.

[n] See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).

[o] If CSF positive or spinal MRI positive, consider alternative systemic chemotherapy regimens and/or intra-CSF chemotherapy (category 2B), especially for patients who cannot tolerate systemic methotrexate ≥3 g/m^2.

[p] Due to a lack of strong evidence, it is not clear which consolidation regimen provides the most benefit.

[q] For CRu criteria, see: Abrey LE, et al. Report of an international workshop to standardize baseline evaluation and response criteria for primary CNS lymphoma. J Clin Oncol 2005;23:5034-5043.

[r] See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).

[s] WBRT may increase neurotoxicity, especially in patients >60 y.

[t] Includes primary CNS lymphoma of the brain, spine, CSF, and leptomeninges.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

CSF ANALYSIS

- Secondary CSF in ~15% to 20% (Cytopathology, Flow cytometry, Protein markers, PCR of rearranged immunoglobulin genes, microRNA)

---Evaluation of the CSF may reveal the presence of malignant lymphoid cells in up to 40 percent of patients with PCNSL

---elevated protein concentration and a lymphocytic predominant pleocytosis Glucose concentration is usually normal, but may be lowered in the presence of leptomeningeal disease

- ocular involvement in 5% to 20% of PCNSL

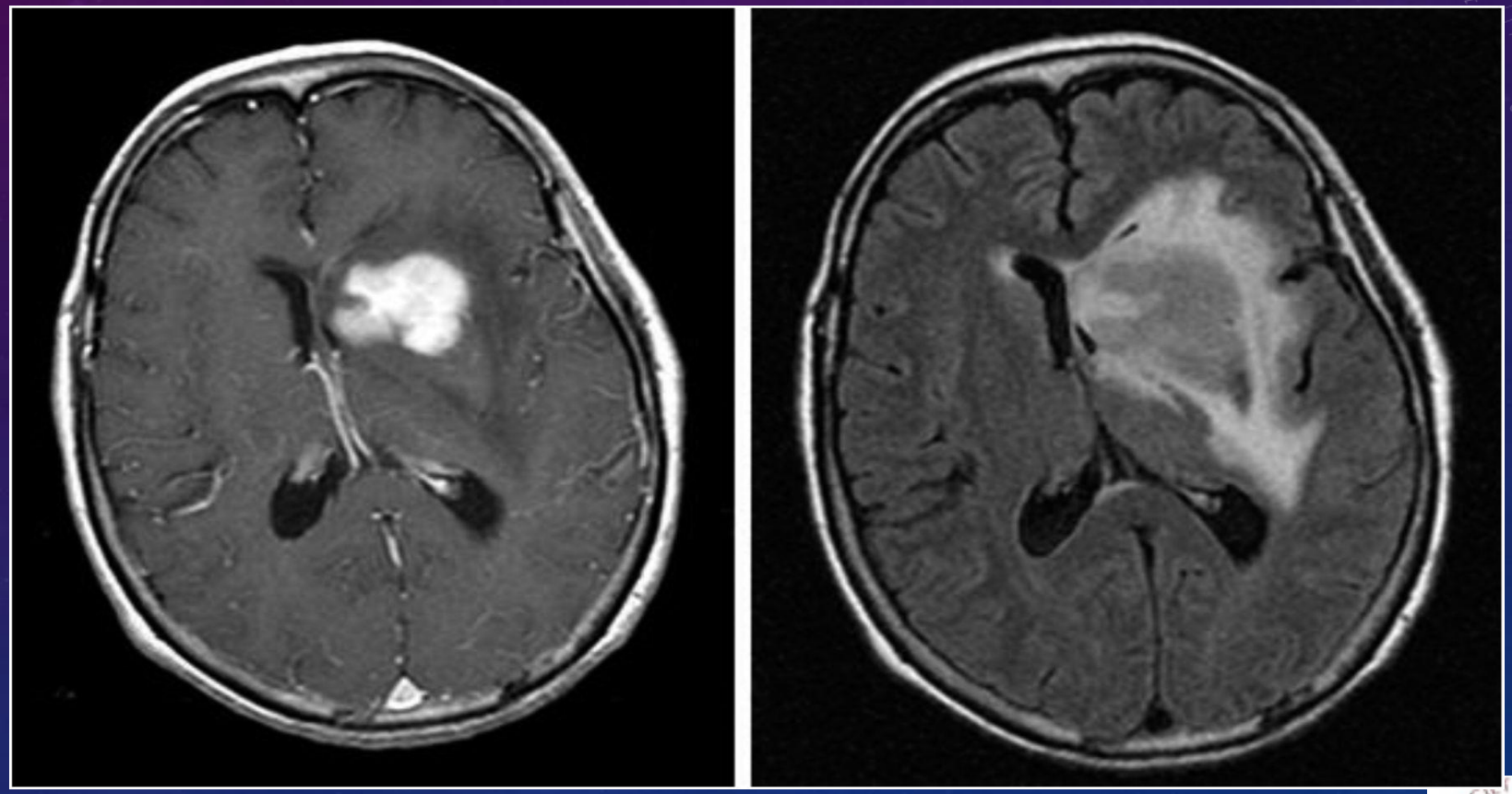
(eye pain, blurred vision, and floaters)

---Slit lamp examination

MRI

- gadolinium-enhanced brain (MRI) scan is the most sensitive radiographic study for the detection of PCNSL
- hypointense lesion, homogeneously with contrast administration
- Lesions are multifocal in 50% of patients with AIDS, whereas only 25% of immunocompetent patients have multifocal disease at presentation

Magnetic resonance images from a patient with PCNSL. A T1-weighted, axial, postcontrast scan (left) demonstrates intense, homogenous enhancement of the tumor in the region of the left caudate nucleus. An axial T2/FLAIR scan at the same anatomical level (right) demonstrates hyperintense signal surrounding the tumor, reflecting vasogenic cerebral edema. (Courtesy Priscilla K. Brastianos, M.D.)



Tracy T. Batchelor Hematology 2016;2016:379-385

MANAGEMENT

- Surgery >>>>Surgical resection has No role , Biopsy only for tissue diagnosis !
- Radiation
  - WBRT
    - WBRT alone OS 11-18 Mo
    - Consolidation in newly dx
      - RTOG 0227: MTR +WBRT 2years OS 81%, 2 year PFS 64%

TREATMENT CHEMOTHERAPY

- The most effective treatment of PCNSL at this time is IV, high-dose methotrexate (HD-MTX) (3-8 g/m^2), typically used in combination with other chemotherapeutic agents and/or WBRT
- Doses of methotrexate ≥3 g/m^2 result in therapeutic concentrations in the brain parenchyma and CSF (DeAngelis LM, Radiation Therapy Oncology Group Study 93-10. Combination chemotherapy and radiotherapy for primary central nervous system lymphoma: Radiation Therapy Oncology Group Study 93-10. J Clin Oncol. 2002)

RITUXIMAB

- Rituximab, a chimeric monoclonal antibody targeting the CD20 antigen, is being incorporated into induction chemotherapy regimens for PCNSL.
- When rituximab is administered IV at doses of 375-800 mg/m^2, has CSF penetration,
- Radiographic responses have been observed in relapsed PCNSL patients treated with rituximab monotherapy.(Batchelor 2014)
- The complete radiographic response rates are higher with induction regimens that include rituximab vs those in which there is no rituximab (Holdhoff , 2014)

High-dose methotrexate with or without rituximab in newly diagnosed primary CNS lymphoma

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ABSTRACT

Objective: To evaluate the efficacy of rituximab (R) when added to high-dose methotrexate (HD-MTX) in patients with newly diagnosed immunocompetent primary CNS lymphomas (PCNSLs).

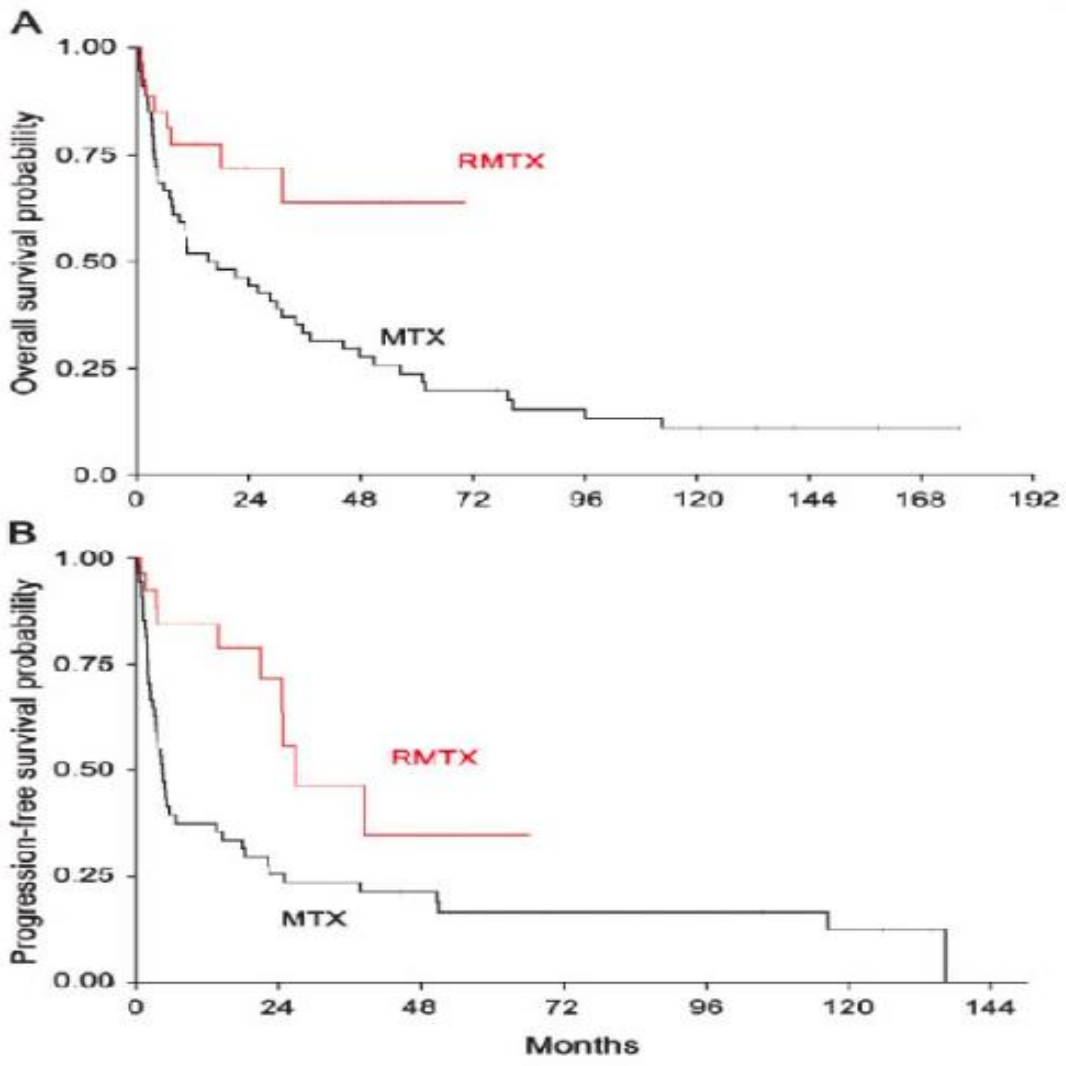
Methods: Immunocompetent adults with newly diagnosed PCNSL treated at The Johns Hopkins Hospital between 1995 and 2012 were investigated. From 1995 to 2008, patients received HD-MTX monotherapy (8 g/m² initially every 2 weeks and after complete response [CR] monthly to complete 12 months of therapy). From 2008 to 2012, patients received the same HD-MTX with rituximab (375 mg/m²) with each HD-MTX treatment. CR rates and median overall and progression-free survival were analyzed for each patient cohort in this single-institution, retrospective study.

Results: A total of 81 patients were identified: 54 received HD-MTX (median age 66 years) while 27 received HD-MTX/R (median age 65 years). CR rates were 36% in the HD-MTX cohort and 73% in the HD-MTX/R cohort ($p = 0.0145$). Median progression-free survival was 4.5 months in the HD-MTX cohort and 26.7 months in the HD-MTX/R cohort ($p = 0.003$). Median overall survival was 16.3 months in the HD-MTX cohort and has not yet been reached in the HD-MTX/R cohort ($p = 0.01$).

Conclusions: The addition of rituximab to HD-MTX appears to improve CR rates as well as overall and progression-free survival in patients with newly diagnosed PCNSL. Comparisons of long-term survival in the 2 cohorts await further maturation of the data.

Classification of evidence: This study provides Class III evidence that in immunocompetent patients with PCNSL, HD-MTX plus rituximab compared with HD-MTX alone improves CR and overall survival rates. **Neurology® 2014;83:235–239**

Figure 1 Overall and progression-free survival in patients with PCNSL treated with HD-MTX with or without rituximab



patients who initiated their treatment at The J Hopkins Hospital and who continued it elsewh These patients could, however, be included in survival analysis. The 2 cohorts showed a sir distribution of age, performance status, and sex (ta

CR was identified in 36% of patients in the I MTX monotherapy cohort and in 73% of pat who received HD-MTX/R ($p = 0.0145$). Ov complete and partial responses were 60% and 8 respectively. The median number of cycles to CR 5 (range, 2–15) in the HD-MTX monothe cohort and 5 (range, 2–21) in the combina cohort.

Median OS (all 81 patients were included in analysis) was 16.3 months (95% CI: 7.4– months) in the HD-MTX monotherapy cohort it has not yet been reached in the HD-MTX/R co ($p = 0.01$; figure 1A). Median PFS was 4.5 mo (95% CI: 2.9–13.6 months) in the HD-MTX mo therapy cohort compared with 26.7 months in combination therapy cohort (95% CI: 20.9 mo to not reached) ($p = 0.003$; figure 1B).

To compare our results with data from previc published studies, we also performed subgroup analysis of patients with an ECOG performance tus of ≤2 (because it had been used as an eligi criterion in prior clinical trials). Including only t better performance status patients, the median O patients treated with HD-MTX alone was months (95% CI: 7.4–50.6 months), and it has yet been reached in the combination therapy gr Median PFS in these patients was 5.2 months (9 CI: 3–22.2 months) in the monotherapy cohort 26.7 months in the combination cohort ($p = 0.0$

We then assessed median OS and PFS in patients who had achieved a CR (both groups c bined) compared with those who did not achie CR. In patients who did achieve a CR, median was 80.4 months vs only 5.8 months (95%

QUESTION :

- A 45-year-old man is evaluated in the emergency department for a 3-week history of headache and impaired vision on the right side. He has not previously had frequent headaches, but the current pain has been constant and worsening since onset. The patient thinks that something is wrong with his eyesight because he has been running into or tripping over objects on the right side. He has no significant medical history and takes no medication.
- On physical examination, vital signs are normal. No papilledema is noted on funduscopic examination. A slit lamp examination shows no cells in the vitreous humor. Other findings from the general medical examination are unremarkable. Neurologic examination reveals the presence of right homonymous hemianopia.
- An MRI of the brain shows a lesion in the left occipital lobe that is highly suspicious for central nervous system lymphoma.
- Results of laboratory studies include a normal leukocyte count and differential and no evidence of HIV antibodies.
- Cytologic analysis of cerebrospinal fluid shows no malignant cells.

- Which of the following is the most appropriate next step in management?

- A: Bone marrow biopsy
- B: Surgical biopsy of the brain lesion
- C: Surgical resection of the brain lesion
- D: Treatment with dexamethasone
- E: Treatment with photon-beam radiation