Evidence Based Guidelines In Contemporary Management of CNS Tumours

Vol. XVII
(Part A)

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Contents

Preface

The Tata Memorial Hospital has pioneered the cause of EBM in oncology in India and has been conducting the annual meeting on EBM in common cancers for the past sixteen years. The 18th conference on "Evidence Based Management of Cancers in India- EBM 2020" is being held from 28th February to 1st March 2020. Each year we have focused on different aspect of cancer care; collated and published the best available evidence in the form of"EBM book" which is also easily accessible at our official website. This year we will be focusing on Contemporary Management in Neuro Oncology, Uro Oncology - Decade of Transformation and Palliative Medicine - Current Concepts and Controversies. This helps busy clinicians from all over the country and abroad to get updated on the best available evidence in oncology in a span of 3-4 days, thereby translating into better overall patient care. Renowned international and national faculty members will cover the above topics in a very focused and succinct manner.

Tumors of the brain and central nervous system (CNS) though relatively uncommon, represent a substantial source of morbidity and mortality worldwide. The last decade or so has witnessed path-breaking, seminal developments that have provided deeper insights and improved the fundamental understanding of disease biology with resultant significant impact on the diagnostic, prognostic, and therapeutic landscape of neuro-oncology. Evidence-Based Medicine (EBM) 2020 will dissect and summarize all the available evidence including recent updates in contemporary neuro-oncologic practice.

This EBM conference will be led by a galaxy of national and international authorities in the field of CNS. The goal is to critically review and present the best available evidence and evolve management practices, which can be easily assimilated into clinical practice across the country. This book outlines and discusses these advances.

Prof R A Badwe
Director,
Tata Memorial Centre

February 2020
Mumbai

Statistical Vignettes of CNS tumours

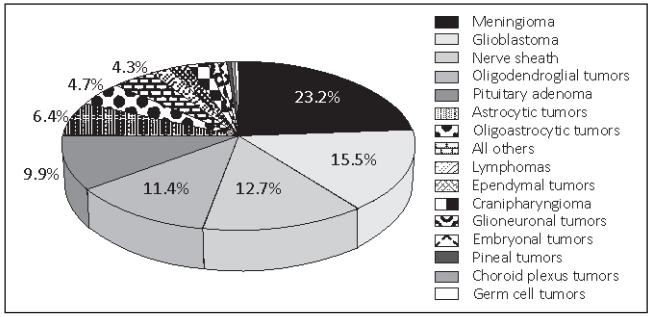
- Tumours of the brain and the CNS comprise only 1-2% of the overall cancer incidence.
- Overall incidence of CNS tumours is low – 4.63 per 100, 000 person years
- Incidence increased between 1990- 2016 by 17.3% and is steadily rising
- China, USA and India have the highest number of incident cases
- Five-fold difference in incidence between high incidence (developed world) and low incidence (developing world) regions
- 2018-In total, 296 851 new cases(1.6% of overall cancer incidence) and 241,037 deaths (2.5%of overall cancer-related mortality) were reported
- 5 yr survival has steadily increased between 2000-2014

Table-1 :				
2016	**Overall (GBD)**	**India (GBD)**	**China (GBD)**	**USA (GBD)**
Incidence (95% UI)	329, 673 (298 ,926 to 348,845)	23,344 (21,446 to 28,329)	106 207 (96,980 to 119 885)	24, 725 (22,447 to 26,908)
Deaths (95% UI)	227, 039 (204 ,784 to 241,279)	21,042 (18,847 to 25,993)	59,120 (53,264 to 66,813)	16,779 (14,745 to 17,556)
DALY burden (95% UI)	7 ,659, 974 (6,922,776 to 8,280, 367)	811,288 (731,493 to 1,008,612)	1,933,243 (1,756,995 to 2,196,524)	453,457 (410,642 to 491,397)

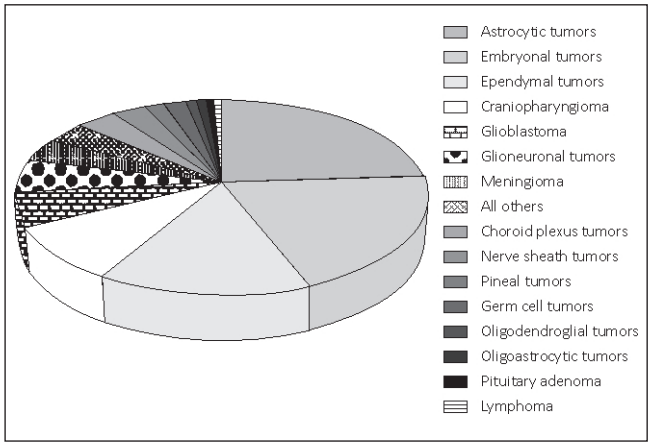
GBD: Global burden disease; **UI**: Uncertainty interval

Representative histopathological spectrum of tumours of the brain central nervous system in the overall population (A, B) and in children (C, D) from the West (USA) and the East (India), respectively. USA data are extracted from the Central Brain Tumour Registry of the United States (CBTRUS) statistical report 2011-2015, whereas Indian estimates are from a hospital-based cancer registry for the overall population and multi Institutional pooling of data for childhood brain tumours**.**

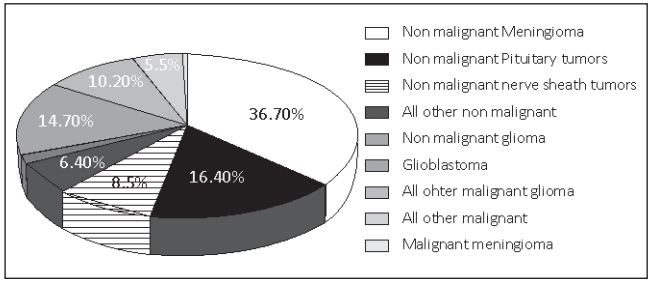
Adult brain tumor India (n=3601)



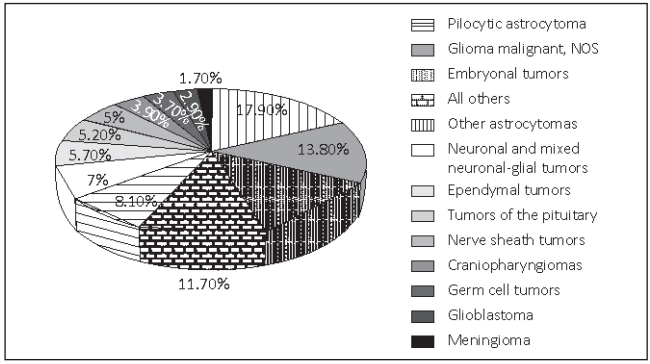
Pediatric Brain tumor India (n=694)



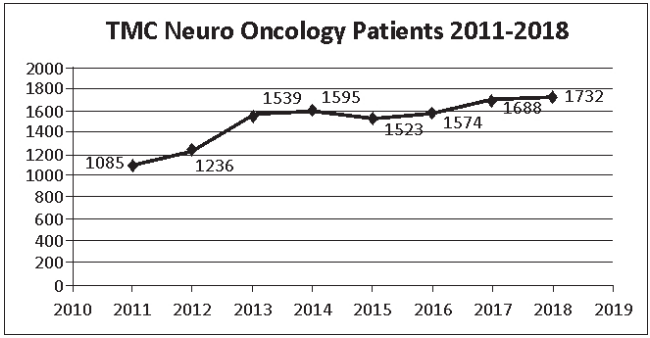
Adult brain tumor CBTRUS (n=392982)



Pediatric Brain tumor CBTRUS (n=17273)



Tata memorial center has witnessed an increasing trend in the annual registration of primary brain tumours. The annual registration in the year 2018 had touched 1700 new patients of brain tumours.



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Contemporary Neuro Imaging

DIAGNOSTIC NEUROIMAGING:

Table-2: Contemporary imaging modalities for CNS tumours

Imaging	Remarks	Pros	Cons
CT scan	First line imaging modality	Good anatomic visualization Cheaper & Faster More widely available Can be used with metal objects	Limited reconstruction ability Exposure to ionizing radiation Poor resolution Contrast reaction
MRI	Gold standard imaging modality	Unparalleled resolution True multiplanar imaging No exposure to ionizing radiation	Susceptible to motion artifacts Cannot be used with metal objects Claustrophobic, noisy, long times Expensive
MR Spectroscopy	Assesses tumour metabolites	Useful for discriminating radiation necrosis from tumour	Limited utility near bone, vessels or air spaces Wide variability in interpretation
MR Perfusion	Assesses blood flow & volume	Generally correlates with grade Useful to distinguish radiation necrosis from tumour progression	Limited utility near bone, vessels

TISSUE CHARECTERSTICS IN NEUROIMAGING

Table-3: Normal tissue

Tissue	CT scan	T1MRI	T2MRI
Bone	bright	Dark	Dark
Air	dark	Dark	Dark
Fat	dark	Bright	Bright
water	dark	Dark	Bright
Normal brain	intermediate	anatomic	Intermediate

Table-4: Abnormal tissue

Type	CT scan	T1MRI	T2MRI	Enhancement
Infarct	Dark	Dark	Bright	Subacute
Bleed	Bright	Bright	Bright	No
Tumour	Dark	Dark	Bright	yes

Table-5: Typical Imaging features of primary brain tumours

Tumour	MRI signal Intensity			Contrast enhancement	Edema	CT density	Calcification
	T1WI	T2WI	FLAIR				
LGG	Hypo	Hypo	Hyper	absent	Minimal	Hypo	infrequent
HGG	Hypo	Hypo	Hyper	Heterogenous	Moderate to severe	Hypo	Rare
Oligodendroglioma	Hypo	Variable Hyper	Hyper	Variable	Present (present in anaplastic)	Hypo-	Common
Ependymoma	Hypo	Variable Hyper	Variable hyper	Variable	variable	Iso-Hypo	Common
Medulloblastoma	Iso-hyper	Hyper	Hyper	Variable Homogenous in WNT, SHH variants Heterogenous in grp-3, grp-4	Variable	Hyper	Uncommon
Metastasis	Iso-Hyper	Hypo	Hyper	Ring like	severe	Hyper-	Rare Iso

LGG: Low grade Gliomas; HGG: High grade Glioma

Table-6: Typical MRI features of intraxial brain tumours

MR Imaging Feature	Neoplasms			Tume-factive Demye-linating Lesion	Abscess*	Ence-phalitis
	Primary	Secondary	Lympho-ma			
MR spectroscopy Lipid signal (ppm)	Elevated at 0.9 and 1.3, especially with high-grade lesion	Elevated at 0.9 and 1.3	Elevated at 0.9 and 1.3			
Lactate signal (ppm)	Elevated at 1,33., especially with high-grade lesion	Elevated at 1.33	Elevated at 1.33		Elevated at 1.33	Elevated at 1.33
NAA signal (ppm)	Reduced at 2.02 more so with high-grade lesion	Reduced or absent at 2.02	Reduced at 2.02	Reduced at 2,02	Absent at 2.02	Reduced at 2.02
Choline signal (ppm)	Elevated at 3.2, more so with high-grade lesion	Elevated at 3.2	Elevated at 3.2	Elevated at 3.2 especially with acute lesions	Absent at 3.2	Elevated at 3.2
Myoinositol signal (ppm)	Elevated at 3.55, more so with glio-matosis and low-grade lesion					Elevated at 3.55

(Contd...)

(Contd...)

MR Imaging Feature	Neoplasms			Tumefactive Demyelinating Lesion	Abscess*	Encephalitis
	Primary	Secondary	Lymphoma			
Diffusion-weighted imaging. ADC value	Variable, 0.82–2.73 X 10^{-3} mm^2/ sec	Elevated	Reduced	Reduced (crescent or concentric areas) for acute lesions; elevated for chronic lesions	Markedly reduced	Variable
Perfusion imaging; rTBV value	Tends to increase with tumor grade	Elevated	Low, compared with primary high-grade neoplasms; high, relative to toxoplasmosis	Low	Low	Unknown

Other typical MR spectroscopic features include elevated signals for amino acid (at 0.9 ppm), alanine (at 1.47 ppm), acetate (at 1.92 ppm), pyruvate (at 2.37 ppm), and succinate (at 2.40 ppm), and absent creatine signal (at 3.0 ppm).

MR spectroscopy: what does each amnoacids depict?

Lipid lactate peaks: The first resonant peak of clinical interest is of *lipids* which resonate at 0.9 ppm (CH3) and

1.3 ppm ((CH2) n). The rise of lipids is detected in various cellular processes such as necrosis, growth arrest, inflammation, malignancy and apoptosis. The lipid peaks detected in most of these processes are saturated lipids arising from increased number of cytoplasmic vesicles. The presence of lipid in lymphoma is postulated to arise from increased membranous component in transformed lymphoid cells.

The methyl group (CH3) of *lactate* produces doublet peak at 1.33 ppm which points upward at short TE and downwards at intermediate TE. It increases rapidly during hypoxia. Increased rates of lactate production signify higher tumor grade.

Alanine peak gives a doublet peak at 1.47 ppm which inverts at intermediate TE. Another small singlet peak of alanine is found at 3.93 ppm. Alanine is produced by transamination of pyruvate in hypoxic tissues showing increased glycolysis to prevent further increase in lactate. Alanine in meningiomas comes from partial oxidation of glutamine or by conversion of pyruvate due to inhibition of the enzyme pyruvate kinase by L-alanine. It is also elevated in central neurocytoma and PNET.

Acetate and Succinate peaks (1.92 ppm and 2.42 ppm respectively) levels reflect anaerobic fermentation of pyruvate generated from glycolysis where it undergoes carboxylation to form acetate and succinate. Clinically markedly raised acetate and succinate peaks in the MR spectra suggest brain abscesses, useful in differentiating from brain tumor mimics.

N-acetyl aspartate (NAA) peak is the largest peak of the spectra at 2.02 ppm. NAA peak also obtains contributions from *N*-acetyl aspartyl glutamate (NAAG), glycoproteins, and amino acid residues in peptides. It is the second most abundant amino acid in the brain and is synthesized in mitochondria, thus can be used as a marker for neuronal density and integrity. In pathologies causing axonal loss including tumors, NAA is markedly reduced due to absence of its synthesizing enzyme.

Creatine peak is seen at 3.03 ppm with major contributions from creatine and phosphocreatine. It is a marker for intracellular energy states as it stores high energy phosphates. Cr peak is utilized as an internal reference standard for characterizing other peaks as its level is high and relatively comparable in different tissue types of brain. Total creatine content is low in non-neuroectodermal tumors such as brain metastases.

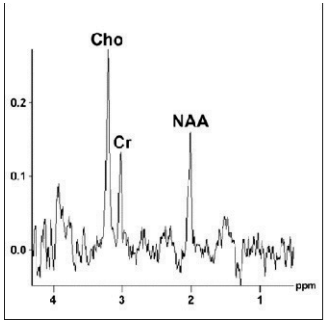
Choline (cho) peak resonance is present at 3.2 ppm and 3.52 ppm. The resonance is attributed to trimethyl ammonium residues of free choline (3.21 ppm), phosphorylcholine (3.23 ppm), glycerophosphorylcholine (3.24 ppm) and other metabolites such as carnitine. The enzyme Choline Kinase is overexpressed in several brain tumors and hence the presence of choline peak in MRS spectra reflects increased cell membrane synthesis and thus increased cellularity.

Myoinositol (mI) peak produces at a quadruplet peak at 3.55 ppm. This is believed to be an osmolyte that is found primarily in astrocytes involved in osmoregulation and volume regulation. Increased levels are believed to reflect

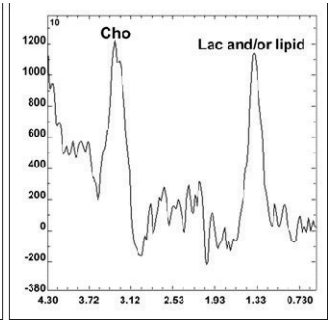
increased numbers of glial cells which contain high levels of mI, thus it is relatively higher in low-grade gliomas and lower in higher grade tumors such as anaplastic astrocytoma/glioblastoma multiforme. MI detected within an intraventricular tumor in a pediatric patient suggests choroid plexus papilloma.

Typical MR spectroscopy Graph depicting glioma, demyelination and abscess

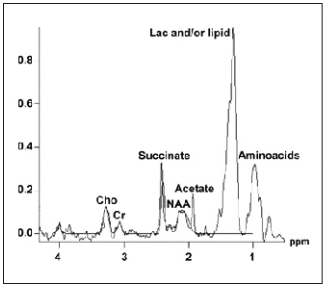
Anaplastic glioma (grade-III)



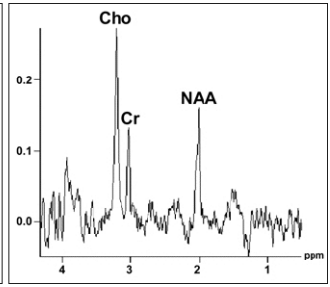
Glioblastoma (Grade-IV)



Brain Abscess



Tumefactive demyelination



MR perfusion imaging in brain tumours

Perfusion imaging is a method for assessing the flow of blood occurring at the tissue level and can be accomplished by both CT and MR perfusion techniques. The use of perfusion imaging has increased substantially in the past decade, particularly in neuro-oncologic imaging, where it is has been used for brain tumor grading and directing biopsies or targeted therapy, as well as for the evaluation of treatment response and disease progression.

Clinical Utility in Neuro-Oncologic Imaging

A. Tumor grading

Both MR and CT perfusion have been successfully used to grade gliomas on the basis of perfusion parameters. It is also found that permeability values for high-grade tumors obtained using a T2*-weighted method were significantly greater than those for low-grade tumors. rCBV value of 1.75 represents high-grade tumors.

B. Differentiating Recurrent Tumor Versus Treatment Effects

Brain tumor enhancement depends on the presence and integrity of the BBB, which can be affected by a number of factors other than disease response or progression, including effects related to particular treatment.

Pseudoprogression is the term applied to a treatment-related increase in enhancing lesion size and/or

edema without a true increase in tumor burden, which shows either improvement or lack of progression on follow-up imaging. Pseudoprogression commonly occurs in the 2- to 6 months period after therapy however, it may happen as long as 2years after therapy

Compared with recurrent tumor, enhancing lesions caused by treatment effects (eg. Pseudoprogression) lack significant neoangiogenesis, which is the hallmark of recurrent tumor. This lack results in a lower microvascular density and lower vessel leakiness, which manifests as lower blood volume and permeability on perfusion imaging.

C. Radiation Necrosis

Radiation necrosis is a delayed effect of radiation injury. Generally occurring between 3 and 12 months after radiation therapy, radiation necrosis most commonly occurs at the site of maximum radiation dose, which is usually in the vicinity of the original tumor and surrounding the surgical cavity.

The most commonly used parameter in this differentiation is relative cerebral blood volume (rCBV), which is reduced in the setting of radiation necrosis. The mechanism behind it is, blood vessels within previously irradiated tissues tend to maintain an intact BBB versus the leaky BBB seen in recurrent tumor with neoangiogenesis, therefore demonstrating a lower perfusion.

Arterial Spin labelling MRI

Arterial spin labeling (ASL) is a non-ionizing and completely non-invasive MRI technique for measuring tissue perfusion (blood flow), which uses magnetically labeled arterial blood water protons as an endogenous tracer. These benefits make ASL very suitable for perfusion studies in healthy individuals, patients with renal insufficiency and those who need repetitive follow-ups. It is also an impressive method for studying perfusion in pediatric populations in which the use of radioactive tracers or exogenous contrasts agents may be restricted.

A pair of images is always acquired: a labeled image, in which the blood water magnetization is inverted, and a control image, in which the blood water magnetization is not inverted. The signal difference between labeled and control images is proportional to the amount of magnetization inverted and delivered to the tissue. If all the labeled blood has arrived at the imaging voxel at the time of image acquisition, the signal difference will be proportional to cerebral blood flow (CBF).

Currently there are four types of ASL techniques that differ, mainly according to the magnetic labeling process. CASL was the very first implementation of ASL. Pseudo continuous ASL (PCASL- most commonly used in clinical practice), PASL and velocity-selective ASL (VS-ASL).

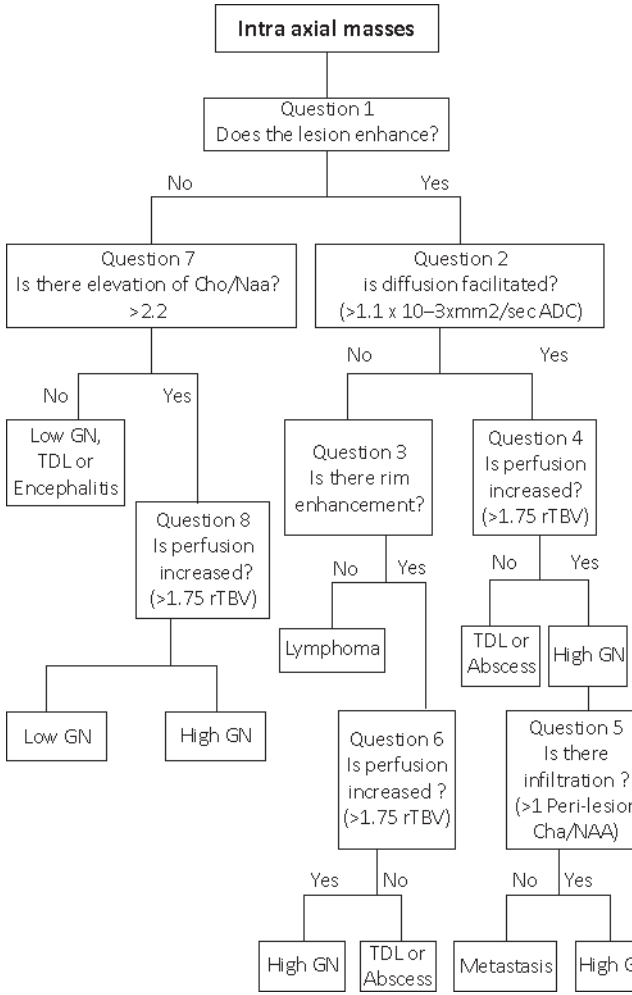
Clinical Applications of ASL MRI In Neoplasms

Glioblastoma is the most common high-grade central nervous system tumor in adults and is associated with high

metabolism and CBF. Initial reports demonstrated that ASL and DSC show largely concordant results in terms of identifying this tumor and distinguishing it from contrast-enhancing mimics. Higher CBF in glioblastoma multiforme correlates with genetic markers (such as epidermal growth factor receptor) and is associated with shorter progression-free survival time . Lower grade tumors typically demonstrate lower CBF. CBF changes may portent transformation to a more aggressive phenotype. In fact, some have suggested that CBF quantification provides a better estimate of event-free survival for a wide range of gliomas than does a histologic grading scale. One exception to this rule of increasing CBF and tumor grade is oligodendroglioma, a grade 2 tumor that often demonstrates increased CBF.

The quantitative nature of ASL has enabled studies of CBF changes over time or with treatment to assess its impact on prognosis and outcome. A particularly important and challenging distinction to make is between radiation necrosis and recurrent tumor in patients with new or increasing contrast enhancement. Since radiation necrosis is associated typically with reduced CBF and most recurrent tumors demonstrate increased CBF, perfusion imaging may be helpful to distinguish the two entities. In the early time period following resection (typically 4 weeks after resection), where any contrast enhancement is probably due to pseudo progression, again ASL is more useful than Dynamic susceptibility contrast imaging.

Radiologic diagnostic algorithm for intracranial mass lesion



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Positron Emission Tomography (PET) in CNS Malignancies

Nuclear Medicine tracers are used for focused indications in neuro-oncology depending upon the metabolic pathway active in the tumor cells. Broadly, depending upon the type of emission, radiotracers are either SPECT (Single Photon Emission Computed Tomography) or PET (Positron Emission Tomography) tracers, which are imaged with a Gamma Camera or PET scanner respectively.

Table-7: Commonly used radiotracers in Neuro-oncology

Tumor	Metabolic pathway	Radiotracer	Indication
Primary CNS lymphoma (PCNSL)	Glucose-dependent (GLUT receptor over-expression)	18F-FDG PET/CT	Diagnosis and staging Treatment response Prognostication
Metastases	Glucose-dependent (GLUT receptor overexpression)	18F-FDG PET/CT	Diagnosis Treatment response
High-grade Glioma (HGG)	Amino-acid transporter over-expression	18F-FET (Fluoro-ethyl-tyrosine) PET/CT 18F-DOPA PET/CT (Fluoro-dopa)	Diagnosis Restaging Radiation necrosis versus recurrence
High grade Glioma	Thymidine-kinase-1 pathway (Proliferation marker)	18F-FLT (Fluoro-thymidine) PET/CT	Radiation necrosis versus recurrence
Meningioma	Somatostatin receptor over-expression	Ga-68-DOTANOC PET/CT	Diagnosis and theranostics

FDG PET/CT in Brain Tumors:

Commonly occurring malignant brain lesions such as PCNSL, HGG, and metastases show characteristic imaging

features on routine MRI in a large proportion of cases. Occasionally, MRI Commonly occurring malignant brain lesions such as PCNSL, HGG, and metastases show characteristic imaging features on routine MRI in a large proportion of cases. Occasionally, MRI features can overlap and an accurate diagnosis becomes difficult. PET using fluorine-18-fluorodeoxyglucose (18 F-FDG) which is the most popular and easily available tracer; measures metabolic activity of tumors and has been used to image brain tumors for indications such as establishing a diagnosis, assessing response to therapy, and as a prognostic marker. Purandare et al (1) studied metabolic characteristics of the brain lesions (standardized uptake value - SUVmax) along with tumor-to-background activity ratios, and concluded that PCNSL can be differentiated from HGG and metastases by their higher metabolic activity. In addition, 18F-FDG PET/CT can potentially impact therapeutic decisions by detecting primary malignancy in patients with metastatic brain lesions and extracranial disease sites in patients with brain lymphoma. Thus, FDG PET has no impact in diagnosis and staging of glial neoplasms.

Amino Acid PET Imaging in Glial Tumors:

18F-fluoroethyl-tyrosine (FET) binds to L-Amino acid transporters which are overexpressed in glial neoplasms; the density of receptors being directly proportional to tumor grade. Puranik et al, in a study of 27 patients with equivocal MR imaging findings showed that tumor-contralateral white-mater ratio (T/Wm) was higher for high-grade glial tumors compared to non-glial tumors (metastases, PCNSL, tuberculoma, anaplastic

meningioma). A cut-off of 1.9 can reliably diagnose a tumor of glial origin with a sensitivity and specificity of 93.8 and 91% respectively. FET PET is especially useful when lesions show overlapping features (PCNSL, metastases, HGG) on MR, and are multifocal and deep-seated, making tissue diagnosis a difficult and risky proposition.

In the setting of treated gliomas, MR imaging with advanced sequences (MR perfusion, arterial-spin labeling, MR spectroscopy) forms the cornerstone for detecting areas of radiation necrosis and recurrence. However, it lacks in specificity and diagnostic accuracy primarily due to co-existence of both pathologies, and inherent technical limitations. FET-PET can accurately distinguish areas of tumor necrosis from active disease. Our unpublished results from TMH in 72 patients with WHO Grade 3 or 4 gliomas show that with a cut-off of 2.65 of T/Wm, FET PET has a sensitivity of 80 % and a specificity of 87.5 % in diagnosing recurrence.

F-DOPA performs equally well, as compared to FET PET, however, its cost of production is high and due to its physiological localization in striatum, it obscures the tracer uptake in tumors in these areas.

Somatostatin-Receptor imaging for Meningiomas

Meningiomas generally express somatostatin receptor subtype 2 (SSTR2), which makes Ga-68 labeled-octreotide analogs ideal tracers for imaging. Ga-68-DOTATATE specifically bind to SSTR; and unlike FDG it does not concentrate in normal brain parenchyma, hence increasing the target to background ratio. In a tertiary care Oncology Center like TMH, there are scenarios where it's important

to distinguish dural-based metastases from meningiomas (especially in breast cancer), where Ga-68-DOTANOC acts as a problem-solving tool.

Sommerauer at al showed that WHO grades I and II meningiomas showed a correlation of SUVmax and tumor growth rate; furthermore, meningiomas with fast tumor growth and trans osseous expansion elicit the highest DOTATATE binding; therefore, they might be especially suited for DOTATATE-based therapy, making it a theranostic tool.

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Contemporary Neuropathology

World health Organization (WHO) classification of CNS Tumours

- 2016 WHO classification of CNS tumours, is a shift in approach to classification system from pure histological features to integrated molecular and histomorphological approach, where canonical genetic alterations were incorporated to identify the entities.
- A summary of the major changes in the updated 2016 WHO classification is provided in table 1.

Table- 8: Summary of the major changes in the 2016 CNS WHO classification

Formulating concept of how CNS tumour diagnoses are structured in the molecular era
Major restructuring of diffuse gliomas, with incorporation of genetically defined entities
Major restructuring of medulloblastomas, with incorporation of genetically defined entities

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Major restructuring of other embryonal tumours, with incorporation of genetically defined entities and removal of the term “primitive
neuroectodermal tumour”
Incorporation of a genetically defined ependymoma variant
Novel approach distinguishing paediatric look-alikes, including designation of novel, genetically defined entity
Addition of newly recognized entities, variants and patterns - IDH-wildtype and IDH-mutant glioblastoma (entities) - Diffuse midline glioma, H3 K27M–mutant (entity) - Embryonal tumour with multi-layered rosettes, C19MC-altered (entity) - Ependymoma, RELA fusion–positive (entity) - Diffuse leptomeningeal glioneuronal tumour (entity) - Anaplastic PXA (entity) - Epithelioid glioblastoma (variant) - Glioblastoma with primitive neuronal component (pattern) - Multinodular and vacuolated pattern of ganglion cell tumour (pattern)
Deletion of former entities, variants and terms - Gliomatosis cerebri - Protoplasmic and fibrillary astrocytoma variants - Cellular ependymoma variant - “Primitive neuroectodermal tumour” terminology
Addition of brain invasion as a criterion for atypical meningioma

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Restructuring of solitary fibrous tumour and hemangiopericytoma (SFT/HPC) as one entity and adapting a grading system to accommodate this change
Expansion and clarification of entities included in nerve sheath tumours, with addition of hybrid nerve sheath tumours and separation
of melanotic schwannoma from other schwannomas
Expansion of entities included in hematopoietic/lymphoid tumours of the CNS (lymphomas and histiocytic tumours)

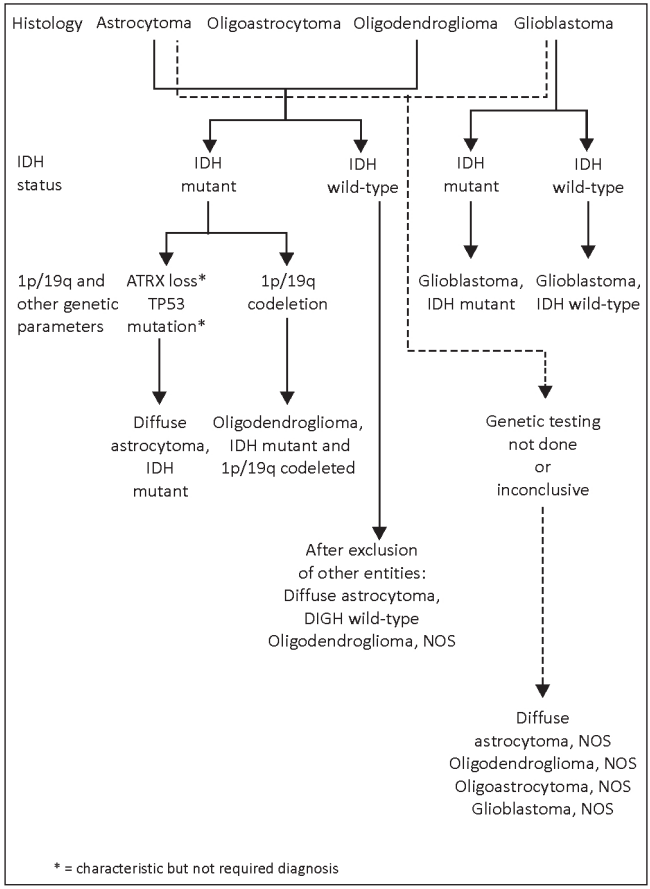
Adult Diffuse Gliomas

- *IDH1R132/IDH2R172*mutations are seen in almost 70-80% of grade II and III diffuse gliomas, and 5-10% of glioblastomas and is now considered as earliest oncogenetic event in the gliomagenesis. IDH1/2 mutant gliomas possess important biological properties. Thus, the each of the diffuse gliomas are based on *IDH1/2* mutation are classified into mutant and wild type respectively (table 9).

Table-9 : Glioma classification based on IDH mutation status and their prognosis

Histological subtype	Grade	Molecular subtype	Prognosis
oligodendroglioma	II &III	IDH mutant, Ip19q co-deleted	Best
Astrocytoma	II & III	IDH mutant & ATRX retained	Intermediate
Astrocytoma	III GBM (Grade IV)	IDH wild type & ATRX retained	Poor

Schematic view of the classification of adult diffuse glioma according to the status of key genes



Source: Acta Neuropathologica; 2017

- **Detection of *IDH* mutations:** Initial basic immunohistochemistry, s directed against a specific point mutation- IDH1R132H (which is the commonest mutation, almost accounting 90% of all IDH mutations in gliomas). Only in cases of negativity for IDH1R132H on immunohistochemistry for all cases with immunohistochemical loss of ATRX protein expression, oligodendroglia morphology, low to intermediate grade morphology and in GBM of <55 years (where clinically indicated)), it should be followed up with sequencing for other IDH1 and IDH2 mutations to provide an integrated diagnosis, for eg. anaplastic astrocytoma, IDH mutant, WHO grade III.
- A diagnosis of "NOS" or not otherwise specified, should only be given if such testing cannot be performed or is inconclusive, however, as far as possible, the use of this designation is discouraged.
- **1p/19q** whole-arm co-deletion in oligodendroglial tumours should be performed on all gliomas with oligodendroglial morphology and presence of IDH mutation (detected on immunohistochemistry or sequencing) to identify the canonical oligo-dendrogliomas

  For detecting 1p/19q co-deletion, the most common and widely available technique is Fluorescence-in-situ hybridization (FISH). Other techniques which may be used, but are not easily available are PCR based detection of loss of heterozygosity (LOH), methylation assay, and next generation sequencing (NGS).

- **MGMT methylation in** High grade gliomas carry epigenetic modification (methylation) of the promoter of the DNA repair enzyme O-6-methylguanine-DNA methyl transferase (MGMT). This correlates with survival following treatment with temozolomide. MGMT methylation detection is a useful predictive/prognostic marker. It is important to know that the frequency of MGMT methylation is very high in IDH-mutant gliomas (with or without 1p/19q co-deletion) and moreover IDH mutation itself is a favourable biological marker, thus MGMT methylation testing may be reserved only for IDH wild-type gliomas. The test to detect MGMT methylation include methylation specific PCR, pyrosequencing and DNA methylation array. All the methods have their own set of technical and interpretive difficulties, and currently there is no consensus on the best assay for MGMT testing.
- **Telomerase Reverse Transcriptase (TERT) promoter mutations** have been also identified in a variety of brain tumours, including diffuse gliomas, medulloblastoma and meningiomas. It has been seen that IDH wild type astrocytic tumours, carrying only TERT mutations show significantly worse outcomes. Hence assessment of TERT mutations in IDH-wild type astrocytic tumours (especially grade II and III) may be useful for treatment stratification.

Table-10: Classification of Diffuse Pediatric Gliomas

Diffuse astrocytic and oligodendroglial tumours	Grade
Diffuse astrocytoma, IDH mutant	II
Gemistocytic astrocytoma, IDH mutant	
Diffuse astrocytoma, IDH wild-type	II
Diffuse astrocytoma, NOS	II
Anaplastic astrocytoma, IDH mutant	III
Anaplastis astrocytoma, IDH wild-type	III
Anaplastic astrocytoma, NOS	III
Glioblastoma, IDH wild-type	IV
Giant cell glioblastoma	
Gliosarcoma	
Epitheloid glioblastoma	IV
Glioblastoma, IDH mutant	IV
Glioblastoma, NOS	IV
Diffuse midline glioma, H3-K27M mutant	IV
Oligodendroglioma, IDH mutant and 1p/19q co-deleted	II
Oligodendroglioma, NOS	II
Anaplastic oligodendroglioma, IDH mutant and 1p/19q co-deleted	III
Anaplastic oligodendroglioma, NOS	III
Oligoastrocytoma, NOS	II
Anaplastic oligoastrocytoma, NOS	III

Pediatric gliomas: Gliomas in pediatric population are predominantly low grade and usually non-infiltrating (non-diffuse) type, which are classified in the 2016 WHO classification under the category of other astrocytic tumours. This also includes the tumours with neuronal differentiation like gangliogliomas. This group of low grade glial and glioneuronal tumours in children are grouped as low grade glial/glioneuronal tumours, which encompasses pilocytic astrocytoma (WHO grade I), ganglioglioma (WHO grade I), dysembryoplastic neuroepithelial tumour (DNET; WHO grade I), angiocentric glioma (WHO grade I), pleomorphic xanthoastrocytoma (WHO grade II). However, there are host of tumours, which may not show typical features, which can be labeled as low grade glial/ glioneuronal tumour, NOS.

Unlike in adults, the diffuse (infiltrative) gliomas in children are very uncommon. Histologically, they are no different from adult diffuse gliomas. Of the diffuse gliomas in children, glioblastomas are common than WHO grade II and grade III tumours. But overall, low grade glial/ glioneuronal tumours are the commonest type of gliomas in children.

Molecularly, pediatric gliomas are distinct from adult gliomas Understanding their distinct molecular biology has modified the nosology of pediatric gliomas and hence even their therapy. Unlike the adult counterparts they are not *IDH-mutated*; (though rarely can be seen in older children, especially of adolescent age). Rather *BRAF, FGFR, MYB/MYB1, NTRK, histone* gene alterations are common (listed in the table below)

Table 11. Overview of genetic alterations in paediatric gliomas

Genetic alteration	Tumours
BRAFV600E and BRAF fusions	*BRAF* gene alterations are more common in non-diffuse gliomas especially in pilocytic astrocytomas, pleomorphic xanthoastrocytoma and gangliogliomas, Fusions are almost exclusive of pilocytic astrocytoma (though it is also reported in diffuse leptomeningeal glioneuronal tumour). *BRAFV600E* mutations is also common in epithelioid glioblastoma
FGFR mutations and structural rearrangement	*FGFR1 mutations and kinase domain duplications are common in pediatric low grade gliomas; the duplications are more* frequent in dysembryoplastic neuroepithelial tumors (DNET) and in tumour with oligo-like histology. Rarely described in pilocytic astrocytomas also. However, it is to be noted that FG*FR1:TACC1* and *FGFR3:TACC3* fusions are also very reported in adult glioblastomas
MYB/MYBL1 rearrangements	Commonly seen in non-pilocytic pediatric low grade gliomas, especially diffuse astrocytomas and angiocentric gliomas (*MYB:*

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Genetic alteration	Tumours
	QKI fusion is the commonet alterations involving MYB gene in pediatric low grade gliomas)
NTRK2/3 fusions	Seen rarely in different subtypes of pediatric low grade gliomas. However it is to be noted that these alterations can be rarely in infantile glioblastomas.
H3F3A (H3.3)/HIST1H3B (H3.1)	*K27/28 point mutations* Commoner in pediatric high grade gliomas than the adult counterparts. As per the current (2016) WHO classification, presence of this mutation assigns the tumour as grade IV irrespective of histological features. These group of high grade gliomas are one of the worst prognostic group.
H3.3G34R	These alterations are also more commonly seen in older children and young adults; however unlike the H3K27M mutation, this alterations is not incorporated in the 2016 WHO classification.
Others	*PDGFRA* amplifications, *ACVR1* mutations, *CDKN2A/B* homozygous deletions, *NMYC* amplifications

Molecular Drivers: Pediatric HGG can be divided into molecular subgroups characterized by distinct oncogenic driver mutations, DNA methylation profiles, and gene expression. While the overall mutation burden in pediatric HGG is significantly less compared to adults, the overall mutation rate is higher than that in other childhood malignancies. The salient features of each subgroup is summarized below:

Histological sub types added in revised classification forPediatric Diffuse Gliomas

Diffuse midline glioma: The WHO 2016 has introduced a new entity, diffuse midline glioma-H3K27M mutant, occurring in childhood and young adulthood, and associated with a significantly worse prognosis, poor response to radiotherapy and earlier relapses. This is a diffusely infiltrating high grade glioma, usually of astrocytic morphology, and occurs in midline locations such as thalamus, brainstem and spinal cord, and shows mutation in histone H3 protein. This entity includes tumours previously referred to as diffuse intrinsic pontine glioma (DIPG), and has rarely been seen in adults as well. The tumours harbor K27M mutation in either H3F3A (H3.3) or HIST1H3B/C (H3.1) genes.

Diffuse midline glioma and Diffuse Intrinsic Pontine Glioma: Despite having significant overlap, subtle differences exist between DMG and DIPG. By convention any intrinsic glioma of the pons comes under DIPG, DMG includes only H3K27 mutated gliomas occurring at midline

location including pons, spinal cord and the thalamus. 80% of DIPGs have been reported to harbor H3K27M mutations, whereas presence of H3K27M mutation is mandatory to be termed as DMG.

Epithelioid Glioblastoma: This term has been added as a provisional new variant of IDH-wild type of glioblastoma. These tumours, morphologically characterized by dyscohesive sheets of large epithelioid cells, are seen in children and younger adults, especially in a superficial cortical or diencephalic location, and have a poor prognosis. About 50% show BRAFV600E mutation.

Anaplastic pleomorphic Xanthoastrocytoma: This has been recognized in the current (2016) WHO classification as distinct from the typical canonical pleomorphic xanthoastrocytoma (PXA) and assigned grade III. It is defined as tumour with typical features of PXA alongwith five or more mitosis/10 high-power fields with or without presence of necrosis. Like in PXA, *BRAFV600E* mutations have also been detected in nearly 40-60% of anaplastic PXA.

Pilocytic astrocytoma and pilomyxoid astrocytoma: The current 2016 WHO classification recognizes pilomyxoid astrocytoma to be biological related to pilocytic astrocytomas, in view of similar frequency and presence of genetic alterations. Thus currently, pilomyxoid astrocytomas are not assigned any WHO grade. Additionally, the current WHO classification identifies anaplastic pilocytic astrocytoma as distinct and higher grade version of the pilocytic astrocytoma.

Ependymal tumours

Ependymal tumours are currently known to have nine distinct molecular subgroups. Three each for supratentorial, posterior fossa and spinal compartments **(table 12).** However, this molecular classification of ependymoma has not been included yet in the WHO since it is based on DNA methylation profiling, which is only available in very select institutions world over. From that classification however, one genetically defined supratentorial ependymoma subtype, the RELA fusion-positive ependymoma has been included in the WHO 2016 classification as a distinct entity, since this alteration can be detected by FISH, and also because of availability of a robust immunohistochemical surrogate marker-L1CAM. The RELA fusion-positive ependymoma is site-specific, and is seen in upto 70% of childhood supratentorial ependymomas, and has poor prognosis. Another clinically significant molecular subgroup is the posterior fossa (PF)-A, seen mostly in infants, and has a poor prognosis, in contrast to PF-B, seen in older children and young adults. PF-A type of posterior fossa ependymoma, can also be identified by immunohistochemical loss of expression for H3K27me3. This is being increasingly used in the clinics for identification of PF-A type of posterior fossa ependymoma. A subset of PF-A subtype of ependymomas are characterized by 1q gains (which can be detected by FISH), which has the worst prognosis of all molecular subtypes of ependymomas. However, this though clinically relevant, have not been included in WHO classification yet.

Table-12: Proposed nine molecular subgroups of ependymoma based on methylation profiling (modified from WHO classification)

Anatomical location	Group	Genetic characteristic	Dominant pathology	Age at presentation	Outcome
Supratentorial	ST-EPN-RELA*	RELA fusion gene	Classic/ anaplastic	Infancy to adulthood	Poor
	ST-EPN-YAP1	YAP1 fusion gene	Classic/ anaplastic	Infancy to childhood	Good
	ST-SE	Balanced genome	Subependy-moma	Adulthood	Good
Posterior fossa	PF-EPN-A	Balanced genome	Classic/ anaplastic	Infancy	Poor
	PF-EPN-B	Genome-wide polyploidy	Classic/ anaplastic	Childhood to adulthood	Good
	PF-SE	Balanced genome	Subependy-moma	Adulthood	Good
Spinal	SP-EPN	NF2 mutation	Classic/ anaplastic	Childhood to adulthood	Good
	SP-MPE	Genome-wide polyploidy	Myxopapillary	Adulthood	Good
	SP-SE	6q deletion	Subependy-moma	Adulthood	Good

*Included in WHO 2016 classification; EPN: ependymoma

Medulloblastomas

Medulloblastomas have undergone major restructuring and incorporation of genetically defined entities in the latest WHO classification of brain tumours

In the updated WHO classification, medulloblastoma (MB) are now classified molecularly, based on clustering on transcriptome or methylome profiling, because of its significant clinical utility. However, in absence of molecular analysis, a histopathological classification has also been retained, since both molecular and histological subgroups of MB show vivid prognostic and predictive differences. In the histological classification, classic, desmoplastic/

nodular, MB with extensive nodularity (MBEN), and large cell/anaplastic (LCA) variants are included. In the molecular classification, three principal groups have been identified- WNT activated (~10%), SHH activated (~30%) and non-WNT/non-SHH tumours, which comprise group 3 (~20%) and group 4 (~40%), both the latter listed as provisional variants, since they are not as well separated in molecular clustering analysis. (**Table-13**) The SHH-activated MB is further divided into p53-mutant and p53-wildtype, having different behavior. Although, as yet, only these four major molecular subgroups are recognized by the WHO, additional studies have highlighted significant heterogeneity within these subgroups, and in the future this classification may be set for an expansion.

Table-13: Molecular classification and characteristics of medulloblastoma

	WNT activated	**SHH activated**		**Non-WNT/non-SHH**	
		P53 mutant	**P53 wild type**	**Group 3**	**Group 4**
Frequency	~10%	Rare (<5%)	~25-30%	~25%	~35%
Age distribution	Childhood (7- 14 years), adults (15% of adults)	Children (4-17 years)	Infants <4 years Adole-scents and young adults	Mostly in infants & childhood	Childhood (5-15 yrs), lower incidence in infants & adults
Histological subtype	Classic	LCA or classic	D/N (infants, adults) MBEN (infants)	LCA or classic	Classic
Expression profiling	WNT signature	SHH signature		Photo-receptor/ retinal GABAergic signature	Neuronal, glutamatergic signature

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	WNT activated	SHH activated		Non-WNT/non-SHH	
		P53 mutant	P53 wild type	Group 3	Group 4
Genetic alterations	CTNNB1 mutation (exon3) (85-90%) Monosomy 6 (85%)	TP53 mutation (50% in exon 4&8) GLI2/MYCN/ SHH amplification Loss of Chr 17p	PTCH1/ SMO/SUFU mutation present GLI2 amplification	MYCN amplification or over expression seen in~25% patients, often associated with MYCN-PVT1 fusion	~80% show copy number alteration in Chr 17 (17p gain, 17p deletion, isodicentric 17q) MYCN amplification (~6%)
Proposed cell of origin	Lower rhombic lip progenitor cell in dorsal brainstem nuclei	Granule neuron precursor cell in external granular layer of cerebellum		Prominin1+/ CD133+ lineage neural stem cell	Premature glutamatergic neuronal networks
5-year OS	>95% (excellent)	~40% (poor)	70-85% (good)	<50% (poor)	50-85% (variable and intermediate)
Risk Stratifi-cation	Low Risk (<16 yrs) Unknown risk- For metastatic	Very high risk (metastatic or non-metastatic)	Standard risk- No MYC amp, non-metastatic High risk- MYC amp and/or Metastatic	Standard risk- No MYC amp, non-metastatic Very high risk- Metastatic Unknown- Non-metastatic with MYC amplifi-cation; anaplasia; isochromo-some 17q	Standard risk- Chr 11 loss, non-metastatic High risk- No Chr 11 loss, non-metastatic Very high risk- Metastatic Unknown- Anaplasia

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Principles of Management of CNS Tumours

Principals of surgical management of brain tumours in the contemporary era

Surgery is usually the first modality of treatment in virtually all CNS tumors. In some patients especially benign tumors, it may be the only treatment required. The principles of surgery remain more or less the same for all tumor types (with differences in approaches and strategies depending on the location and occasionally the biological nature of the tumors).

Evolution

Neurosurgical oncology is a rapidly evolving subspecialty and akin to other neurosurgical sub-specialities, it has witnessed significant change due to introduction and adoption of newer technologies and techniques in the last two decades.

The significant advancements were introduction of microscopic neurosurgical techniques by Yasargil in 1970's and use of image guided surgical techniques like

neuronavigation in 1990's. Theseadvances coupled with advancements in neuroanaesthesia and intensive care management and introduction of sophisticated radio-oncological and interventional radiology treatments have changed and widened the scope of neurosurgical practice

Surgery serves the following goals:

- Provides tissue diagnosis so as to guide further adjuvant treatment.
- Relieves compressive symptoms and improve neurological symptoms– which is a major indication of cytoreductive surgery
- Cytoreductive surgery also facilitates subsequent adjuvant therapies by improving neurological status, reducing the tumor burden and eliminating the hypoxic (therapy-resistant) core.
- Surgery also provides an opportunity to deliver novel local therapies (many of which are currently experimental) like Gliadel wafers
- Extent of resection of the primary tumor has been shown to be an independent prognostic factor affecting survival especially in gliomas [Please refer to the suggested reading section for references]

General Principles of Neuro-oncological - surgery

- Meticulous pre-surgical evaluation consisting of detailed neurological examination, adequate preoperative radiologic workup for surgical planning and counselling of the patient's family are essential

components of preoperative workup. Neuropsychological evaluation is preferable in lobar tumors where neurocognitive outcomes are important.

- Maximizing the tumor resection with preservation neurologic function should be the objective which can be achieved with the use of intraoperative adjuncts.
- Due to the unique location of these tumors, it is often not possible resect them radically (as in other oncological surgeries) and the underlying tenet always remains "Safe Maximal Resection".
- The suspected histology also plays an important role in deciding the extent of resection. Eg . In a suspected low grade tumor, completely excising it with resultant mild deficits which are likely to improve over time with plasticity may be acceptable as compared to deficits in a high grade tumor where poor KPS will make the patient unfit to receive the adjuvant treatment.
- Post-operative imaging (MRI preferably) should be performed within 72 hours of the surgery. Regular neurologic assessment and monitoring post operatively is essential to diagnose and treat post-operative complications early.
- Intensive rehabilitation measures instituted promptly help in improvement of overall quality of life (QOL) and help consolidate further adjuvant treatment

Intra-operative Adjuncts

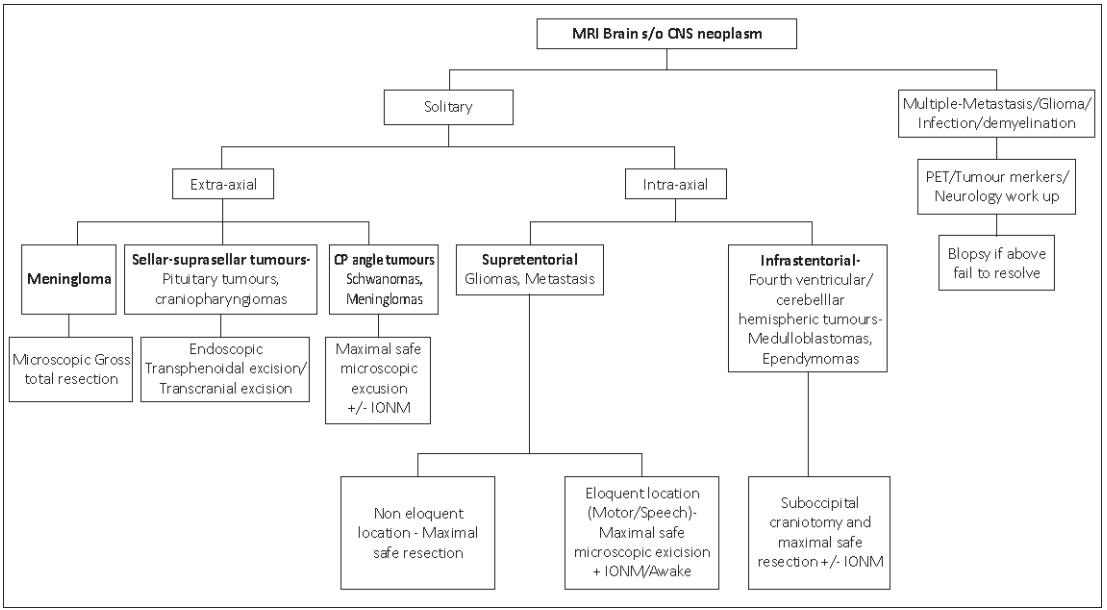
Many adjuncts have been used routinely in neurosurgical practice to achieve the goal of maximal safe resection. The

use of the adjuncts can be tailored as per the requirement in individual case –

- Microscope: It has been routinely used in neurosurgical procedures. It provides improved illumination, magnification and stereoscopic view at depth thus facilitating more radical and complex surgeries safely.
- Intra-operative navigation: Intra-operative navigation systems are based on pre-operative imaging and help to plan the incision, localize tumor intra-operatively and assess completeness of the resection. However due to technical limitations (brain shift) their role in guiding resections is usually limited.
- Intraoperative Imaging: This allows real-time updates and guides resection control overcoming the limitations of navigation. Intra-operative MRI is the gold standard, but remains a logistical challenge at most centers. Intra-operative US is a useful, cost-effective alternative and maybe more easily available in most setups. (Please refer to the suggested reading section for references)
- Fluorescence guided surgery: Use of fluorescence (5-aminolevulinic acid) administered before surgery to patient helps to guide and maximize tumor resections especially in high grade gliomas. Other dyes used for image guided surgeries are fluorescein and Indo-cyanine green and evidence is evolving with respect to their role.

- Intra-operative Neuro-monitoring: It helps to identify eloquent areas (motor strip), cranial nerves and white matter tracts (corticospinal tracts) intra-operatively and allows prediction and prevention of neural injury. Awake surgery with mapping of speech and other higher mental functions is invaluable in most tumors around eloquent areas. There has been progressive increase in the published literature supporting the role of neuro-monitoring for maximal safe resection.
- Endoscopy- Endoscopic techniques have been frequently used as minimally invasive tool for resection of brain tumours especially skull base tumors, pituitary adenomas, craniopharyngiomas and intraventricular tumors.
- Local surgical therapies – Various local surgical therapies have been developed and many more are under development for treating malignant brain tumors. Some of these include Carmustine wafer (Gliadel wafers), nanotherm therapy, and laser interstitial thermal therapy (LITT), especially in recurrent glioblastomas.

Algorithm for general neurosurgical approach to CNS tumours



Principles of radiation therapy for CNS tumours in the contemporary era.

Radiotherapy is an integral component of the multimodality management of primary brain tumours with potential impact upon local control, symptom improvement, and progression free survival for low-grade and benign neoplasm and also overall survival for malignant brain tumours. Following maximal safe resection, adjuvant radiotherapy is indicated for all high-grade primary brain tumours in the postoperative setting. For completely excised benign tumours, such as pituitary adenomas and benign meningiomas, currently there is no role of upfront adjuvant radiotherapy. For low grade gliomas too, with no residual tumour on neuroimaging, surveillance alone is a reasonable option. However, radiotherapy is recommended in such tumours either if a macroscopic residual tumour is evident on postoperative imaging or if tumour progression is documented on serial imaging. For tumours in the eloquent cortex where only a partial excision or biopsy if possible, radical radiotherapy is needed to improve outcome.

Radiotherapy planning

Radiotherapy planning includes appropriate positioning of the patient's head and immobilization with thermoplastic mask. In the present era, all the brain tumours are treated with precision-based delivery techniques which includes Three-dimensional (3D) conformal radiotherapy (3DCRT), Intensity modulated radiotherapy (IMRT), Stereotactic conformal radiotherapy (SCRT) andStereotactic radiosurgery (SRS), volumetric arc radiotherapy(VMAT) and

tomotherapy. High precision radiation therapy techniques are undertaken by delineation of the target volume using CT/MRI fusion. The MRI sequence used is either T2FLAIR for gliomas and 3DFSPGR with contrast for enhancing tumours like embryonal tumours, ependymoma, Pituitary adenomas and craniopharyngiomas.

Volume delination: Gross tumour volume (GTV) comprises of contrast enhancing tumor on preoperative CT/MRI for all high-grade tumors and any residual visible tumour on the post-operative planning images for benign and low grade tumors. Clinical Target Volume (CTV) that encompasses any subclinical microscopic extension is variable depending upon the infiltrating nature of the tumor. Generally, it is 2cm margin to the GTV for high-grade tumors, 0.5-1cm for low grade, and 0.5 cm for benign tumors, which is edited where no spread is possible (e.g. intact bone, tentorium). Planning Target Volume (PTV) is generated 3-dimensionally over CTV to account for set-up errors in daily reproducibility and should ideally be generated in each department individually. For brain, a PTV margin of 5 mm seems safe for routine treatment. For conformal treatments with facility for serial verification, it can be further reduced to 3 mm and should be in the range of 2 mm for fractionated stereotactic radiosurgery depending upon equipment specification and tolerance. Critical structures such as optic chiasm, optic nerves, temporal lobes, brainstem, eyes and lenses, normal brain, cochlea, pituitary hypothalamic axis, hippocampus etc. should be drawn and doses to these structures also calculated to compare different plans.

Field arrangement: For simulated patients, either a 2-field or 3-field conformal arrangement with appropriate wedges is the norm. In case of CT planning, conventional beam arrangement can be substituted with non-coplanar techniques for improving conformity. For stereotactic treatments, 6-9 field non coplanar arrangement gives the most optimal dose distribution. For benign tumours like craniopharyngiomas or patients undergoing re-irradiation Intensity modulated radiotherapy(IMRT) with Image guidance(IGRT) is the norm.

Principles of Chemotherapy & biological therapy and other newer therapy for CNS tumours in the contemporary era.

The role of chemotherapy and biological therapy in the multidisciplinary management of primary brain tumors continues to evolve rapidly. The goal of chemotherapy is to kill tumor cells directly by making them unable to replicate or to enhance normal process of cell death - apoptosis. Some chemotherapy drugs act during specific parts of the cell cycle (cell-cycle specific drugs). Other drugs are effective at any time during the cell cycle and are referred to as non-cellcycle specific drugs. Combining non cross-resistant drugs to improve efficacy and reduce toxicity is the basis of contemporary multi-agent chemotherapy regimens.

Cytotoxic and biological agents for primary brain tumors

- Alkylating agents act by forming a molecular bond which prevents them from reproducing: Cisplatin, carboplatin, cyclophosphamide, temozolomide

- Anti-tumor antibiotics stop the action of enzymes needed for cell growth: Rapamycin Mitotic inhibitors usually disrupt microtubule assembly and interferewith the production of proteins: Etoposide (VP-16) and vincristine
- Nitrosoureas stop tumor cells from repairing themselves: Carmustine (BCNU), and lomustine (CCNU).

Miscellaneous: Procarbazine

Cytostatic agents used for primary brain tumors

Reducing drug resistance: O6-benzylguanine (O6-BG)

Angiogenesis inhibitors: Thalidomide, interferon, CC-5013, COL-3, PTK-787, and bevacizumab

PDL1 inhibitors: Nivolumab

CART cell therapy: C7R-GD2.CAR T cells, CART-EGFRvIII, CART- (IL-13 Rá2)

There are tremendous difficulties and challenges in treating primary brain tumors with systemic chemotherapy. The brain has a natural defense mechanism called the blood brain barrier, which protects the brain by acting as a filter. For a drug to be effective in treating these brain tumors, a sufficient quantity must either pass through the blood brain barrier or bypass it entirely. Blood brain barrier disruption is a technique used to temporarily disrupt this barrier in order to allow chemotherapy to flow into the brain. During blood brain barrier disruption, high osmotic agents such as mannitol are used to temporarily open the barrier. Very high doses of chemotherapy drugs

are then injected systemically, which passes through the blood brain barrier into the tumor area. The barrier is restored naturally as the effects of the osmotic agent wanes.

One of the newer methods of delivering drugs to a tumor is convection enhanced delivery (CED). CED uses the principles of constant pressure to flow or infuse substances through brain tumor tissue. The procedure begins with surgery, during which a catheter (or multiple catheters, depending on the tumor size) is placed into the tumor area. The neurosurgeon then connects a pump-like device to the catheter, filling it with the therapeutic substance to be delivered to the tumor. The fluid flows, by use of pressure and gravity, through the tumor tissue. This convective-delivery method bypasses the blood brain barrier, placing the therapeutic substance in direct contact with tumor tissue. Receptor-mediated permeabilizers offer another way of delivering drugs through the blood brain barrier. They are laboratory created, but modeled after natural substances which temporarily increase the openings of the blood brain barrier, allowing drugs to pass into the brain.

Chemotherapy can also be delivered directly into the cerebrospinal fluid (CSF). This treatment is used for meningeal tumors involving the ventricles or spine, and tumors that tend to seed or spread, through the CSF. A small container system, such as an Ommaya Reservoir, is surgically placed under the scalp. A tube leads from the reservoir into a ventricle of the brain. Medications are injected via syringe into the reservoir and then the

reservoir is pumped. The pumping begins the flow of drug through the ventricles and lining of the spine.

Tumour treating fields (TTF)

TTF is a relatively new, non-invasive technique for adults having glioblastoma. It uses alternating electrical fields to disrupt tumour cell division, or cause cell death, thereby preventing the tumour from growing or spreading so quickly. TT Fields selectively targets cells within mitosis through interacting with key mitotic proteins to cause mitotic arrest and cell death. TTFields therapy may be used for the combinational therapy route due to the lack of overlapping toxicities associated with electric fields. TTFields can be used in combination with alkylating agents, radiation, anti-angiogenics, mitotic inhibitors, immunotherapies, and also with novel agents.

In a randomized trial of 695 patients, use of TTF with TMZ in glioblastoma patients improved the median Progression free survival without causing any additional toxicity.

Evidence Based Management Guidelines of Individual Brain Tumours

A) DIFFUSE NON-CIRCUMSCRIBED GLIOMAS

Treatment of diffuse gliomas in children

Gliomas in children are histologically classified as high-grade (HGG) and low-grade gliomas (LGG). Based on the extent of brain infiltration, these are further categorized into “non-diffuse” or “diffuse”.

Diffuse gliomas (majority HGG; sometimes LGG) are associated with less favorable clinical outcomes, including recurrence after primary surgery, because of extensive infiltration and invasion into the brain.

While pediatric LGGs with diffuse growth patterns include diffuse astrocytoma grade II (DA), angiocentric gliomas (AGs), pleomorphic xanthoastrocytoma (PXAs), and several other rare glioma types, pediatric HGGs are a heterogeneous group with well-defined molecular drivers (discussed below). The new WHO classification on CNS tumours incorporates both genotype and phenotype to include the WHO grade II and grade III astrocytic tumours, the grade II and III Oligodendrogliomas, the grade IV

glioblastomas, as well as the related diffuse gliomas of childhood under a common rubric of **diffuse gliomas.**

Unlike other LGGs that are predominantly found in the cerebellum, diffuse LGGs are most commonly hemispherical (54%) in location, followed by diencephalon (16%), brainstem (12%), cerebellum (12%) and the spinal cord (6%). Location is one of the most important determinants in survival; cerebellum and hemispherical lesions are amenable to complete excision and have 5-year survival rates of 75-80%, in contrast to lesions in brainstem which are inaccessible and need adjuvant radiation or chemotherapy.

Treatment Approach in Diffuse LGG:

Surgical resection remains the mainstay of treatment in all low-grade gliomas. In diffuse PLGGs however, surgery is difficult due to its infiltrative nature and inaccessible locations.

Adjuvant therapies include radiotherapy and chemotherapy. Owing to the long-term side effects of radiotherapy including endocrine abnormalities, cognitive deficits and growth impairment, it has fallen out of favor.

Chemotherapy agents (vincristine and carboplatin, vincristine, carboplatin and TMZ, vincristine, carboplatin, thioguanine, procarbazine and CCNU, single agent vinblastine) have had a demonstrable benefit in non-diffuse PLGGs.

Diffuse PLGGs however are an attractive option for targeted therapies. BRAFv600E inhibitors (dabrafenib, vemurafenib) that are of use in melanoma and histiocytic

disorders, have had encouraging results when used as a single agent diffuse LGGs. Other agents that are useful in diffuse LGGs include Selumitinb and everolimus.

Pediatric High-Grade Gliomas:

Of all the brain tumours in children, pediatric HGG account for about 10%, with majority being "primary" HGG. Pediatric HGG include anaplastic astrocytoma (Grade III) and glioblastoma (Grade IV). In addition to these two, this category includes WHO grade II, III, and IV gliomas of the brain stem that have dismal outcomes and together comprise diffuse intrinsic pontine glioma (DIPG). The 2016 WHO classification has adjusted that nomenclature in favor of diffuse midline gliomas, as diffuse gliomas of the pons, thalamus, and spinal cord may form a more biologically distinct category when H3K27M mutations are present.

Location: The most common locations include the cerebral white matter and deep midline structures. The chances of drop metastases into the spine and leptomeningeal spread are higher in HGG vis-à-vis LGG with up to 10-20% in glioblastoma and 20% in DIPG.

Histology: The two most important pediatric high-grade gliomas are supratentorial glioblastoma (GBM) and diffuse intrinsic pontine glioma (DIPG). Though relevant in the past, limitations exist in classifying HGG purely on the basis of morphology. While histological classification dictates grade III and above in any glioma as being high-grade, certain subtypes like pleomorphic xanthoastrocytoma shares the genotype and clinical behavior with that of a

low-grade glioma despite being grade III. Majority of infants (age < 3 years) with HGG behave clinically like LGG because they lack molecular abnormalities seen in a HGG older than 3 years. Identification of IDH1 mutation supersede the clinical behavior in a pediatric glioblastoma making it favorable compared to a "typical" GBM. Summarily, discovery and identification of distinct molecular drivers that have a robust phenotype-genotype correlation in pediatric HGG have rendered the conventional histology-based classification archaic.

Radiotherapy for Pediatric HGG

The section is divided into:

a. Radiotherapy for HGG

b. Radiotherapy for DIPG

A. Radiotherapy for HGG

Pediatric HGG's include Diffuse midline gliomas (H3K27 mutant) and glioblastomas. Radiation dose of 59.4 GY/33 Fractions or 60 Gy in 30 fractions using 3D conformal therapy is delivered to the tumour concurrent with Temozolamide, However, the role of TMZ in pediatric GBM and midline gliomas (H3K27 mutant) is controversial. The target volume delineation is based on the EORTC or the RTOG guidelines for target delineation for Glioblastomas.

B. Radiotherapy for DIPG

Radiation therapy is definitive treatment in DIPG as surgery is very rarely contemplated in DIPG. Steroids are frequently used during the course of RT to alleviate symptoms of

peritumoral edema, and usually stopped with dose tapering after treatment completion. Overall, RT remains to play a central role in DIPG management.

Conventionally fractionated RT Most common and traditional dose-fractionation scheme for DIPG includes conventionally fractionated RT to a total dose of 54 Gy delivered with daily fractions of 1.8 to 2 Gy over approximately 6 weeks. There have been attempts to improve outcomes of RT with integration of systemic agents before, during, or after RT. Although results of combined modality management with incorporation of systemic agents into radiotherapeutic management of DIPG has not yet been satisfactory to justify its incorporation in routine clinical practise, there is ongoing extensive research on this issue without a widely accepted consensus. Despite the slow progress in terms of prolongation of survival, ongoing trials are assessing the role of single and multi-agent chemotherapy in DIPG management. Multicenter collaborative efforts are warranted to shed light on optimal DIPG management using multimodality therapy.

Hyperfractionated RT:The rationale of hyper fractionated RT is the delivery of potentially higher biologically equivalent doses of radiation without causing excessive RT-induced toxicity. In an attempt to improve outcomes of RT for DIPG, several studies investigated the role of hyper fractionated RT for DIPG. Hyper fractionated RT with higher radiation doses was delivered as a twice-daily treatment. Total delivered dose ranged between 64 to 78 Gy in hyper fractionation trials, however, multicenter

collaborative studies reported that children succumbed to their disease within 18 months of diagnosis and revealed no significant advantage of hyper fractionation over conventionally fractionated RT.

Hypofractionated RT: While late effects of irradiation may be considered as an important concern for a mostly young patient group, there have been attempts to shorten the overall RT time for DIPG since duration of conventionally fractionated RT may be considered long particularly when the short lifespan of patients (typically limited to less than a year) is concerned. Late effects of irradiation may not be observed in the majority of patients due to their limited lifespan, and hypofractionation may be a viable radiotherapeutic strategy for prompt relief of symptoms to improve patients' quality-of-life with reduced burden on patients and families.

Reirradiation Although prognosis of recurrent DIPG is grim, selected patients may benefit from reirradiation. It may be pertinent to consider focal radiation delivery with either conventional or hypo fractionated regimen for effective palliation achievement with reduced overall treatment time despite the need for optimization of RT dose and patient selection.

Chemotherapy in pediatric HGG:

The section is divided into:

a. Chemotherapy for HGG
b. Chemotherapy for DIPG

Table-14: Table summarizing the evidence and the response rates in various therapy regimens in pediatric HGG:

Study and Year	Sample Characteristics	Study arms	Dose	Results
Sposto et al 1989 **CCG-943**	58 patients total 28 (RT+Chemo) 30 (RT alone)	Phase I: Initial Surgery followed by RT vs RT + 12 months of chemotherapy (CCNU, VCR, Prednisone) Phase II (for recurrence): Procarbazine, VCR, CCNU for children who received RT; Single agent procarbazine who received chemotherapy	RT: 52.5 Gy in 28# (45 Gy for children 2-3 years) VCR: 1.5mg/m^2/ week x 6 weeks during RT Chemotherapy **Phase I (6 week cycle)** VCR: 1.5 mg/m^2 D1, D8, D15; CCNU: 100mg/m^2 PO on D2; Prednisone: 40mg/m^2x14 days **Phase II (6 week cycle)** Procarbazine 100mg/m^2/day x 14 days	5 yr EFS: RT+Chemo: 46% RT alone: 18%
Finlay JL et al 1995 **CCG-945**	172 patients 85 (Control) 87 (Intervention)	Phase III Randomized trial Control: As per CCG-943 Intervention: 8-in-1 regimen	Intervention: VCR, CCNU, PCZ, CDDP, Hydroxyurea, Ara-C, Dacarbazine, Methylprednisolone Control: Same as CCG-943 Phase I	5 yr PFS 33% 5 yr OS 36% No difference in either arms
Cohen et al 2011 **ACNS 0126**	90 children (31 AA; 55 GBM; 4 others)	Single Arm Phase II Chemoradio-therapy with TMZ followed by adjuvant TMZ	TMZ @ 90mg/m^2/day starting 7 days after RT and on every day of RT. Adjuvant TMZ at 200mg/m^2 PO for 5 days administered upto 10 cycles every 4 weeks	3 yr EFS: 11% 3 yr OS: 22%

(Contd...)

(Contd...)

Study and Year	Sample Characteristics	Study arms	Dose	Results
Jakacki et al 2016 **ACNS 0423**	108 children 3-21 years (46 AA: 62 GBM)	Single Arm Phase II Chemoradio-therapy with TMZ followed by adjuvant TMZ+ Lomustine	TMZ @ 90mg/m^2/day starting 7 days after RT and on every day of RT. Adjuvant TMZ at 160mg/m^2 PO for 5 days Adjuvant Lomustine 90mg/m^2 PO on day 1 administered upto 6 cycles ever 6 weeks	3 yr EFS: 22% 3 yr OS: 28%

A. Chemotherapy for DIPG

While numerous clinical trials have been undertaken and some are underway in pediatric DIPG, the clinical impact besides radiation therapy remains unproven. No chemotherapy agent (including adjuvant, neo-adjuvant, concurrent, immunotherapy or high dose chemotherapy and stem cell transplant) has led to a measurable long-term survival for children with DIPG.

Potential new therapies include epigenetic therapy, immunotherapy, use of stem cells-nanoparticle combination and targeted inhibitors.

Supportive Care in High Grade Gliomas:

1. Steroids: The steroid of choice is Dexamethasone at 6-12 mg per day in 3 divided doses. It helps in reducing peritumoural edema. And is also useful in reducing radiation associated edema. After being on the starting dose for 72 hours, dexamethasone is gradually tapered (during the 1st week of radiation) and the lowest effective dose is continued.

2. Gastroprotection with H2 inhibitors or PPI must be given with steroids if the anticipated duration is more than 2 weeks.
3. Early integration into palliative care services if the tumour in case of progression/relapse.
4. Generous analgesic use: Paracetamol at 10–15 mg/kg orally every 4–6 h. Opiates should be used in moderate-severe pain at 0.3 mg/kg orally or PR every 3–4 h.

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TREATMENT OF DIFFUSE GLIOMAS IN ADULTS

Surgical management of diffuse gliomas

Surgical resection is considered the first step to be done when dealing with either LGG or HGG. Currently, it is assumed that surgery should aim for the greater extent of resection as it would: (a) increase survival and potentially alter the natural history of the disease: gross total removal or subtotal tumor removal (when feasible and safe) is superior to biopsy in terms of decreasing the rate of tumor progression (evidence -Level II) and also have positive impact in overall survival (evidence Level III). (b) Assure histological diagnosis and molecular analysis (Level III). (c) Ameliorates mass effect and intracranial hypertension. (d) Control of seizures (Level III). Patients with LGG and seizures would have Engel class 1 outcome (seizure-free) in 67–70% of cases and improvement in another 20–25%. Biopsy is indicated when diagnosis is needed in deep lesions (including brainstem), diffuse and/or multicentric tumor or any other contraindication for open resection. Biopsy can be stereotactic (framed or frameless) or open. Neuronavigated non-framed biopsy is gaining acceptance.

Adjuvant Treatment paradigm in adult diffuse gliomas in contemporary era

1. **IDH-wild type low/lower grade gliomas**

   The absence of IDH mutation in grade II/III gliomas marks a distinct IDH-wild type subgroup, which when compared to IDH-mutant gliomas, has been shown to be associated with relatively poor prognosis than is expected for low/lower grade gliomas. Such patients

   a. In cases where IHC for IDH is negative, management of these patients need caution. These cases should be reviewed if there is a high index of suspicion for IDH to be mutant based on clinico-radiological features (any enhancement/T2 signal abnormality). It is strongly encouraged to confirm the IHC findings by DNA sequencing in such cases. If IDH is indeed found to be wild type even on DNA sequencing, they are likely to behave aggressively and extreme caution must be exercised if the treating team is considering an observation/conservative protocol. IDH-wild type WHO grade II tumors postoperatively on observation alone have been shown to exhibit much more rapid increase in their velocity of tumour growth than IDH1 mutant tumors and the mutation acts as an independent prognostic factor for progression-free survival (PFS) and overall survival (OS)

   b. Where feasible, the IDH-wild type lower-grade gliomas could be considered for testing with other molecular markers on an individual case-to-case basis to look for the presence of markers

suggestive of aggressiveness such as EGFR amplifications, mutations of histone H3F3A, and TERT promoter, as these markers identify the molecularly favorable group (lacking molecular alterations) and an unfavorable group (those having either EGFR amplification, histone mutation, or TERT mutation). However, if additional testing is not feasible, it is advisable to err on the side of caution and offer protocols similar to that utilized for high risk low-grade gliomas, i.e., RT along with chemotherapy, either with adjuvant "PCV" [procarbazine-CCNU (lomustine)- vincristine] regimen or concurrent and adjuvant temozolomide (TMZ).

2. IDH-mutant WHO grade II glioma

IDH-mutant adult diffuse WHO grade II low-grade gliomas are relatively slow growing tumors. It is important to characterize their lineage (astrocytoma vs. oligodendroglioma) as the median survival in grade II oligodendroglioma is >15 years and grade II astrocytoma is 7-10 years.

a. Observation alone in IDH-mutant histologically confirmed **low risk WHO grade II diffuse glioma** may be a reasonable option but must be done after careful evaluation of all the known clinico-radiological factors. Those most amenable for this strategy include patients with a **small tumor (less than 6 cm) on initial scans, either none or minimal residual disease post-surgery, age < 40 years, tumors not crossing the midline, absence/minimal enhancement, favorable molecular profile with IDH mutation,**

oligodendroglioma histology with confirmed 1p19q codeletion status, low MIB-1 labeling index, and consensus decision as per a multidisciplinary team meeting. Initial results from the RTOG group (RTOG) 9802 of postoperative observation for favorable risk patients with grade II gliomas (age less than 40 years, no/small residual disease) [RTOG 9802] have shown more than half of the patients even with gross tumor resection having a > 50% risk of tumor progression within 5 years of resection if no adjuvant treatment was prescribed. This makes it, therefore, critical to assess the likelihood of a close follow-up of relevant patients, and final decision-making should be done after due discussion with the patients and their families bearing in mind the need for adjuvant therapy at a later stage if the wait and watch policy is applied.

b. The unfavorable risk patients should be treated as having a **"high risk" low grade glioma** with adjuvant therapy. The long-term results of RTOG 9802 has shown a significant overall survival (OS) benefit with addition of PCV chemotherapy comprising of procarbazine, lomustine (CCNU), and vincristine to focal RT and is, therefore, now the standard-of-care for these patients. IDH-mutant cases, particularly in this group, were associated with the greatest survival advantage. While the trial perse used PCV chemotherapy, increasingly TMZ has been used as an alternative

to PCV as well due to lesser toxicity and the ease of oral administration. The initial results of the RTOG 0424 study using TMZ in high risk, lower grade gliomas (LGG) showed significantly superior survival (both progression free survival [PFS] and OS) as compared to a matched historic comparable cohort treated with RT alone because TMZ is generally tolerated better and may be used as an alternative to PCV, as well.

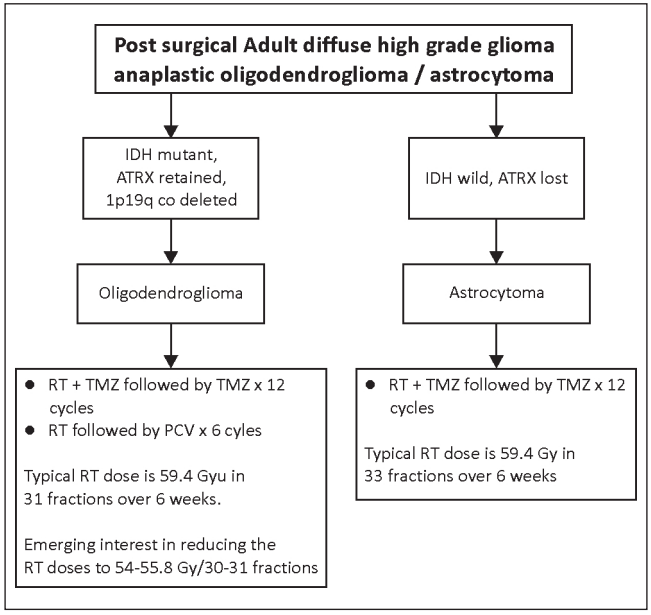
3. **World Health Organization (WHO) grade III anaplastic gliomas with IDH mutation and 1p19q codeletion (anaplastic oligodendrogliomas)**

   This group of tumors do generally well with median survivals reported to be more than 10 years with postoperative adjuvant chemo-radiation post-surgery.

   It is recommended to give radiation therapy and chemotherapy, either in the form of RT followed by PCV or RT concurrently with TMZ followed by adjuvant 12 cycles of monthly TMZ, as per the standard Stupp regimen. The phase III intergroup study of RT with concomitant and adjuvant TMZ versus RT with adjuvant PCV chemotherapy in patients with 1p/19q codeleted anaplastic glioma or low-grade glioma (CODEL study) is currently ongoing and should eventually answer the question of the relative efficacy of TMZ versus PCV chemotherapy. **Radiation doses typically have been 59.4 Gy/33 fractions over 6 weeks**but in view of good long-term survivals in these patients; there is emerging interest in reducing the RT doses to 54–55.8 Gy/30–31 fractions.

4. **World Health Organization grade III anaplastic gliomas with IDH mutation and 1p19q non co-deletion (Anaplastic Astrocytomas)**

This group has a median survival of 3.5 years. The interim results from the Phase III trial on concurrent and adjuvant TMZ chemotherapy in 1p/19q non-codeleted anaplastic glioma (CATNON trial) was associated with a significant survival benefit at 5 years to be 56% in the RT + TMZ arm vs. 44% with RT alone, and hence, is the recommendation in these patients. **RT doses are typically 59.4Gy in 33fractions in this group of patients.**



5. IDH-wild type glioblastoma

IDH-wild type glioblastoma, also known as primary glioblastoma, is the most aggressive of alldiffuse gliomas. The recommended adjuvant treatment in IDH-wild type glioblastoma is conformal **RT with 59.4 Gy/33 fractions and chemotherapy with TMZ**, **followed by cyclical TMZ of atleast 6 cycles,** unless contraindicated.

6. IDH-mutant glioblastoma

IDH-mutant glioblastomas (about 10% of cases) are secondary glioblastoma with a longer history of prior lower grade diffuse glioma, and arises in relatively younger patients. Evidence demonstrates that survival of IDH-mutated GBM to be more favorable than that for non-mutated grade III astrocytoma, thus showing the strong prognostic value of this finding. However, the concurrence of both mutated-IDH and methylated MGMT promoter has stronger prognostic value than either one of these genetic aberrations alone and is associated with improved survival irrespective of the treatment administered. These patients although have a better prognosis than the IDH wild GBM's, they should still be treated aggressively with conformal **RT dose of 59.4 Gy/33 fractions and chemotherapy with TMZ**, **followed by cyclical TMZ of at least 12 cycles,** unless contraindicated.

7. Elderly patients with glioblastoma

- For patients up to 70 years of age with a good performance status and without serious comorbidity, we recommend to give standard

radiation therapy (59.4 Gy/33 fractions) with concurrent and adjuvant TMZ

- For older patients > 70 years of age with a good performance status and without serious comorbidity, hypofractionated radiation (40 Gy in 15 fractions) with concurrent and adjuvant TMZ may be optimal given that radiation therapy can be completed within a reasonable period of time without compromising on the biologically effective dose.
- For older patients who are having a poor functional status or significant comorbidity, the treatment is based on the MGMT promoter methylation status of the tumor. We recommend that MGMT promoter methylated patients should be given TMZ alone and unmethylated cases should be given a short course of radiation therapy alone.

Radiation therapy doses for adult diffuse gliomas in the contemporary era

1. IDH wild type low grade Gliomas: Typical RT dose is 55.8Gy in 31 fractions over 6 weeks.
2. (WHO) grade III anaplastic gliomas with IDH mutation and 1p19q codeletion (anaplastic oligodendrogliomas): Typical RT doses is 59.4 Gy/33 fractions over 6 weeks
3. World Health Organization grade III anaplastic gliomas with IDH mutation and 1p19q non-codeletion (anaplastic astrocytomas) :Typical RT doses is 59.4 Gy/33 fractions over 6 weeks

4. IDH-wild or mutant type glioblastoma: Typical RT doses is 59.4 Gy/33 fractions over 6 weeks

Chemotherapy for adult diffuse gliomas

Indications of chemotherapy in adult glioma

1. Adjuvant setting
    a. Grade 2 Glioma - High risk
    b. Grade 3 Glioma (Anaplastic Glioma)
    c. Grade 4 Glioma (Glioblastoma)
2. Recurrent setting

Agent used

1. Adjuvant setting
    a. The option of participation in a clinical trial is the preferred treatment
    b. Grade 2 Glioma - Either PCV (Preferred) or Temozolomide
    c. Grade 3 Glioma- Either PCV or Temozolomide (Preferred)
    d. Grade 4 Glioma- Temozolomide or Temozolomide + CCNU (option in MGMT methylated patients)

Recurrent setting

The option of participation in a clinical trial is the preferred treatment

a) Chemotherapy- PCV, Temozolomide, CCNU
b) Targeted therapy- Avastin alone or in combination with CCNU or irinotecan or TMZ

Doses used

1. Concurrent use of TMZ with radiation - 75 mg/m^2 per oral (PO) daily(OD)from day 1 of radiation till end

Supportive measures-

- High-risk antiemetic prophylaxis
- Pneumocystis Carnii Pneumonia prophylaxis- Septran double strength twice daily on Saturday and Sunday till completion of radiation. An alternative schedule- alternating days 3 times a week can also be offered.

Temozolomide for adjuvant or salvage settings

- Cycle 1- 150 mg/m^2 PO OD day 1 to day 5 for 28-day cycle
- Cycle 2 onwards- 200 mg/m^2 PO OD day 1 to day 5 for 28-day cycle if tolerated well

Supportive measures-

- High-risk antiemetic prophylaxis
- Dose levels for reduction - 200 mg/m^2, 150 mg/m^2 and 100 mg/m^2

Temozolomide with CCNU

- Cycle 1- CCNU 100 mg/m^2 PO OD day 1 followed by TMZ100 mg/m^2 PO OD day 2 to day 6 for 42-day cycle
- Cycle 2- CCNU 100 mg/m^2 PO OD day 1 followed by Temozolamide 100-200 mg/m^2 PO OD day 2 to day 6 for 42-day cycle
- CCNU alone 110 mg/m^2 PO OD day 1for 42-day cycle

Supportive measures

- High-risk antiemetic prophylaxis
- PCV (RTOG PCV regimen)
- Procarbazine 60 mg/m^2 PO OD on days 8 through 21, CCNU 110 mg/m^2 PO OD on day 1, and vincristine 1.4 mg/m^2 maximum dose, 2.0 mg administered intravenously on days 8 and 29 of each cycle. The cycle length 8 weeks
- Bevacizumab :10 mg/kg IV 2 weekly **(Preferred)**

  Alternative schedules of dose 5-15 mg/kg IV 2-3 weekly have also been used.

  A flat dose of 100 mg IV 2-3 weekly can also be given

Duration of Treatment

1. Adjuvant setting

   Grade 2 Glioma - High risk

   - PCV (RTOG)- 6 cycles
   - Concurrent with radiation followed by Temozolomide -12 cycles

   Grade 3 Glioma (Anaplastic Glioma)

   - PCV (RTOG)- 6 cycles (48 weeks)
   - Concurrent with radiation followed by Temozolomide -12 cycles

   Grade 4 Glioma (Glioblastoma)

   - Concurrent with radiation followed by Temozolomide -6 cycles

2. Recurrent setting
   - Till progression of the disease or intolerable side effects

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B) EPENDYMOMAS

Ependymomas are glial tumors that arise from ependymal cells within the CNS. The WHO classification scheme for these tumors includes 4 divisions based on histologic appearance: grade I (myxopapillary ependymoma and subependymoma); grade II (cellular, papillary, and clear cell variants); grade III (anaplastic ependymoma); and grade IV (ependymoblastoma). Myxopapillary ependymomas are considered a biologically and morphologically distinct variant of ependymoma, occurring almost exclusively in the region of the cauda

equina and behaving in a more benign fashion than grade II ependymoma. Sub-ependymomas are uncommon lesions that share the benign features of myxopapillary ependymomas. However, recent molecular classification based on methylation profiling classifies ependymomas into 9 molecular subgroups (table-11).However the treatment of ependymomas is still based on the extent of resection and histological grade of the tumour. Histologically.

Intracranial ependymomas present as intraventricular masses with frequent extension into the subarachnoid space, while spinal ependymomas present as intramedullary masses arising from the central canal or exophytic masses at the conus and cauda equina. In children, approximately 90% of ependymomas are intracranial, with the majority of these usually arising from the roof of the fourth ventricle (infratentorial). In adults and adolescents, 75% of ependymomas arise within the spinal canal, with a significant minority occurring intracranially in the supratentorial compartment. Intracranial ependymomas represent 6-9% of primary CNS neoplasms and account for 30% of primary CNS neoplasms in children younger than 3 years. They generally present in young children with a mean age of diagnosis of 4 years. Spinal ependymomas are most common in patients aged 15-40 years, most of which are of myxopapillary subtype.Dissemination of the tumor through the cerebrospinal fluid (CSF) is observed in <10% of patients at diagnosis, most of which are infratentorial.Depending on the patient population, the reported 5-year overall survival rate for ependymoma varies from 45-65%.

Surgical resection of ependymomas

Surgical resection remains a critical component of ependymoma management for all histological grades. The surgical procedure is essential to establish a pathological diagnosis and collect tissues for a genomic analysis to determine each ependymoma's unique molecular profile. If the tumor cannot be resected safely due to its location, a biopsy of the lesion is still warranted prior to the initiation of treatment. Where tumor resection is feasible, the most extensive resection is always desirable as many clinical studies have reported that extensive resection is associated with both PFS and OS. Gross total resection is the most significant prognostic factor that determines PFS in supratentorial tumours.

Staging of ependymomas is highly recommended with imaging of the entire neuraxis and cerebrospinal fluid (CSF) analysis. The CSF analysis should be delayed for a minimum of 2 weeks after surgery to avoid confusing findings in the CSF. Dissemination through the CSF is not common and is estimated to occur in 15% of patients, but impacts treatment planning.

Radiation therapy for ependymomas

Postoperative radiation has been established as an effective adjuvant therapy for patients with grade III ependymomas or those with low-grade ependymomas who cannot undergo a complete resection. There is less clarity for grade II ependymomas with GTR. The optimal radiation field and dosage are still matters of debate. However, the consensus as of now is to treat patients with focal radiation therapy, rather than whole brain or

craniospinal radiation, unless there is a sign of tumor dissemination. RT Doses of 5400 cGy in 30 fractions for low-grade ependymomas and 5940 cGy in 33 fractions for high-grade tumors have been tested in the treatment protocols. Results from multivariate analysis of PFS by tumor location, conducted by CERN investigators, demonstrated that radiation following GTR significantly increase PFS for infratentorial ependymomas but not supratentorial and spinal ependymomas.

In the setting of GTR, Grade-I & grade-II ependymomas can be observed however, due to poor prognosis in (WHO grade III) anaplastic ependymomas, there is a consensus that tumor resection should be followed by radiotherapy. Focal radiation therapy can be delivered by precision-based techniques like IMRT or Proton therapy. Retrospective studies have shown similar tumour volume coverage with both techniques. However, studies have shown substantial sparing of normal tissue in ependymomas treated with proton therapy when compared with IMRT. Use of IMPT allows additional sparing of some critical structures.

The Role of Chemotherapy in Ependymomas

The role of chemotherapy in the management of ependymomas has not been well defined. Chemotherapy has been used in younger patients in an attempt to defer radiation to the developing nervous system. In a prospective clinical trial conducted by the French Society of Pediatric Oncology, 73 children younger than age 5 years with ependymomas were treated with 16 months of multiagent chemotherapy, including alternating procarbazine and carboplatin, etoposide and cisplatin, and

vincristine and cyclophosphamide after surgery. The 2- and 4-year survival rates were 40% and 23%, respectively. The benefit of chemotherapy for adults with ependymomas has not been studied prospectively. In patients with recurrent disease, retrospective analyses suggested that platinum-based chemotherapy regimens appear to result in higher response rates with lower rates of progression than nitrosourea-based regimens. However, cisplatin-based chemotherapy did not prolong PFS or OS, despite achieving a higher objective response rate.

A recent retrospective study of response to TMZ in 18 patients with recurrent ependymomas suggested that TMZ has a role in recurrent ependymomas. Chemo-naive adult patients with intracranial ependymoma should be considered for TMZ as the possible first-line salvage treatment in the recurrent setting.

Role of targeted therapy in Ependymomas

CERN investigators developed a novel clinical trial for adults with recurrent ependymoma, testing a combination treatment of lapatinib, a dual tyrosine kinase receptor inhibitor of EGFR/ ERBB1 and ERBB2, and dose-dense TMZ with the intention of depleting MGMT (CERN 08-02, NCT00826241). Treatment was well-tolerated and the results using PFS as a metric demonstrated activity in the spectrum of ependymoma defined by location and tumor grade, which was most efficacious in spinal cord tumors. Preliminary gene expression analysis of a tumor subset showed a statistically significant correlation of better treatment response with a higher ERBB2 expression. Ongoing molecular profiling will determine whether ERBB2

is a predictive marker for response to this treatment regimen. Lapatinib, combined with bevacizumab has been tested on children in a clinical trial by pediatric neuro-oncologists at the CERN Foundation (CERN 08-01, NCT00883688). However, the study accrual was stopped because of low response rate. CERN investigators are now accruing adult patients with recurrent ependymomas to test a combination of carboplatin with bevacizumab, a humanized VEGF monoclonal antibody (CERN 09-01, NCT01295944)

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C) MEDULLOBLASTOMAS

- Commonest primary malignant tumour of brain in children with a small proportion of adult patients
- Small round blue cell tumours of posterior fossa with significant predilection for leptomeningeal dissemination and aggressive behavior
- Understanding from a molecular standpoint has revolutionized classification and prognostication
- Aggressive multimodality therapy can lead to encouraging outcomes with the caveat of long-term debilitating toxicities
- Molecular biology and refined risk stratification likely to personalize treatment in the future

Initial presentation

- Signs of raised intracranial tension – headache, nausea, vomiting,seizures
- Signs of leptomeningeal dissemination- cranial nerve palsies, altered sensorium, backache, paraplegia, incontinence

Initial stabilization

- Head end elevation
- Medical decompression
  - Steroids – initially intravenous Dexamethasone 0.5 -1mg /kg , later reduce to 0.25-0.5 mg /kg in divided doses Q6H-Q8H with PPI
  - Osmotic diuresis – Mannitol – 0.25 – 2 gm/kg body weight IV over 30- 60 minutes thrice daily
- Temporary CSF diversion – External ventricular drain or Endoscopic third ventriculostomy
- Best to avoid VP shunting in view of dependency and long term shunt related morbidity unless referral is planned to a higher centre and no other options are feasible

Work up / Investigations

- Blood: Complete Hemogram, biochemistry, coagulation profile:
- Imaging:
  - CT scan
    - Initial investigation usually done in emergency setting
    - Appears as a hyper dense mass in the posterior fossa with intense post contrast enhancement
    - Leptomeningeal dissemination may be seen as nodules or folial enhancement
    - Always preferable to get an MRI done except in cases of emergency decompressive surgery for an obtunded patient

- MRI Scan
  - Initial investigation of choice due to excellent soft tissue resolution, multi-parametric capability and multi – planar imaging
  - Entire neuraxis (brain & spine) must be imaged pre-operatively to avoid false positive findings that might appear post-operatively
  - The tumor appears T1 hypointense with variable degree of contrast enhancement, T2 hypointense (dark) , with restriction on diffusion sequences
  - Leptomeningeal dissemination appears as plaque like folial or spinal enhancement or discrete nodules
  - Possible to predict molecular subgrouping on the basis of semantic radiological features (see consolidated table on molecular subgrouping)
- Cerebrospinal fluid (CSF) analysis:
  - Despite absence of radiological evidence of disease in spine, 10% of patients can have malignant cells in CSF making CSF studies an useful adjunct to spine MRI. CSF analysis for cytology is done in between 2^{nd} – 3^{rd} week of surgery to avoid contamination secondary to surgical procedure.

- Lumbar puncture preferable to ventricular tap

- Additional preoperative workup:
  - Audiometry: Baseline assessment and monitoring for hearing loss that might occur due to cranial irradiation and cisplatin chemotherapy.
  - Endocrine evaluation
  - Cognitive evaluation
- Occupational therapy for strength and balance training Additional preoperative workup- Perimetry, audiometry, Endocrine evaluation, Cognitive evaluation, Occupational therapy for strength and balance training

PRINCIPLES OF MANAGEMENT

Surgery

Principles of Surgical management:

1. The collaborative effort of neurosurgeons, neuro-oncologists, radiation oncologists, neuroradiologists, and neuropathologists is crucial for delivering appropriate and timely multimodality therapy to patients with MB. Currently, most patients are treated with a combination of maximal surgical resection, craniospinal irradiation (CSI), and chemotherapy
2. Goals of the surgery include obtaining a tissue diagnosis, achieving maximal safe tumor resection, relieving critical structures from mass effect, and addressing any associated hydrocephalus.

3. Majority of the children at the time of presentation may be symptomatic due to hydrocephalus. Depending on the severity of symptoms a decision must be made to treat the hydrocephalus before hand or at the time of tumour resection.
4. Options for surgically treating hydrocephalus at presentation are external ventricular drain (ETV), ventriculo-peritoneal shunt (VPS) or endoscopic third ventriculostomy (ETV).
5. However majority of the patients with symptomatic hydrocephalus can be managed with cerebral decongestant therapy (Corticosteroid and mannitol) alone and definitive surgery can be performed on semielective basis as only 10 % -40% of the ultimately need a permanent CSF diversion follow tumour resection.

Principles of Surgical management:

6. Currently, most patients are treated with a combination of maximal surgical resection, craniospinal irradiation (CSI), and chemotherapy
7. Goals of the surgery include obtaining a tissue diagnosis, achieving maximal safe tumor resection, relieving critical structures from mass effect, and addressing any associated hydrocephalus.
8. Majority of the children at the time of presentation may be symptomatic due to hydrocephalus. Depending on the severity of symptoms a decision must be made to treat the hydrocephalus before hand or at the time of tumour resection. Some institutes

prefer to surgically treat the hydrocephalus first (if patient is symptomatic) and address the tumour electively.

9. Options for surgically treating hydrocephalus at presentation are external ventricular drain (EVD), ventriculo-peritoneal shunt (VPS) or endoscopic third ventriculostomy (ETV).
10. However majority of the patients with symptomatic hydrocephalus can be managed with cerebral decongestant therapy (Corticosteroid and mannitol) alone and definitive surgery can be performed on semielective basis as only 10 % -40% of the ultimately need a permanent CSF diversion follow tumour resection.

Surgery

- Medulloblastoma typically arise from the roof of the fourth ventricle and are surgically approached by a midline suboccipital craniotomy.
- Surgery can be performed in prone (more common) or sitting position.
- Goal of the surgery is maximal safe tumour resection using the standard microsurgical principles.
- Operative adjuncts which may be needed during the surgery are microscope, cavitron ultrasonic aspirator, evoked potentials/ neuromonitoring(if brain stem invasion anticipated on MRI) and ultrasound (especially for hemispheric lesions).
- Fourth ventricular mass lesion can be approached by a telo-velar approach. A cerebellar hemispheric MB

is typically approached with transcortical incision through the cerebellar cortex that is the shortest distance from the tumor

- Its essential to identify the floor of the fourth ventricle early and avoid resection of tumour infiltrating into the cerebellar peduncles or the floor of the fourth ventricle.
- Post-operative imaging, preferably MRI brain with contrast should be performed within 48 hours or else deferred till 4 weeks post op to allow post-operative changes to resolve.
- Presence of significant residual tumor may be considered for early repeat resection, unless the procedure was stopped because invasion of tumor into critical structures like brainstem. However, recent published literature does not demonstrate prognostic importance of extent of resection on survival in medulloblastomas. (please refer the suggested reading)

Post op CSF sampling for staging-to defer till 3 weeks post op to avoid false positivity

Pathology, molecular classification and risk stratification

Conventional histo-morphological classification recognizes the following subgroups of MB:

- Desmoplastic nodular (DN)
- Medulloblastoma with extensive nodularity (MBEN)
- Large cell anaplastic (LCA): Associated with disseminated disease and poor outcomes
- Classical: Intermediate between the two

Molecular subtyping has presently taken precedence in classification of MB and the present WHO 2016 classification identifies 4 distinct subgroups of MB:

- Wingless(WNT)
- Sonic Hedge Hog (SHH)-TP53 wild
- Sonic Hedge Hog (SHH)-TP53 mutant
- Non WNT Non SHH (includes Canonical Group 3& 4)

All DN-MB are SHH-driven while the converse is not true. Only about one-third of SHH-MB are DN; majority are classic (40%), MBEN is seen in 10% and LC/A in 20%. Similarly, WNT-driven MBs are usually of classic subtype and rarely are LC/A. Group 3/4 MBs can either be classic or LC/A.

Despite defined molecular drivers for each subgroup, classical subgroups on histopathology should always be reported even in the presence of molecular sub-grouping to allow comparability with historical data sets & to allow prognostication in the absence of molecular subgrouping. Molecular classification-based risk stratification and treatment optimization while still being useful, are at present avoided outside the context of a clinical trial. Currently they would form a basis for prognostication alone.

The table below summarizes the clinico-pathological and radio- genomic features of the broad molecular subgroups:

Staging Evaluation & Risk Stratification:

Staging:

Staging is decided on the basis of extent of disease dissemination and presence of residual disease.

Modified Chang staging is used across all protocols to stage the disease:

M0: No dissemination

M1: Only CSF cytology positive for malignant cells

M2: Gross nodular seeding in the cerebellar-cerebral subarachnoid space and/or lateral ventricle and/or third ventricle (limited to intracranial compartment)

M3: Gross nodular seeding in the spinal subarachnoid space (spill-over to the spinal compartment)

M4: Extra-neural metastases (bone, bone marrow, skin)

Incidence of M1-M4: 30%

Incidence of M4 alone: <1%

Residual disease:

Gross total resection (GTR): No residual tumor identified

Near Total resection (NTR): Residual tumor < 1.5 cm^2

Subtotal resection (STR): Residual tumor ≥ 1.5 cm^2

Risk Stratification: Detailed in Table 16.

Molecular subgroup guided risk stratification: Emerging role in prognostication but not yet clinically validated. Summarized in Table 17.

The most recent risk stratification takes into account molecular subtype, age, extent of metastatic disease and divides MB into 5 groups:

1. Very Low-risk: WNT M0
2. Low-risk: WNT M+, SHH-MBEN, iSHH-II (γ), Group 4-Low Risk,
3. Intermediate Risk: SHH-TP53WT, SHH-non-MBEN, Group 4-Others
4. High-risk: Group 3 MYC non-amplified, iSHH-I (β), Group 4-High Risk
5. Very High-risk: SHH-TP53 mutant, Group 3 M+ or MYC amplified.

Table-15: The table below summarizes the clinico-pathological and radio- genomic features of the broad molecular subgroups

Parameter	WNT	SHH		Non WNT Non SHH	
		TP53 mutant	TP53 wild	Group 3	Group 4
Frequency	10%	<5%	25-30%	25%	35%
Age distribution	Older children (85%); Adults (15%)	Children (4-17 yrs); Un-common in adults	Infants <4 yrs Adole-scents & Young Adults	Infants	Children(5-15yrs) Lower incidence in infants and adults
Gender	Equal	Equal	Equal	More in males (>2 fold)	More in males (2-8-fold)

(Contd...)

(Contd...)

Parameter	WNT	SHH		Non WNT Non SHH	
		TP53 mutant	TP53 wild	Group 3	Group 4
Radiology	Vermian origin Extension to CP angle and foramen of Luschka Homoge-nous enhance-ment Bleed on GRE Superior location on sagittal images	Midline origin in infants; Lateralized origin in adults Contact with tentorium Edema on T2 sequences		Inferior placement on sagittal images with fluffy enhancement Folial enhancement and propensity for leptomeningeal disease	Inferior location on sagittal MRI with dilatation of superior recess of 4th ventricular Poor to patchy enhancement; isolated deposits (suprasellar) -contrast mismatch pattern between primary and mets
Histo-pathology	Mainly classic, very rarely LCA	LCA or classic DN-rare	DN-infants, adults MBEN-infants Rarely classic or LCA	LCA or classic	Classic-common LCA- rare
Expression profiling	WNT signature	SHH Signature		Photoreceptor/ GABAergic signature	Neuronal/ Glutaminergic signature
Survival (5yr)	>95%	40%	70-85%	<50%	50-85%

Risk stratification

Table-16 : Conventional clinical and tumour factors for risk stratification of medulloblastomas still forms the basis of clinical practise

Risk grouping	Features	5 year overall survival
Average risk	Age >3 yrs Residue <1.5 cm^2on axial CT No neuraxial dissemination	70-80%
High risk	Age <3 yrs Residue >1.5 cm^2on axial CT Neuraxial dissemination	40-60%

Table-17: Molecularclassification in medulloblastomas – emerging role in prognostication but not yet clinically validated

Risk group	WNT	SHH	Group 3	Group 4	Other
Low	<16 yr			All of the following - Non metastatic - Chr 11 loss	
Standard		-Non metastatic -No MYC N ampli-fication -TP53 wild type	Both -No MYC ampli-fication -Non-Metastatic	All of the following -Non metastatic -No Chr 11 loss	
High		One or both -MYCN ampli-fication -Metastatic	Metastatic		

(Contd...)

Risk group	WNT	SHH	Group 3	Group 4	Other
Very high		TP53 mutation -metastatic or non-metastatic	Metastatic		
Unknown	metastatic		-Non metastatic with MYC amplification -Significance of anaplasia -Isochromosome 17q	Significance of anaplasia	-Melanotic medulloblastoma Medullomyoblastoma Boundary Group 3/4

Table-18: TMH approach for Adjuvant Radiation therapy& chemotherapybased on risk stratification

Risk stratification	Paradigm	Radiotherapy	Chemotherapy
Average risk Children	Low dose Cranio- spinal Irradiation (CSI) followed by adjuvant systemic chemotherapy	CSI- 23.4Gy/13# Tumour bed boost (1.5 cm margin) -30.6Gy/17# Total dose -54Gy	4-8 cycles adjuvant systemic chemotherapy) Lomustine/ Cisplatin / Vincristine or Cyclophosphamide/ Cisplatin/ Vincristine

(Contd...)

(Contd...)

Risk stratification	Paradigm	Radiotherapy	Chemotherapy
Adults	Standard dose Cranio- spinal Irradiation (CSI)	CSI- 35Gy/21# -40Gy/24# (extensive leptomeningeal disease) followed by Tumour bed boost (with 1.5 cm margin) - 19.8Gy/11#	No chemotherapy
High risk	Standard dose Cranio- spinal Irradiation (CSI) followed by adjuvant systemic chemotherapy	CSI- 35Gy/21# -40Gy/24# (extensive leptomeningeal disease) followed by Tumour bed boost (with 1.5 cm margin) -10.8Gy/6# -19.8Gy/11# Posterior fossa boost -10.8Gy/6 #-19.8Gy/ 11# (if extensive leptomeningeal disease in posterior fossa) Boost to sites of gross lepto- meningeal disease -10.8Gy/6# -19.8Gy/11# Total Dose – 54Gy	4-8 cycles adjuvant systemic chemotherapy) Lomustine/ Cisplatin/ Vincristine or Cyclophosphamide/ Cisplatin/Vincristine

(Contd...)

(Contd...)

Risk stratification	Paradigm	Radiotherapy	Chemotherapy
Very high risk High risk + any of the features • NMYC amp • P53 positive SHH • Large cell anaplastic variant • Diffuse anaplasia	Standard dose Cranio-spinal Irradiation (CSI) with concurrent carboplatin for first 15 days followed by adjuvant systemic chemotherapy	CSI- 35Gy/21# -40Gy/24# (extensive leptomeningeal disease) followed by Tumour bed boost (with 1.5 cm margin) -10.8Gy/6# -19.8Gy/11# Posterior fossa boost -10.8Gy/6 # -19.8Gy/11# (if extensive leptomeningeal disease in posterior fossa) Boost to sites of gross leptomeningeal disease -10.8Gy/ 6# -19.8Gy/11# Total Dose – 54Gy	4-8 cycles adjuvant systemic chemotherapy) Lomustine/ Cisplatin/ Vincristine or Cyclophosphamide/ Cisplatin/ Vincristine

(Contd...)

(Contd...)

Risk stratification	Paradigm	Radiotherapy	Chemotherapy
Infants and young children <3 years of age	Systemic chemotherapy (Baby brain protocol) and deferred RT (till child has attained the age of atleast 3 yrs to mitigate debilitating toxicities of CSI on developing brain)		Multi agent chemotherapy including carboplatin/ cisplatin, etoposide, cyclophosphamide, vincristine with or without the use of HD-MTX or IT-MTX

Follow up

- Neuraxial imaging – to be repeated 1-month post RT and then again at 1-month post completion of adjuvant chemotherapy. Further imaging annually or at suspicion of clinical progression
- Clinical follow up- 3 monthly for 2 years, thereafter 6 monthly till 5 years, thereafter annually

Table-19: Toxicities associated with treatment of medulloblastomas

Acute toxicity			Late toxicity
Surgery	**Radiotherapy**	**Chemotherapy**	
➢ Air embolism ➢ Haemorrhage Wound dehiscence ➢ CSF leak ➢ Brainstem dysfunction ➢ Infection ➢ Mutism	➢ Myelo-suppression ➢ Emesis	➢ Myelo suppression ➢ Ototoxicity ➢ Nephrotoxicity ➢ Neurotoxicity	➢ Cognitive dysfunction ➢ Hypothalamic & pituitary dysfunction ➢ Visual and auditory dysfunction ➢ Disuse atrophy and ataxia ➢ Cataract ➢ Infertility ➢ Second malignancy

Recurrent medulloblastoma

- Relapses tend to be local in 33% of cases, whereas 67% is associated with dissemination.
- Early relapses (within 3 years more common in children) whereas adults may have late relapses with extra – neuraxial dissemination.
- Infants and young children who have not received RT may be salvaged with CSI and this may translate into long term survival.
- High dose chemotherapy with autologous hemato-poietic cell transplantation has been attempted in small series with encouraging disease free survival.
- Alternatively, patients with longer disease free interval, good general condition and favorable biology

disease may be considered for re-excision, systemic chemo and irradiation (focal/CSI) with encouraging outcomes reported in small prospective series.

Other aggressive embryonal tumours (CNS-PNET/ATRT/ ETMR)

- Management algorithms are on the same lines as high risk medulloblastoma.
- Early RT in Infants and toddlers as opposed to a delayed RT strategy is associated with improved outcomes and must be weighed against the significant toxicities consequential to CSI on the developing brain.

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D) BRAIN METASTASIS

Brain metastases (BM) are the most common intracranial tumors and occur in 20–40% of all cancer patients, significantly affecting the quality of life and survival. Lung cancer (20-56%), breast cancer (5-20%), and melanoma (7-16%) are the most frequent primary cancers to develop BM. Among lung cancers, small cell lung cancer contributes to 50% of all BM. In Breast cancers about 50% are HER2 (human epidermal growth factor-2) overexpressing breast cancer, followed by triple negative breast cancer and hormone receptor positive breast cancer. The highest frequency of BM is seen in patients with metastatic melanoma, with approximately 50% of metastatic melanoma patients detected with BM at baseline, while additional 40% are noted at autopsy.

Treatment

Various treatment options are exercised in various permutations and combinations including surgical resection, radiation therapy, and/or chemotherapy. The choice of therapies and aggressiveness is guided by an estimation of a patient's prognosis or survival, where generally more localized (surgery, stereotactic radiosurgery) and aggressive therapies are offered to patient's with better prognoses. There are several prognostic scoring systems that have been developed

including the Recursive Partitioning Analysis (RPA), Score Index for Radiosurgery (SIR), Basic Score for BM (BSBM), Rotterdam system (ROTTERDAM), Golden Grading System (GGS), Rades classification (RADES), and Graded Prognostic Assessment (GPA) classification systems.

Table-20: Median survivals stratified by diagnosis and diagnosis-specific GPA score for patients with newly diagnosed BM and modified GPA scoring. (Adapted from ASTRO guidelines, 2012)

Diagnosis	GPA scoring	Overall Median Survival	GPA 0-1	GPA 1.5-2	GPA 2.5-3	GPA 3.5-4
NSCLC	Age: <50:1,50-60:0.5, >60:0 KPS: 90-100:1, 70-80:0.5, <70:0 Extra Cranial Mets: ab:1; pr:0 No BM: 1:1, 2-3:0.5, >3:0	7	3	5.5	9.4	14.8
SCLC	As NSCLC	4.9	2.8	4.9	7.7	17.1
Melanoma	KPS: 90-100:2, 70-80:1, <70:0 No BM: 1:2, 2-3:1, >3:0	6.7	3.4	4.7	8.8	13.2
RCC	As Melanoma	9.6	3.3	7.3	11.3	14.8
GI	KPS: 90:3, 80:2, 70:1, <70:0	5.4	3.1	4.4	6.9	13.5
Breast	KPS: 90-100:1.5, 70-80:1, 60:0.5, <60:0 Triple +:2, Her2+: 1.5, ER/PR+:1, Triple -: 0 Age: <70: 1, >70:0	13.8	3.4	7.7	15.1	25.3
Total		**7.2**	**3.1**	**5.4**	**9.6**	**16.7**

Surgery

Surgery plays a significant role in the management of BM. It helps in achieving decompression and relief of symptoms secondary to mass effect, tissue diagnosis including relevant molecular analysis, local control in select cases such as larger lesions, and/or for a combination of these

reasons. Surgeryfor BM is indicated for patients with good prognosis and accessible locations and low potential surgical morbidity. For metastatic lesions that are small with minimal edema and mass effect, radiation therapy, namely stereotactic radiosurgery, is preferred.

A subset of BM are present in deep-seated locations where accessing and resecting them can lead to significant morbidity. In large cystic BM, an option of cyst aspiration can help in substantially decreasing the tumor volume and improving the feasibility of SRS. This can also be used in large post-operative cavity to facilitate better dose delivery with adjuvant radiotherapy.

One of the early randomized trials by Patchell et al. demonstrated complete resection at surgery as the best management strategy for single BM. Patients with a single BM were randomized to surgery plus WBRT or biopsy plus WBRT which showed an overall survival (OS) benefit to surgical resection (40 vs. 15 weeks, $p < 0.01$) and local control improvement. Subsequently, the same group studied single BM with complete surgical resection randomized to WBRT or observation. The post-operative WBRT reduced intracranial failure from 70 to 18% ($p < 0.001$) and local recurrence (LR) from 46 to 10% ($p < 0.001$).

Indication for surgery in brain metastasis

- Ideal Indication for radical surgery- solitary brain met with well-controlled primary and good KPS, where a safe resection is possible.

  In deep-seated lesion /or eloquent area metastasis-surgery is not recommended/preferable.

- Biopsy- in case of diagnostic dilemma after appropriate investigations.
- In case of a large metastasis with multiple smaller lesion- surgery may be offered for the larger lesion to facilitate RT/SRS to others.
- Reservoir placements for intrathecal medications in leptomeningeal disease.
- Other cases- where solitary brain lesion progresses, but systematically the disease responds with treatment (e.g chemo in lung ca). Here surgery can be offered as the brain serves as a sanctuary site.

Adjuvant Radiotherapy [Cavity SRS (Post-operative SRS)]

The rate of recurrence for surgery alone is close to 50%. To reduce this rate of recurrence, postoperative radiosurgery or radiotherapy is generally recommended. WBRT as adjuvant therapy for surgically resected BM has traditionally been considered the standard of care. But WBRT comes with substantial cost of neurocognitive decline due to in advent dose to the normal functioning brain parenchyma. Randomized trial N107c, demonstrated equivalent OS for postoperative SRS and WBRT (median OS: 12.2 vs. 11.6 months, respectively; p=0.70) where 85% of WBRT patients experienced cognitive deterioration at 6 months post-treatment as compared to only 52% with SRS ($p<0.001$). Postoperative SRS is thus now considered a standard of care and is becoming a more frequently employed modality after surgically resected metastases.

In contemporary series, the rate of local recurrence has considerably declined with SRS to 28% at 1-year and 44% for >3cm lesions at 2-years. This may be due to improved cross-sectional imaging, surgical advances, targeted systemic therapy, and advanced delivery of radiation treatments. The size of post-operative cavity >3cm, volume >10c.c, CTV margin <2mm, >3 weeks' post-surgery and meningeal contact have been associated with increased local failures. The first two factors may be related to choice of lower dose for larger volume and less homogeneity index. Recently published consensus guidelines for contouring in cavity SRS by Soliman et al. is recommended.

Recommendations for CTV contouring for postoperative completely resected cavity SRS

- CTV should include the entire contrast-enhancing surgical cavity using the T1-weighted gadolinium-enhanced axial MRI scan, excluding edema determined by MRI.
- CTV should include entire surgical tract seen on postoperative CT or MRI If the tumor was in contact with the dura preoperatively.
- CTV should include a 5- to 10-mm margin along the bone flap beyond the initial region of preoperative tumor contact if the tumor was not in contact with the dura.
- CTV should include a margin of 1 to 5 mm along the bone flap If the tumor was in contact with a venous sinus preoperatively.
- CTV should include a margin of 1 to 5 mm along the sinus.

Radiation doses in cavity radiosurgery (Brown et al Lancet Oncology 2017)

Cavity volume	SRS dose
<4.2ml	20Gy
4.2-7.9 ml	18Gy
8.0-14.3 ml	17Gy
14.4-19.9ml	15Gy
20-29.9ml	14Gy
>30ml	12Gy

Upto a Maximum cavity size of 5cm

Tumor progression has been reported in three ways for brain metastasis, local, elsewhere brain parenchyma and lepto-meningeal carcinomatosis. The elsewhere recurrences remain predominant location post SRS, similar for both intact SRS alone and post-operative scenario. The data suggests that leptomeningeal carcinomatosis is higher with post resection of BM and surgical violation of the tumor capsule. The overall rate of leptomeningeal disease is estimated to be 5–15%, depending on several clinical and pathologic features such as breast and rectal cancer histology, posterior fossa location to name a few. These rates increase to 8 to 24% in post-surgical scenario.

Large BM: unsuitable/unwilling for surgery

General definition for large mets varies in literature from size ≥2 or ≥3 cm in diameter or ≥4 cm. The WBRT alone

used traditionally, is associated with a poor local control. With SRS alone, efficacy also decreases with increasing size due to inability to deliver higher doses safely. In RTOG 90-05, lesions measuring ≤2, 2.1–3, and 3.1–4 cm were treated by radiosurgery with doses of 24, 18, and 15 Gy, respectively. The local control rates were 49% and 45% in lesions 2.1–3 and 3.1-4 cm in diameter, while 85% in ≤2 cm with dose of 24 Gy.

Recommendation for the SRS doses in intact brain Metastasis based on RTOG 90-05 study	
Size	**Dose**
<2cm	24 Gy
2.1-3 cm	18 Gy
3.1-4 cm	15Gy

Hypofractionated radiotherapy (typically 2–6#) is recently seen as one of the options to allow safer dose escalation for large mets to improve outcomes. Hypofractionated SRS has been associated with a median OS of 7–17 months and a 1-year LC of 64 to 100%. In a review of 448 patients treated in eight series found it to be safe for lesions measuring >1 cm and furthermore it was found to be a preferable method of treatment for tumors with diameter >2 cm over SRS. The local control rates were 68.2–93%.The dose schedules range from 25- 42 Gy in 3-5#. The series using doses upto 42-46 Gy/5# demonstrated that at these levels, the size of tumor no longer related to control rates (90% at 1 year irrespective of size). Similarly, excellent

control rates of 95% were seen when fractionation was chosen to provide a biologically equivalent dose (BEDGy10) > 50 Gy.

Another possible alternative to single fraction SRS and hypofractionation for large BM is a planned multiple treatment radiosurgery over two or more sessions separated by weeks or months. In one of the initial studies including tumors measuring e”10 cm3 and delivering 30 Gy in 3 fx every 2 weekly showed almost 18.8 and 40% volume reduction after 10 and 20 Gy respectively with 1-yr control rates of 75.9%. Two stages treatment at 3-4 weeks in >10cc with total 20–30 Gy showed 1-yr control rates of 64%. Similarly, 24-33 Gy (Median 30Gy, BEDGy10: 44–73; median 62.5 Gy) in 2–3 fx over a month has been used. In this technique, replanning is needed for each fraction.

In fractionated SRT, the generally followed dose constraints include maximum doses of 21–25 Gy in 5 fx or 15–18 Gy in 3 fx for the optical apparatus and 31 Gy in 5 fx or 23 Gy in 3 fx for the brainstem. Other possible dose limits that have been described for the brainstem are D1% (dose administered to 1% of the volume) ≤20 Gy or V26Gy (volume of the brainstem receiving 26 Gy) <1 cc, D1% ≤15 Gy or V20Gy (volume receiving 20 Gy) <0.2 cc for the optical nerves and D1% <1 Gy for the lenses (7, 45). Maintaining a V14Gy < 3 cm^3 for the brain parenchyma and <1 cm^3 for critical areas such as motor cortex, basal ganglia or thalamus has been described.

Data has showed that large tumors treated with 9 Gy in 3 fx had a 14% risk of RN vs. 33% for lesions treated in a

single fraction. The risk of RN when treated with 3 fractions seems to be related to the volume receiving 18 Gy. Rates of RN are estimated to be 5% for V18 ≤30.2 cm3 and up to 14% for V18 > 30 cm^3.

The risk of RN was estimated to be: 0, 6, 13, and 24% for V18 < 22.8, 22.8–30.2, 30.3–41.2, and >41.2 cm^3, respectively. When surrounding brain volume treated to the equivalent of a single dose of 14 Gy (V14Gy) can be predictive of the risk of RN, with V14 ≥7.0 cm^3 being a risk factor for developing extensive brain edema and RN. It has been concluded that the risk of RN can be maintained under 2–15% when a BED of 90–127 Gy3 (a/b=3) is used (dose of 24–35 Gy in 3–5 fx).

The Grade 1–3, toxicity of 2–52% has been reported. Age (>60), treatment with less than five fractions, and a greater treated volume (possibly of >20 cm^3) have been suggested to be predictive of brain edema necessitating steroids. Lesions located deep within the white matter are perhaps more likely to cause edema necessitating corticosteroids, and it has been suggested for these to keep V14Gy to ≤3 cm^3.

One to four BM

Despite decades of proofs available in literature for feasibility, safety and success of treatment for multiple BM, substantial nihilism exists in practice. One of the initial studies treated 2 to 4 BM, all <2.5 cm with WBRT vs. WBRT plus SRS boost showed better control with SRS boost (100% vs. 8%) and survival (11 vs 7.5 months). RTOG 95-08 randomized 300patients with 1-3 BM and showed improved local control at 1-yr from71 to 82% but no

survival difference. In the subset of patients with single BM or recursive partition analysis (RPA) Class I, there was improved survival with SRS boost arm.. On secondary analysis, patients were classified by GPA score and patients with a high GPA (3.5–4) had improved survival regardless of number of BMs. This study further strengthened conclusion that SRS boost improves LC and OS, particularly in patients with good performance status. A Cochrane database updated review in 2017 of the three randomized trials (n = 358) showed decreased local failure in the WBRT plus SRS group (HR 0.27 95% CI 0.14–0.52) as well as an improvement in performance status scores and decreased steroid use (RR 0.64 CI 0.42–0.97). There was no difference in OS in either group, though in participants with single BM had significantly longer median survival in the WBRT plus SRS group ($p = 0.04$).

In a phase III study (Aoyama et al; n=132), BM of 4 or less and BM <3 cm, local failure decreased from 76 to 47% with the addition of WBRT to SRS ($p < 0.001$). WBRT also improved 1-year freedom from new BM from 41.5% in SRS group to 64% with the addition of WBRT ($p = 0.003$) with no noted differences in toxicities between the groups. Conflicting conclusions were drawn by various groups from this data, with the authors concluding that WBRT could be omitted safely, while others felt that WBRT improved LC and brain tumor recurrence and should be delivered routinely. In a secondary analysis of the data, published 9 years later, in the subset of patients with non-small cell lung cancer (NSCLC) with GPA score of 2.5–4, there was an improvement in OS from 10.6 to 16.7 months ($p = 0.04$) in patients receiving SRS plus WBRT. As expected, this group of patients had a lower rate of BM recurrence

($p < 0.01$) which may have contributed to improved OS. There was no improvement in survival for patients with lower GPA scores.

In another phase III study in patients (n=58) with 1–3 BM and followed with neurocognitive outcomes with the Hopkins Verbal Learning Test Revised (HVLT-R) at interim analysis demonstrated 96% probability for decline in neurocognition with WBRT and was stopped. There was a higher rate of CNS recurrence with SRS alone (73 vs. 27%; p=0.0003). Median OS was surprisingly improved in SRS alone group at 15.2 vs. 5.7 months in the SRS plus WBRT group (p=0.003) probably associated with more surgical salvage and/or earlier start to systemic therapy in SRS alone arm. Given improved neurocognitive scores as well as potential for OS benefit, the authors concluded the SRS alone should be preferred over SRS plus WBRT provided patients undergo close and careful follow up.

In EORTC phase III study for patients with 1–3 BM who underwent SRS or surgery and then randomized patients to WBRT or observation again showed no difference in OS between the groups. Further it showed that patients in the observation arm had higher HRQOL scores in global health at 9 months (p=0.148), as well as improved physical function and fatigue at 8 weeks, and cognitive functioning at 12 months compared to those in WBRT arm. An individual patient-level meta-analysis of the above three studies showed that patients younger than 50 years old had an improved survival with SRS alone when compared to SRS plus WBRT (10 vs. 8.2 months, p = 0.04). This patient group also had no difference in distant BM rate. It was concluded from this data set that the side effect profile of

WBRT coupled with no improvement in distant BM rate may lead to the survival advantage seen in younger patients receiving SRS alone.

The most recent phase III study investigating SRS vs. SRS plus WBRT, (N0574) randomized patients with 1–3 BM to SRS vs. SRS plus WBRT (n=280) with the primary endpoint of neurocognitive function (defined as decline of >1 standard deviation from baseline in any of 7 cognitive domains at 3 months follow up) showed that 91.7% of patients in the SRS plus WBRT arm had cognitive decline vs. 63.5% in SRS alone group ($p < 0.001$).

Particular cognitive domains that were most affected by the addition of WBRT included immediate recall, delayed recall, and verbal fluency. In patients living 12 months or more, there was more frequent cognitive decline with the addition of WBRT, most notably in executive functioning ($p = 0.05$). However, there was improvement in 12 months intracranial control with addition of WBRT (84.6%) vs. SRS alone (50.5%). There was a numerical, though not statistically significant, improvement in median OS for SRS alone of 10.4 vs. 7.4 months ($p = 0.92$), though the study was not powered to detect OS differences. This larger study confirmed previous results, with a larger patient population, that in patients with 1–3 BM, SRS alone may be preferred treatment modality.

From these four trials, we are able to glean several important points regarding the preferred treatment of patients with 1– 4 BM. First, there is no negative impact on OS by eliminating WBRT. Next, there is additive benefit in terms of local control with SRS plus WBRT, though SRS alone has similarly high rates. Thirdly, when WBRT is

withheld, there is increased rate of new distant BM which leads to more frequent salvage treatment, and about a quarter of patients will ultimately require WBRT. Finally, the risk of neurocognitive decline is lower with SRS alone.

With growing data as outlined above, ASTRO consensus guidelines were updated recommending against the routine use of WBRT in addition to SRS in patients with limited BMs. SRS alone is favored in patients with limited BM burden and WBRT to be reserved for salvage options.

Neurocognitive sparing

For patients requiring WBRT, multiple approaches can be used for neurocognitive sparing.

- Use of Memantine which is an antagonist of the N-methyl-D-aspartate (NMDA) receptor.The RTOG 0614 explored memantine for reducing neurocognitive decline, there was a trend toward delayed recall (the primary endpoint) improvement but did not reach statistical significance ($p = 0.059$). As a result, the NCCN CNS and small-cell lung cancer guidelines acknowledge the potential role of memantine to promote cognitive preservation for patients undergoing both WBRT and PCI.
- Donepezil, a reversible acetylcholine esterase inhibitor. In a phase 2 study, it did not improve cognitive composite scores (the primary endpoint), but improved modestly memory decline.
- Hippocampal sparing during RT: Preliminary data from a multi-institutional single-arm phase II RTOG 0933 demonstrated superior cognitive preservation with

hippocampal avoidance WBRT (HA-WBRT) as compared to historical WBRT controls. Currently, two separate NRG Oncology trials have been launched evaluating the impact of HA-WBRT in the randomized setting. Similar trials are ongoing for prophylactic cranial irradiation indications as well.

More than 4 metastases

Whether SRS or WBRT is the optimal radiation modality for patients with five to fifteen BM remains an open question. The Canadian Cancer Trials Group (CCTG)-lead North American intergroup trial is an ongoing prospective study testing this. Various retrospective and prospective papers have already shown feasibility of SRS alone in patients with up to 10 BM. Additionally, radiosurgery for as many as 15 BM has been found to be safe, notably in a series of more than 300 patients. Yamamoto et al. prospective observational study of SRS alone for treatment of 5–10 BM showed that overall survival was similar between patients with 2–4 metastases as compared to 5–10 metastases with no difference in acute toxicities. Future study is necessary to optimize appropriate settings for SRS alone.

Radiation Necrosis (RN)

The true incidence of RN is hard to estimate and probably lies between 5 and 25%. The rates of radiographic RN post-SRS (for intact BM) can go upto 24%, while in postoperative-SRS these range from 1.5 to 18.5%. The infratentorial location and doses/volumes like V12, V14Gy volume has been associated with increased RN.

The risk factors associated with increased risk of RN include tumor volume, location, prescribed dose, fraction size, volume of normal brain irradiated (PTV margin), previous use of radiation and the use of concurrent systemic therapy. It is generally recommended to restrict doses for SRS as per volume as < 20mm with 24 Gy, 21–30mm with 18 Gy and 31–40mm with 15 Gy. The risk of RN is higher when V10 > 10.5 cm^3 or V12 > 7.9 cm^3. The risk of RN with SRS in the setting of prior SRS (to the same lesion) was reported to be 20% at 1 year, 4% when prior WBRT had been used and 8% when concurrent WBRT.

The management of RN primarily depends on the presence of symptoms. Symptomatic patients may experience headaches, nausea, cognitive impairment, seizures or focal deficits relating to the location of the lesion. About 1/3rd or less of patients may have spontaneous regression over time. For more symptomatic patients, oral corticosteroids (such as dexamethasone) is the preferred first line. Gradual tapering of the dose is suggested as long duration can lead to systemic side effects like myopathy, iatrogenic Cushing's syndrome, gastric ulcers etc.

Bevacizumab (humanized monoclonal antibody against VEGF) is used to treat steroid-refractory RN. The radiographic response rate, clinical improvement rate is reported as 97% and 79% respectively with a mean decrease in dexamethasone dose of 6 mg. However, the durability of response and toxicities associated with bevacizumab, such as hemorrhage, thrombosis and impaired wound healing must be considered. Hyperbaric oxygen therapy (HBOT) use is mostly limited to case reports

where the efficacy is not well-documented. For patients who remain symptomatic despite conservative management, or in whom there is diagnostic uncertainty, surgical resection can be considered. LITT is an image guided approach which generates high temperatures using a laser fiber, and facilitates ablation of both tumor tissue, and VEGF producing reactive glial cells.

Systemic therapy

In general, the chemotherapy is not considered an effective mode of controlling BM due to limited penetration of BBB. The typical approach for management of systemic disease with BM is treatment of CNS disease first, followed by initiation of systemic therapy. A recent randomized trial from Korea, specifically evaluated timing of SRS relative to the start of chemotherapy in patients with limited number of asymptomatic BM. Patients with NSCLC randomized to upfront SRS prior to chemotherapy initiation vs. initiation of chemotherapy without treatment of CNS disease showed equivalent median OS in two groups though there was a trend toward longer CNS PFS, lower symptomatic brain progression rate and lower CNS salvage rates in the upfront SRS group. It appears from this data, that upfront SRS may be preferable, though in cases that urgent chemotherapy is needed; delaying CNS treatment is likely safe.

In newly diagnosed cancer patients found to have BM, treatment with concurrent systemic therapy and SRS had improved survival compared to SRS alone (41.6 vs. 21.5 months, $p < 0.05$). In a larger retrospective review of 1,650 patients with 27% of patients receiving concurrent systemic

therapy, similar results were found. In patients who received SRS plus WBRT, there was a higher rate of RN, compared to SRS alone when patients received concurrent vascular endothelial growth factor receptor, tyrosine kinase inhibitors (TKIs; 14.3 vs. 6.6%, p = 0.04) or epidermal growth factor receptor TKIs (15.6 vs. 6% p = 0.04). There was no association between other systemic therapies, including hormonal therapy, cytotoxic chemotherapy or other targeted agents. Similar results were seen in secondary analysis of patients enrolled on RTOG 0320 and concurrent use of temozolomide or erlotinib with concurrent SRS or SRS plus WBRT.

A recent multi-institutional retrospective review evaluated 351 patients with EGFR-mutant NSCLC with new BM who were TKI naive. Patients were treated with SRS or WBRT followed by TKI therapy or TKI therapy alone with radiation reserved at time of progression. Outcomes showed that delaying radiation, WBRT or SRS alone, is associated with significantly worse OS in this patient population. Patients treated with SRS followed by TKI had the longest median OS at 46 months, compared to 30 months with WBRT + TKI and 25 months with TKI alone ($P < 0.001$ for each group). Further randomized data is needed to better define the optimal timing and sequencing of radiation and systemic therapy, particularly in the setting of new targeted therapies.

Medical management with targeted therapy

As of now, insufficient data exists to support the recommendation of targeted therapies in the treatment of BM. Paradoxical literature is available hypothesizing

targeted therapy playing a role in the development of BM. This may be an effect of longer survival in metastatic patients treated with targeted therapy increasing chances of developing BM. It is also postulated that this relegates the brain as a "sanctuary" site in which undetected intracranial micromets are sheltered from systemic treatment that is unable to penetrate the "sanctuary" of the BBB (Her-2 Breast Cancer, BRAF mutant melanoma). This data is much more controversial in EGFR mutant lung cancer. Recently some newer targeted agents have been demonstrated to cross BBB and may help in controlling BM. The limited data available in literature at this time is not convincing for standard recommendation in clinical practise. Low dose Bevacizumab has been tried with little success in brain metastasis.

Table-21: targeted agents in BM

Targeted therapy	Primary malignancy	Level of evidence	Best available outcome
ALK DIRECTED THERAPY Crizotinib Ceritinib Alectinib Brigatinib	Non-small cell Lung cancer	Subgroup Phase 3 Sub group P2 Pooled Ph2 Subgroup Ph2	12-week DCR 85% vs. 45% with chemo RR: 45% RR: 64% RR: 78% vs. 29% with crizotinib
EGFR DIRECTED THERAPY Erlotinib Osimertinib	Non-small cell Lung cancer	Phase 2 Phase 3 Phase 3	PFS: 10.1 months alone, 60% RR with RT RT+ Erlotinib: med OS: 6.1 m PFS at 6 months: 87% vs. 71%. (std E-TKI) PFS at 18 months: 58% vs. 40%

(Contd...)

(Contd...)

Targeted therapy	Primary malignancy	Level of evidence	Best available outcome
HER2 DIRECTED THERAPY			
Lapatinib+Capecitabine	Breast cancer	Phase 2	BM IC-RR: 66%
Neratinib+Capecitabine		Phase 2	12-month OS: 63%
BRAF-MEK			
Vemurafenib	Melanoma	Phase 2	RR: 18%
Dabrafenib		Phase 2	RR of 40% in Rx naïve & 30% in prev Rx
Dabrafenib + Trametinib		Phase 2	RR- 44-59%
VEGF Pathway			
Bevacizumab+ Carboplatin	Breast cancer	Phase 2	RR – 45%

The newer methods of drug delivery across the BBB are also being explored. One of these is a focused delivery augmented by combination of low intensity MR-guided focused ultrasound and i.v microbubbles of drugs. The safety, feasibility and preliminary efficacy have been demonstrated in animal models but clinical utility is still far experimental.

Immunotherapy

Brain has long been viewed as an immune-privileged environment. Emerging clinical data also suggest existence of stimulation of peripheral T cells leading to anti-tumor effects in the brain across BBB by using immune checkpoint inhibitors. The anti-programmed cell death-1 (PD-1) monotherapy with pembrolizumab has shown intracranial response rates of 20–30% in patients with melanoma or non-small cell lung cancer (NSCLC) BM. The combination

of nivolumab and ipilimumab [anti-PD-1 and anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)] showed an intracranial response rate of 55% in patients with melanoma BM. Similarly, prolonged control rates are reported in lung, melanoma, RCC BM when patients on immunotherapy and received various types of radiotherapy for BM. At present, more data are needed to confirm these results, determine mechanisms of efficacy and resistance and for concrete recommendations. The role of combining immunotherapy with radiotherapy as direct local therapy as well as immune modulator, abscopal effect present an exciting venue for future research.

Follow-up

Table-22: Follow up schedule BM post treatment (adapted from NICE guidelines 2018)

	Years after end of treatment		
	0-1	1-2	>2
Frequency	Every 3 months	4-6 monthly	Annually
Routine	Standard structural MRI (T2 weighted, FLAIR, DWI series and T1 pre- and post-contrast) clinical review		
Special investigations When Findings from standard imaging are unclear	Advanced MRI techniques (perfusion, DTI, spectroscopy) FET-PET-CT		

SUGGESTED READING

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E) MENINGIOMAS

Meningiomas are the most common primary intracranial tumors, of which most are classified as WHO grade I lesions, with a minority classified as WHO grade II or grade III lesions on the basis of local invasiveness and cellular features of atypia.

- The most common primary brain tumours, amounting to 37% of all brain tumours, with the annual incidence rates ranging from 1.3/100,000 to 7.8/100,000 across various population-based registries.
- The median age at diagnosis is 66 years.
- They are more common in women with a female-to-male ratio of approximately two or three to one.
- These tumours are believed to arise from the arachnoid cap cells.

Presentation

- Most often, meningiomas are asymptomatic tumours, owing to their slow growing nature, and are detected incidentally on imaging, or at autopsy.
- Common presenting features are seizures, seen in approximately 30% patients; and focal neurological deficits. Large tumours in the posterior fossa may cause obstructive hydrocephalus.

Imaging

- Meningiomas have a characteristic appearance on CT as well as MRI.
- On CT, a meningioma appears as a well -defined extra-axial mass, that is smooth in contour, and displaces the normal brain, and homogeneous, bright post contrast enhancement. Calcification, hyperostosis of the adjacent bone and intraosseous tumour growth are better appreciated on CT.
- On MRI, meningiomas appear iso- to hypointense on T1, and typically iso- to hypointense on T2.
- Most meningiomas are characterized by the dural tail sign, seen on contrast enhanced T1 images, seen as a marginal thickening of the dura adjacent to the tumour that tapers peripherally.
- MRI has limited sensitivity and specificity for detecting osseous and parenchymal invasion, as well as differentiating recurrent disease from post treatment changes. [68Ga]- DOTATATE PET targeting somatostatin receptor 2A is a useful imaging modality in these settings.

Table -23: The WHO Classification of Tumours of the CNS classifies meningiomas into three grades.

	Grade 1(80%)	**Grade 2 (atypical) (10-18%)**	**Grade 3 (anaplastic) (2-4%)**
Mitotic activity	Low mitotic rate, less than 4 per ten high-power fields (HPFs)	Mitotic rate 4- 19 per HPF	Mitotic rate more than 20 per HPF
Brain invasion	Absence of brain invasion	Brain invasion	Brain invasion
Histological features	No sinister features	spontaneous necrosis, sheeting, prominent nucleoli, high cellularity, and small cells	Frank anaplasia (focal or diffuse loss of meningo thelial differentiation, resembling sarcoma, carcinoma or melanoma
Histological subtypes	Meningothelial Fibrous Transitional (mixed) Psammomatous Angiomatous Microcystic Secretory Lympho-plasmacyte rich	Clear cell	Papillary Rhabdoid
5 yr. estimate of local recurrence	5-10%	30-40%	50-60%

Molecular markers

- Mutations in the telomerase reverse transcriptase (TERT) gene promoter are associated with increased risk of recurrence and progression. DNA methylation analysis now segregates meningiomas into six methylation classes (MC) – MC benign 1,2,3, MC

intermediate A; which together comprise Group A, while Group B is comprised of MC intermediate B and malignant MC. Methylation classes have shown to be a better predictor of clinical outcomes than the WHO grading. However, their use has not been validated in clinical practice

PRINCIPLES OF MANAGEMENT

Observation

Many asymptomatic, incidentally discovered meningiomas can be managed by observation using annual clinical and MRI tests

Surgery

The treatment of choice for symptomatic or progressive benign meningiomasis complete surgical resection. The vast majority of patients can be cured by surgery alone, particularly patients with WHO grade I tumours in favourable location (eg, convexity meningiomas, and easily accessible skull-base meningiomas). Beyond surgery, various radiotherapy approaches are often used to increase local control, especially if surgery alone seems insufficient. Micro-neurosurgical resection of the meningiomas remains the main stay of the surgical treatment.

Table-24 : The extent of surgical resection of meningiomas is given by the Simpson's grading.

Grading	Extent	Symptomatic recurrence at 10 yrs
I	Complete macroscopic removal of the tumour along with its dural attachment, and any abnormal bone.	9%
II	Complete macroscopic removal of the tumour, with coagulation of its dural attachment.	19%
III	Complete macroscopic removal of the intradural tumour, without addressing its dural attachment or extradural extensions.	29%
IV	Sub –total removal	44%
V	Simple decompression/biopsy	

The inclusion of an additional 2-cmdural margin has been denoted grade 0 removal. Extent of resection is an important prognostic factor for the risk of tumour recurrence. It is particularly influenced by its location. Resection of tumours in the skull base location (sphenoid wing and Suprasellar) is limited by its proximity to neurovascular structures. Also, tumours in the parasagittal location with involvement of dural sinus have high rate of recurrence.

Radiotherapy

- Fractionated adjuvant radiotherapy to a dose of 50-54 Gy (for Grade I meningiomas in the setting of

residual disease) with escalation upto 59.4-60Gy for Gd II-III meningiomas forms the standard line of management

- Hypofractionated RT may be used in very small lesions in regions remote from critical structures (optic apparatus and brain stem) may be judiciously used
- CTV margins typically encompass 1-2 cm around the areas of gross disease or tumor bed with editing from critical structures. It is important not to exclude bone, dura or sinus tissue from the CTV. Additionally, 3-5mm PTV margins should be used depending on institutional data and precision of image guidance.
- SRS has proven to be highly effective for patients with small benign (WHO grade I) meningiomas where there is a surgical risk of mortality. The SRS dose is around 15Gy single fraction.

Follow-Up

- The recommended follow up is an MRI Brain at 3, 6- and 12-months post treatment.
- Thereafter, an MRI Brain is recommended every 6 to 12 months for 5 years, then every 1-3 years or as clinically indicated.

Management of Recurrence

- Re-surgery and radiotherapy form the mainstay of management of recurrent meningiomas. Achieving a satisfactory excision is of paramount importance in achieving durable control

- Systemic therapies have been investigated in the recurrent setting. Antiangiogenic drugs, peptide receptor radionuclide therapy, and targeted agents are promising candidates for future pharmacological approaches to treat refractory meningiomas across all WHO grades
    - Hormonal Therapy - Estrogen receptors are expressed in 10% of meningiomas, while progesterone and hormone receptors are expressed in two-thirds of meningiomas. However, neither hormonal agents, nor chemotherapy has shown encouraging results in the clinical setting.
    - Somatostatin analogues - Somatostatin receptors are expressed in 90% meningiomas, but the use of somatostatin analogues in the recurrent setting has shown mixed results.
    - PRRT - This abundance of somatostatin receptor expression has been employed to treat patients with PRRT (peptide receptor radionuclide therapy) using Yttrium-90 or Lutetium-177 labelled peptides.

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F) CRANIOPHARYNGIOMAS

Craniopharyngioma is a benign tumor typically treated with both surgery and radiation, an approach that offers 5-year progression-free survival (PFS) rates exceeding 90%

Craniopharyngioma is a histologically benign, extra-axial, slow-growing tumor that predominately involves the sella and suprasellar space. Three distinct subtypes primarily based on histologic appearance have been described: adamantinomatous, papillary, and mixed. The commonest type is the adamantinomatous tumor which is partly solid, partly cystic with characteristic machine oil fluid. Craniopharyngioma represents approximately 3-5% of intracranial tumors and 6-10% of pediatric brain tumors. A bimodal age distribution is seen, with the first peak occurring in childhood and early adolescence, predominately at age 5-10 years. The second peak (for papillary types) occurs at age 40-60 years. The most common presenting symptoms are headache, nausea, vomiting, and visual disturbances. The most common visual disturbances are bitemporal hemianopsia, homonymous hemianopsia, and amblyopia.

Craniopharyngiomas have been surgically divided into 3 groups: sellar, prechiasmatic, and retrochiasmatic. Three specific growth categories have also been described based on the relationship of the tumor to the vascular structures and the optic chiasm: type A, type B, and type C. In type A, the anterior communicating artery and the A1 segment of the anterior cerebral artery are not disturbed. In type B, the anterior communicating artery and the A1 segment of the anterior cerebral artery are elevated, but no posterior displacement of the basilar artery is observed. The tumor protrudes anteriorly between the optic nerves and pushes the optic chiasm posteriorly. In type C, the anterior communicating artery and the A1 segment of the anterior cerebral artery are elevated, with posterior displacement of the basilar artery and stretching of the posterior communicating arteries. The tumor protrudes posteriorly, pushing the chiasm forward and causing it to abut the tuberculum sellae.

The primary treatment of choice is complete surgical excision. Local recurrence is common after surgical excision alone, with reported recurrence rates of 25-40% without adjuvant radiation. The size of the tumor at presentation also impacts upon local recurrence (70% for tumors >5 cm and 20% for tumors <5 cm). Cystic degeneration and enlargement is a common finding on follow up scans and needs intervention in almost 20% of patients. In recent times conservative surgery (maximal safe resection) followed by adjuvant radiation therapy is preferred to aggressive radical excision to improve outcome. A 5-year survival rate of 70-80% is achieved with contemporary

microsurgery and adjuvant radiation therapy. The 10-year overall survivalis60-75%.

Proton therapy compared with photon therapy, offers a better opportunity to preserve IQ scores in patients with craniopharyngioma without compromising efficacy.

Craniopharyngioma is a curable tumor treated primarily by conservative resection and radiotherapy. Reducing the late toxicities of radiotherapy remains of pivotal importance in treating craniopharyngioma. Recent technological advances in radiotherapy offer the promise of reducing side effects while maintaining high cure rates.

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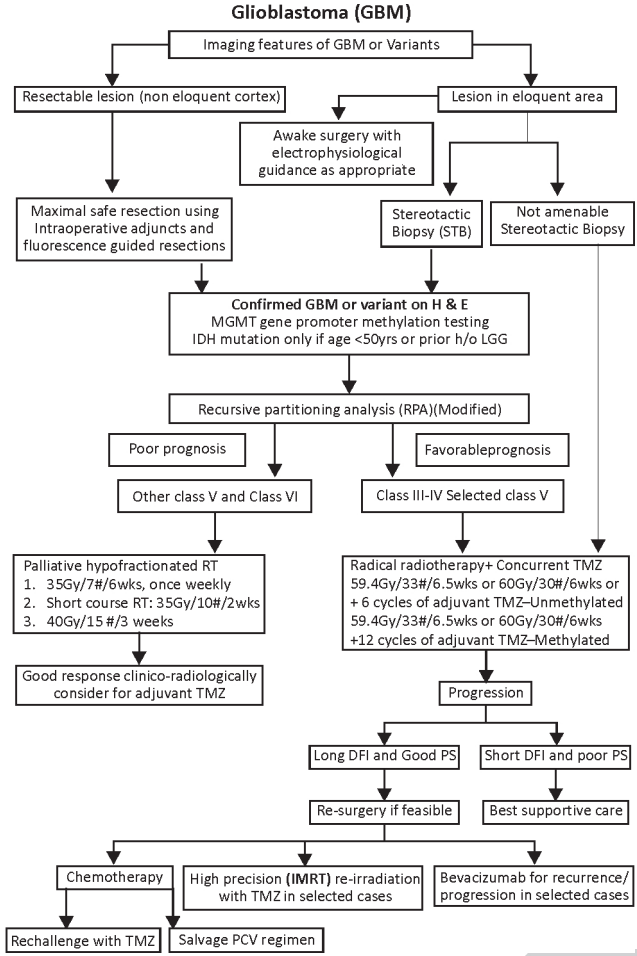
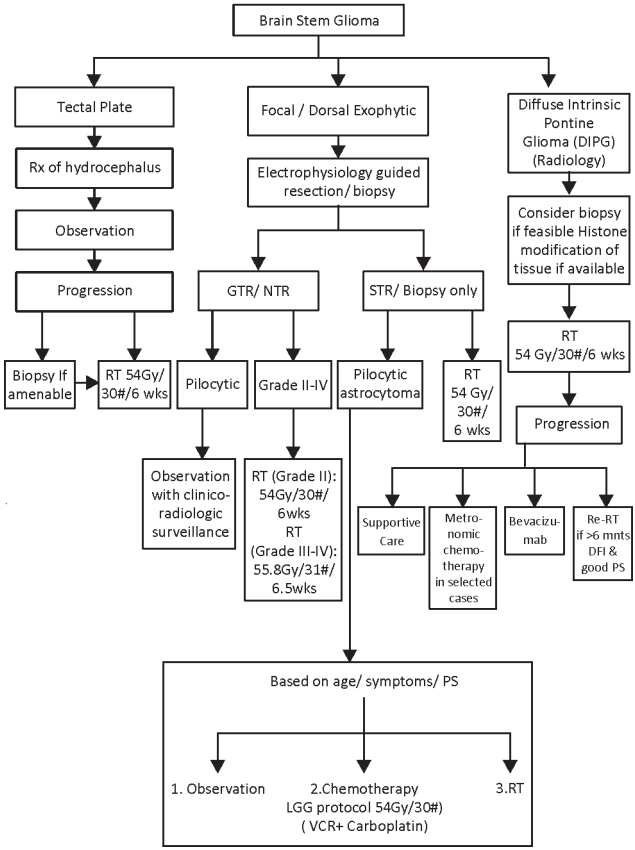
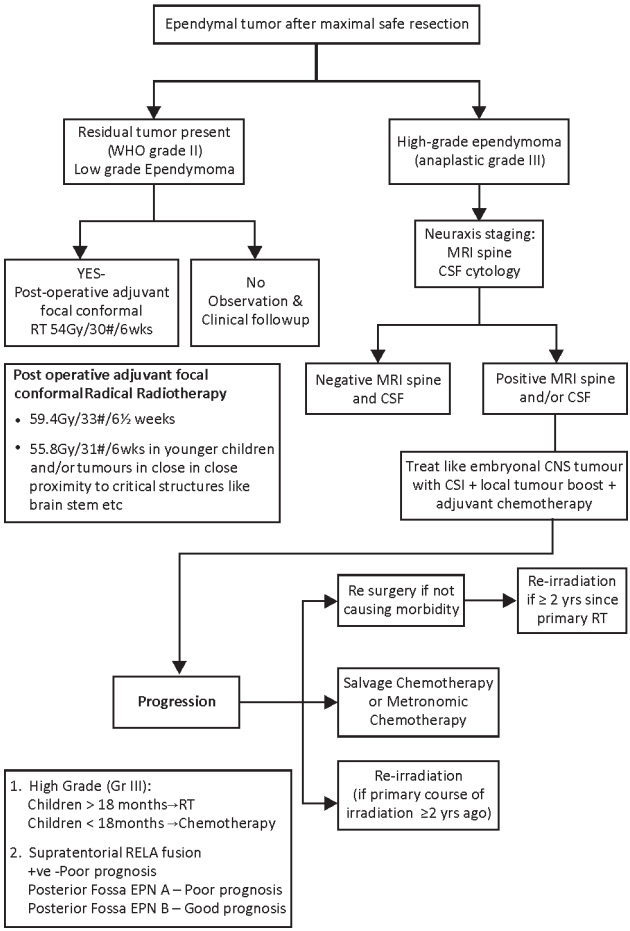
- Hermann L. Müller. Craniopharyngioma *Endocrine Reviews*, Volume 35, Issue 3, 1 June 2014, Pages 513–543.


Glioblastoma (GBM)
Imaging features of GBM or Variants
Resectable lesion (non eloquent cortex)
Lesion in eloquent area
Awake surgery with electrophysiological guidance as appropriate
Maximal safe resection using Intraoperative adjuncts and fluorescence guided resections
Stereotactic Biopsy (STB)
Not amenable Stereotactic Biopsy
Confirmed GBM or variant on H & E
MGMT gene promoter methylation testing
IDH mutation only if age <50yrs or prior h/o LGG
Recursive partitioning analysis (RPA)(Modified)
Poor prognosis
Favorableprognosis
Other class V and Class VI
Class III-IV Selected class V
Palliative hypofractionated RT
1. 35Gy/7#/6wks, once weekly
2. Short course RT: 35Gy/10#/2wks
3. 40Gy/15 #/3 weeks
Radical radiotherapy+ Concurrent TMZ
59.4Gy/33#/6.5wks or 60Gy/30#/6wks or
+ 6 cycles of adjuvant TMZ–Unmethylated
59.4Gy/33#/6.5wks or 60Gy/30#/6wks
+12 cycles of adjuvant TMZ–Methylated
Good response clinico-radiologically consider for adjuvant TMZ
Progression
Long DFI and Good PS
Short DFI and poor PS
Re-surgery if feasible
Best supportive care
Chemotherapy
High precision (IMRT) re-irradiation with TMZ in selected cases
Bevacizumab for recurrence/ progression in selected cases
Rechallenge with TMZ
Salvage PCV regimen

(DIPG / focal exophytic / Tectal plate gliomas)

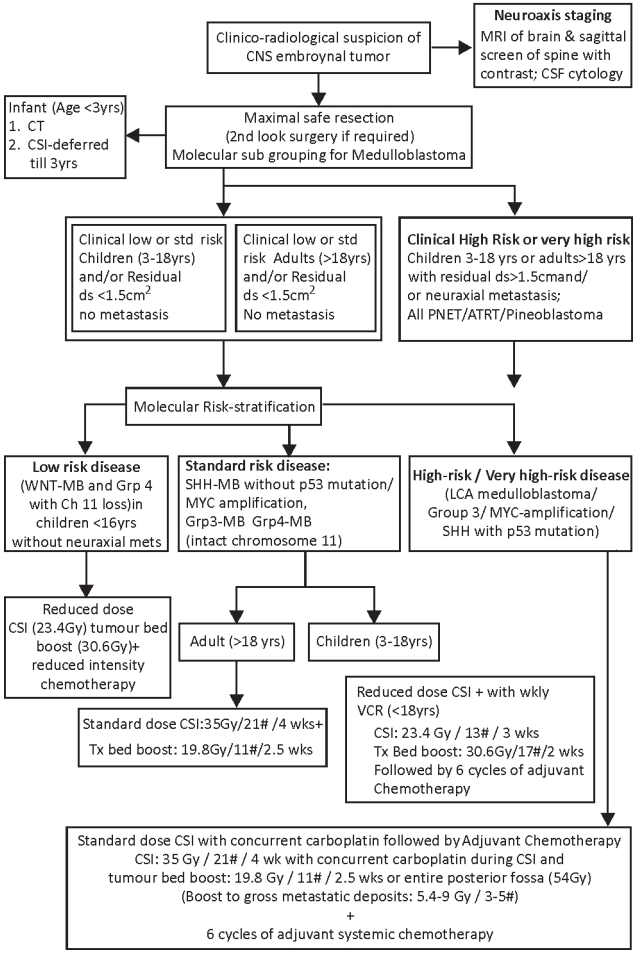


Ependymoma

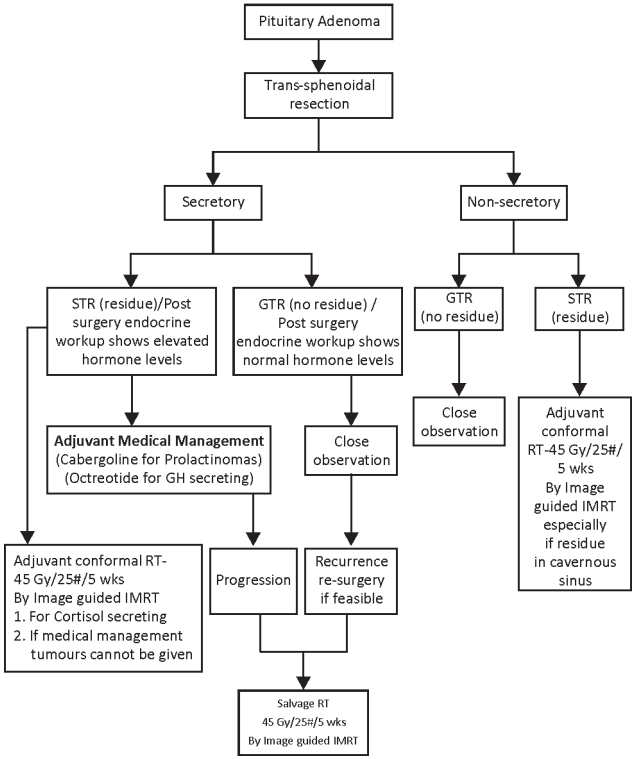

Ependymal tumor after maximal safe resection
Residual tumor present (WHO grade II) Low grade Ependymoma
High-grade ependymoma (anaplastic grade III)
YES- Post-operative adjuvant focal conformal RT 54Gy/30#/6wks
No Observation & Clinical followup
Neuraxis staging: MRI spine CSF cytology
Post operative adjuvant focal conformal Radical Radiotherapy
• 59.4Gy/33#/6½ weeks
• 55.8Gy/31#/6wks in younger children and/or tumours in close in close proximity to critical structures like brain stem etc
Negative MRI spine and CSF
Positive MRI spine and/or CSF
Treat like embryonal CNS tumour with CSI + local tumour boost + adjuvant chemotherapy
Re surgery if not causing morbidity
Re-irradiation if ≥ 2 yrs since primary RT
Progression
Salvage Chemotherapy or Metronomic Chemotherapy
Re-irradiation (if primary course of irradiation ≥2 yrs ago)
1. High Grade (Gr III): Children > 18 months→RT Children < 18months →Chemotherapy
2. Supratentorial RELA fusion +ve -Poor prognosis Posterior Fossa EPN A – Poor prognosis Posterior Fossa EPN B – Good prognosis

CNS Embryonal tumours

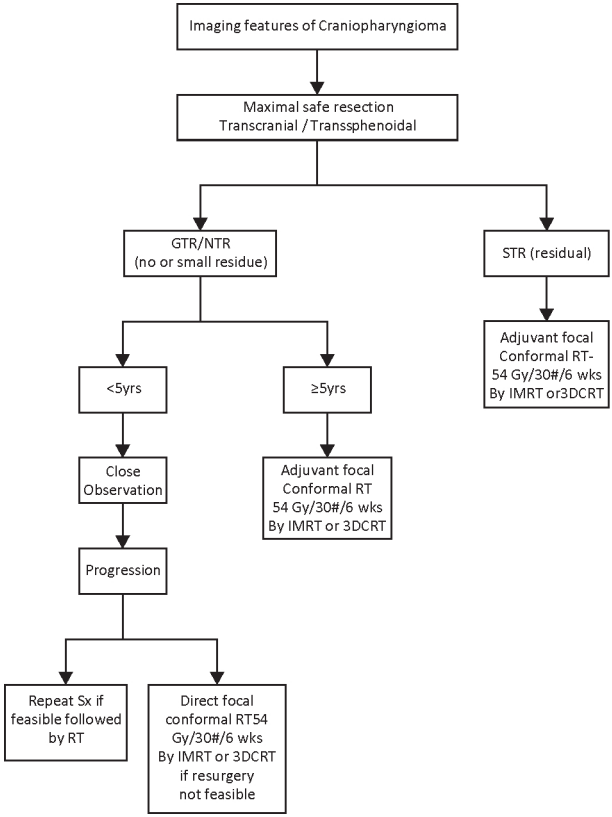
(Medulloblastoma / PNET / ATRT / Pineoblastoma)



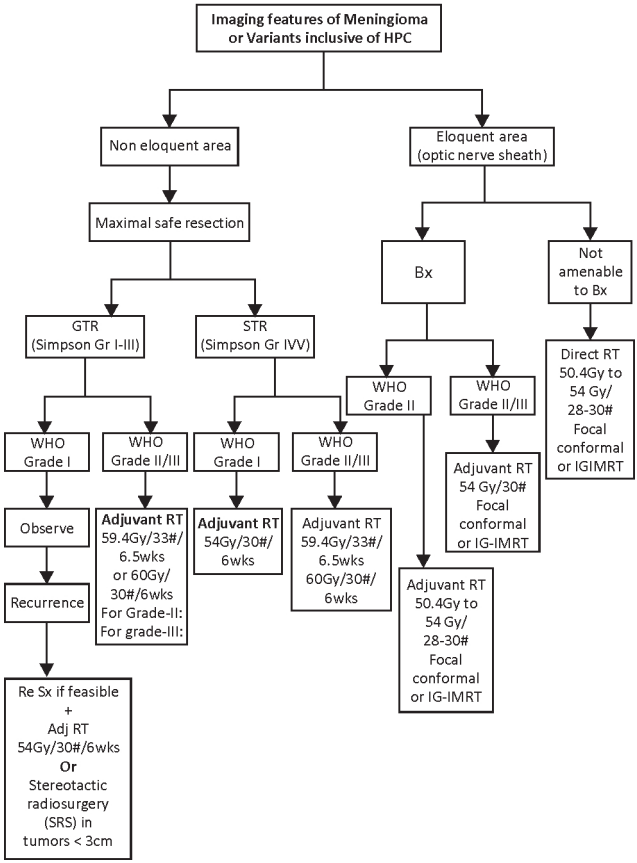
Pituitary Adenoma



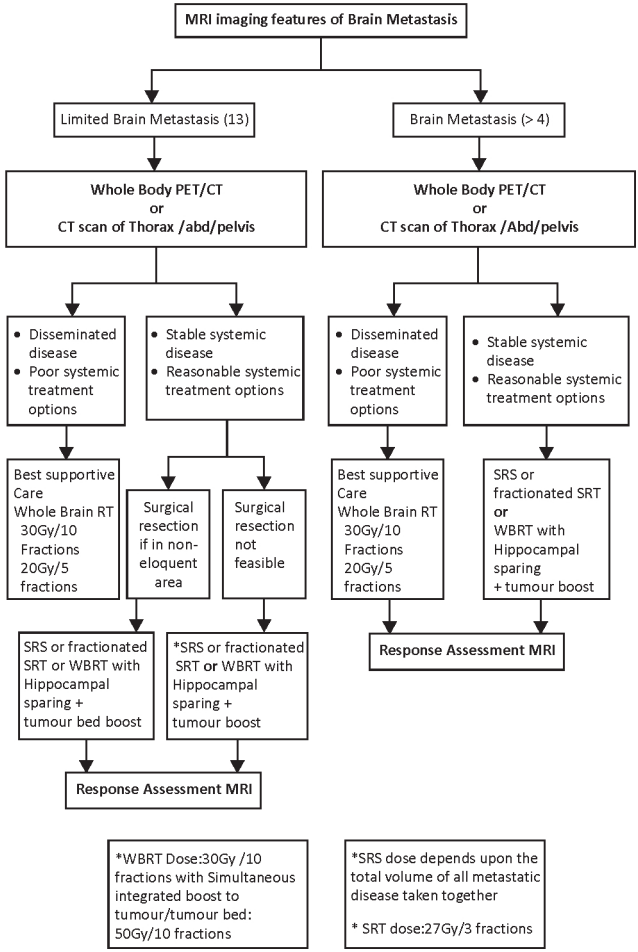
Craniopharyngioma



Imaging features of Meningioma or Variants including Hemangiopericytoma (HPC)



Management of brain metastasis from solid primaries



Appendices

APPENDIX-I

The 2016 World Health Organization Classification of Tumors 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	9362/3
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	
Medulloblastoma, SHH-activated and TP53-mutant	9475/3’ 9476/3’
Medulloblastoma, SHH-activated and TP53-wildtype	9471/3
Medulloblastoma, non-WNT/non-SHH Medulloblastoma, group 3 Medulloblastoma, group 4	9477/3’
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
Melanotic schwannoma	9560/1
Neurofibroma	9540/0
Atypical neurofibroma	9540/0
Plexiform neurofibroma	9550/0
Perineurioma	9571/0
Hybrid nerve sheath tumours	
Malignant peripheral nerve sheath tumour	9540/3
Epithelioid MPNST	9540/3
MPNST with perineurial differentiation	9540/3
Meningiomas	
Meningioma	9530/0
Meningothelial meningioma	9531/0
Fibrous meningioma	9532/0
Transitional meningioma	9537/0
Psammomatous meningioma	9533/0

Angiomatous meningioma	9534/0
Microcystic meningioma	9530/0
Secretory meningioma	9530/0
Lymphoplasmacyte-rich meningioma	9530/0
Metaplastic meningioma	9530/0
Chordoid meningioma	9538/1
Clear cell meningioma	9538/1
Atypical meningioma	9539/1
Papillary meningioma	9538/3
Rhabdoid meningioma	9538/3
Anaplastic (malignant) meningioma	9530/3

Mesenchymal, non-meningothelial tumours

Solitary fibrous tumour / haemangiopericytoma"	
Grade 1	8815/0
Grade 2	8815/1
Grade 3	8815/3
Haemangioblastoma	9161/1
Haemangioma	9120/0
Epithelioid haemangioendothelioma	9133/3
Angiosarcoma	9120/3
Kaposi sarcoma	9140/3
Ewing sarcoma / PNET	9364/3
Lipoma 8850/0	
Angiolipoma	8861/0
Hibernoma	8880/0
Liposarcoma	8850/3
Desmoid-type fibromatosis	8821/1
Myofibroblastoma	8825/0
Inflammatory myofibroblastic tumour	8825/1
Benign fibrous histiocytoma	8830/0
Fibrosarcoma	8810/3
Undifferentiated pleomorphic sarcoma / malignant fibrous histiocytoma	8802/3

Leiomyoma	8890/0
Leiomyosarcoma	8890/3
Rhabdomyoma	8900/0
Rhabdomyosarcoma	8900/3
Chondroma	9220/0
Chondrosarcoma	9220/3
Osteoma	9180/0
Osteochondroma	9210/0
Osteosarcoma	9180/3
Melanocytic tumours	
Meningeal melanocytosis	8728/0
Meningeal melanocytoma	8728/1
Meningeal melanoma	8720/3
Meningeal melanomatosis	8728/3
Lymphomas	
Diffuse large B-cell lymphoma of the CNS	9680/3
Immunodeficiency-associated CNS lymphomas	
AIDS-related diffuse large B-cell lymphoma	
EBV-positive diffuse large B-cell lymphoma, NOS	
Lymphomatoid granulomatosis	9766/1
Intravascular large B-cell lymphoma	9712/3
Low-grade B-cell lymphomas of the CNS	
T-cell and NK/T-cell lymphomas of the CNS	
Anaplastic large cell lymphoma, ALK-positive	9714/3
Anaplastic large cell lymphoma, ALK-negative	9702/3
MALT lymphoma of the dura	9699/3
Histiocytic tumours	
Langerhans cell histiocytosis	9751/3
Erdheim-Chester disease	9750/1
Rosai-Dorfman disease	
Juvenile xanthogranuloma Histiocytic sarcoma	9755/3

Germ cell tumours

Germinoma	9064/3
Embryonal carcinoma	9070/3
Yolk sac tumour	9071/3
Choriocarcinoma	9100/3
Teratoma 9080/1	
Mature teratoma	9080/0
Immature teratoma	9080/3
Teratoma with malignant transformation	9084/3
Mixed germ cell tumour	9085/3

Tumours of the sellar region

Craniopharyngioma	9350/1
Adamantinomatous craniopharyngioma	9351/1
Papillary craniopharyngioma	9352/1
Granular cell tumour of the sellar region	9582/0
Pituicytoma	9432/1
Spindle cell oncocytoma	8290/0

Metastatic tumours

The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) i742A|. Behaviour is coded 10 for benign tumours:

/1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma insitu and grade III intraepithelial neoplasia; and /3 for malignant tumours.

The classification is modified from the previous WHO classification, taking into account changes in our understanding of these lesions.

*These new codes were approved by the IARC/WHO Committee for ICD-O. Italics. Provisional tumour entities. **Grading according to the 2013

WHO Classification of Tumours of Sott Tissue and Bone.

APPENDIX II

Approaches and Evidence in Average Risk MB (Selected Trials):

Study	Sample	Study arms	Dose	Results
Evans et al. 1990 (CCSG-942)[2]	179 patients	Phase III Randomized trial Regimen I: Radiotherapy + concurrent VCR + Adjuvant Chemotherapy (VCR, CCNU, Prednisolone) 8 cycles, 6 weekly for a total of 1 year Regimen II: Radiotherapy and concurrent VCR	RT: CNS axis – 35-40 Gy; PF boost – 50-55 Gy Concurrent VCR: 1.5 mg/m2 Adjuvant Chemotherapy: VCR 1.5 mg/m2 on D1, D8, D15 CCNU 100mg/m2 PO on D1 Prednisolone 40mg/m2 PO * 14 days	Overall:5-year EFS/OS:55%/65% Regimen I: 59%/65% Regimen II: 50%/65%
Taylor et al. 2003 (SIOP PNET-3)[3]	179 patients Chang M0-M1 90: Arm A 89: Arm B 3-16 years	Arm A: Pre-radiation chemotherapy followed by standard dose RT Arm B: Radiotherapy alone	Pre-RT chemotherapy: Four 3-weekly cycles VCR 1.5mg/m2 D1, D7, D14; Etoposide 100mg /m2 D1-D3; Carboplatin 500mg/m2 D1-D2 ALTERNATING WITH VCR 1.5mg/m2 D1, D7, D14; Etoposide 100mg/m2 D1-D3; Cyclophosphamide 1.5gm/m2 D1 only CSI: 35 Gy; PF boost: 50-55 Gy total	3 yr EFS/OS: Overall: 71.6%/79.5% Arm A: 3 yr EFS 78.5% Arm B: 3 yr EFS 64.8% No difference in overall survival

(Contd...)

(Contd...)

Study	Sample	Study arms	Dose	Results
Packer et al 2000[6]	65 patients 3 – 10 years of age M0 patients	Prospective non-randomized study to analyze role of reduced dose 23.4 Gy CSI followed by 8 cycles of maintenance chemotherapy	RT: 23.4 Gy with concurrent weekly VCR at 1.5mg/m2 Maintenance CT (6-weekly cycles): VCR 1.5mg/m2 D1, D8, D15 CCNU 75mg/m2 PO D1 Cisplatin 75mg/m2 IV D1	3 yr PFS: 86 ± 4% 5 yr PFS: 79 ± 7%
Packer et al. 2006[8] **A9961**	379 patients 3 – 21 years M0 patients AND GTR	Radiotherapy with concurrent weekly VCR followed by either of the chemotherapy regimens: Arm A: CCNU, VCR, Cisplatin OR Arm B: VCR, Cisplatin, Endoxan Total of eight 6-weekly cycles	Standard dose CSRT (23.4GY) with 55.8 Gy PF RT followed by either chemotherapy regimens Arm A: CCNU 75mg/m2 PO D0; CDDP 75mg/m2 on D1; VCR 1.5 mg/m2 D1, D7, D14 OR Arm B: CDDP 75mg/m2 IV D0; VCR 1.5 mg/m2 D1, D7, D14; Endoxan 1 gm/m2 IV on D21-D22	5 yr EFS/OS: 81%/86% Cyclo-phosphamide arm had more infections Lomustine arm had more electrolyte abnormalities

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Study	Sample	Study arms	Dose	Results
Gajjar et al. 2006[9]	86 patients 3 – 21 years M0 patients and GTR	All AR-MB (M0 and GTR) received RT followed by dose-intense chemotherapy followed by stem cell rescue (Total of four 4-weekly cycles)	Day (-4): CDDP 75mg/m2; VCR 1.5mg/m2 Day (-3 & -2): Cyclophosphamide 2gm/m2 Day (-1): Hydration Day 0: Stem cell infusion (2*106 cells/kg) Day (+1): Inj. G-CSF 5 mcg/kg Day (+6): Inj. VCR 1.5 mg/m2	5 yr EFS/OS: 83%/85%

APPENDIX III

Approaches and Evidence in High-risk Medulloblastoma (Selected Studies):

Study	Sample	Study arms	Dose	Results
Bailey et al. 1995 **SIOP-II**	133 patients	Prospective randomized trial of chemotherapy followed by radiation alone V/s Radiotherapy alone Arm A: CT followed by RT (Sandwich) Arm B: RT alone	PCV: 100mg/m^2 D1-D14 PO VCR: 1.5 mg/m^2 IV D 1,8,15,22,29,36 MTX: 2gm/m^2 as a 6 hour infusion with leucovorin rescue Prednisolone: 100mg/m^2 2 hours before MTX infusion RT dose: 35 Gy to the neuraxis and 20 Gy to the posterior fossa.	5 yr EFS Arm A: 56.3 % Arm B: 52.8 % In Chang M2/3: 5 yr EFS: 40%
Taylor et al. 2005. SIOP-PNET 3	68 patients; 2 – 16 years Chang M2–M3 MB	Non-randomized single arm study of 4 cycles of pre-radiation CT followed by RTComparison done with other cohorts of HR-MB	CT Doses same as in Ref (9) Craniospinal RT: 35 Gy; PF RT: 20 Gy	3 yr EFS/OS: 40%/50% 5 yr EFS/OS: 34%/44%
Kortmann et al. 2000. HIT-91	26 patients in total*	Arm I: 1 or 2 cycles of sandwich chemotherapy followed by radiation therapy (22 weeks of planned delay) Arm II: Radiation therapy followed by maintenance chemotherapy	Arm I: 1 or 2 cycles of 8 weeks each (with 4 weeks in between): Ifosfamide 3gm/m2 D1-3; Etoposide 150mg/m^2 D4-6; High Dose MTX 5gm/m^2 on D28, D35; CDDP 40mg/m^2 D42-44; Ara-C 400mg/m2 D42-44 Arm II: Packer protocol (14) CSRT: 35.2 Gy; PF boost: 20 Gy	Overall 3 yr OS in M2/M3 patients was 30%.

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Study	Sample	Study arms	Dose	Results
Stewart et al. 2004[10]	44 patients (36 analyzable)	Prospective Phase II window study	Topotecan 5.5mg/m2/d as a 4-hr SD: 47%	CR: 11% PR: 16% infusion * 5 days
Gajjar et al. 2006. SJMB 96	48 HR-MB	6 weeks of Topotecan monotherapy followed by RT followed by dose-intense chemotherapy followed by stem cell rescue each time (Total of four 4-weekly cycles)	Topotecan dose same as Ref (17) Remaining chemotherapy doses same as ref (15) CSRT: 39.6 Gy PFRT: 55.8 Gy	5 yr EFS/OS: 70%/70%. Topotecan therapy did not impact the EFS.
Jakacki et al. 2012	161 HR-MB	Phase I/II dose escalation study of carboplatin followed by maintenance chemotherapy with or without CDDP	Recommended Phase 2 dose: 35mg/m2/dose for 30 days Regimen A: Endoxan 1gm/m2 D0, D1; VCR 1.5mg/m2 D0, D7 Regimen B: Regimen A + CDDP 75mg/m2 CSRT: 36 Gy; PFRT: 19.8 Gy	5 yr PFS/OS: Regimen A: 71%/82% Regimen B: 59%/68%

APPENDIX IV

Approaches and evidence in infant medulloblastoma

Study	Sample	Study arms	Dose	Results
Duffner et al. 1993. Baby POG-1	62 children	Prospective single arm study with surgical resection followed by chemotherapy (AABAAB) 2-4 weeks after surgery	Cycle A: VCR 0.065 mg/kg on D1, D8; Endoxan 65 mg/kg on D1; Cycle B: CDDP 4 mg/kg on D1, VP-16 6.5 mg/kg on D3,D4 Planned duration: 2 years for children < 2 yrs.; 1 year for children 2-3 years	2 yr EFS/OS: 34%/46% Complete resection in 38% 13/62 (M0R0): 5 yr OS: 69% 5 yr OS (GTR vs STR): 60% vs 32%
Rutkowski et al. HIT-87. 2009	29 children < 3 years	Prospective risk-stratified post-operative chemotherapy followed by radiation at 72 months of age or at salvage. Arm 1: Low risk: maintenance chemotherapy until 3 years or progression Arm 2/Arm 3: 2 cycles of induction chemotherapy followed by maintenance chemotherapy	Induction (10 weeks): PCV: 100mg/m2/day D1-10 Ifosphamide: 3gm/m2/day D15-19 Etoposide: 150mg/m2 on D15-17 Methotrexate: 5gm/m2 on D29, D43 Cisplatin: 40mg/m2 on D57-59 Ara-C: 400mg/m2 D57-59 Maintenance (8 weeks): PCV: 100mg/m2/day D1-8 Methotrexate: 5 gm/m2/day D15, 29,43 VCR: 1.5mg/m2 D1, 8,15,29,43	10 yr EFS/OS in Arm 1: 52.9%/58.8% In Arm 3, no long-term survivors (10 yr OS: 0%) Desmoplastic histology (n=9) superior to classic MB (n=20): 88.9% vs 30%

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Study	Sample	Study arms	Dose	Results
Rutkowski et al. HIT-92. 2009	43 children < 3 years	Prospective risk-stratified post-operative chemotherapy. Three 2-month (8 weeks) cycles. Total of 36 IVt Mtx doses.	HIT SKK: 8-week cycles of 4 blocks: Block 1: IVt MTX 2mg/day D1-4; Endoxan 800mg/m2 D1-3; VCR 1.5mg/m2 D1 Block 2: Starts from 3rd week. IVt MTX 2mg/day D1-2; HD MTX 5gm/m2 over 24 hrs D1; VCR 1.5 mg/m2 D1 Block 3: Starts from 5th week. Same as Block 2 Block 4: Starts from week 7. IVt MTX 2mg/day D1-4. Carboplatin 200mg/m2 D1-3; Etoposide 150mg/m2 D1-3	5-year PFS/OS: Overall: 58%/66% R0: 82.9%/93.6% M0: 68%/77% R+: 50.3%/56% M+: 33%/38%
Dhall G et al. Head Start I & II. 2008	21 patients HS I followed by HD	Prospective risk-stratified post-operative chemotherapy. RT reserved for relapses	HS I: 5 cycles of 21 days each with CDDP 3.5 mg/kg on D1; VCR 0.05 mg/kg on D1, D8, D15; VP-16 4 mg/kg on D2-D3; Endoxan 65mg/kg on D2-D3 HS II: HS I + HD Mtx 400mg/kg/cycle HD Chemotherapy: Thiotepa 300mg/m2/day, Etoposide 250mg/m2/day, Carboplatin (AUC of 7/day) for 3 days.	5yr EFS/OS: 52%/70% 5 yr RT free survival: 52% GTR vs <GTR: 64% vs 29%

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Study	Sample	Study arms	Dose	Results
Dhall G et al. Head Start III **(abstract only)**	92 children < 10 years	Prospective trial of multi-agent chemo therapy with HD metho-trexate, HD chemo-therapy and stem cell rescue	5 induction cycles (vincristine,cisplatin, endoxan, VP-16, HD Mtx-cycles 1, 3, 5), and vincristine, Endoxan, oral VP-16 and TMZ (cycles 2, 4), followed by 1 consolidation cycle of myeloablative chemotherapy (Thiotepa, carboplatin, VP-16) and AuHCR. Children 6 -10 years old or with residual tumor pre-consolidation, were to receive irradiation after consolidation.	3 yr EFS/OS Overall: 47%/65% M0: 63%/80% M1: 33%/54% 3 yr EFS as per histology DN vs Classic vs LCA: 89% vs 26% vs 36%
Gajjar et al. 2018. SJYC07.	81 patients	Prospective phase II trial of post-operative chemo-therapy with risk-based deference, delay or reduced RT Initial therapy consisted of 4 28-day cycles of high dose methotrexate, vincristine, CDDP, cyclopho-sphamide	LR: Carboplatin AUC < 5mg/mL on D2, Endoxan 1.5gm/m2 on D1, VP-16 100mg/m2 D1-2 IR: Same as P9934 HR: Topotecan AUC 120-160 ng-h/mL D1-5; Endoxan 600mg/m2 D1-5 followed by CSRT. Later, LR: Carboplatin + Endoxan + VP-16 IR: Same as P9934 + focal RT HR: Topotecan + Endoxan + CRT All risk groups received 6 cycles of oral maintenance chemotherapy (Endoxan+VP-16+ Erlotinib).	5 yr EFS of entire cohort: 31.3% LR/IR/HR: 55.3%/ 24.6%/16.7% SHH/Group 4/ Group 3: 51.1%/ 13.3%/8.3%.