Role Of Chemotherapy in CNS Tumors

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Presentation at ICRO

Epidemiology

Table 15-1 World Health Organization Classification and Grading of Selected Primary CNS Tumors

	I	II	III	IV
Diffuse astrocytic tumors				
Diffuse astrocytoma, *IDH* mutant		X		
Anaplastic astrocytoma, *IDH* mutant			X	
Glioblastoma, *IDH* mutant				X
Glioblastoma, *IDH* wild type				X
Diffuse midline glioma, H3K27M mutant				X
Oligodendroglial tumors				
Oligodendroglioma, *IDH* mutant and 1p/19q codeletion		X		
Anaplastic oligodendroglioma, *IDH* mutant and 1p/19q codeletion			X	
Other astrocytic tumors				
Pilocytic astrocytoma	X			
Subependymal giant cell astrocytoma	X			
Pleomorphic xanthoastrocytoma		X		
Anaplastic pleomorphic xanthroastrocytoma			X	
Ependymal tumors				
Subependymoma	X			
Myxopapillary ependymoma	X			
Ependymoma		X		
Ependymoma, RELA fusion–positive (II or III)		X	X	
Anaplastic ependymoma			X	
Embryonal tumors				
Medulloblastoma (all subtypes)				X
Atypical teratoid/ rhabdoid tumor				X
Tumors of the cranial and paraspinal nerves				
Schwannoma	X			
Neurofibroma	X			
Malignant peripheral nerve sheath tumor (II, III, or IV)		X	X	X
Meningiomas				
Meningioma	X			
Atypical meningioma		X		
Anaplastic (malignant) meningioma			X	
Tumors of the sellar region				
Craniopharyngioma	X			

With permission of Springer from Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Classification of tumors of the central nervous system: a summary. *Acta Neuropathol.* 2016;131:803-820.
Abbreviations: IDH, isocitrate dehydrogenase.

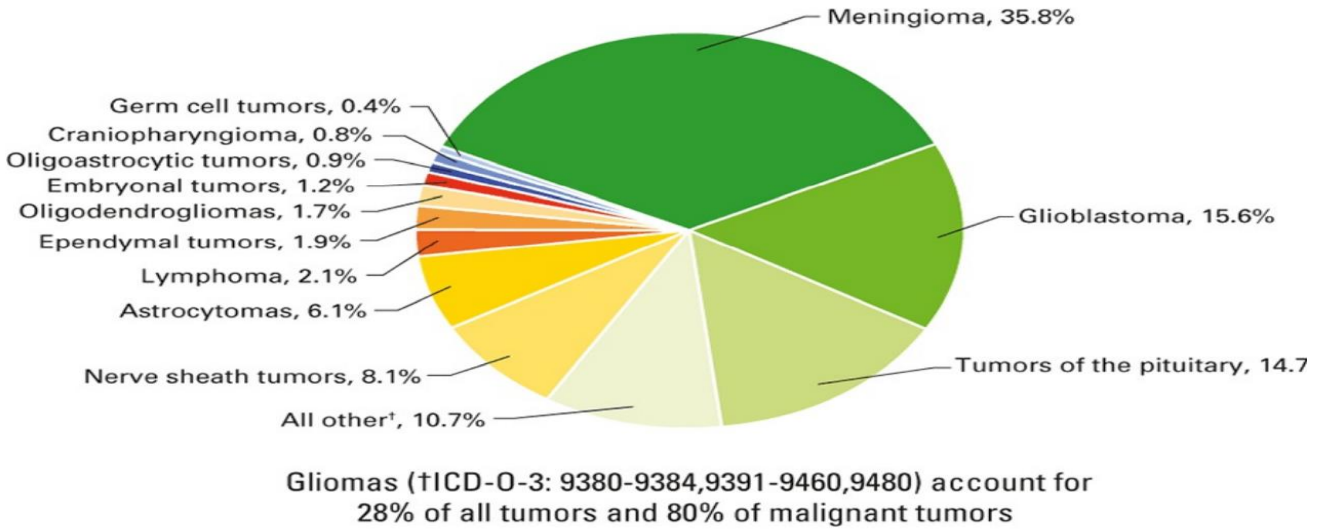

Fig. 15-1 Distribution of primary brain and CNS tumors by histology (326,711 patients).
Abbreviation: CNS, central nervous system.
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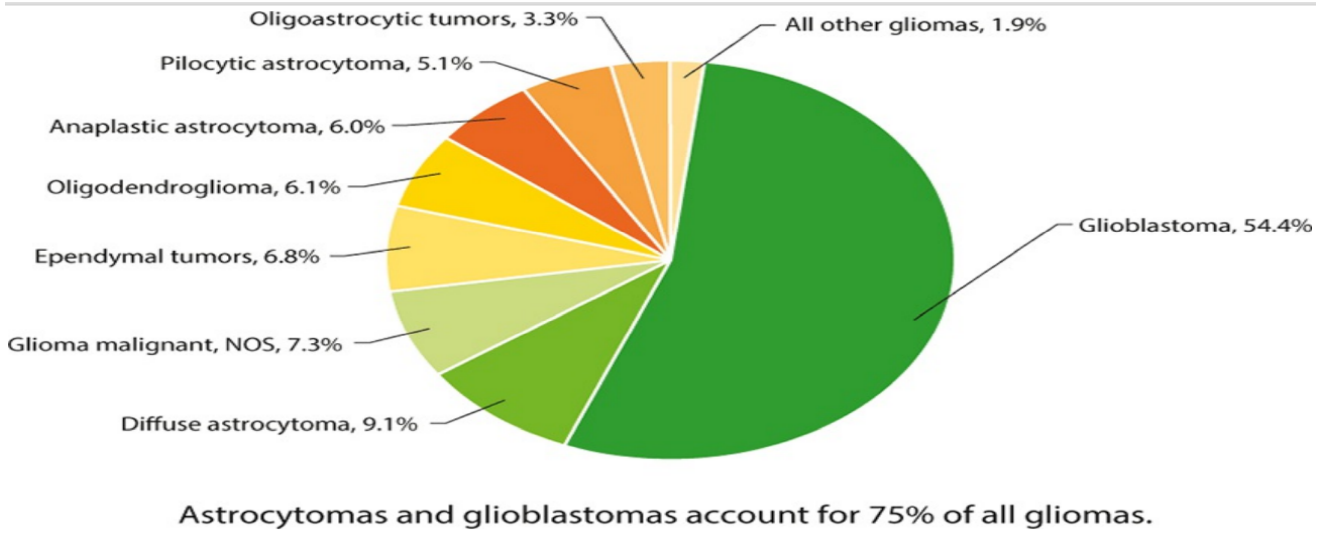


Fig. 15-2 Distribution of primary brain and CNS gliomas by histology subtypes (92,504 patients).
Abbreviations: CNS, central nervous system; NOS, not otherwise specified.
Reprinted with permission from Oxford University Press for Ostrom QT, Gittleman H, Farah P et al. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2006-2010. Neuro Oncol. 2013;15 Suppl 2:ii1-ii56. PMID: 24137015.

Overview

- Tumors of neuroepithelial tissue- malignant primary CNS tumors
  - astrocytic tumors (including glioblastoma),
  - oligodendroglial tumors, and
  - embryonal tumors (e.g., medulloblastoma)
- Tumors of the meninges (e.g., meningioma) represent the most common benign primary CNS tumor.
- Other less common primary CNS tumor categories include
- Tumors of the cranial and paraspinal nerves (e.g., vestibular schwannoma), Tumors of the sellar region (e.g., craniopharyngioma),
- Hematopoietic neoplasms (e.g., primary CNS lymphoma), and
- Germ cell tumors. Metastatic tumors,

Genetics

Table 15-2 **Genetic Syndromes Associated with Primary CNS Tumors**

Genetic Syndrome	Gene Alteration(s)	Associated Primary CNS Tumors
Basal cell nevus (Gorlin) syndrome	*PTCH1*	Medulloblastoma
Cowden syndrome	*PTEN*	Gangliocytoma
Li-Fraumeni syndrome	*TP53*	High-grade glioma Medulloblastoma
Neurofibromatosis 1	*NF1*	Malignant peripheral nerve sheath tumor Low-grade astrocytoma (usually pilocytic astrocytoma)
Neurofibromatosis 2	*NF2*	Vestibular schwannoma (frequently bilateral) Meningioma
Tuberous sclerosis	*TSC1, TSC2*	Subependymal giant cell astrocytoma
Familial adenomatous polyposis	*APC*	Medulloblastoma
Lynch syndrome (hereditary nonpolyposis colorectal cancer)	*MSH2, MLH1, MSH6, PMS2*	Glioblastoma
Von Hippel-Lindau syndrome	*VHL*	Hemangioblastoma

1) epidermal growth factor receptor (EGFR) mutation and amplification, (2) loss of the PTEN tumor suppressor gene, (3) RB1 gene deletion and mutation, (4) CDKN2A and CDKN2B gene deletions, and (5) NF1 gene mutations and deletions. Other abnormalities such as TP53

Investigations

- CT scan
- MRI
- MRS
- PET differentiate high-grade glioma from radiation necrosis, as tumor is more likely to be hypermetabolic

The sensitivity and specificity of MRS in differentiating tumor histology or radiation necrosis are currently too low to recommend its routine use. However, other types of MRS and PET imaging may be more useful in specific situations. For example, the development of proton MRS for evaluation of 2-hydroxyglutarate (2HG) has provided a noninvasive biomarker to assess tumor status and treatment response in IDH-mutant gliomas

IHC markers

Glial markers

- **GFAP**
- **Oligo I**
- **Oligo 2**
- **S 100**
- **SOX 10**

Neuronal markers

- **Synaptophysin**
- **Neu-N**
- **NF-4**
- **MAP -2**

Glial neoplasm
“GFAP, IDH, ATRX, P53, Ki-67”

Classification of Diffuse glioma (2016).....

- Diffuse astrocytoma (WHO grade II) or Anaplastic astrocytoma(gradeIII): ***IDHm, wild-type, NOS***
- Oligodendroglioma (WHO grade II) or Anaplastic oligodendroglioma (WHO grade III) : ***IDHm and 1p/19q-codeleted or NOS***
- GBM (WHO grade IV): *IDHm, wildtype, or NOS*
- Diffuse midline glioma (WHO grade IV): ***H3K27M-mutant***

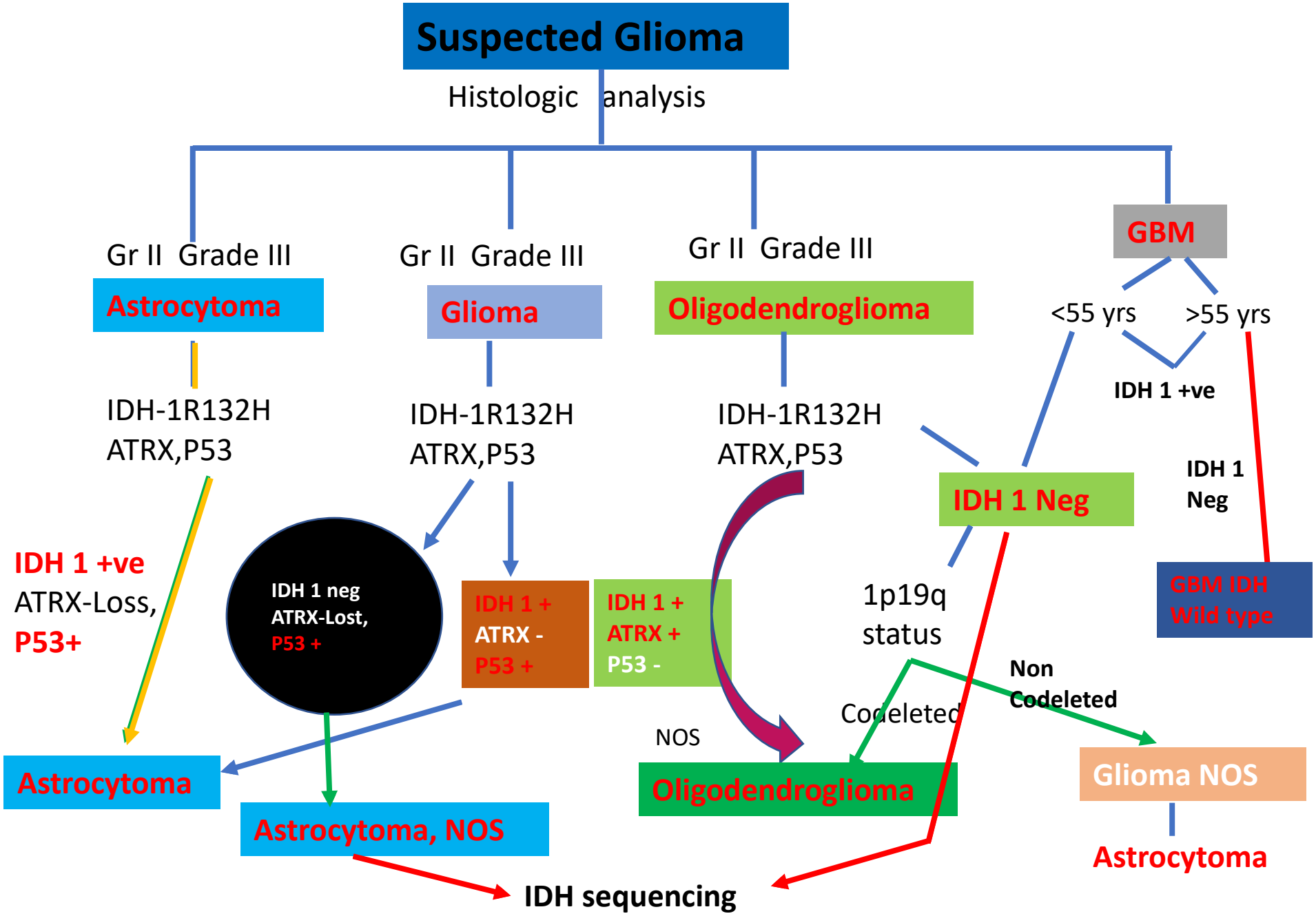
Diagnostic Pathology

Markers of good prognosis in gliomas include

- 1p/19q codeletion,
- MGMT promoter hypermethylation, and
- IDH mutation.

Furthermore, 1p/19q codeletion and IDH mutation independently predict response to chemotherapy in anaplastic oligodendroglioma, whereas MGMT promoter hypermethylation is associated with a greater likelihood of benefit from temozolomide in glioblastoma. Current clinical trials are using these biomarkers for either stratification or clinical Inclusion

Algorithm for classification of adult Diffuse Glioma *(IHC based in a resource poor setting)*



Role of radiology findings

- **Intra axial** – from brain parenchyma itself

- **Extra axial** – from meninges, skull etc compressing the brain

✓Single – more likely to be primary

✓Multiple – more likely to be metastasis or disseminated infection

✓Location- cerebral hemispheres,ventricles,cerebellum,suprasellar, meningeal etc

✓Cyst/cystic lesion – benign non neoplastic cysts show no contrast enhancement

The Importance of clinical history
Relative frequency of intracranial tumors

Age <3yrs	3-15yrs	15-65	>65
MB	PA	GBM	Mets
PA	MB	Anaplastic astrocytoma	GBM
Ependymoma	Ependymoma	Astrocytoma	Anaplastic astrocytoma
Choroid plexus tumors	Astrocytoma	Meningioma	Meningioma
Teratoma	Choroid plexus tumors	Pituitary tumors	Acoustic schwannoma

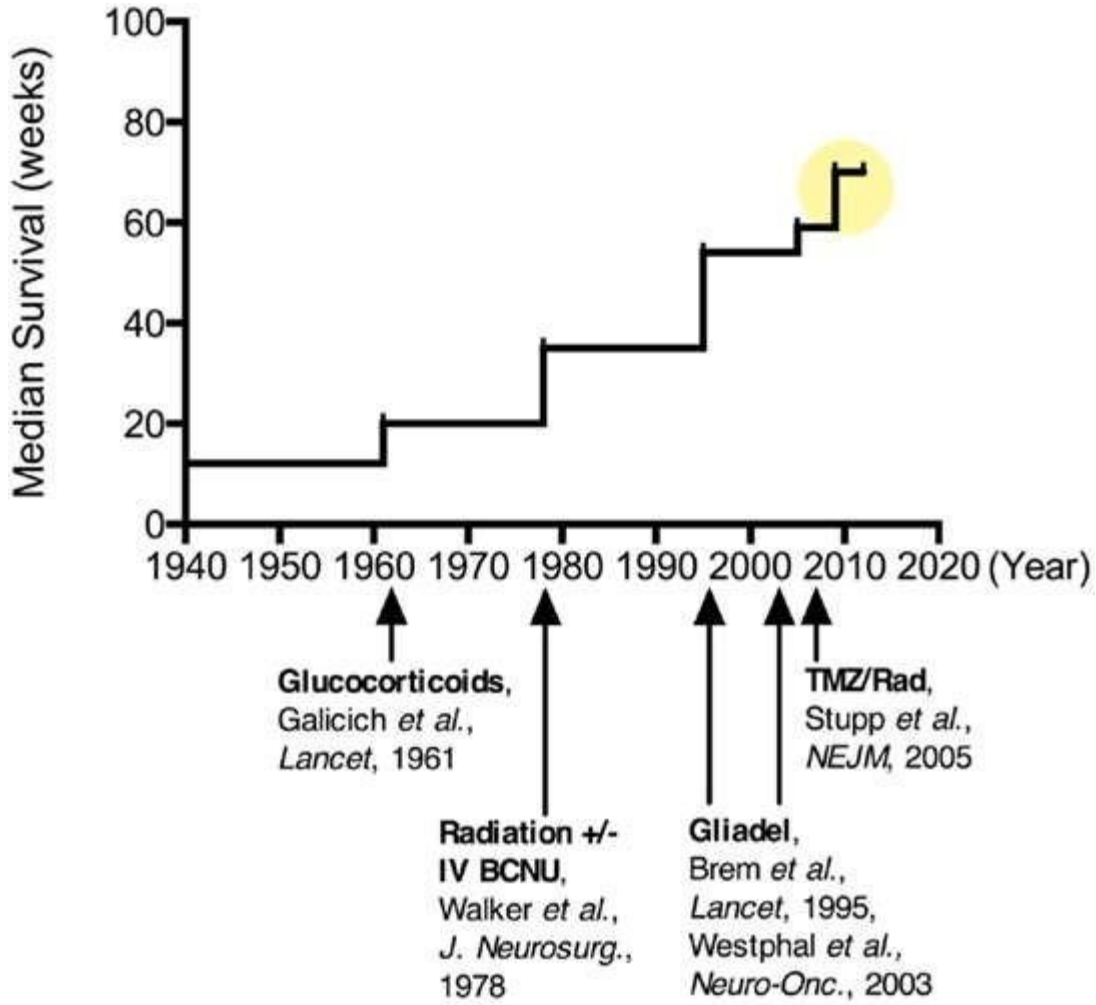
Distribution of Intracranial lesions: Intraparenchymal

Intraparenchymal Supratentorial	Intraparenchymal Infratentorial
Astrocytoma, anaplastic astro,GBM	Cerebellar astrocytoma
Oligodendroglioma	MB
Ependymoma	Epedymoma
Mets	Hemangioblastoma
lymphoma	Mets
Inflammatory lesions	Lymphoma
Vascular disorders	Inflammatory lesions, vascular disorders
Extra parenchymal Supratentorial	**Extra parenchymal Infratentorial**
Meningioma	Schwannoma
Metastatic neoplasms	Meningioma
Epidermoid/dermoid cysts	Metastatic neoplasms
	Glomus jugulare tumor

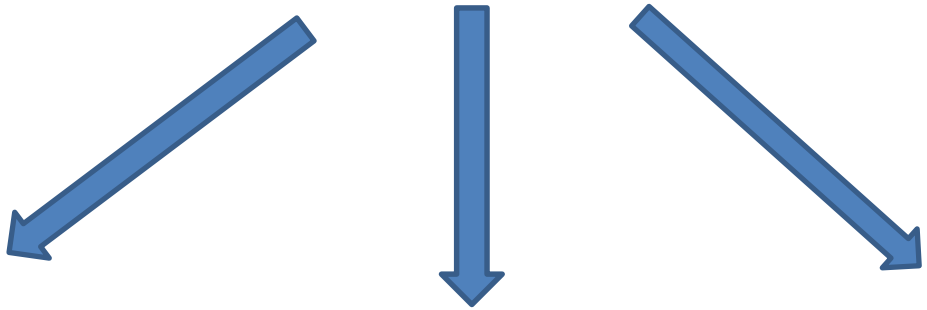
Overview

1. Chemotherapy history
2. CNS active drugs
3. Therapeutic challenges in CNS chemotherapy
4. Strategies for increased drug delivery to brain tumor
5. Targeted /Antiangiogenic therapy
6. Chemotherapy in common CNS cancers

1.History of Chemotherapy in CNS tumors



ROLE OF CHEMOTHERAPY IN CNS MALIGNANCY

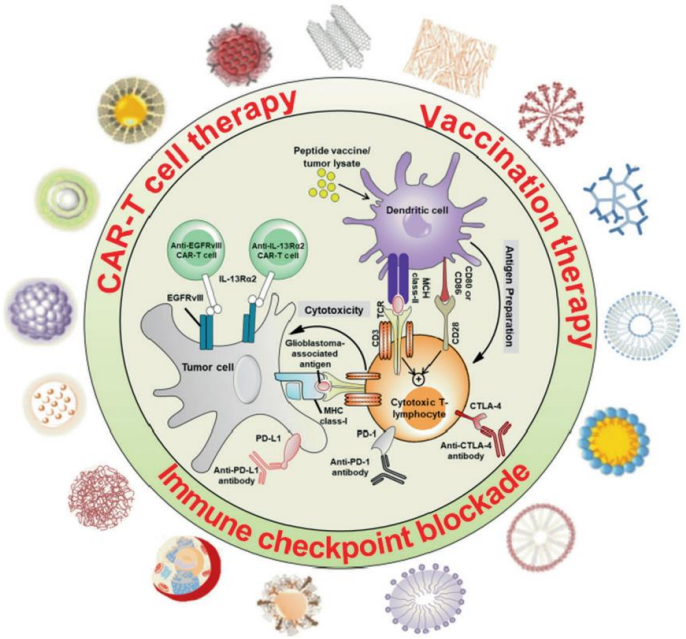


Neoadjuvant	Adjuvant	Primary
• Germinoma ??	• GBM • Anaplastic Glioma • ODG • Medulloblastoma • Ependymoma • Gliomas • Metastasis	• PCNSL • Germinoma

CNS Active drugs

Agent	CSF:Plasma ratio (%)
Alkylating agents	
Cyclophosphamide	50
Total drug	15
Active metabolite	30
Ifosfamide	15
Total drug	>90
Active metabolite	50
Thiotepa	40
Carmustine	<5
Cisplatin	30
Free platinum	<5
Total platinum	
Carboplatin	3
Free platinum	25
Total platinum	15
Antimetabolites	
Methotrexate	50
6-Mercaptopurine	15
Cytarabine	
5-Fluorouracil	
Bolus Infusio	

Antitumor antibiotics	ND[b]
Anthracyclines	ND
Dactinomycin	5
Plant alkaloids	<5
Vinca alkaloids	
Topoisomerase I inhibitors	
Etoposide/Teniposide	
Topotecan	32
Irinotecan	
CPT-11	14
lactone SN-38 lactone	<8
Miscellaneous	<10
Prednisolone	15
Dexamethasone	N
Asparaginase	



timal design of nanoparticle-based delivery of drugs, cargoes/or adjuvants, and immunotherapy of glioblastoma. Diverse types ale materials can serve as vehicles for targeted delivery of tumor-cytotoxic nanomedicines

Table 2. Comparison of multiple nanomedicine-based immunotherapies for glioblastoma

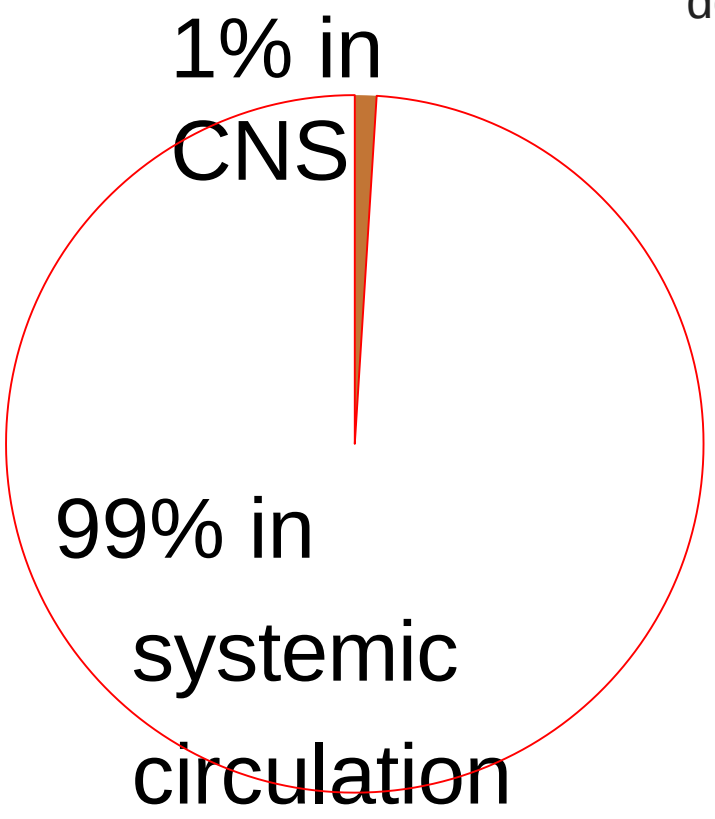
Immunotherapy	Advantages	Disadvantages
Immune checkpoint inhibition	Enhanced PD-L expression in glioblastoma Can overcome glioblastoma immune evasion Development of novel immune checkpoints The slow occurrence of side effects Combination of immunotherapy with radiotherapy or chemotherapy is more effective	Complex immune evasion strategies Responsive evaluations Immune-related side events The balance between self-tolerance and autoimmunity
Vaccination therapy	Multitude characterized Elicits potent, robust, and specific immune responses Available for most patients Ability to combine multiple targets into a cocktail vaccine Lowered risk of immune escape Safe, multivalent, and patient-specific Fully defined composition	Reduced immune response due to central tolerance if expressed by normal tissues Available for a subset of patients Possible immune evasion (growth of tumor cells that lack antigen expression) Instability of peptides in vivo being rapidly degraded by peptidases High production costs
CAR T-cell therapy	MHC-independent Overcomes tumor MHC molecule downregulation Potent in recognizing any cell-surface antigen (protein, carbohydrate, or glycolipid) Applicable to a broad range of patients and T-cell populations Production of large numbers of tumor-specific cells in a moderately short period	Capable of targeting only cell-surface antigens Lethal toxicity due to cytokine storm reported Difficulties of target selection Most mutations occur in intracellular proteins

Targeted agents like
Breast –Abemaciclib, TDM1,
Lung-Lorlatenib, Osemertinib

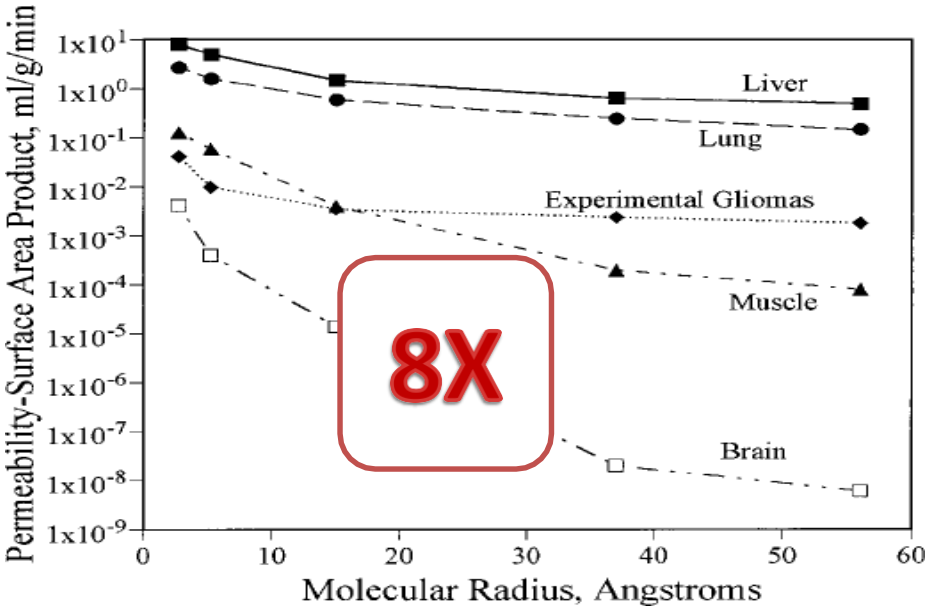
Newer

- immunotherapy in cancer is expanding rapidly, its efficacy in glioma is still unclear. One promising example is chimeric antigen receptor (CAR) T cells—one patient with multifocal glioblastoma had significant regression of tumor after both intracranial and intrathecal infusions of interleukin-13 receptor alpha 2–targeted CAR T cells.
- intra-arterial chemotherapy with or without blood–brain barrier disruption, intratumoral administration of agents by convection-enhanced delivery, and placement of intratumoral biodegradable polymers.
- FDA has approved the use of carmustine-impregnated degradable polymers for the treatment of newly diagnosed highgrade gliomas and recurrent glioblastoma
- Tumor-Treating Fields (TTFields). This is a device that delivers alternating electromagnetic fields to electrodes placed on the shaved scalp. It is approved for use inthe treatment of patients with both newly diagnosed (after concurrent chemoradiation) and recurrent glioblastoma. The intervention has also been investigated in the postresection setting for patients with newly diagnosed glioblastoma. A randomized, phase III trial of temozolomide with or without TTFields alongside adjuvant temozolomide enrolled 695 patients who had completed concurrent chemoradiation. The final data demonstrated a significant increase in median OS of the patients treated concurrently with temozolomide and TTFields compared with patients treated with temozolomide alone (21 months vs. 16 months, $p < 0.00062$)

DRUG CONCENTRATION IN CNS

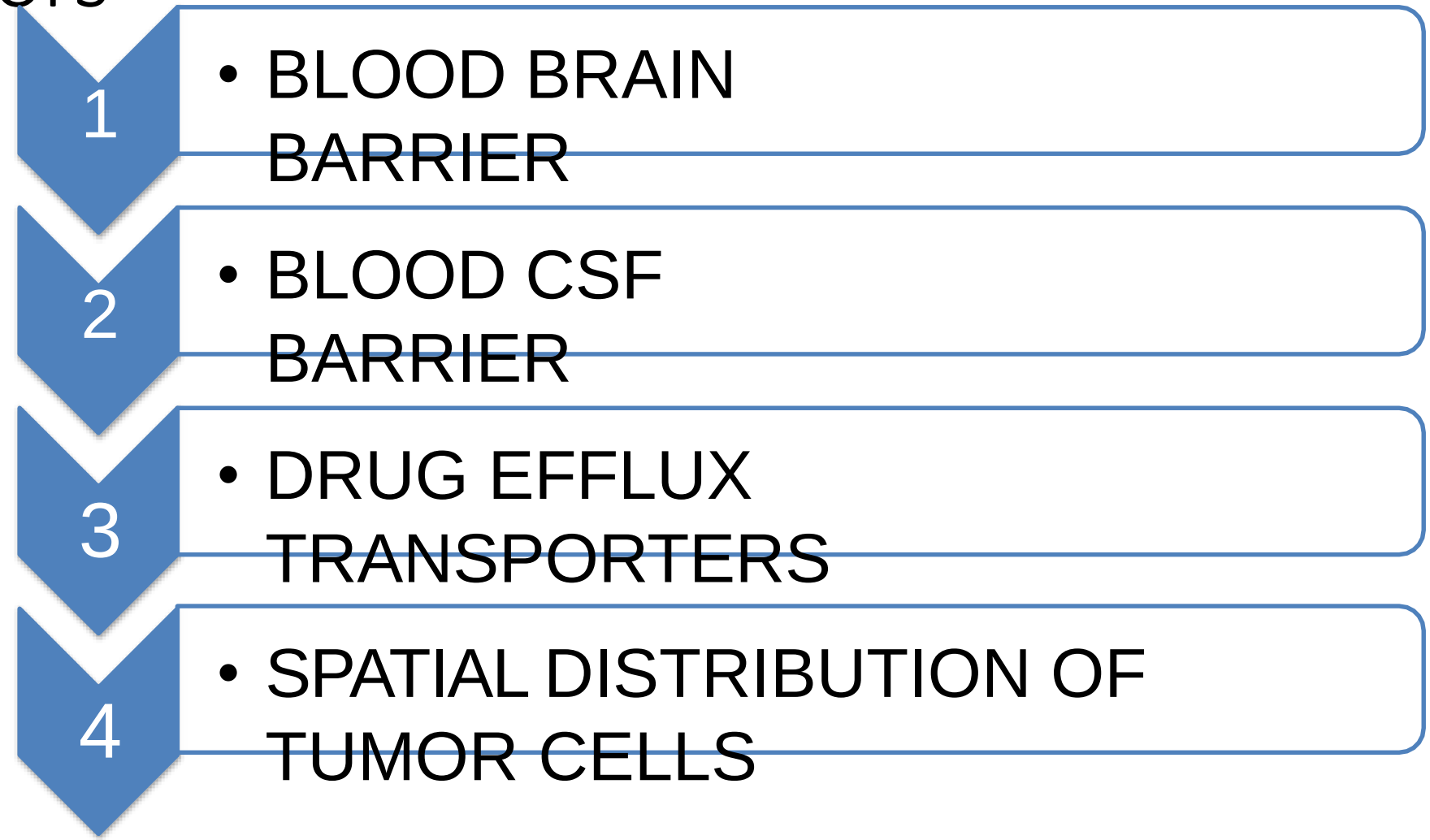


transient disruption of the BBB eg radiation , is likely insufficient to deliver effective intratumoral concentrations of anticancer drugs

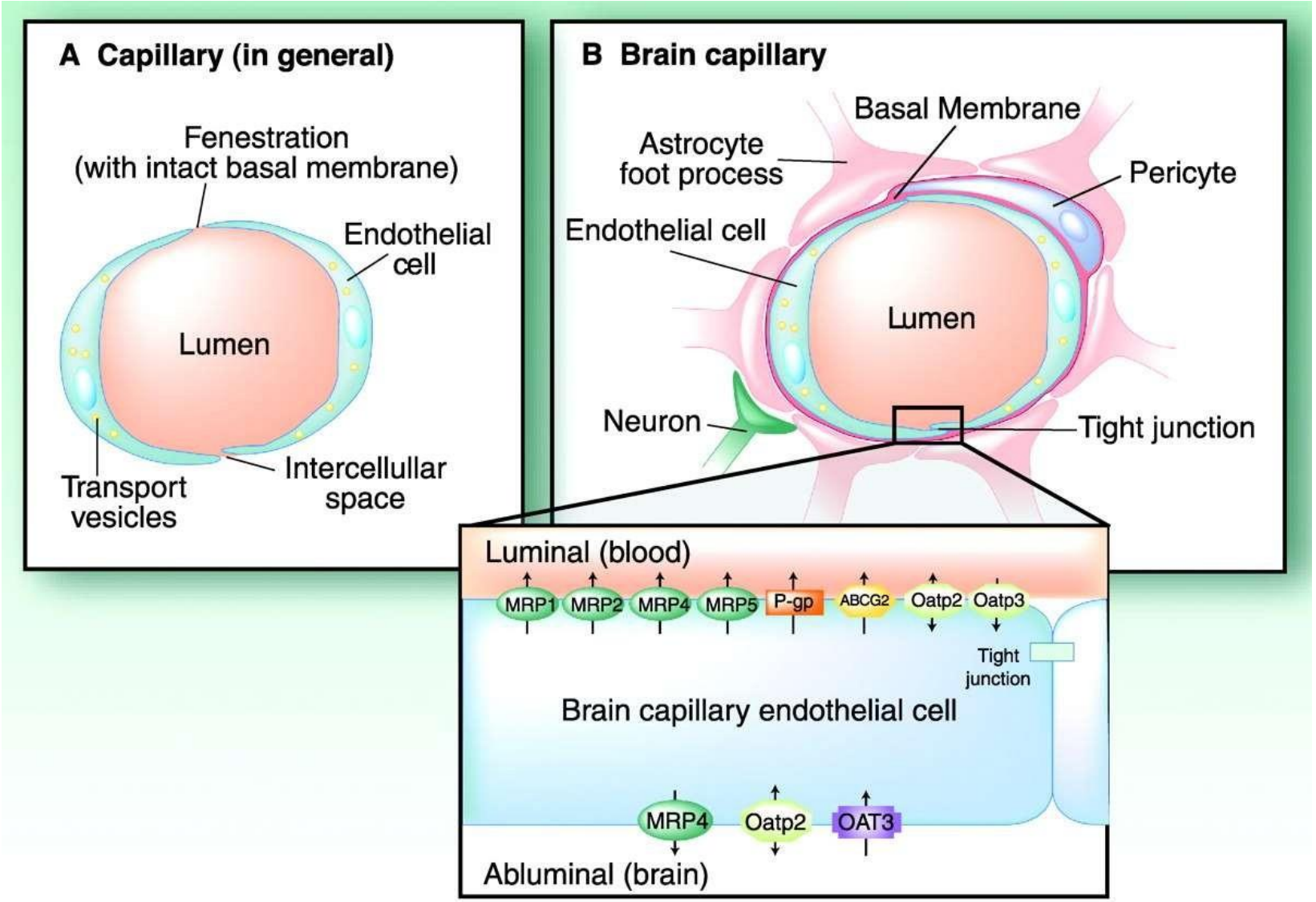


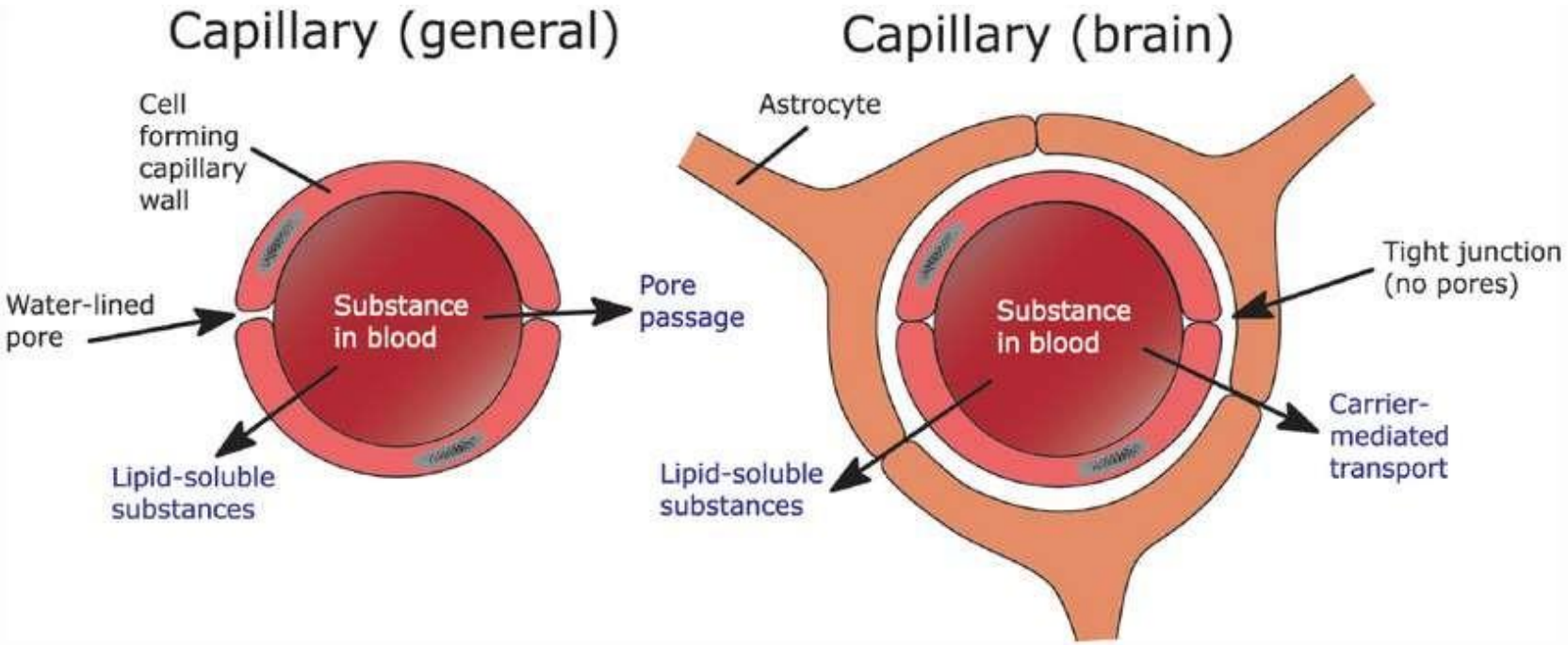
Passive Diffusion

Therapeutic challenges in management of brain tumors



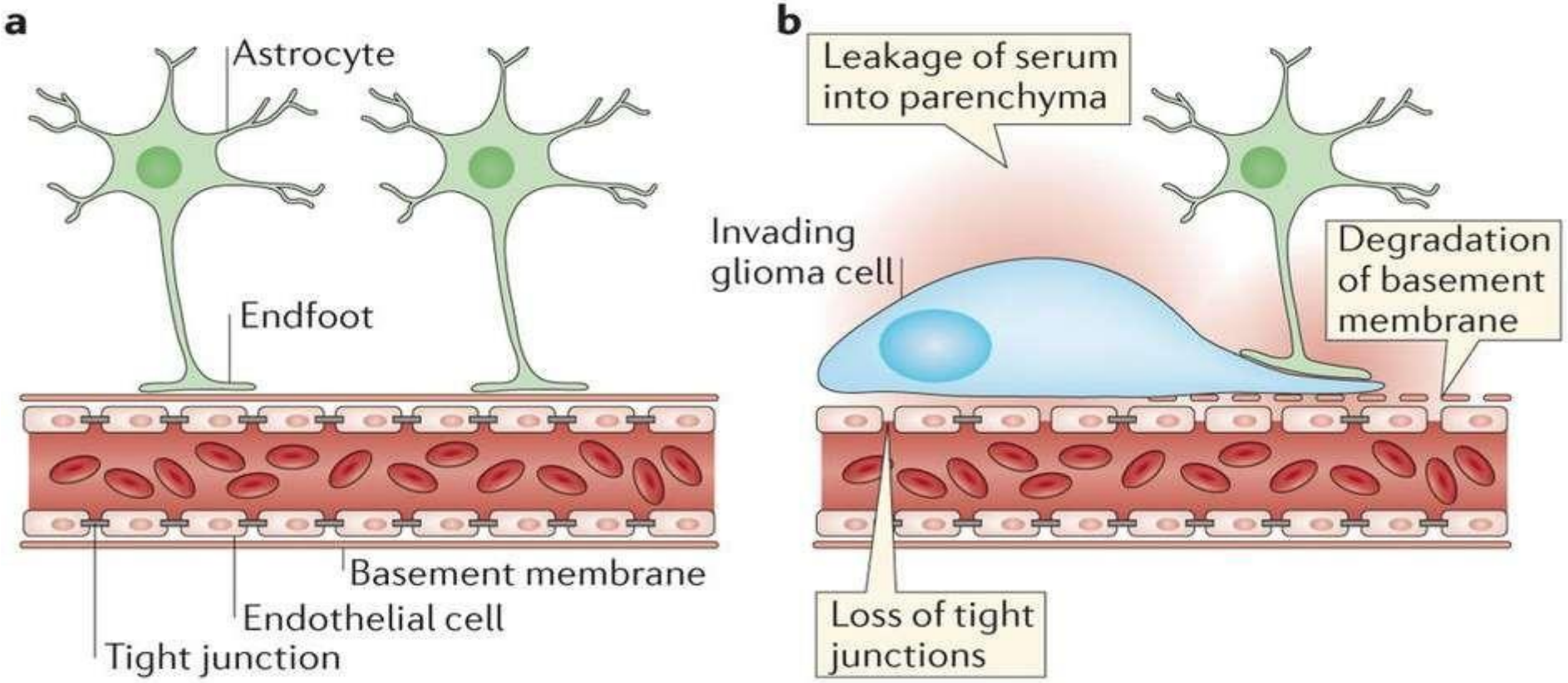
BLOOD BRAIN BARRIER





Intracellular junction	Loose	Tight
Pinocytic vesicles	Present	Absent
Fenestrae	Present	Absent
Electrical resistanc	Low	High

Blood Tumor Barrier



Increases in perivascular space Increased fenestrations
Increased number of pinocytic vacuoles
Expression of transporter also altered in endothelial

TYPES OF BTB

1. Continuous nonfenestrated capillaries in BBB

   Eg : grade 2 astrocytoma, oligodendroglioma

2. Continuous fenestrated in Blood

   CSF barrier

   capillaries Eg : medulloblastoma

2. Capilaries having intraepithelial gap as large as

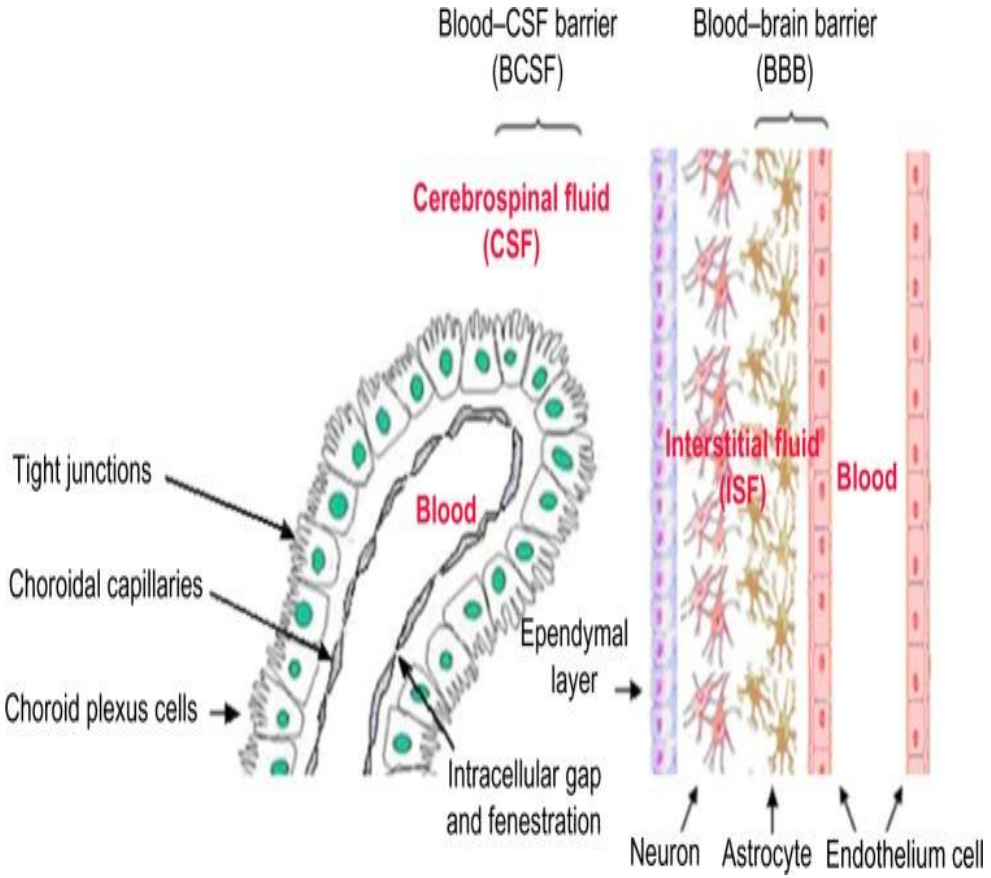
   1µm

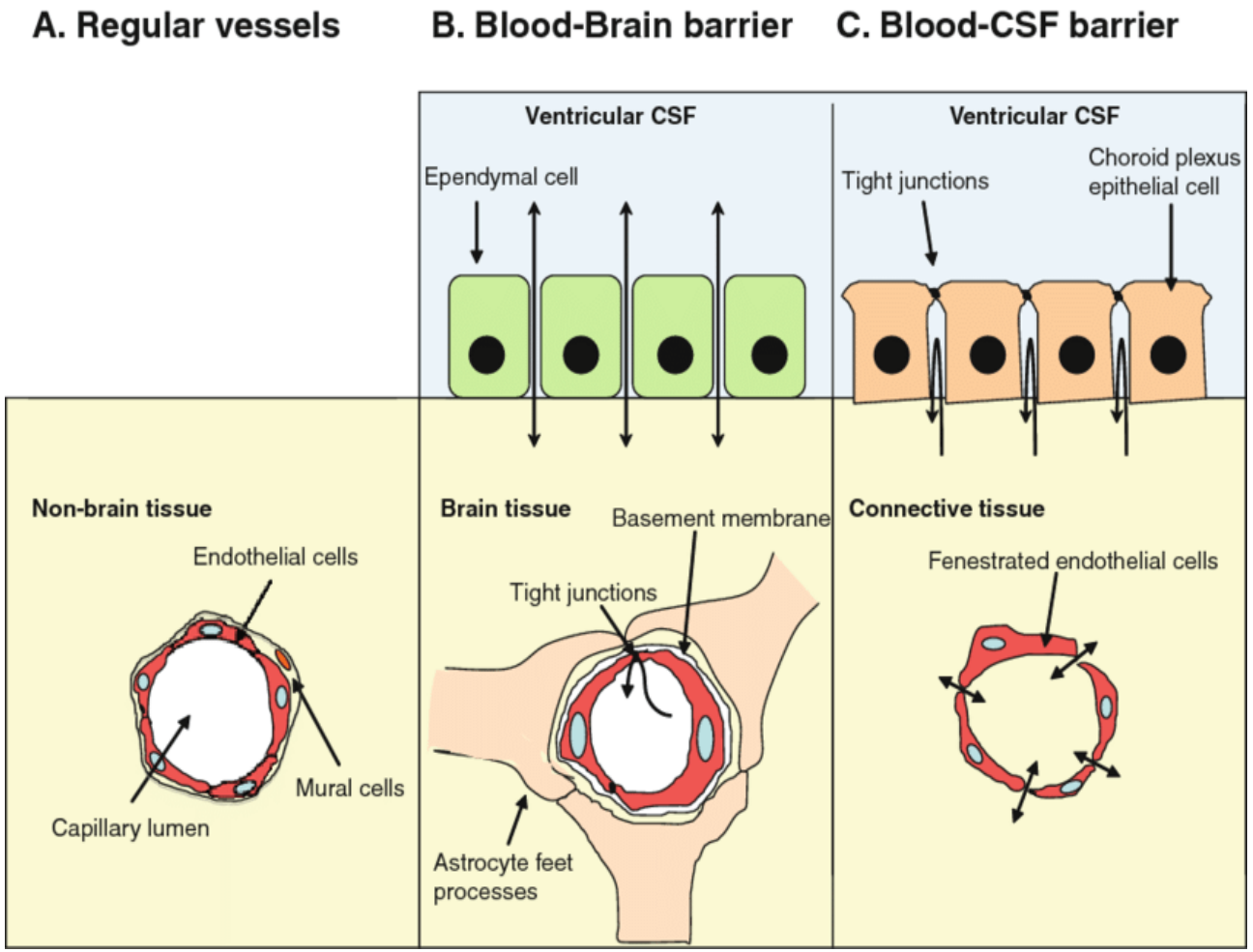
   Eg : high grade glioma

Blood barriers in the CNS

- **Blood-CSF barrier:**
  - A selective barrier of substances formed by the tight junctions between the choroidal epithelial cells.
- **The blood brain barrier (BBB)**
  - A selective barrier between the blood and the brain tissue.
  - Formed by the tight junctions between the endothelial lining of the capillaries.
- The function of the BBB & blood-CSF barrier is to provide a stable environment for the normal function of the CNS.

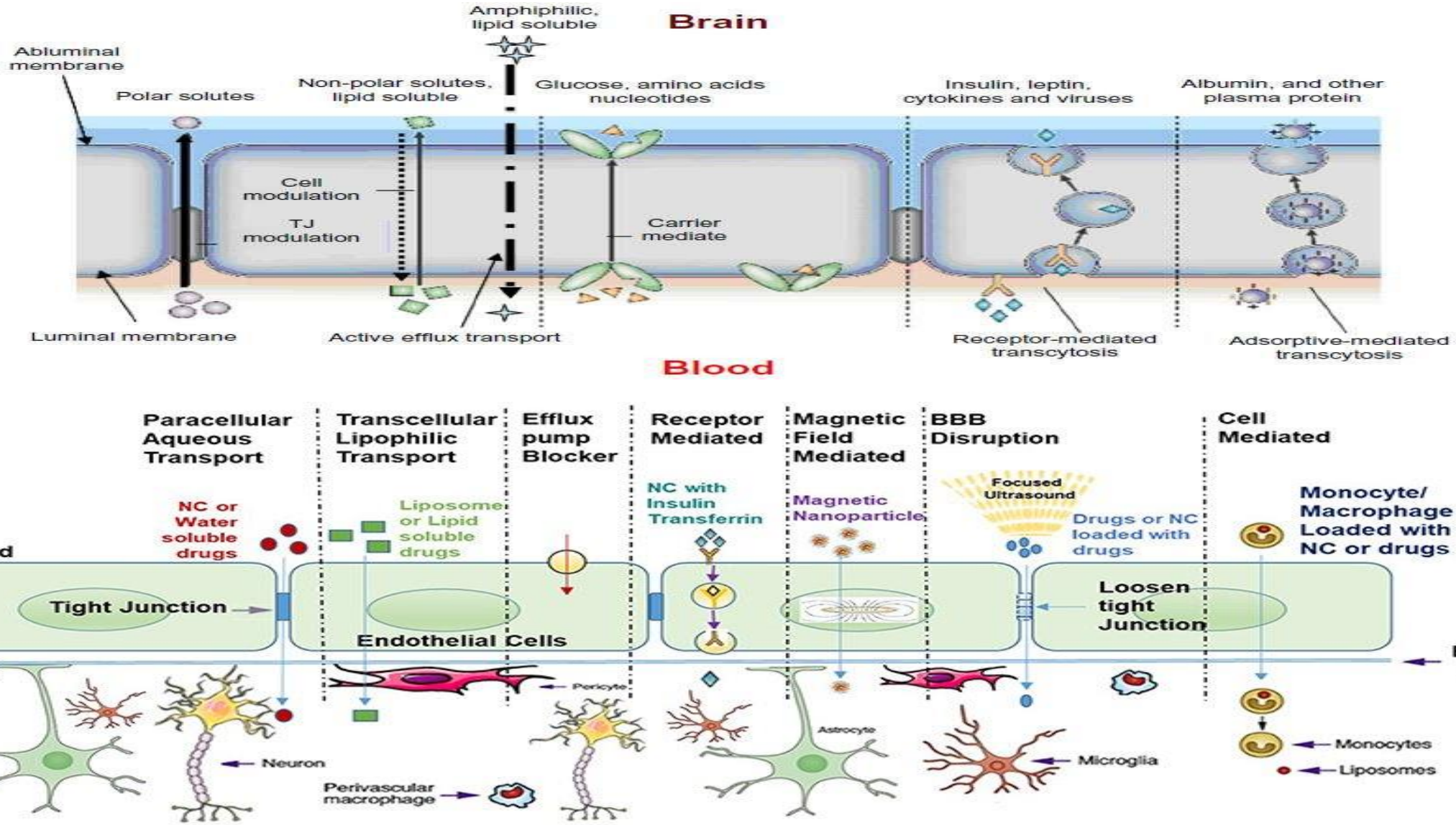
BLOOD CSF BARRIER



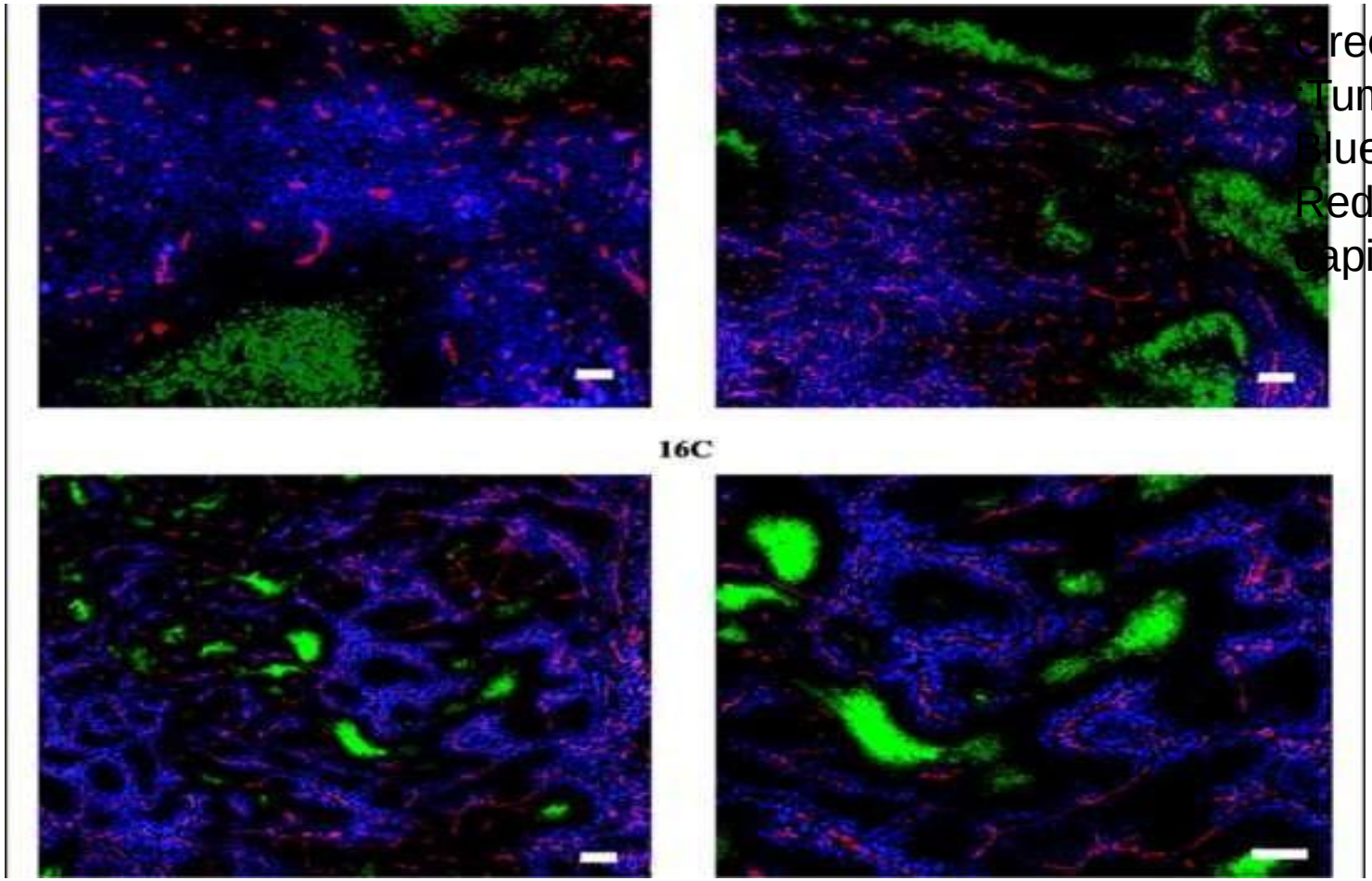


Drug efflux transporters

Multidrug resistance protein decreases drugs delivered inside



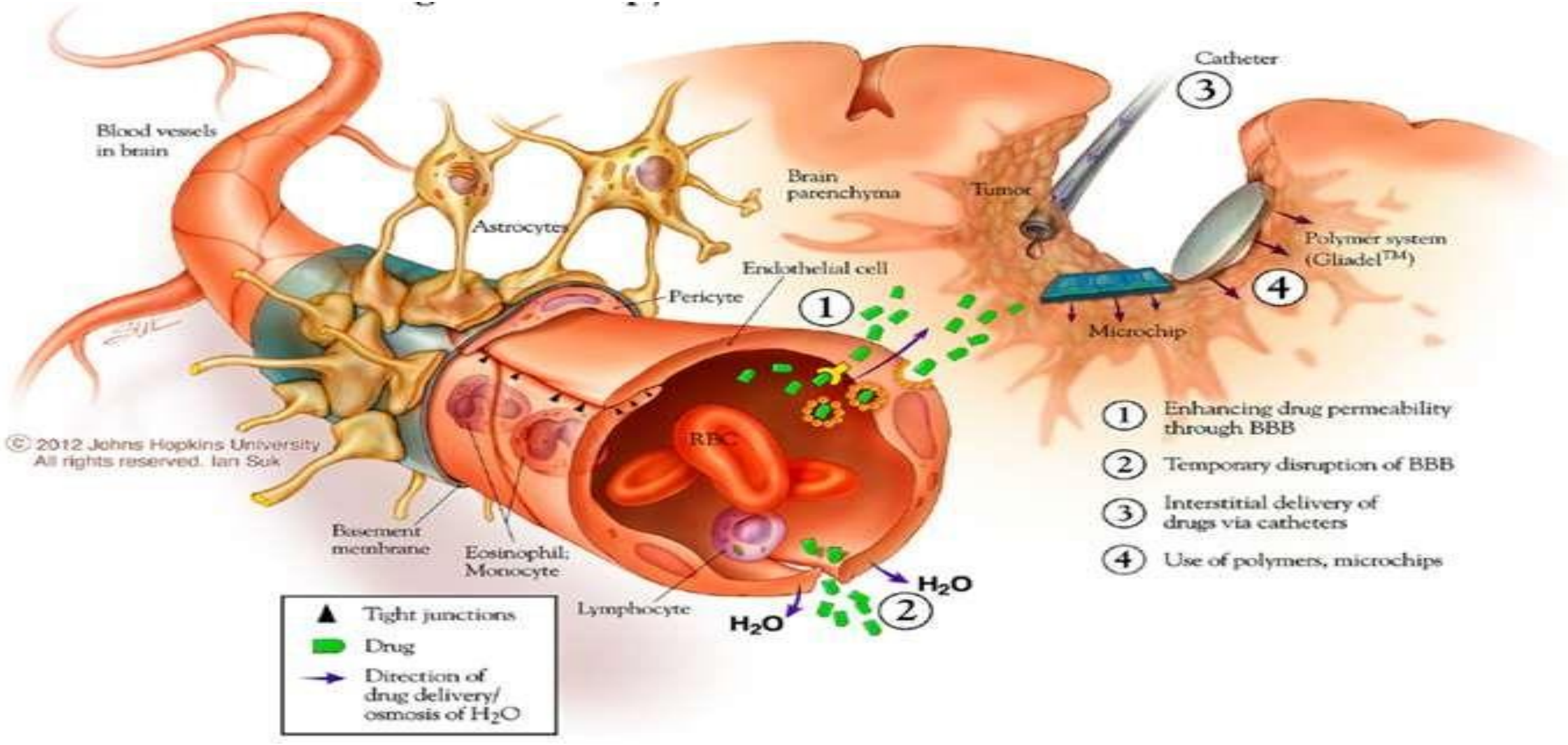
Spatial distribution of the target capillaries

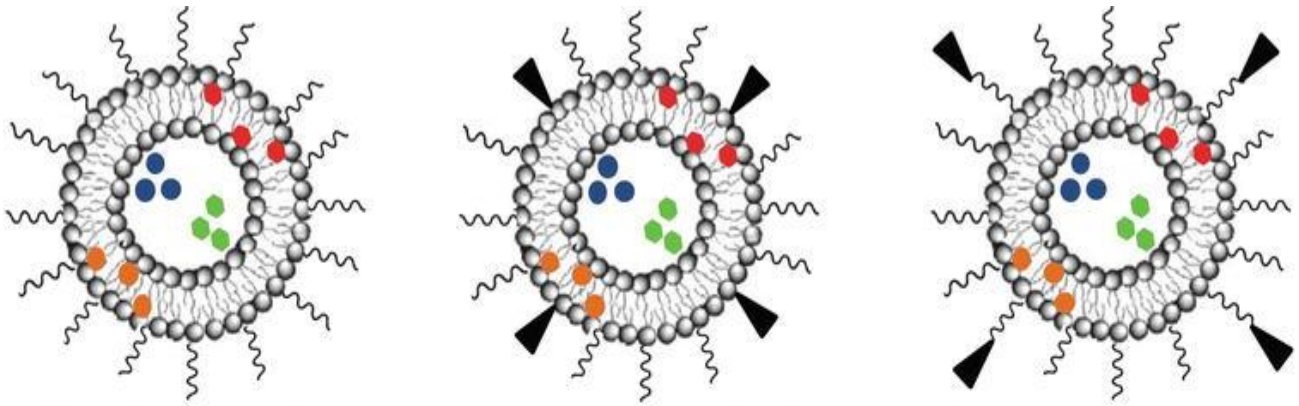


Green: Tumor
Blue: drug
Red: capillary

Andrew J. Primeau et al. Clin Cancer Res 2005;11:8782-8788

STRATEGIES FOR INCREASED DRUG DELIVERY TO BRAIN TUMOR





Passive targeting

Active targeting

= Hydrophilic therapeutic compound,

= Lipophilic therapeutic compound

= Hydrophilic imaging/contrast agent,

= Lipophilic imaging/contrast agent

= Long-circulating polymer coating, ie PEG, PVP or PAA

= Monoclonal antibody,

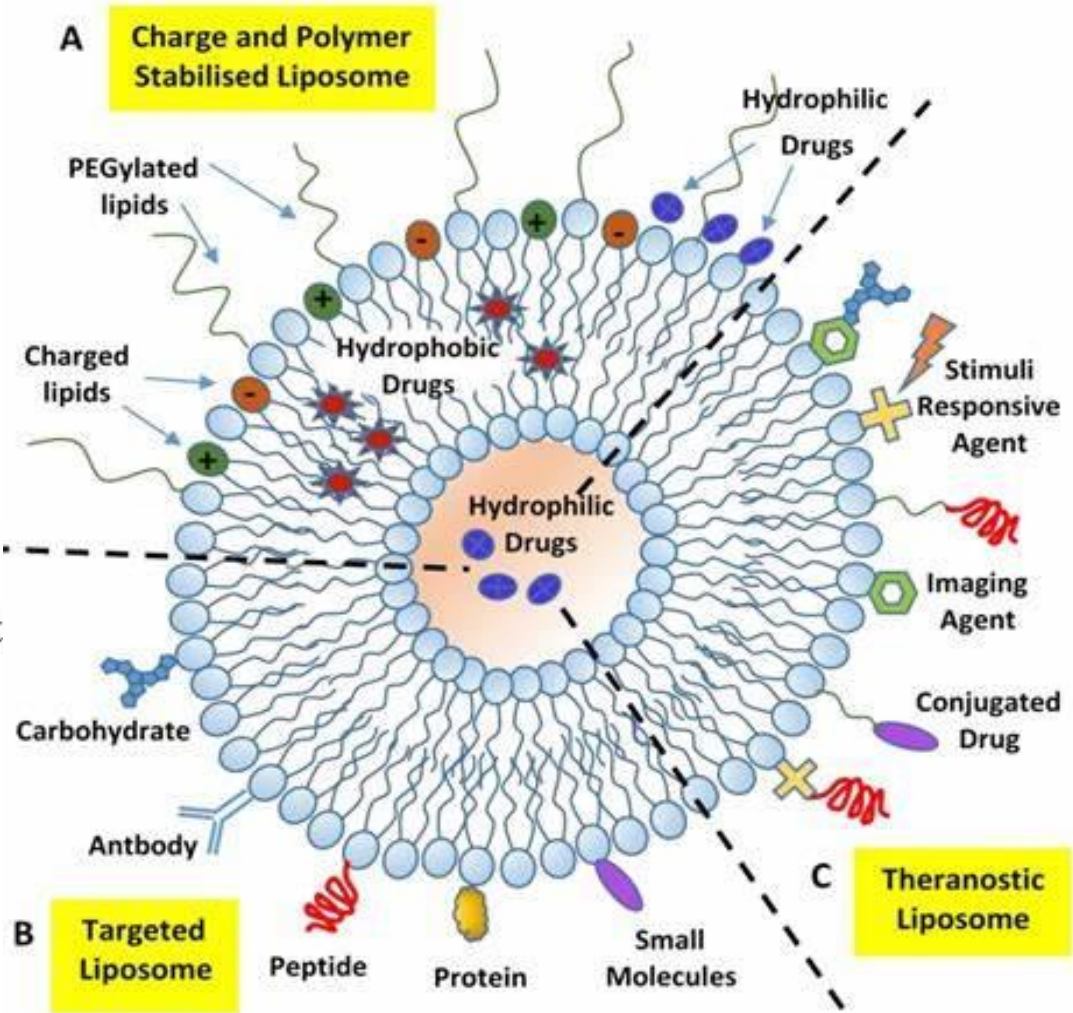
= $F(ab')_2$ fragments,

= Fab' fragments

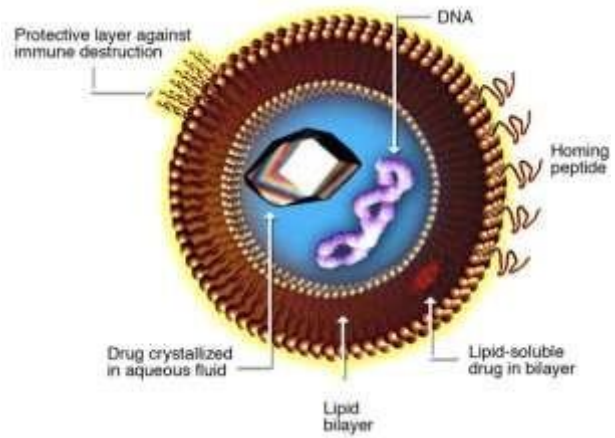
= Aptamers,

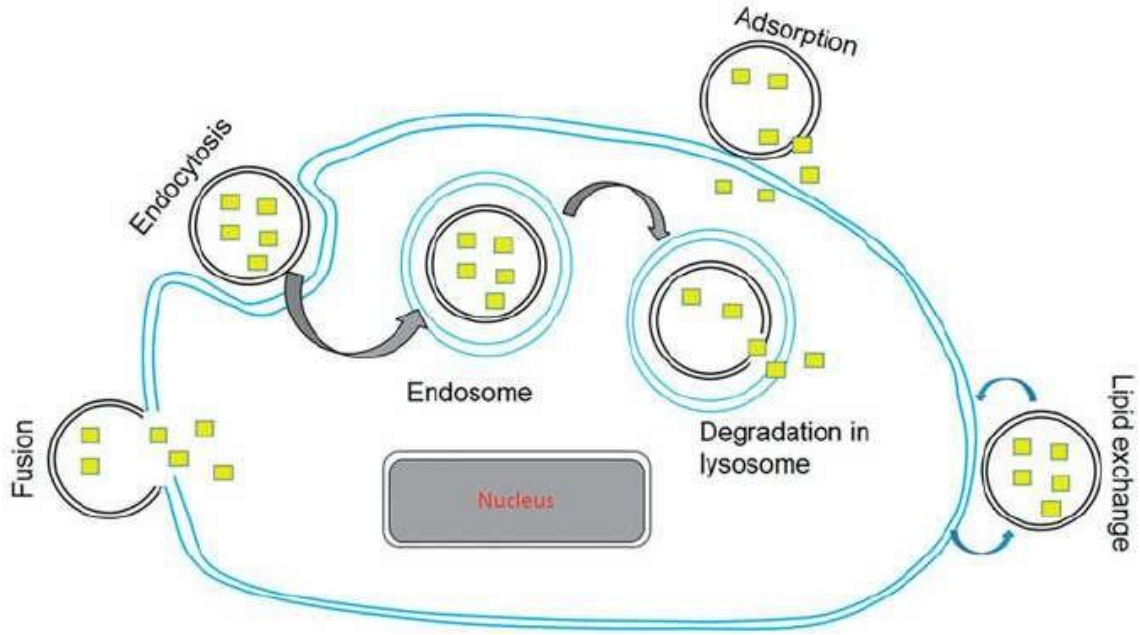
= Peptides

= Proteins



Liposomal Drug





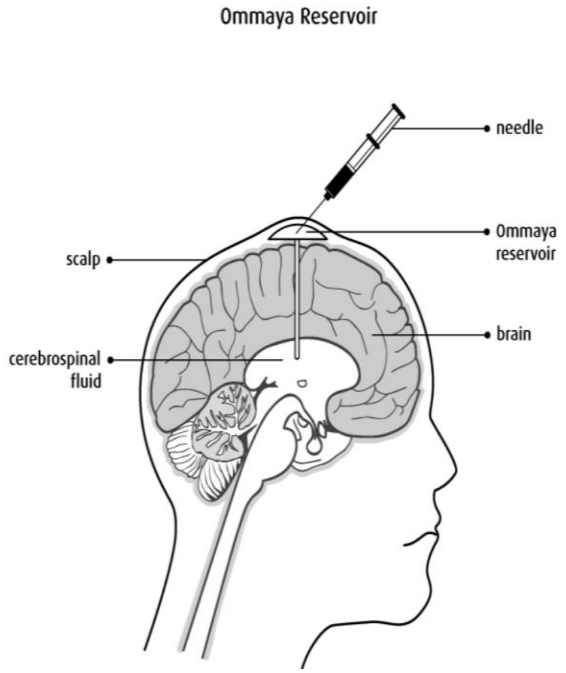
Drug	Disease	Status	Source(s)
Vincristine	Medulloblastoma/ODG	FDA Approved in 2012	Allen and Cullis, 2013; Wang et al., 2015
Irinotecan	GBM	Phase I/II	Zhang et al., 2004; Suenaga et al., 2015
Daunorubicin	Leukemia and solid tumors	FDA Approved in 1996	Chang and Yeh, 2012; Allen and Cullis, 2013
Cytarabine	Neoplastic meningitis and lymphomatous meningitis	FDA Approved	Chang and Yeh, 2012; Jahn et al., 2015
Lurtotecan	Metastatic Ovarian cancer, head, and neck cancer	Phase I/II	Dark et al., 2005; Chang and Yeh, 2012
Vinorelbine	relapsed solid tumors	Phase I	Allen and Cullis, 2013
Topotecan	Advanced solid tumors	Phase 1/II	Seiden et al., 2004; Allen and Cullis, 2013

Types of Chemo in CNS disease

- Systemic
- Local wafers
- Regional
- Intrathecal
- Intraventricular Ommaya Reservoir
- SIACI

Intraventrical chemotherapy

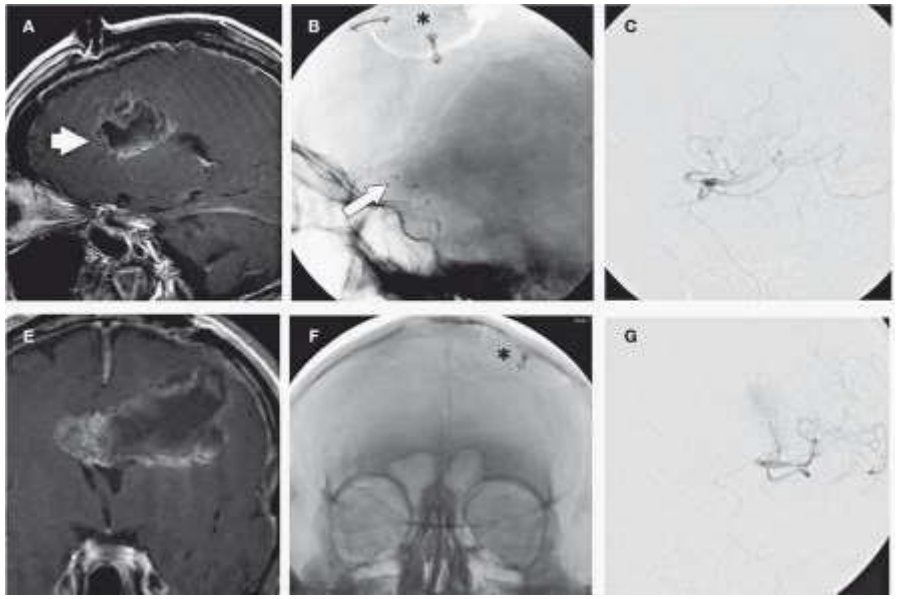
Chemotherapy for brain tumours may be given directly into the cerebrospinal fluid (CSF) in the ventricles of the brain. It is given through an Ommaya reservoir, which is a small, dome-shaped device with a short tube (catheter) attached to it that is placed during surgery. The chemotherapy drug is injected using a small needle inserted through the scalp into the Ommaya reservoir.

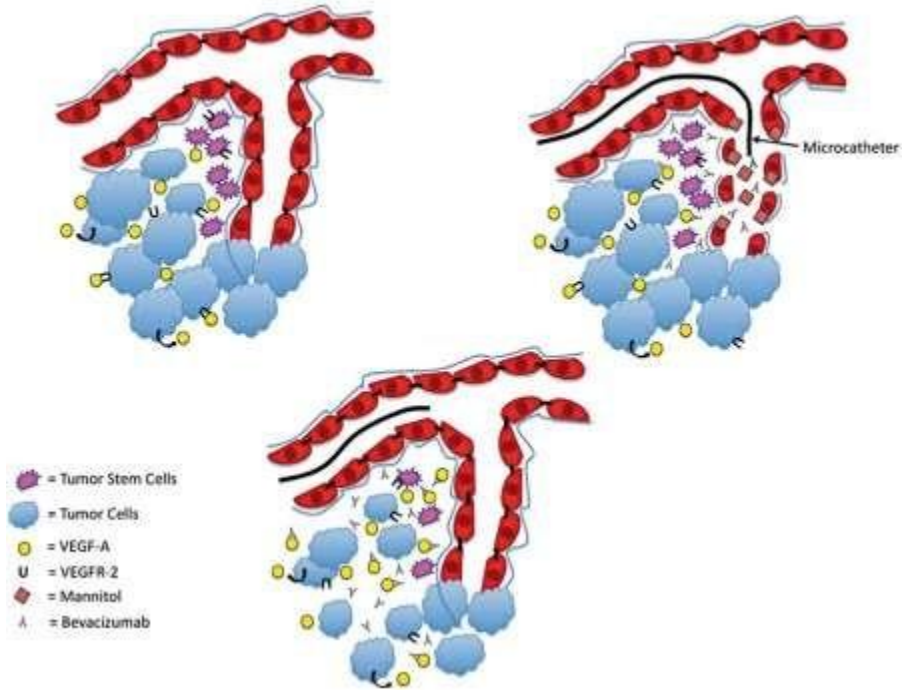


Increasing drug permeability

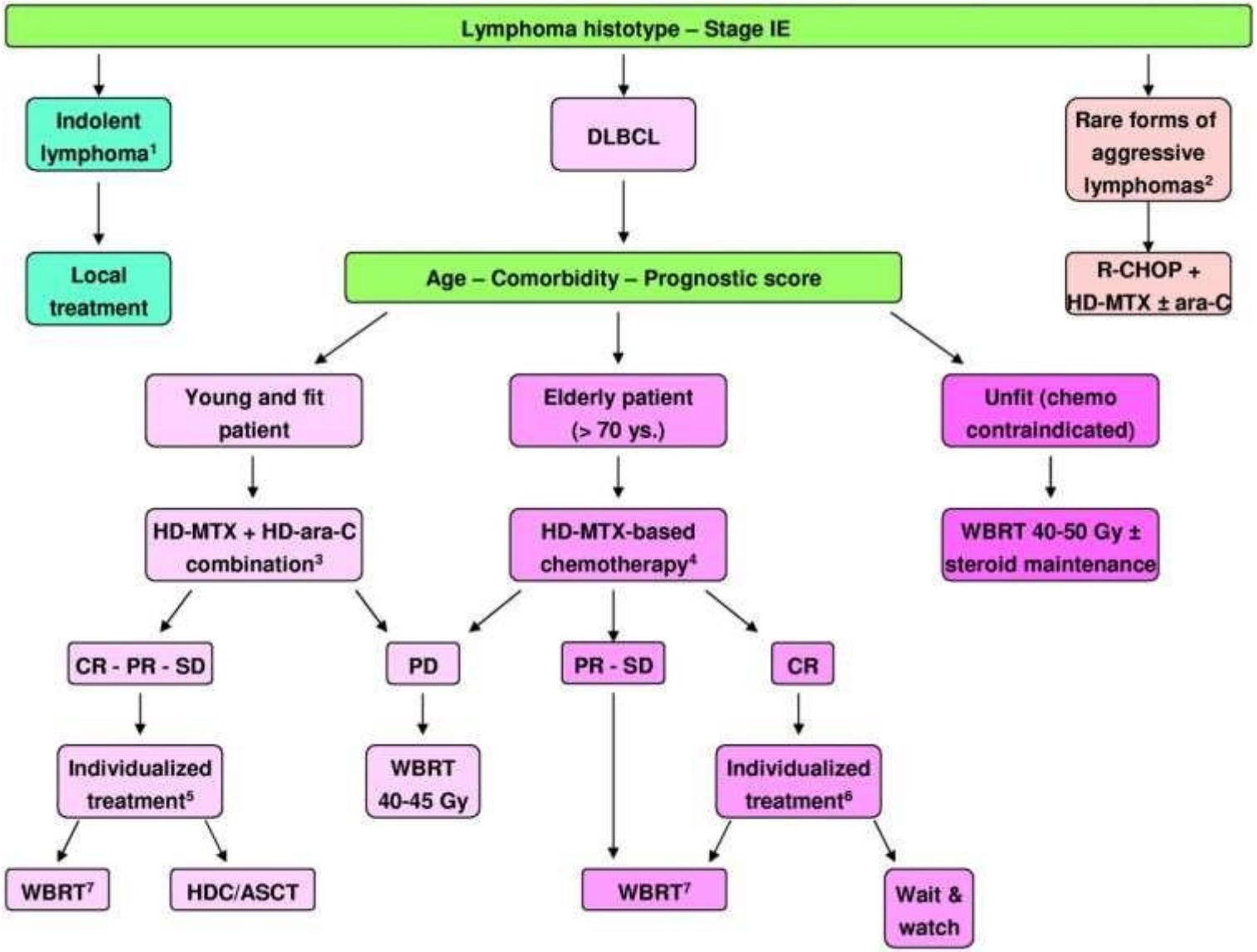
1. Liposomal Drug
2. High dose chemotherapy
3. Selective intra-arterial cerebral infusion (SIACI) technique
4. Inhibiting drug efflux

Selective intra-arterial cerebral infusion (SIACI) technique



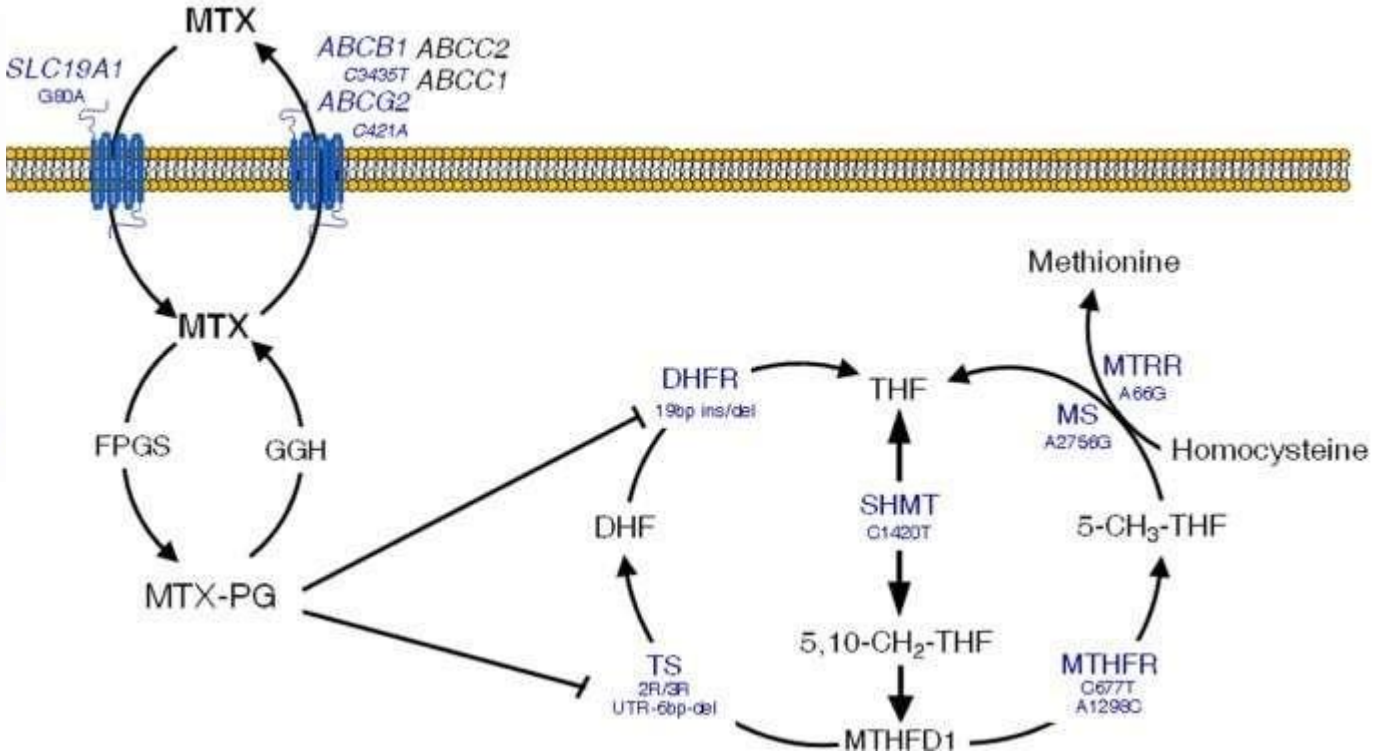


PCNSL-HD MTX


Lymphoma histotype – Stage IE
Indolent lymphoma[1]
DLBCL
Rare forms of aggressive lymphomas[2]
Local treatment
Age – Comorbidity – Prognostic score
R-CHOP + HD-MTX ± ara-C
Young and fit patient
Elderly patient (> 70 ys.)
Unfit (chemo contraindicated)
HD-MTX + HD-ara-C combination[3]
HD-MTX-based chemotherapy[4]
WBRT 40-50 Gy ± steroid maintenance
CR - PR - SD
PD
PR - SD
CR
Individualized treatment[5]
WBRT 40-45 Gy
Individualized treatment[6]
WBRT[7]
HDC/ASCT
WBRT[7]
Wait & watch

High Dose Chemotherapy

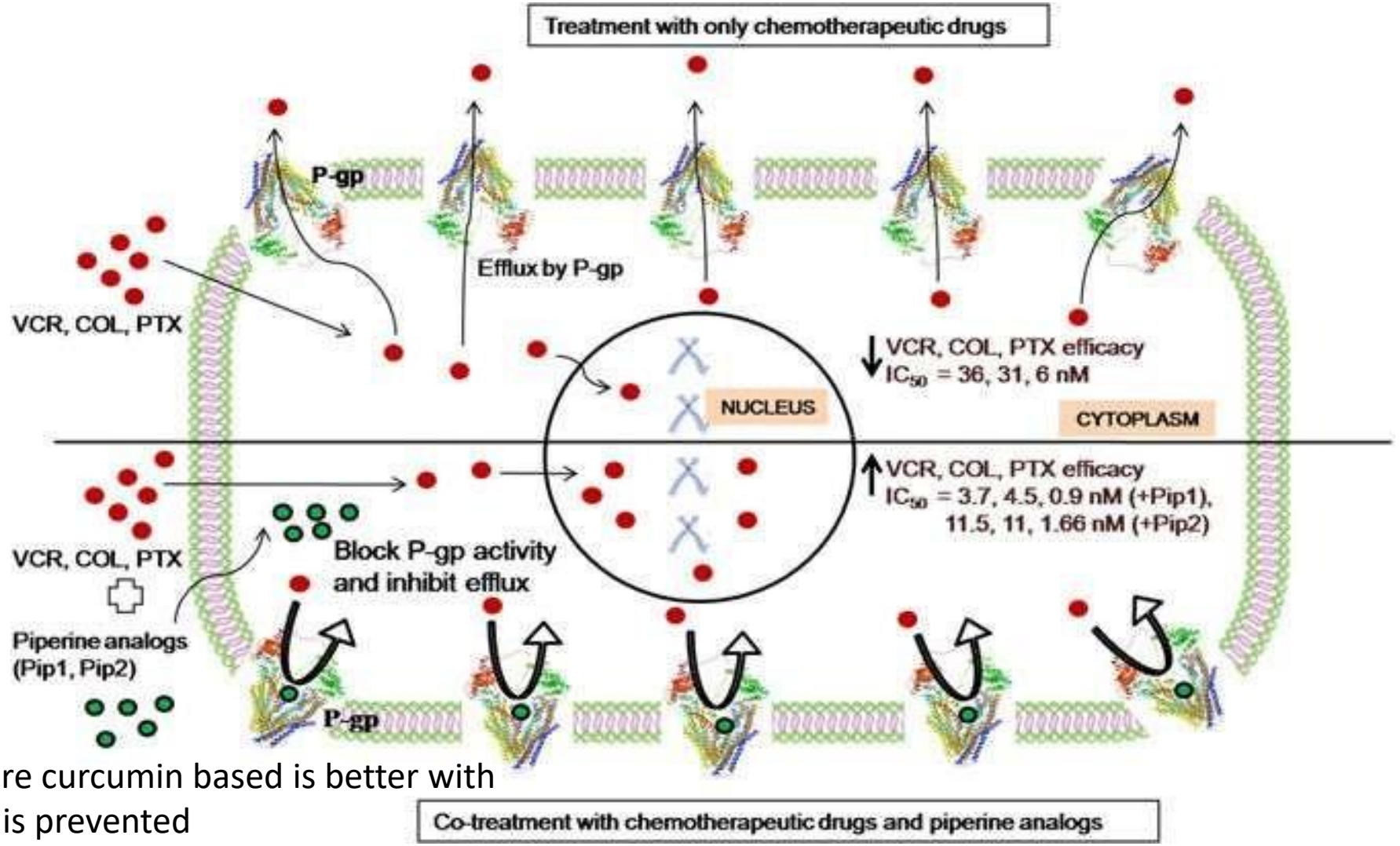
Methotrexate is an antimetabolite that penetrates the blood brain barrier when given in high doses intravenously. MTX exerts its chemotherapeutic effect by counteracting and competing with folic acid in cancer cells, resulting in folic acid deficiency and cell death. Normal cells are not spared; thus, significant side effects can occur.



HD MTX Trials of PCNSL

Trial	Chemotherapy	n	PFS	OS
Regimens with WBRT				
Abrey (2000)	MTX 3.5 g/m^2, pcb, vinc, IT MTX, cytarabine, WBRT	52	129	51
DeAngelis (2002)	MTX 2.5 g/m^2, pcb, vinc, IT MTX, WBRT	98	24	37
Ferreri (2006)	MTX 3.5 g/m^2, cytarabine, idarubicin, thiotepa, WBRT	41	13	15
Ferreri (2009)	MTX 3.5 g/m^2, WBRT	40	5	10
	or			
	MTX 3.5 g/m^2, cytarabine, WBRT	39	9	31
Reduced-dose WBRT				
Morris (2013)	MTX 3.5 g/m^2, ritux, vinc, pcb, cytarabine, reduced-dose WBRT	52	40	79

Drug efflux inhibition



Piperine analogues are curcumin based is better with CNS chemo as efflux is prevented

Table 2. Drug transporters putatively involved in forming the BBB, as well as chemotherapy agents that are substrates for each transporter, and compounds used as potential inhibitors of transporter function

Transporter	HUGO name	Substrates	Inhibitors
P-glycoprotein	ABCB1	Doxorubicin, daunorubicin, docetaxel, paclitaxel, epirubicin, idarubicin, vinblastine, vincristine, etoposide	Verapamil, cyclosporine A, quinidine, PSC 833 (valspodar), GF120918 (elacridar), VX-710 (biricodar), LY335979 (zosuquidar), XR9576 (tariquidar)
MRP1	ABCC1	Etoposide, teniposide, daunorubicin, doxorubicin, epirubicin, melphalan, vincristine, vinblastine	Probenecid, sulfinpyrazone, MK-571, some P-glycoprotein inhibitors (e.g., cyclosporin A, verapamil, PSC 833)
MRP2	ABCC2	Similar to MRP1	Probenecid, MK-571, leukotriene C4
MRP3	ABCC3	Similar to MRP1	Sulfinpyrazone, indomethacin, probenecid
MRP4	ABCC4	Methotrexate, 6-mercaptopurine, thioguianine	Probenecid
MRP5	ABCC5	6-Mercaptopurine, thioguanine	Probenecid, sildenafil
MRP6	ABCC6	Actinomycin D, cisplatin, daunorubicin, doxorubicin, etoposide	Probenecid, indomethacin
BCRP	ABCG2	Mitoxantrone, methotrexate, SN-38, topotecan, imatinib, erlotinib, gefitinib	GF120918, fumitremorgin C

DIRECT ADMINISTRATION INTO CNS

- Intratumoral or intracavitory injection
- Intrathecal or intraventricular injection
- Convection enhanced delivery

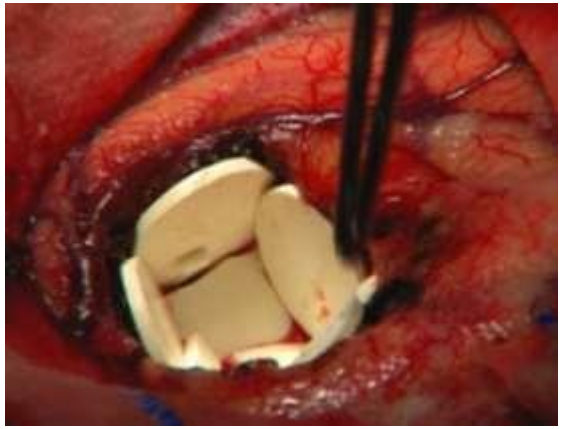
CARMUSTINE WAFERS

- Polifersan Wafer slowly undergoes biodegradation releasing active BCNU

- Used in high grade glioma

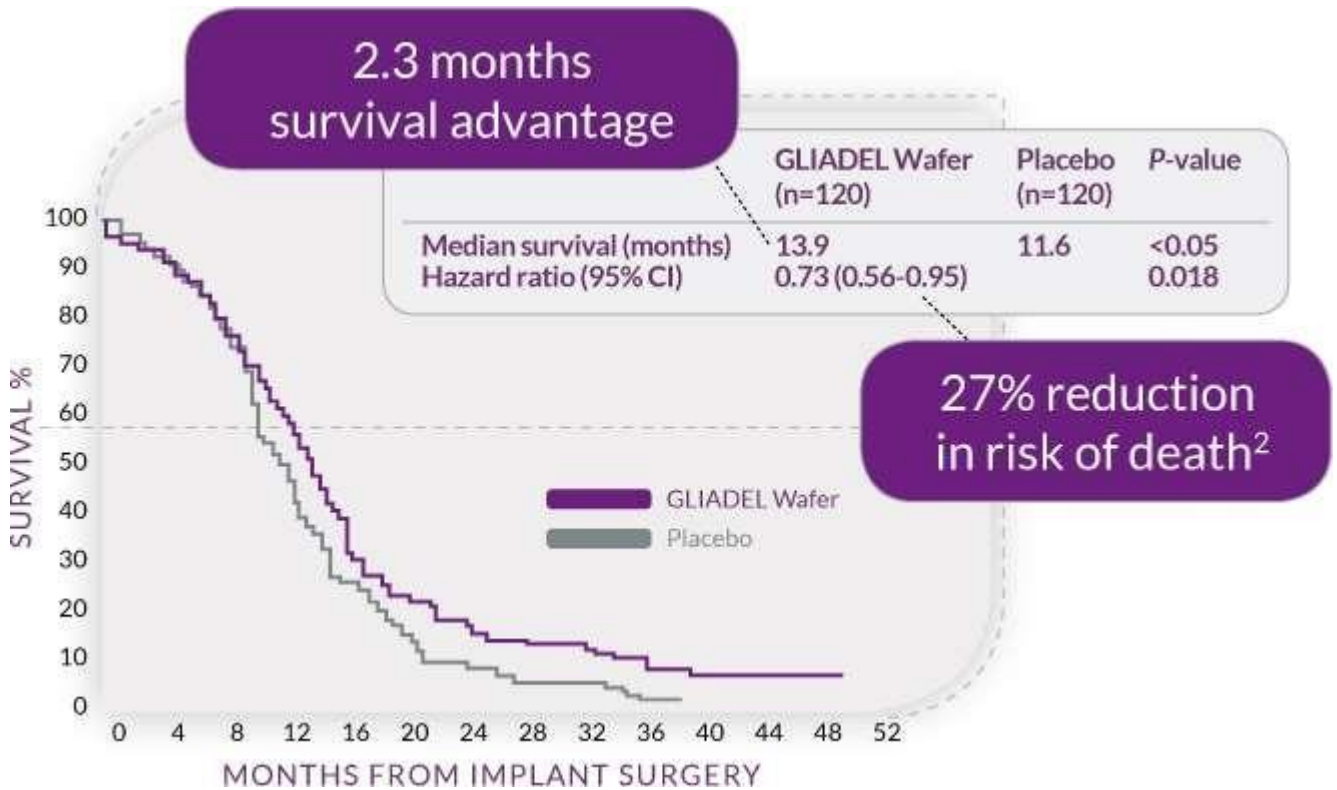
- Advantages
  a. minimal systemic toxicity
  b. No limitation posed by BBB
  c. High local concentration

S/E – seizures, cerebral infection



A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma[1,2]

Manfred Westphal,[3] Dana C. Hilt, Enoch Bortey, Patrick Delavault, Robert Olivares, Peter C. Warnke, Ian R. Whittle, Juha Jääskeläinen, and Zvi Ram



Chemotherapy wafers for high grade glioma (Review)

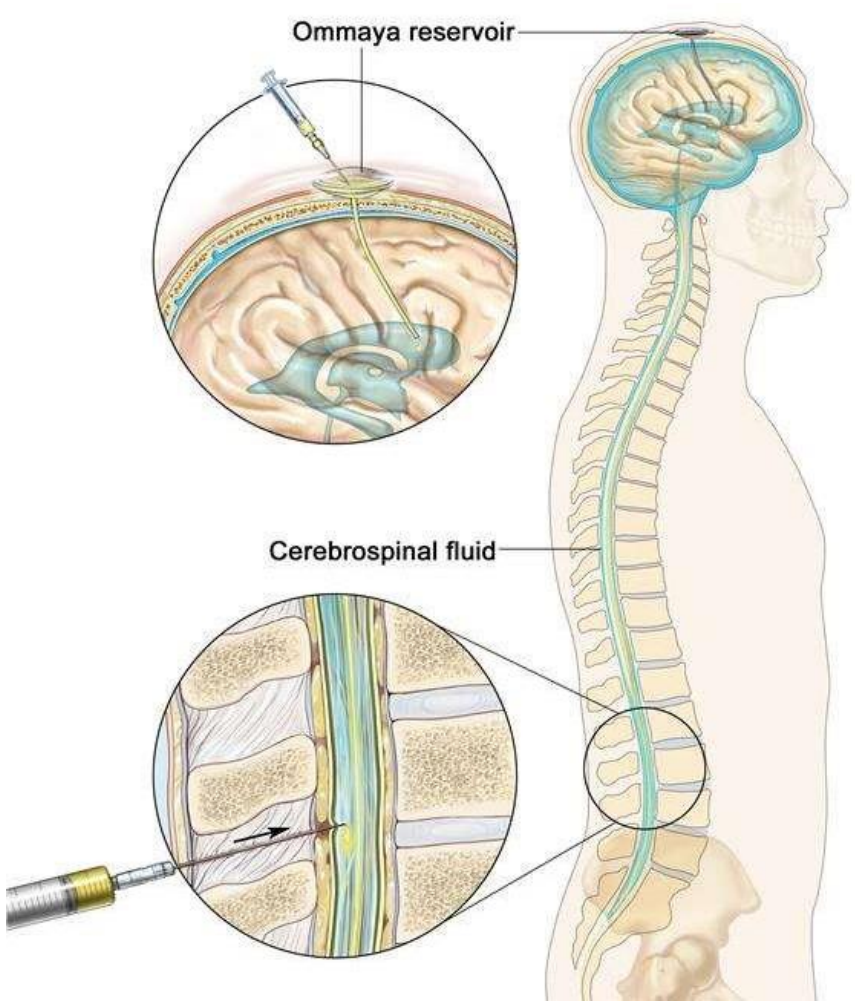
Cochrane Library

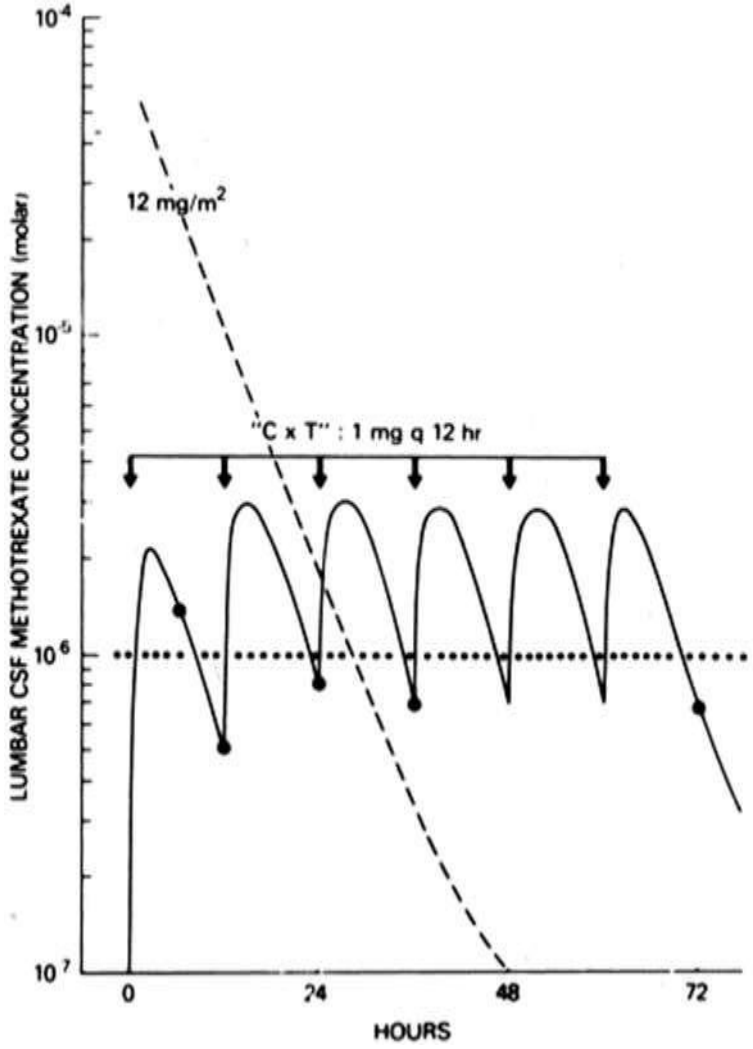
Cochrane Database of Systematic Reviews

CONCLUSION

- There is evidence that Gliadel increases survival in primary therapy for HGG but not for recurrent disease, and that this benefit is without a significant increase in adverse events

Intrathecal Therapy

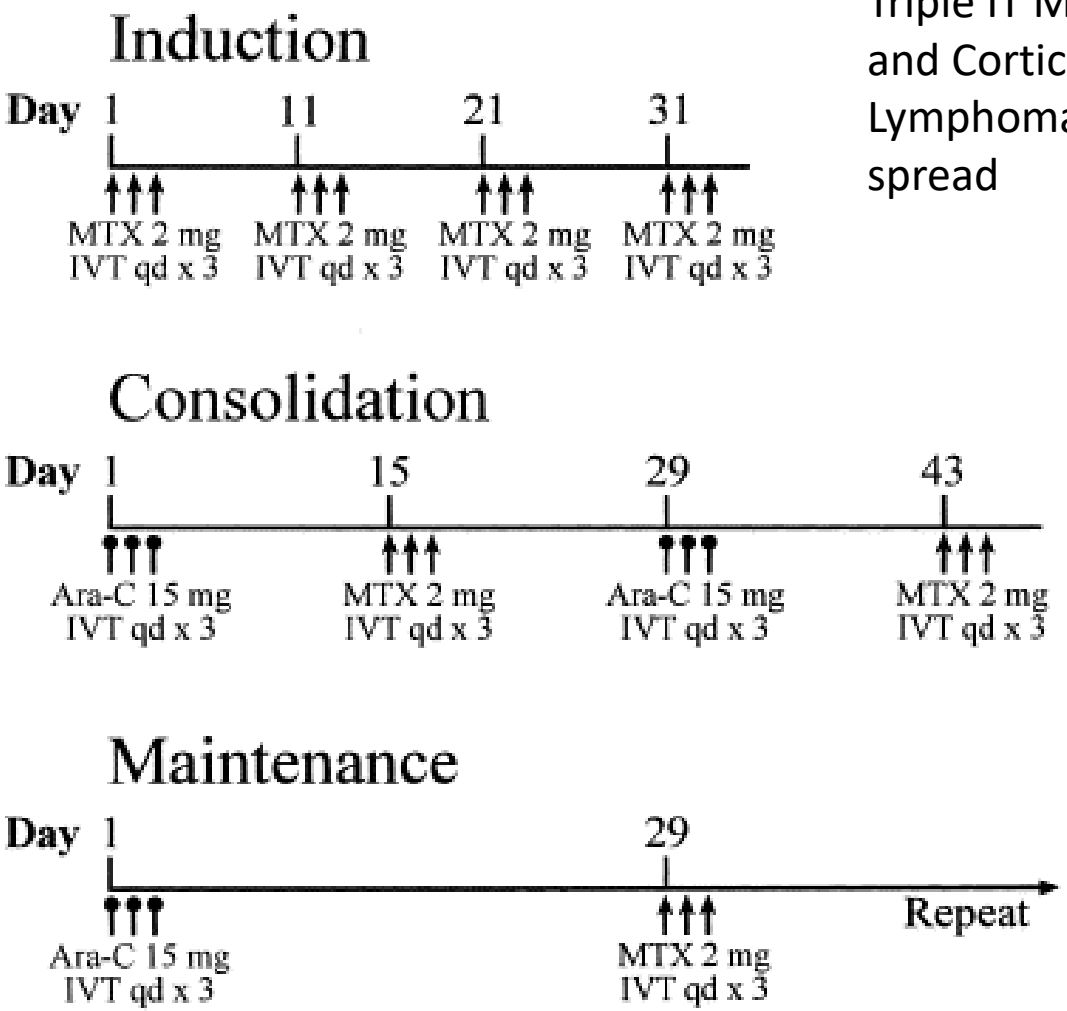




Intrathecal drugs

Drugs	Dose	Indication
Methotrexate	15 mg/week	Lymphoma/Breast/Ovary/ SCLC/NSCLC/GI
Cytarabine	30 mg/week	Lymphoma
Thiotepa		Solid malignancy
Topotecan		neuroblastoma
Mafosfamide	20 mg/week	RMS/PNET
Busulfan		CML
Rituximab		PCNSL
Trastuzumab	50-100 mg/week	Her2+ CA breast

ITMtx-ITAraC Protocol



Triple IT MTX, Cytosine arabinoside and Corticosteroids
Lymphoma n Leptomeningeal spread

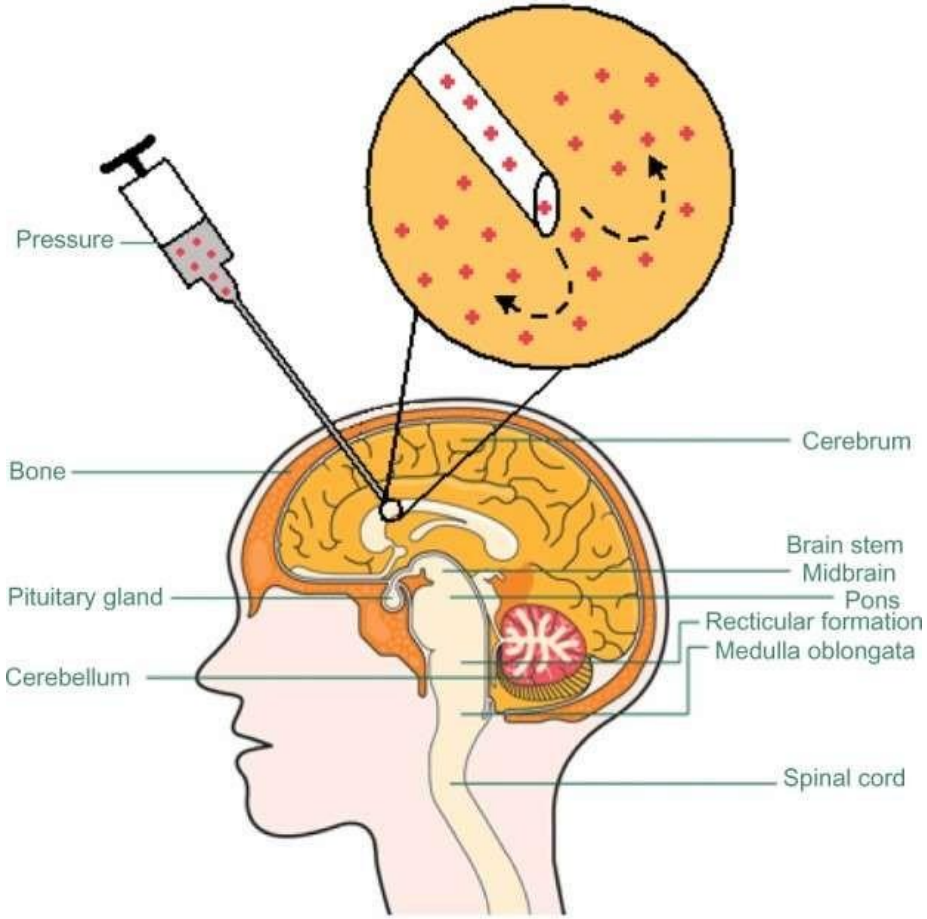
Leptomeningeal metastasis

- Local injury to nerves traveling through the spinal fluid (cranial nerve palsies, weakness, paresthesias, or pain).
- Direct invasion into the brain or spinal tissues or interruption of blood supply to thosetissues (focal findings or seizures).
- Obstruction of normal CSF flow pathways, increased intracranial pressure, and hydrocephalus (headache, nausea, vomiting, and dizziness).
- Interference with cognitive function (encephalopathy).
- Leptomeningeal metastases are manifested by symptoms and signs of injury to brain parenchyma, cranial nerves, and/or spinal nerves.
- Treatment of leptomeningeal metastases from solid tumors is often limited to symptom control because it is minimally effective and because leptomeningeal metastases frequently occur in the context of widespread systemic metastases intrathecal therapy with methotrexate, liposomal cytarabine, or thiotepa may increase the median survival to 3 to 6 months
- Leptomeningeal metastases from hematologic malignancies may have a much better response to systemic (e.g., high-dose methotrexate in secondary CNS lymphoma)
- Drugs can be administered intrathecally through an Ommaya reservoir or by repeated lumbar punctures. Liposomal cytarabine is a sustained-release formulation of the drug that requires less frequent administration, but it is more likely to cause an acute aseptic meningitis

ITM for Lepto Meningeal spread of Solid tumors

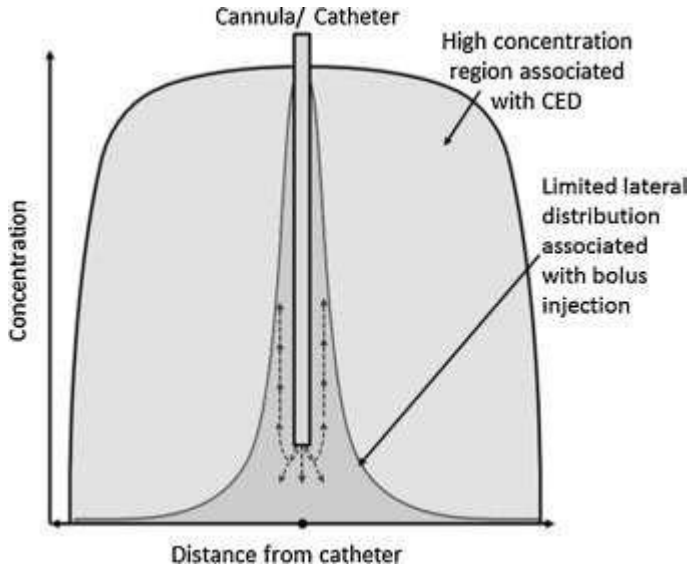
Author (year)	Primary cancer	Treatment (No. of patients)	Median survival	Response
Wasserstrom et al.[66] (1982)	Breast >> lung > melanoma	Intraventricular MTX* (n=90)	5.8 months	50% (clinical) 23% (cytological)
Ongeroboer de Visser et al.[50] (1982)	Breast	Intraventricular/intrathecal MTX (n=25/33†)	6 months for intraventricular MTX (n=16) 2 months for intrathecal MTX (n=9)	80% (clinical) 81% (cytological)
Hitchins et al.[38] (1987)	SCLC, breast >> others	Intraventricular MTX vs. triple (n=44)	8 weeks	55% (clinical) 50% (cytological)
Fizazi et al.[23] (1996)	Breast ca.	Intrathecal MTX (n=62)	7 weeks for low-dose (n=21) 14 weeks for high-dose (n=41)	32% (clinical) 24% (cytological)
Chamberlain and Kormanik[17] (1998)	NSCLC	Intraventricular MTX* (n=32)	5.0 months	32% (clinical) 53% (cytological)
Waki et al.[65] (2009)	Lung, breast >> others	Intrathecal MTX* (n=31/85†)	144 days for intrathecal-treated	55% (mixed clinical & cytological criteria)
Gauthier et al.[26] (2010)	Breast ca.	Intrathecal MTX* (n=80/91†)	4.5 months	73% (clinical) 20% (cytological)
Gwak et al.[34] (2013)	NSCLC	Intraventricular MTX* (n=105)	3.0 months	29% (ICP) 13% (cytological)

Convection-Enhanced Delivery



ADVANTAGES OF CED

- ✓ Less size dependent
- ✓ Large volume of brain tissue
- ✓ More uniform drug concentration
- ✓ paclitaxel, topotecan



PRECISE Trial:significant improvement in PFS(17.7 vs
11.4 weeks; P = .0008

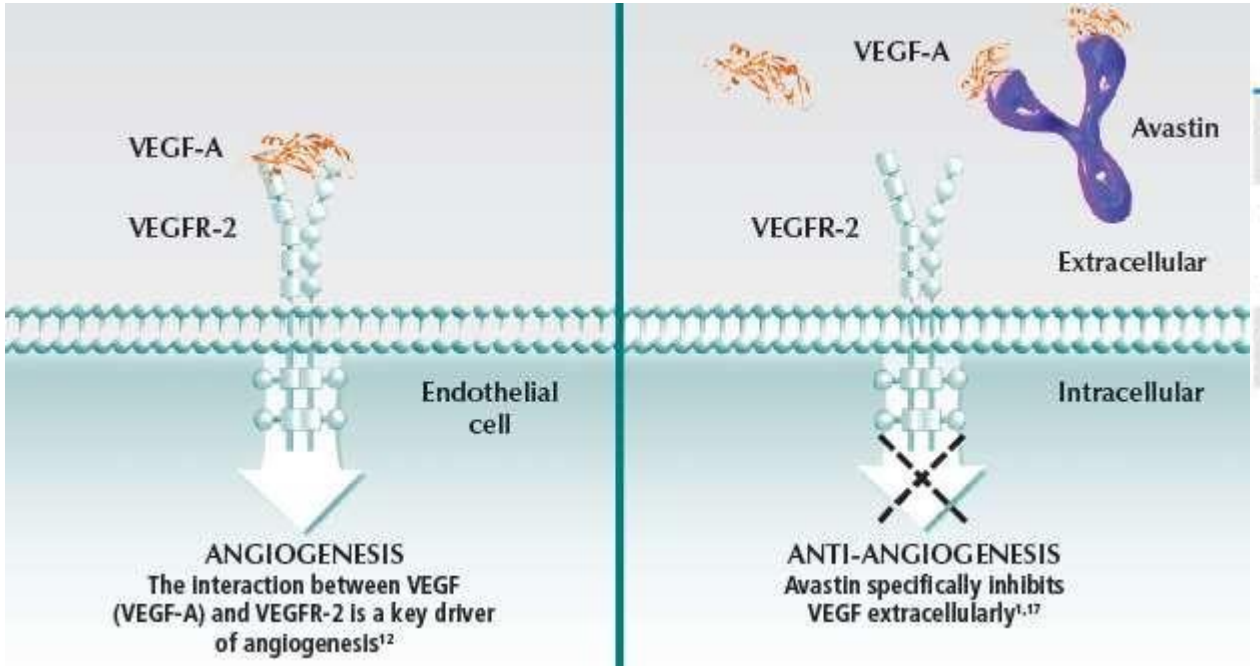
Kunwar S Neuro Oncol. 2010 Aug;12(8):871-81

Angiogenesis Inhibitors in CNS tumor

Angiogenesis inhibitors in Glioma

Target	Agent	Disease Setting	Study Phase
Integrins	Cilengitide	nGBM rGBM	Phase III Phase I/II
Angiopoietin/Tie 2	CVX-060	rGBM	Phase I/II
VEGF	VEGF-trap (aflibercept)	rGBM nGBM	Phase II Phase I
	VEGFR TKIs (cabozantinib, cediranib, axitinib, pazopanib)	rGBM, nGBM	Phase I, II, III
	Bevacizumab + strategies	nGBM, rGBM	Phase I, II, III
Endothelial cell proliferation	Metronomic temozolomide	nGBM, rGBM	Phase II, III

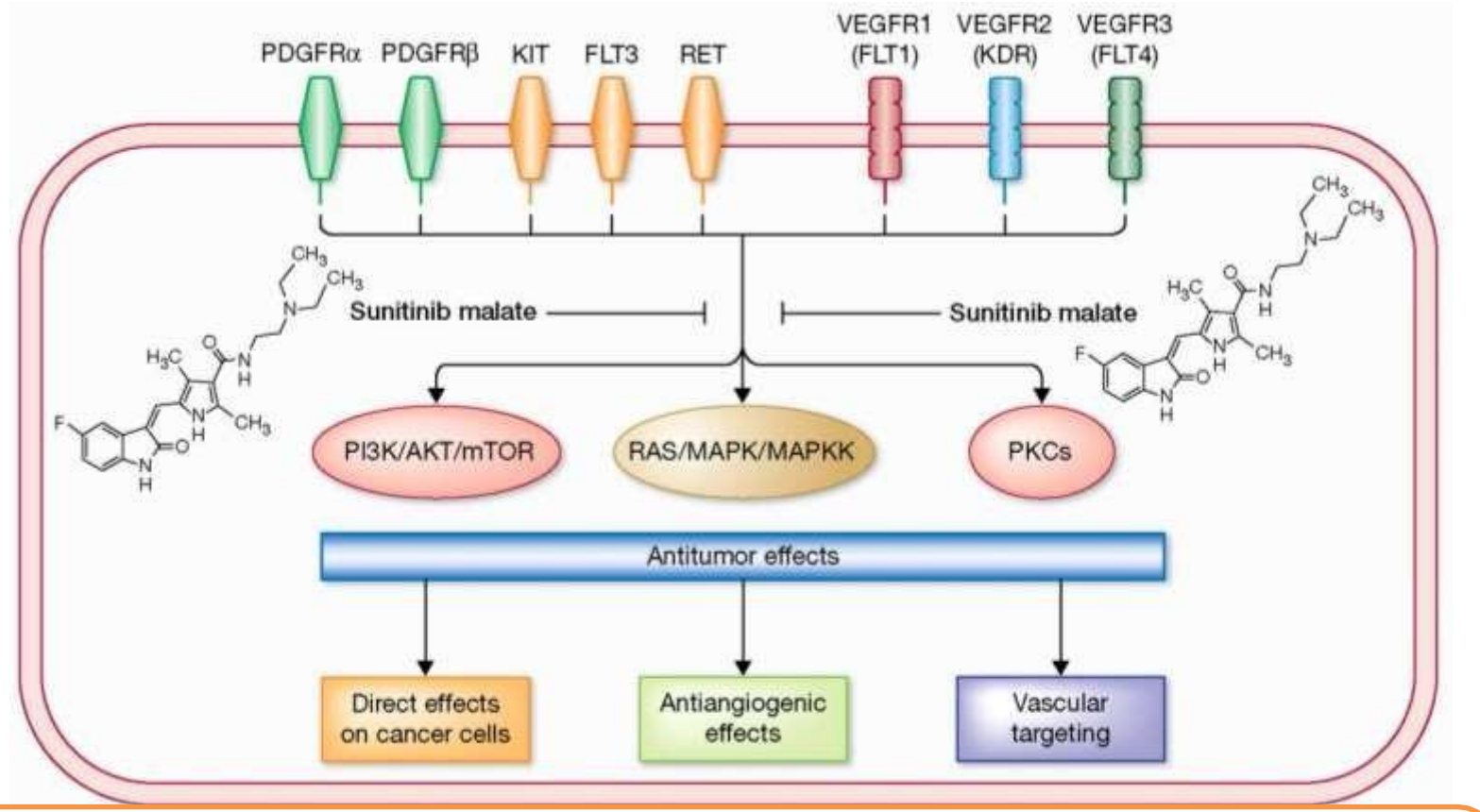
Angiogenesis Inhibitor- Bevacizumab



	Bevacizumab* (N = 85)	Bev + Irinotecan (N = 82)
Overall response rate	28.2%	37.8%
6-month progression-free survival	42.6%	50.3%
Overall survival	9.2 mo	8.7 mo
Duration of response	5.6 mo	4.3 mo

Friedman HS, Prados MD, Wen PY, et al. J Clin Oncol. 2009;27:4733-4740.Cloughesy, et al,Journal of Clinical Oncology 26, no. 15

Sunitinib in recurrent Meningioma



Sunitinib :50 mg/d for days 1–28 of every 42-day
PFS6 rate : 42% Median PFS : 5.2 months (95% CI: 2.8–8.3 mo) median overall survival : 24.6 months (95% CI: 16.5–38.4 mo).

Sunitinib ref: Kaley TJ, Wen P, Schiff D, et al. Phase II trial of sunitinib for recurrent andprogressive atypical and anaplastic meningioma. Neuro-Oncology 2014; 17:116-121

Chemotherapy Protocols for common CNS tumors

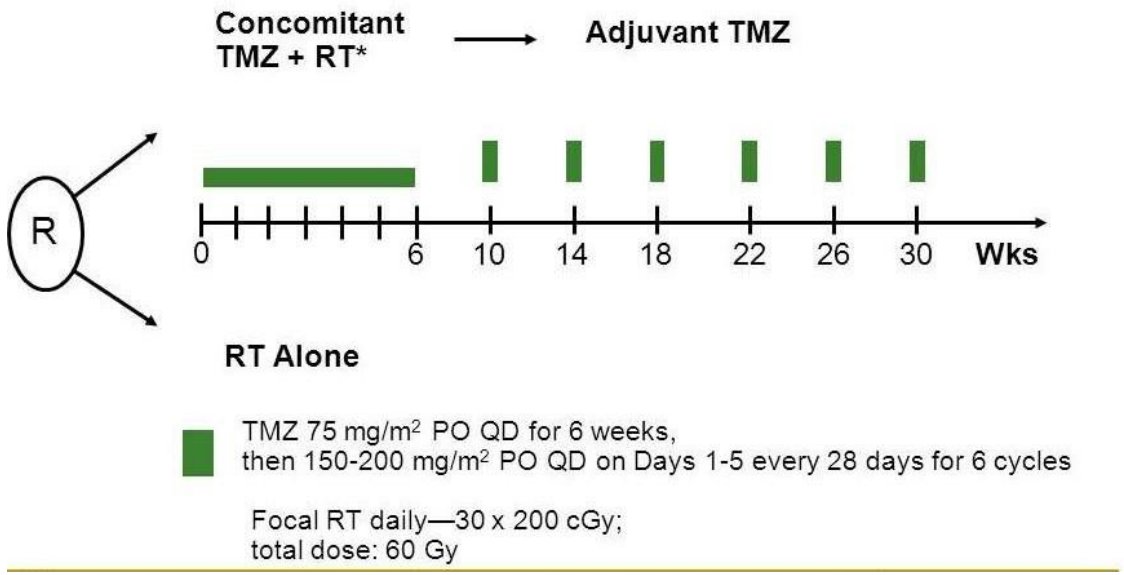
RT-TMZ

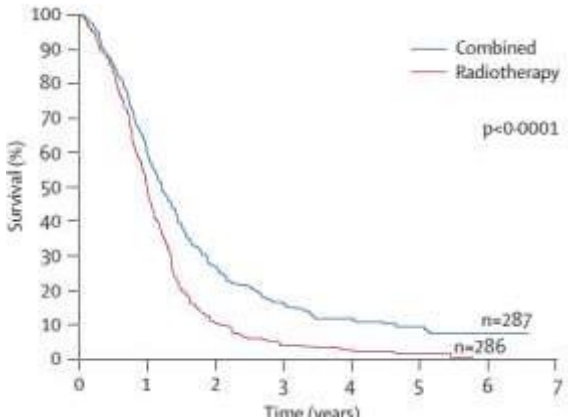
INDICATION

GBM

Anaplastic Glioma

Low-Grade Infiltrative Supratentorial Astrocytoma/ Oligodendroglioma





	Deaths/ patients	Hazard ratio (95% CI)	Median (months; 95% CI)	2 years (%)	3 years (%)	4 years (%)	5 years (%)
Overall							
Radiotherapy	278/286	1·0	12·1 (11·2-13·0)	10·9 (7·6-14·8)	4·4 (2·4-7·2)	3·0 (1·4-5·7)	1·9 (0·6-4·4)
Combined	254/287	0·6 (0·5-0·7)	14·6 (13·2-16·8)	27·2 (22·2-32·5)	16·0 (12·0-20·6)	12·1 (8·5-16·4)	9·8 (6·4-14·0)

Stupp et al Journal of Clinical Oncology 22, no. 14_suppl (July 2004) 2-2. Stupp et al Lancet Oncol. 2009 May;10(5):459-66. doi: 10.1016/S1470-2045(09)70025-7. Epub 2009 Mar 9.
Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial.

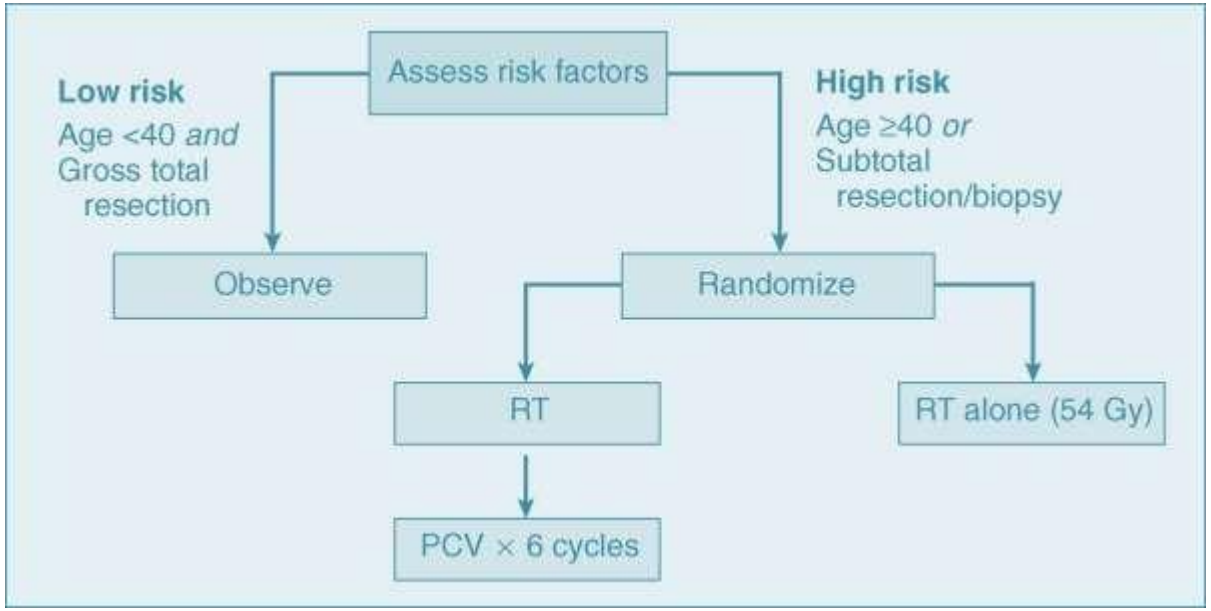
PC

INDICATION

Anaplastic Oligoastrocytoma/Anaplastic Oligodendroglioma Adjuvant/Recurrent

Low-Grade Infiltrative Supratentorial Astrocytoma/Oligodendroglioma Adjuvant/Recrrent

GBM Recurrent Anaplastic Glioma Adjuvant/Recrrent Medulloblastoma



RTOG 98-02 Updated 2014:
median survival (13.3 vs. 7.8 years, p = 0.03; HR = 0.59)
PFS (10.4 vs. 4.0 years, p = 0.002; HR = 0.50)

Shaw EG, Wang M, Coons SW, et al., Randomized trial of radiation therapy plus procarbazine, lomustine, and vincristine chemotherapy for supratentorial adult low-grade glioma: initial results of
RTOG 9802. J Clin Oncol 2012;30:3065-3070 Mehta et al Mature Survival Data from RTOG 9802: A Phase III Study of Radiation Therapy (RT) With or Without Procarbazine, CCNU, and Vincristine (PCV) for Adult Patients with High-Risk Low-Grade Glioma (LGG)
van den Bent MJ, Brandes AA, Taphoorn MJ. Adjuvant Procarbazine, Lomustine, and Vincristine Chemotherapy in Newly Diagnosed Anaplastic Oligodendroglioma: Long-Term

Targeted therapy for CNS Metastasis

Drug	Mechanism of action	Cancer
Capecitabine ± lapatinib,	HER2	Her2+Ca Breast
Ceritinib, alectinib	ALK	ALK +NSCLC
Crizotinib	ALK/ROS-1	ALK/ROS-1 +NSCLC
Osimertinib	T790M EGFR	T790M+ NSCLC Adeno Carcinoma
Erlotinib, afatinib, gefitinib	EFGR	EGFR+NSCLC
Dabrafenib/Vemurafanib	BRAF	BRAF Mutant Melanoma/NSCLC
Pembrolizumab	PD-1	Melanoma/NSCLC
Ipilimumab + nivolumab (melanoma)	CTLA4/PDL1	Melanoma

Adult Astrocytoma

Systemic Therapy for Adult Low-Grade Infiltrative Supratentorial Astrocytoma/Oligodendroglioma[1]	
Note: All recommendations are Category 2A unless otherwise indicated.	
Adjuvant Treatment	
REGIMEN	**DOSING**
Combination PCV (lomustine + procarbazine + vincristine) (Category 1)[2]	**Day 1:** Lomustine 110mg/m² orally **Days 8–21:** Procarbazine 60mg/m² orally once daily **Days 8 and 29:** Vincristine 1.4mg/m² (maximum 2mg) IV. Repeat every 6 weeks.
Temozolomide[3–5]	**Days 1–49:** Temozolomide 75mg/m² orally. Repeat cycle every 11 weeks (7 weeks on/4 weeks off) for 6 cycles. **OR** **For children/adolescents:** Temozolomide monthly 5-day courses at doses of 200mg/m²/day (patients with no prior craniospinal irradiation [CSI]) or 180mg/m²/day (prior CSI). **OR** **Days 1–21:** Temozolomide 75mg/m²/day orally. Repeat cycle every 28 days.
Recurrent or Progressive, Low Grade Disease	
Temozolomide[3,6a]	**Days 1–49:** Temozolomide 75mg/m² orally. Repeat cycle every 11 weeks (7 weeks on/4 weeks off) for 6 cycles. **OR** **Days 1–5:** Temozolomide 150mg/m² to 200mg/m²; when patients progress during conventional temozolomide treatment, change temozolomide to a 50mg/m² daily regimen. Repeat cycle every 28 days.
Combination PCV regimens (lomustine + procarbazine + vincristine)[7]	**Day 1:** Lomustine 110mg/m² orally **Days 8–21:** Procarbazine 60mg/m² orally once daily **Days 8 and 29:** Vincristine 1.4mg/m² (maximum 2mg) IV. Repeat every 6 weeks.
Platinum-based regimen: Carboplatin[8]	**Day 1:** Carboplatin 350mg/m² IV **Days 1–3:** Teniposide 50mg/m² IV. Repeat cycle every 4 weeks.
Platinum-based regimen: Carboplatin[9]	Carboplatin 560mg/m² IV at 4-week intervals; continued until disease progression, unacceptable toxicity, or for 12 additional courses after achieving maximal response.
Platinum-based regimen: Cisplatin[10]	**Days 1–3:** Cisplatin 25mg/m²/day IV + etoposide 100mg/m²/day IV. Repeat cycle every 4 weeks for first 3 cycles, then repeat every 5 weeks for next 3 cycles, then repeat every 6 weeks for the last 3 cycles; total 10 cycles over approximately 10–11 months (total dose 750mg/m² cisplatin and 3,000mg/m² etoposide).
Lomustine[11]	Lomustine 130mg/m² orally every 6 weeks.
Carmustine[12]	Carmustine 150–200mg/m² IV as a single dose or divided over 2 days given every 6 weeks OR 75–100mg/m²/day IV for 2 days every 6 weeks.
Systemic Therapy for Anaplastic Gliomas[1]	
Adjuvant Treatment	
Temozolomide[13,14]	**Days 1–5:** Temozolomide 200mg/m²/day orally. Repeat cycle every 4 weeks until disease progression or for up to 24 cycles.
PCV with deferred RT[13]	**Day 1:** Lomustine 110mg/m² orally **Days 8–21:** Procarbazine 60mg/m² orally once daily **Days 8 and 29:** Vincristine 1.4mg/m² (maximum 2mg) IV. Repeat every 6 weeks.
Concurrent temozolomide (with RT)[15]	2 Gy given 5 days/week for 6 weeks plus continuous daily oral temozolomide (75mg/m²/day, 7 days per week from the first to the last day of radiotherapy), followed by 6 cycles of adjuvant temozolomide 150–200mg/m²/day for 5 days. Repeat cycle every 28 days.

continued

Anaplastic Recurrent Glioma

Systemic Therapy for Anaplastic Gliomas[1] (continued)

Recurrence Therapy

REGIMEN	DOSING
Temozolomide[4,6,16]	Temozolomide 50mg/m² daily for up to 1 year or until disease progression. **OR** **For children/adolescents:** Temozolomide monthly 5-day courses at doses of 200mg/m²/day (patients with no prior CSI) or 180mg/m²/day (prior CSI). **OR** **Days 1–5:** Temozolomide 150mg/m² to 200mg/m² 5 days of each 28-day cycle; when patients progress during conventional temozolomide treatment, change temozolomide to a 50mg/m² daily regimen. **OR** **Days 1–5:** Temozolomide 150mg/m² to 200mg/m². Repeat cycle every 28 days.
Lomustine or carmustine[11,12,17]	**Day 1:** Lomustine 100–130mg/m²/day orally. Repeat cycle every 6 weeks. **OR** Carmustine 150–200mg/m² IV as a single dose or divided over 2 days given every 6 weeks OR 75–100mg/m²/day IV for 2 days every 6 weeks.
Combination PCV regimens (lomustine + procarbazine + vincristine)[7]	**Day 1:** Lomustine 110mg/m² orally **Days 8–21:** Procarbazine 60mg/m² orally once daily **Days 8 and 29:** Vincristine 1.4mg/m² (maximum 2mg) IV. Repeat every 6 weeks.
Bevacizumab[18–20b]	**Day 1:** Bevacizumab 10mg/kg IV. Repeat cycle every 14 days.
Bevacizumab + irinotecan[21,22c]	**Day 1:** Bevacizumab 10mg/kg IV plus irinotecan 125mg/m² IV. Repeat cycle every 2 weeks. **OR** Bevacizumab 10mg/mg² IV plus irinotecan 340mg/m² IV in patients receiving enzyme-inducing antiepileptic drugs (EIAED). Repeat cycle every 14 days.
Bevacizumab + nitrosurea[23]	**Days 1 and 15:** Bevacizumab 10mg/kg IV **Days 1 and 8:** Fotemustine 75mg/m² IV Followed after a 3-week interval by a maintenance phase of bevacizumab 10mg/kg IV plus fotemustine 75mg/m² IV. Repeat cycle every 3 weeks.
Bevacizumab + carboplatin (Category 2B)[24,25]	**Day 1:** Bevacizumab 10mg/kg IV plus carboplatin AUC 4–6mg·min/mL, depending on the patient's prior treatment history and bone marrow reserves; cycle 2 doses of carboplatin (every 28 days) and 3 doses of bevacizumab (every 14 days) and lasted 6 weeks.
Irinotecan[26,27]	**Day 1:** Irinotecan 350mg/m² IV to patients on non-enzyme-inducing antiepileptic drugs (NEIAED) or 600mg/m² to patients on EIAED. Repeat cycle every 21 days. **OR** **Day 1:** Irinotecan 350mg/m² IV. Repeat cycle every 21 days.
Platinum-based regimen: Carboplatin[8]	**Day 1:** Carboplatin 350mg/m² IV **Days 1–3:** Teniposide 50mg/m² IV. Repeat cycle every 4 weeks.
Platinum-based regimen: Carboplatin[9]	Carboplatin 560mg/m² IV at 4-week intervals; continued until disease progression, unacceptable toxicity, or for 12 additional courses after achieving maximal response.
Platinum-based regimen: Cisplatin[10]	**Days 1–3:** Cisplatin 25mg/m²/day IV + etoposide 100mg/m²/day IV. Repeat cycle every 4 weeks for first 3 cycles, then repeat every 5 weeks for next 3 cycles, then repeat every 6 weeks for the last 3 cycles; total 10 cycles over approximately 10–11 months (total dose 750mg/m² cisplatin and 3,000mg/m² etoposide).
Cyclophosphamide (Category 2B)[28,29]	**Days 1–2:** Cyclophosphamide 750mg/m² IV. Repeat cycle every 28 days.
Etoposide[30]	Etoposide 50mg/day IV given until the neutrophil count dropped to < 1.0 × 10⁹/L or the platelets fell to < 75 × 10⁹/L and resumed when the counts rose to normal levels.

A phase III international trial (EORTC 26053 or “CATNON”) is ongoing, in which patients with anaplastic glioma without 1p/19q codeletion are randomly assigned to either radiation alone or radiation with temozolomide during radiation and/or after radiation. Interim results indicate improved OS with post-RT temozolomide (HR reduction for OS of 0.645, p= 0.0014), further supporting adjuvant chemotherapy. Anaplastic astrocytomas have a high propensity to transform into glioblastoma. ■ Although standard therapy has not yet fully been established, anaplastic astrocytomas (both IDH wild-type and IDH mutant) are often treated like glioblastoma, with maximal safe resection followed by radiation with concurrent and adjuvant TMZ

In patients with anaplastic oligodendroglioma or oligoastrocytoma with IDH mutation and 1p/19q codeletion, chemotherapy with procarbazine, lomustine, and vincristine (PCV) after radiation significantly improves OS.

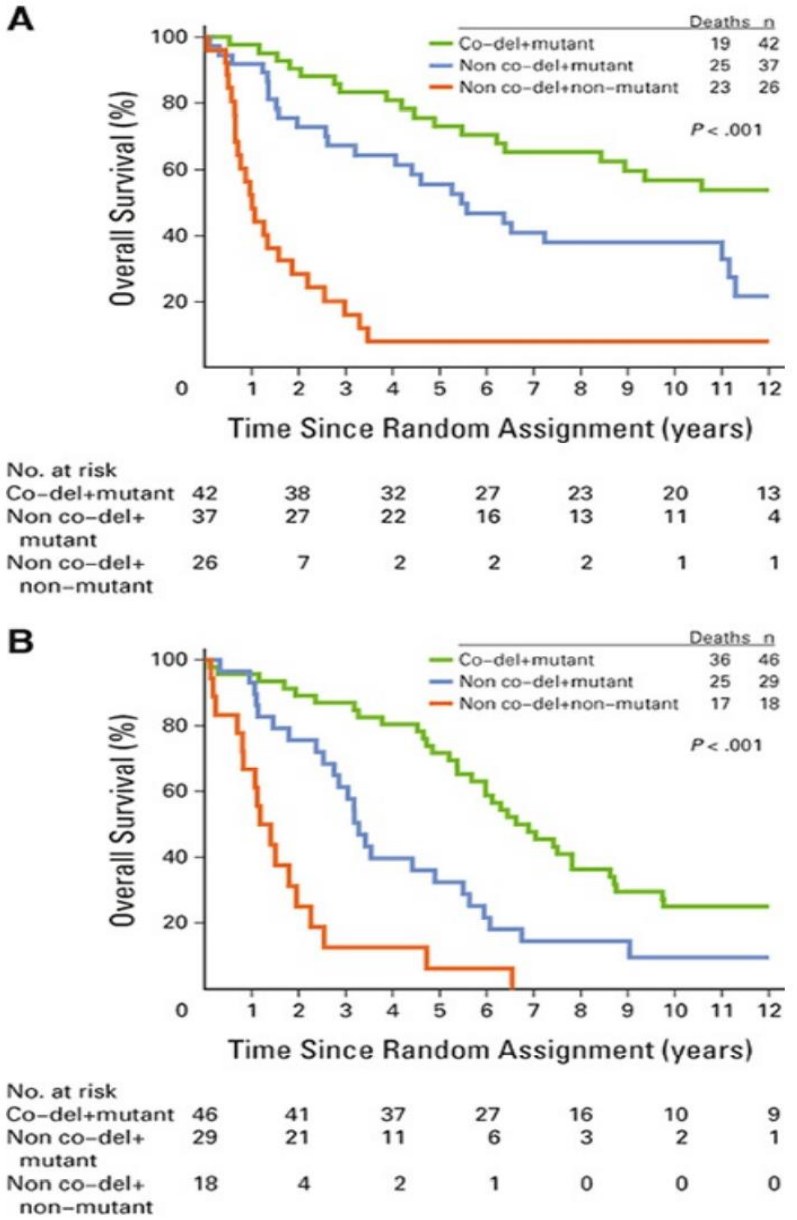
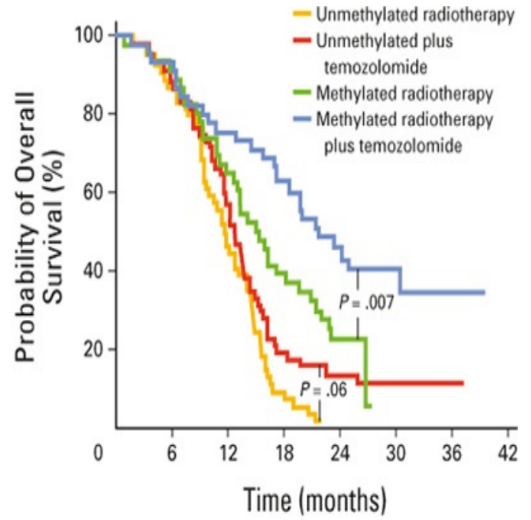


Fig. 15-7 Kaplan–Meier estimates of OS for patients with anaplastic oligodendroglioma or anaplastic astrocyto whose tumors were *IDH* mutants with 1p/19q codeletion, mutants with no codeletion, and nonmutants with no codeletion after procarbazine–lomustine–vincristine (PCV) plus radiotherapy (RT) and RT alone.

GBM

Systemic Therapy for Glioblastoma[1]	
Adjuvant Treatment	
Concurrent temozolomide (with RT)[15]	2 Gy given 5 days/week for 6 weeks plus continuous daily oral temozolomide (75mg/m²/day, 7 days per week from the first to the last day of radiotherapy), followed by 6 cycles of adjuvant temozolomide 150–200mg/m²/day for 5 days. Repeat cycle every 28 days.
Post-RT temozolomide[32]	**Days 1–5:** Temozolomide 150–200mg/m²/day orally for 5 days. Repeat cycle every 28 days.
Temozolomide + standard RT[33]	**Days 1–5:** Temozolomide 200mg/m², orally plus: Standard RT: 60.0 Gy administered in 2.0 Gy fractions over 6 weeks.
Recurrence Therapy	
Bevacizumab[34–36b]	**Day 1:** Bevacizumab 10mg/kg IV. Repeat cycle every 14 days.
Bevacizumab + irinotecan[22,34–36c]	**Day 1:** Bevacizumab 10mg/kg IV. Repeat cycle every 14 days. After tumor progression, immediately treat with bevacizumab 10mg/kg IV plus irinotecan 340mg/m² or 125mg/m² IV every 14 days, depending on use of EIAEDs.
Bevacizumab + nitrosurea[23c]	**Days 1 and 15:** Bevacizumab 10mg/kg IV **Days 1 and 8:** Fotemustine 75mg/m² IV Followed after a 3-week interval by a maintenance phase of bevacizumab 10mg/kg IV plus fotemustine 75mg/m² IV. Repeat cycle every 3 weeks.
Bevacizumab + carboplatin (Category 2B)[24,25c]	**Day 1:** Bevacizumab 10mg/kg IV plus carboplatin AUC 4–6mg·min/mL, depending on the patient's prior treatment history and bone marrow reserves; cycle 2 doses of carboplatin (every 28 days) and 3 doses of bevacizumab (every 14 days) for 6 weeks.
Temozolomide[6,32,37]	**Days 1–5:** Temozolomide 150mg/m² to 200mg/m²; when patients progress during conventional temozolomide treatment, change temozolomide to a 50mg/m² daily regimen. Repeat cycle every 28 days. **OR** 2 Gy given 5 days/ week for 6 weeks plus continuous daily oral temozolomide (75mg/m²/day, 7 days per week from the first to the last day of radiotherapy), followed by 6 cycles of adjuvant temozolomide 150–200mg/m²/day for 5 days. Repeat cycle every 28 days. **OR** **Chemotherapy-naive patients:** **Days 1–5:** Temozolomide 200mg/m²/day. **Chemotherapy-experienced patients:** **Days 1–5:** Temozolomide 150mg/m²/day, increasing to 200mg/m²/day in the absence of grade 3/4 toxicity. Repeat cycle every 28 days.
Lomustine or carmustine[11,12,17]	**Day 1:** Lomustine 100–130mg/m²/day orally. Repeat cycle every 6 weeks. **OR** Carmustine 150–200mg/m² IV as a single dose or divided over 2 days given every 6 weeks **OR** 75–100mg/m²/day IV for 2 days every 6 weeks.
Combination PCV regimens (lomustine + procarbazine + vincristine)[7]	**Day 1:** Lomustine 110mg/m² orally **Days 8–21:** Procarbazine 60mg/m² orally once daily **Days 8 and 29:** Vincristine 1.4mg/m² (maximum 2mg) IV. Repeat every 6 weeks.
Cyclophosphamide (Category 2B)[28]	**Days 1–2:** Cyclophosphamide 750mg/m² IV. Repeat cycle every 28 days.

continued



No. at risk							
Unmethylated radiotherapy	54	47	25	5	0	0	0
Unmethylated radiotherapy plus temozolomide	60	53	34	11	7	4	1
Methylated radiotherapy	46	42	30	18	8	0	0
Methylated radiotherapy plus temozolomide	46	42	34	28	16	7	1

Fig. 15-5 Survival in patients with glioblastoma.

By *MGMT* promoter methylation status and treatment (radiation alone or radiation plus temozolomide).

Abbreviation: MGMT, O^6-methylguanine–DNA methyltransferase.

From Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med. 2005;352:997–1003. Copyright 2005. Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. PMID: 15758010.

Recurrent GBM

Ependymoma , Medulloblastoma

BRAIN CANCER TREATMENT REGIMENS (Part 4 of 9)	
Systemic Therapy for Glioblastoma[1] (continued)	
Recurrence Therapy (continued)	
REGIMEN	**DOSING**
Platinum-based regimen: Carboplatin[8]	**Day 1:** Carboplatin 350mg/m² IV **Days 1–3:** Teniposide 50mg/m² IV. Repeat cycle every 4 weeks.
Platinum-based regimen: Carboplatin[9]	Carboplatin 560mg/m² IV at 4-week intervals; continued until disease progression, unacceptable toxicity, or for 12 additional courses after achieving maximal response.
Platinum-based regimen: Cisplatin[10]	**Days 1–3:** Cisplatin 25mg/m²/day IV + etoposide 100mg/m²/day IV. Repeat cycle every 4 weeks for first 3 cycles, then repeat every 5 weeks for next 3 cycles, then repeat every 6 weeks for the last 3 cycles; total 10 cycles over approximately 10–11 months (total dose 750mg/m² cisplatin and 3,000mg/m² etoposide).

Systemic Therapy for Intracranial and Spinal Ependymoma (excluding supependymoma)[1]	
Recurrence Therapy	
Platinum-based regimen: Carboplatin[8]	**Day 1:** Carboplatin 350mg/m² **Days 1–3:** Teniposide 50mg/m². Repeat cycle every 4 weeks.
Platinum-based regimen: Carboplatin[9]	Carboplatin 560mg/m² IV at 4-week intervals; continued until disease progression, unacceptable toxicity, or for 12 additional courses after achieving maximal response.
Platinum-based regimen: Cisplatin[10]	**Days 1–3:** Cisplatin 25mg/m²/day IV + etoposide 100mg/m²/day IV. Repeat cycle every 4 weeks for first 3 cycles, then repeat every 5 weeks for next 3 cycles, then repeat every 6 weeks for the last 3 cycles; total 10 cycles over approximately 10–11 months (total dose 750mg/m² cisplatin and 3,000mg/m² etoposide).
Etoposide[30]	Etoposide 50mg/day given until the neutrophil count dropped to $<1.0 \times 10^9$/L or the platelets fell to $<75 \times 10^9$/L and resumed when the counts rose to normal levels.
Bevacizumab[34–37b]	**Day 1:** Bevacizumab 10mg/kg IV. Repeat cycle every 14 days.
Temozolomide[3–5]	**Days 1–49:** Temozolomide 75mg/m² orally. Repeat cycle every 11 weeks (7 weeks on/4 weeks off) for 6 cycles. **OR** **Days 1–21:** Temozolomide 75mg/m²/day orally. Repeat cycle every 28 days.
Systemic Therapy for Adult Medulloblastoma and Supratentorial Primitive Neuroectodermal Tumor (PNET)[1]	
Adjuvant Treatment	
Weekly vincristine during craniospinal radiation therapy followed by either of the following regimens. Note that omission of vincristine during radiation therapy phase of therapy or dose modification may be required for adults because they do not tolerate this regimen as well. Data supporting the use of vincristine has been found in pediatric trials only. Patients should be closely monitored for neurologic toxicity with periodic exams.	
Vincristine + cisplatin + lomustine[38]	During craniospinal radiotherapy (RT) **Day 1:** Lomustine 75mg/m² orally **Day 2:** Cisplatin 75mg/m² IV **Days 2, 8 and 15:** Vincristine 1.5mg/m² IV bolus, max 2mg bolus; up to max 8 doses.
Vincristine + cisplatin + cyclophosphamide[39]	**Day 1:** Cisplatin 75mg/m² IV **Days 2, 8 and 15:** Vincristine 1.5mg/m² IV bolus, max 2mg bolus **Days 22, 23:** Cyclophosphamide 1,000mg/m² IV.
Recurrence Therapy	
No prior chemotherapy: Consider high-dose chemotherapy with autologous stem cell reinfusion in patients who achieve a complete remission with conventional doses of salvage chemotherapy or have no residual disease after re-resection.[35]	
High dose cyclophosphamide ± etoposide	
Carboplatin + etoposide + cyclophosphamide	
Cisplatin + etoposide + cyclophosphamide	
Prior chemotherapy: Consider high-dose chemotherapy with autologous stem cell reinfusion in patients who achieve a complete remission with conventional doses of salvage chemotherapy or have no residual disease after re-resection.[35]	
High dose cyclophosphamide ± etoposide	
Temozolomide[3]	Temozolomide 75mg/m² orally in 11-week cycles of 7 weeks on followed by 4 weeks off.
Oral etoposide[40,41]	**Days 1–21:** Etoposide 50mg orally daily. Repeat cycle every 4 weeks.

continued

- Ependymomas are currently separated into five categories by the WHO classification. Subependymomas and myxopapillary ependymomas are rare grade I tumors that are usually curable with complete resection alone. Ependymomas (grade II), ependymomas-RELA fusion–positive (grade II or III, seen mostly in children) and anaplasticependymomas (grade III) should be completely resected if possible.
- Supratentorial ependymomas are divided into RELA fusion–positive and RELA fusion–negative tumors.
- For infratentorial ependymomas, Group A tumors are characterized by relatively increased DNA methylation and usually occur in infants and young children; they are associated with a poorer prognosis. Group B tumors do not have the increased DNA methylation and have much better outcomes; they primarily occur in older children and adults
- The genetically define medulloblastoma subtypes have been incorporated into the new WHO 2016 classification: WNT, sonic hedgehog (SHH), Group 3, and Group 4 (Fig. 15-8). 138 The WNT group has the best prognosis, with long-term survival in more than 90% of patients. Patients in the SHH group and Group 4 have an intermediate prognosis, and Group 3 patients, with overexpression of MYC, have the worst prognosis

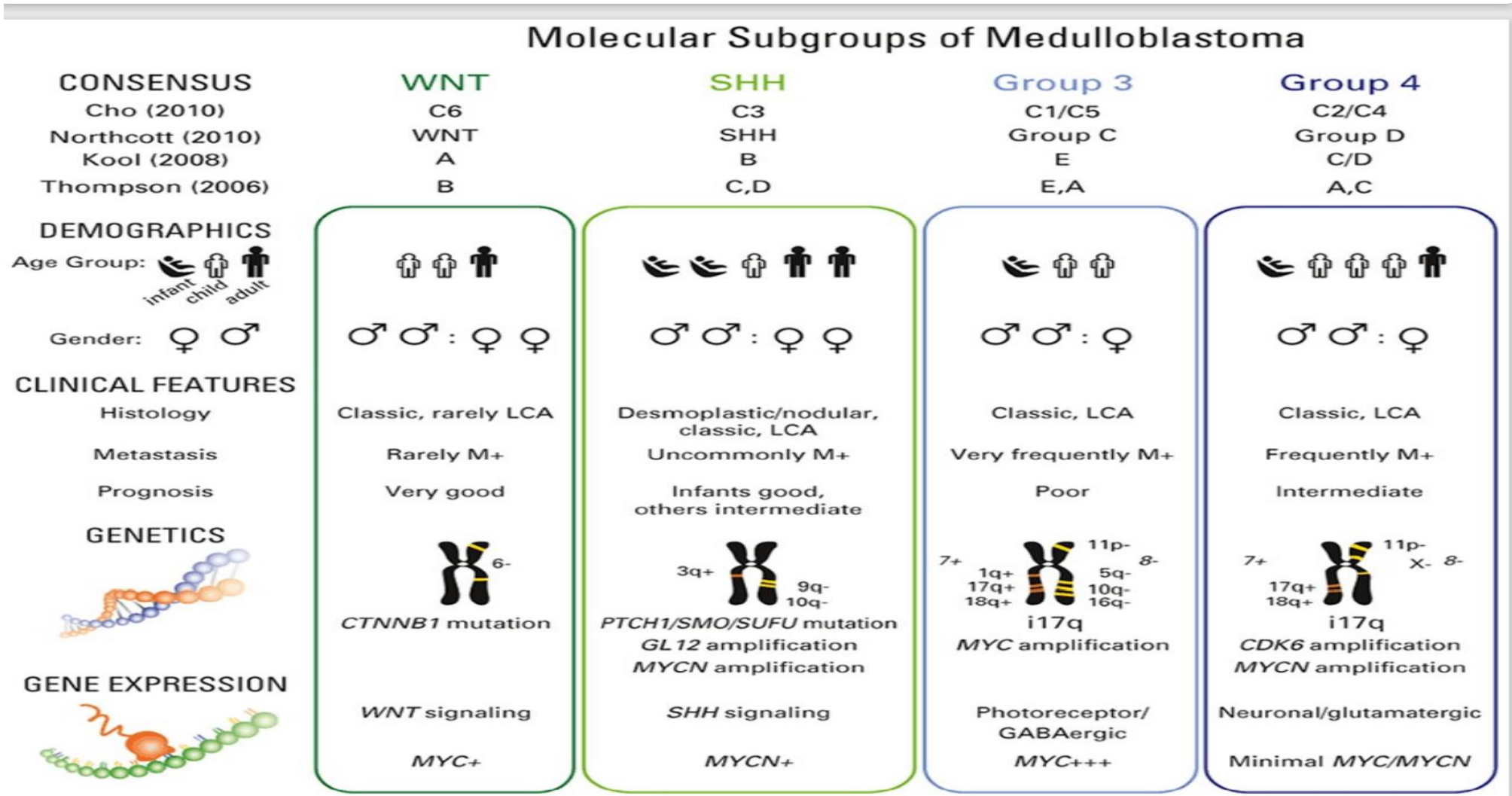


Fig. 15-8 Comparison of the various subgroups of medulloblastoma, including their affiliations with previously published papers on medulloblastoma molecular subgrouping.

Abbreviations: LCA, large cell/anaplastic; M+, metastatic; SHH, sonic hedgehog.

Reprinted with permission from Taylor MD, Northcott PA, Korshunov A, et al. Molecular subgroups of medulloblastoma: the

CNS Lymphoma

BRAIN CANCER TREATMENT REGIMENS (Part 5 of 9)

Primary CNS Lymphoma[1]

Primary Treatment

REGIMEN	DOSING
High dose methotrexate + chemotherapy[42–44]	**High dose methotrexate combined with the following plus radiation therapy:** **Weeks 1, 3, 5, 7, and 9:** MTX 2.5g/m² + vincristine 1.4mg/m² with a cap of 2.8mg (2m²) **Weeks 1, 5, and 9:** Procarbazine 100mg/m²/day orally for 7 days **Weeks, 2, 4, 6, 8, and 10:** Methotrexate 12mg intraventicularly **Weeks 1, 3, 5, 7, and 9:** Leucovorin 20mg every 6 hours orally for 12 doses **Weeks, 2, 4, 6, 8, and 10:** Leucovorin 10mg orally twice daily for 8 doses **Weeks 11–15:** Whole-brain RT in 1.80-Gy fractions for a total dose of 45 Gy **Weeks 16 and 19:** Cytarabine 3mg/m²/day IV for 2 days. Repeat for 5 cycles. **OR** **Day 1:** MTX 3.5g/m² **Days 2–3:** Cytarabine 2g/m² IV twice a day. **OR** **Day 1:** MTX 4gm/m² IV, followed by leucovorin 20–25mg IV every 6 hours starting 24 hours after MTX for 72 hours or until serum MTX level <1 × 10–8mg/dL. Increase leucovorin to 40mg every 4 hours if MTX level >1 × 10–5mg/dL at 48 hours or >1 × 10–8mg/dL at 72 hours. **Days 3–5:** Ifosfamide 1.5gm/m² IV + mesna 400mg IV before ifosfamide, then 4 hours and 8 hours after.
High dose methotrexate (MTX 2.5–4.0mg/m²) + chemotherapy ± monoclonal antibody[45]	**Day 1:** Rituximab 500mg/m² IV **Day 2:** MTX 3.5mg/m² IV plus vincristine 1.4mg/m² Procarbazine 100mg/m²/day was administered for 7 days with odd-numbered cycles.
High dose methotrexate (MTX 8.0mg/m²) + chemotherapy ± monoclonal antibody[46–47]	**High dose methotrexate combined with the following plus radiation therapy deferred radiation therapy:** **Induction therapy** MTX 8g/m² IV administered every 2 weeks until complete response achieved or max of 8 cycles reached. **Consolidation** MTX 8g/m² IV administered every 2 weeks for 2 cycles. **Maintenance therapy** MTX 8g/m² IV administered every 4 weeks for 11 cycles. **Plus** **Day 1:** Rituximab 375mg/m² IV. Repeat cycle every 4 weeks for 4 cycles. **OR** **Induction therapy** **Day 1:** Rituximab 375mg/m² IV, **followed by** **Days 1–5:** Temozolomide 150–200mg/m² orally daily, after rituximab infusion. Repeat cycle every 4 weeks for 4 cycles. **Maintenance therapy** **Days 1–5:** Temozolomide 150–200mg/m² orally daily. Repeat cycle every 4 weeks for 8 cycles.
Consider urgent glucarpidase (carboypeptidase G2) for prolonged MTX clearance due to MTX-induced renal toxicity[48]	Glucarpidase, one 50U/kg dose IV, 2 doses 24 hours apart, or 3 doses every 4 hours; thymidine 8 g/m²/day IV administered as continuous IV infusion for ≥48 hours after the last dose of glucarpidase; leucovorin 1g/m² IV every 6 hours before administration of glucarpidase and at a dose of 250mg/m² IV every 6 hours for 48 hours after administration of the last dose of glucarpidase.

Recurrent or Progressive Disease

Consider high-dose chemotherapy with autologous stem cell reinfusion in patients who achieve a complete remission with conventional doses of salvage chemotherapy or have no residual disease after re-resection.[35]

Re-treat with high-dose methotrexate[46]	**Induction therapy** MTX 8g/m² IV administered every 2 weeks until complete response achieved or max of 8 cycles reached. **Consolidation** MTX 8g/m² IV administered every 2 weeks for 2 cycles. **Maintenance therapy** MTX 8g/m² IV administered every 4 weeks for 11 cycles.

continued

Primary CNS Lymphoma[1] (continued)

Recurrent or Progressive Disease (continued)

REGIMEN	DOSING
Rituximab ± temozolomide[49]	**Induction therapy** **Day 1:** Rituximab 375mg/m² IV, **±** **Days 1–5:** Temozolomide 150–200mg/m² orally daily, administered after rituximab infusion. Repeat cycle every 4 weeks for 4 cycles. **Maintenance therapy** **Days 1–5:** Temozolomide 150–200mg/m² orally daily, administered after rituximab infusion. Repeat cycle every 4 weeks for 8 cycles.
Topotecan[50]	**Days 1–5:** Topotecan 1.5mg/m² IV. Repeat cycle every 21 days.
High-dose cytarabine[51]	Cytarabine 3g/m² IV.
Dexamethasone + high-dose cytarabine + cisplatin[52]	**Day 1:** Cisplatin 100mg/m² continuous IV infusion over 24 hours, followed by 2 pulses each of cytarabine at a dose of 2g/m² given 12 hours apart. **Days 1–4:** Dexamethasone 40mg PO or IV. Repeat cycle every 3–4 weeks for 6–10 courses.
Pemetrexed[53]	Pemetrexed 900mg/m² IV every 21 days for 6 weeks.

Meningioma

Meningioma[1]	
Interferon-alfa (Category 2B)[54]	α-IFN 106 units/m² SC every other day for 4 weeks. Repeat cycle every 4 weeks.
Somatostatin analog[55]	Sandostatin LAR Depot 10–30mg IM every 4 weeks.
Sunitinib (Category 2B)[56]	**Days 1–28:** Sunitinib 50mg orally daily. Repeat cycle every 42 days.

Metastasis

Systemic Therapy for Limited (1–3) Metastatic or Multiple (>3) Metastatic Lesions[1]	
Recurrent disease—Treatment as per the regimens of the primary tumor (‡ Bevacizumab + chemotherapy can be considered for patients who have failed monotherapy with bevacizumab)	
Carmustine wafer[57]	8 wafers (7.7mg) for a total of 61.6mg implanted intracranially.
High-dose methotrexate (MTX; breast and lymphoma)[58,59]	**Breast:** MTX 3.5g/m² IV. **Lymphoma:** Treatment based on weekly high-dose MTX 3.5g/m² and weekly intra-CSF cytarabine; oral procarbazine 100mg/m² days 2–15 was added to patients whose bone marrow reserve could tolerate this drug.
Capecitabine ± lapatinib, cisplatin, etoposide[60–68]	**Days 1–14:** lapatinib 1,250mg orally plus capecitabine 1,000mg/m² orally twice per day. Repeat cycle every 21 days. **OR** **Days 1–14:** Capecitabine 2,000mg/m²/day in 2 divided doses for 14 days, followed by a 7-day rest and lapatinib 1,250mg once daily continuously. **OR** **Day 1:** Cisplatin 100mg/m² IV **Days 4, 6, and 8:** Etoposide 100mg/m². Repeat cycle every 21 days. **OR** **Day 1:** Cisplatin 100mg/m² IV **Days 1, 3, and 5 OR Days 4, 6, and 8:** Etoposide 100mg/m² IV. Repeat cycle every 21 days. **OR (breast)** Capecitabine orally starting at a dose of 1,800mg/m²/day (up to 2,000mg/m²/day) in 2 divided doses, and temozolomide given orally once daily at a starting dose of 75mg/m²/day. Concomitant daily doses given on days 1–5 and days 8–12, with cycles repeated every 21 days until disease progression. **OR (breast)** **Days 1–14:** Capecitabine 2,000mg/m²/day orally once daily. Repeat cycle every 21 days. **OR (breast)** **Days 1–21:** Capecitabine 2,400mg/m²/day orally once daily. Repeat cycle every 28 days.
Ipilimumab (melanoma)[69]	**Day 1:** Ipilimumab 10mg/kg IV. Repeat cycle every 21 days for a maximum 4 cycles. Individuals who were clinically stable at week 24 were eligible to receive ipilimumab 10mg/kg every 12 weeks.

continued

Organ-specific Systemic Chemotherapy; Emphasizing Drugs with Good CNS Penetration	
Intra-CSF chemotherapy: Liposomal (slow-release) cytarabine (lymphoma/ leukemias)[72,73]	**Induction** Liposomal cytarabine 50mg intrathecally once every 14 days for 2 doses. **Maintenance** Liposomal cytarabine 50mg every 14 days for 2 doses, followed by 50mg every 28 days for 2 doses. **OR** **Induction** Liposomal cytarabine 50mg intraventricularly every 14 days for 3 doses plus rituximab 25mg intraventricularly twice per week for 8 doses. **Maintenance** Liposomal cytarabine 50mg intraventricularly once weekly plus rituximab 25mg intraventricularly twice weekly for 4 weeks. Repeat cycle every 4 weeks until disease progression
Intra-CSF chemotherapy: topotecan[74]	Topotecan 400 µg intraventricularly twice weekly for 6 weeks.
Intra-CSF chemotherapy: etoposide[75]	**Induction** **Days 1–5:** Etoposide 0.5mg/day intra-CSF every other week for 8 weeks. **Maintenance** **Days 1–5:** Etoposide 0.5mg/day every 4 weeks.
Intra-CSF chemotherapy: trastuzumab[76]	Cumulative dose of intrathecal trastuzumab given in clinical studies was 1,040mg (SD 697.9, median 1,215, range 55–1,675)
Intra-CSF chemotherapy: Interferon-alfa (category 2B)[77]	IFN-α 1 × 106 IU subcutaneously every other day 3 times per week for 4 weeks by induction.
High-dose methotrexate for lymphoma and breast[58]	**Breast:** MTX 3.5g/m² IV.
Erlotinib (Category 2B)[78]	Weekly pulse erlotinib for EGFR exon 19 or exon 21 L858R mutation non-small cell lung cancer; trial demonstrates that a new schedule of erlotnib administration may overcome acquired resistance to erlotinib. Pulsatile high-dose erlotinib was found to be effective against brain metastases in patients who had progressed while on treatment with standard-dose erlotinib. Pulsatile high-dose erlotinib 1,500mg (median dose with range of 900–1,500mg) once weekly.
Systemic Therapy for Metastatic Spine Tumors[1]	
Use regimen for disease specific site	

a For patients not previously treated

b Patients who have good performance status but evidence of radiographic progression may benefit from continuation of bevacizumab to prevent rapid neurologic deterioration

c Bevacizumab + chemotherapy can be considered for patients who have failed monotherapy with bevacizumab

- Brain metastases are 10 times more common than primary brain tumors. The most common primary tumors are lung and breast cancers, melanoma, and cancer of unknown primary origin. ■ Surgical resection and SRS are of benefit to patients with a single brain metastasis who have a good Karnofsky performance score and controlled or absent systemic tumor. ■ The addition of SRS after resection of brain metastasis decreases local recurrence and has better cognitive outcomes compared to WBRT. ■ ALK inhibitors and EGFR tyrosine kinase inhibitor can be effective in ALK-rearranged and EGFR-mutant NSCLC, respectively. ■ Patients with BRAF-mutant melanoma metastatic to the brain benefit from treatment with Dabrafenib.

IMPORTANT SUPPORTIVE CARE AGENTS

- Corticosteroids, antiepileptic drugs, and anticoagulant drugs are important ancillary agents
- phenytoin, phenobarbital, and carbamazepine induce common hepatic enzyme systems, including warfarin and small-molecule inhibitors such as cytochrome P450 enzymes. In contrast, valproate inhibits cytochrome P450 and may reduce chemotherapy metabolism with a consequent increase in toxicity. Newer antiepileptic drugs, such as levetiracetam, zonisamide, lacosamide, lamotrigine, topiramate, and pregabalin, do not typically interact with current treatment regimens. These agents are preferred when feasible because they may avoid the enzyme interactions previously noted.
- If antiepileptics are initiated perioperatively, current practice recommendations are to taper and discontinue use after the first postoperative week. Patients who have had a seizure should be maintained on antiepileptic therapy after surgery.
- venous thromboembolism (VTE) or pulmonary emboli that require anticoagulation may occur in 20 to 30% of patients with primary brain tumors.Low-molecular weight heparin is generally considered to be more effective than warfarin in patients with active malignancy. Patients with CNS tumors should receive anticoagulation for established VTE as recommended for other patients with cancer. Anticoagulation should be avoided in the setting of active intracranial bleeding (or, especially, hemorrhagic brain tumors), thrombocytopenia, or coagulopathy. Clinical trials evaluating newer oral anticoagulants, including factor Xa inhibitors (e.g., apixaban, edoxaban, and rivaroxaban) and direct thrombin inhibitors (e.g., dabigatran) have not assessed the safety of these drugs in patients with brain tumors.

Pseudo progression

- Pseudoprogression When concern for tumor progression arises after first-line therapy, it is essential to consider pseudoprogression prior to initiating alternative therapy. It is now well established that pseudoprogression can mimic true tumor growth, especially in patients whose tumors exhibit MGMT promoter methylation.
- On MRI, both progression and pseudoprogression are characterized by increased contrast enhancement, T2 -weighted signal abnormality, and mass effect, with or without clinical deteriorationNo imaging method can reliably distinguish the difference.
- For patients whose MRI scans appear worse within 1 to 3 months after completion of radiation, especially in tumors with MGMT promoter methylation, it is reasonable to continue adjuvant temozolomide with or without increasing the corticosteroid dose and to perform a repeat MRI scan in 1 to 2 months.
- In addition, both pseudoprogression and radiation necrosis may improve with bevacizumab, 7.5 mg/kg intravenously every 3 weeks. Only patients with continued deterioration in imaging should proceed with different therapy.

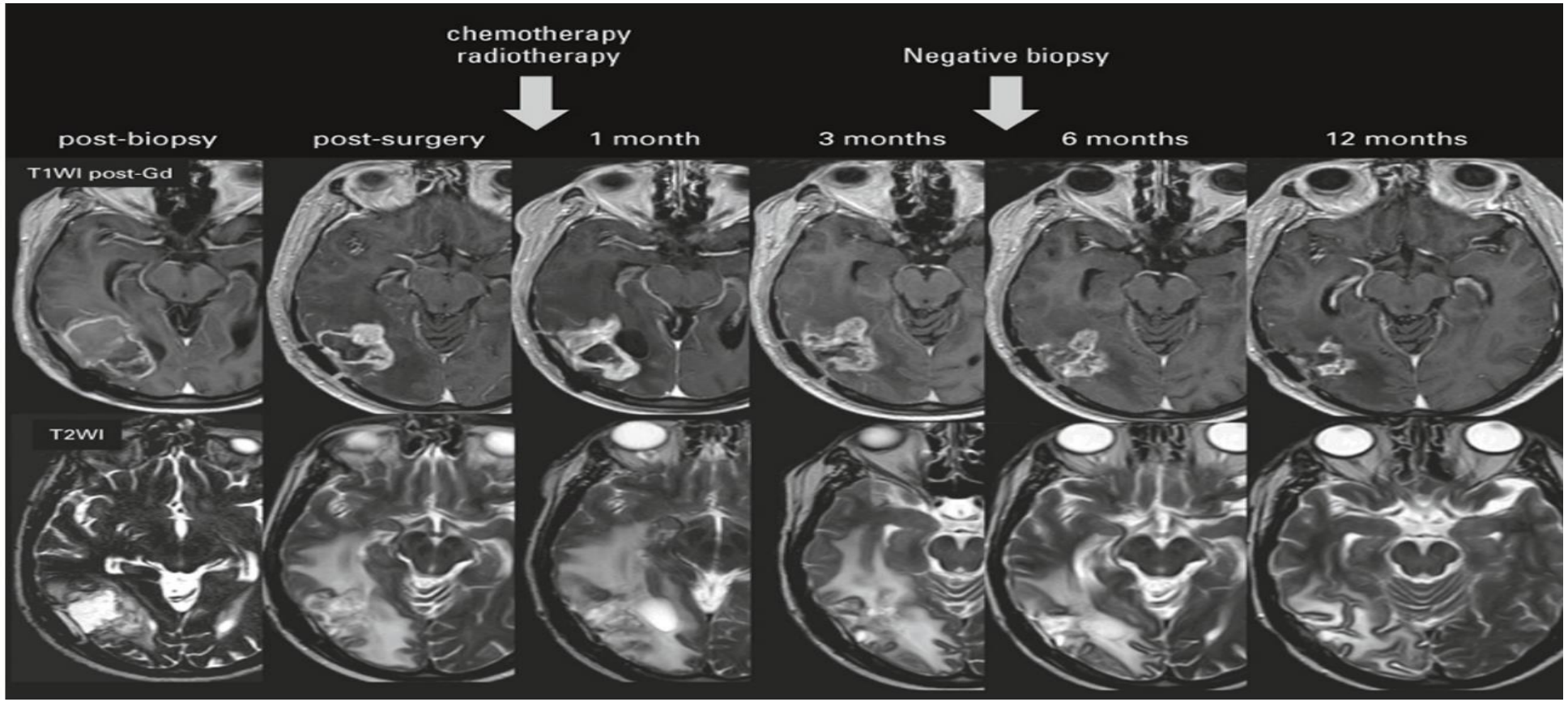


Fig. 15-6 Pseudoprogression in a 59-year-old man with glioblastoma.

MRI obtained 1 month after concurrent radiation and temozolomide demonstrated an expansion of the right temporal lesion. Reductions in both the enhancing portion and the surrounding abnormal hyperintense area in the T_2-weighted imaging were seen in the follow-up MRI examination.

Abbreviations: MRI, magnetic resonance imaging; T1WI post-Gd, T_1-weighted image post-gadolinium; T2WI, T_2-weighted image.