ICRO Teaching course 2025

# Pediatric Ependymoma & other Pediatric Gliomas

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# Basics of Pediatric Gliomas

Any diffuse gliomas- IDH driven in adults

Most Pediatric if not all are IDH-Wild (not IDH driven)

- Pediatric "circumscribed" Gliomas
- Pediatric "diffuse" low-grade Gliomas
- Pediatric "diffuse" high-grade Gliomas
- Pediatric neuronal/neuro-epithelial tumors
- Pediatric ependymal tumors

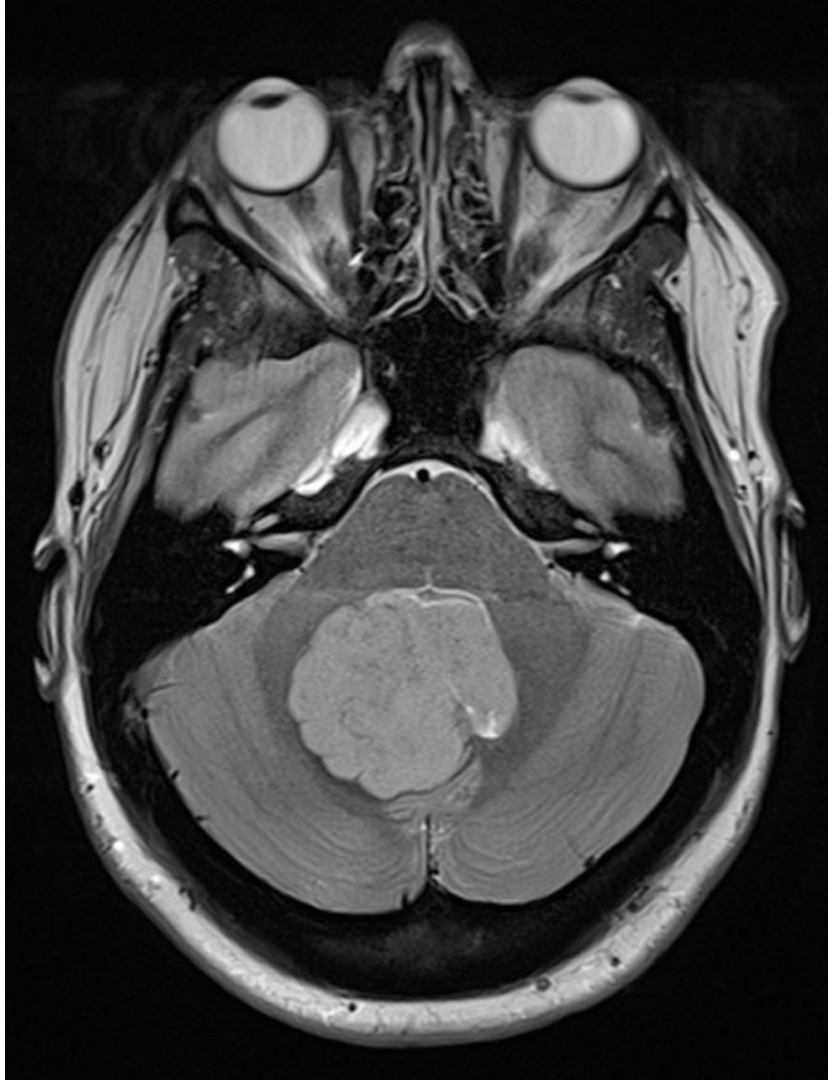
# Ependymoma- Introduction

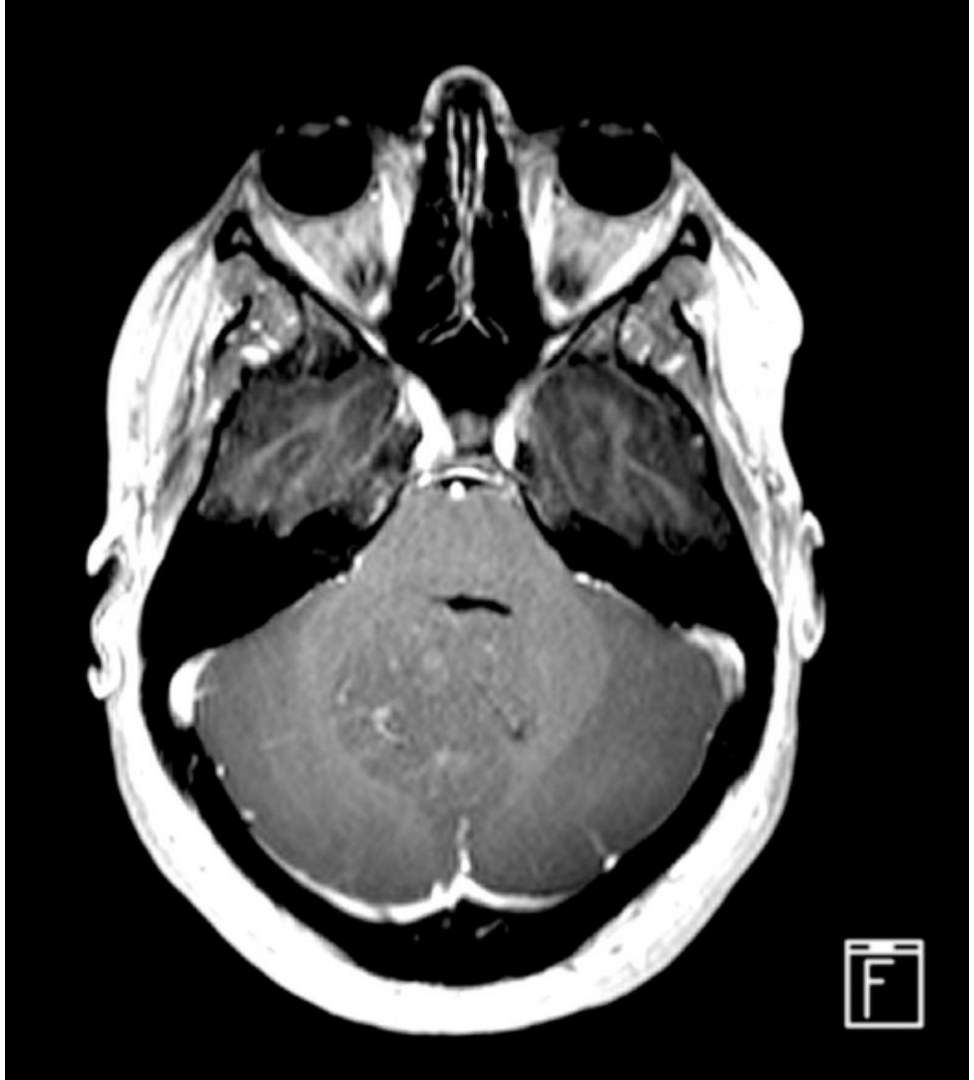
Ependymomas are **glial tumors** that arise from the **ependymal cells** lining the ventricular system and central canal of the spinal cord.

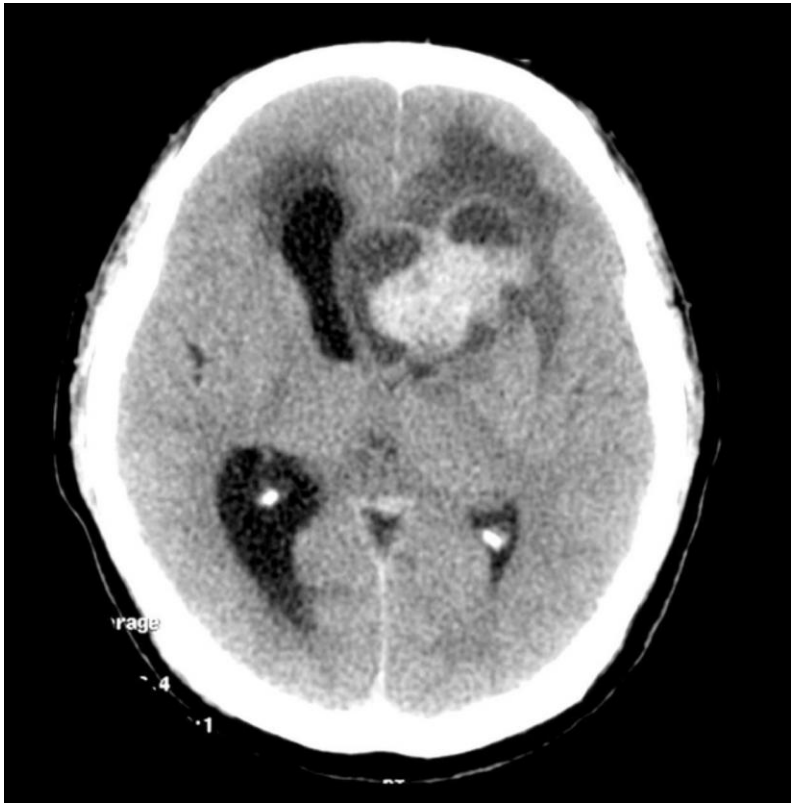
They account for about **6–10% of pediatric CNS tumors** and **1–2% of adult intracranial tumors**.

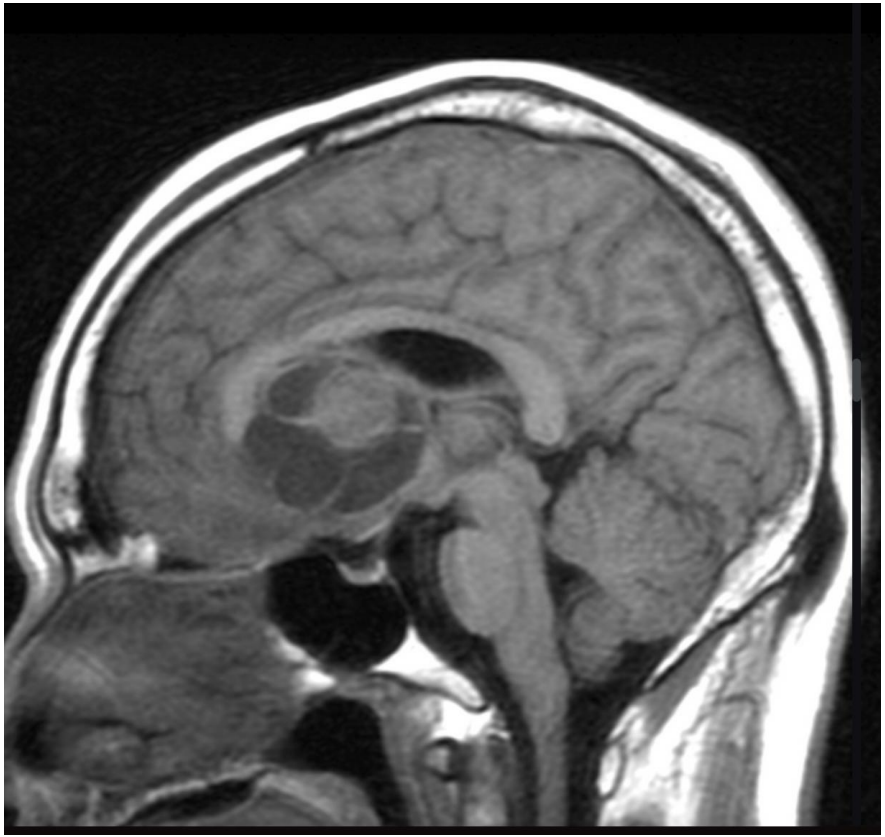
Although they can occur anywhere along the neuraxis, their **location and molecular profile** strongly influence both behavior and prognosis.

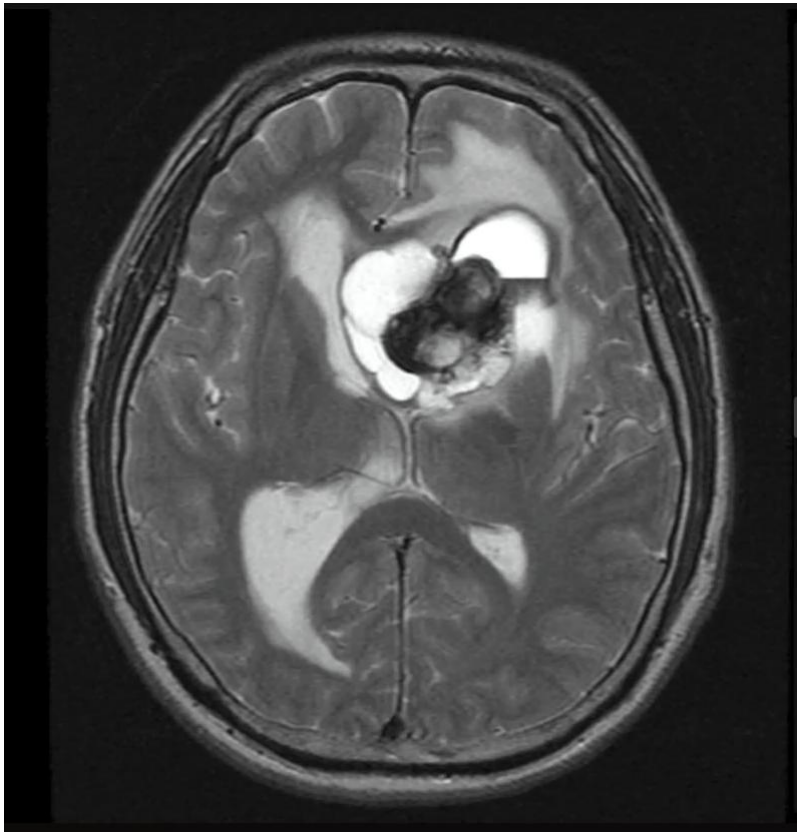
- **Supratentorial** – cerebral hemispheres (about 30%)
- **Posterior fossa (infratentorial)** – cerebellum and fourth ventricle (about 60% of pediatric cases)
- **Spinal cord** – intramedullary or filum terminale (more common in adults)

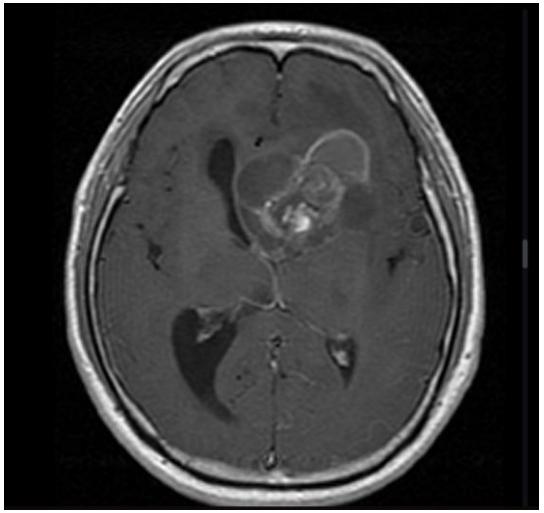


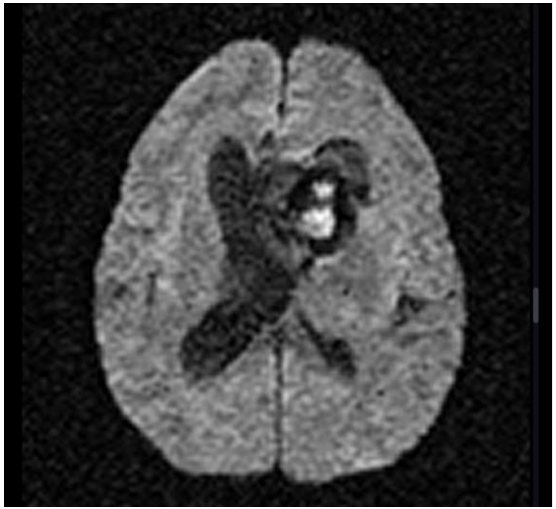


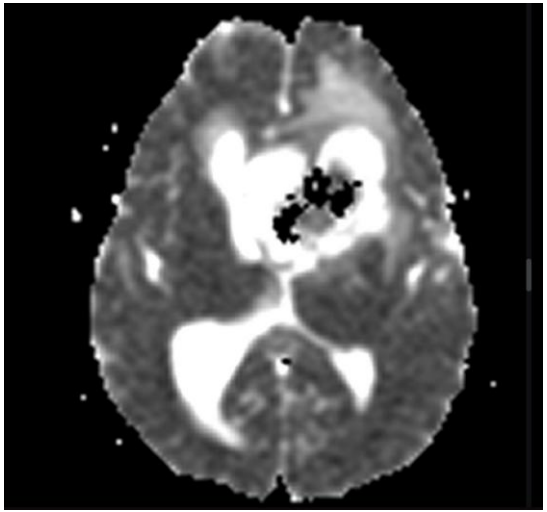




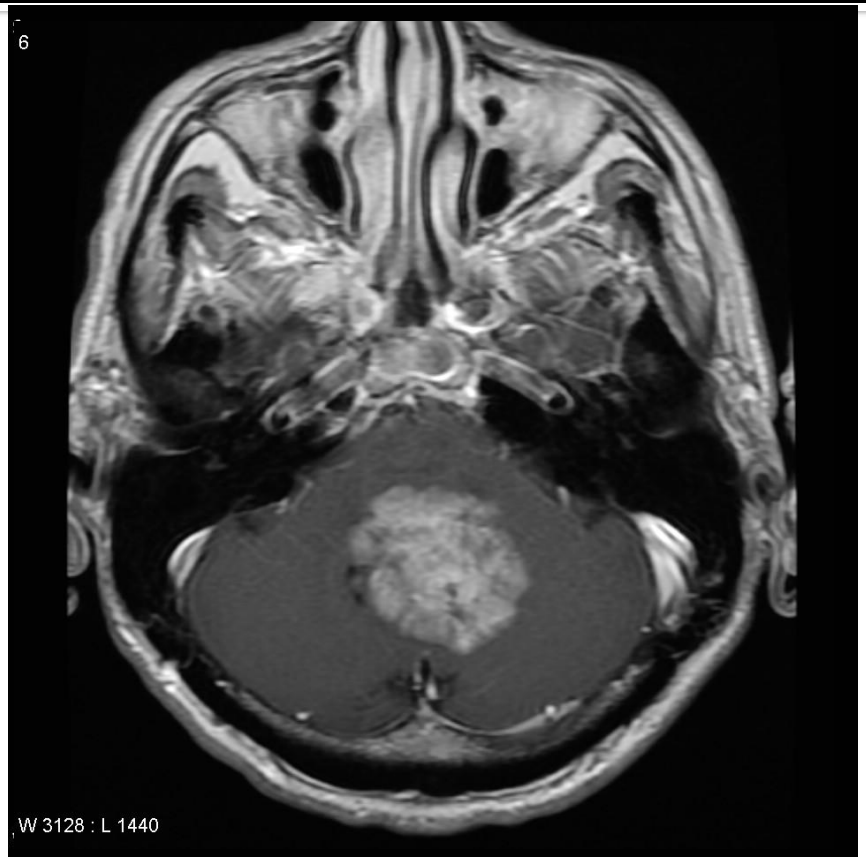








# Radiology of Ependymoma



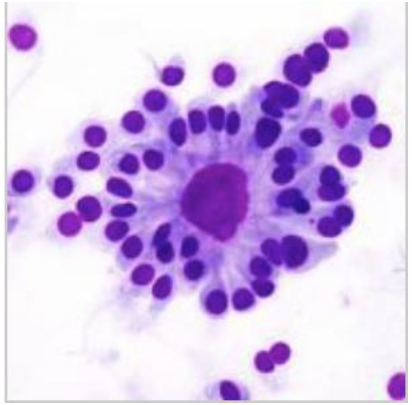

## MRI

- **T1**
  - solid portions of ependymoma typically are isointense to hypointense relative to white matter [7]
- **T2**
  - hyperintense to white matter
  - more reliable in differentiating tumor margins than non-contrast T1-weighted images (but less reliable than contrast enhanced T1)
- **T2* (e.g. SWI)**
  - foci of blooming from hemorrhage or calcification
- **T1 C+ (Gd)**
  - enhancement present but heterogeneous
  - enhancement with gadolinium is useful in differentiating tumor from adjacent vasogenic edema and normal brain parenchyma
- **DWI/ADC**
  - restricted diffusion may be seen in solid components, especially in anaplastic tumor
  - diffusion should be interpreted with caution in masses with significant hemorrhage or calcification
- **MRS**
  - Choline peak elevation according to the cellularity of tumor
  - NAA peak reduction
  - elevated Cho/Cr ratio
  - lipid and lactate rise when degeneration occurs

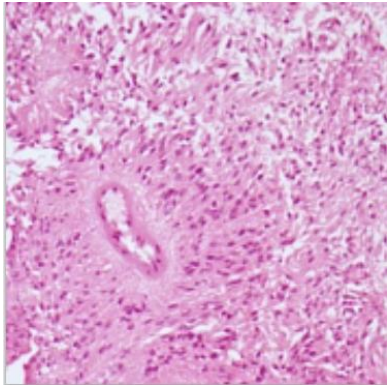
Although it is uncommon when compared to tumors like medulloblastomas, careful examination of the entire neuraxis is required to assess for the presence of CSF seeding.

# Pathology

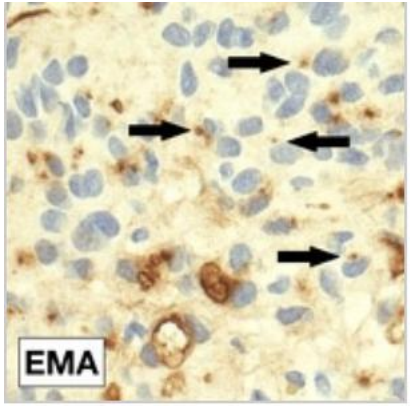
Ependymal rosettes



Perivascular pseudo rosettes



Intracytoplasmic micro rosettes




<u>Immunohistochemistry</u>

GFAP

EMA-dot like positivity

S100

Vimentine

OLIG2: Negative

- Perivascular pseudo-rosettes and true ependymal rosettes
- Monomorphic cells with salt-and-pepper chromatin
- GFAP-positive cytoplasmic processes radiating toward vessels

If PF lesions: h3K27 me3

# Pathology- molecular pathology

Neuro-Oncology

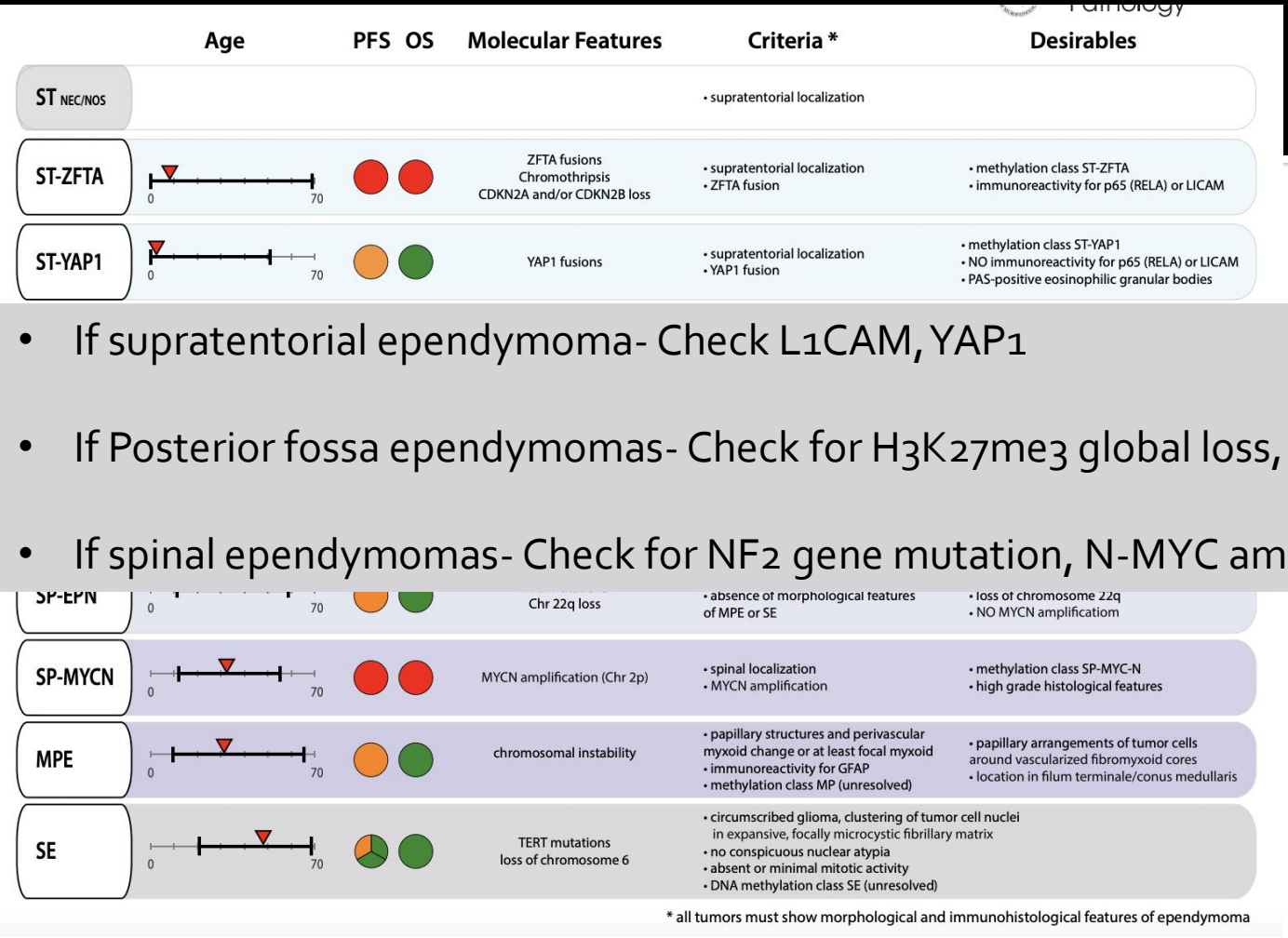
23(8), 1231–1251, 2021 | doi:10.1093/neuonc/noab106 | Advance Access date 29 June 2021

## The 2021 WHO Classification of Tumors of the Central Nervous System: a summary

David N. Louis, Arie Perry, Pieter Wesseling, Daniel J. Brat, Ian A. Cree, Dominique Figarella-Branger, Cynthia Hawkins, H. K. Ng, Stefan M. Pfister, Guido Reifenberger, Riccardo Soffietti, Andreas von Deimling, and David W. Ellison

DNA-methylation profiling underpins this scheme and outperforms histology for prognosis

| | |
|---|---|
| Supratentorial ependymomas | *ZFTA*, *RELA*, *YAP1*, *MAML2* |
| Posterior fossa ependymomas | H3 K27me3, *EZHIP* (methylome) |
| Spinal ependymomas | *NF2*, *MYCN* |

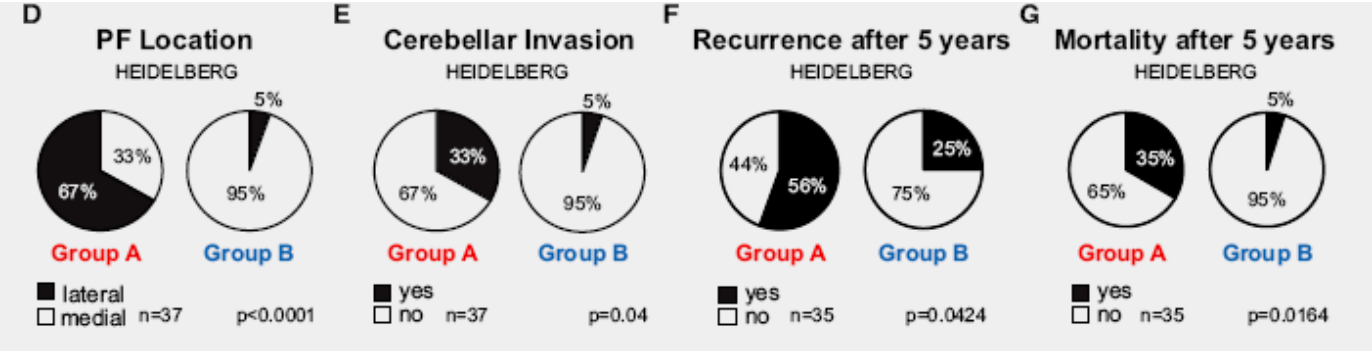


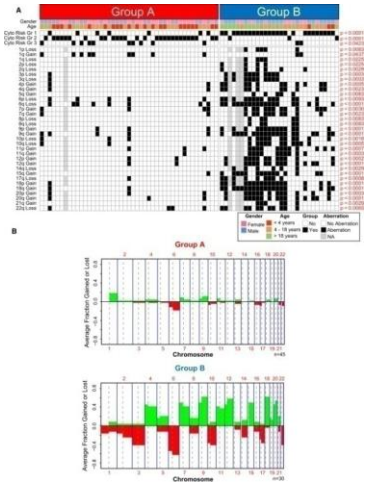

- If supratentorial ependymoma- Check L1CAM, YAP1
- If Posterior fossa ependymomas- Check for H3K27me3 global loss, 1q gain, 6q loss
- If spinal ependymomas- Check for NF2 gene mutation, N-MYC amplification

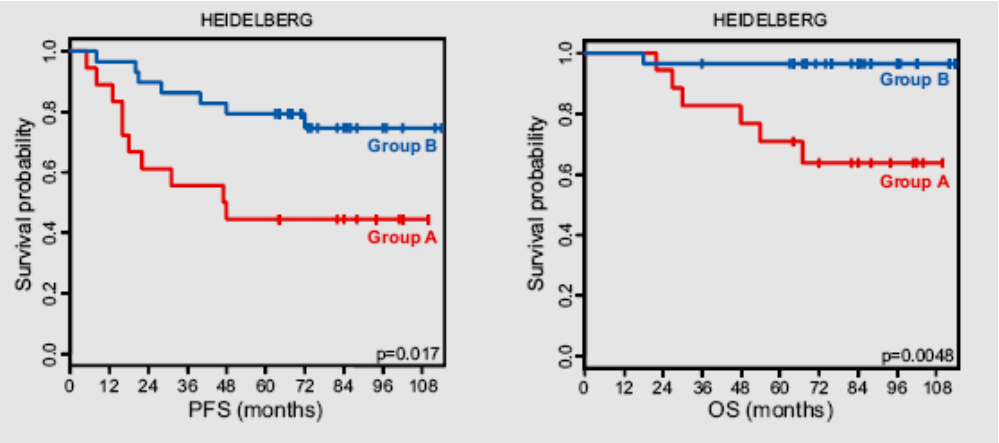
| PF Group A (CpG island methylator phenotype) | PF Group B (with extensive chromosomal aberrations) |
| --- | --- |
| ▪ Young age (2.5 - 4 yrs)<br>▪ Laterally located<br>▪ Invasive<br>▪ Increased recurrence<br>▪ Metastasis<br>▪ Increased mortality<br>▪ Balanced genome<br>▪1 q gain<br>▪LAMA2 over-expression | ▪ Older (18 yrs)<br>▪ Midline<br>▪ Less aggressive<br><br>▪Frequent chromosomal aberrations<br>▪6q-, 22q-, 9q+, 15q+, 18q+<br>▪NELL2 |

➢Histologically indistinguishable

➢Grade II and III tumors equally distributed in both groups




Hendrik et al, Cancer cell 2011; 20: 143-157

# Molecular Classification Hazards Model for PFS/OS

| PFS | | | |
|---|---|---|---|
| 1q gain (yes versus no) | 1.79 | 1.27–2.52 | 0.001 |
| WHO III versus WHO II | 0.89 | 0.63–1.27 | 0.547 |
| Age, years (< 4 versus > 18) | 1.18 | 0.55–2.53 | 0.665 |
| Age, years (4-18 versus > 18) | 1.39 | 0.68–2.83 | 0.364 |
| Resection (STR versus GTR) | 1.79 | 1.31–2.45 | <0.0001 |
| Chemotherapy (yes versus no) | 0.93 | 0.64–1.34 | 0.715 |
| Radiotherapy (yes versus no) | 0.75 | 0.50–1.10 | 0.149 |
| PF-SE versus PF-EPN-B | 1.23 | 0.30–5.024 | 0.771 |
| PF-EPN-A versus PF-EPN-B | 2.50 | 1.13–5.56 | 0.024 |
| ST-SE versus PF-EPN-B | 0.29 | 0.01–5.27 | 0.407 |
| ST-EPN-YAP versus PF-EPN-B | 0.68 | 0.11–3.95 | 0.67 |
| ST-EPN-RELPOS versus PF-EPN-B | 2.66 | 1.21–5.86 | 0.015 |
| Likelihood Ratio Test | | | |
| Full model versus model without methylation subgroups (PFS) | | | 0.01 |
| Full model versus model without WHO (PFS) | | | 0.56 |

| Variable | Hazard Ratio[a] | 95% CI | p Value[b] |
|---|---|---|---|
| OS | | | |
| 1q gain (yes versus no) | 2.44 | 1.49–4 | <0.0001 |
| WHO III versus WHO II | 1.06 | 0.61–1.82 | 0.827 |
| Age, years (<4 versus >18) | 0.46 | 0.14–1.53 | 0.21 |
| Age, years (4–18 versus >18) | 0.63 | 0.20–1.95 | 0.429 |
| Resection (STR versus GTR) | 1.79 | 1.11–2.90 | 0.017 |
| Chemotherapy (yes versus no) | 1.44 | 0.81–2.56 | 0.205 |
| Radiotherapy (yes versus no) | 0.81 | 0.43–1.52 | 0.528 |
| PF-SE versus PF-EPN-B | 1.45 | 0.06–33.87 | 0.814 |
| PF-EPN-A versus PF-EPN-B | 6.65 | 1.35–32.56 | 0.019 |
| ST-SE versus PF-EPN-B | 1.89 | 0.08–44.09 | 0.691 |
| ST-EPN-YAP versus PF-EPN-B | 1.97 | 0.08–46.31 | 0.673 |
| ST-EPN-RELPOS versus PF-EPN-B | 6.22 | 1.32–29.27 | 0.021 |
| Likelihood Ratio Test | | | |
| Full model versus model without methylation subgroups (OS) | | | 0.03 |
| Full model versus model without WHO (OS) | | | 0.79 |

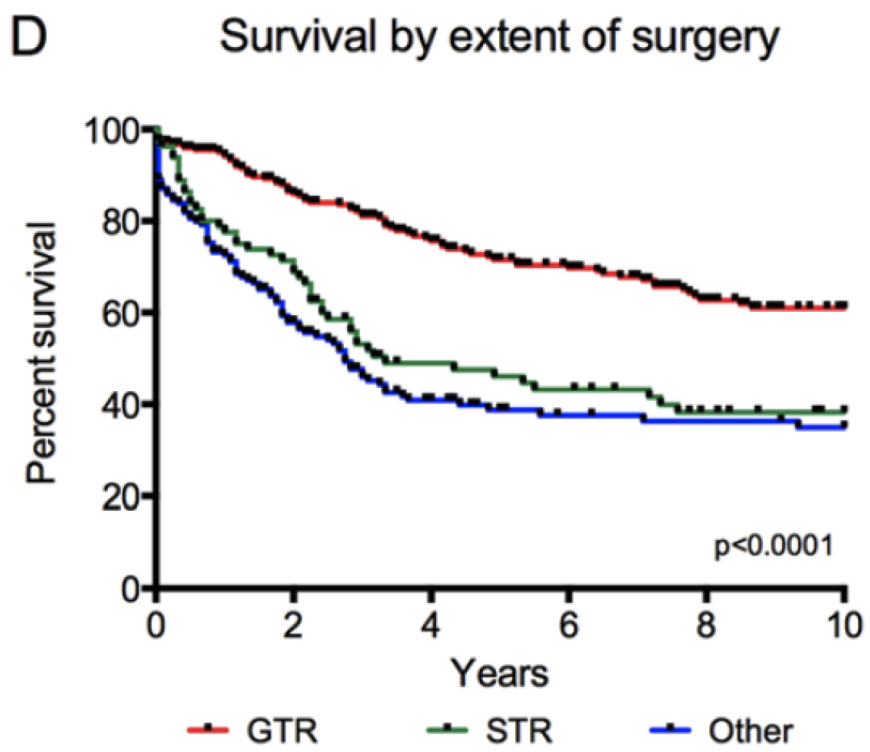
Pajtler KW, Witt H, Sill M, et al (2015), Molecular Classification of Ependymal Tumors across All CNS Compartments, Histopathological Grades, and Age Groups. Cancer Cell, 27(5):728-43.

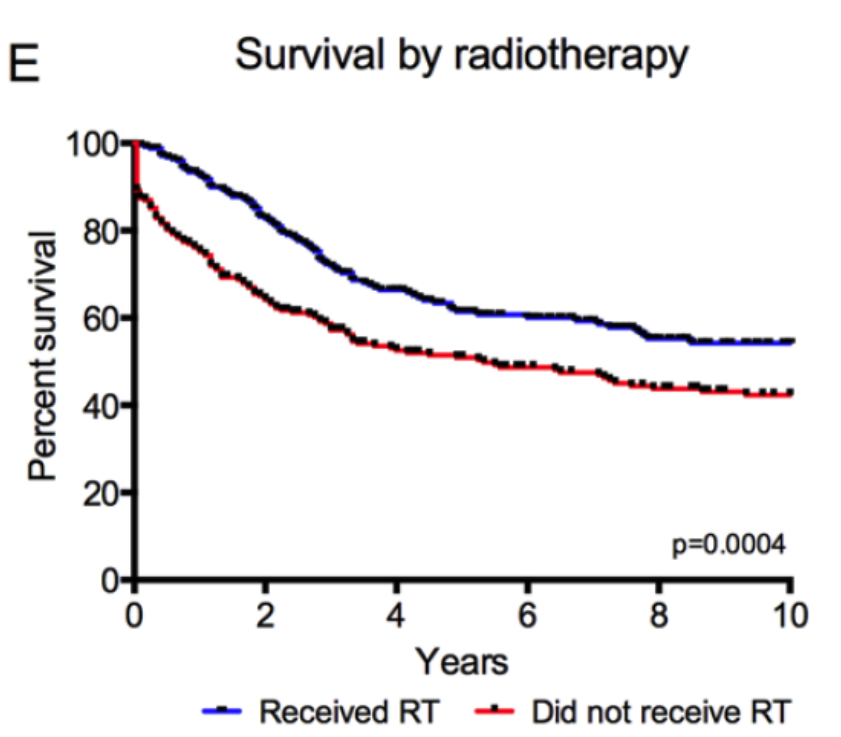
# Management of Ependymomas

Gross total Resection- single most important predictor of outcome that can be altered.

Despite its tough location, in 75-80% of the times, surgeons are able to achieve GTR/NTR

GTR- defined as no residual disease seen intra-op as well on postop imaging.




Snider et al . *Ped Blood Cancer*. 2018; 65: e26880

# Historically…. After surgery

**Age < 3 years**

↓

**Chemotherapy**

| | |
|---|---|
| 5YR EFS: | 24% ± 5% |
| 5YR OS: | 43% ± 5% |

Neuro Oncol 2014 16:457-65
Study Dates 1992-1997

**Age > 3 years**

↓

**Radiation Therapy**

| | |
|---|---|
| 5YR EFS: | 57% ± 6% |
| 5YR OS: | 71% ± 6% |

Pediatr Blood Cancer 2012 59:1183-9
Study Dates 1995-1999

# Evidence for Adjuvant radiotherapy in Ependymoma

Preliminary Results From a Phase II Trial of Conformal Radiation Therapy and Evaluation of Radiation-Related CNS Effects for Pediatric Patients With Localized Ependymoma

*Thomas E. Merchant, Raymond K. Mulhern, Matthew J. Krasin, Larry E. Kun, Tani Williams, Chenghong Li, Xiaoping Xiong, Raja B. Khan, Robert H. Lustig, Frederick A. Boop,*

- 64 Ependymoma (of a phase 2 trial)
- 5 failures local only with 59.4 Gy – conformal radiotherapy
- **Dose of 59.4 Gy is necessary**.
- Adverse effects- long term. Better RT techniques to spare normal tissue toxicity

- To see if irradiated volumes **could be reduced** to minimize CNS related side effects at the same local control rates
- 3-year PFS- 75%
- Local failure was 14%
- Preserved NC outcomes at 2 years
- **Limited volume radiation is enough (1cm margin enough)**

# Management of Ependymomas

**A Prospective Study of Conformal Radiation Therapy for Pediatric Ependymoma**

**Prof. Thomas E. Merchant, DO, Chenghong Li, PhD, Prof. Xiaoping Xiong, PhD, Prof. Larry E. Kun, MD, Frederic A. Boop, MD,** and **Robert A. Sanford, MD**
Department of Radiological Sciences (Prof T Merchant DO, Prof L Kun MD, F Boop MD, R Sanford MD) and Department of Biostatistics (C Li PhD, Prof X Xiong PhD), St. Jude Children's Research Hospital, Memphis, TN, USA

153 pts, median age 2.9 yrs

7yr LC-84%, EFS-69.1%, OS-81%

| | | | Event-Free Survival (%) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Factors | Sub-Group | N | 5-Year | | 7-year | | | Hazards Ratio | |
| | | | estimate | 95% CI | estimate | 95% CI | P-Value | Estimate | 95% CI |
| Tumor grade | Differentiated | 68 | 86·4 | 76·8–96·0 | 79·2 | 69·6–88·8 | 0·005 | 1·0 | |
| | Anaplastic | 85 | 61·3 | 46·4–76·2 | 61·3 | 46·4–76·2 | | 2. ·58 | 1·30–5·12 |
| Tumor Location | Infratentorial | 122 | 71·1 | 60·5–81·7 | 65·8 | 55·2–76·4 | 0·16 | 1·0 | |
| | Supratentorial | 31 | 82·9 | 66·6–99·2 | 82·9 | 66·6–99·2 | | 0·52 | 0·20–1·32 |
| Race | White | 126 | 75·5 | 66·3–84·7 | 70·4 | 61·2–79·6 | 0·26 | 1·0 | |
| | Other | 27 | 64·5 | 30·8–98·2 | 64·5 | 30·8–98·2 | | 1·55 | 0·71–3·38 |
| Gender | Female | 58 | 84·7 | 73·9–95·5 | 81·0 | 70·2–91·8 | 0·018 | 1·0 | |
| | Male | 95 | 66·7 | 53·4–80·0 | 61·0 | 47·7–74·3 | | 2·4 | 1·13–5·06 |
| Age at CRT | ≥ 3 years | 75 | 79·0 | 66·8–91·2 | 69·4 | 57·2–81·6 | 0·37 | 1·0 | |
| | < 3 years | 78 | 68·6 | 55·7–81·5 | 68·6 | 55·7–81·5 | | 1·34 | 0·71–2·52 |
| Total Dose | 54 | 22 | 80·7 | 61·5–99·9 | 70·6 | 51·4–89·8 | 0·67 | 1·0 | |
| | 59·4 | 131 | 72·4 | 62·4–82·4 | 68·8 | 58·8–78·8 | | 1·04 | 0·87–1·24 |
| Surgery Number | 1 | 87 | 79·7 | 69·3–90·1 | 74·4 | 64·0–84·8 | 0·056 | 0·55 | 0·29–1·02 |
| | 2~4 | 66 | 65·6 | 49·5–81·7 | 62·0 | 45·9–78·1 | | 1·0 | |
| Surgery Extent | GTR | 125 | 81·5 | 72·7–90·3 | 77·3 | 68·5–86·1 | <0·0001 | 0·21 | 0·11–0·40 |
| | NTR or STR | 28 | 41·0 | 17·7–64·3 | 34·2 | 10·9–57·5 | | 1·0 | |
| Pre-CRT Chemotherapy | Yes | 35 | 59·4 | 39·6–79·2 | 48·7 | 28·9–68·5 | 0·008 | 1·0 | |
| | No | 118 | 78·1 | 68·3–87·9 | 75·9 | 66·1–85·7 | | 0·43 | 0·22–0·81 |

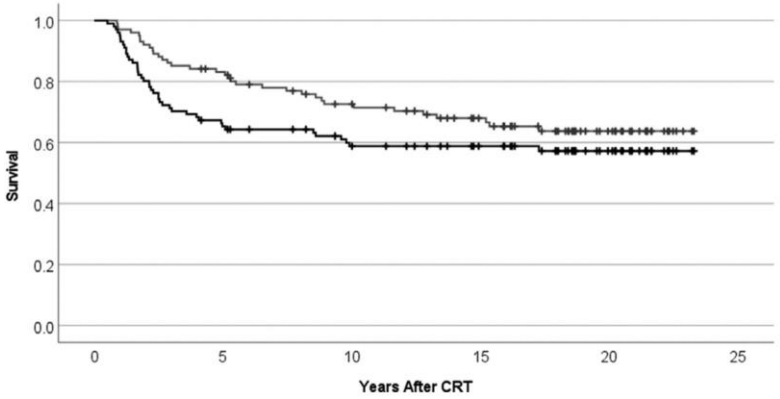
Lancet Oncol 2009

CLINICAL INVESTIGATION

IJROBP 2023

# Conformal Radiation Therapy for Ependymoma at Age ≤3 Years: A 25-Year Experience

Gabrielle N. Howe, BS,* Drucilla Y. Edmonston, MD,‡ Grace C. Dirks, BS,* Frederick A. Boop, MD,† and Thomas E. Merchant, DO, PhD*




The 10-year event-free and overall survivals were 58.5% and 72.6% respectively, with a median follow-up of 18.4 years (range, 4.2-23.3 yrs).

Death occurred in 34 patients from ependymoma (n = 24), secondary malignancy (n = 6), necrosis (n = 2), shunt failure (n = 1), & anaphylactic reaction (n = 1).

23 patients developed a secondary tumor including 6 cases of fatal high-grade glioma.

Of the surviving cohort and those ≥18 years old, 98% obtained a high school diploma, 64% had a current driver's license, 89% were students or employed full or part time, 32% were living independently, and 70% received higher education or training

# Conformal Radiation Therapy for Pediatric Ependymoma, Chemotherapy for Incompletely Resected Ependymoma, and Observation for Completely Resected, Supratentorial Ependymoma

Thomas E. Merchant, DO, PhD[1]; Anne E. Bendel, MD[2]; Noah D. Sabin, MD, JD[1]; Peter C. Burger, MD[3]; Dennis W. Shaw, MD[4]; Eric Chang, MD[5,6]; Shengjie Wu, MS[1]; Tianni Zhou, PhD[7]; David D. Eisenstat, MD[8,9]; Nicholas K. Foreman, MD[10]; Christine E. Fuller, MD[11]; Edwina Templeton Anderson, BS[1]; Juliette Hukin, MB[12]; Ching C. Lau, MD, PhD[13-15]; Ian F. Pollack, MD[16]; Fred H. Laningham, MD[17]; Robert H. Lustig, MD[18]; Floyd D. Armstrong, PhD[19]; Michael H. Handler, MD[10]; Chris Williams-Hughes, BA[20]; Sandra Kessel, BA[21]; Mehmet Kocak, PhD[1]; David W. Ellison, MD, PhD[1]; and Vijay Ramaswamy, MD[22]

ACNS 0121 study

J Clin Oncol 37. © 2019

# Role of surgery

- GTR 1 was defined as no visible residual tumor identified under the operating microscope and no evidence of disease in postoperative neuroimaging.
- GTR 2 was defined as microscopically visible residual tumor identified under the operating microscope and no evidence of disease in postoperative neuroimaging.
- NTR was defined as residual tumor evident on postoperative neuroimaging with thickness or nodularity measuring 0.5 cm or smaller in the greatest dimension.
- STR was defined as residual tumor measuring greater than 0.5 cm on postoperative imaging.

# Treatment Strata

356 new pts, 1-21 yrs old

| Stratum | 1 11 pts | 2 64 pts | 3 118 pts | 4 163 pts |
|---|---|---|---|---|
| Surgery | GTR1 | STR | NTR/GTR2 | GTR1 |
| WHO Grade | II | II-III | II-III | II-III |
| Site | Supratentorial | Any | Any | Supratentorial III<br>Infratentorial II-III |
| Treatment | Observation | Chemotherapy<br>↓<br>± 2nd Surgery<br>↓<br>Radiation Therapy | Radiation Therapy | |
| Treatment Group | 1 | 2 | 3 | |

| | EFS (95% CI) | | |
|---|---|---|---|
| **Category** | **5 Year** | **7 Year** | **10 Year** |
| All patients | **62.7 (57.4 to 68.0)** | 60.4 (54.5 to 66.3) | 55.6 (36.8 to 74.4) |
| S1: observation | **61.4 (33.2 to 89.6)** | 51.1 (16.0 to 86.2) | |
| S2: STR and CT | **37.2 (24.8 to 49.5)** | 33.3 (19.0 to 47.6) | 33.3 (0.0 to 70.9) |
| S2: STR and CT (second surgery positive) | **50.5 (30.3 to 70.7)** | 45.9 (24.9 to 66.9) | 45.9 (0.0 to 100.0) |
| S2: STR and CT (second surgery negative) | **28.5 (14.2 to 42.8)** | 25.0 (6.0 to 44.0) | 25.0 (0.0 to 55.0) |
| S2: STR and CT (second surgery GTR) | **50.0 (25.5 to 74.5)** | 50.0 (23.7 to 76.3) | 50.0 (0.0 to 100.0) |
| S3: NTR | **67.3 (58.5 to 76.1)** | 65.4 (56.0 to 74.8) | 58.9 (34.2 to 83.6) |
| S4: GTR | **69.5 (62.1 to 76.9)** | 67.9 (59.7 to 76.1) | 62.1 (31.5 to 92.7) |
| S3 and S4: NTR and GTR | **68.5 (62.8 to 74.2)** | 66.8 (60.5 to 73.1) | 60.9 (40.9 to 80.9) |
| S3 and S4: NTR and GTR (WHO grade 2) | **74.6 (67.5 to 81.7)** | 73.1 (65.5 to 80.7) | 68.8 (47.0 to 90.6) |
| S3 and S4: NTR and GTR (WHO grade 3) | **60.7 (51.5 to 69.9)** | 58.6 (48.6 to 68.6) | 49.8 (9.8 to 89.8) |
| S3 and S4: NTR and GTR (age < 3 years) | **62.9 (51.9 to 73.9)** | 61.4 (49.6 to 73.2) | 53.8 (24.6 to 83.0) |
| S3 and S4: NTR and GTR (age ≥ 3 years) | **70.5 (63.8 to 77.2)** | 68.8 (61.5 to 76.1) | 63.8 (38.7 to 88.9) |
| S2: STR and CT/1q gain positive | 20.0 (0.0 to 44.7) | NA | NA |
| S2: STR and CT/1q gain negative | 16.3 (0.0 to 33.2) | 16.3 (0.0 to 37.1) | NA |
| S3 and S4: NTR and GTR/1q gain (positive) | **47.4 (26.0 to 68.8)** | 47.4 (23.7 to 71.1) | 47.4 (0.0 to 100.0) |
| S3 and S4: NTR and GTR/1q gain (negative) | **82.8 (74.4 to 91.2)** | 78.6 (69.0 to 88.2) | 78.6 (49.6 to 100.0) |
| PFA + 1q gain (positive) | **35.7 (12.8 to 58.6)** | 35.7 (10.6 to 60.8) | 35.7 (0.0 to 91.8) |
| PFA + 1q gain (negative) | **81.5 (71.5 to 91.5)** | 75.8 (64.0 to 87.6) | 75.8 (43.1 to 100.0) |
| | **Cumulative Incidence LF** | | |
| | **5 Year (95% CI)** | **7 Year (95% CI)** | **10 Year (95% CI)** |
| S3 and S4: NTR and GTR/1q gain (positive) | **31.58 (9.78 to 53.38)** | 31.58 (9.78 to 53.38) | 31.58 (9.78 to 53.38) |
| S3 and S4: NTR and GTR/1q gain (negative) | **12.29 (5.10 to 19.48)** | 13.69 (6.10 to 21.28) | 13.69 (6.10 to 21.28) |

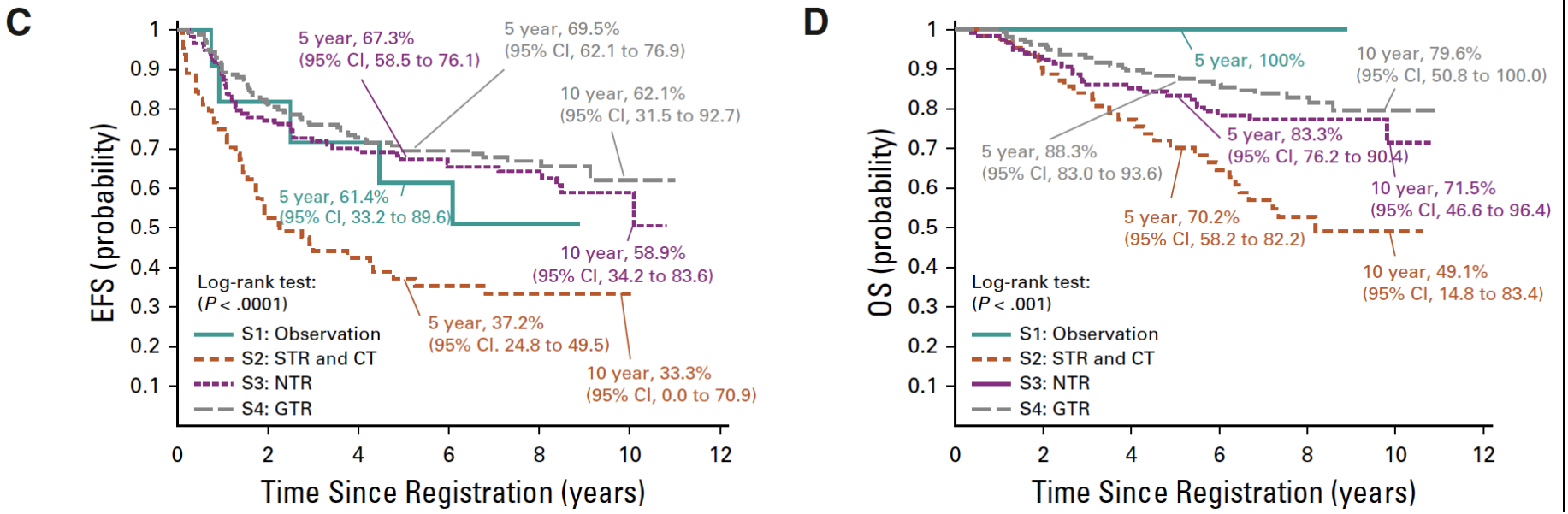
| S (95% CI) | | |
|---|---|---|
| **OS 5 Year** | **OS 7 Year** | **OS 10 Year** |
| **83.8 (79.7 to 87.9)** | 77.4 (72.3 to 82.5) | 71.2 (53.0 to 89.4) |
| 100 | 100 | |
| **70.2 (58.2 to 82.2)** | 57.0 (42.9 to 71.1) | 49.1 (14.8 to 83.4) |
| 66.4 (47.6 to 85.2) | 62.0 (42.0 to 82.0) | 57.2 (5.3 to 100.0) |
| 72.5 (57.6 to 87.4) | 53.0 (34.0 to 72.0) | 43.5 (6.5 to 80.5) |
| 71.4 (48.9 to 93.9) | 64.3 (39.2 to 89.4) | 56.3 (0.0 to 100.0) |
| **83.3 (76.2 to 90.4)** | 77.4 (69.0 to 85.8) | 71.5 (46.6 to 96.4) |
| **88.3 (83.0 to 93.6)** | 83.9 (77.4 to 90.4) | 79.6 (50.8 to 100.0) |
| **86.2 (81.9 to 90.5)** | 81.2 (75.9 to 86.5) | 75.3 (55.7 to 100.0) |
| 89.4 (84.3 to 94.5) | 85.1 (78.8 to 91.4) | 82.2 (62.6 to 100.0) |
| 82.0 (74.7 to 89.3) | 76.1 (67.5 to 84.7) | 59.7 (16.8 to 100.0) |
| **87.4 (79.6 to 95.2)** | 82.7 (71.5 to 93.9) | 79.4 (50.6 to 100.0) |
| **85.8 (80.4 to 90.9)** | 80.7 (74.4 to 87.0) | 73.2 (48.5 to 97.9) |
| **20.0 (0.0 to 44.7)** | NA | NA |
| **84.6 (65.8 to 100.0)** | 50.8 (24.3 to 77.3) | NA |
| **68.4 (48.2 to 88.6)** | 57.0 (32.5 to 81.5) | 57.0 (0.0 to 100.0) |
| **91.3 (85.0 to 97.6)** | 85.9 (77.7 to 94.1) | 76.4 (46.6 to 100.0) |
| **64.3 (40.6 to 88.0)** | 50.0 (21.8 to 78.2) | 50.0 (0.0 to 100.0) |
| **91.6 (84.3 to 98.9)** | 86.0 (76.4 to 95.6) | 73.7 (40.6 to 100.0) |
| | **Cumulative Incidence DF** | |
| **5 Year (95% CI)** | **7 Year (95% CI)** | **10 Year (95% CI)** |
| **21.05 (2.12 to 39.98)** | 21.05 (2.12 to 39.98) | 21.05 (2.12 to 39.98) |
| **6.09 (0.88 to 11.30)** | 6.09 (0.88 to 11.30) | 6.09 (0.88 to 11.30) |

# 1. Outcomes improved over time

| Age < 3 years | POG9233 (1992-97)† | ACNS0121 (2003-07) | |
|---|---|---|---|
| | All Patients | All Patients | Strata 3-4 |
| 5 year EFS | 24% | 57% | 63% |
| 5 year OS | 43% | 85% | 87% |

| Age ≥ 3 years | CCG9942 (1995-99)‡ | ACNS0121 (2003-07) | |
|---|---|---|---|
| | All Patients | All Patients | Strata 3-4 |
| 5 year EFS | 57% | 65% | 71% |
| 5 year OS | 71% | 83% | 85% |

# 2. Outcomes for each strata

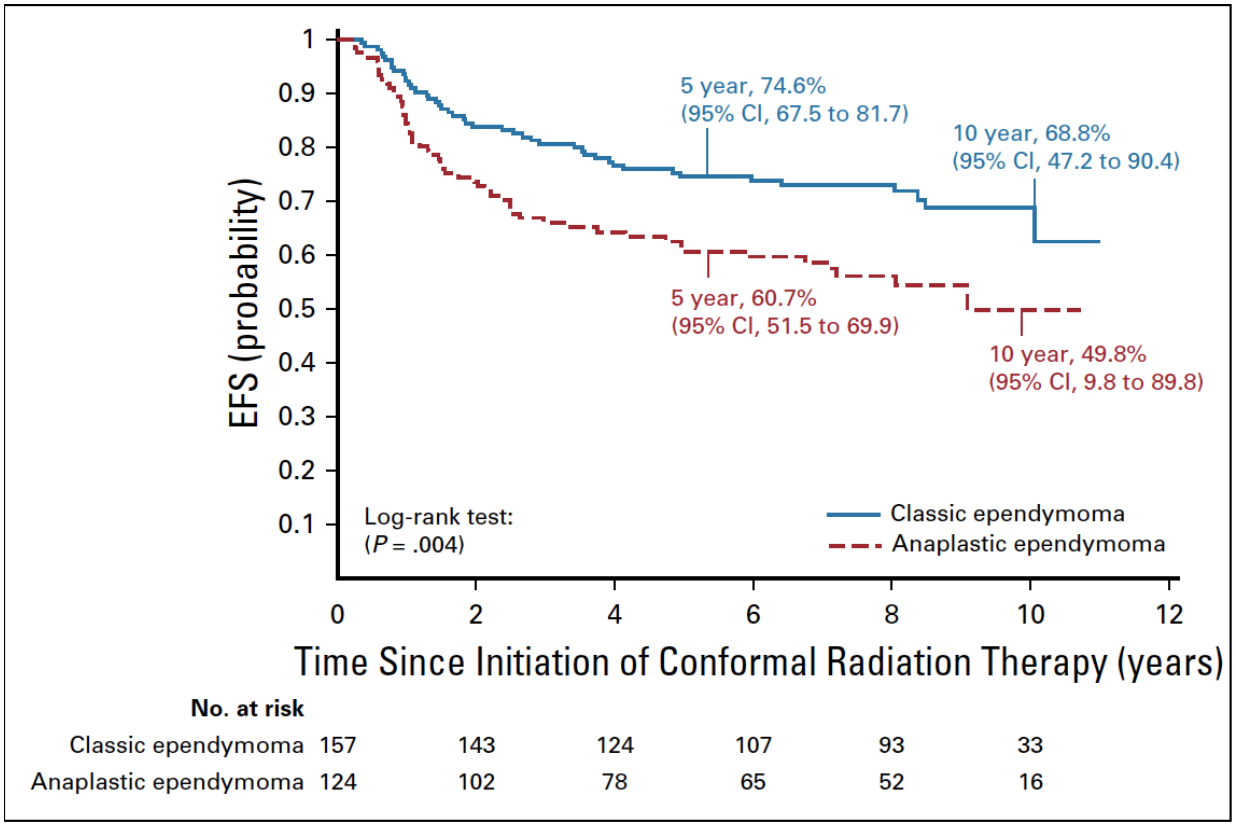


# 3. Impact of age

| | <3 yrs | >3 yrs | P value |
|---|---|---|---|
| 5 yr EFS | 62.9% | 70.5% | NS |
| 5 yr OS | 87.4% | 85.8% | NS |

Immediate postoperative radiation nullified the effect of age

# 4. Impact of grade



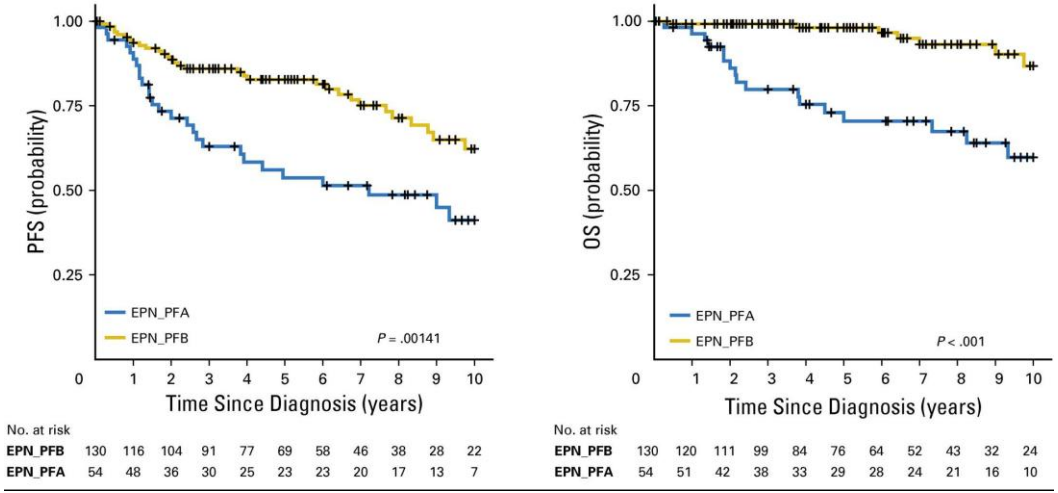

Grade still very relevant in strata 3 and 4

# 5.1 Impact of molecular subgroups

79% of ST tumors had RELA fusion

No impact of RELA fusion status on outcome of patients

# 5.2 Impact of Molecular subgroups



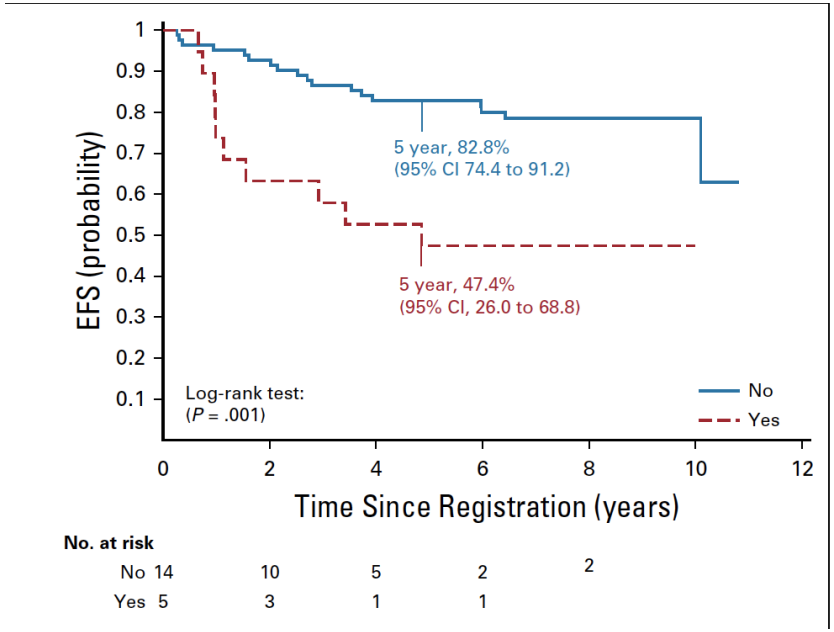

ACNS 0121

There was no impact of classifying PF lesions to A and B

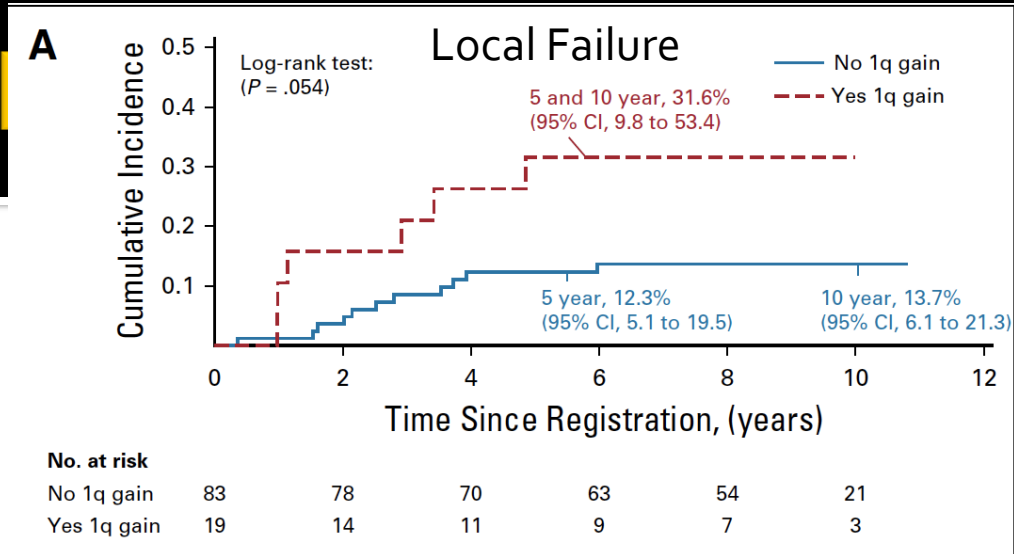
PF-A lesions did as well as others with immediate Postop RT

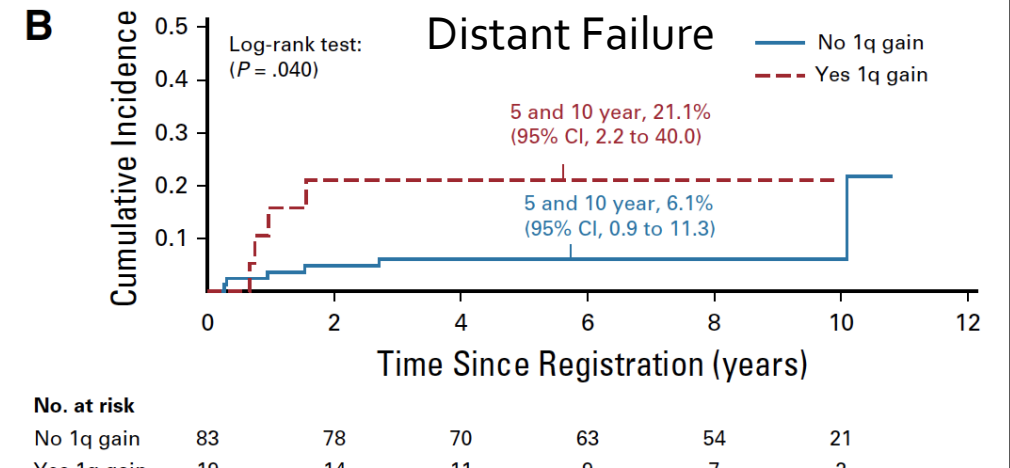
Ramaswamy et al, *J Clin Oncol*, 2016; 34(21):2468-2477

# 5.2 Impact of Mol




Impact of 1q gain



# 5.2 Impact of Molecular subgroups

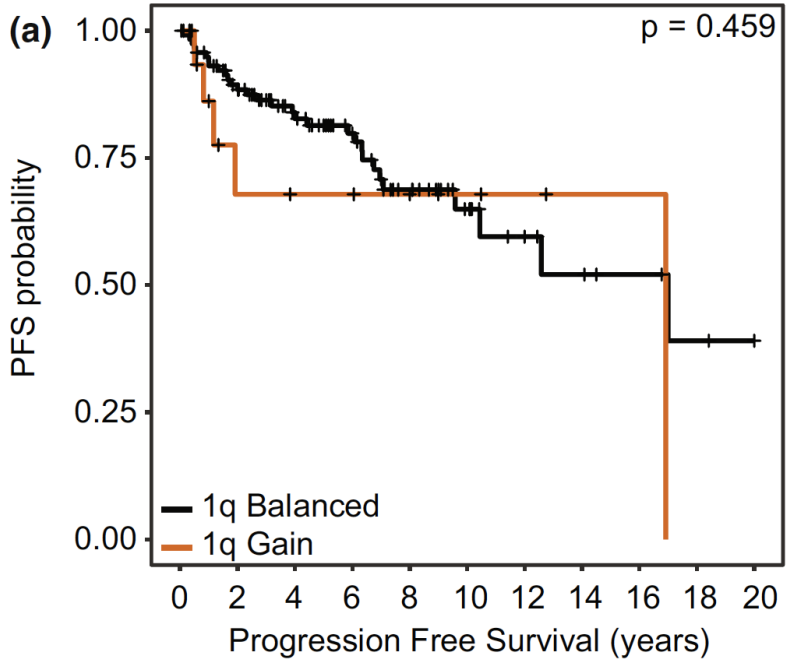
Strata 2- STR followed by chemo followed by Surgery & RT

No impact of 1q gain on EFS, failure patterns

OS: 20% vs. 84.6% (p=0.019)

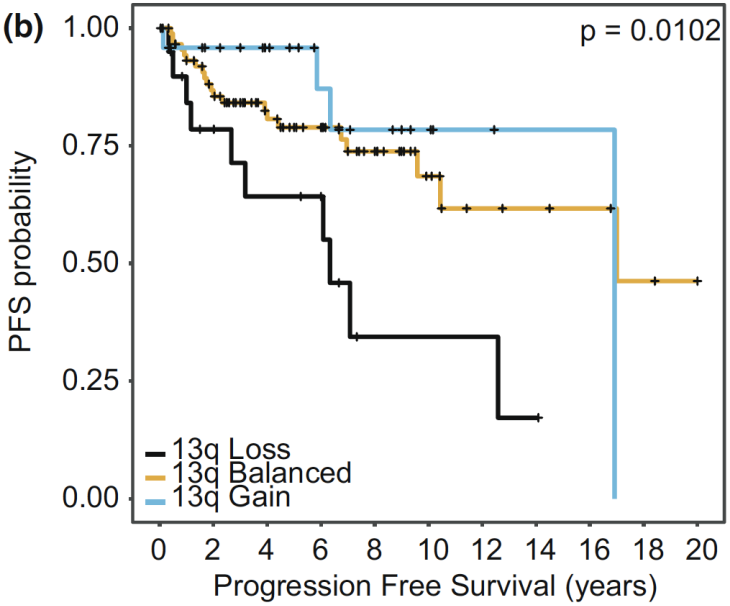
Impact of 1q gain

# Additional Information- PF-B




No. at risk

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Gain 1q** | 20 | 7 | 6 | 6 | 5 | 3 | 2 | 1 | 1 | 0 | 0 |
| **No gain** | 117 | 93 | 66 | 51 | 28 | 16 | 10 | 7 | 5 | 3 | 2 |



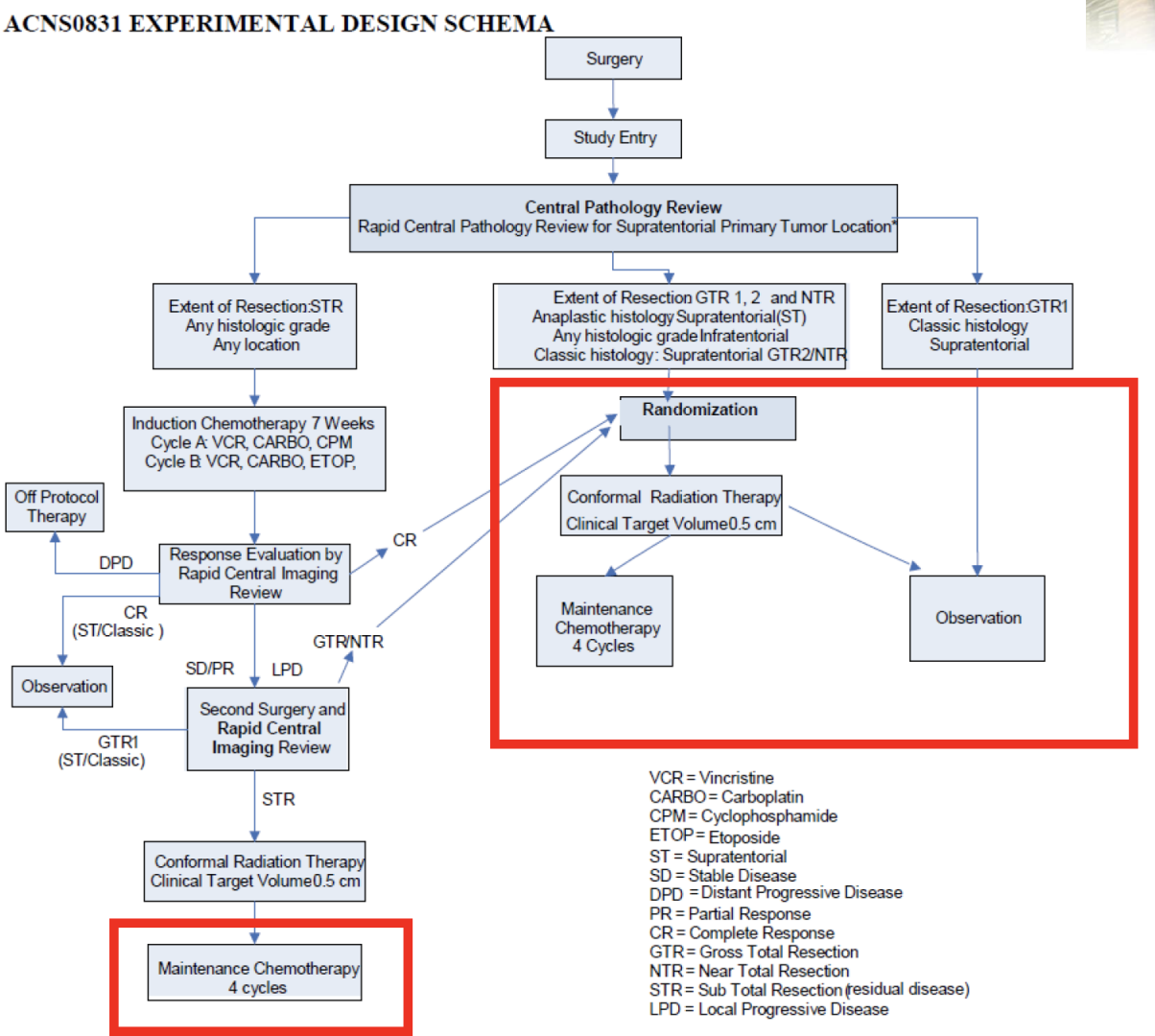

No. at risk

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **13q gain** | 24 | 19 | 15 | 10 | 7 | 4 | 2 | 1 | 1 | 0 | 0 |
| **13q bal** | 91 | 67 | 47 | 38 | 23 | 12 | 7 | 6 | 5 | 3 | 2 |
| **13q loss** | 20 | 12 | 9 | 8 | 2 | 2 | 2 | 1 | 0 | 0 | 0 |

Cavalli, et al Acta Neuropath 2018

# ACNS 0831

Role of Maintenance chemotherapy after surgery & radiation is being evaluated



# Issue of radiation dose

54 Gy vs. 59.4Gy, the practice varies

Current ACNS0831 protocol

CTV1: Residual tumor and resection bed + 0.5cm
CTV2: Residual tumor and resection bed, excluding the cord

Dose: 54Gy to PTV1 and 5.4Gy boost to PTV2
(previously 54Gy to children <3yrs)

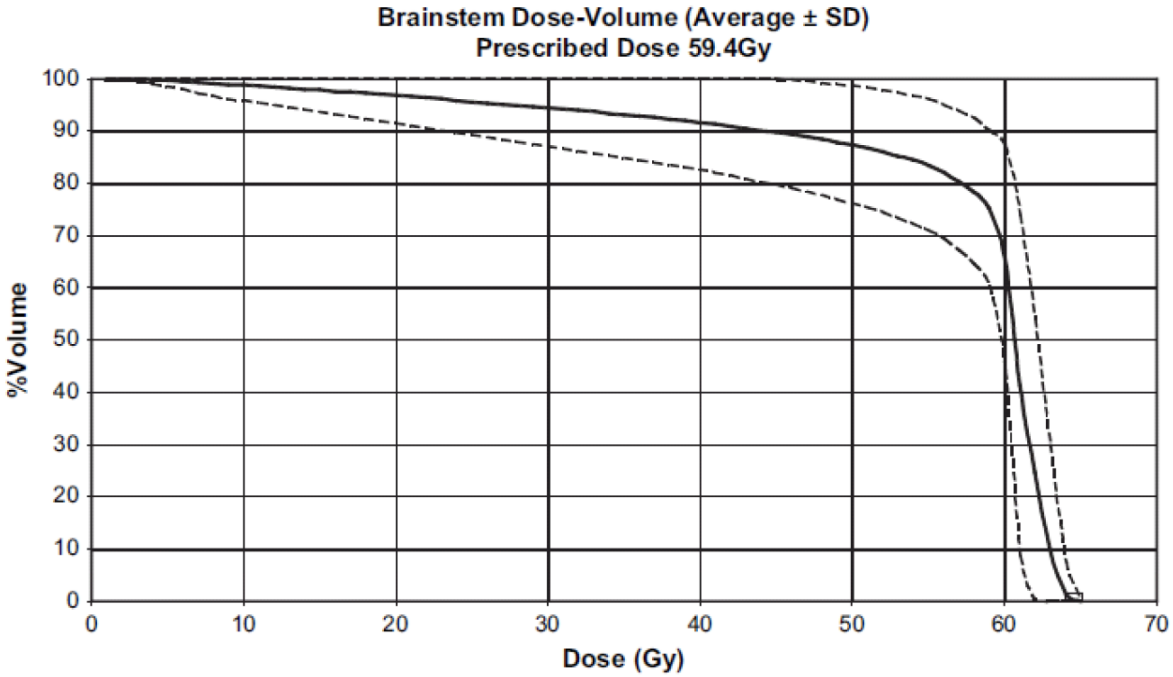
# Impact of higher dose

Phase 2 study local postop RT for 1-21 yrs

74/88 pts had GTR

59.4Gy to 73 pts and 54Gy to <3yrs old

75% 3 yrs PFS,
8/20 recurrences local only




J Clin Oncol 22:3156-3162. © 2004

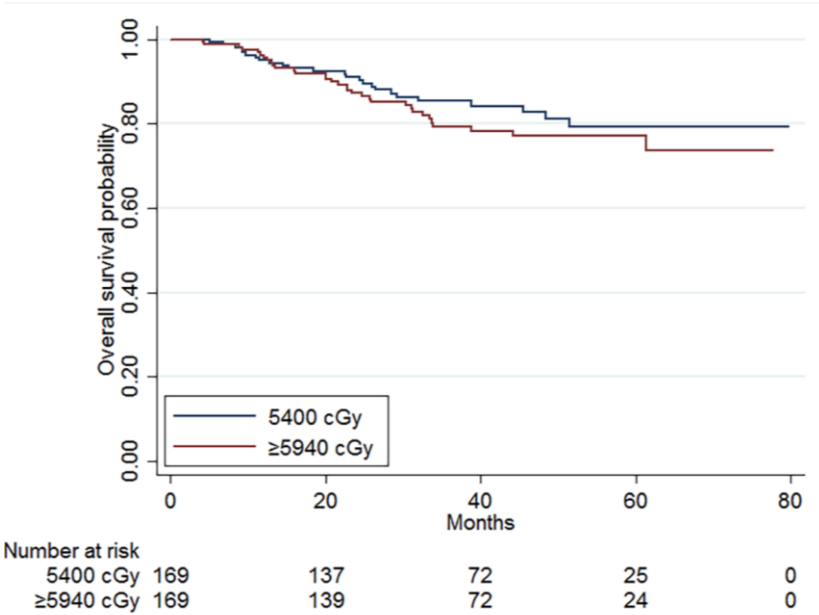
# Impact of higher dose

- POG-9132: 6960cGy through Hyperfractionation
- SIOP 59.4Gy followed by 8Gy/2#

- NCDB study 548 patients

  Did not show a benefit w.r.to OS

  No data regarding local control




Kovnar, et al JNO 1997
Massimino M, et al IJROBP 2004, Neuro Oncol 2016
Vogel, et al ARO 2019,

# Impact of higher dose on brainstem

Table 3. Impact of brainstem dose–volume on functional recovery for patients with infratentorial ependymoma treated with postoperative irradiation

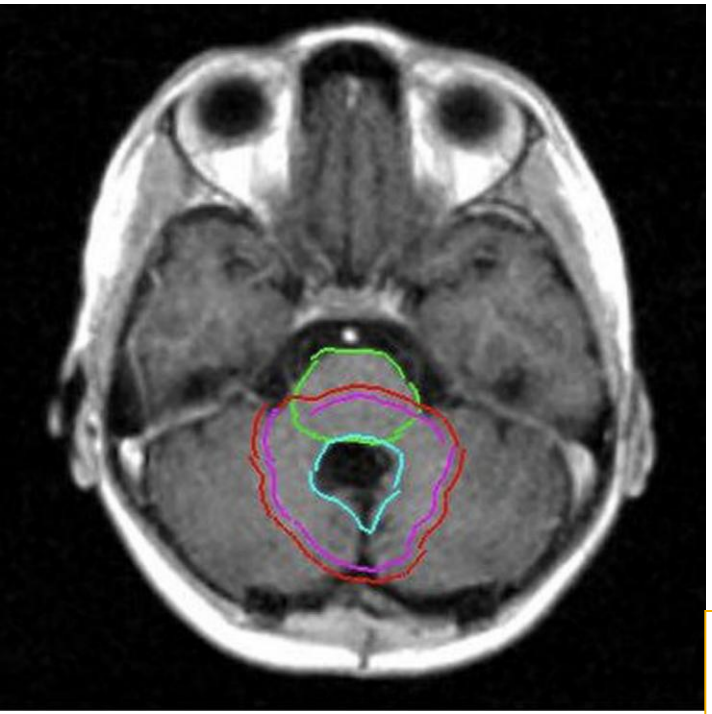
| Dose factor | Mean ± SD volume (ml) | Odds ratio (95% CI) of response at 12 months ($n$ = 62 patients) | $p$ value | Odds ratio (95% CI) of response at 24 months ($n$ = 56 patients) | $p$ value |
|---|---|---|---|---|---|
| Volume (ml) >54Gy | 15.06 + 4.15 | 1.052 (0.928 to 1.192) | 0.43 | 0.993 (0.877 to 1.125) | 0.92 |
| Volume (ml) >56Gy | 13.34 + 6.09 | 1.045 (0.953 to 1.146) | 0.35 | 0.993 (0.912 to 1.082) | 0.88 |
| Volume (ml) >58Gy | 12.24 + 6.28 | 1.014 (0.932 to 1.104) | 0.75 | 0.974 (0.897 to 1.058) | 0.54 |
| Volume (ml) >60Gy | 7.64 + 6.53 | 1.055 (0.972 to 1.145) | 0.2 | 1.031 (0.949 to 1.120) | 0.47 |
| % volume >54Gy | 79.95 + 15.66 | 0.986 (0.954 to 1.020) | 0.42 | 0.964 (0.927 to 1.002) | 0.06 |
| % volume >56Gy | 69.89 + 28.99 | 1.002 (0.983 to 1.020) | 0.87 | 0.989 (0.971 to 1.008) | 0.25 |
| % volume >58Gy | 64.03 + 30.21 | 0.996 (0.979 to 1.013) | 0.64 | 0.986 (0.969 to 1.004) | 0.12 |
| % volume >60Gy | 39.60 + 32.47 | 1.006 (0.989 to 1.022) | 0.49 | 1.001 (0.985 to 1.018) | 0.88 |

| | | |
|---|---|---|
| Wenkel[14¶,**,††] | CGE Surface ≤64 | |
| 46 | CGE Center ≤53 | |
| | CGE | |

QUANTEC paper IJROBP 2010

Merchant, et al. IJROBP 2009

# Impact of dose on brainstem toxicity



Gender, GTV volume were factors at 12 months
No. of resections, age were factors at 24 months
CSF shunting, GTV volume were factors at 60 months

<u>No differences in outcomes based on DVH parameters to Brainstem</u>

Total 68 pts
17 without deficits did not develop any deficit
4 pts developed progressive deficits

Conclusions: Incomplete recovery of brainstem function is related to surgical morbidity and the volume and the extent of tumor.

Merchant, et al IJROBP 2010

# Timing of radiation therapy

Advances in Radiation Oncology (2021) 6, 100691

advances in radiation oncology

www.advancesradonc.org

Scientific Article

## Effect of Postoperative Radiation Therapy Timing on Survival in Pediatric and Young Adult Ependymoma

Sunny Shah, MS,[a,1] Kevin Gates, MS,[a,1] Chase Mallory, BHS,[a,1] Muni Rubens, PhD, MPH,[a] Ossama M. Maher, MD,[b] Toba N. Niazi, MD,[c] Ziad Khatib, MD,[b] Rupesh Kotecha, MD,[a] Minesh P. Mehta, MD,[a] and Matthew D. Hall, MD, MBA[a,*]

[a]*Department of Radiation Oncology, Miami Cancer Institute, Baptist Health South Florida, Miami, Florida;* [b]*Department of Pediatric Oncology,* [c]*Department of Pediatric Neurosurgery, Nicklaus Children's Hospital, Miami, Florida*

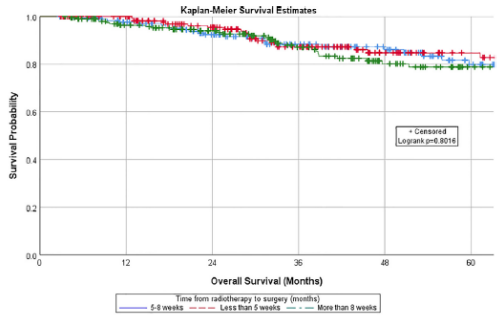



**Figure 3** Overall survival curves as a function of postoperative radiation therapy timing in patients treated between 2010 and 2016 (n = 565), when extent of surgical resection was known in all patients.

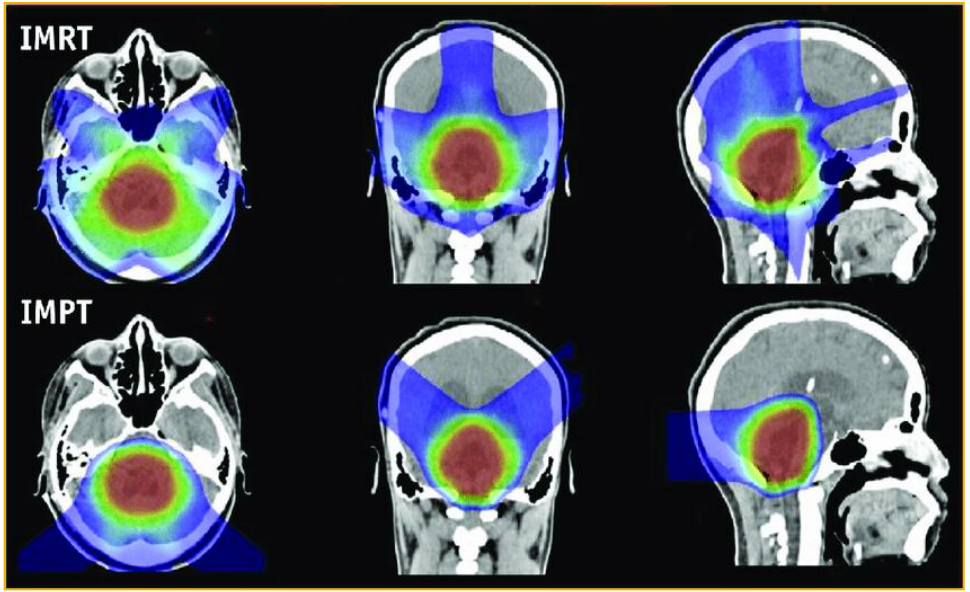
- No clear detriment with delayed RT in pediatric and young adult patients with localized intracranial ependymoma
- Given the importance of NTR/GTR on survival, we advise complete surgical resection whenever feasible, even if second look surgery is required, leading to a delay in adjuvant RT
- **Routine delays in postoperative RT should be avoided,** but these data suggest that it may be considered in selected patients who may benefit from second look surgery, require additional time for adequate healing, or to facilitate referral to a high-volume RT center.

# Impact of technique

Conformal technique preferred

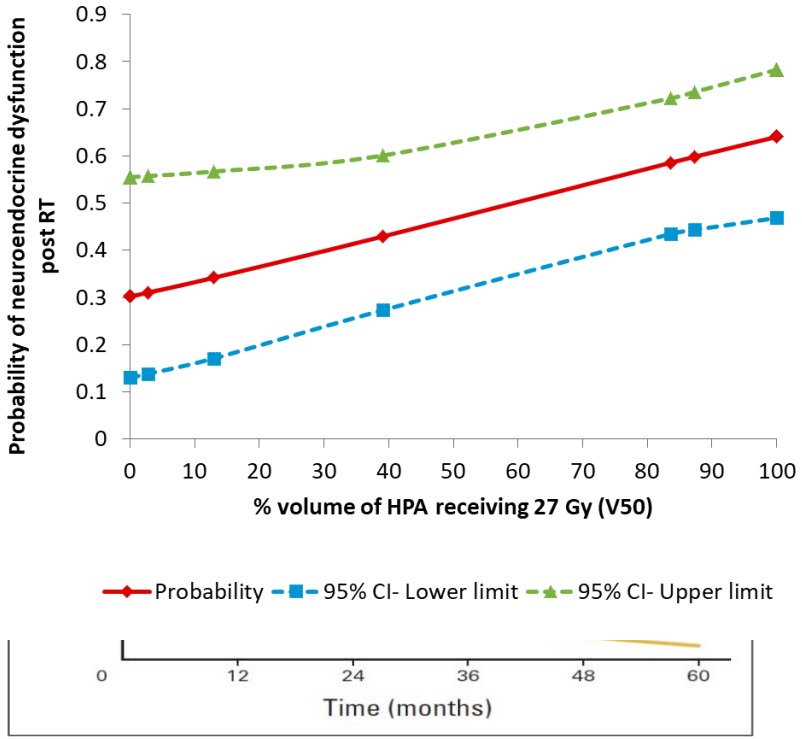
IMRT was preferred in ACNS 0121 due to wide availability

Proton therapy encouraged wherever possible- 20/356



# Impact of Proton therapy

- Hearing loss
- Impaired Cognition
- Impaired academic performance
- Endocrine Dysfunction
- Growth abnormalities
- Vasculopathy- CVA
- Brain stem necrosis
- Optic pathway dysfunction
- Social issues
- Psychological issues
- Impaired overall QOL
- Second Malignant neoplasms



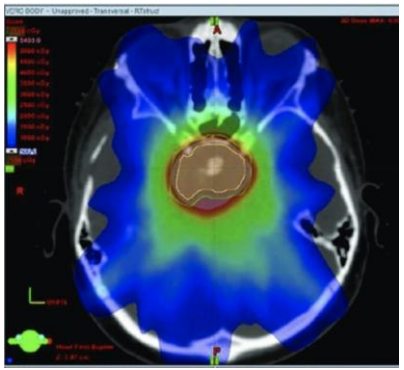

JCO 2016,JCO 2011, R Jalali, et al PRO 2019

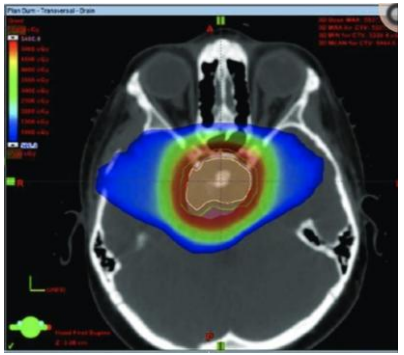
## Superior Intellectual Outcomes After Proton Radiotherapy Compared With Photon Radiotherapy for Pediatric Medulloblastoma

Lisa S. Kahalley, PhD[1,2]; Rachel Peterson, PhD[3]; M. Douglas Ris, PhD[1,2]; Laura Janzen, PhD[3]; M. Fatih Okcu, MPH, MD[1,2]; David R. Grosshans, MD, PhD[4]; Vijay Ramaswamy, MD, PhD[3,5]; Arnold C. Paulino, MD[4]; David Hodgson, MD[6]; Anita Mahajan, MD[7]; Derek S. Tsang, MD, PhD[6]; Normand Laperriere, MD[6]; William E. Whitehead, MPH, MD[1,2]; Robert C. Dauser, MD[1,2]; Michael D. Taylor, MD, PhD[3,5]; Heather M. Conklin, PhD[8]; Murali Chintagumpala, MD[1,2]; Eric Bouffet, MD[3,5]; and Donald Mabbott, PhD[3,5]

- Superior long-term outcomes in global IQ, perceptual reasoning, and working memory compared with the XRT group (all P < .05).
- XRT group exhibited a significant decline whereas PRT group exhibited stable scores over time in all domains with the exception of processing speed (P = .003)

| Endocrine axis | X-ray | Proton | P value |
|---|---|---|---|
| Hypothyroidism | 69% | 23% | 0.01 |
| Sex hormone deficiency | 19% | 3% | 0.02 |
| Any hormone replacement | 78% | 55% | 0.03 |
| Height SDS score | -2 | -1.19 | 0.02 |

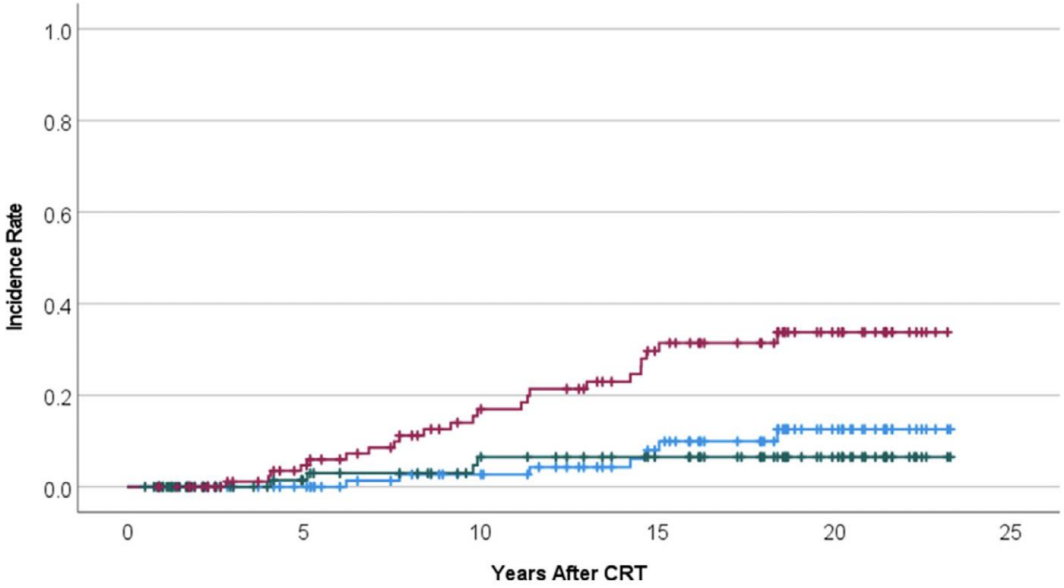




Eaton, et al Neuro Oncol 2016, JCO 2019

# Conformal Radiation Therapy for Ependymoma at Age ≤3 Years: A 25-Year Experience

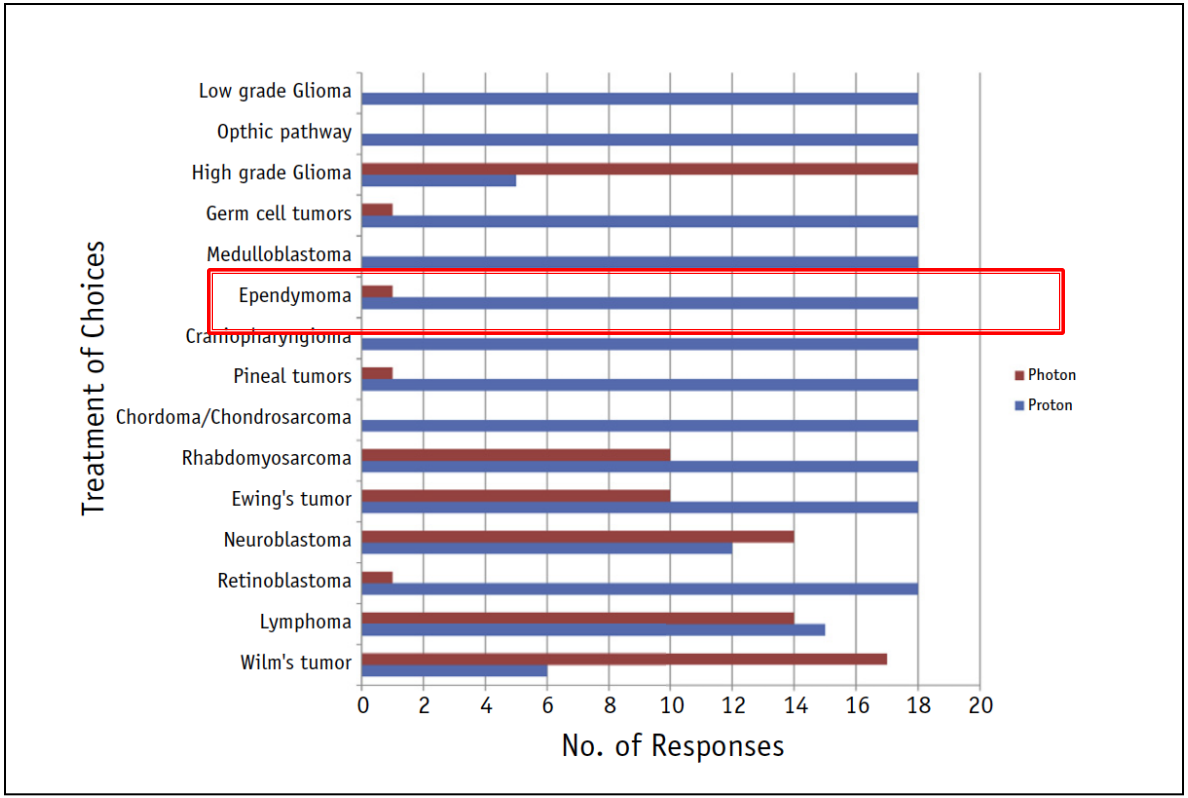
Gabrielle N. Howe, BS,* Drucilla Y. Edmonston, MD,‡ Grace C. Dirks, BS,* Frederick A. Boop, MD,† and Thomas E. Merchant, DO, PhD*




| | | |
|---|---|---|
| Secondary tumor, y | | |
| Benign thyroid nodule | 5 | 14.4 (4.00-16.19)* |
| Meningiomatosis | 1 | 4.92 |
| Cholesteatoma | 1 | 13.01 |
| Low-grade glioma | 1 | 2.80 |
| High-grade glioma, y | 6 | 9.79 (4.05-14.53)† |
| Meningioma, y | 7 | 14.25 (6.19-18.39) |
| Papillary thyroid cancer, y | 3 | 9.16 (6.84-11.32) |
| Vestibular schwannoma, y | 1 | 11.14 |

**Fig. 2.** Incidence rate for the development of any neoplasm (upper curve, red), meningioma (middle curve, blue), or high-grade glioma (lower, green) after conformal photon radiation therapy for ependymoma, age <3 years.

# Consensus Report From the Stockholm Pediatric Proton Therapy Conference



ACTA ONCOLOGICA, 2018
VOL. 57, NO. 5, 644–648
https://doi.org/10.1080/0284186X.2017.1413248

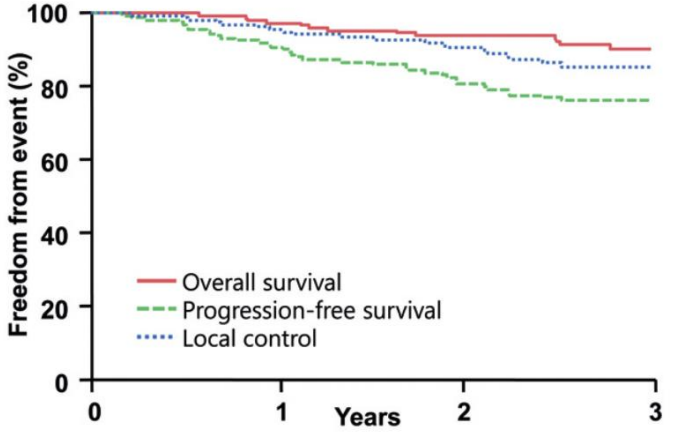
Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

OPEN ACCESS Check for updates

## Outcomes following proton therapy for pediatric ependymoma

Daniel J. Indelicato[a], Julie A. Bradley[a], Ronny L. Rotondo[a], Ronica H. Nanda[a], Natalie Logie[a], Eric S. Sandler[b], Philipp R. Aldana[c], Nathan J. Ranalli[c], Alexandra D. Beier[c], Christopher G. Morris[a] and Nancy P. Mendenhall[a]




No. of patients at risk after…

| | 0 years | 1 year | 2 years | 3 years |
|---|---|---|---|---|
| Local control | 179 | 145 | 115 | 85 |
| Progression-free survival | 179 | 138 | 107 | 83 |
| Overall survival | 179 | 149 | 121 | 94 |

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

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## Evaluating the safety and efficacy of proton radiotherapy for intracranial pediatric ependymomas: A single-arm *meta*-analysis

Lucca B. Palavani[a], Gabriel Semione[b], Gustavo de Oliveira Almeida[c], Henrique L. Lepine[d,*], Pedro Borges[e], Bernardo Vieira Nogueira[f], Gisele Lúcia[g], Márcio Yuri Ferreira[h], Anna Pereira[i], David Abraham Batista da Hora[g], Matheus de Jesus Leone Pereira[j], Fabio Torregrossa[k,l], Fernando De Nigris Vasconcellos[m], Raphael Bertani[n], Raphael Bastianon[o], Carolina Benjamin[p], Cleiton Formentin[q]

Ten cohorts comprising 908 patients with ependymoma were included. The patient population had an average age of 3.5 years, and 53.4 % were male.

| Endpoints | Proportion |
|---|---|
| 5 yr LC | 79% |
| 5 yr EFS | 65% |
| 5 yr OS | 83% |
| Neurological AE | 17% |
| Brainstem AE | 3% |

# Recurrence common phenomenon & re-irradiation a necessity

| Tumor Location / Subtype | Approx. 5–10 Year Local Recurrence Rate | Approx. Distant (Spinal/CSF) Recurrence Rate | Comments / Key Insights |
|---|---|---|---|
| **Posterior Fossa (Overall)** | **35–55%** | **8–15%** | Majority of relapses are local, even after GTR and adjuvant RT; higher in young children due to residual microscopic disease. |
| **Posterior Fossa Group A (PFA)** | **50–70%** | **10–20%** | Highest relapse risk among all subtypes; often within 2–3 years post-RT; driven by H3K27me3 loss and 1q gain; recurrence usually local and aggressive. |
| **Posterior Fossa Group B (PFB)** | **10–20%** | **<5%** | Much lower recurrence risk; older children/adolescents; long-term disease-free survival common after GTR ± RT. |
| **Supratentorial (Overall)** | **30–45%** | **10–20%** | Local relapse predominant; risk influenced by molecular fusion status. |
| **Supratentorial ZFTA fusion–positive** | **40–50%** | **10–15%** | Moderate–high recurrence; typically local; tends to recur within radiation field. |
| **Supratentorial YAP1 fusion–positive** | **<10%** | **<5%** | Excellent outcomes; recurrence rare after GTR; radiation often omitted in infants. |
| **Spinal Cord (NF2-mutant / Sporadic)** | **20–30% (local)** | **<5%** | Recurrence often along the same spinal segment; durable control after complete resection. |
| **Spinal MYCN-amplified** | **>70% (local ± distant)** | **20–30%** | Highly aggressive; early recurrence common despite multimodality therapy. |

Re-surgery followed by re-irradiation is the usual standard

# Pearls on Recurrence

1. **Time to first recurrence is one of the strongest prognostic factors** in ependymoma.

2. **Early failures** (within 24 months) typically indicate **radioresistant, molecularly aggressive disease** (especially PFA or ZFTA+).

3. **Late recurrences** tend to have **prolonged post-recurrence survival**, often with durable control after surgery and re-irradiation.

4. **Post-recurrence PFS** is roughly **one-third to one-half** of the initial PFS in most series, but **may equal or exceed it** in late-relapsing indolent subtypes (PFB, YAP1+, spinal).

5. **Re-irradiation is safe and beneficial** for localized relapse, especially with **proton therapy** minimizing cumulative dose to critical structures.

6. Long-term **surveillance (>10 years)** is essential — some PFB recurrences appear after a decade.

# Re-irradiation setting

49% progressed after salvage RT

29% neuraxis dissemination
20% local progression

- Systemic chemo to delay re-RT in salvage setting was detrimental

| | |
|---|---|
| After completion of re-RT | 16 (29%) |
| No systemic chemotherapy | 19 (35%) |
| Median (range) interval between RT1 and re-RT | 35 months (11–169 months) |
| Extent of re-RT | |
| Uni-focal | 49 (89%) |
| Multi-focal | 03 (5.5%) |
| Craniospinal irradiation | 03 (5.5%) |
| Dose of re-RT with equivalent dose in 2 Gy fraction (EQD2) | |
| Median (range) physical re-RT dose | 54 Gy (40–60 Gy) |
| Median (range) cumulative EQD2 | 106.2 Gy (92.4–117.6 Gy) |

**Extent of re-excision, sequence/timing of salvage re-irradiation, and disease-free interval impact upon clinical outcomes in recurrent/ progressive ependymoma**

Tejpal Gupta[1] · Madan Maitre[1] · Priyamvada Gupta[1] · Rahul Krishnatry[1] · Abhishek Chatterjee[1] · Aliasgar Moiyadi[2] · Prakash Shetty[2] · Vikas Singh[2] · Girish Chinnaswamy[3] · Sridhar Epari[4] · Ayushi Sahay[4] · Vijay Patil[5] · Jayant GodaSastri[1]

Median follow up of 37 months
3-yr PFS and OS were 40% and 51%.

- GTR at recurrence
- early salvage re-RT
- longer (> 2 years) DFI

Better Outcomes

Salvage re-RT was well tolerated with 5.5% developing symptomatic radiation necrosis

JNO 2020

# Re-irradiation Key take aways

- St.Jude's data (101 children) and Sick Kids data (31 children) demonstrate better EFS in pts treated with CSI for focal recurrence

Tsang, et al IJROBP 2017, Neuro Oncol 2019

- Need for full doses of RT in salvage RT setting, generally well tolerated.
- Molecular markers dictate survival
- Systemic chemotherapy to delay re-RT is detrimental

# APCC Experience

**Table 3-Average dose to organ at risk**

| | Posterior Fossa (PF-PBT) | Supratentorial (ST-PBT) |
|---|---|---|
| Brain stem (D Max)-Avg | 51 GyE | 36 GyE |
| C/L Hippocampus-( Dmean)-Avg | 27 GyE | 7 GyE |
| I/L Hippocampus-( Dmean)-Avg | 30 GyE | 31 GyE |
| C/L Cochlea( Dmean)-Avg | 29 GyE | 0.5 GyE |
| I/L Cochlea( Dmean)-Avg | 32 GyE | 10 GyE |
| Pituitary (Dmean)-Avg | 23 GyE | 14 GyE |
| Optic Chiasm (Dmax)-Avg | 23 GyE | 29 GyE |

**Table 1- Patient, tumour and treatment characteristics at initial diagnosis**

| Patient characteristics | N-31 |
|---|---|
| Median age at diagnosis (range) | 11.7 years(11 months- 53 years) |
| <3 years | 12(39%) |
| 3-18 years | 13(42%) |
| 18 above | 6(119%) |
| Gender | |
| Male | 19(61%) |
| Female | 12(39%) |
| Location | |
| Posterior fossa | 20(64%) |
| Supratentorial | 7(23%) |
| Spinal | 4(13%) |
| Tumour Grade | |
| 2 | 11(36%) |
| 3 | 20(64%) |
| Molecular Pattern | |
| H3K27Me3 Global loss | 14(45%) |
| H3K27Me3 reduced | 2(7%) |
| EZHIP | 2(7%) |
| ZFTA Fusion(L1CAM) | 3(9%) |
| NF2 | 1(3%) |
| Spinal Myxopapillary ependymoma | 1(3%) |
| Spinal with Leptomeningeal deposit-N-myc-negative | 2(7%) |
| Recurrent Pattern | |
| Local | 9(82%) |
| Distal | 2(18%) |
| Surgery before Re-RT | 8 (82%) |
| GTR/NTR | 6(54%) |
| Subtotal resection | 2(37%) |
| Chemotherapy | 6 (54%) |
| Before Re-RT | 2 (33%) |
| After Re-RT | 4(67%) |
| Radiation details | |
| Median interval RT after the first Radiation | 36 months (range -17 -47 months) |
| Craniospinal Irradiation | 8 (72%) |
| Focal RT | 3(28%) |

# APCC experience

25 pts, were treated between 2018-2023; 17 males, 8 females

17 newly diagnosed, 6-local recurrences, 2-distant recurrences

Median age-10.8 yrs (9mo-52 yrs); <3yrs-24%, 3-18yrs-56%, and >18years-20%

18pts- PF ependymoma, 4 pts- ST ependymoma & 3-spinal ependymoma

| | Posterior fossa | Supra-tentorial | Spinal |
|---|---|---|---|
| Grade 2 -11(44%) | 10(40%) | 1(4%) | 1 |
| Grade 3-14(60%) | 9(36%) | 3(12%) | 2(8%) |

Molecular Alteration:

All 10 PF-A Ependymomas had H3K27me3 global loss, of which 3 had 1q gain.

Among ST Ependymomas- 2 patients had ZAFTA fusion, 1 had Yap1 fusion.

# Surgical details

New Cases-Total-17

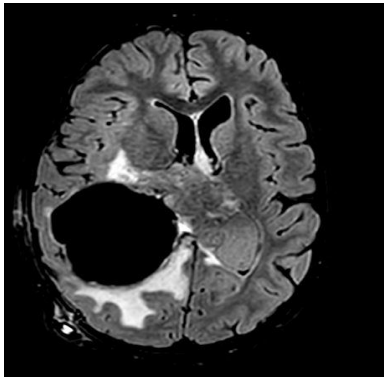
- 29.4%(5 patients) underwent multiple surgeries to maximize the extent of resection at APCC

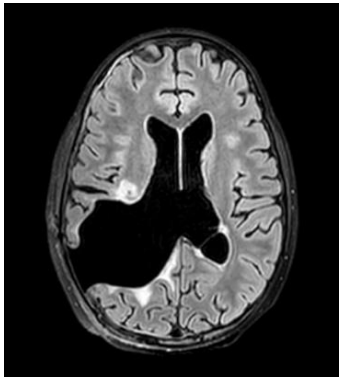
(1 patient had systemic chemotherapy before 2-nd surgery)

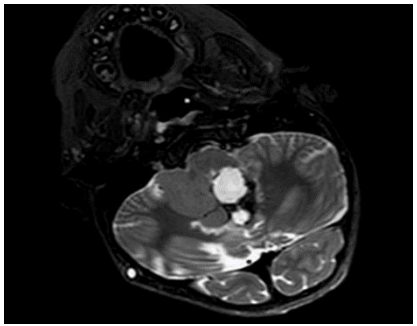
- 94.1 % (16 patients) had a gross total or near total tumour resection before radiotherapy
- 41.2%(7 patients ) had a shunt insertion

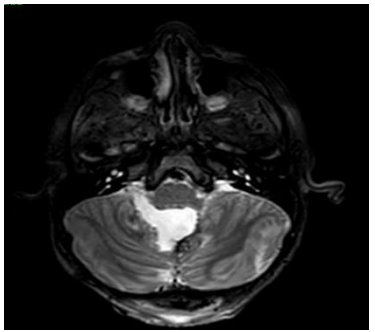
Recurrent Cases-Total-8 (Local recurrence-6, Distal recurrence-2)

- 62.5 % (Total-5 patients) underwent surgery for local recurrence
- 1 patient refused Surgery
- 2 patients had multi-site recurrences- not offered surgery
- 2 (25%) patients achieved GTR









# Proton therapy details

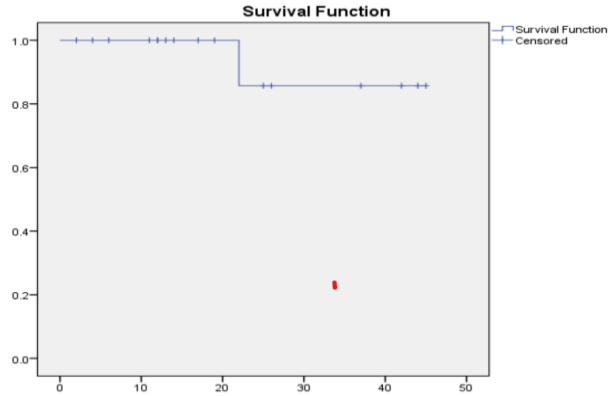
- Radiation dose to postop bed-54 GyE/30# to 59.4 GyE/33#
- Craniospinal irradiation 35 Gy/21# followed by boost(18 GyE/10# or 19.8 GyE/11#)
- The median time for Re RT From Initial radiation-37 months
- 28 % (7 patients) needed IV sedation under the care of a pediatric anesthesiologist (< 5 Years)

| Target Volume; | Definition |
|---|---|
| GTV | Residual gross tumor plus the tumor bed |
| CTV | GTV plus a 15 to 20 mm expansion, modified for anatomic barriers to tumor spread<br><br>Posterior fossa-Upto C2 |
| PTV1 | Clinical target volume (CTV) plus a 3mm symmetric expansion-54 GyE/30# |
| PTV2 | GTV plus a 3mm symmetric Expansion-1.8 GyE/1# Or 5.4 GyE/3#(Age,resection status,Grade and molecular pattern) |

# Early Outcomes

- Median Follow up- 18 months
- Two years of local control rate of newly diagnosed ependymoma was 85.7% after proton therapy. (One patient had local progression after 22 months)
- One year and two years local control rates were 62.5% and 28.6% in recurrent ependymoma

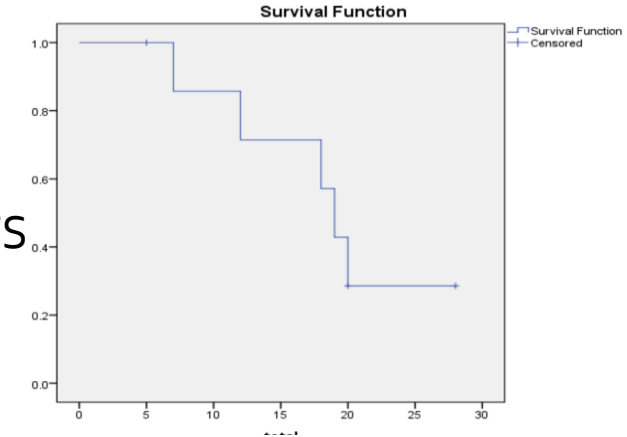
PFS after 1st-Proton therapy




PFS

Months

PFS following Proton re-irradiation




PFS

Months

# Re-irradiation: CSI

# Summary of the talk

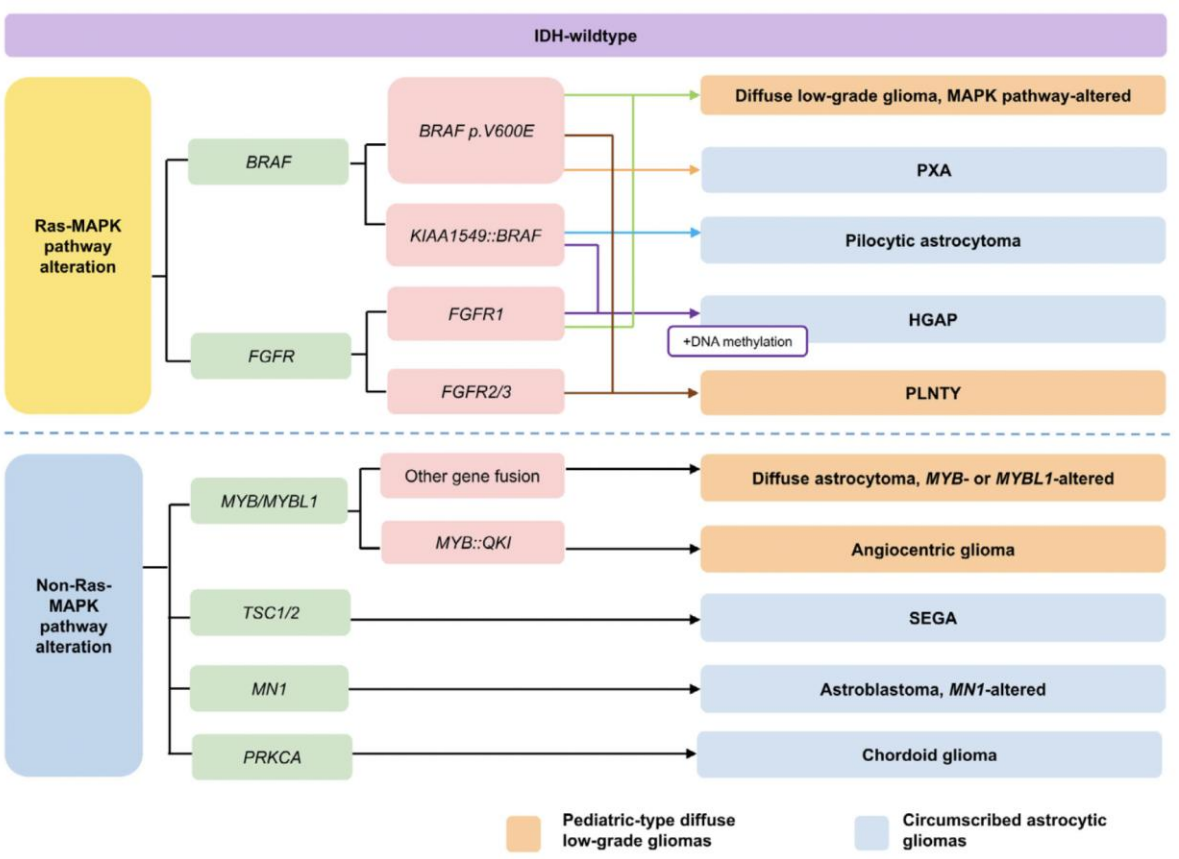
| Surgery | GTR/NTR is the key |
| --- | --- |
| Impact of postoperative radiation: GTR/NTR, STR | Huge impact on outcome |
| Impact of grade, age, molecular classification | Discussed |
| Radiation Dose and volume | 54-59.4Gy, focal RT1 unless disseminated |
| Impact of technique | Advanced techniques must<br>Proton therapy preferable in RT1 and RT2 |
| Recurrent setting | CSI preferable, full doses<br>Don't delay re-RT |

# Other Pediatric gliomas

Pediatric Gliomas

- Pediatric "circumscribed" Gliomas
- Pediatric "diffuse" low-grade Gliomas
- Pediatric "diffuse" high-grade Gliomas
- Pediatric neuronal/neuro-epithelial tumors
- Pediatric ependymal tumors

# Pediatric Low-grade Glioma



# Pediatric High-grade Glioma