Survival Analysis of CNS patients in Bangladesh – focusing the multidisciplinary approaches among 149 patients in a single center retrospective analysis from 2018- 2023.

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Contents

Introduction, Incidents & Etiology

- Brain and other CNS tumours are the 2nd most common cancer in adolescents and young adults, and represent the 8th most common cancer in older adults.
- Average annual age-adjusted incidence rates for all glial tumours is 5·95 per 100 000 people in the USA.
- Most primary brain tumours are sporadic and without a known cause. Cancer-causing mutations in glioma primarily originate as a consequence of endogenous, rather than exogenous, factors.

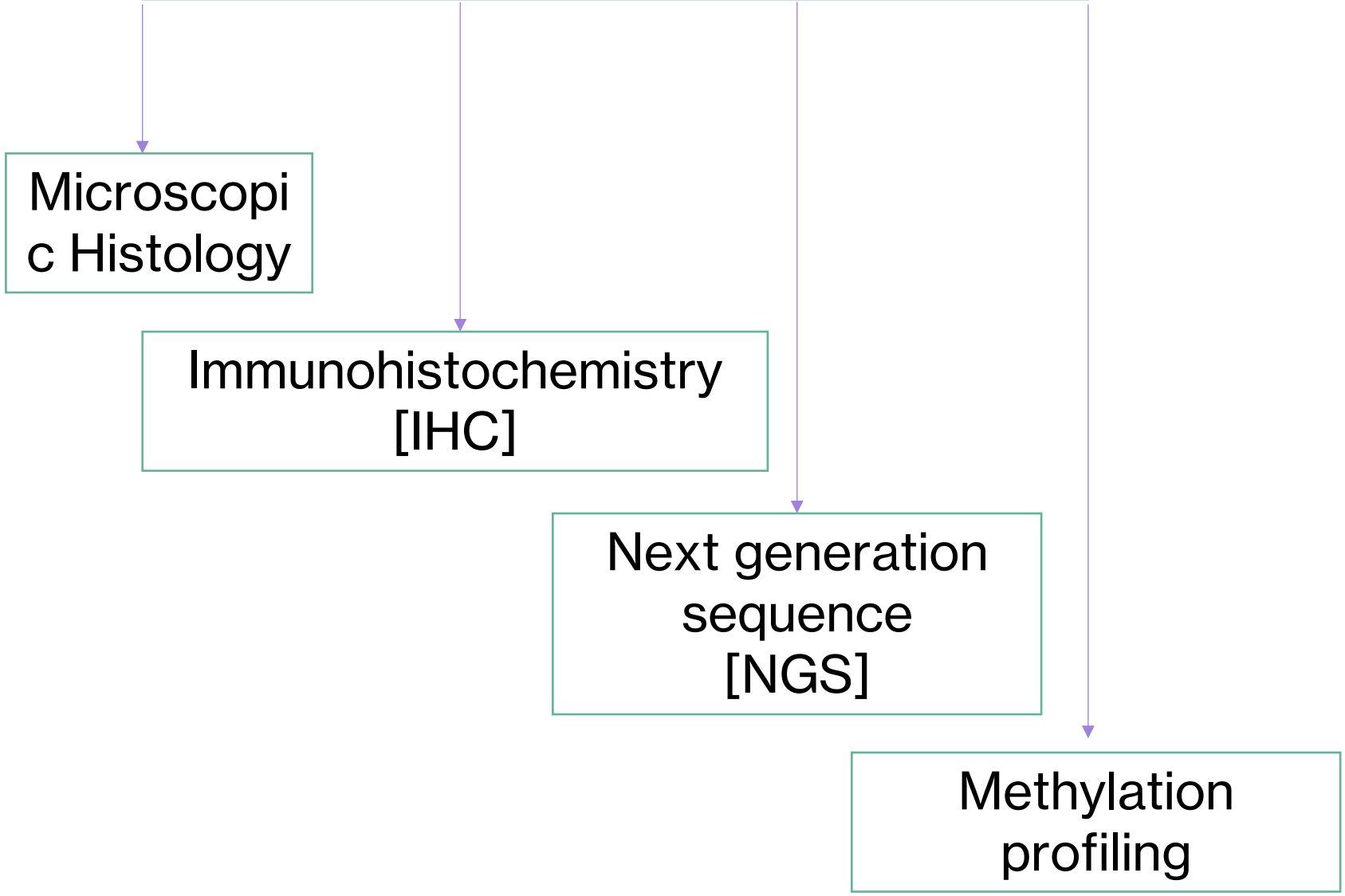
Iorgulescu JB, Sun C, Neff C, et al. *Neuro Oncol* 2022; **24:** 1989–2000.

Pathological Classifications

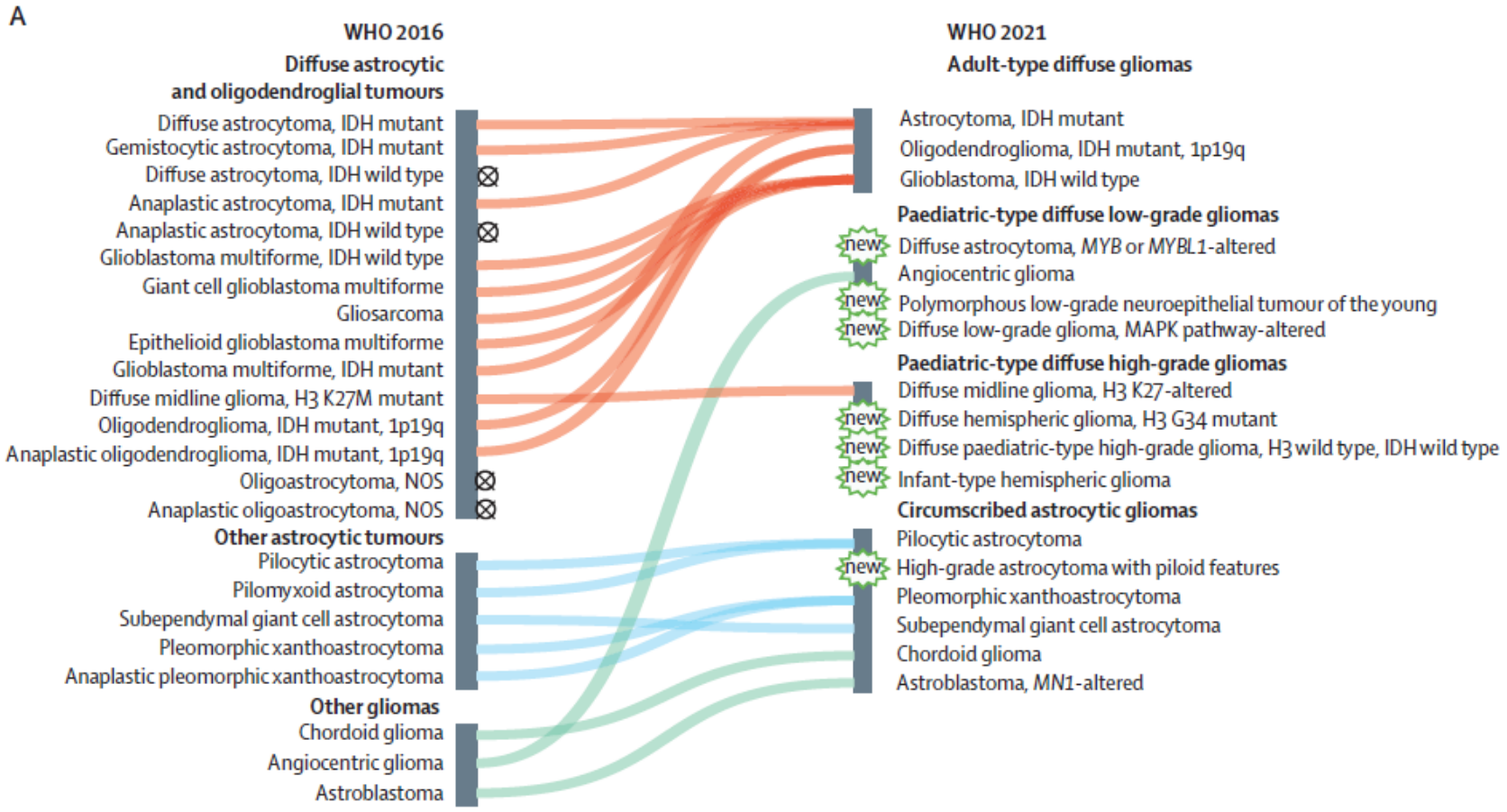
- CNS tumor classification is based on the World Health Organization Classification of CNS tumors
- First published in 1979, last revised in 2021
- 2021 version incorporated a combination of molecular and histologic parameters

Louis, et al. Acta Neuropathologica, 2007

Brain tumor diagnosis



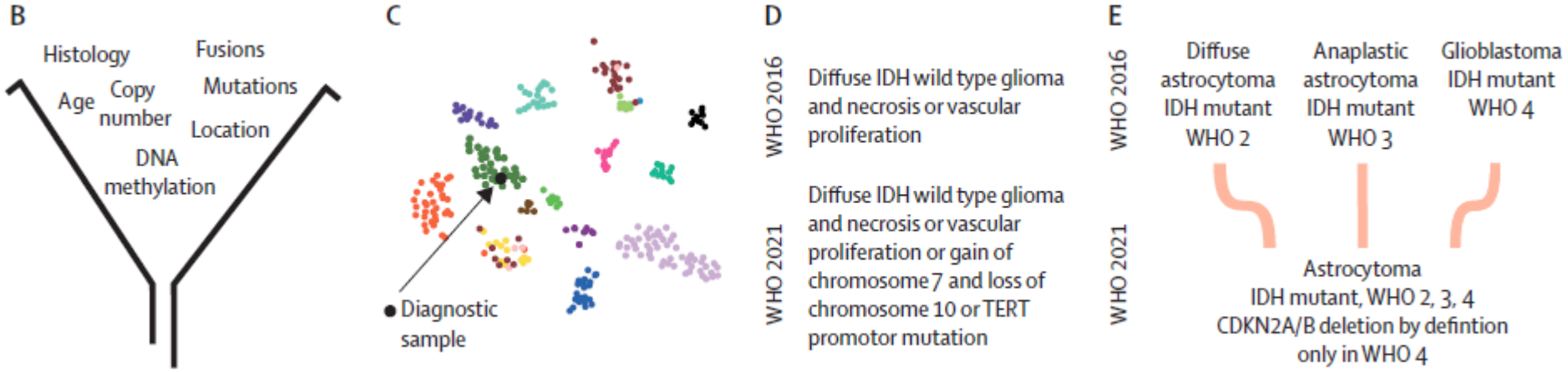
Classifications of CNS tumours - WHO 2021



Central changes between the WHO 2016 and WHO 202169 classifications of CNS tumours :
(A) Overview of new sorting of diffuse and circumscribed gliomas from WHO 2016 to WHO 2021 and overview of newly introduced tumour classes. The symbol signifies an abandoned diagnostic term.

Primary brain tumours in adults van den Bent, Martin J et al. The Lancet, Volume 402, Issue 10412, 1564 - 1579

Central changes between the WHO 2016 and WHO 202169 classifications of CNS tumours



(B) Distillation of essential diagnostic criteria for every tumour class. (C) Introduction of DNA methylation-based tumour classification. (D) Introduction of molecular defining features for glioblastoma, IDH wildtype that allow diagnosis if histological features of glioblastoma (vascular proliferation or necrosis, or both) are lacking. (E) Consolidation of astrocytoma, IDH mutant into one type with three WHO grades. IDH=isocitrate dehydrogenase. NOS=not otherwise specified.

Primary brain tumours in adults van den Bent, Martin J et al. The Lancet, Volume 402, Issue 10412, 1564 - 1579

Survival Analysis of CNS patients in Bangladesh – focusing the multidisciplinary approaches among 149 patients in a single center retrospective analysis from 2018- 2023

- **Aims and Objective**
  - This study evaluates the overall survival (OS) of patients with central nervous system (CNS) malignancies in Bangladesh.
  - The study seeks to identify key prognostic factors affecting survival outcomes, providing insights to improve diagnostic, therapeutic, and resource allocation strategies in low-resource settings.

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Methods

- Central Nervous Tumor (CNS) tumor is variable survival status due to its location and age groups.
- We tried to find selected CNS tumors among adult and child with tri-modalities treatment and compared the survival and prognostic factors among 149 patients first time in Bangladesh.

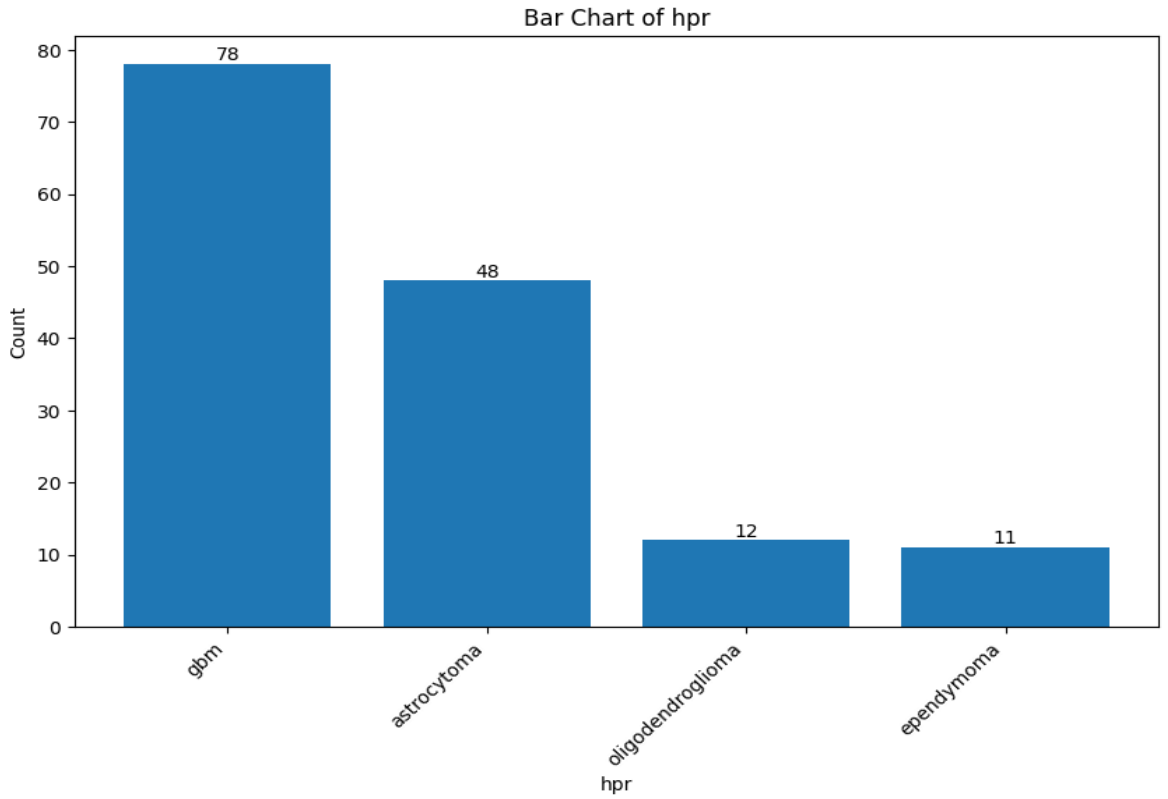
Data Analysis

- A model with python created to analyze the survival in different groups.
- Kaplan-Meier survival analysis was used to estimate overall survival (OS), and the log-rank test was applied to compare survival curves between different patient subgroups.
- Cox proportional hazards regression was employed to assess the significance of potential prognostic factors on survival outcomes, A p-value of <0.05 was considered statistically significant for all tests.
- Descriptive statistics were used to summarize the demographic and clinical characteristics of the study population, and results were presented as hazard ratios (HR) with 95% confidence intervals (CI).

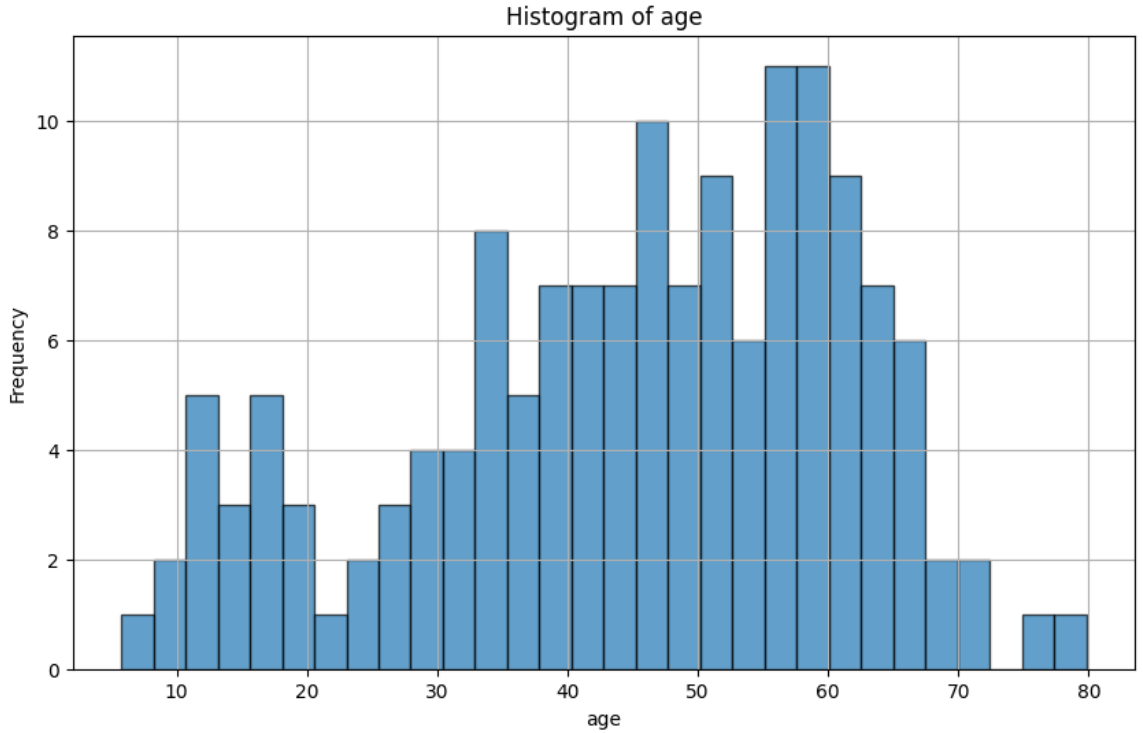
Results

Among the 149 cases the median age 46.89 years with histology grouped in 4 major divisions of

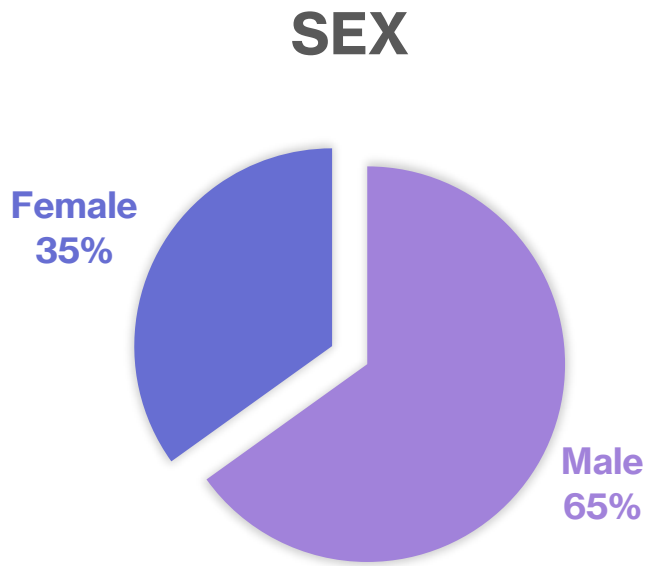
- Ependymoma 11(7.4%),
- Oligodendroglioma 12(8.1%),
- Astrocytoma 48(32.2%),
- Glioblastoma (GBM) 78(52.3%).



Age, Sex Distribution



Distribution of patients according to age median age 46.89 years, ranging from 5-79 years

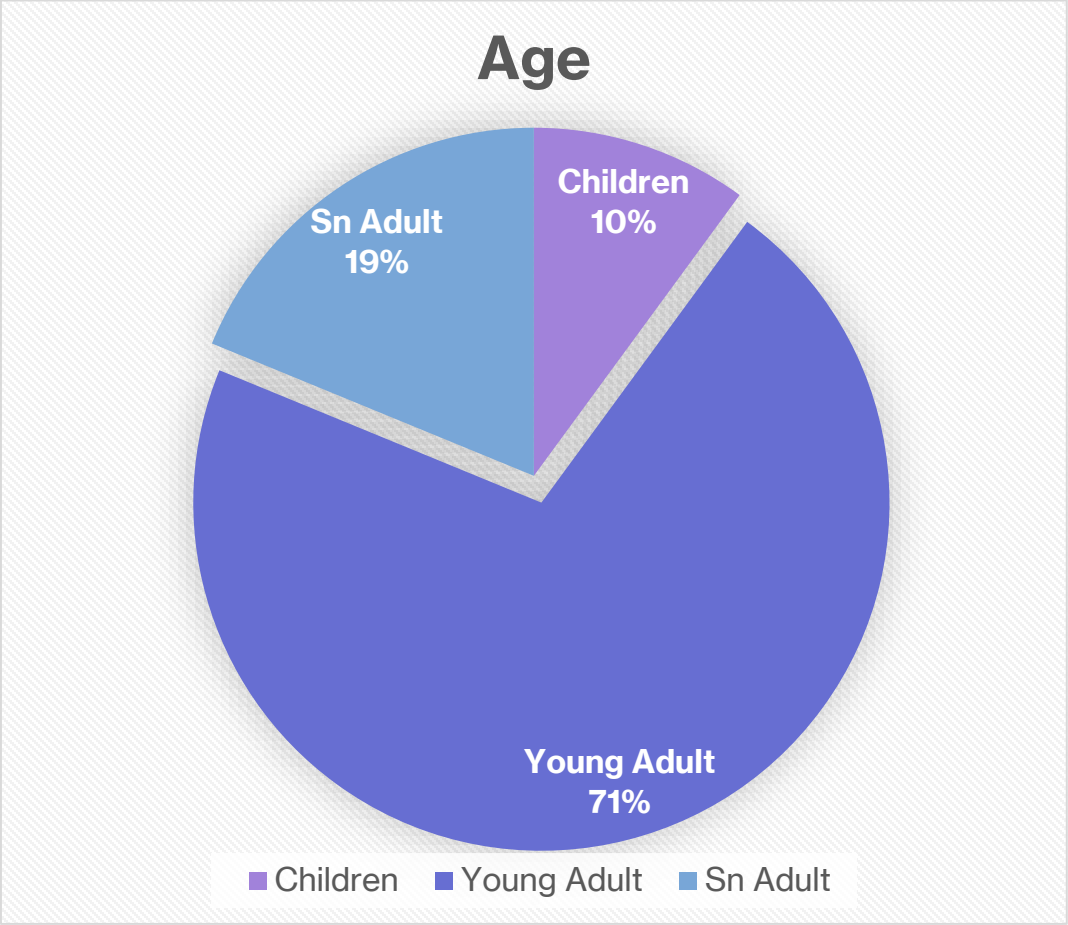


Distribution of patients according to sex

Results

Age group is proposed :

- 1-18 children (10%)
- 18-60 young adult (71%) &
- Above 60 Sn. Adult (19%).



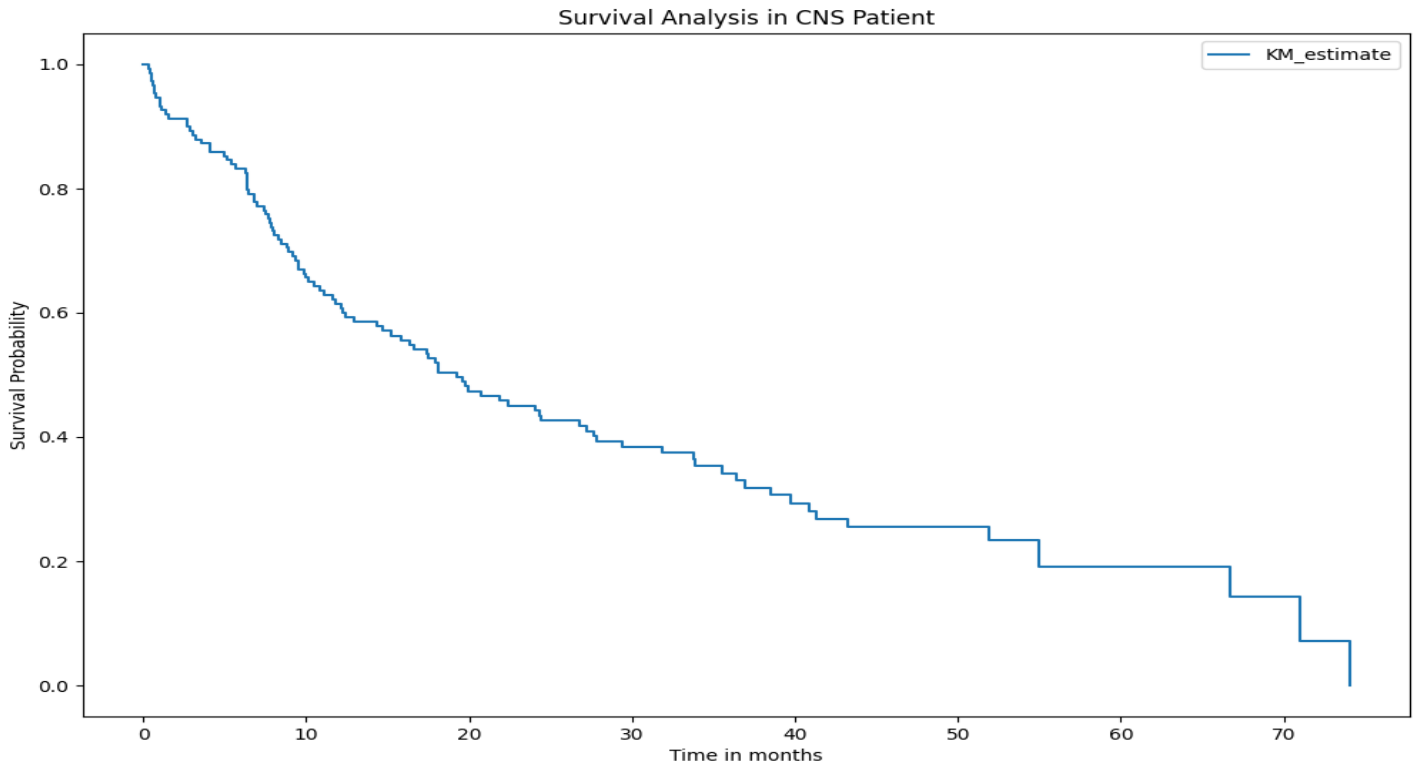
The median overall survival was found 19.2m (95% CI, 14.3-26.7) and the male: female gender ratio is 17.9m:24.4m.

The individual histological median survival was lowest in GBM 11.7m & in Astrocytoma- 21.9m.

Median Survival Time and Confidence Intervals

Description	Value
Median Survival Time	19.23
95% CI Lower Bound	14.30
95% CI Upper Bound	26.77

Median Over Survival of CNS Patient in Bangladesh



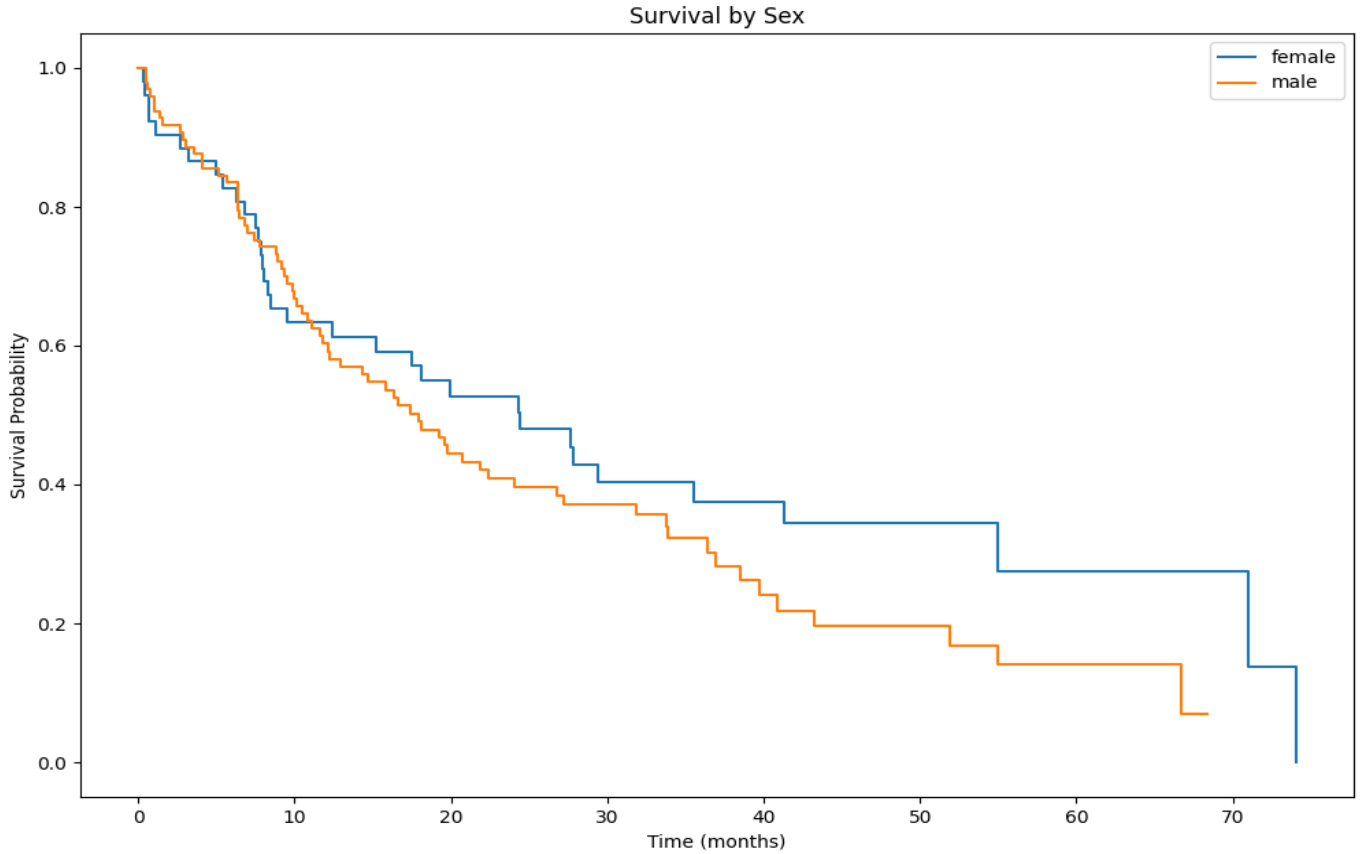
Median Survival of CNS Patient in Bangladesh based on Gender

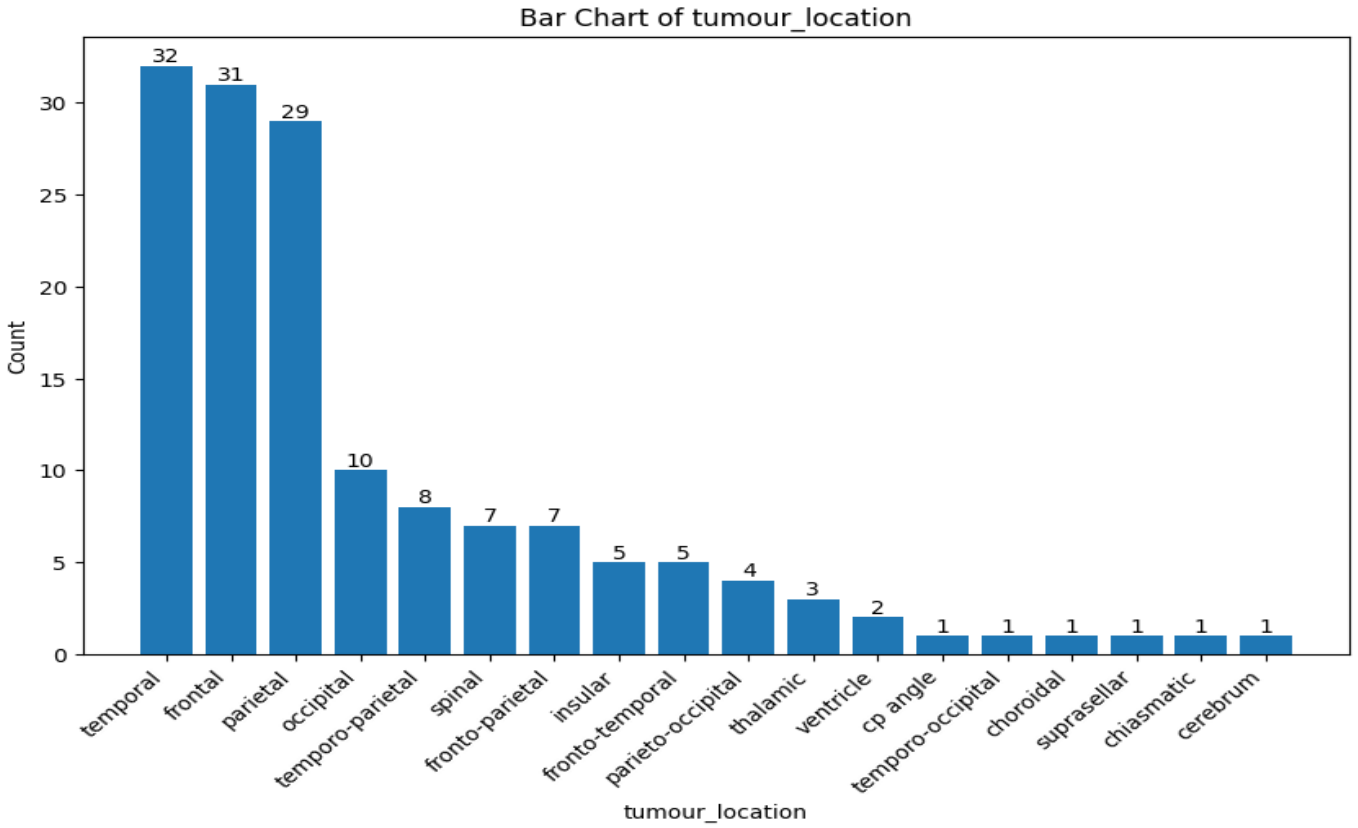
Sex	Median Survival Time	95% CI Lower	95% CI Upper
Female	24.4	9.5	41.33
Male	17.93	11.77	24.07

Log rank p test results on Survival of different Gender Group

Group1	Group2	p-value	Significant
Male	Female	0.2349	False

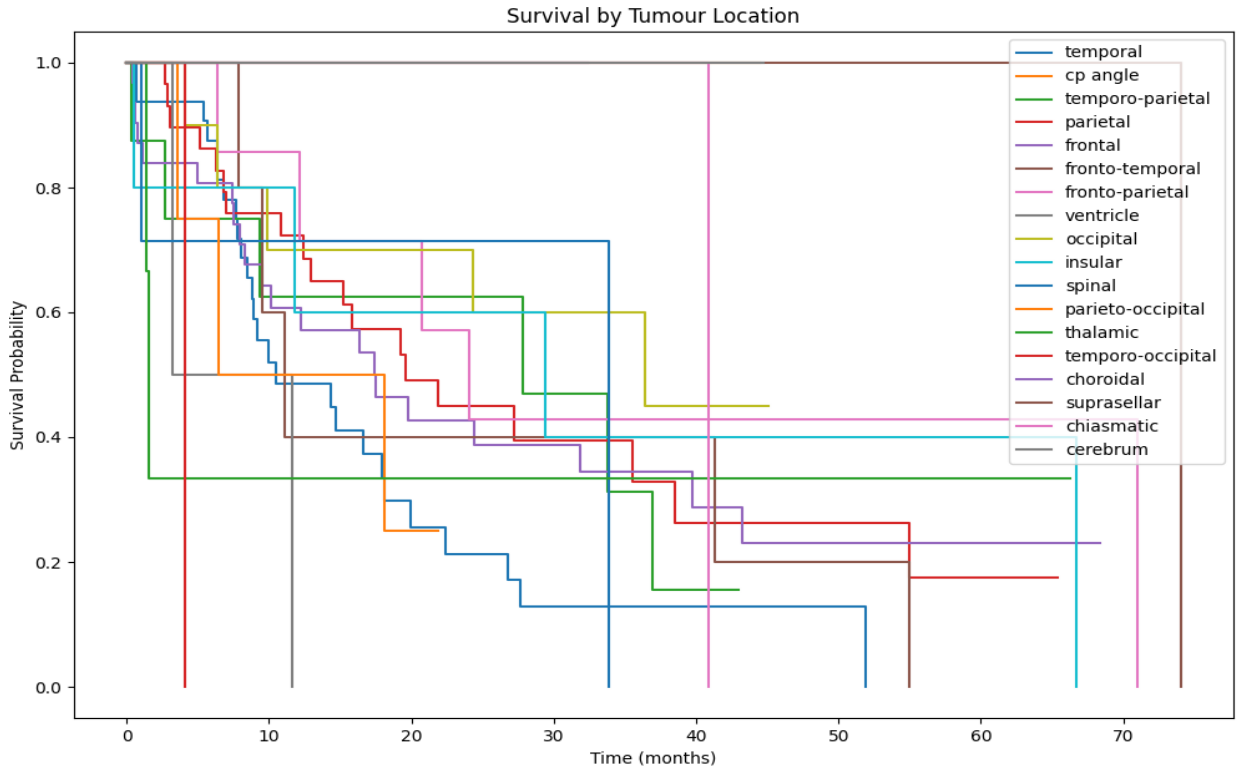
Median Over Survival of CNS Patient in Bangladesh based on Gender





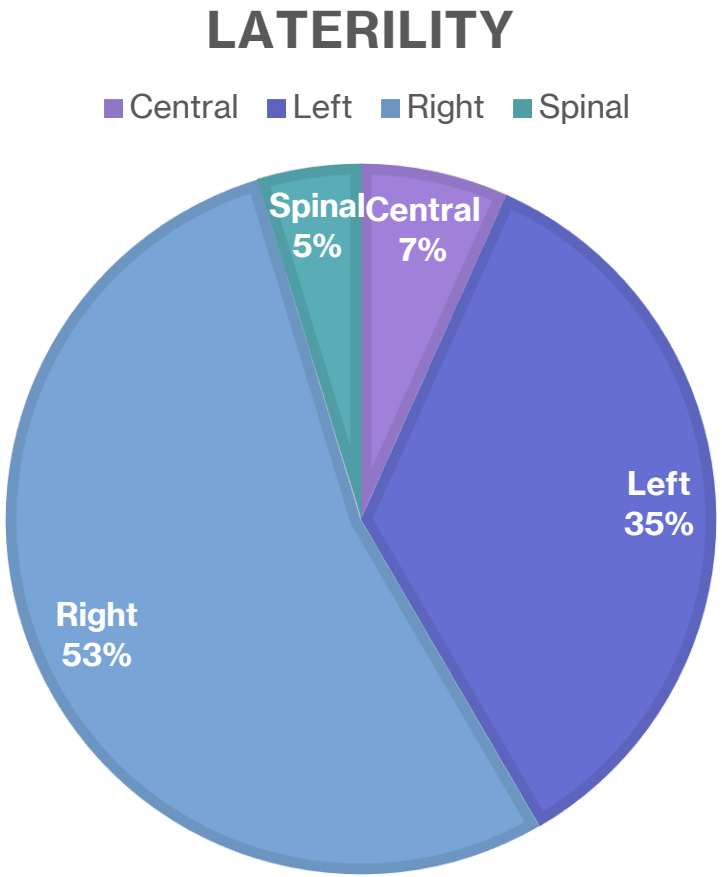
- Position of tumor predominantly in right side of brain 53.7%.
- 70.5% of them achieved GTR due to the use of neuronavigation and 4% patients have only biopsy due to inoperability.
- Highest location of tumor was found to have in temporal, frontal & parietal region about 62% together.

Median Overall Survival of CNS patient in Bangladesh based on Tumour Location



Tumour Location	Median Survival Time	95% CI Lower	95% CI Upper
temporal	10.47	8.03	18.1

Laterality


LATERILITY
Central
Left
Right
Spinal
Spinal 5%
Central 7%
Left 35%
Right 53%

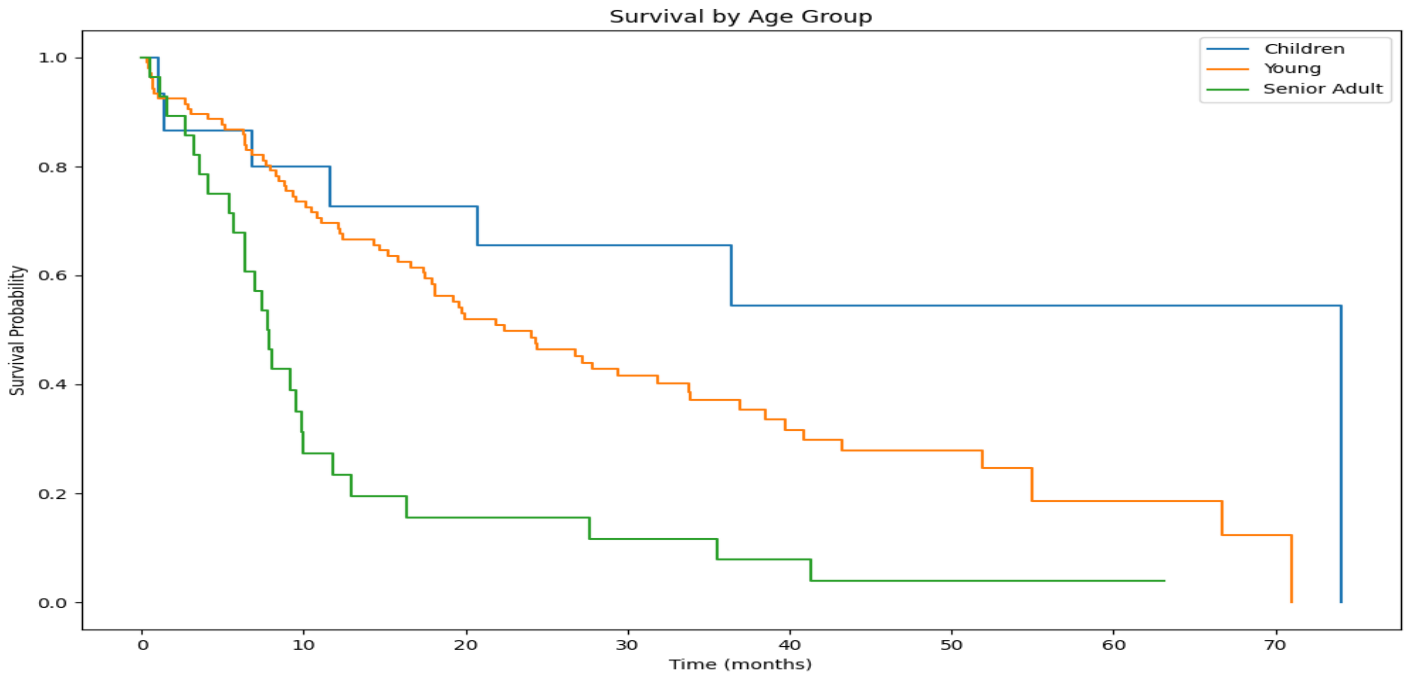
Median Survival of CNS Patient in Bangladesh based on Different Age Group

Age Group	Median Survival Time	95% CI Lower	95% CI Upper
Children	74.03	6.77	74.03
Young	22.4	17.47	31.87
Senior Adult	7.73	5.7	9.83

Log rank p test results on Survival of Different Age Group

Group1	Group2	p-value	Significant
Children	Young	0.1239	False
Children	Senior Adult	0.005	True
Young	Senior Adult	0.0004	True

Survival Analysis of CNS patient in Bangladesh based on Age Group



If we compare with the histology with grading the results of median survival also similar like in G-IV 11.7m (95% CI-8.93-17.47) whereas in case of G-III 24.4m (95% CI 18.1-66.67) & in G-II 54.97m (95% CI- 21.9-74.03).

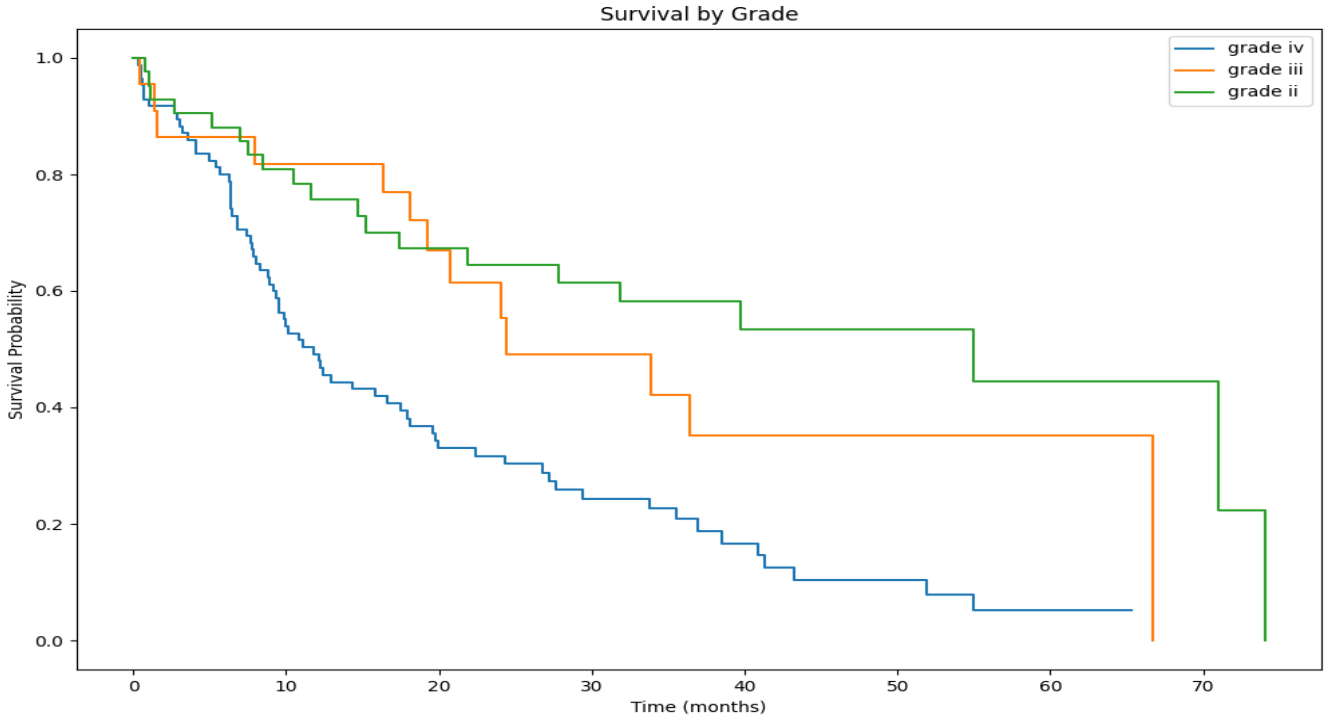
Median Survival of CNS Patient in Bangladesh based on Different Tumor Grade

Grade	Median Survival Time	95% CI Lower	95% CI Upper
Grade iv	11.77	8.93	17.47
Grade iii	24.4	18.1	66.67
Grade ii	54.97	21.9	74.03

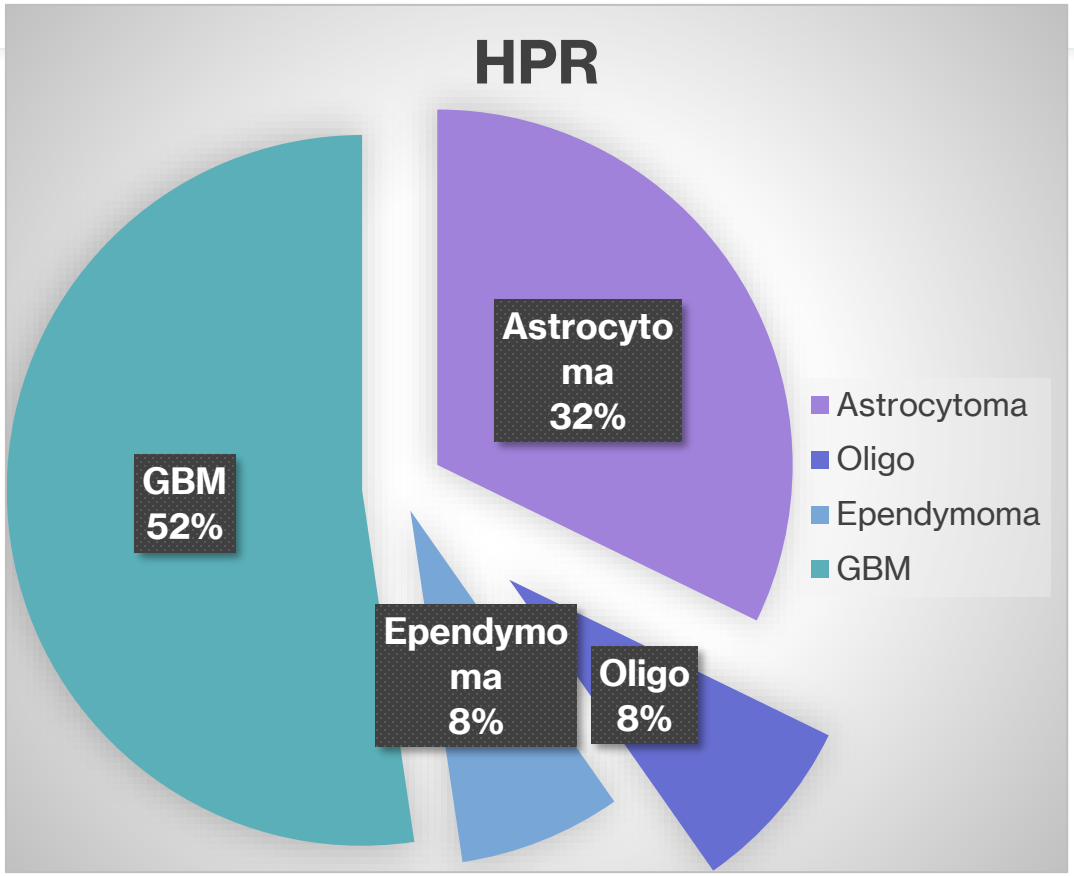
Log rank p test results on Survival of Different Tumor Grade

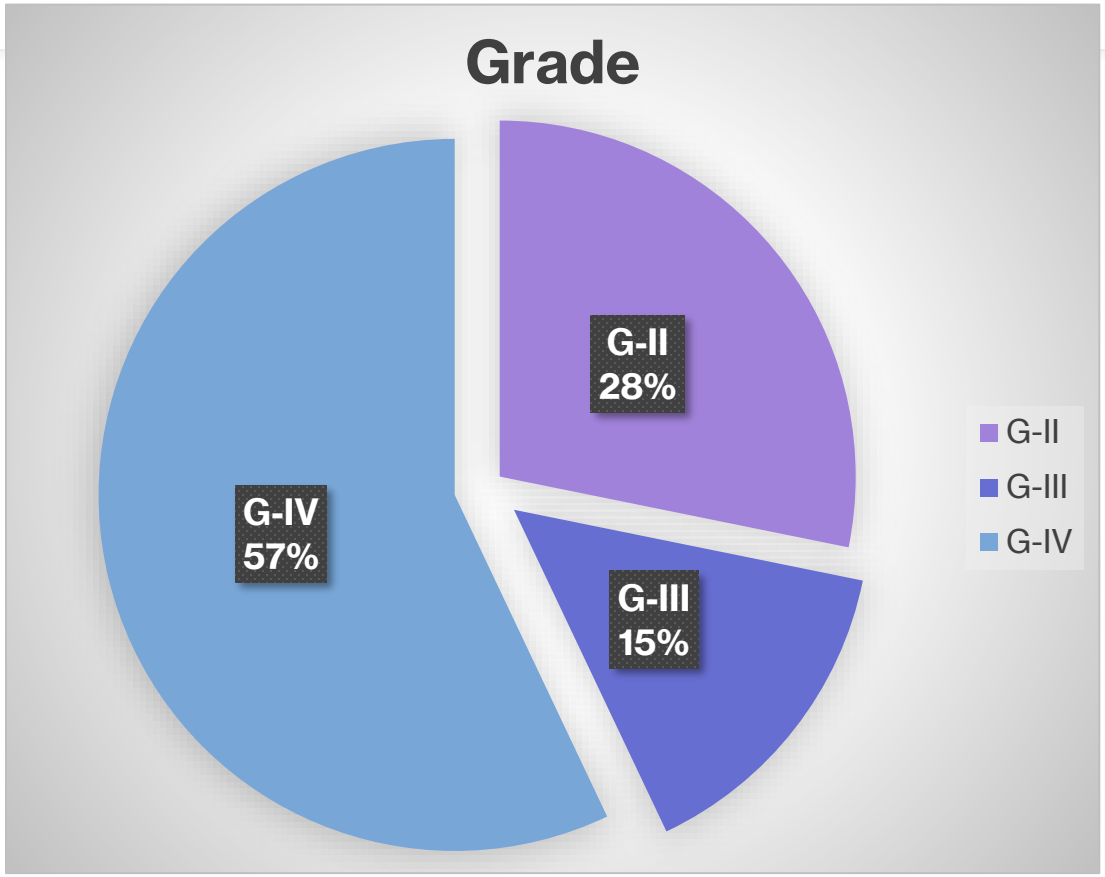
Group1	Group2	p-value	Significant
Grade iv	Grade iii	0.035	True
Grade iv	Grade ii	0.0006	True
Grade iii	Grade ii	0.3655	False

Grade Median Overall Survival of CNS patient in Bangladesh based on Tumor Grade



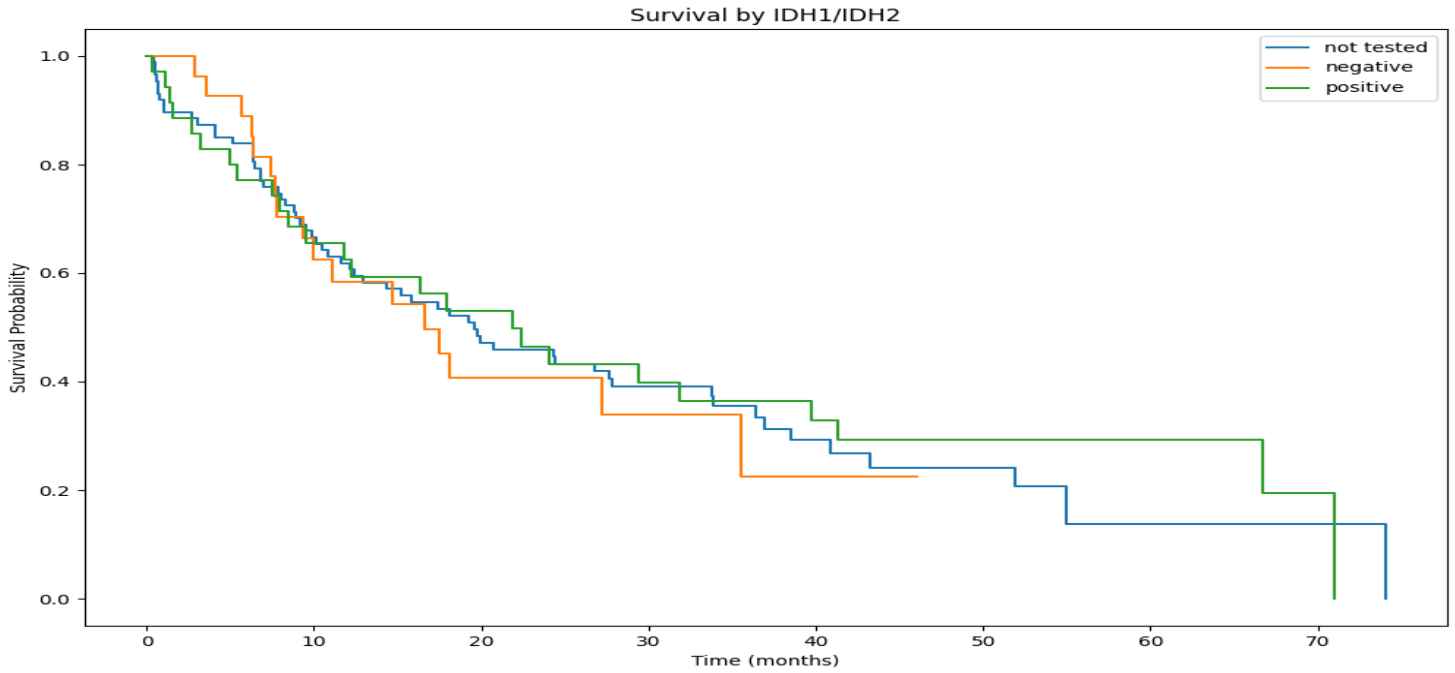
HPR & Grade Distribution





Surgery type also plays an important role in our study, STR & GTR 18.07m vs 19.73m, however the NTR group showed the lowest survival 5.4m as expected in biopsy only group too. 23.5% of IDH mutation positive patients has better survival than 18.1% negative patients (21.9m vs 16.63m)

Median Overall Survival of CNS patient in Bangladesh based on IDH Mutation Status



Survival Analysis of CNS Patient in Bangladesh based on IDH Mutation Status

IDH1/IDH2	Median Survival Time	95% CI Lower	95% CI Upper
Not tested	19.57	12.13	27.8
Negative	16.63	7.73	35.53
Positive	21.9	9.5	39.73

Log rank p test results on Survival based on IDH Mutation Status

Group1	Group2	p-value	Significant
Not tested	Negative	0.1189	False
Not tested	Positive	0.2813	False
Negative	Positive	0.0686	False

COX proportional hazard ratio in Forest Plot also in favor of in case of IDH & Surgery type & Histology as well.

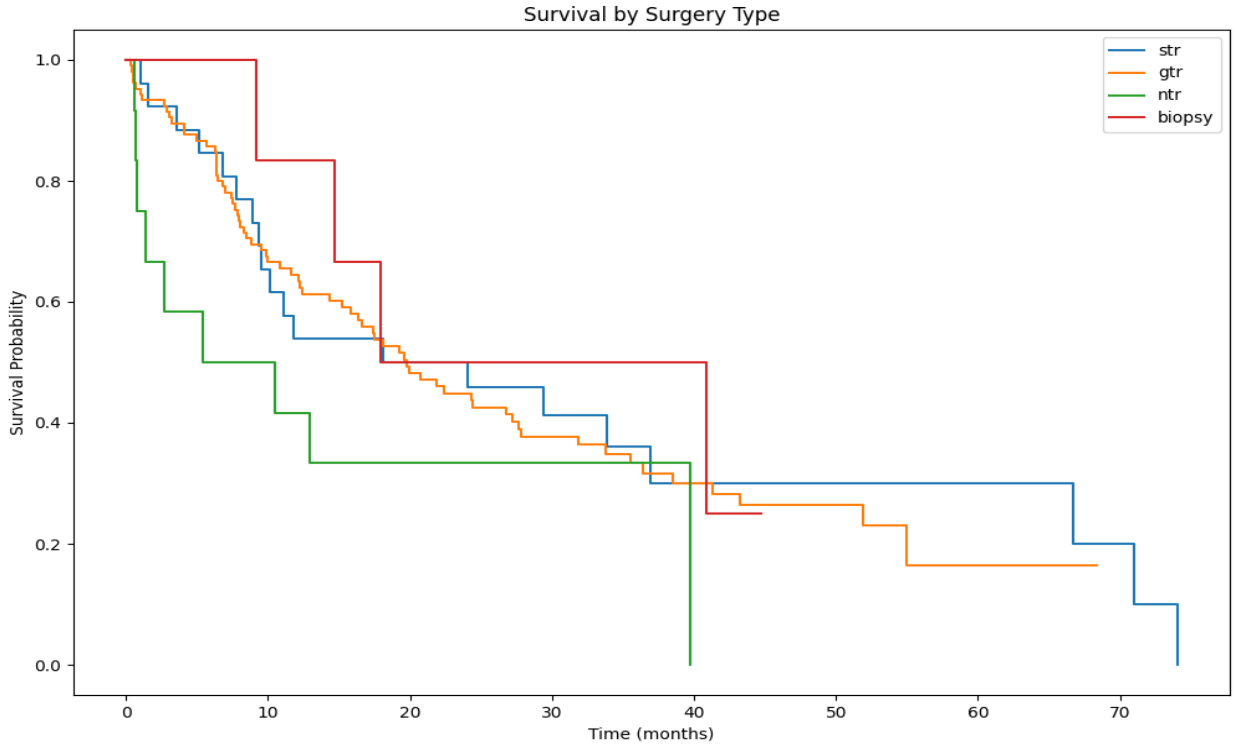
Survival Analysis of CNS Patient in Bangladesh based on Surgery Type

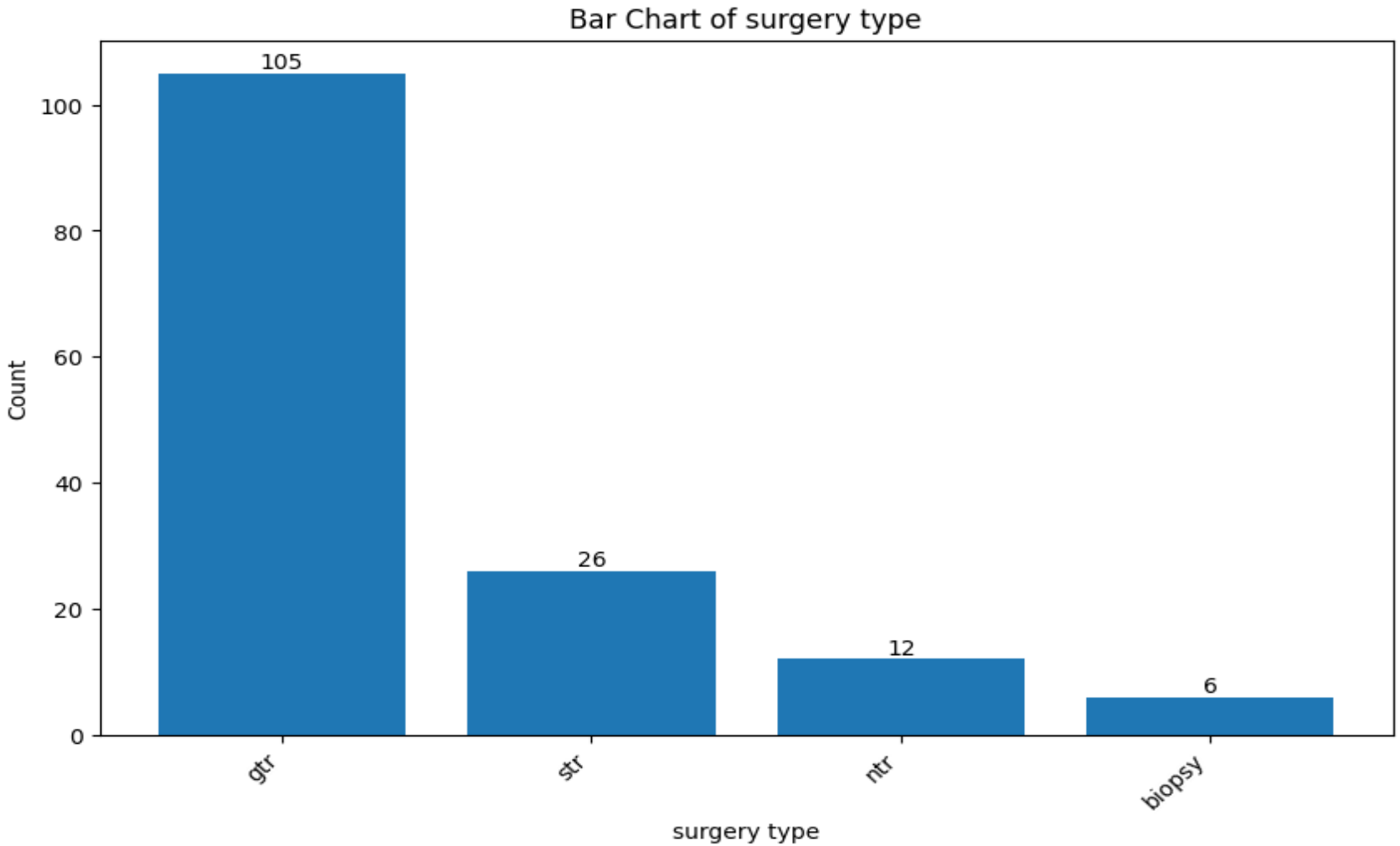
Surgery Type	Median Survival Time	95% CI Lower	95% CI Upper
STR	18.07	9.37	36.9
GTR	19.73	15.23	27.2
NTR	5.4	0.7	39.73

Log rank p test results on Survival based on IDH Mutation Status

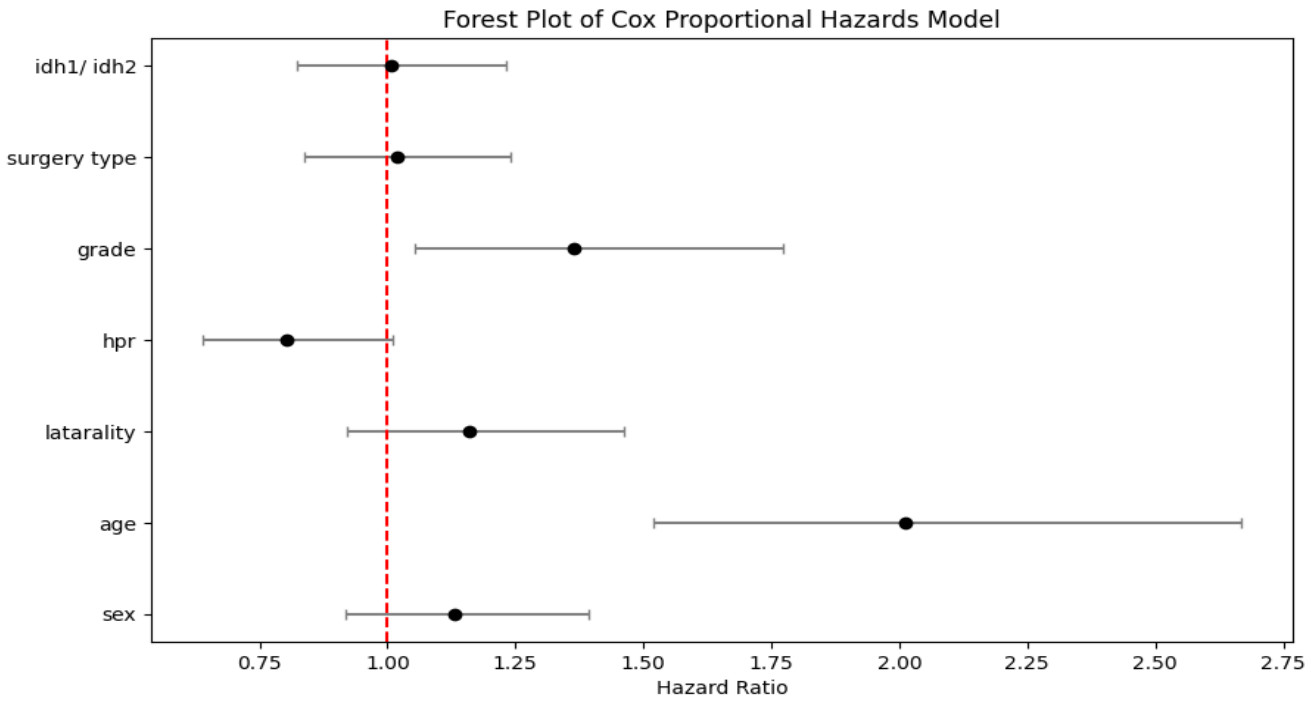
Group1	Group2	p-value	Significant
STR	GTR	0.1337	False
STR	NTR	0.065	False
STR	Biopsy	0.9918	False
GTR	NTR	0.0585	False
GTR	Biopsy	0.8201	False
NTR	Biopsy	0.088	False

Median Overall Survival of CNS patient in Bangladesh based on Surgery Type




Bar Chart of surgery type
105
26
12
6
100
80
60
40
20
0
Count
gtr
str
ntr
biopsy
surgery type

Forest Plot of COX proportional hazard ratio



Age has the strongest association, with a hazard ratio (HR) of 2.0 ($p < 0.001$), indicating that as age increases, the risk of mortality also rises significantly. **Histopathology (HPR)** also impacts survival, with an HR of 0.78 ($p = 0.0293$), suggesting that certain tumor types are associated with reduced risk.
Tumor grade shows an HR of 1.35, nearing significance ($p = 0.0982$), indicating that higher grades may slightly elevate risk.
Variables such as **sex**, **surgery type**, and **IDH mutation** status had no significant impact on survival outcomes in this analysis.

Radiotherapy +-concurrent (CRT) and/or adjuvant chemotherapy (AdChT) with TMZ

- RT doses varies in 50Gy to 60Gy according to histology or group grade with 3DCRT/ IMRT/ VMAT facilities.
- Completion of majorities of group 106/149 patients completed 50-60Gy prescribed doses among them
  - 59.4-60Gy in 33-30# 74/106 patients,
  - 54Gy in 30-27# 22/106 patients and
  - rest of them 10 patients 45-50.4 Gy received.
- Incompletion of 5/149 patients due to poor general condition and completed 10-40Gy with prescribed doses of 45-60Gy.
- RT was not received among 23/149 patients.
- CRT/ AdChT was most of the time with Temozolamide (TMZ) and PCV also given only few patients.
  - CRT was given 96 patients whereas
  - 53 patients did not receive any form of CRT.
  - AdChT was received 84 patients.

Radiotherapy +-concurrent (CRT) and/or adjuvant chemotherapy (AdChT) with TMZ

- Patients who received radiotherapy had a median survival of 27.5 months, significantly higher than those who did not receive radiotherapy (12.4 months, p = 0.008)

Conclusion

The analysis is little complicated in case of heterogeneous histology and location of CNS tumors. But with the model that created by python showed significant relationship and survival outcome. If the sample size also increases in number and the single histology selected to find out the comparison with other parameters, then the best survival outcome can be estimated.

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patient first

Thank you

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Clinical Relevane of Molecular Diagnostics in Gliomas

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Consultant for Neuropathology

Center for Human Genetics/ CeGaT GmbH

27 July 2025

Agenda

1. IDH-mutant Glioma
2. Histone H3-altered Glioma
3. MAPK-altered Glioma (e.g. PXA*)
4. Glioblastoma
5. Case Examples

*PXA is mentioned exemplarily. Please be aware that the CNS WHO classification also lists further MAPK-altered gliomas and glioneuronal tumors which will not be mentioned in this presentation due to time constraints.

IDH-mutant Glioma

Astrocytoma, IDH-mutant	*IDH1, IDH2, ATRX, TP53, CDKN2A/B*

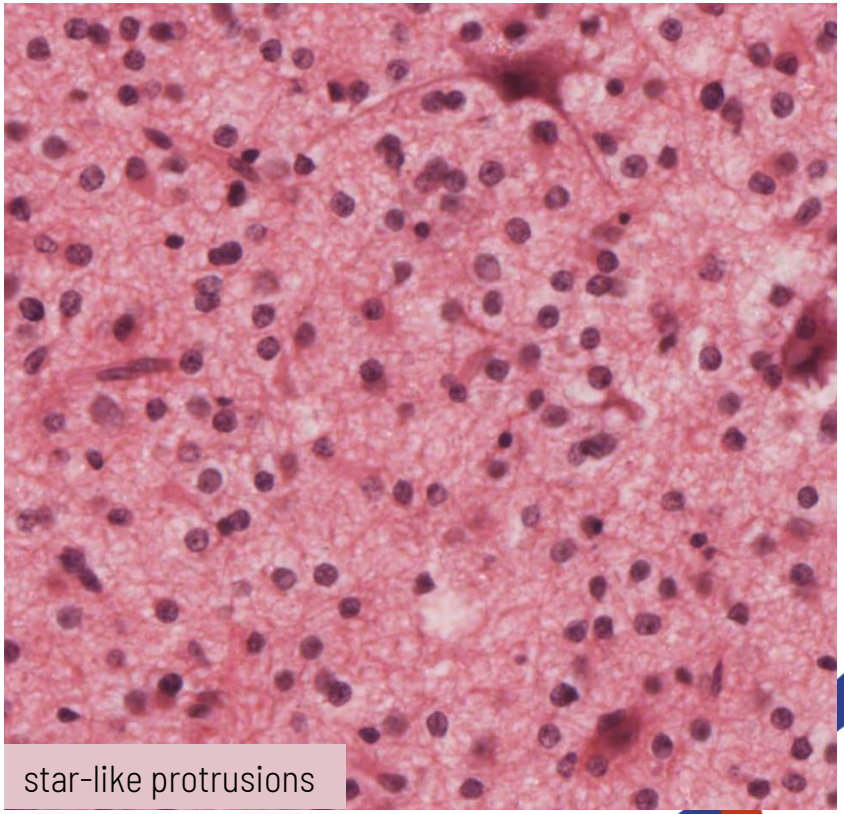
Clinical and Epidemiological Data

- mostly hemispheric location
- mostly adolescents/young adults

Diagnostic criteria

- Essential:
  diffusely infiltrating glioma
  + IDH1 R132 or IDH2 R172 mutation
  + loss of ATRX expression or ATRX mutation

- Desirable:
  astrocytic differentiation by morphology
  overexpression of p53 or TP53 mutation
  DNA methylation profile of IDH-mutant astrocytoma



star-like protrusions

IDH-mutant Glioma

Astrocytoma, IDH-mutant	*IDH1, IDH2, ATRX, TP53, CDKN2A/B*

Grading criteria

- Grade 2: no anaplasia, no/very low mitotic activity
- Grade 3: at least focal anaplasia, significant mitotic activity
- Grade 4: microvascular proliferation or necrosis or homozygous deletion of CDKN2A/B

➢ if CDKN2A/B homozygous deletion is present in an astrocytoma, this tumor is categorized as grade 4, irrespective of histology

➢ CDKN2A mutations may have equivalent prognostic significance

Prognosis

- Grade 2: 10.2 y
- Grade 3: 8.1 y
- Grade 4: 4.7 y
  - ➢ CDKN2A balanced → 5.5 y
  - ➢ CDKN2A loss → 1.8 y
- copy number variation load correlates with malignancy

IDH-mutant Glioma

Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted	*IDH1*, *IDH2*, 1p/19q, *TERT* promoter, *CIC*, *FUBP1*

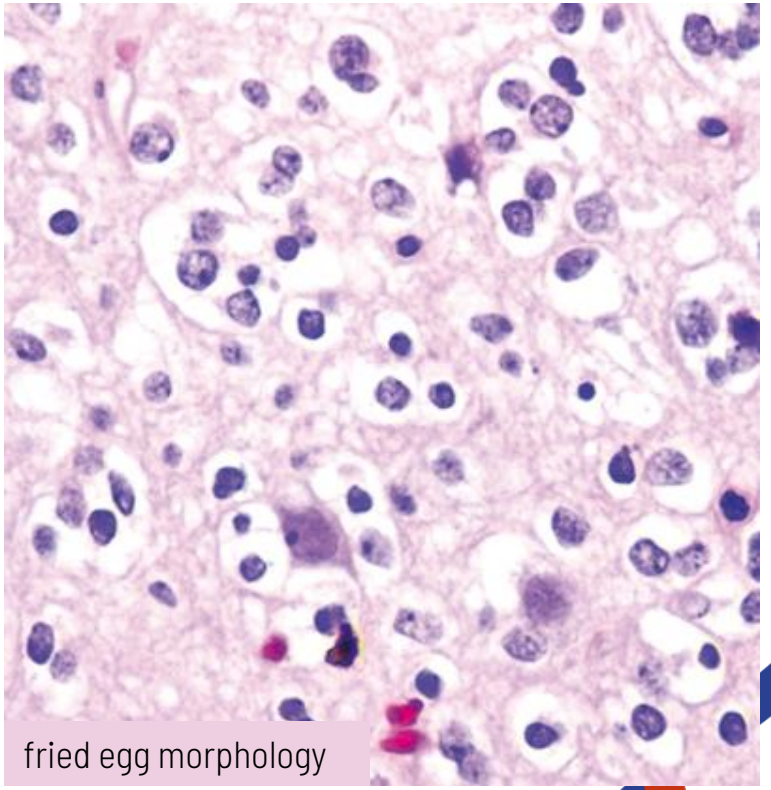
Clinical and Epidemiological Data

- mostly hemispheric location
- patients of all ages

Diagnostic criteria

- Essential:
  diffusely infiltrating glioma
  + IDH1 R132 or IDH2 R172 mutation
  + combined whole-arm deletions of 1p and 19q

- Desirable:
  TERT promoter mutation
  retained ATRX expression or ATRX wildtype
  DNA methylation profile of IDH-mutant oligodendroglioma



fried egg morphology

IDH-mutant Glioma

Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted	*IDH1*, *IDH2*, 1p/19q, *TERT* promoter, *CIC*, *FUBP1*

Grading criteria

- Grade 2: no/very low mitotic activity
- Grade 3: brisk mitotic activity, microvascular proliferation, necrosis

➢ CDKN2A/B homozygous deletion is found in a subset of grade 3, but not grade 2 oligodendrogliomas

➢ CDKN2A/B homozygous deletion may serve as a molecular marker of grade 3 in oligodendrogliomas

Prognosis

- over 10 years
- CDKN2A/B homozygous deletion is linked to reduced survival in oligo-dendroglioma, independent of histological grading

6

IDH-mutant Glioma

Treatment Options

Legend:

PCV = Procarbazine, Lomustine (CCNU), Vincristine
RT = Radiotherapy
TTF = Tumor Treating Fields (Optune device)
TMZ = Temozolomide

Astrocytoma, IDH mutant	Grade 2	observation possible (if low-risk) RT + PCV or TMZ (if high-risk) vorasidenib (FDA)
	Grade 3	RT + TMZ maintenance
	Grade 4	RT (+ concurrent TMZ) + TMZ maintenance TTF (off-label)
Oligodendroglioma, IDH mutant and 1p/19q co-deleted	Grade 2	observation possible (if low-risk) RT + PCV (if high-risk) vorasidenib (FDA)
	Grade 3	RT + PCV or PCV + RT

Histone H3-altered Glioma

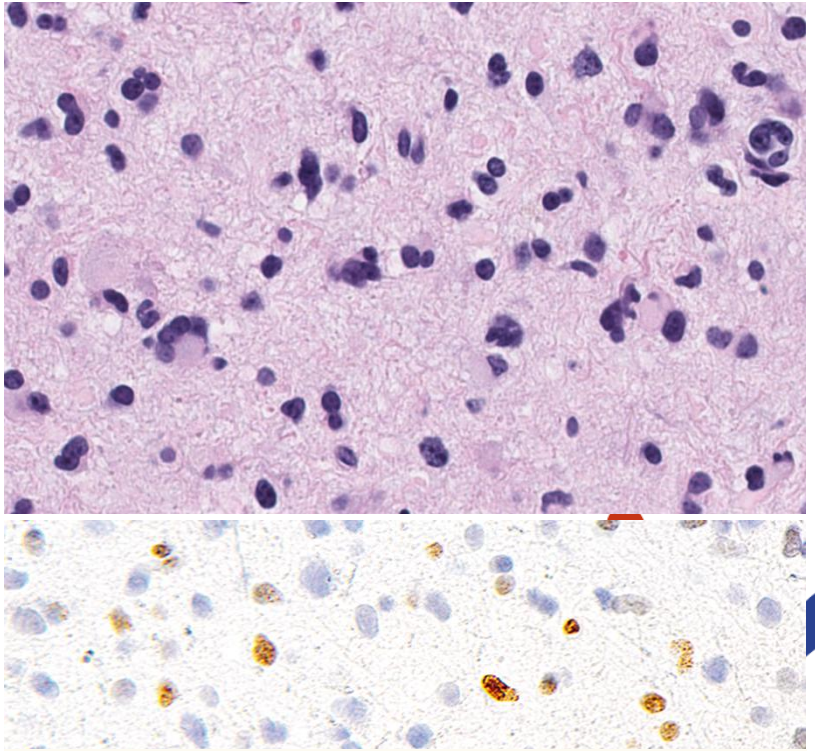
Diffuse midline glioma, H3 K27-altered	H3 K27, *TP53*, *ACVR1*, *PDGFRA*, *EGFR*, *EZHIP*

Diagnostic criteria

- Essential:
  diffuse glioma located in the midline
  + loss of nuclear expression of H3 K27me3 (IHC)
  + H3 p.K27M or p.K27I mutation
    OR EGFR amplification
    OR EZHIP overexpression (RNA/IHC)
    OR DNA methylation profile of diffuse midline glioma

- Desirable:
  molecular analyses that enable discrimination of K27 alterations in the histone family members H3.3, H3.2 and H3.1

- some cases may have concurrent ATRX or TP53 alterations



loss of H3K27me3 in the tumor cell nuclei

Histone H3-altered Glioma

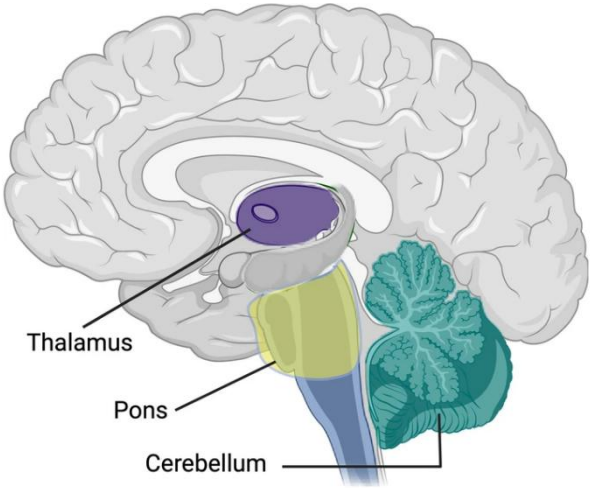
Diffuse midline glioma, H3 K27-altered	H3 K27, *TP53*, *ACVR1*, *PDGFRA*, *EGFR*, *EZHIP*

Clinical and Epidemiological Data

- midline location (thalamus, cerebellum, brainstem, pons, spine)
- children and young adults frequently affected
- former synonym of this entity: diffuse intrinsic pontine glioma (DIPG)

Grading and Prognosis

- poor outcome with OS of 11-16 months
- Grade 4



https://jneuroinflammation.biomedcentral.com/articles/10.1186/s12974-022-02630-8

Histone H3-altered Glioma

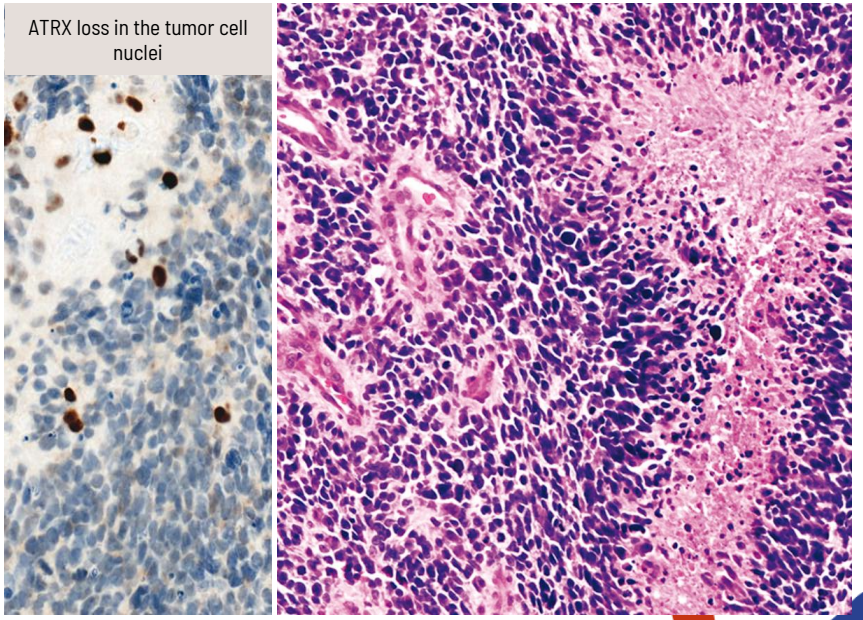
Diffuse hemispheric glioma, H3 G34-mutant	H3 G34, *TP53*, *ATRX*

Diagnostic criteria

- Essential:
  cellular, infiltrative glioma with mitotic activity
  + H3.3 p.G34R or p.G34V mutation
  + hemispheric location
  in unresolved cases DNA methylation profile of H3 G34–mutant diffuse hemispheric glioma

- Desirable:
  Olig2 positivity
  loss of ATRX expression or ATRX mutation
  overexpression of p53 or TP53 mutation

ATRX loss in the tumor cell nuclei



Histone H3-altered Glioma

Diffuse hemispheric glioma, H3 G34-mutant	H3 G34, *TP53*, *ATRX*

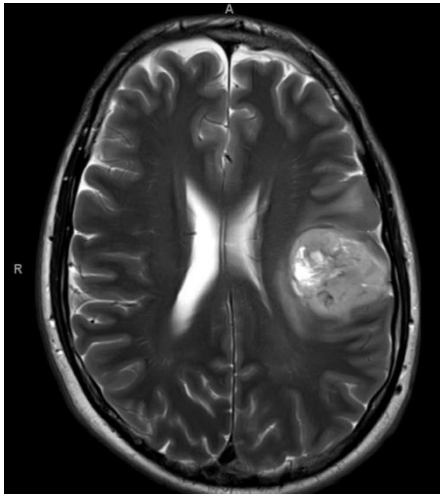
Clinical and Epidemiological Data

- located in the cerebral hemispheres
- adolescents and young adults frequently affected (rare in elderly patients)
- former synonym of this entity: glioblastoma, IDH-wildtype, H3 G34 mutant

Due to the use of different reference transcripts for sequencing ananysis, H3 K27 alterations are sometimes referred to as K28 and H3 G34 alterations as G35.

Grading and Prognosis

- poor outcome with OS of 18-22 months
- Grade 4



https://www.pathologyoutlines.com/topic/cnstumordiffuseH3G34mutant.html

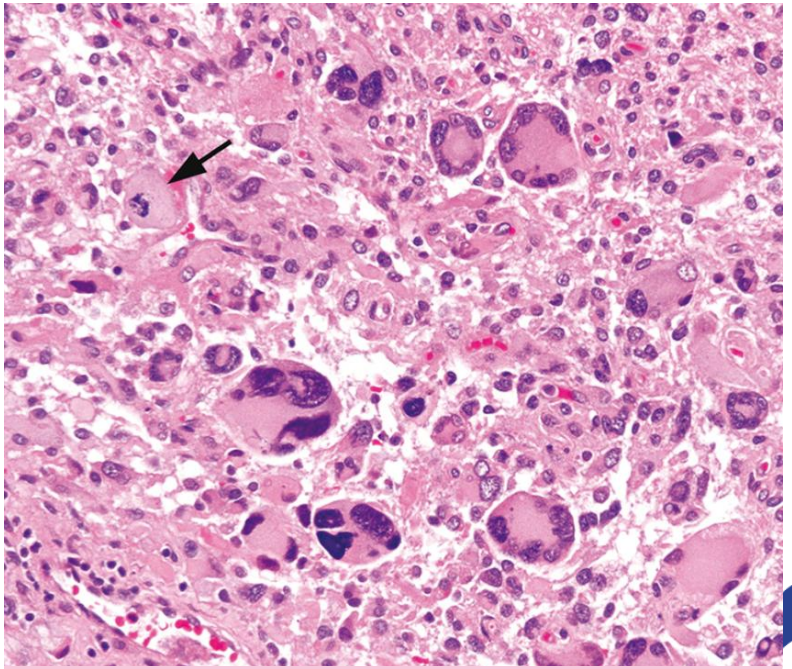
MAPK-altered Glioma (e.g. PXA)

Zentrum für Humangenetik Tübingen

Pleomorphic xanthoastrocytoma (PXA) *BRAF, CDKN2A/B*

Diagnostic criteria

- Essential:
  astrocytoma with pleomorphic tumor cells and eosinophilic granular bodies
- Desirable:
  reticuline deposition
  BRAF mutation (mostly V600E) or other MAPK alteration combined with homozygous deletion of CDKN2A/B
  DNA methylation profile of pleomorphic xanthoastrocytoma
- alterations typical for glioblastoma should be absent



highly pleomorphic and xanthomatous tumor cells

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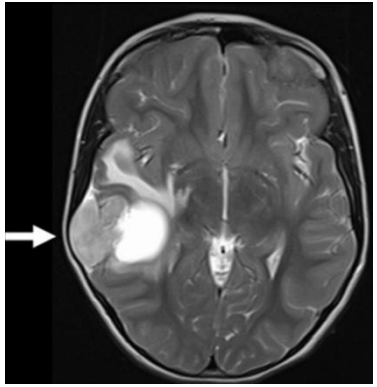
MAPK-altered Glioma (e.g. PXA)

Zentrum für Humangenetik Tübingen

Pleomorphic xanthoastrocytoma (PXA) *BRAF, CDKN2A/B*

Clinical and Epidemiological Data

- located in the cerebral hemispheres, often superficially involving the leptomeninges
- often occurs in children and young adults, rarely observed in elderly patients



doi: 10.21037/tp-24-306

Grading and Prognosis

- grading according to mitotic count
- Grade 2: 5-year OS 90%
- Grade 3: 5-year OS 57%
- rare cases may have a TERT promoter mutation or TERT copy number gain (may predict worse outcome)

Despite PXA is mainly defined by histology in the current CNS WHO classification, molecular studies focusing on DNA methylation-based classification suggest a wider morphological spectrum of this entity. Therefore, comprehensive molecular testing is recommended.

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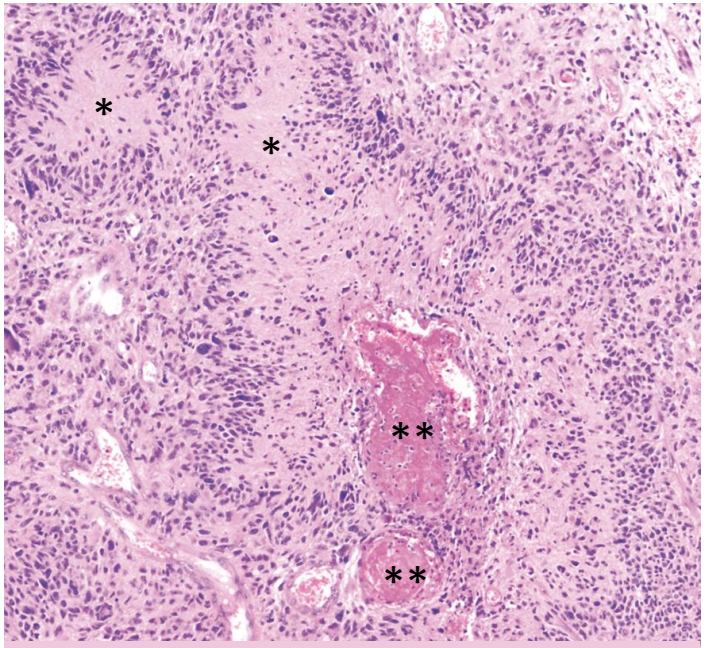
Glioblastoma, IDH-wildtype (GBM)

Glioblastoma, IDH-wildtype	IDH-wildtype, *TERT* promoter, chromosomes 7/10, *EGFR*

Diagnostic criteria

- Essential:
  IDH-wildtype, H3-wildtype, diffuse astrocytic glioma
  + one or more of the following
    - microvascular proliferation
    - necrosis
    - TERT promoter mutation
    - EGFR amplification
    - chromosome 7 gain combined with chromosome 10 loss

- Desirable:
  DNA methylation profile of glioblastoma, IDH-wildtype



glial tumor with palisading necrosis* and thrombosed vessels**

Glioblastoma, IDH-wildtype (GBM)

Glioblastoma, IDH-wildtype	IDH-wildtype, *TERT* promoter, chromosomes 7/10, *EGFR*

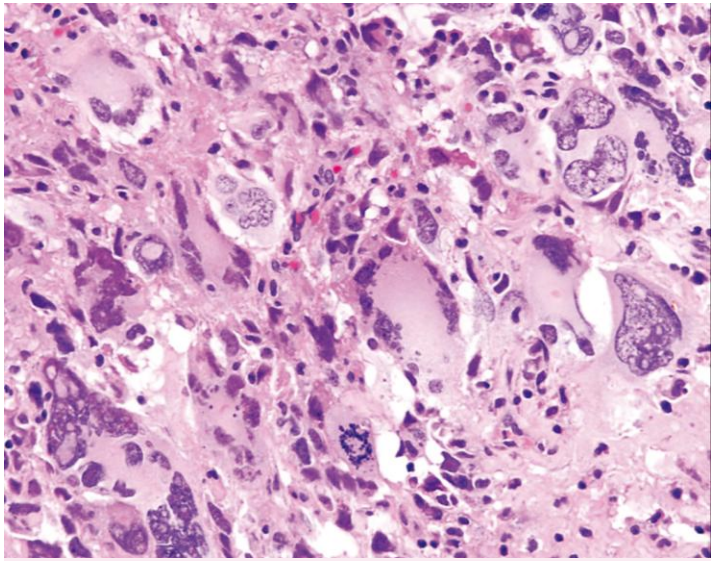
Clinical and Epidemiological Data

- mostly located in the cerebral hemispheres
- rarely located in the cerebellum or spinal cord (<10%)

Rarely, glioblastomas may have a BRAF mutation and may also histologically look like PXA. In order to enable distinction from PXA, diagnostic glioblastoma criteria must apply regardless of the BRAF mutation.

Grading and Prognosis

- poor outcome with OS of 1.6 years
- Grade 4



histological variant with bizarre and multi-nucleated tumor cells

IDH-wildtype Glioma

Treatment Options

Legend:

CCNU = Lomustine
RT = Radiotherapy
TTF = Tumor Treating Fields (Optune Device)
TMZ = Temozolomide
CAR-T = chimeric antigen receptor T-cell

H3-altered Glioma	diffuse midline glioma, H3 K27-altered	RT only, clinical trials (ONC201, ONC206, GD2-CAR-T, H3.3 K27M peptide vaccine +/- immune checkpoint inhibitor)
	diffuse hemispheric glioma, H3 G34-mutant	RT + TMZ (glioblastoma-like protocols) clinical trials (neoantigen-targeted peptide-pulsed dendritic cell vaccine)
Pleomorphic Xanthoastrocytoma (Grade 2 or 3)		RT (+ adjuvant TMZ or CCNU) dabrafenib/trametinib clinical trials (BRAF/MEK inhibitors)
Glioblastoma, IDH wildtype		RT (+ concurrent TMZ) + TMZ maintenance ± TTF in patients up to 70 years of age MGMT+ → TMZ only, MGMT- → RT only in patients over 70 years of age in case of progression TMZ, bevacizumab, regorafenib, CCNU, clinical trial

Case Examples

Case 1

External Diagnosis: Glioblastoma, IDH-wildtype, CNS WHO Grade 4

Histological Diagnosis: Diffuse glioma with singular mitoses
Molecular Findings: BRAF V600E, homozygous CDKN2A/B deletion, lack of molecular GBM markres

Revised Integrated Diagnosis: Pleomorphic Xanthoastrocytoma, CNS WHO Grade 2

- BRAF V600E as therapeutic option in case of progression/recurrence

Case 2

External Diagnosis: Suggestive of low-grade glioma

Histological Diagnosis: CNS tissue with diffusely elevated cell denstity
Molecular Findings: EGFR amplification, TERT promoter mutation

Revised Integrated Diagnosis: Infiltration Zone of Glioblastoma, IDH-wildtype, CNS WHO Grade 4

Further Molecular Alterations With Potential Relevance in Gliomas

Options that can be discussed in a molecular tumor board

Altered Gene	Inhibitor
EGFR (activating varinats, e.g. vIII)	Osimertinib, Afatinib
PTEN, PIK3CA	Temsirolimus, Everolimus
NF1	Selumetinib, Trametinib
FGFR	Erdafitinib
MET	Capmatinib, Crizotinib
NTRK	Entrectinib, Larotrectinib
CDK4, CDK6, CDKN2A/B	Abemaciclib
PDGFRA	Regorafenib, Dasatinib
VEGFA (overexpression)	Bevacizumab

https://staging.asiabiotech.com/collective-wisdom-in-action/

Literature

- WHO Classification of Tumours Editorial Board. Central nervous system tumours. Lyon (France): International Agency for Research on Cancer; 2021 (WHO classification of tumours series, 5th ed.; vol. 6). Available from: https://tumourclassification.iarc.who.int/chapters/45.
- The 2021 WHO Classification of Tumors of the Central Nervous System: a summary (PMID: 34185076)
- Improved prognostic stratification of patients with isocitrate dehydrogenase-mutant astrocytoma (PMID: 38183430)
- Novel, improved grading system(s) for IDH-mutant astrocytic gliomas (PMID: 29687258)
- CDKN2A mutations have equivalent prognostic significance to homozygous deletion in IDH-mutant astrocytoma (PMID: 37550258)
- Pleomorphic xanthoastrocytoma is a heterogeneous entity with pTERT mutations prognosticating shorter survival (PMID: 35012690)
- Wick W. et al, Glioma, S2k guideline, 2021, in: German Society of Neurology, Guidelines for Diagnosis and Therapy in Neurology. Online: www.dgn.org/leitlinien (accessed on 03.07.2025
- https://clinicaltrials.gov/

Thank You!

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BANGLADESH SOCIETY FOR BREAST CANCER STUDY BSBCS

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CME on

Management of Brain tumors in New Era 2025

Sunday, 27th July, 2025 || 2:00 to 4:00 PM (Lunch will be served from 2:00 PM)

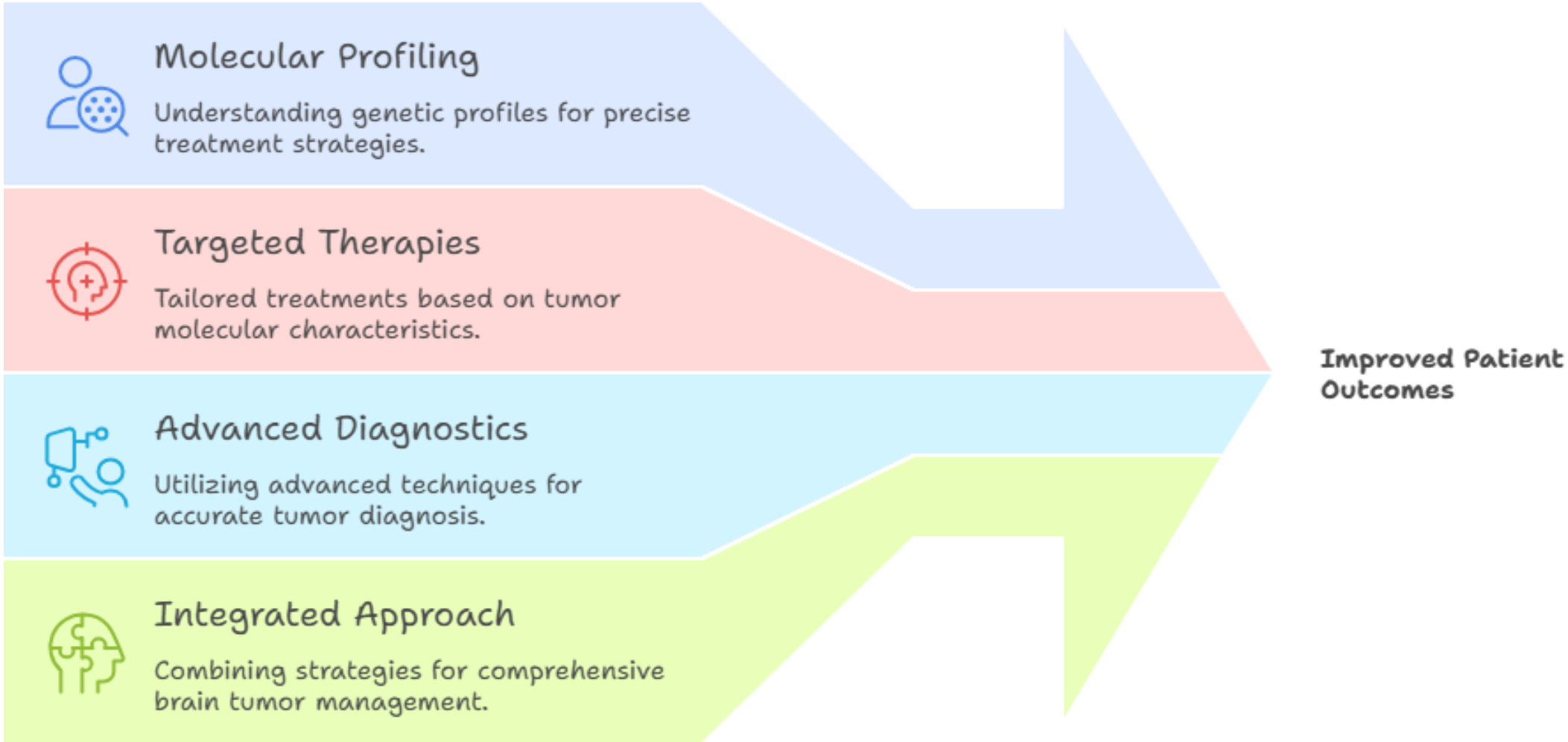
Dr. Mukut Hall, Bangladesh Specialized Hospital PLC

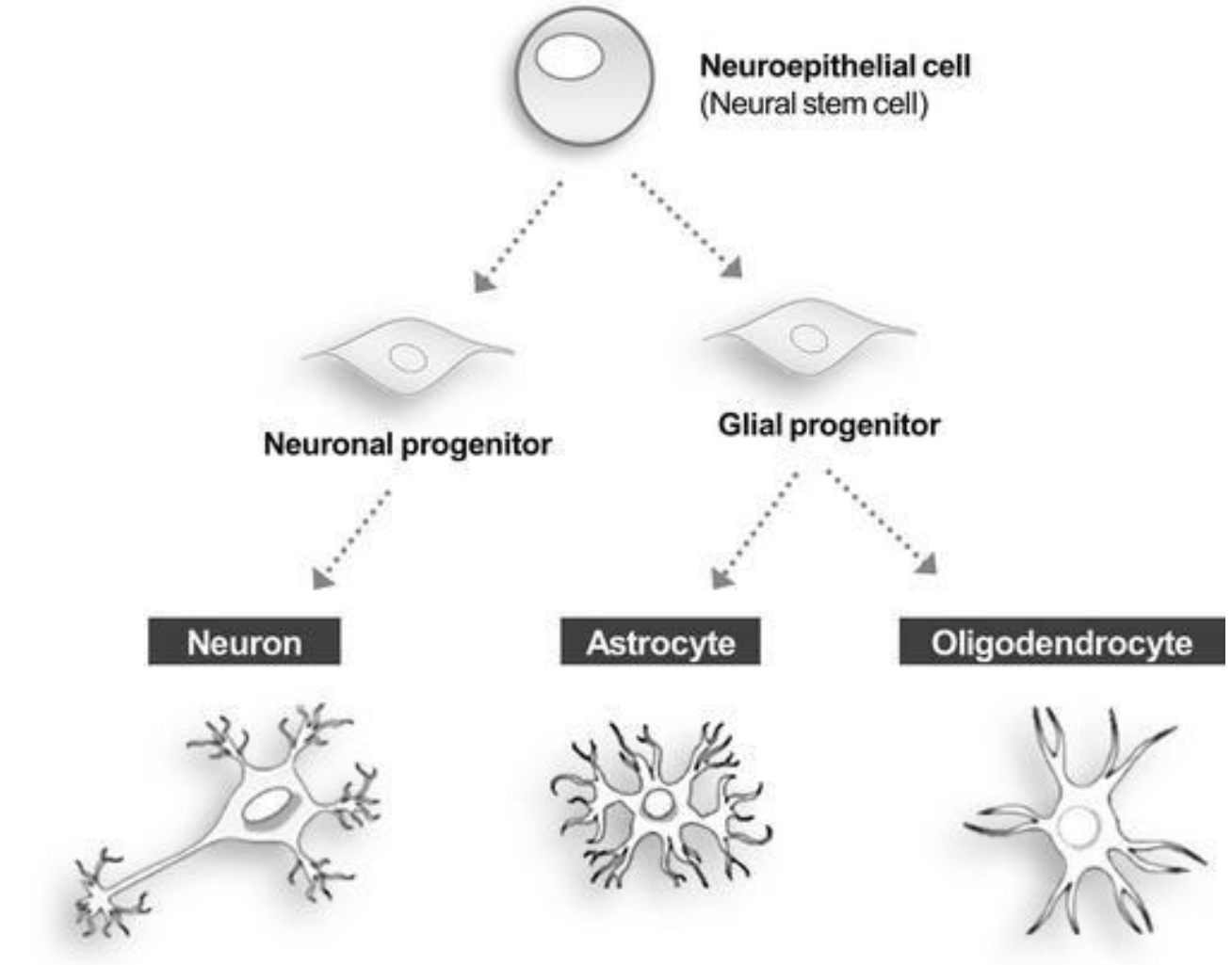
Integrated Management of Brain tumors based on Molecular signature

Dr Rajesh Balakrishnan
Professor - Radiation Oncology
DMG - Breast / Neuro-oncology / Paed Rad Onc
CMC Vellore

rajeshb@cmcvellore.ac.in

Precision in Brain Tumor Management

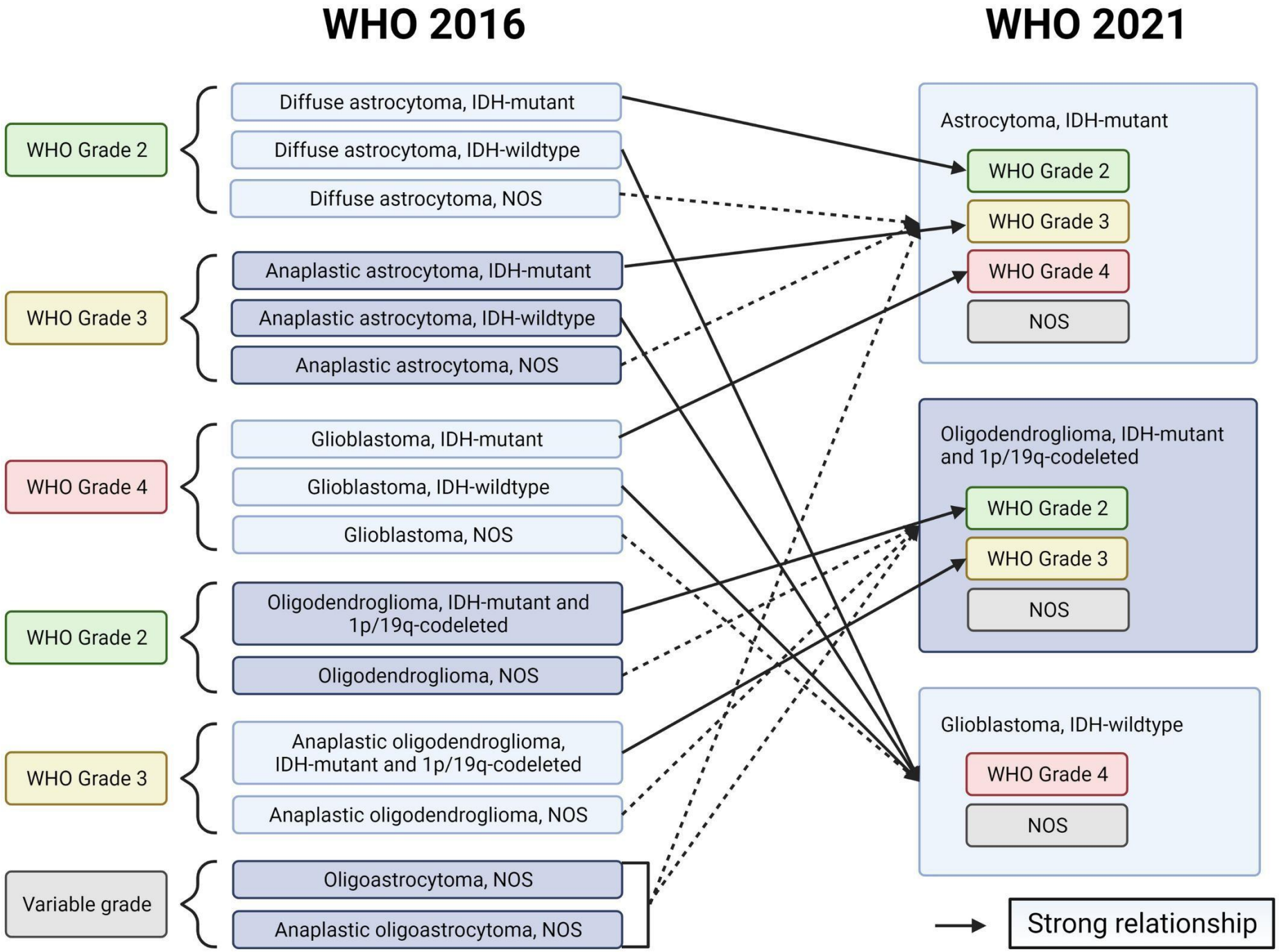




Glioneuronal Tumors | Gliomas | Oligodendrogliomas

https://onlinelibrary.wiley.com/doi/full/10.1002/jmri.29016

2016 Vs 2021



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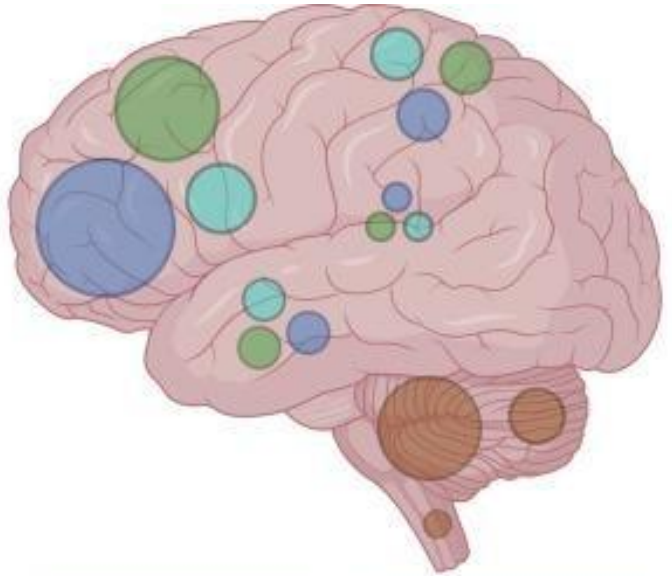
7 Molecular tests required
Classification - Gliomas - (WHO 2021)

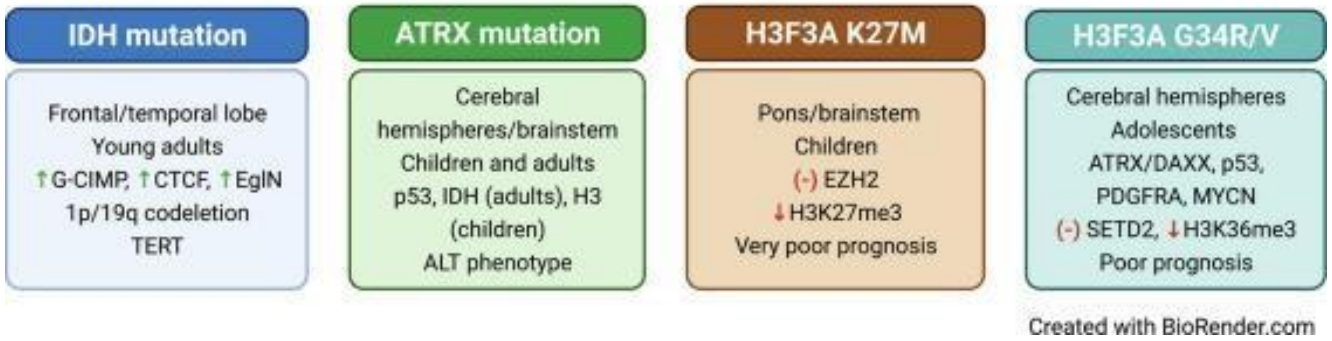
Isocitrate Dehydrogenase (IDH 1/ IDH2) mutations	IHC
Alpha Thalassemia /Mental retardation syndrome X related gene Expression (ATRX)	IHC
1p /19 q codeletion	MLPA /FISH
CDKN2A/B homozygous deletion on 9p21	MLPA /FISH
TERT mutation /EGFR Gene amplification and/or Chromosome 7 gain and 10 loss (+7/ -10)	MLPA /FISH
Histone H3 K27M mutations	IHC
Histone H3 G34R/V mutations	IHC

Multiplex Ligation dependent Probe Amplification

Location of Tumors and Mutations

IDH mutations – Frontal / Temporal lobes
ATRX mutations – Brainstem / Cerebral hemispheres
H3K27 mutations – Midline – pons / brainstem
H3G34 mutations – Cerebral hemispheres





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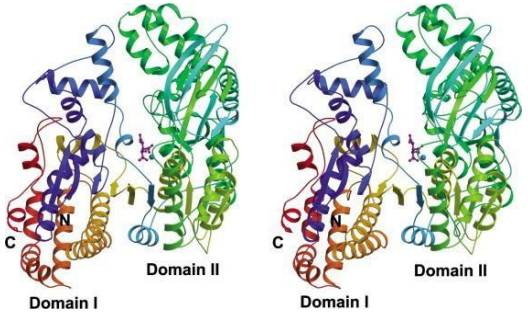
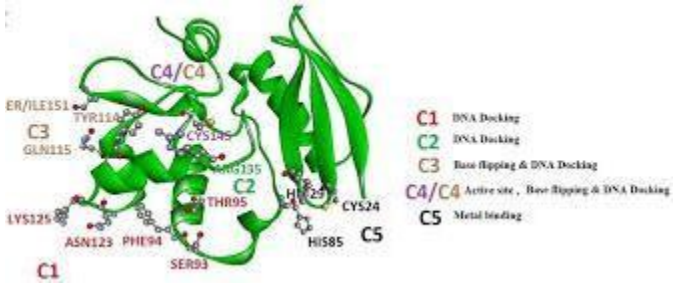
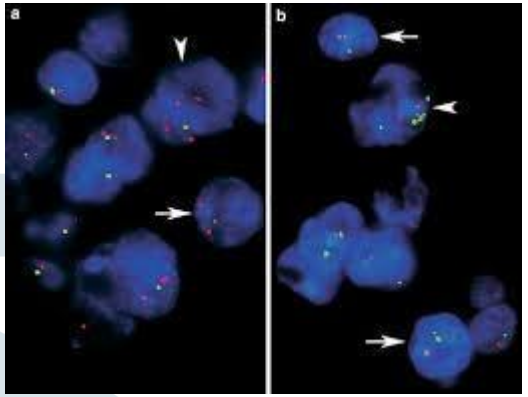
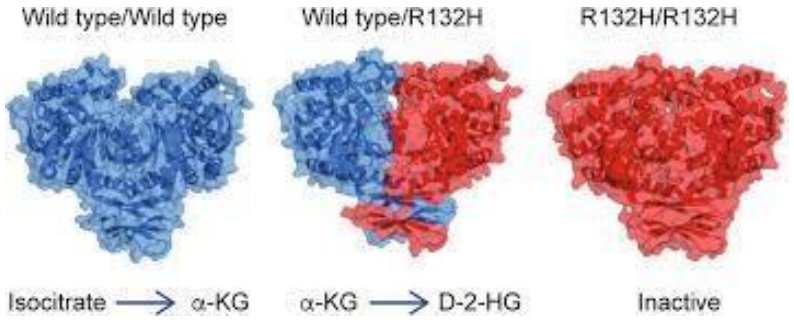
Dharmaiah S, Huse JT. The epigenetic dysfunction underlying malignant glioma pathogenesis. Laboratory Investigation. 2022 Jul 1;102(7):682-90.







Management based on Molecular classification



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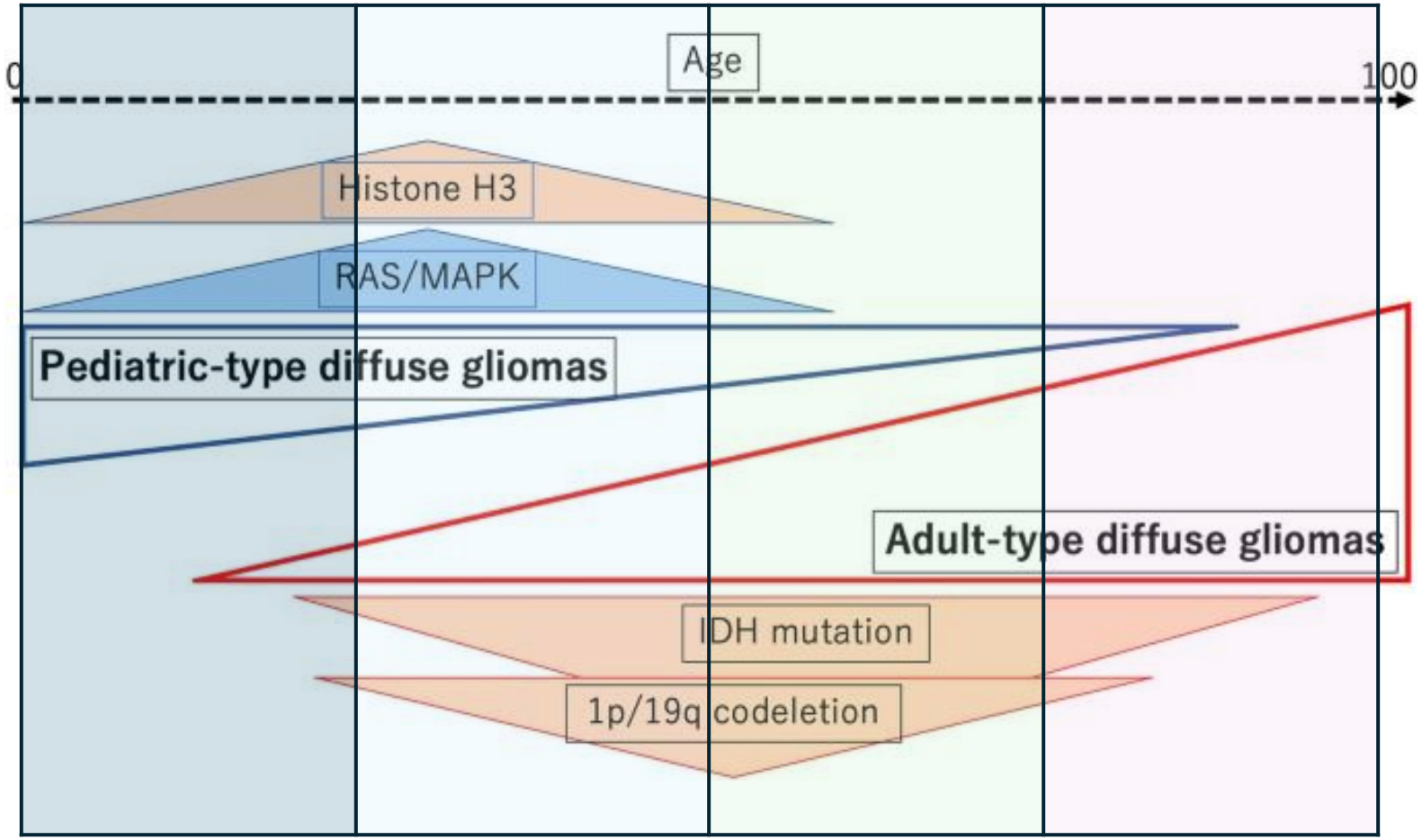
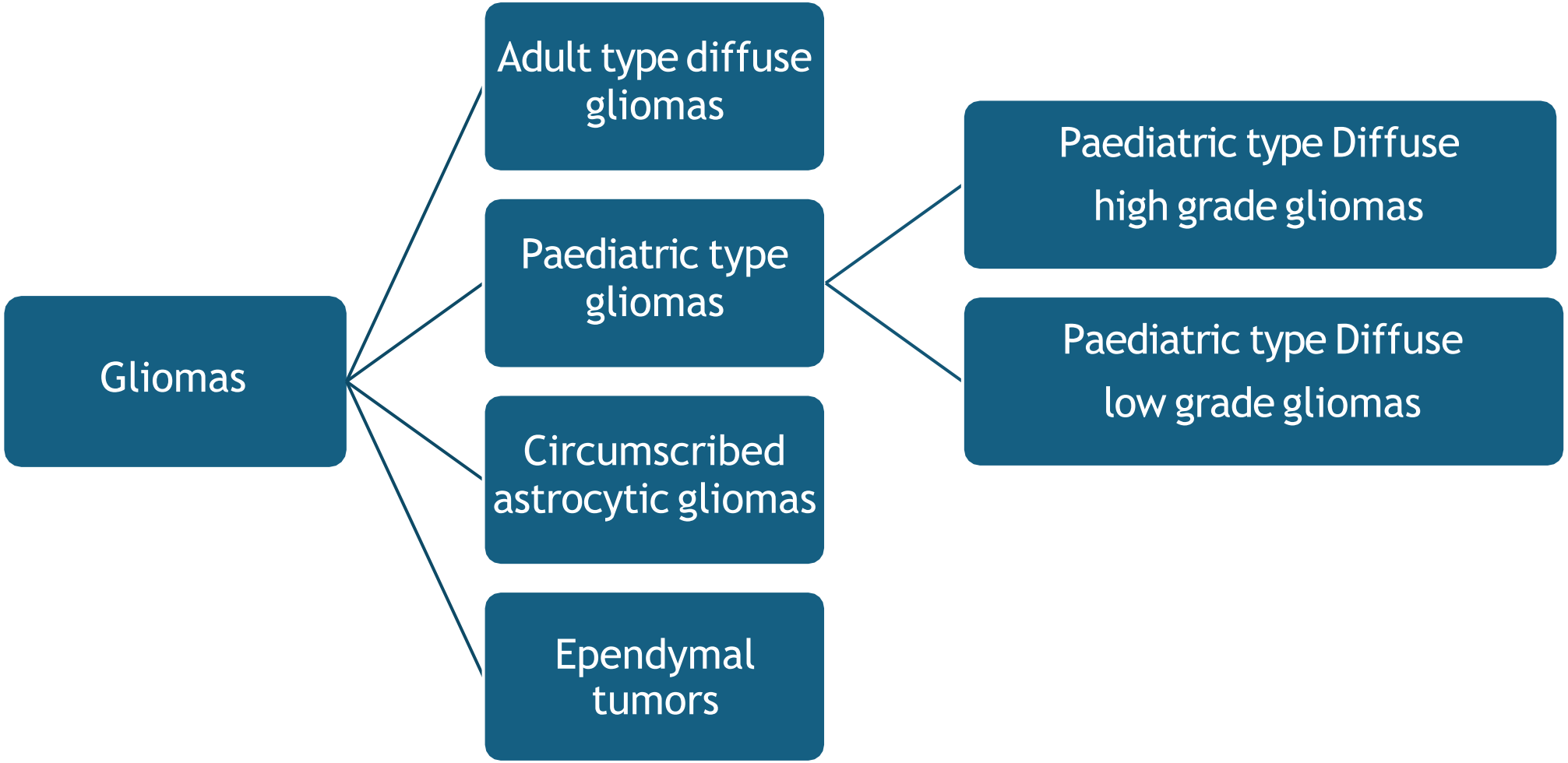
Note that the pediatric type may occur in adults, and vice versa

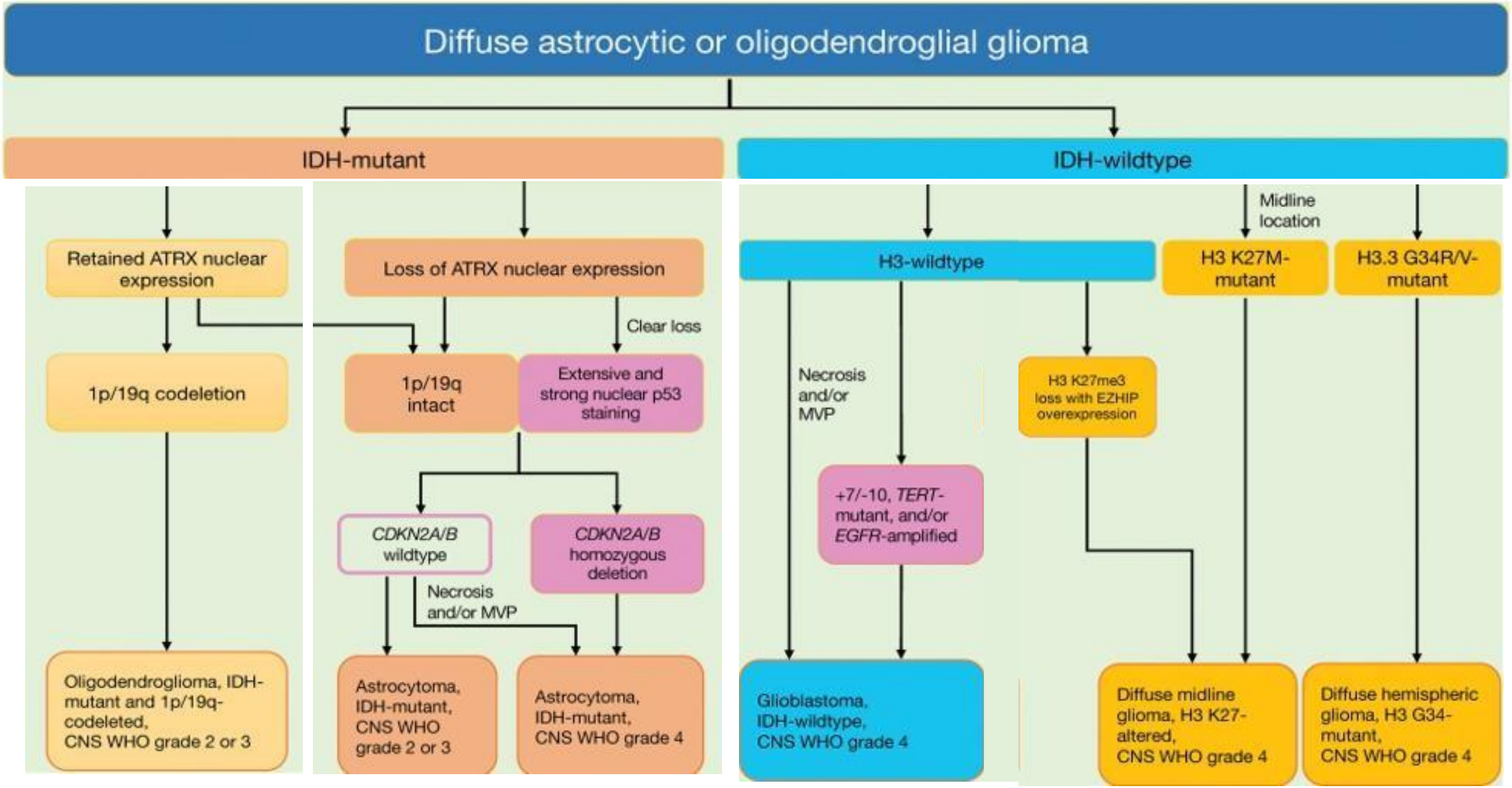


Komori T. The molecular framework of pediatric-type diffuse gliomas: shifting toward the revision of the WHO classification of tumors of the CNS. Brain Tumor Pathology. 2021 Jan;38(1):1-3.

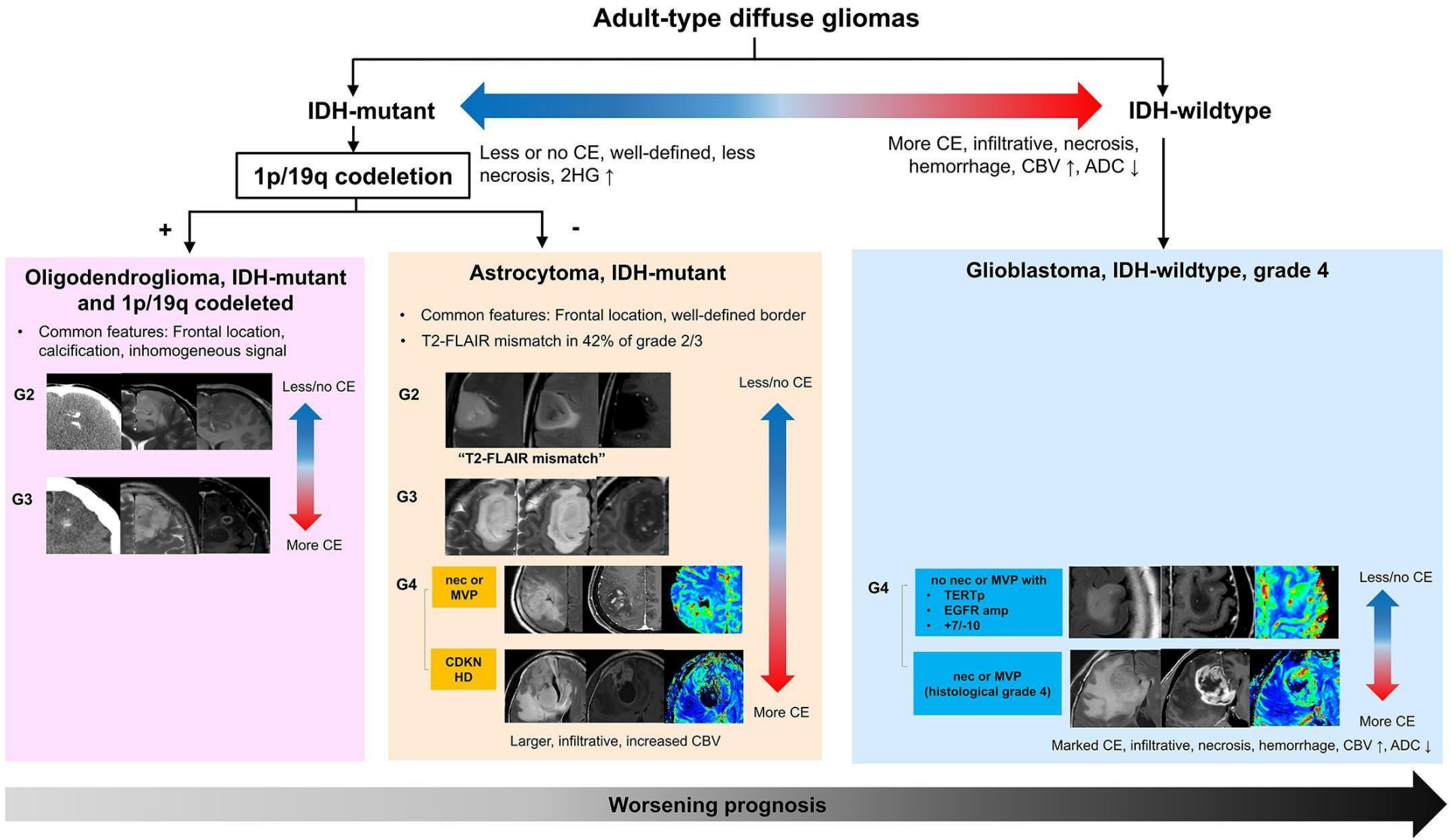
WHO CNS 5 - 2021 Classification



Kurokawa R. Published Online: July 08, 2022
https://doi.org/10.1148/rg.210236



Adult-Type Diffuse Gliomas



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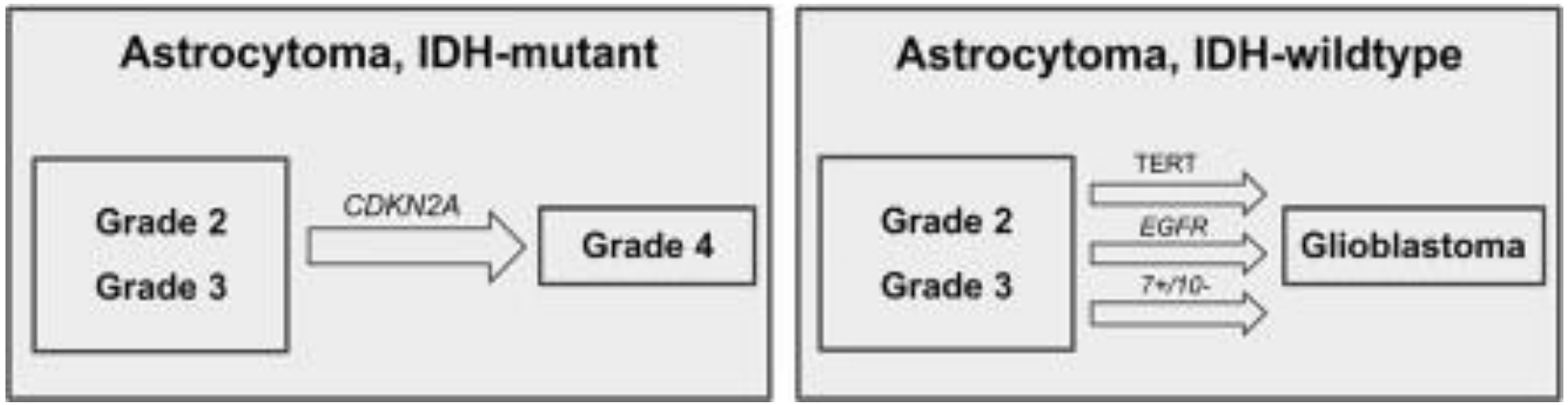
Astrocytoma grading based on genetic alterations WHO CNS5 2021



https://link.springer.com/article/10.1007/s40291-022-00612-3

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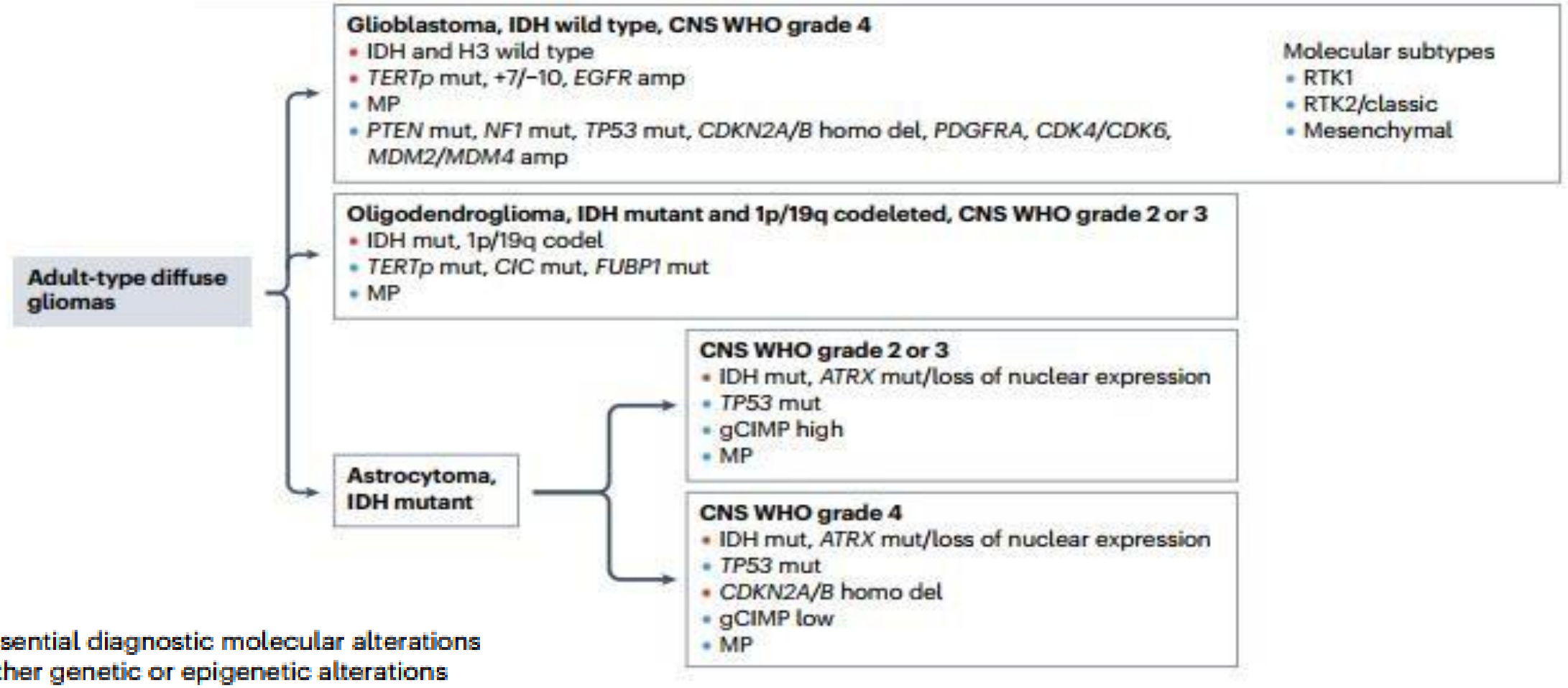
Adult Type Diffuse Gliomas



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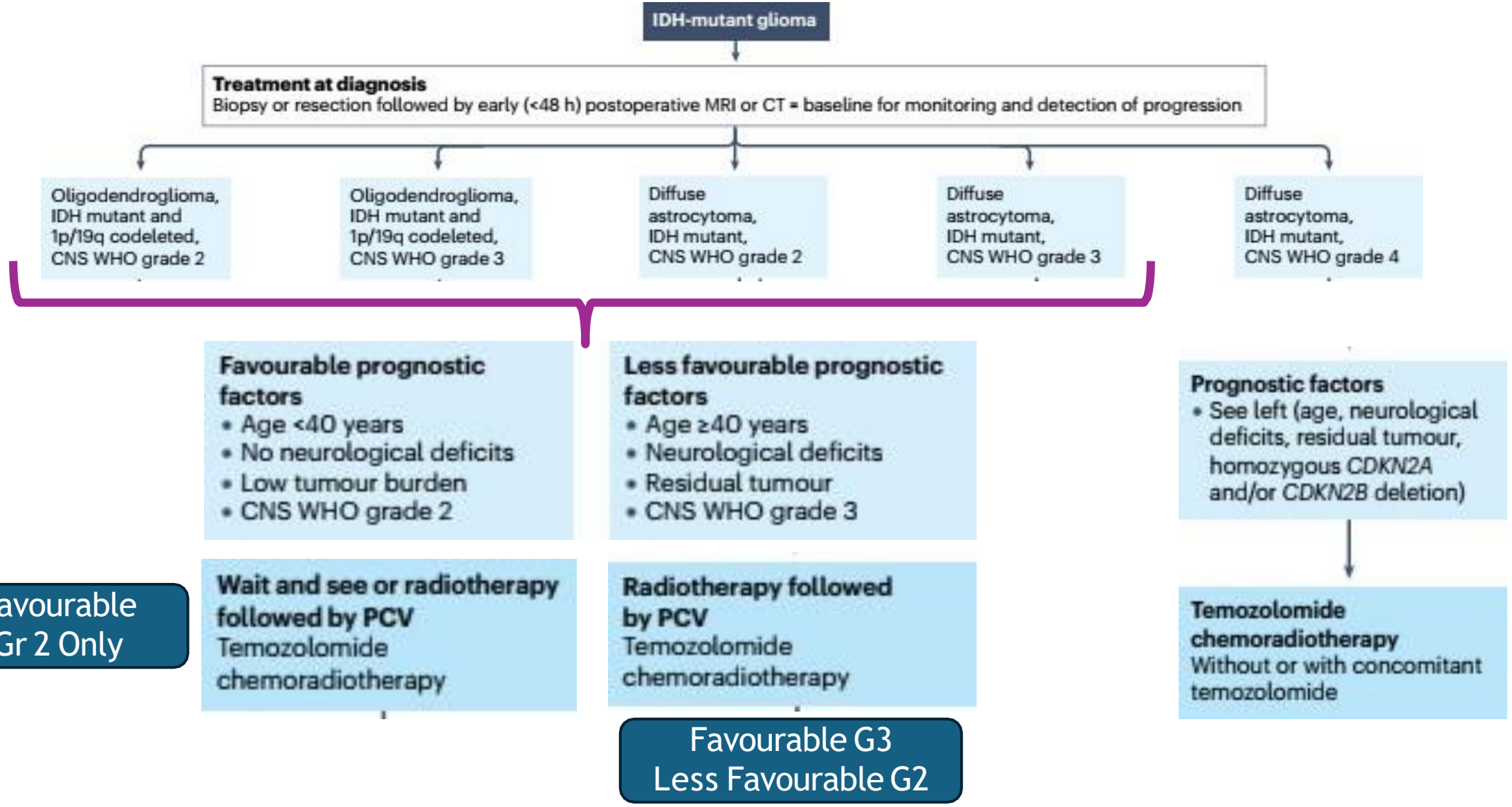
Nature Reviews Disease Primers | (2024) 10:33

IDH Mutant Glioma
Management



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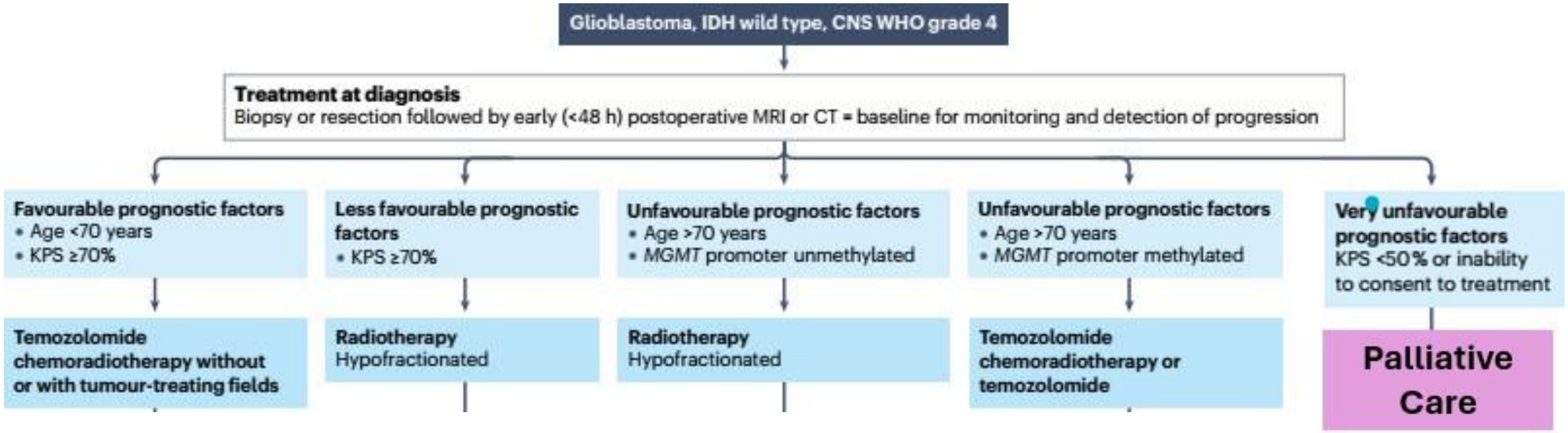
IDH wt / Glioblastoma
Management



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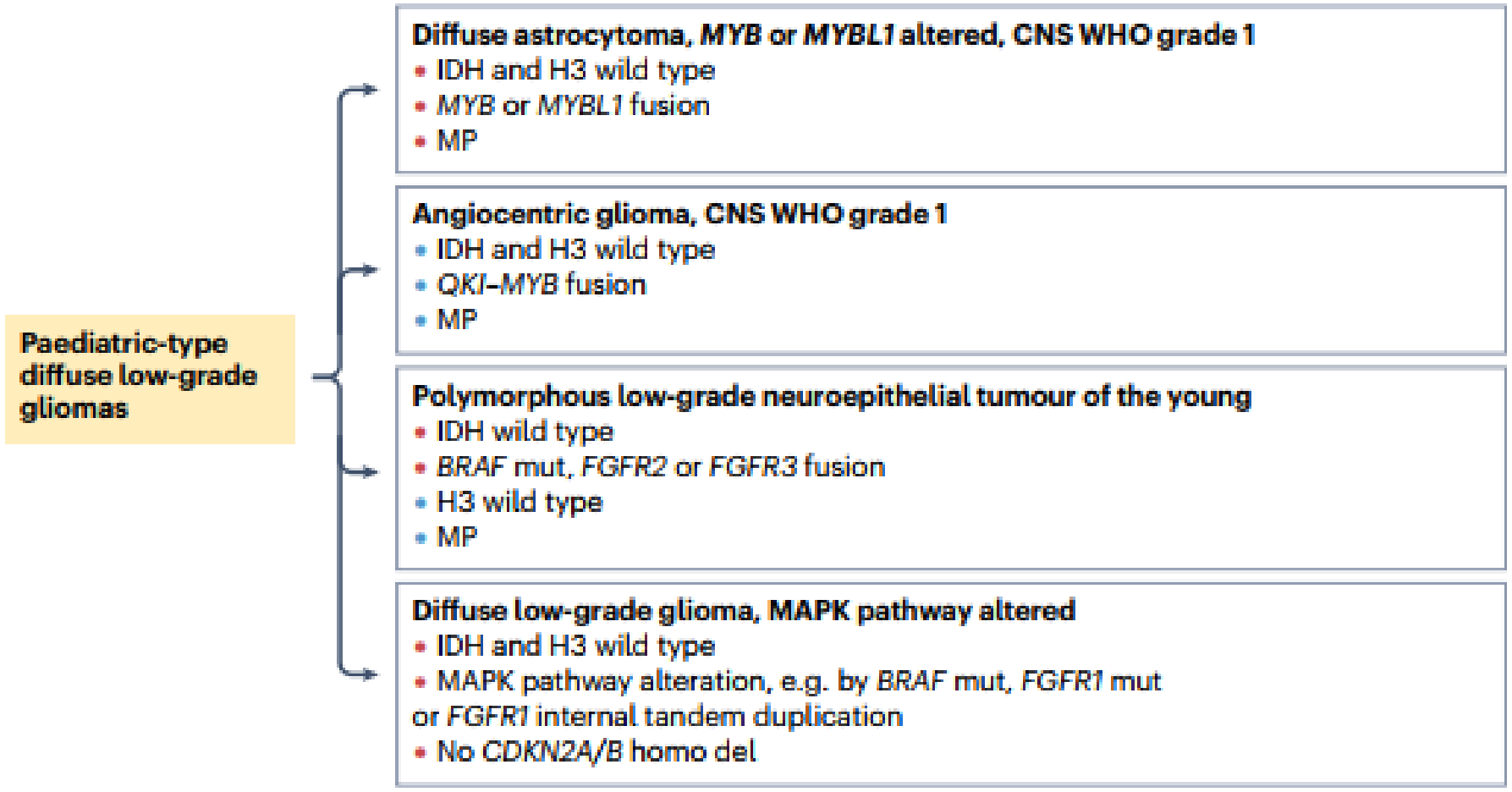
Paediatric Type Diffuse Low Grade Gliomas



- Essential diagnostic molecular alterations
- Other genetic or epigenetic alterations

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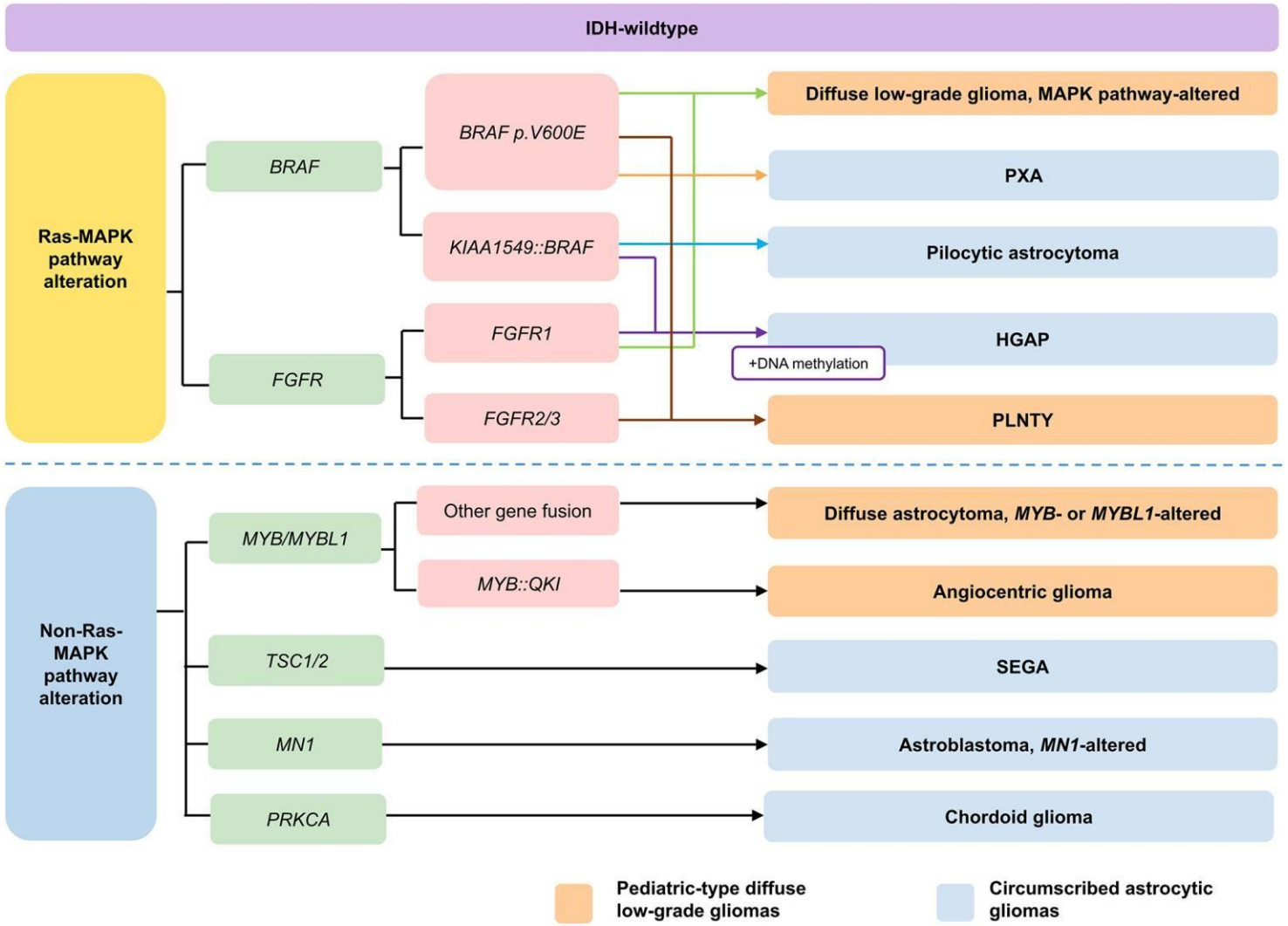
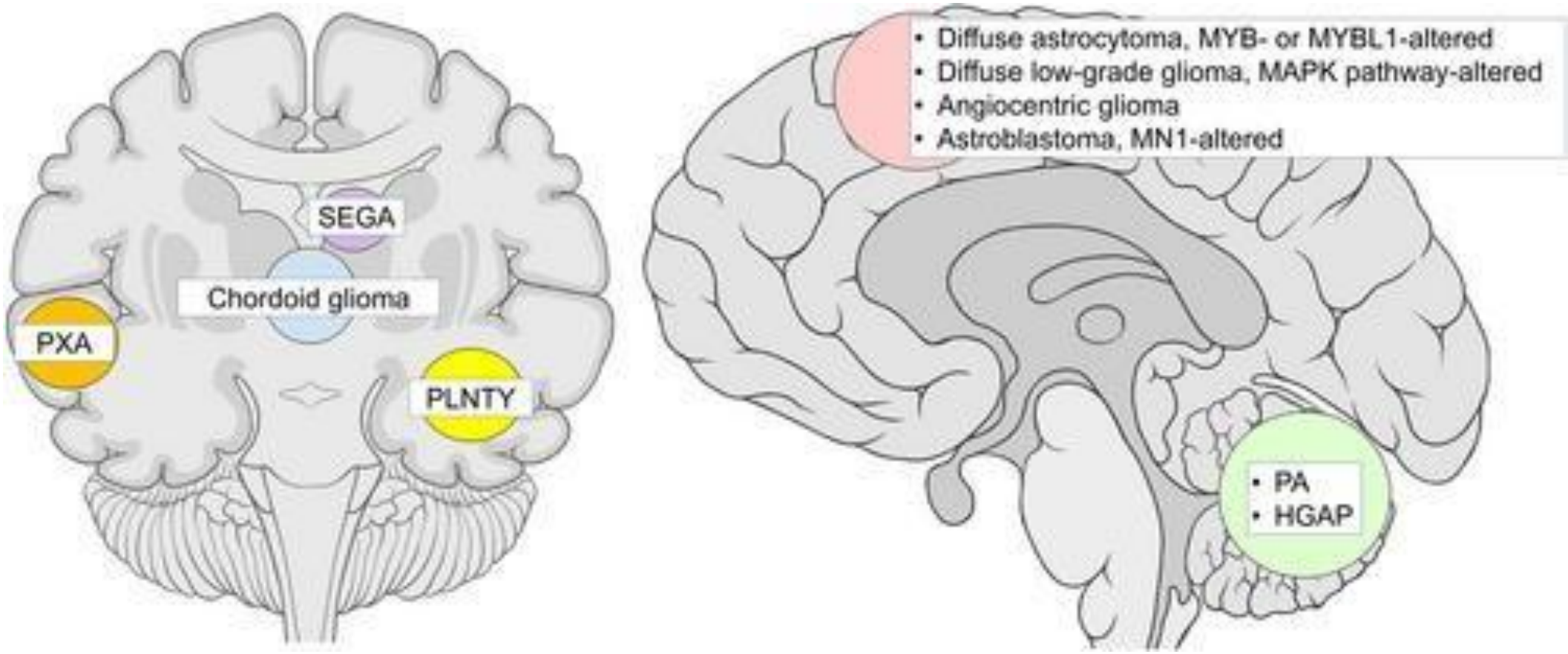
Paediatric Type Diffuse Low Grade Gliomas



https://doi.org/10.1002/jmri.28740

Paediatric Type Diffuse Low Grade Gliomas



https://doi.org/10.1002/jmri.28740

Paediatric-type Diffuse Low grade gliomas
Management

Low Risk for Progression

High Risk for Progression

1

Carboplatin and Vincristine

Carboplatin and Vincristine are used for high-risk, traditional chemotherapy.

2

MEK Inhibitors

MEK Inhibitors are effective for high-risk, targeted therapy.

3

Monitoring

Monitoring is suitable for low-risk, traditional management.

4

Molecularly Targeted Agents

Molecularly Targeted Agents are effective for low-risk, targeted therapy.

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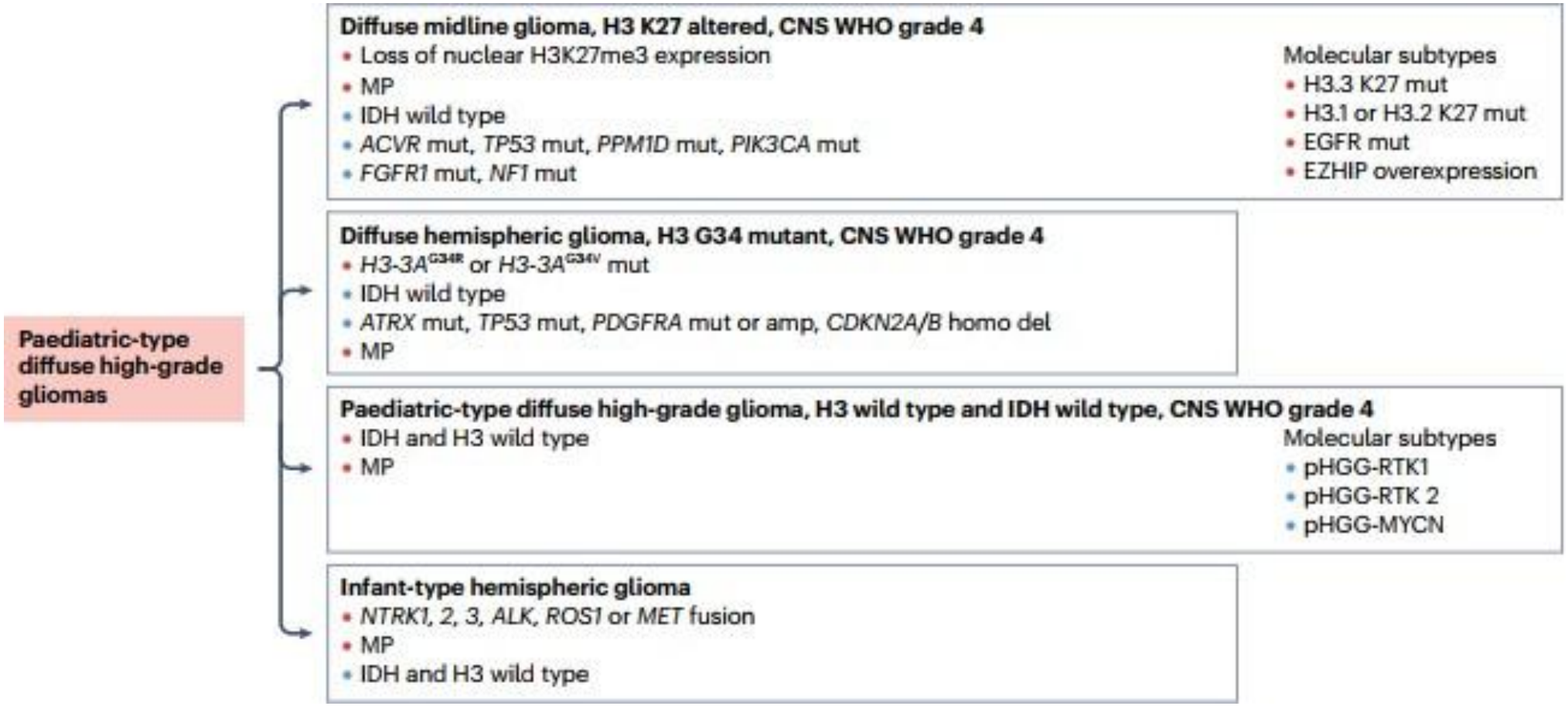
Paediatric Type Diffuse High Grade Gliomas



- Essential diagnostic molecular alterations
- Other genetic or epigenetic alterations

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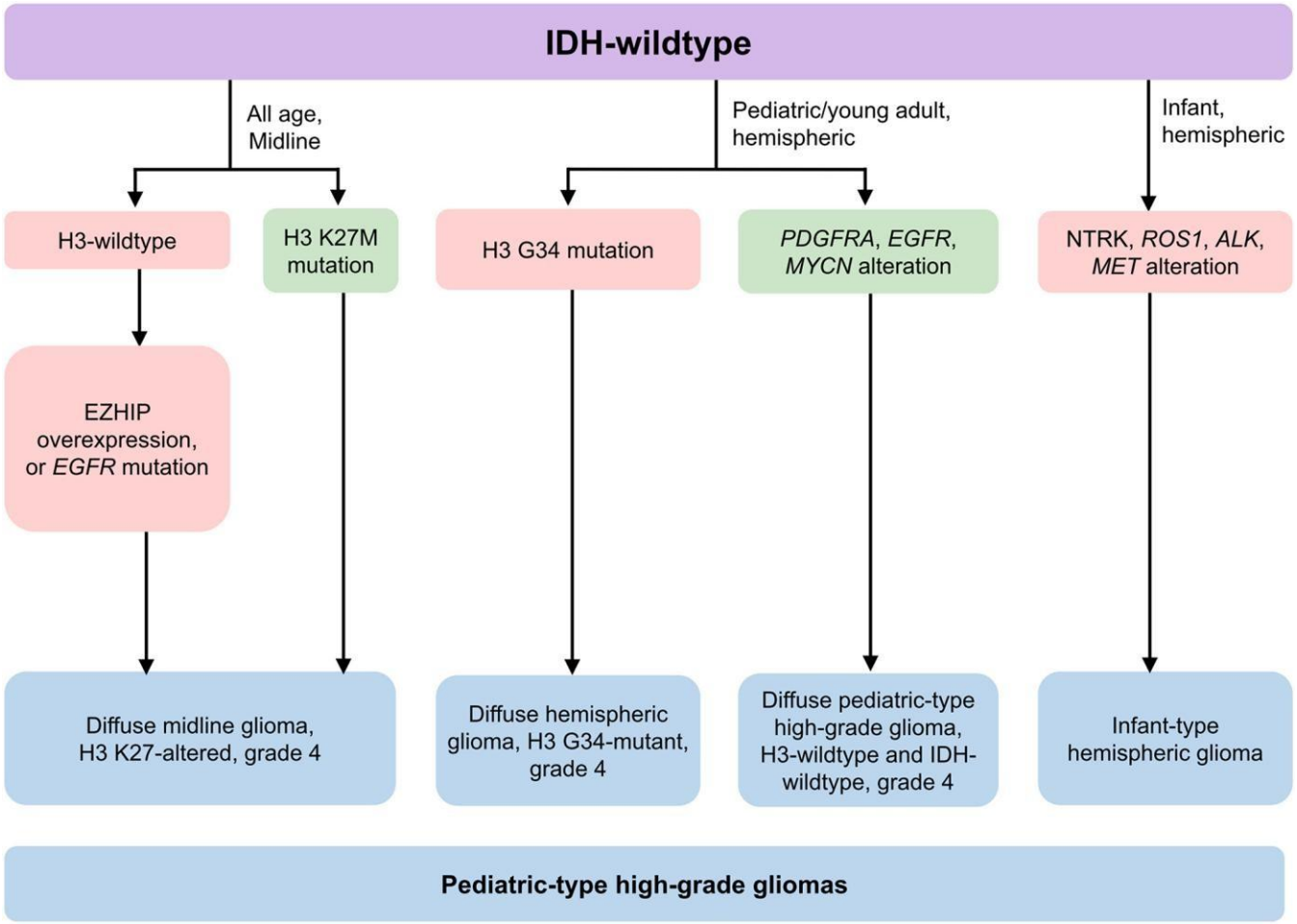
Paediatric Type Diffuse High Grade Gliomas
Classification



https://doi.org/10.1002/jmri.28740

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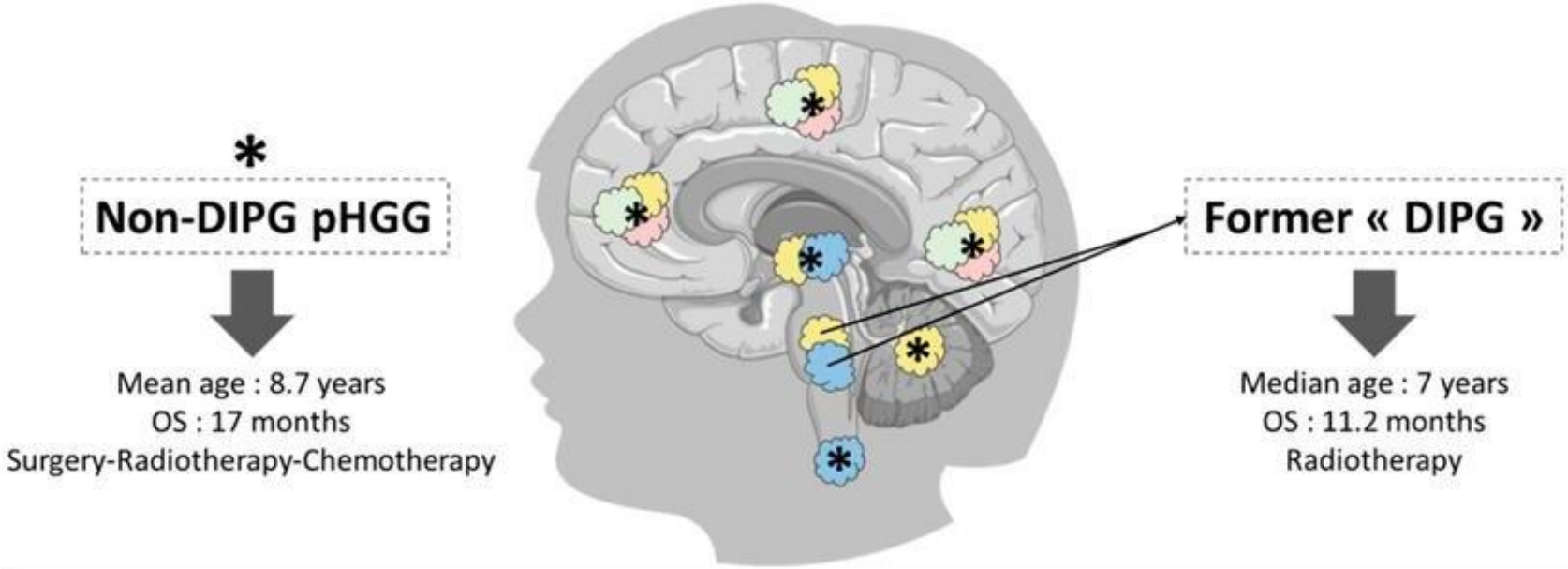
Paediatric Type Diffuse High Grade Gliomas
Prognosis

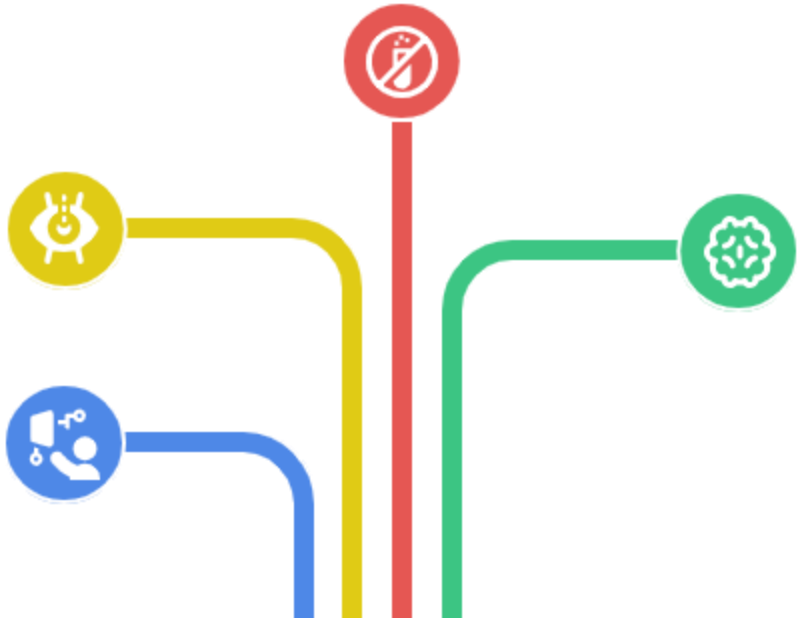


WHO CNS5 pHGG subtypes	Locations	Molecular characteristics
(a) DMG H3 K27-Altered	Thalamus, brainstem or spinal cord	Mutation K27M in *H3F3A* or *HIST1H3B* ; *EZHIP* overexpression
(b) Diffuse hemispheric glioma, H3 G34-mutant	Cerebral hemispheres	Mutation G34R or G34V in *H3F3A*
(c) Diffuse pHGG H3-WT and IDH-WT	Supratentorial, brain stem or cerebellum	MYCN or RTK1 or RTK2 amplification etc.
(d) Infant-type hemispheric glioma	Cerebral hemispheres	Fusion genes *ALK*, *ROS1*, *NTRK1/2/3*, or *MET*

Paediatric-type diffuse High grade gliomas
H3K27 Altered / Diffuse midline glioma
Management

Avoid Chemotherapy

Traditional chemotherapeutics like TMZ are ineffective due to lack of MGMT promoter methylation.



Focal Radiotherapy

Standard of care for these tumours.

Stereotactic Biopsy

Essential for molecular diagnosis and clinical trial enrolment due to infeasibility of surgical resection.

Re-irradiation

Offers potential benefits in symptom improvement and survival at progression.

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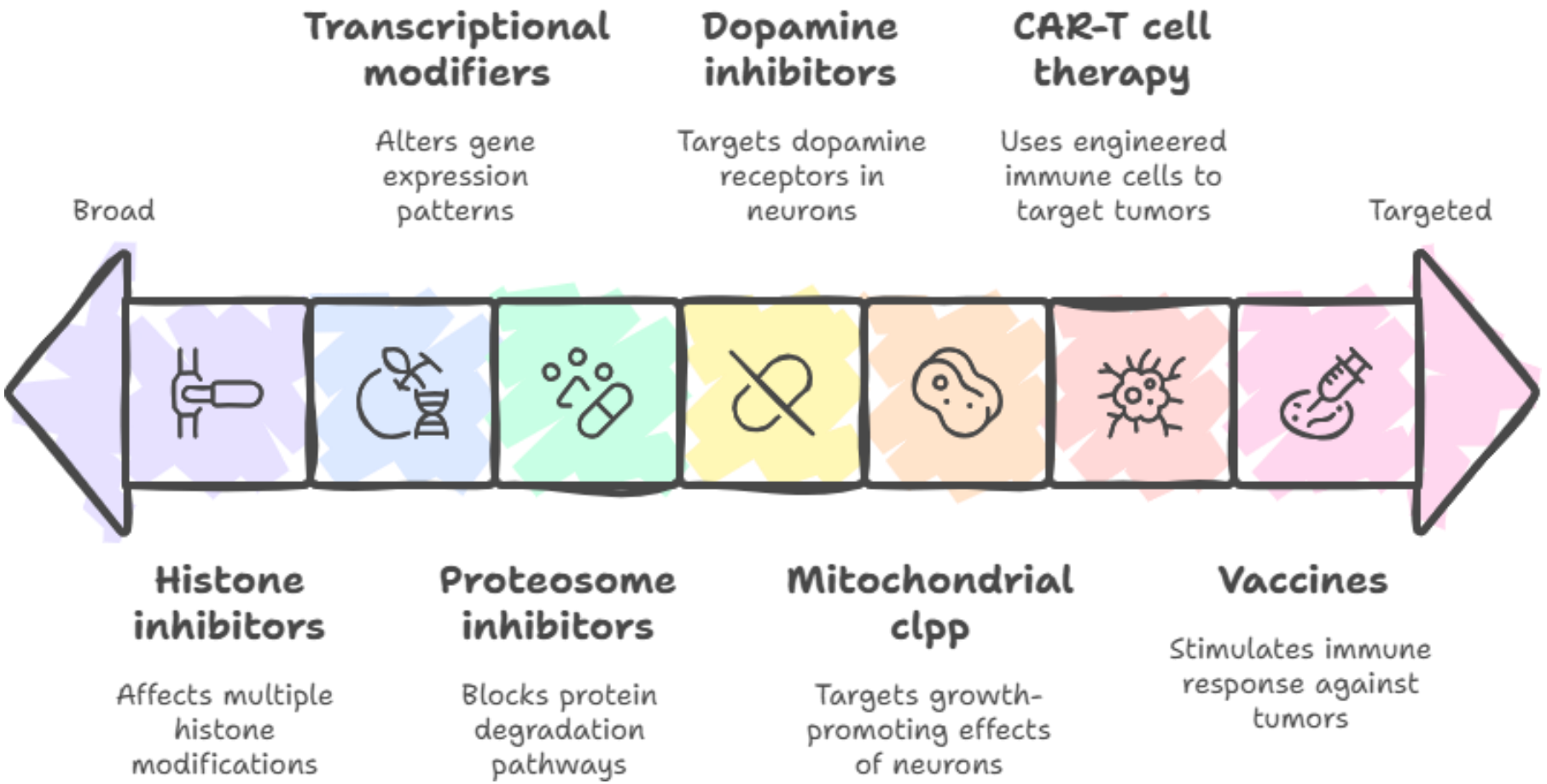
Paediatric-type diffuse High grade gliomas
Management - Epigenetic Therapy



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H3 G34-mutant Diffuse hemispheric gliomas
Management

Disseminated Disease

Whole-Brain Radiotherapy

Whole-brain radiotherapy addresses widespread disease with low methylation.

MGMT Unmethylated

Focal Radiotherapy

Local field radiotherapy targets localized disease with low methylation.

Limited Disease

Temozolomide with Radiotherapy

Temozolomide enhances radiotherapy effectiveness in widespread, methylated tumors.

MGMT Methylated

Surgical Resection

Surgical resection is effective for localized, methylated tumors.

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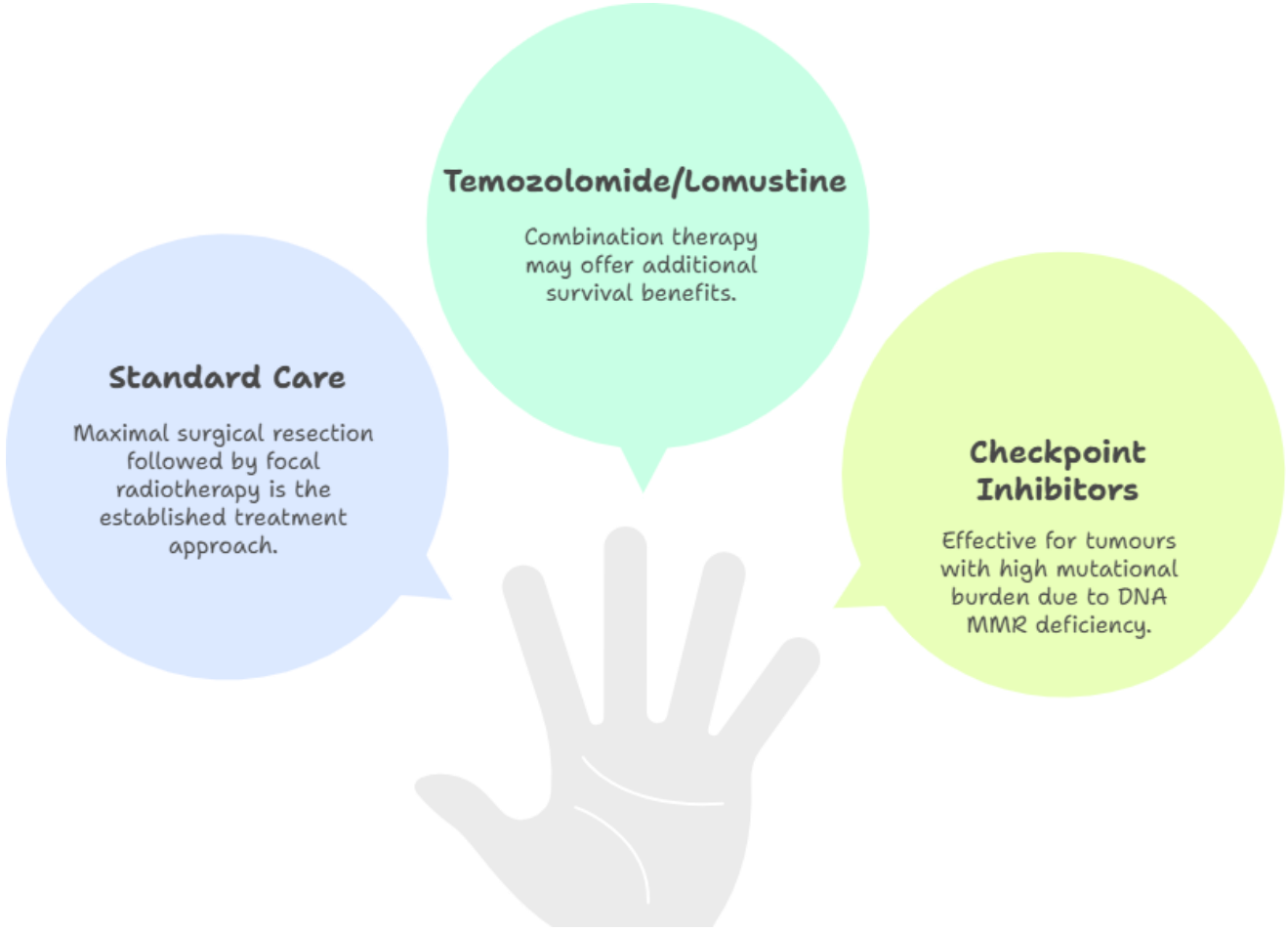
Paediatric-type diffuse High grade gliomas H3 Wild type / IDH wt

Management



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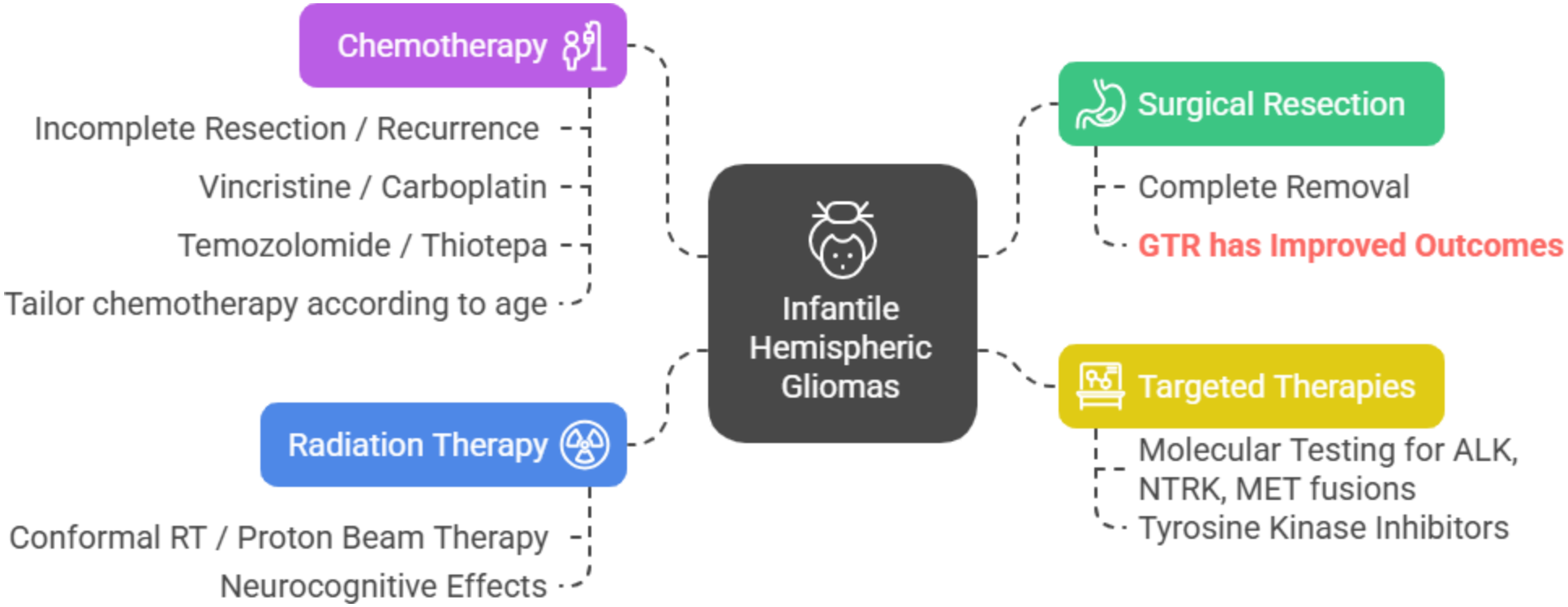
Paediatric-type diffuse High grade gliomas
Infantile Hemispheric Gliomas
Management



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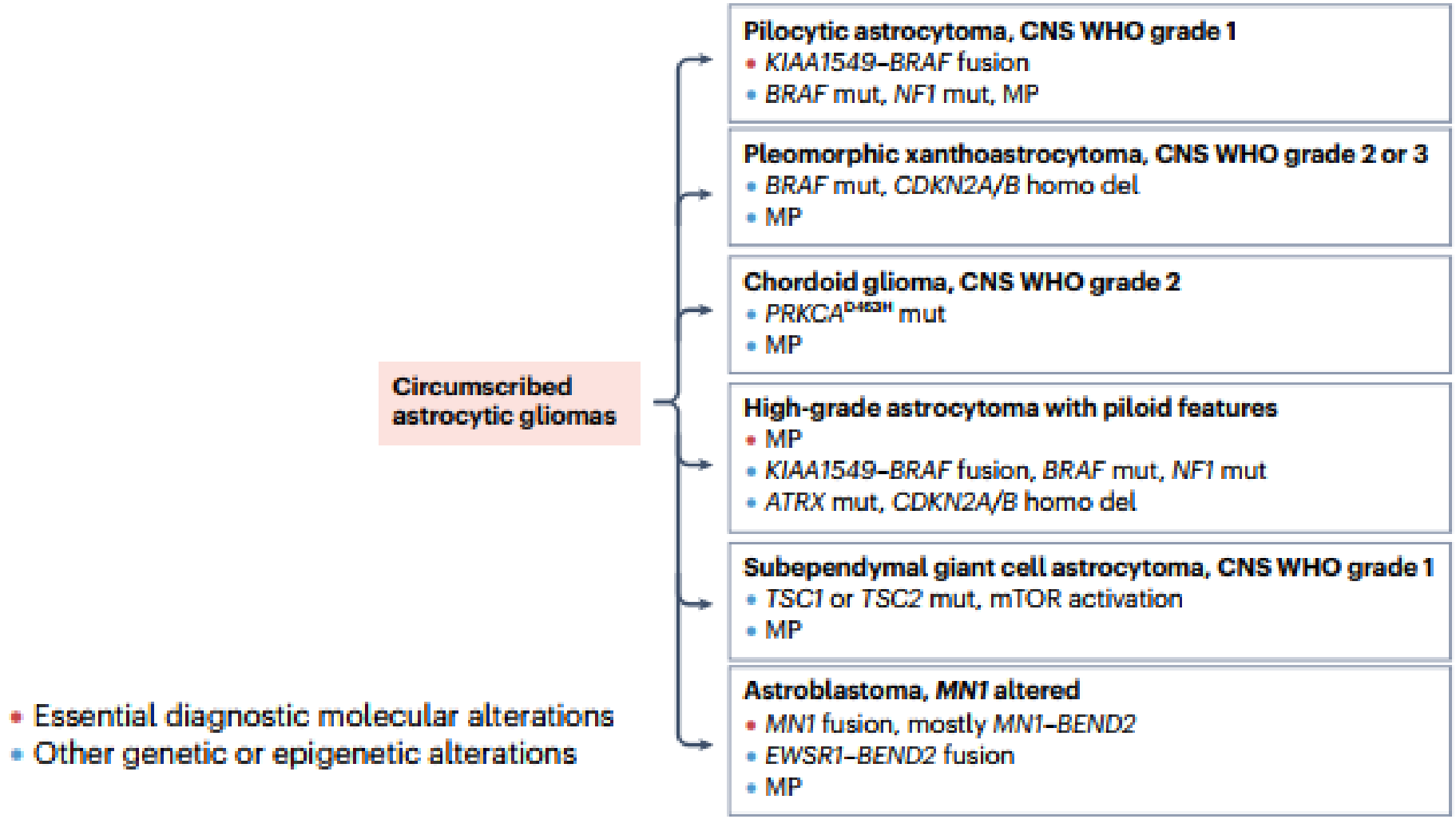
Circumscribed Astrocytic Gliomas



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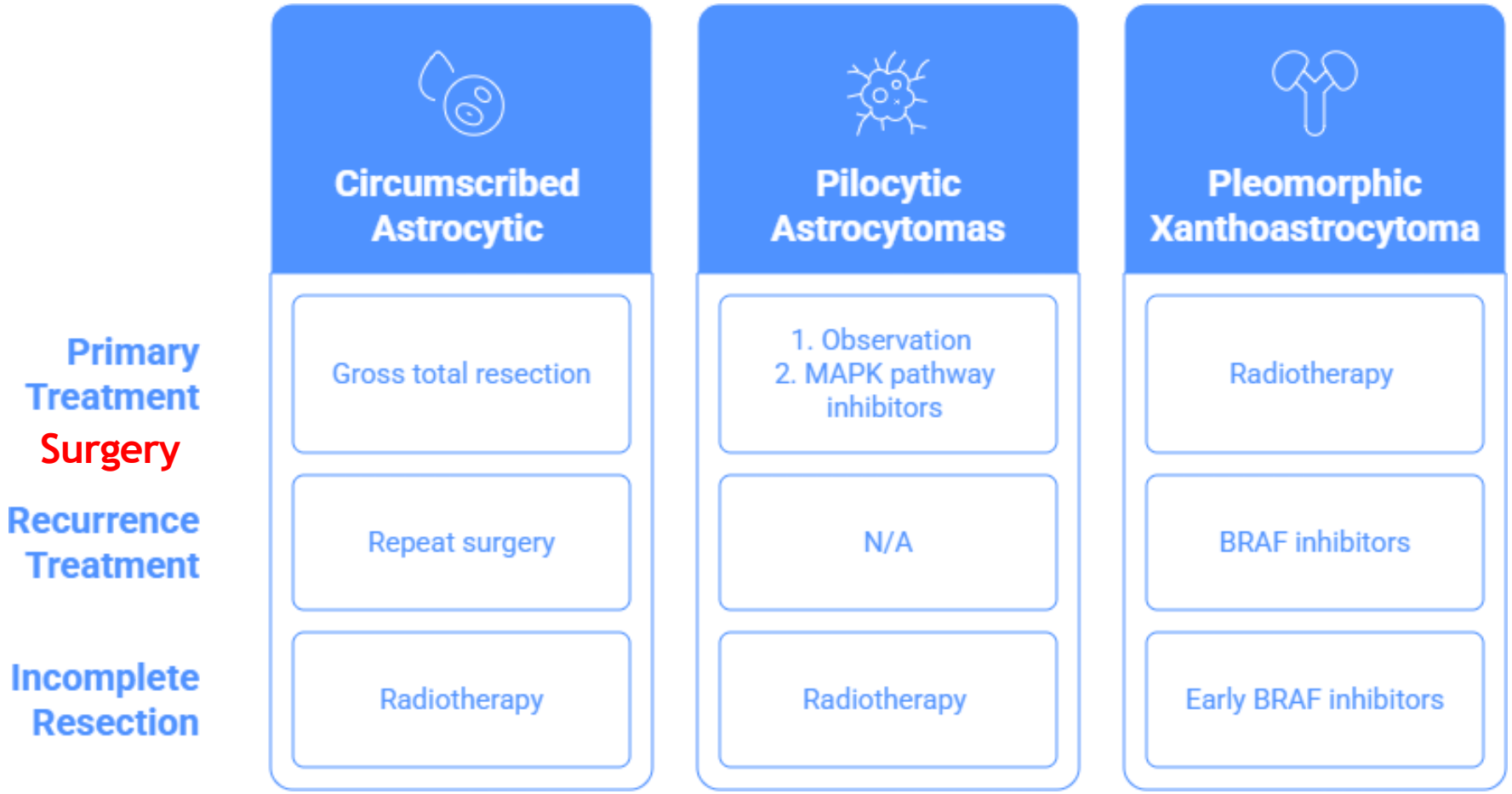
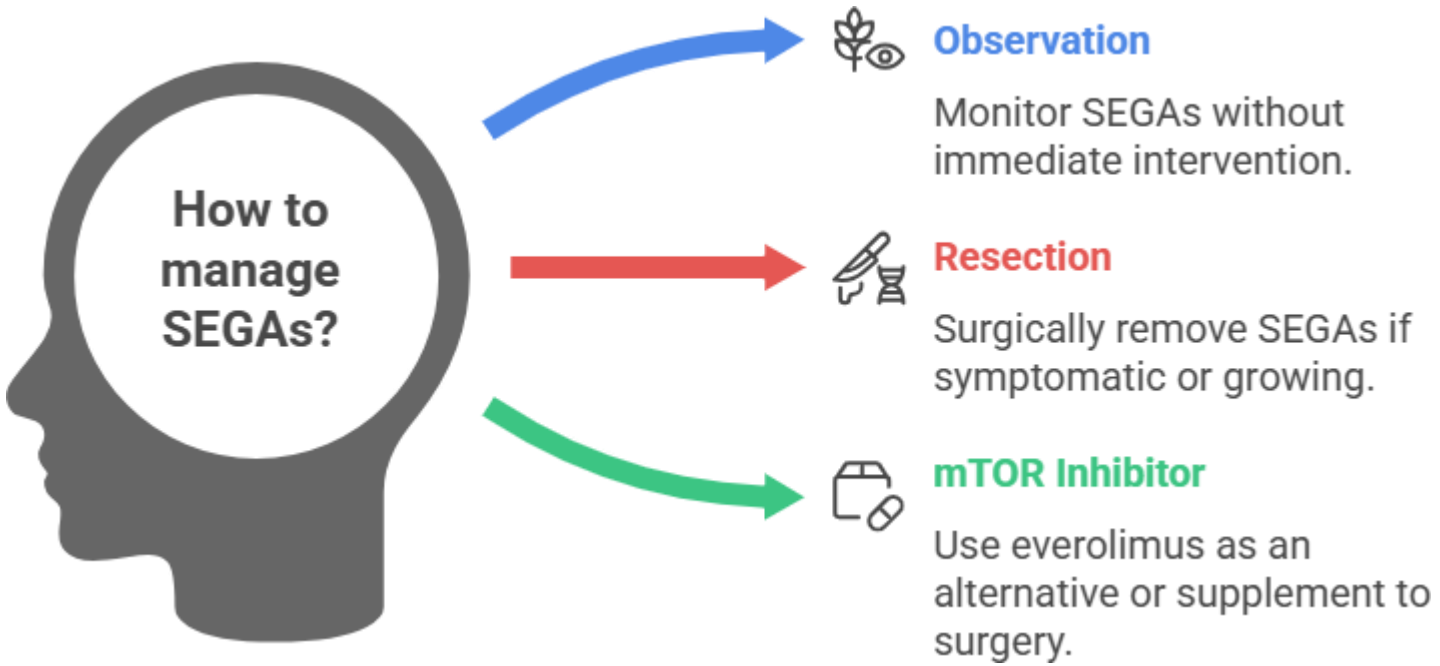
Circumscribed astrocytic gliomas

Management

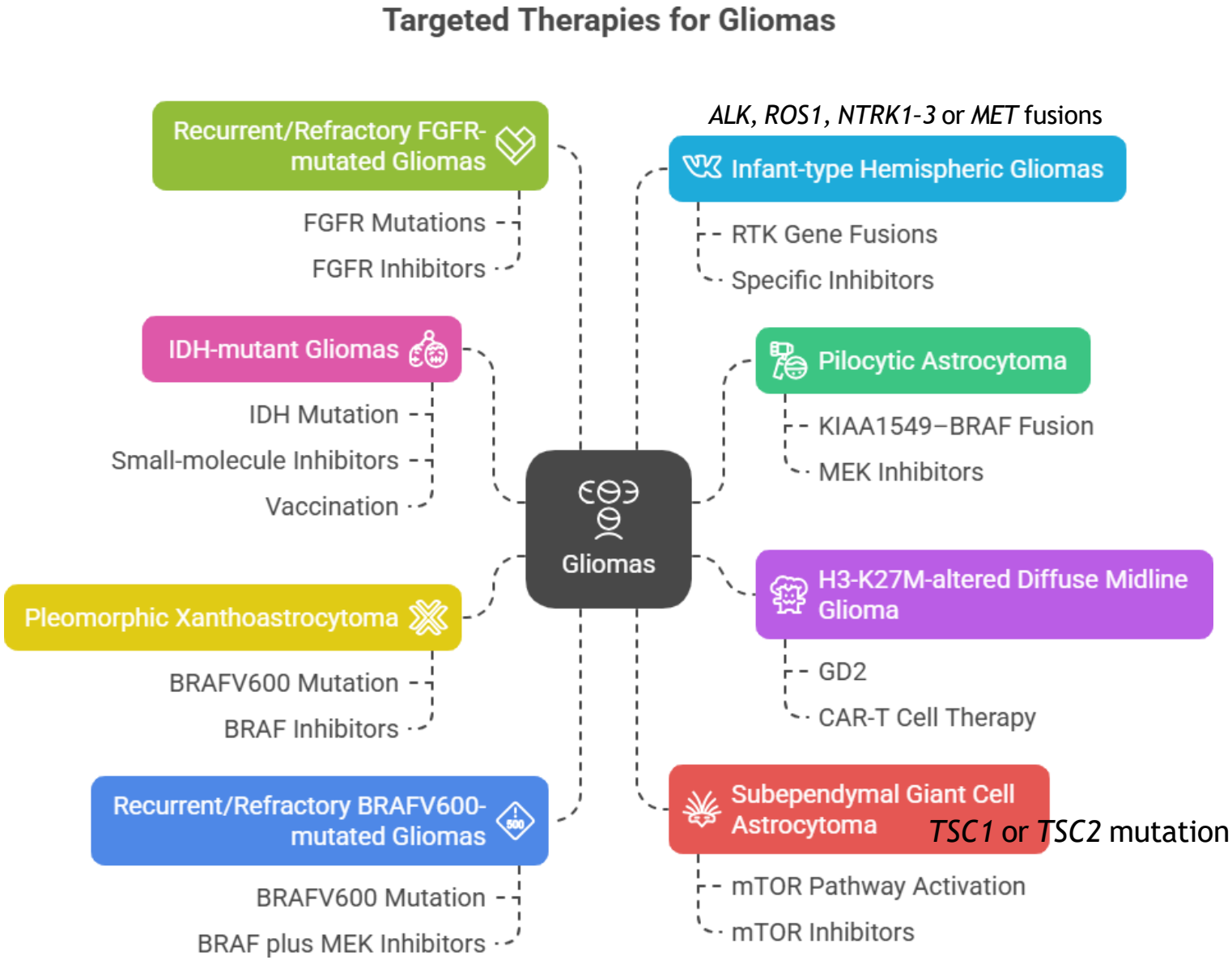


Circumscribed astrocytic gliomas

Management



Emerging molecularly targeted treatment options for patients with glioma



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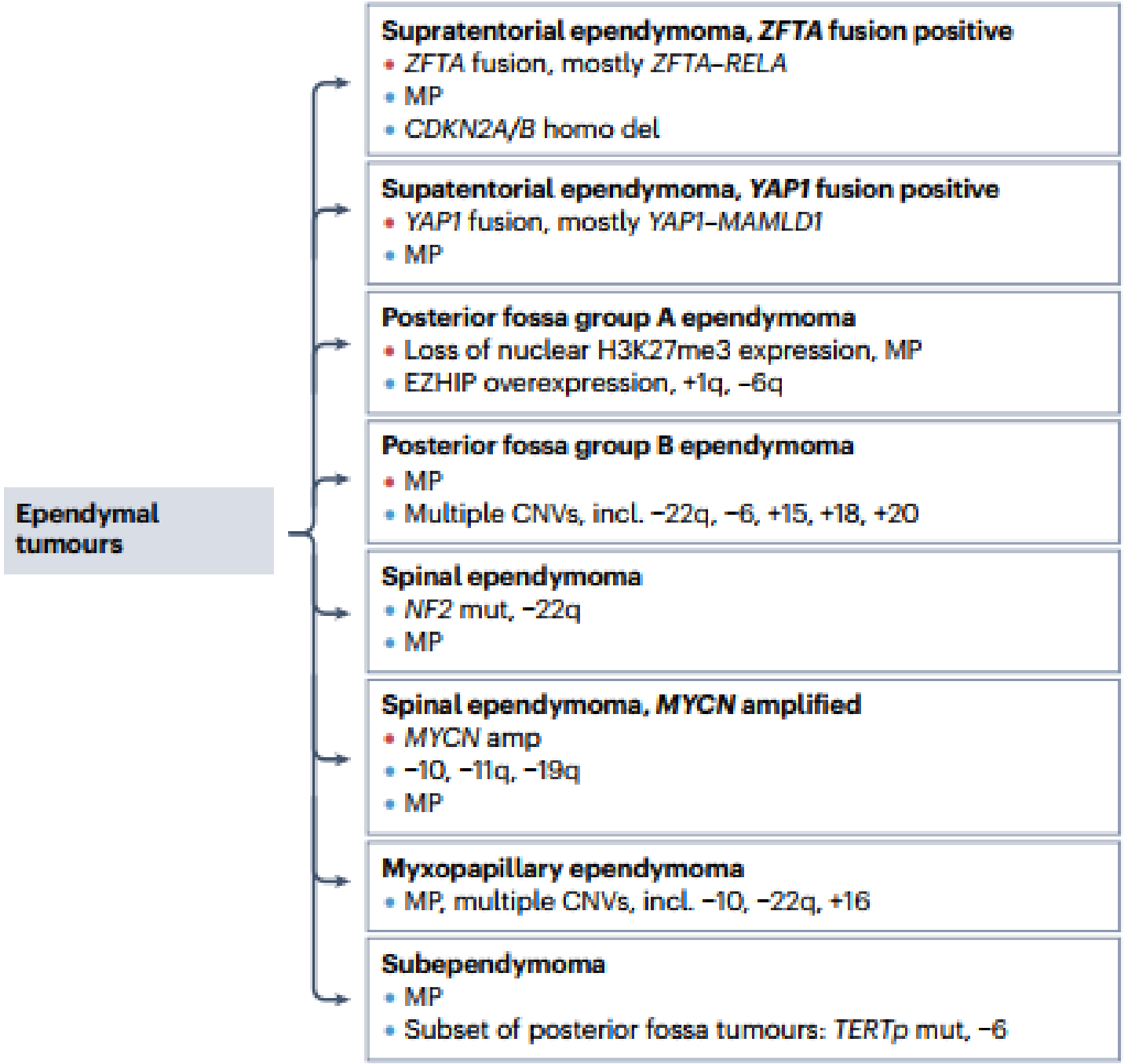
Ependymal Tumors

- Essential diagnostic molecular alterations
- Other genetic or epigenetic alterations



Ependymomas
Workup required

- History C Physical Examination – evaluate for symptoms of elevated ICP

- **Imaging –** MRI of brain C spine with and without contrast
- Lumbar puncture for CSF cytology
- If Raised ICT – Consider Endoscopic Third ventriculostomy Vs VP Shunt

If ICP elevated, wait 10-14 days postop to do LP to avoid risk of herniation

- **Maximal safe resection!!**
- Postoperative MRI to assess extent of resection (Within 48 hrs)
- CSF Cytology if not done preoperatively (After 2 weeks postop)
- MRI Spine with contrast if not done preoperatively (After 2 weeks postop)

European standard clinical practice recommendations for newly diagnosed ependymoma of childhood and adolescence. EJC Paediatric Oncology. 2025 Apr 9:100227

Ependymomas
Staging - Residual disease and metastases

Residual disease stage	Definition
R0	No residual tumour
R1	No residual tumour based on imaging, but small remaining lesion described by neurosurgeon; or unknown neurosurgical result
R2	Residual tumour <5mm in all diameters, not measurable in 3 planes
R3	Measurable residual tumour in 3 planes or one diameter ≥5mm
R4	No relevant changes compared to pre-surgery imaging
RX	Presence of residual tumour cannot be assessed

Metastatic stage	Definition
M0	No evidence of metastatic disease
M1	Microscopic tumour cells found in CSF
M2	Gross nodular seeding in cerebellum, cerebral subarachnoid space, or in the third or fourth ventricles
M3	Gross nodular seeding in spinal subarachnoid space
M4	Metastasis outside the central nervous system

European standard clinical practice recommendations for newly diagnosed ependymoma of childhood and adolescence. EJC Paediatric Oncology. 2025 Apr 9:100227

Ependymomas
Management

Maximal Safe Resection
Prognostic!

	5 yr OS	5 yr PFS
GTR	67 - 80%	51 - 75 %
STR	22 - 47 %	0-26 %

Surgery	Aim for GTR	STR is worse [Think of Resurgery Chemo→ Surgery]	
Complete workup s determine stage/risk	MRI spine (Staging)	MRI brain (postop within 72 hours) To assess Residual	LP postop (10–14 days postop) Staging
Radiation	Tumor bed 59.4 Gy (54 Gy if 12-18 mon)	CSI to 36 Gy if M+	Start 1 month postop
Chemotherapy	To convert STR to resectable disease, or on trial	Bridging Chemotherapy if Age < 12 months	Pre- or post-RT, not concurrent

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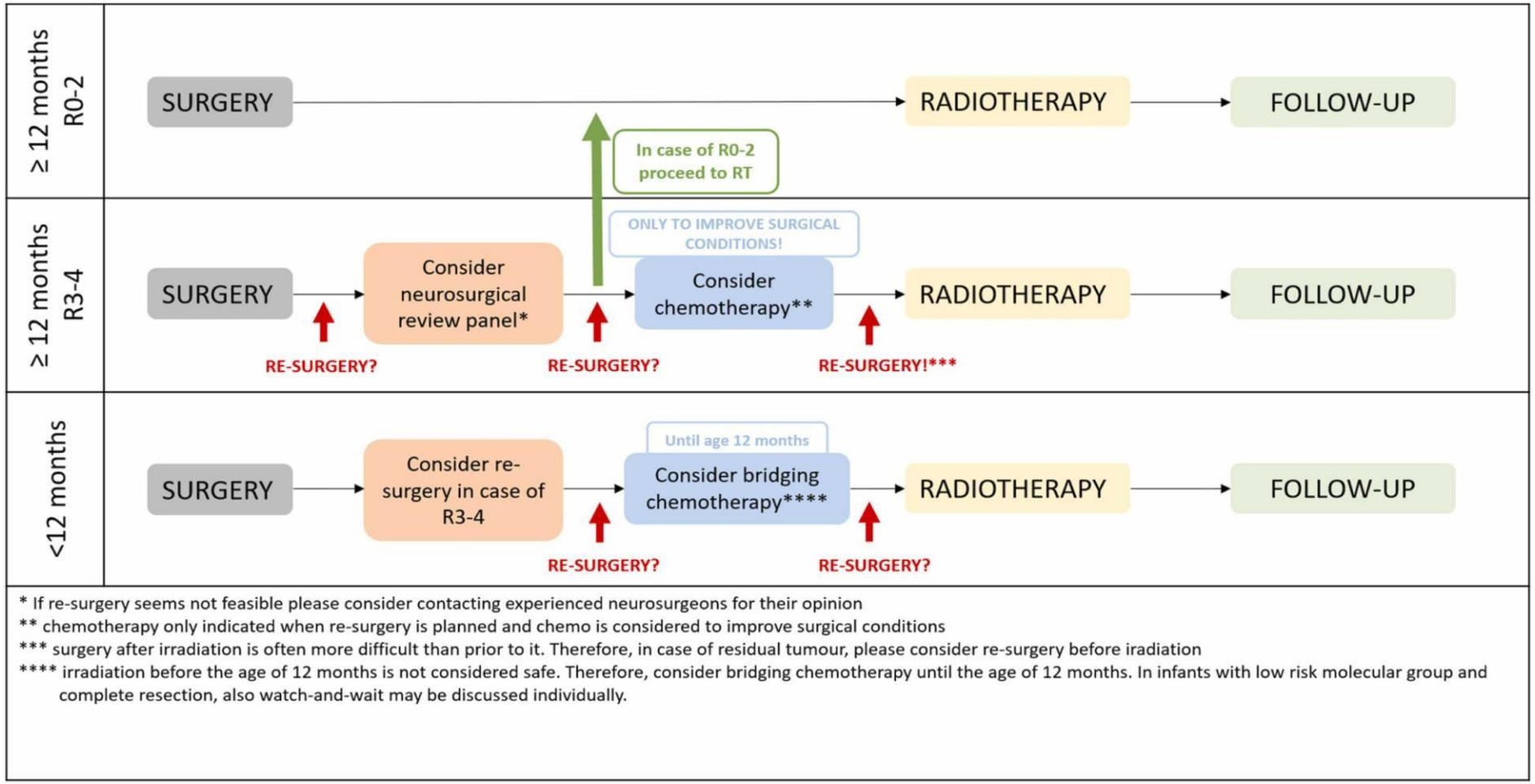
Intracranial ependymomas
Management

R Stage	Definition
R0	No residual tumor
R1	No residual on imaging. Surgeon describes a small residual
R2	Residual <5mm. Not measurable in 3 planes
R3	Residual > 5mm in one plane OR Measurable in 3 planes
R4	Same as Presurgery
Rx	Cannot be assessed



* If re-surgery seems not feasible please consider contacting experienced neurosurgeons for their opinion
** chemotherapy only indicated when re-surgery is planned and chemo is considered to improve surgical conditions
*** surgery after irradiation is often more difficult than prior to it. Therefore, in case of residual tumour, please consider re-surgery before iradiation
**** irradiation before the age of 12 months is not considered safe. Therefore, consider bridging chemotherapy until the age of 12 months. In infants with low risk molecular group and complete resection, also watch-and-wait may be discussed individually.

European standard clinical practice recommendations for newly diagnosed ependymoma of childhood and adolescence. EJC Paediatric Oncology. 2025 Apr 9:100227

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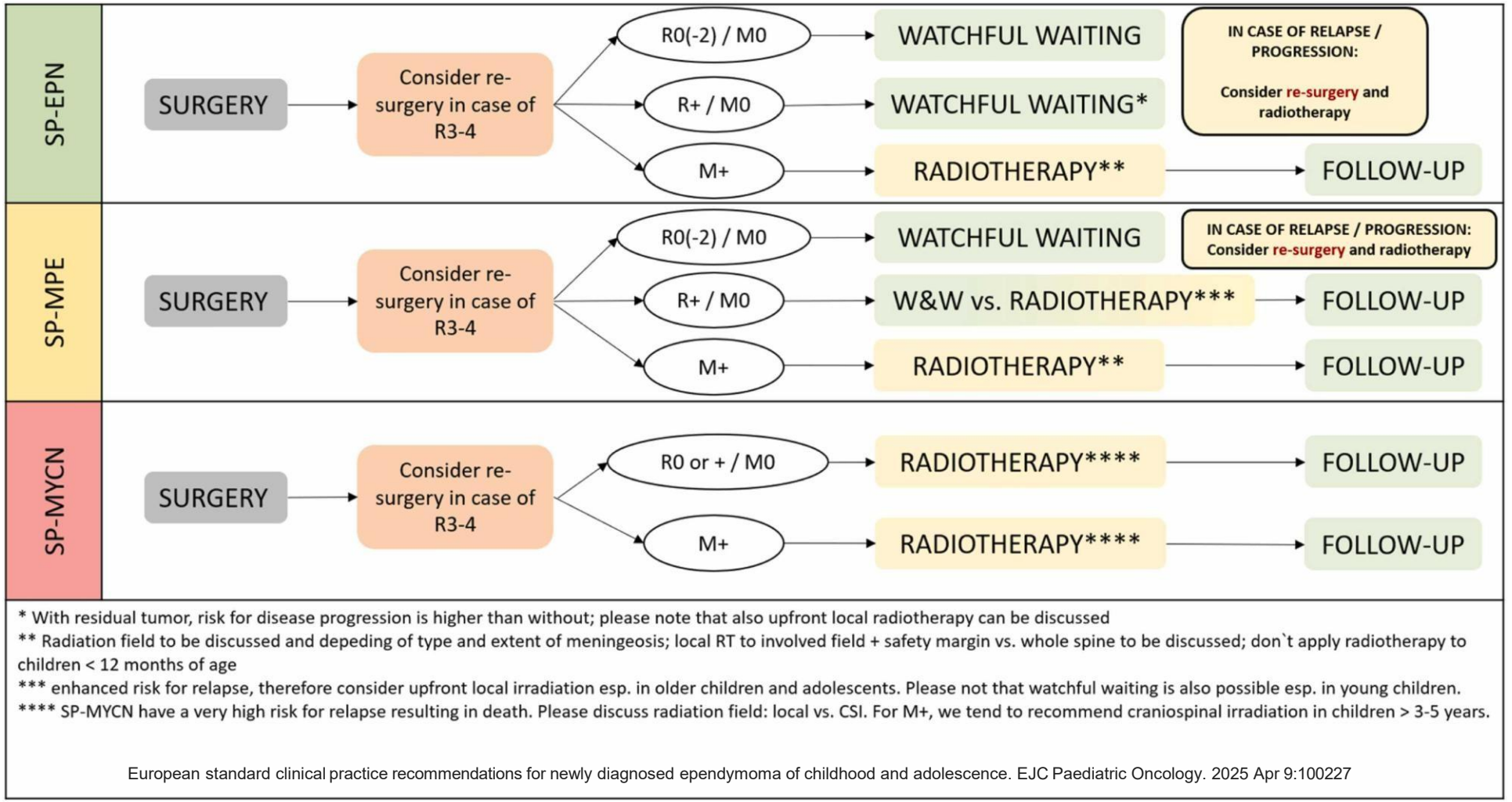
Spinal ependymomas
Management

R Stage	Definition
R0	No residual tumor
R1	No residual on imaging. Surgeon describes a small residual
R2	Residual <5mm. Not measurable in 3 planes
R3	Residual > 5mm in one plane OR Measurable in 3 planes
R4	Same as Presurgery
Rx	Cannot be assessed



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Ependymomas
RT Doses and Margin

Trial	Trial Period	Age Restriction (months)	Target Volume	CTV Margin (cm)	Dose (cGy/CcGE)
US Cooperative Group Studies					
POG-9132	1991-1994[43]	> 36	Preoperative	2.0	69.6/1.2 BID
CCG-9942	1995-1999[42]	> 36	Preoperative	1.5	59.4/1.8 55.8/1.8
ACNS0121	2003-2007[2]	> 12	Postoperative	1.0	59.4/1.8 54.0/1.8
ACNS0831	2010-present[3]	> 12	Postoperative	0.5	59.4/1.8 54.0/1.8
Single- or multi-institutional studies					
St Jude Children's Research Hospital	1997-2003[5]	> 12	Postoperative	1.0	59.4/1.8 54.0/1.8
PSI	2004-2013[39]	> 12	Postoperative	0.5-1.0	59.4/1.8
French cohort	2000-2013[40]	> 36	No details	No details	59.4/1.8 54.0/1.8
Italian cohort	2003-present[41]	> 36	No details	No details	59.4/1.8 67.8/1.8-2.0

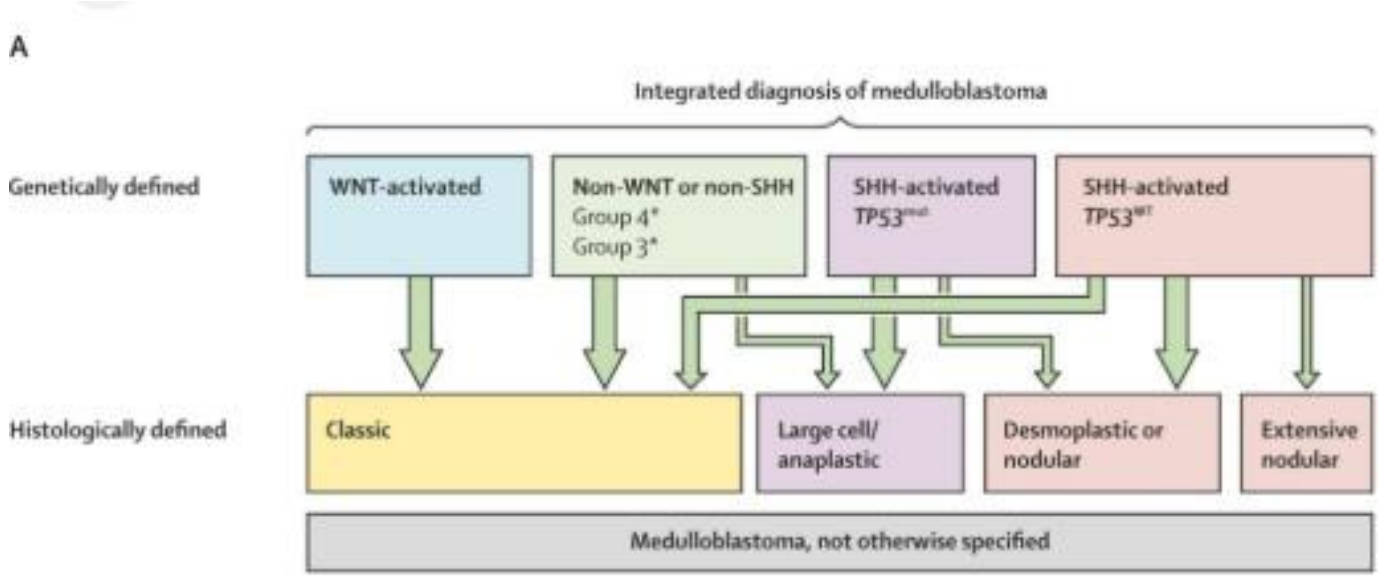
GTV
CTV
PTV

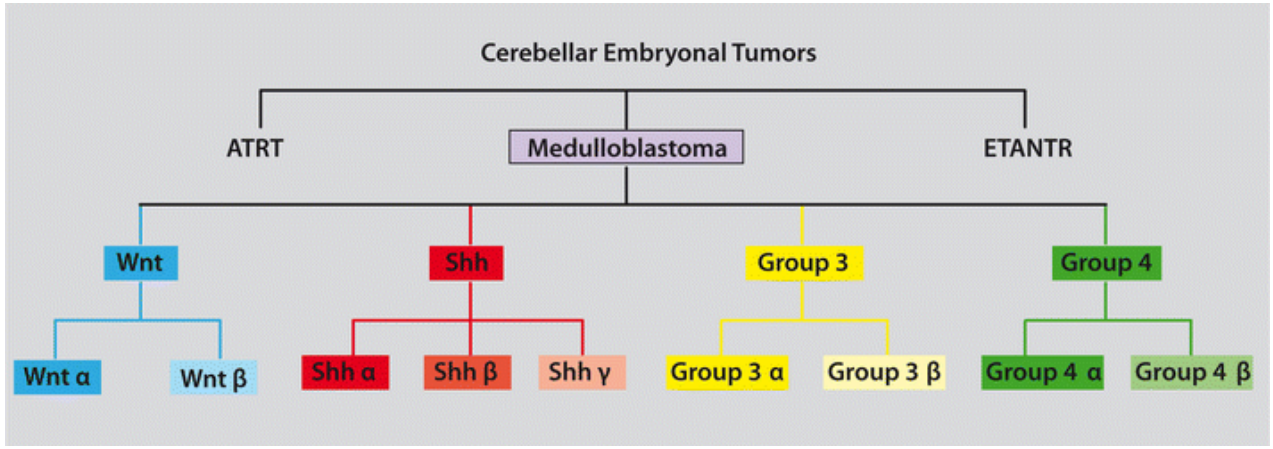
Photons 59.4 Gy
Age < 18m - 54 Gy
Protons 54 Gy

Ependymomas
Management – Focal RT Vs CSI

Scenario / Factor	Preferred RT Modality	Rationale / Notes
Age < 3 years	Generally avoid CSI	CSI is generally avoided in this age group. When used protons preferable
PF-A ependymoma, localized	Focal RT	Poor prognosis, but CSI not standard unless disseminated.
ST-ZFTA, localized (ST-EPN)	Focal RT	No CSI even with molecular risk factors, unless metastases are present.
ST-YAP1 (ST-EPN)	Focal RT	Excellent prognosis; de-escalation may be considered in clinical trials.
MYCN-amplified spinal ependymoma	CSI + boost	Aggressive behavior; CSI considered, due to frequent dissemination.
Disseminated myxopapillary ependymoma	CSI + boost	Especially in sacrococcygeal variants with high dissemination risk.
Metastatic disease (M1+, M2, M3)	CSI + boost	CSI recommended.
1q gain alone (PF-A)	Borderline	Does not indicate CSI by itself.
13q loss (PF-B)	Borderline	Does not indicate CSI by itself.

Medulloblastoma Classification





https://doi.org/10.1016/S1470-2045(19)30669-2

Medulloblastoma
Risk Stratification - Developing Countires

Table 3
Risk stratification in Medulloblastoma as per the SIOP Pediatric Oncology in Developing Countries (PODC) Committee.

Standard risk Medulloblastoma	High-risk Medulloblastoma
All of the following:	**Any one** of the following
➢ > 3yrs of age	➢ < 3yrs of age
➢ < 1.5cm2 residual tumor after resection (complete resection)	➢ >1.5cm2 residual (Subtotal resection)
➢ CSF negative for tumor cells	➢ CSF positive for tumor cells
➢ MRI spine negative for leptomeningeal spread	➢ MRI spine with leptomeningeal spread
➢ Classic or Desmoplastic pathology	➢ Large cell or anaplastic subtype
➢ Complete staging if possible	➢ Incomplete staging

Pediatric Hematology Oncology Journal
Volume 8, Issue 2, June 2023, Pages 121-128

Medulloblastoma
Risk Stratification - Molecular Era

Chromosome 11 - Group 4 (Loss is Good)

Chromosome 14 - SHH (Loss is Bad)

	Low risk (<90% survival)	Standard risk (75-90% survival)	High risk (50-75% survival)	Very high risk (<50% survival)
WNT	Non-metastatic			
SHH		Non-metastatic **AND** *TP53* WT **AND** No *MYCN* amplification **No Chr 14 loss**	Metastatic **AND** *TP53* WT **-- OR --** Non-metastatic **AND** *MYCN* amplification	*TP53* mutation **Chr 14 loss**
Group 3		Non-metastatic **AND** No *MYC* amplification		Metastatic **AND** *MYC* amplification
Group 4	Non-metastatic **AND** Chromosome 11 loss	Non-metastatic **AND** No chromosome 11 loss	Metastatic	

Fig. 2. Patient risk stratication based on molecular and outcome criteria[61]. WNT : wingless, SHH : sonic hedgehog, M : male, F : female.

Medulloblastoma Management

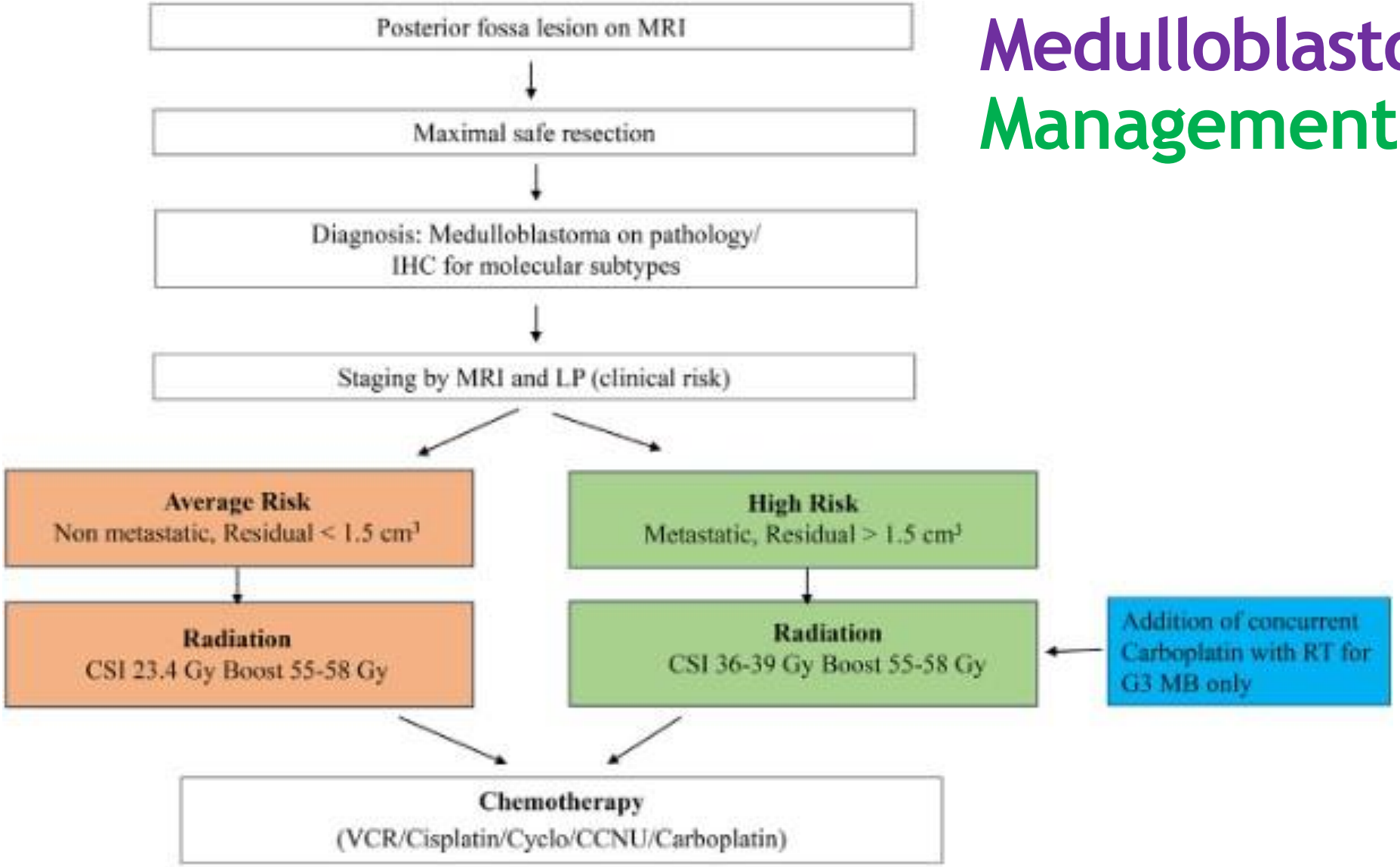


Fig. 1. Current schematic treatment for childhood MB (3yrs–21yrs).

Pediatric Hematology Oncology Journal
Volume 8, Issue 2, June 2023, Pages 121-128

Meningioma Classification

Grade 1 / Benign

Mitosis < 4 per 10 HPF

Grade 2 / Atypical

Mitosis 4-19 per 10 HPF

OR

Clear cell or chordoid histology
Brain invasion

OR

3/5 of the following
1. Necrosis
2. High NC ratio
3. Prominent Nucleoli
4. Architectural Sheeting
5. Hypercellularity

Grade3 / Anaplastic

Mitosis ≥20 per HPF

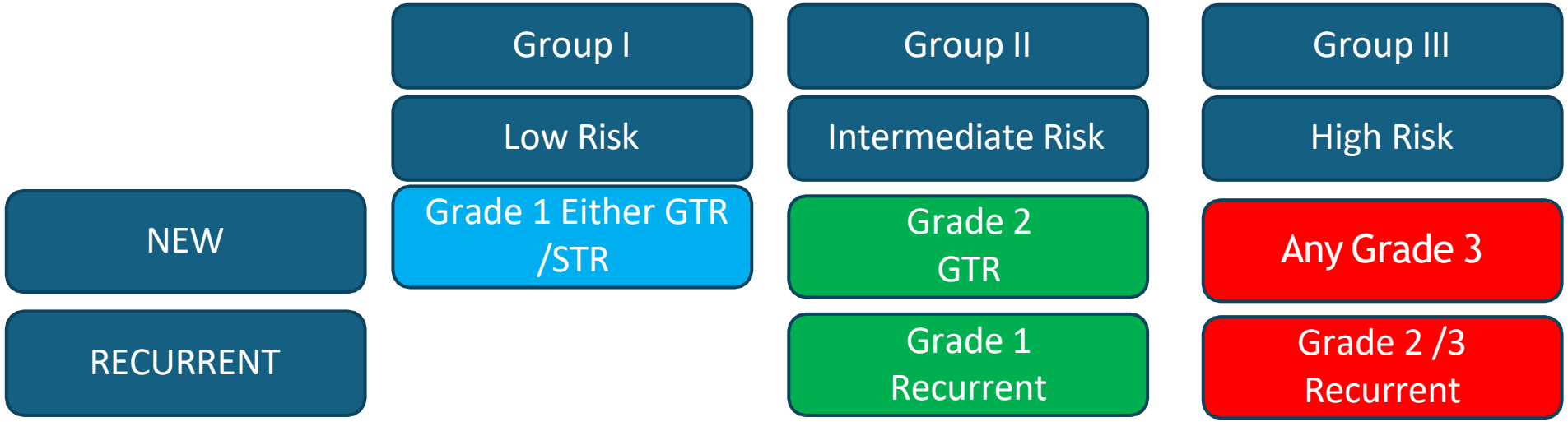
OR

Papillary or Rhabdoid histology

OR

Anaplasia

Meningiomas
RTOG 053G - Risk Categories

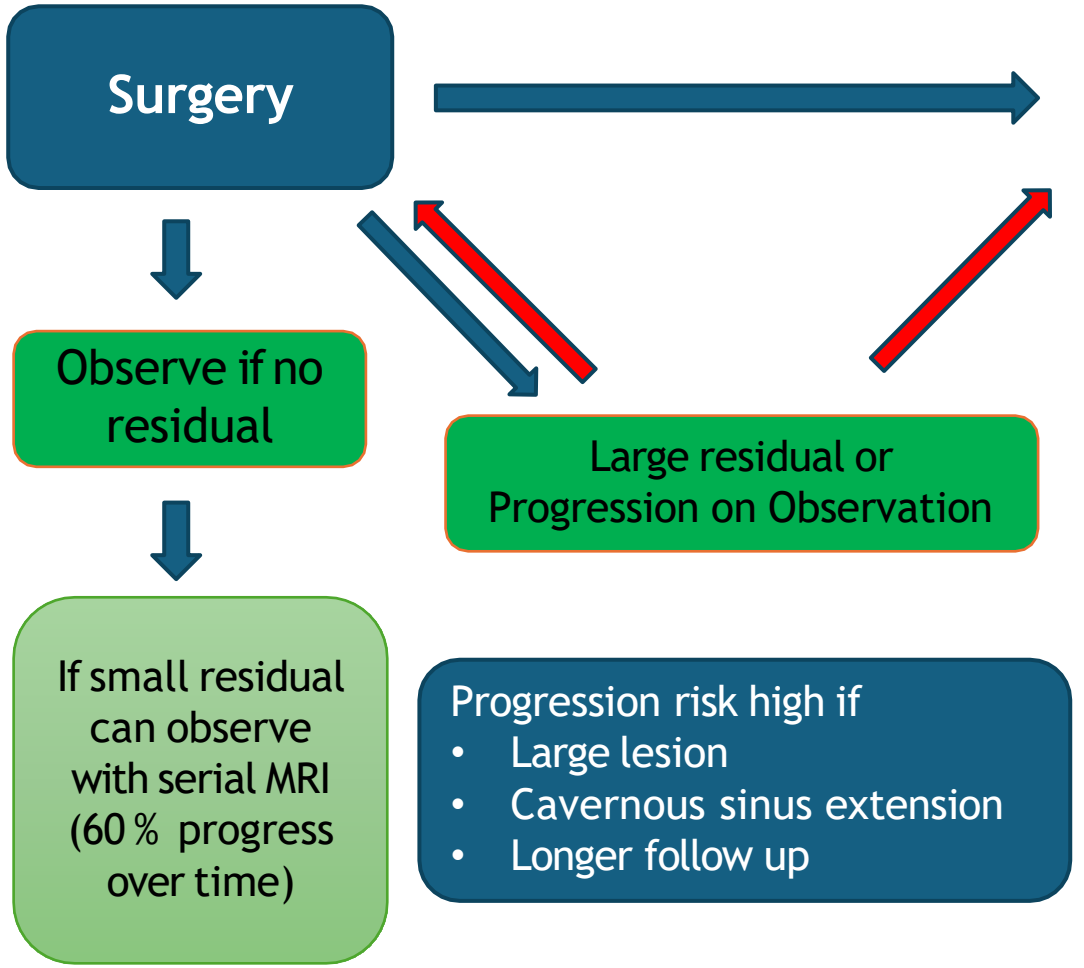


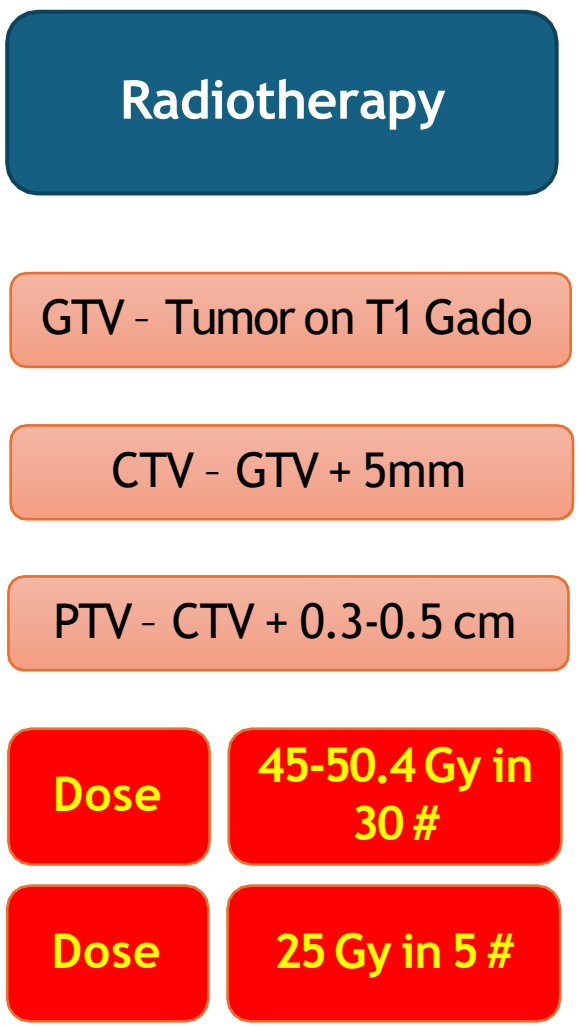
Meningiomas

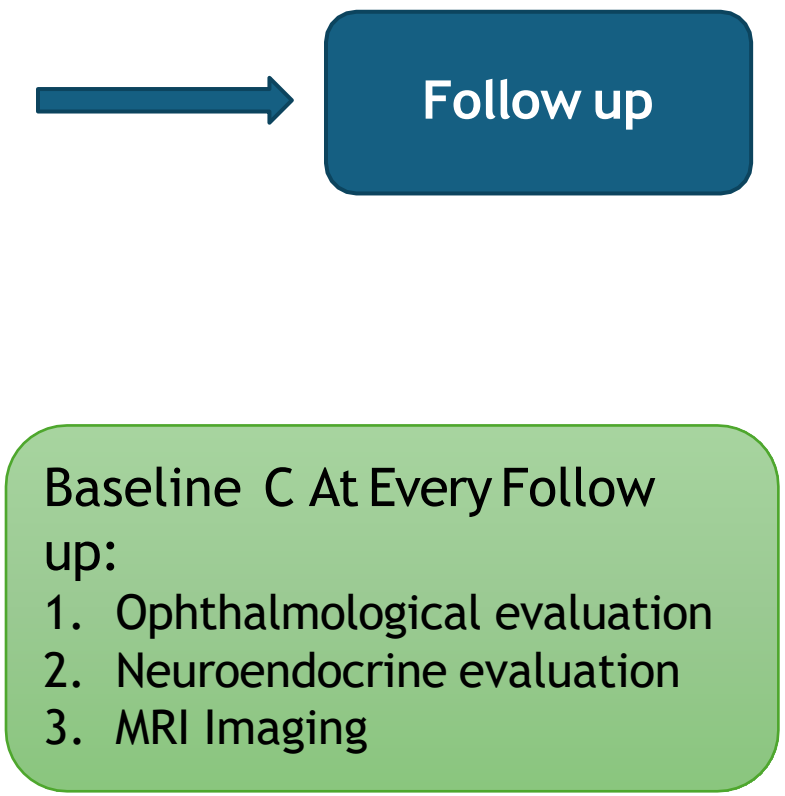
Management as per RTOG 053G - Risk Categories

Group I	Group II	Group III
Low Risk	Intermediate Risk	High Risk
GTR – Observation	3DCRT /SRT /IMRT /Proton	IMRT - SIB
STR – Observation SRS RT	54 Gy in 30 #	PTV 60 : 60Gy in 30 fractions, 2 Gy/ # PTV 54 : 54Gy in 30 fractions, 1.8 Gy/#

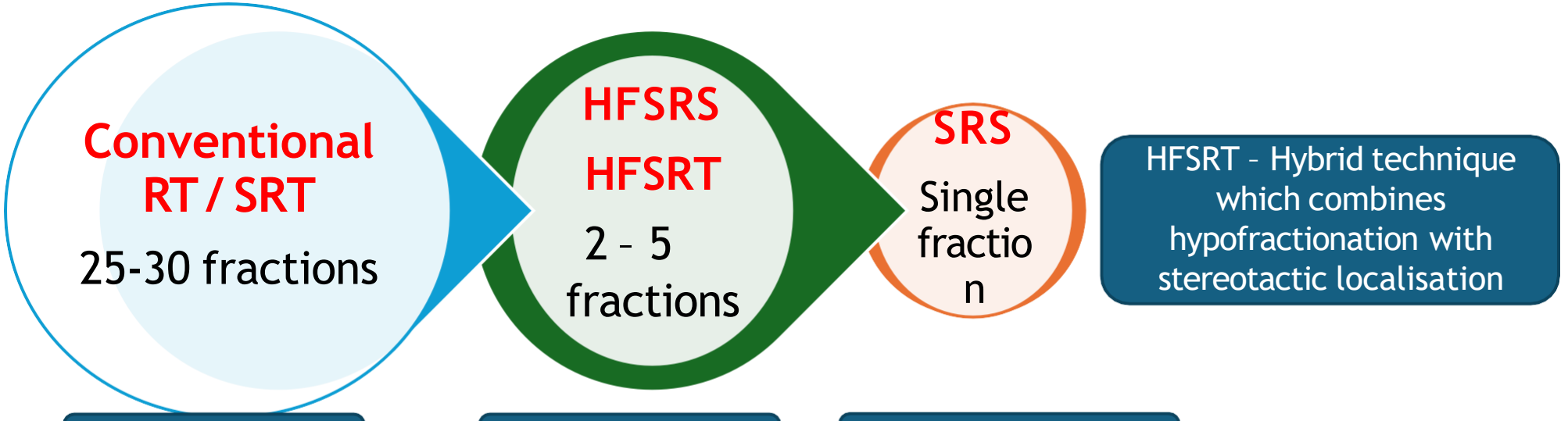
Pituitary Adenomas
Management







Pituitary Adenomas
Fractionation Schedules



Craniopharyngiomas
Management

Maximal Safe Surgery → Radiotherapy if residual → Follow up

Maximal Safe Surgery → Observe if no residual

Radiotherapy if residual:

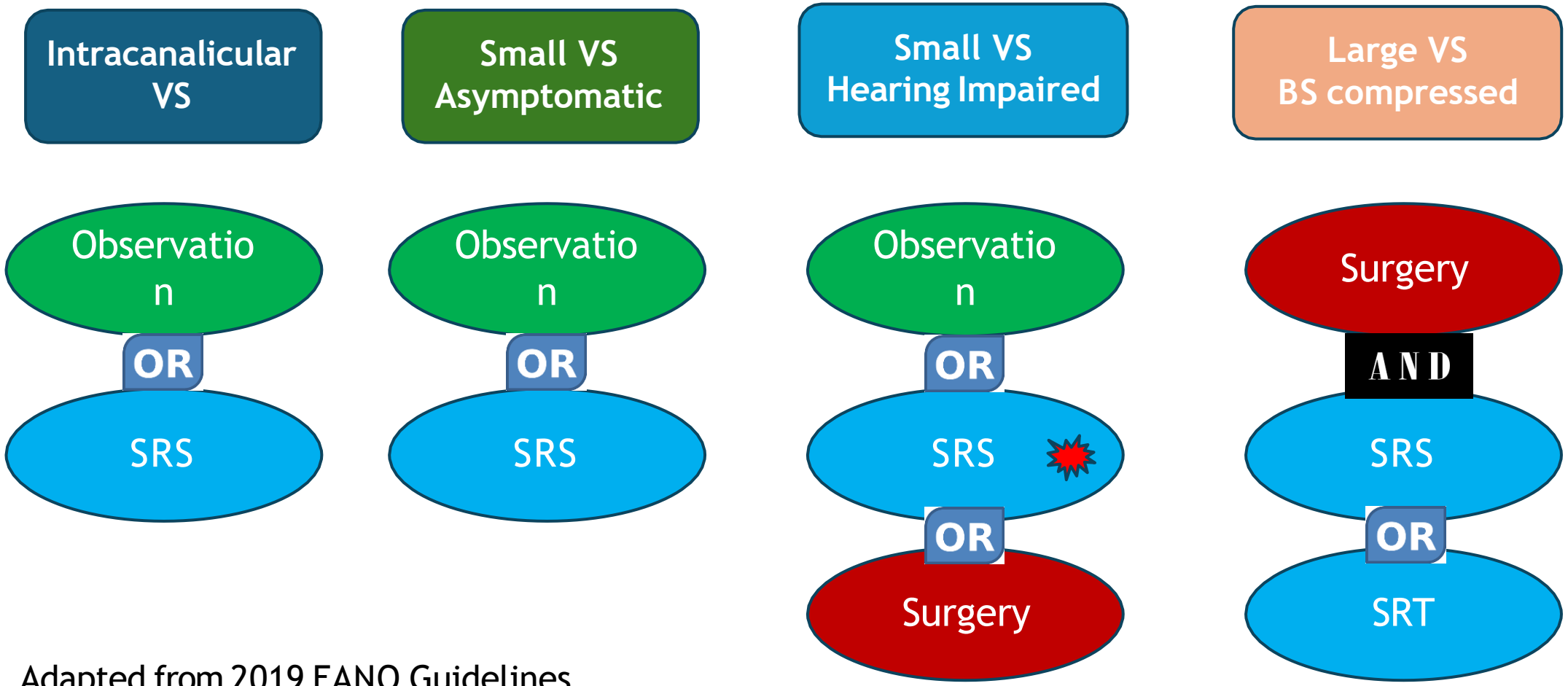
- GTV – Tumor on T1 Gado
- CTV – GTV + 5mm
- PTV – CTV + 0.3-0.5 cm
- Dose: 54 Gy in 30 #
- Interim CT Scan If Cystic

Follow up:

Baseline C At Every Follow up:

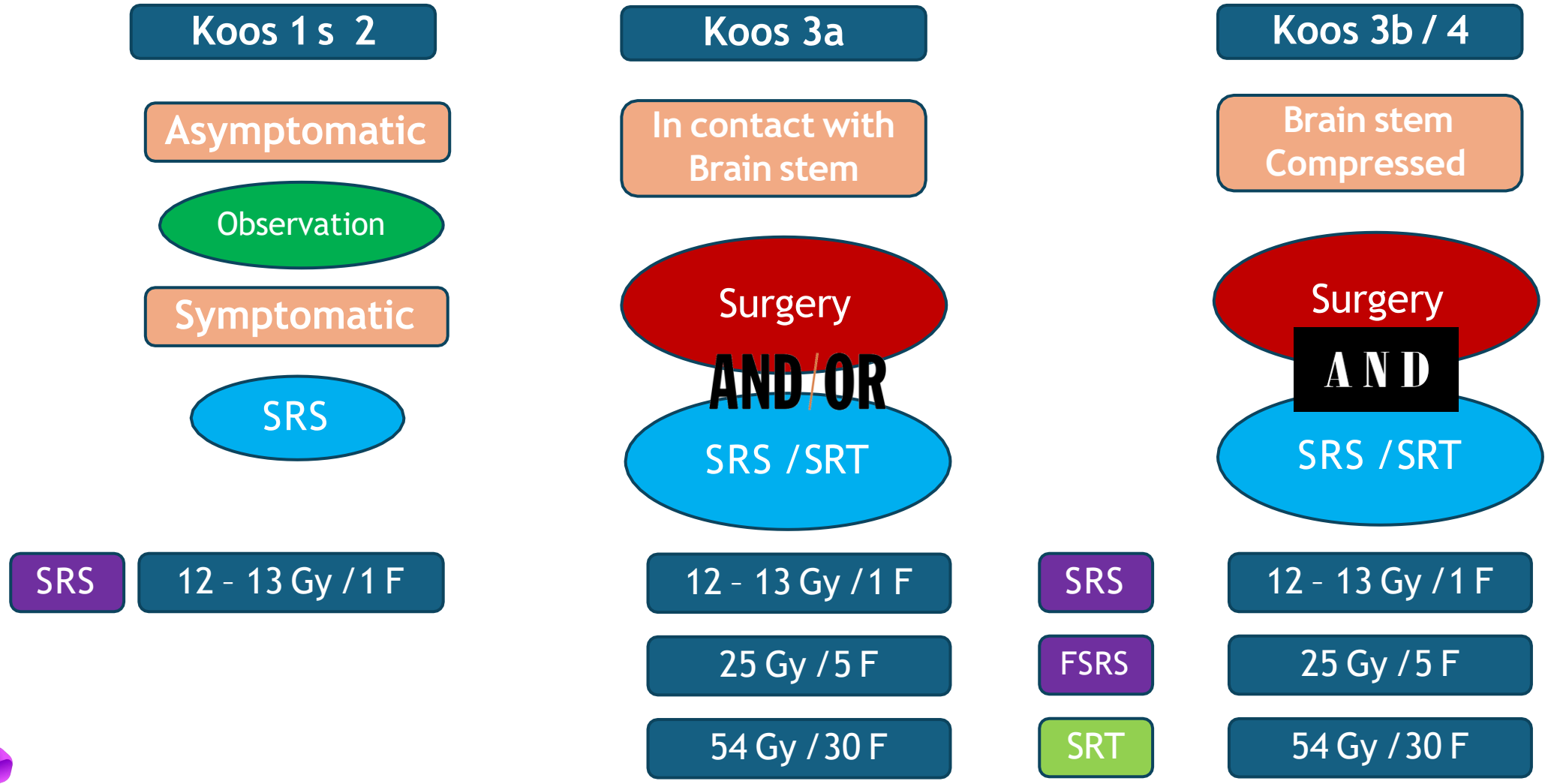
1. Ophthalmological evaluation
2. Neuroendocrine evaluation
3. MRI Imaging

Vestibular Schwannomas
Management

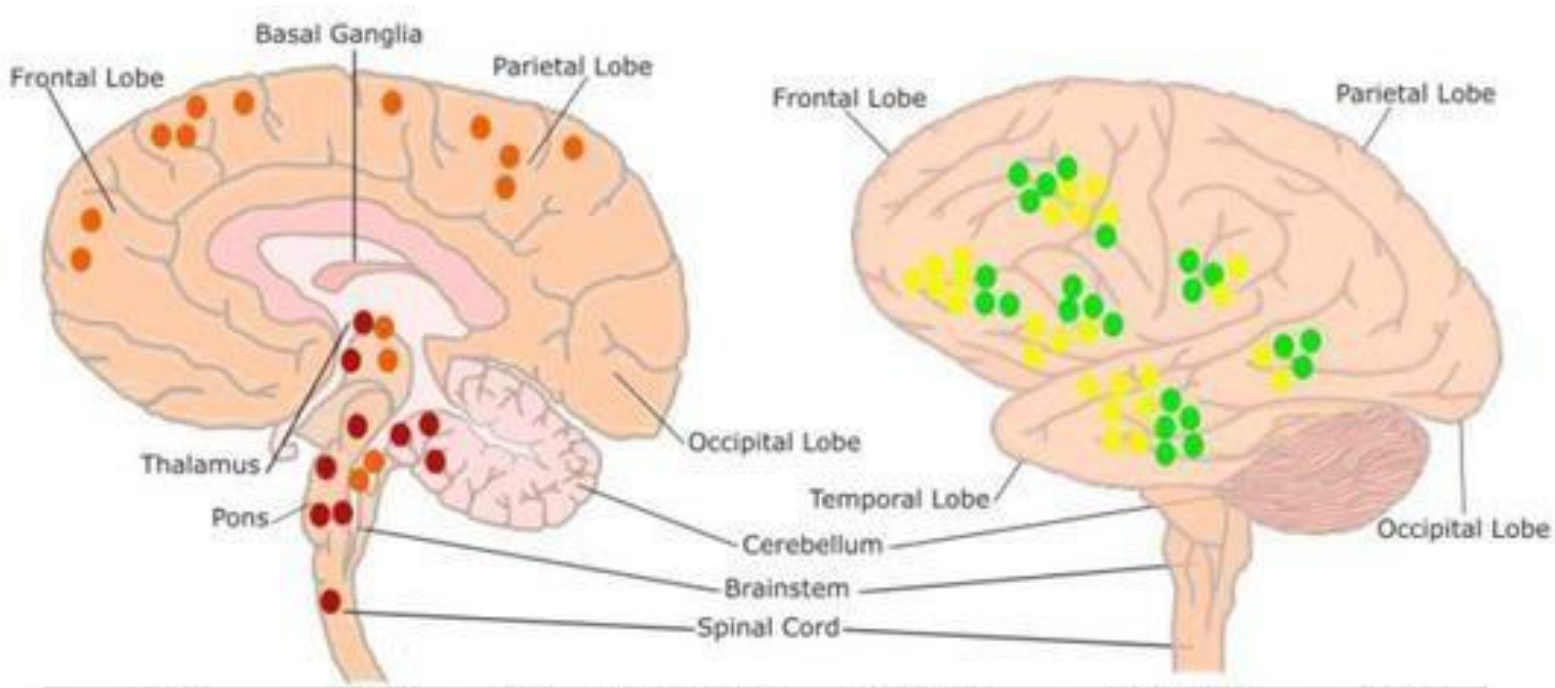


Adapted from 2019 EANO Guidelines

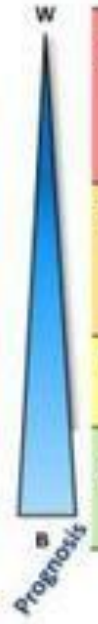
Vestibular Schwannomas
Fractionation Schedules



Paediatric Type Diffuse High Grade Gliomas Prognosis



Subtype	Molecular characteristics	Associated somatic mutations	Histopathological classification	Growth pattern	Grade according to WHO
Diffuse Midline Gliomas H3 K27-altered	H3.1K27M	HIST1H3B, *PI3K, ACVR1, ATRX*	Astrocytic morphology with oligodendroglial-like features	Midline structure (thalamus, brainstem, cerebellum, pons), spinal cord	4
	H3.3K27M	H3F3A, *FGFR1, TP53, PPMD1, PDGFRalpha, CCND2, TOP3A, EZHIP, EGFR*			4
Diffuse paediatric-type high-grade glioma, H3-wildtype and IDH wildtype	H3K27WT	*MYCN, EGFR, PDGFRA*, H3-wildtype, IDH-wildtype	Astrocytic morphology with oligodendroglial-like features	Cerebral hemispheres and midline structures	4
Infant-type hemispheric glioma	NTRK family	NTRK family, *ALK, ROS, MET*	Astrocytic morphology	Cerebral hemispheres	4
Diffuse hemispheric glioma, H3 G34- mutant	H3.3G34R/V	H3F3A, *TP53, ATRX, FBXW7, MGMT promoter methylation*	Neuro-glial heterogeneity	Cerebral hemispheres	4



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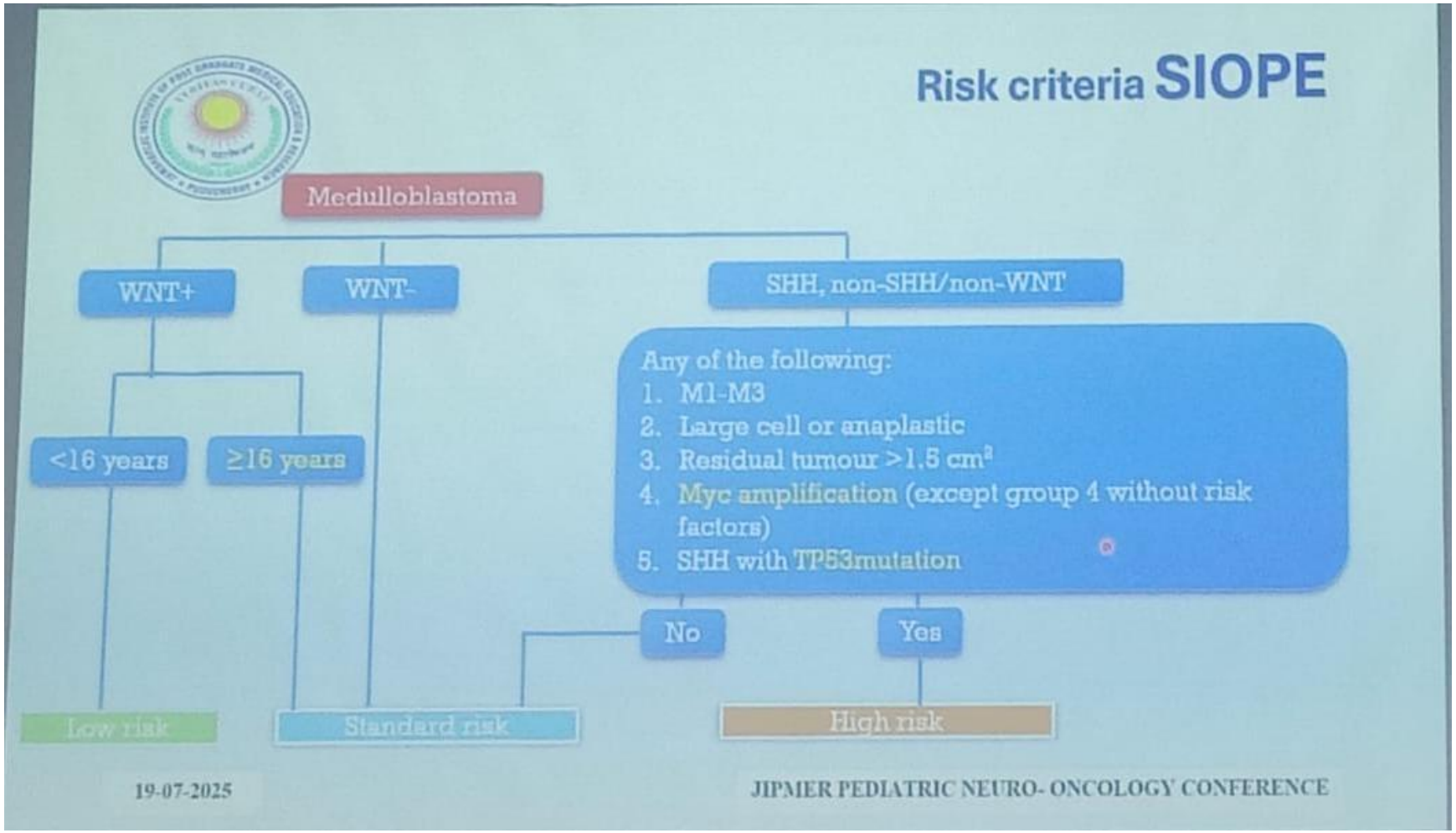
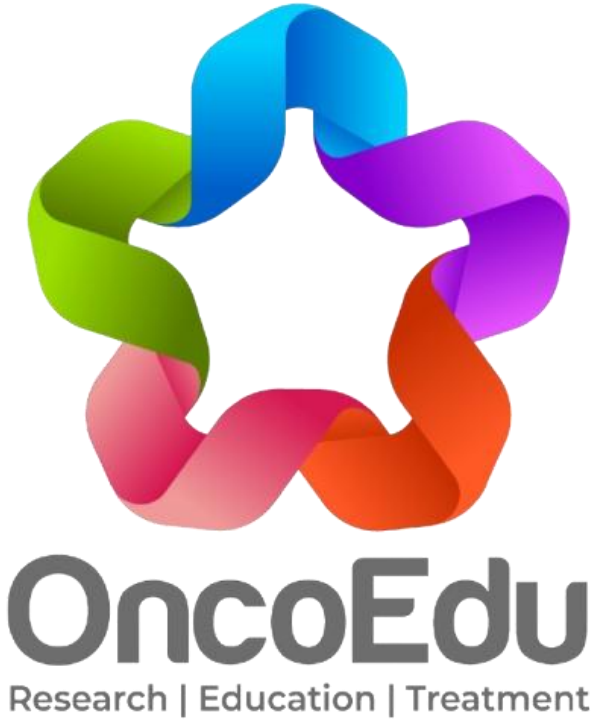
Medulloblastoma
Risk Stratification – Molecular Era



Slide Courtesy – Dr Thankamma Ajitkumar

RTOG 053G - Volume Delineation

	Group II /Intermediate Risk	Group III / High Risk
	3DCRT /SRT /IMRT	IMRT - SIB
	54 Gy in 30 #	PTV 60 : **60Gy** in 30 fractions, 2 Gy/ # PTV 54 : **54Gy** in 30 fractions, 1.8 Gy/#
GTV	1. Tumor bed on post op MRI 2. Any residual nodular enhancement 3. Hyperostotic or directly invaded bone	1. Tumor bed on post op MRI 2. Any residual nodular enhancement 3. Hyperostotic or directly invaded bone
CTV	GTV + 1 cm (reduced to 0.5 cm around natural barriers to tumor growth such as skull)	CTV 60: GTV + 1 cm CTV 54: GTV + 2 cm (reduce to 1cm at natural barriers)
PTV	CTV + 0.3cm	CTV + 0.3cm



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