38TH AROI-ICRO PG TEACHING COURSE

MOLECULAR PROFILING & MANAGEMENT OF EPENDYMOMA

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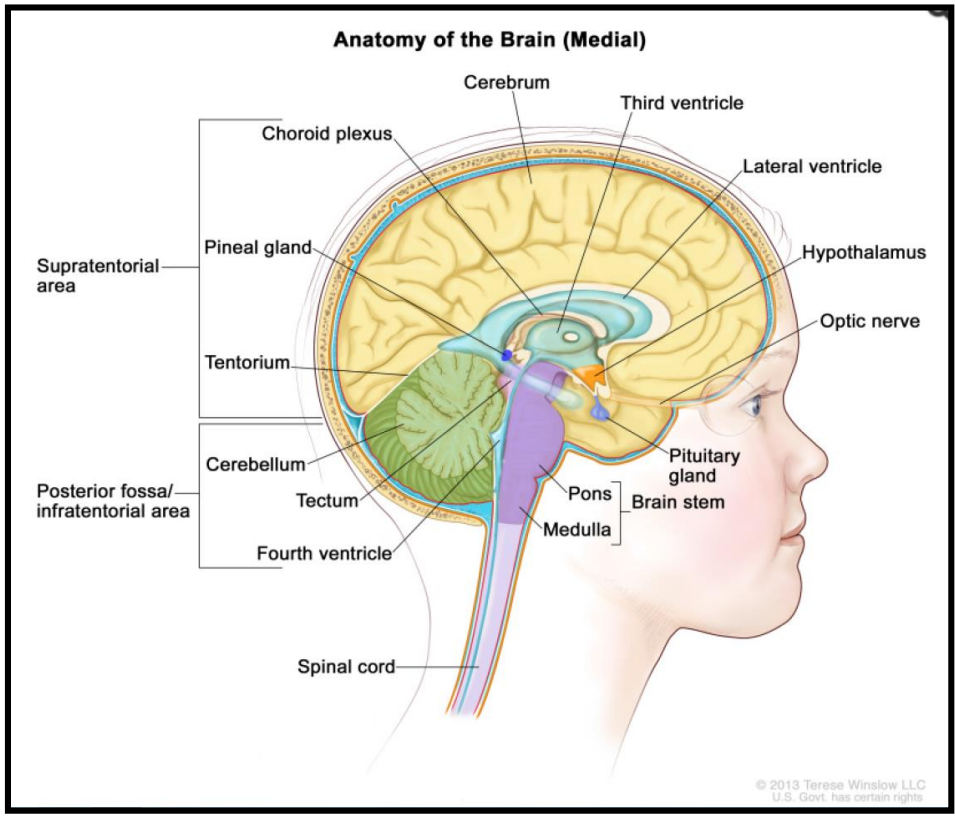
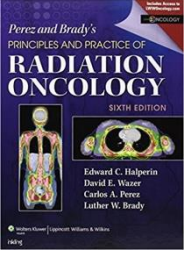
INTRODUCTION

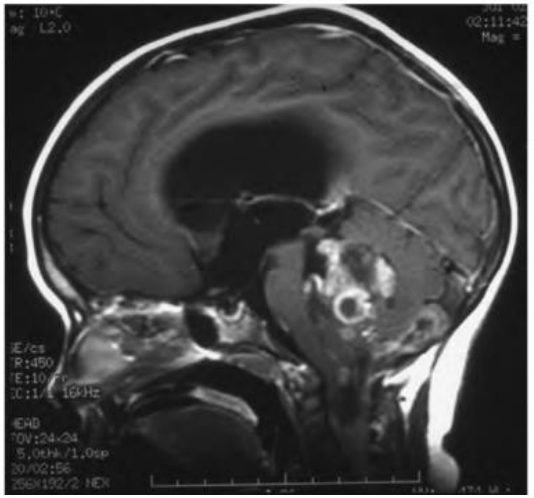
- Ependymoma→ third most common CNS tumor in children
- About half of all cases arise in children younger than 5 yrs
- Sites:
  - Intracranial
    - Supratentorial
    - Infratentorial
  - Spinal canal Tumors
- In children approximately 2/3rd arises in the ependymal lining of 4th ventricle
- Posterior fossa tumours typically present with symptoms & signs of ↑ed intracranial pressure

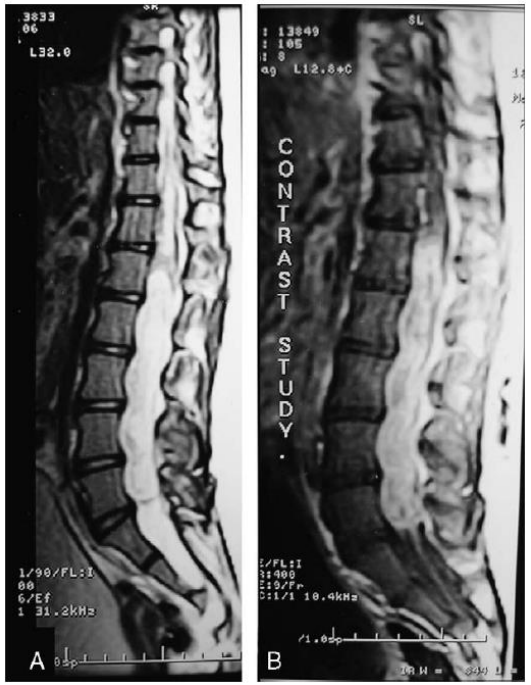




IMAGING

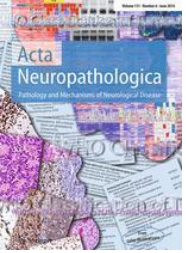
- MRI: imaging modality of choice
- The entire neuraxis needs to be imaged to rule out leptomeningeal spread
- Large, relatively well circumscribed tumor with displacement rather than invasion of adjacent structures
- Extension through the foramen magnum into the upper cervical region not uncommon





-Courtesy: Perez & Brady's Principles & Practice of Radiation Oncology 6E(2013)

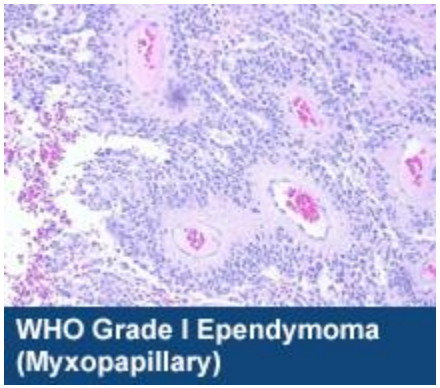
-Biswas et al. J Pediatr Hematol Oncol 2010;32:e38–e41.

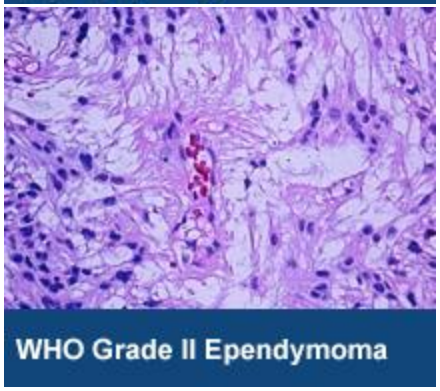


HISTOLOGICAL SUBTYPES OF EPENDYMOMA

- Myxopapillary ependymoma/subependymoma (WHO grade I)
- Ependymoma (WHO grade II)
- Anaplastic ependymoma (WHO grade III)
- Changes in 2016 WHO classification system:

Ependymal tumours	
Subependymoma	9383/1
Myxopapillary ependymoma	9394/1
Ependymoma	9391/3
Papillary ependymoma	9393/3
Clear cell ependymoma	9391/3
Tanycytic ependymoma	9391/3
Ependymoma, *RELA* fusion–positive	9396/3*
Anaplastic ependymoma	9392/3





-Louis DN et al. Acta Neuropathol 2016;131:803-20.

-courtesy: CERN foundation

MYXOPAPILLARY EPENDYMOMA

- Myxopapillary ependymomas commonly located in the conus filum terminale region of the spinal cord
- Usual presenting symptom: back pain
- Despite LG histology, leptomeningeal spread is not uncommon
- Surgical resection→ mainstay of treatment
  - complete resection usually possible for tumour in the filum
  - complete resection difficult & may be associated with significant neurological sequel for tumour in the conus
- If tumour not resected en bloc/ macroscopic residual tumor→ Post-op RT ↑es local control in this high risk situation
- RT dose: 50.4Gy/28#/5.5 weeks
- RT volume: GTV+1.5 cm/1 vertebrae craniocaudal margin+ IM+ SM
- Patients with leptomeningeal seeding at diagnosis/relapse: curative intent CSI →boost to the primary site

EPENDYMOMA

- Surgical resection→ mainstay of treatment
- The completeness of surgical resection → most powerful prognostic factor
- Currently, complete resection achieved in 70% -90% of supratentorial & spinal ependymomas
- Complete resection-less frequently possible in patients with infratentorial ependymomas
- “Second-look” surgery may be considered, if feasible, either after the realignment of structures that takes place following resection of an initially bulky tumor in an often unstable young child or after chemotherapy

ROLE OF RADIOTHERAPY IN EPENDYMOMA

- Postoperative radiotherapy → standard of care for all children (>12 months) with ependymoma
- Omission of RT may be considered acceptable in:
  - complete resection in patients with ependymoma of the spinal cord (DFS approaches 100%)
  - selected patients with supratentorial ependymoma in non-eloquent areas, which can be resected with a wider margin
- In the past, CSI recommended for treatment of infratentorial (HG) ependymoma
- However local conformal RT is the present standard of care

RADIOTHERAPY TARGET VOLUME

- GTV: tumour bed + residuum + any extension caudal to the foramen magnum
- CTV: GTV+0.5-1 cm margin
- PTV: CTV+ IM+SM (usually 3 mm)

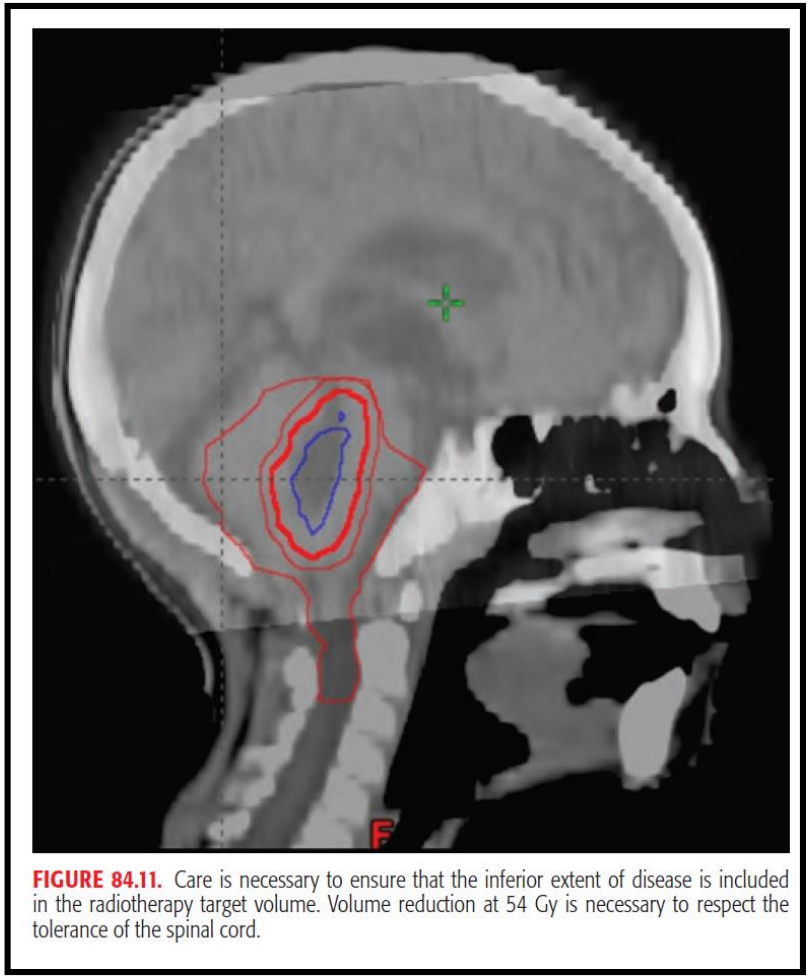


FIGURE 84.11. Care is necessary to ensure that the inferior extent of disease is included in the radiotherapy target volume. Volume reduction at 54 Gy is necessary to respect the tolerance of the spinal cord.

-*Courtesy: Perez & Brady's Principles & Practice of Radiation Oncology 6E(2013)*

RADIOTHERAPY TIME DOSE FRACTIONATION SCHEDULE

- Evidence for a dose–response in ependymoma, with improved tumor control with doses >45 to 50 and even 54 Gy
- The current standard for children with intracranial ependymoma older than 18 months is a dose of at least 54 Gy/30#/6wks
- Higher dose desirable in patients with macroscopic residual disease-59.4Gy/33#/6.5wks (CTV beyond the foramen magnum may be reduced at 54Gy)
- Hyperfractionated radiotherapy up to a total dose of 60-70Gy feasible but without clear evidence of benefit, particularly in the context of improved surgery and modern radiotherapy

ROLE OF CHEMOTHERAPY IN EPENDYMOMA

- The role of chemotherapy in ependymoma remains to be defined.
- Indications:
  - Infants with ependymoma to delay/avoid cranial RT
  - Post-operative residual disease to facilitate complete resection during second-look surgery
- Active agents: Vincristine, Etoposide, Cyclophosphamide, Cisplatin/Carboplatin
- Outcome: Use of post-op chemotherapy alone to delay/avoid cranial RT associated with inferior PFS compared with surgery followed by post-op RT approach

PATTERNS OF FAILURE & SALVAGE TREATMENT

- Failure:
  - Local
  - Leptomeningeal
  - Local & leptomeningeal
- Salvage treatment:
  - Resurgery
  - Reirradiation: local/CSI for local/leptomeningeal failure
  - Chemotherapy

RECENT UPDATES

- Molecular classification of ependymoma
- Current SIOP studies
- Current ACNS studies
- Current consensus on the clinical management of ependymoma in the era of molecular pathology

MOLECULAR CLASSIFICATION OF EPENDYMOMA

CellPress

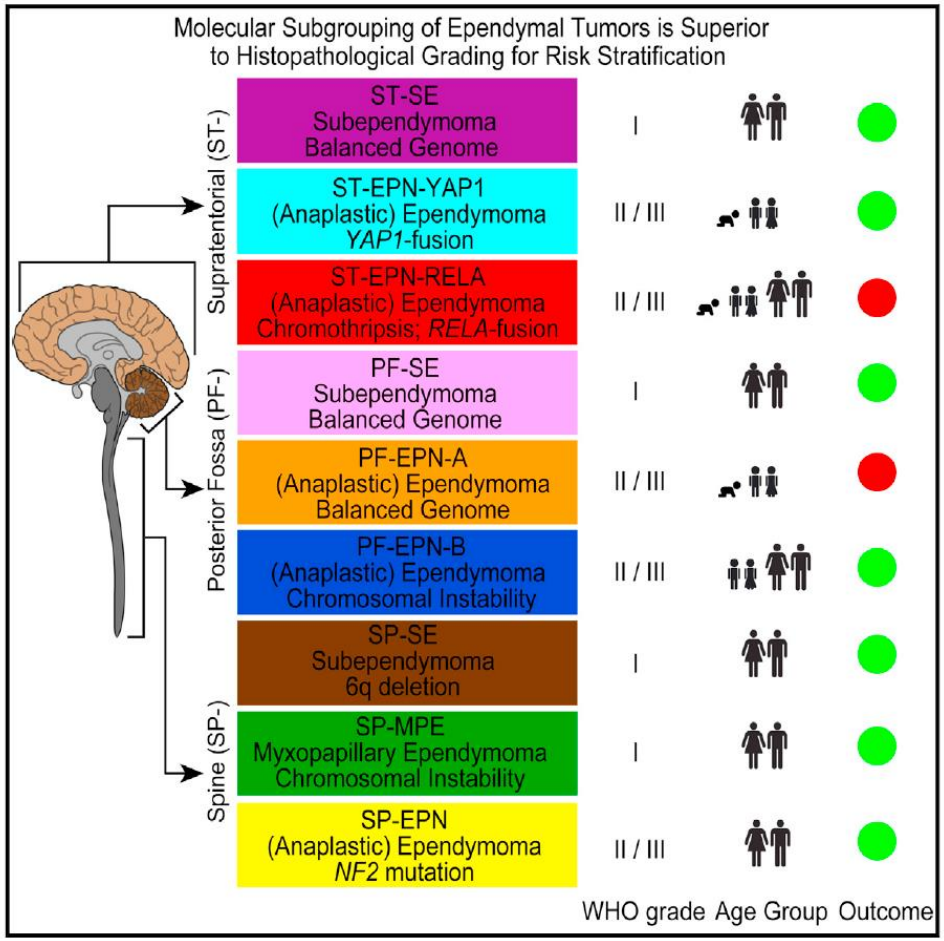
Cancer Cell
Article

Molecular Classification of Ependymal Tumors across All CNS Compartments, Histopathological Grades, and Age Groups

Kristian W. Pajtler,[1,2,37] Hendrik Witt,[1,3,4,37] Martin Sill,[5,37] David T.W. Jones,[1] Volker Hovestadt,[6] Fabian Kratochwil,[1] Khalida Wani,[7] Ruth Tatevossian,[8] Chandanamali Punchihewa,[8] Pascal Johann,[1] Jüri Reimand,[9] Hans-Jörg Warnatz,[10] Marina Ryzhova,[11] Steve Mack,[12] Vijay Ramaswamy,[12,13] David Capper,[14,15] Leonille Schweizer,[14,15] Laura Sieber,[1] Andrea Wittmann,[1] Zhiqin Huang,[6] Peter van Sluis,[16] Richard Volckmann,[16] Jan Koster,[16] Rogier Versteeg,[16] Daniel Fults,[17] Helen Toledano,[18] Smadar Avigad,[19] Lindsey M. Hoffman,[20] Andrew M. Donson,[20] Nicholas Foreman,[20] Ekkehard Hewer,[21] Karel Zitterbart,[22,23] Mark Gilbert,[24] Terri S. Armstrong,[24,25] Nalin Gupta,[26] Jeffrey C. Allen,[27] Matthias A. Karajannis,[28] David Zagzag,[29] Martin Hasselblatt,[30] Andreas E. Kulozik,[3] Olaf Witt,[3,31] V. Peter Collins,[32] Katja von Hoff,[33] Stefan Rutkowski,[33] Torsten Pietsch,[34] Gary Bader,[9] Marie-Laure Yaspo,[10] Andreas von Deimling,[14,15] Peter Lichter,[4,6] Michael D. Taylor,[12] Richard Gilbertson,[35] David W. Ellison,[8] Kenneth Aldape,[36] Andrey Korshunov,[14,15,38] Marcel Kool,[1,38,*] and Stefan M. Pfister[1,3,4,38,*]

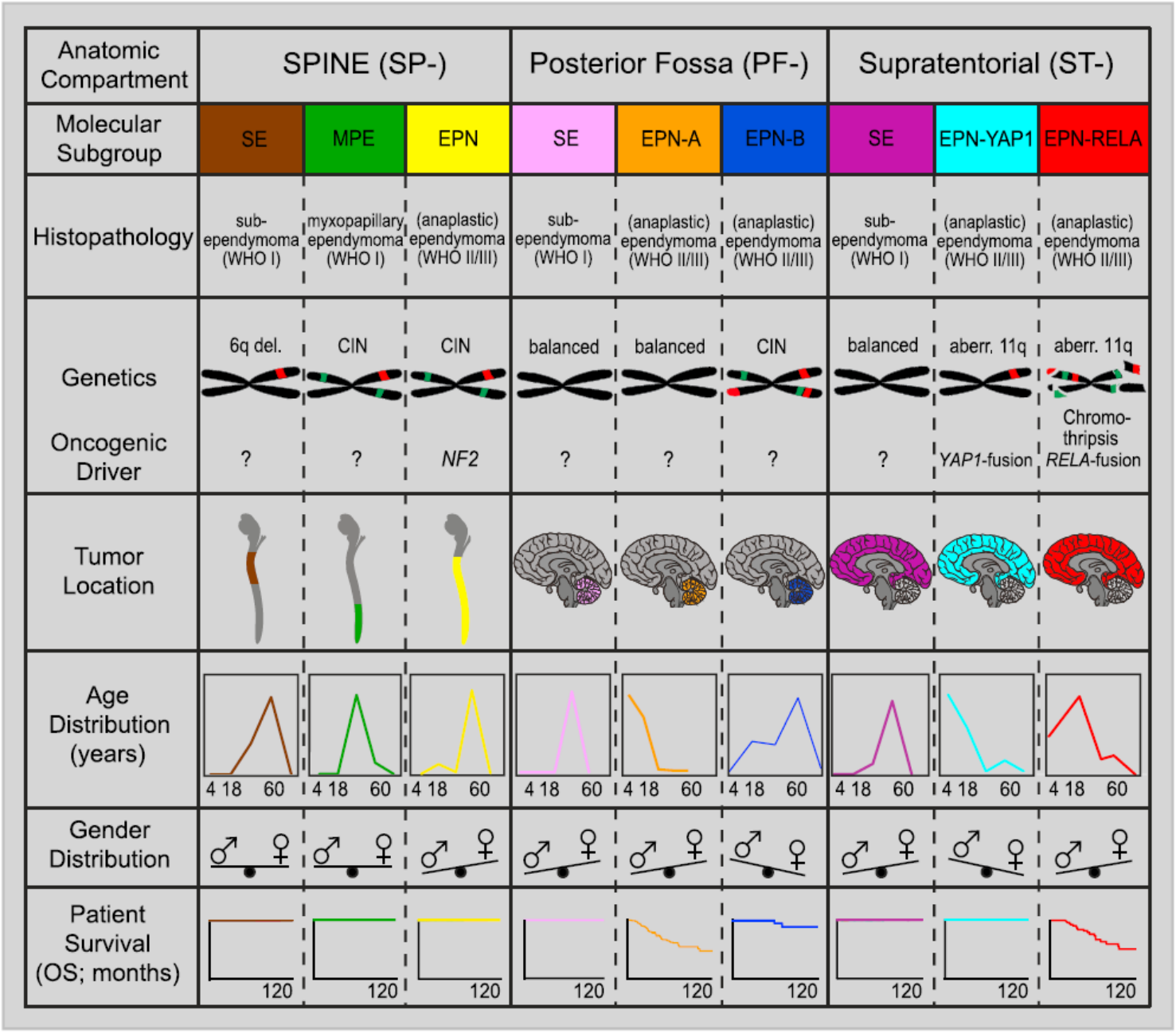
-Cancer Cell 2015;27, 728–743.

Graphical Abstract



In Brief

Pajtler et al. classify 500 ependymal tumors using DNA methylation profiling into nine molecular subgroups. This molecular classification outperforms the current histopathological grading in the risk stratification of patients.


Anatomic Compartment
SPINE (SP-)
Posterior Fossa (PF-)
Supratentorial (ST-)
Molecular Subgroup
SE
MPE
EPN
SE
EPN-A
EPN-B
SE
EPN-YAP1
EPN-RELA
Histopathology
sub-ependymoma (WHO I)
myxopapillary ependymoma (WHO I)
(anaplastic) ependymoma (WHO II/III)
sub-ependymoma (WHO I)
(anaplastic) ependymoma (WHO II/III)
(anaplastic) ependymoma (WHO II/III)
sub-ependymoma (WHO I)
(anaplastic) ependymoma (WHO II/III)
(anaplastic) ependymoma (WHO II/III)
Genetics
6q del.
CIN
CIN
balanced
balanced
CIN
balanced
aberr. 11q
aberr. 11q
Oncogenic Driver
?
?
NF2
?
?
?
?
YAP1-fusion
Chromo-thripsis RELA-fusion
Tumor Location
Age Distribution (years)
4 18 60
Gender Distribution
Patient Survival (OS; months)
120

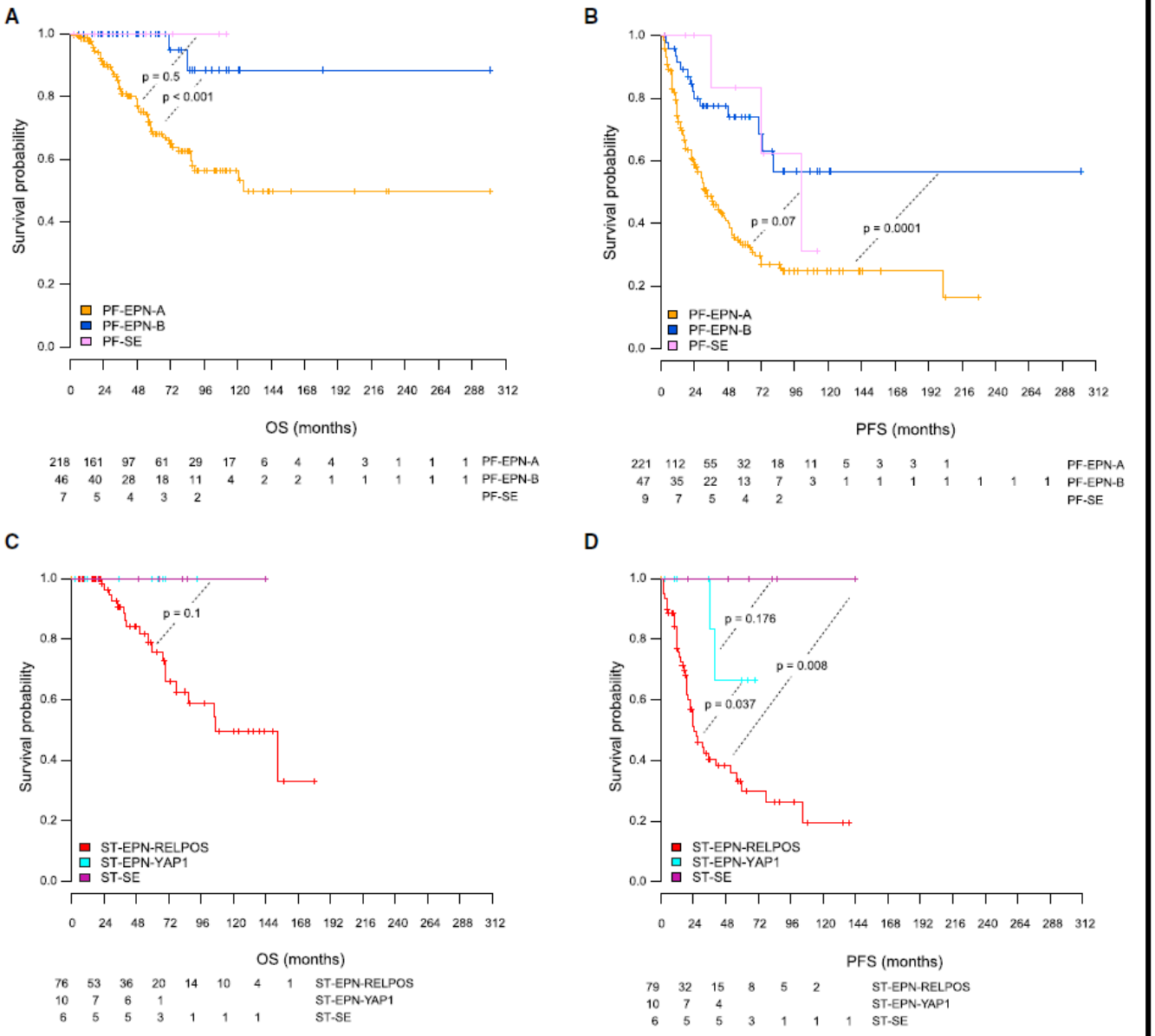
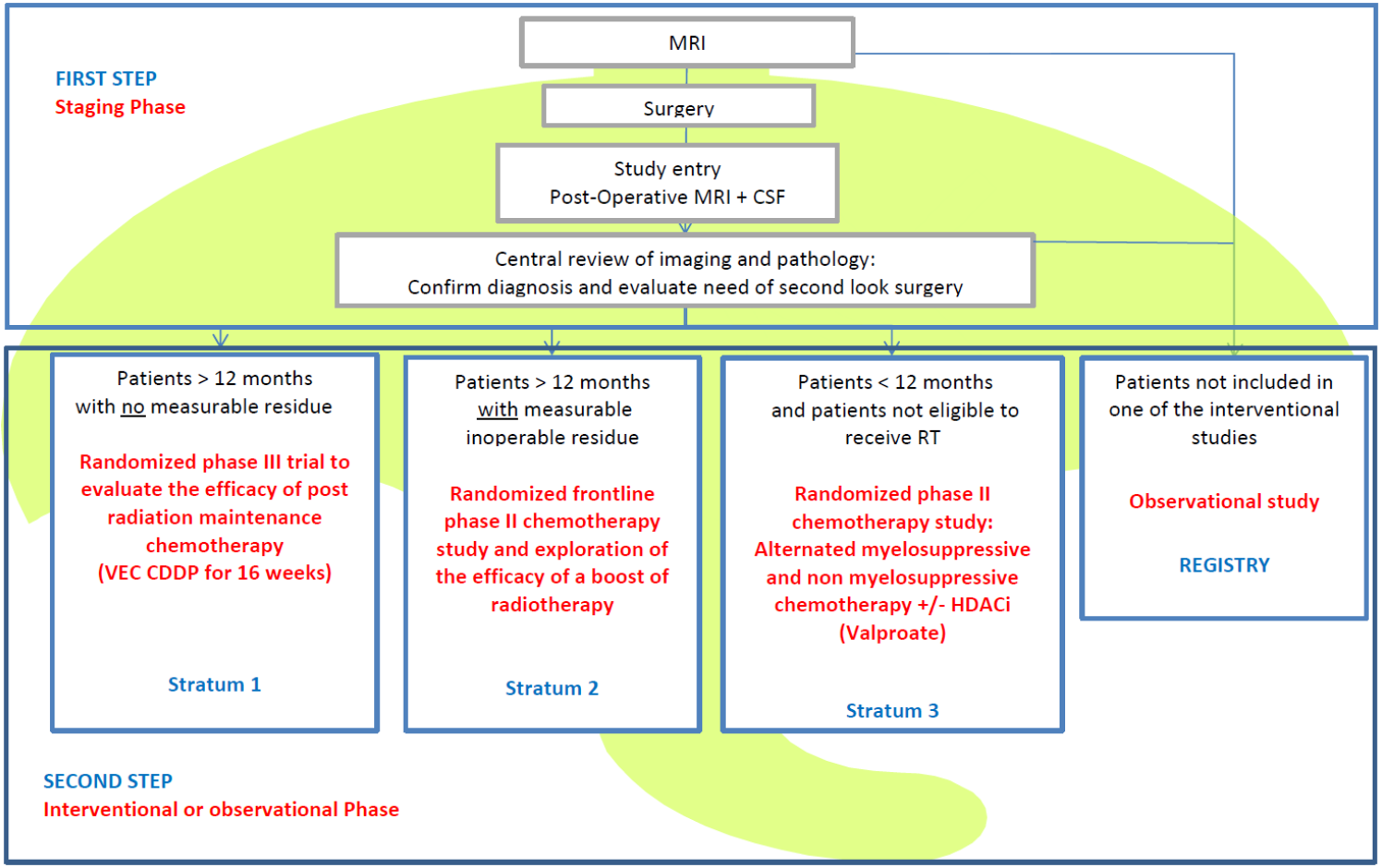
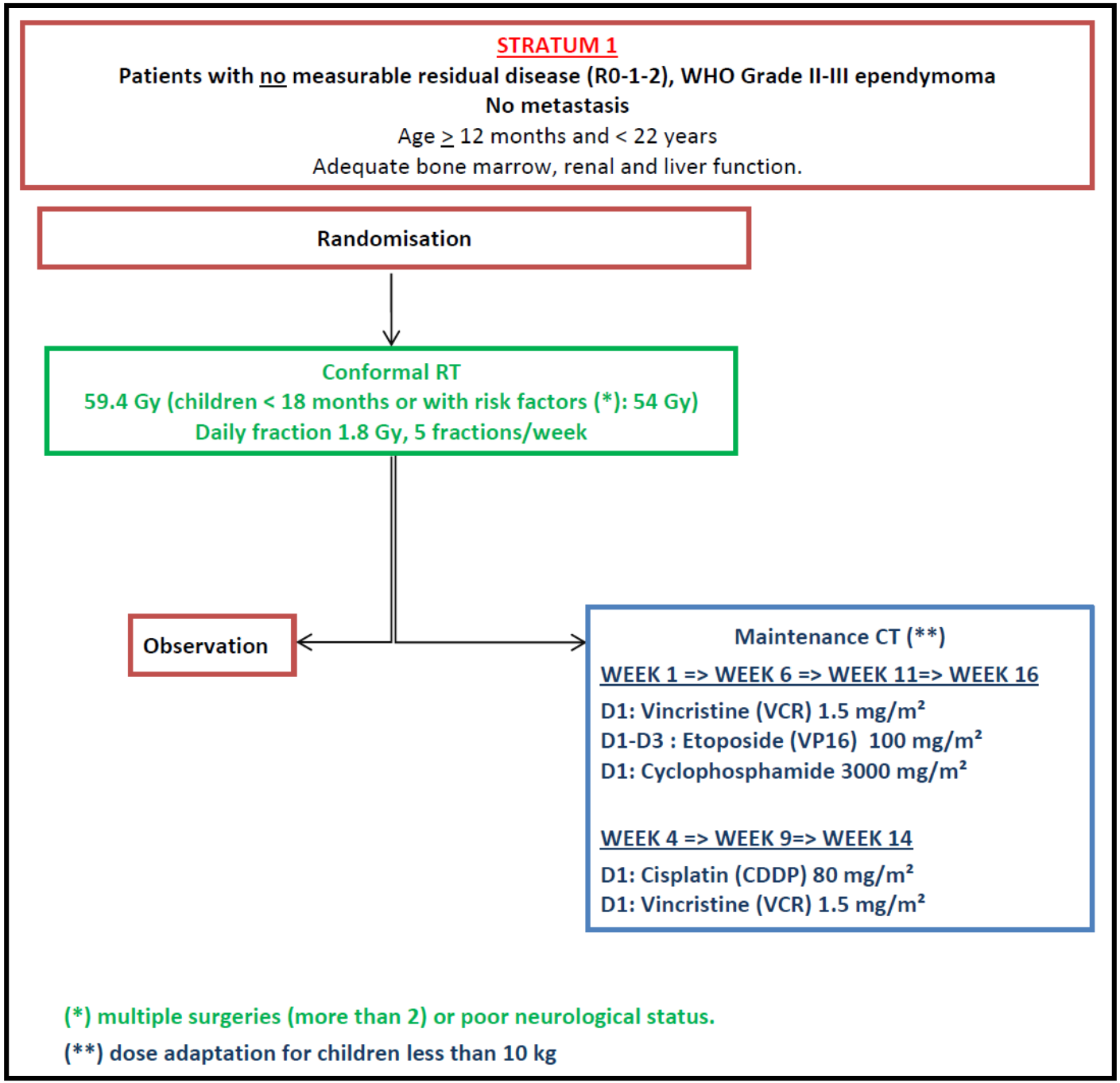


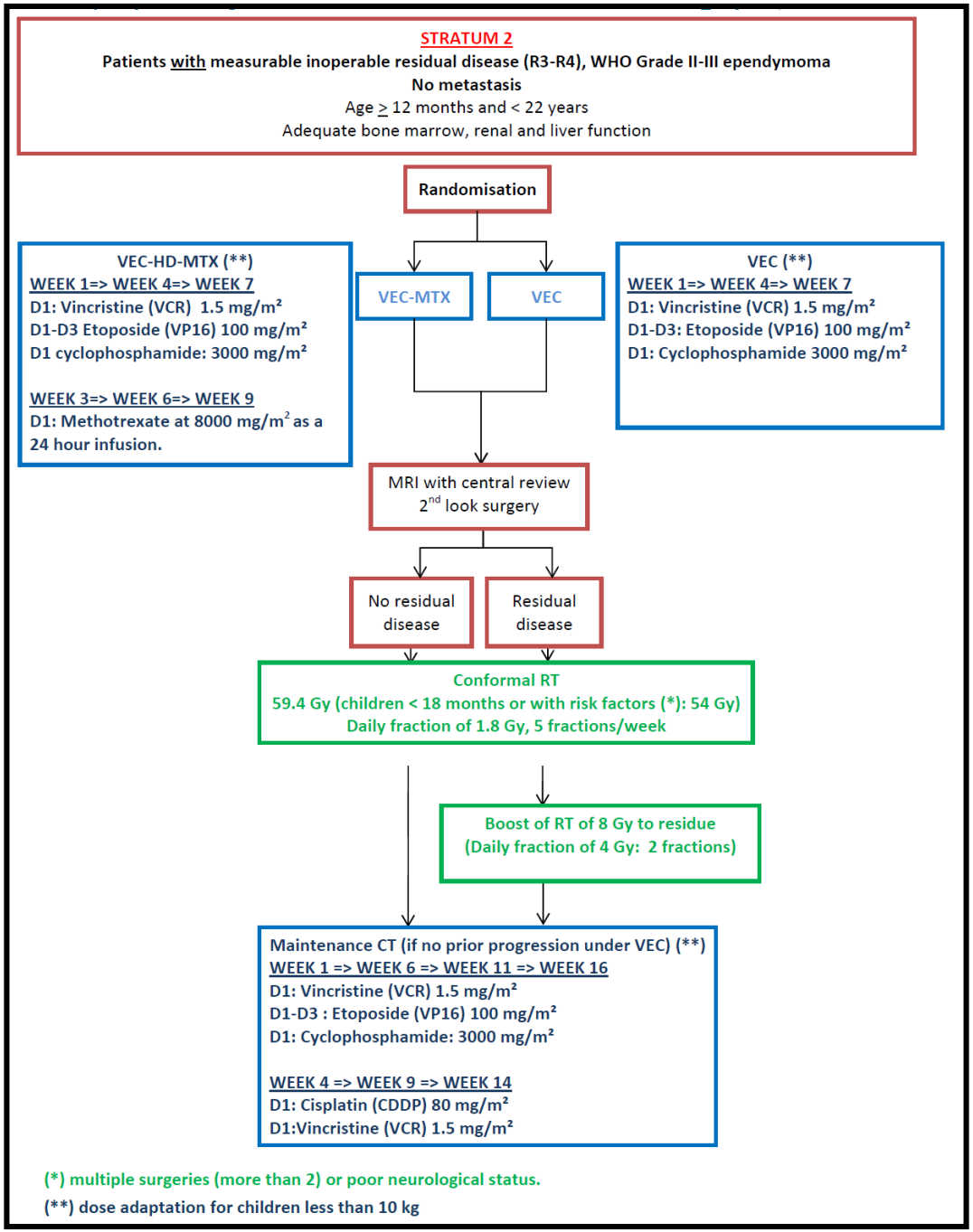
Figure 5. Molecular Subgroups of Ependymal Tumors Correlate with Distinct Clinical Outcome

(A–D) Kaplan-Meier curves for overall (A and C) and progression-free (B and D) survival for infratentorial (A and B) and ST (C and D) molecular ependymal tumor subgroups defined by methylation profiling. The p values were computed by log rank tests between subgroups. Numbers of patients at risk are indicated. See also Figure S5.

SIOP EPENDYMOMA STUDY II




STRATUM 1
Patients with no measurable residual disease (R0-1-2), WHO Grade II-III ependymoma
No metastasis
Age ≥ 12 months and < 22 years
Adequate bone marrow, renal and liver function.
Randomisation
Conformal RT
59.4 Gy (children < 18 months or with risk factors (*): 54 Gy)
Daily fraction 1.8 Gy, 5 fractions/week
Observation
Maintenance CT (**)
WEEK 1 => WEEK 6 => WEEK 11=> WEEK 16
D1: Vincristine (VCR) 1.5 mg/m²
D1-D3 : Etoposide (VP16) 100 mg/m²
D1: Cyclophosphamide 3000 mg/m²
WEEK 4 => WEEK 9=> WEEK 14
D1: Cisplatin (CDDP) 80 mg/m²
D1: Vincristine (VCR) 1.5 mg/m²
(*) multiple surgeries (more than 2) or poor neurological status.
(**) dose adaptation for children less than 10 kg


STRATUM 2
Patients with measurable inoperable residual disease (R3-R4), WHO Grade II-III ependymoma
No metastasis
Age ≥ 12 months and < 22 years
Adequate bone marrow, renal and liver function
Randomisation
VEC-HD-MTX (**)
WEEK 1=> WEEK 4=> WEEK 7
D1: Vincristine (VCR) 1.5 mg/m²
D1-D3 Etoposide (VP16) 100 mg/m²
D1 cyclophosphamide: 3000 mg/m²
WEEK 3=> WEEK 6=> WEEK 9
D1: Methotrexate at 8000 mg/m² as a 24 hour infusion.
VEC-MTX
VEC
VEC (**)
WEEK 1=> WEEK 4=> WEEK 7
D1: Vincristine (VCR) 1.5 mg/m²
D1-D3: Etoposide (VP16) 100 mg/m²
D1: Cyclophosphamide 3000 mg/m²
MRI with central review
2nd look surgery
No residual disease
Residual disease
Conformal RT
59.4 Gy (children < 18 months or with risk factors (*): 54 Gy)
Daily fraction of 1.8 Gy, 5 fractions/week
Boost of RT of 8 Gy to residue
(Daily fraction of 4 Gy: 2 fractions)
Maintenance CT (if no prior progression under VEC) (**)
WEEK 1 => WEEK 6 => WEEK 11 => WEEK 16
D1: Vincristine (VCR) 1.5 mg/m²
D1-D3 : Etoposide (VP16) 100 mg/m²
D1: Cyclophosphamide: 3000 mg/m²
WEEK 4 => WEEK 9 => WEEK 14
D1: Cisplatin (CDDP) 80 mg/m²
D1:Vincristine (VCR) 1.5 mg/m²
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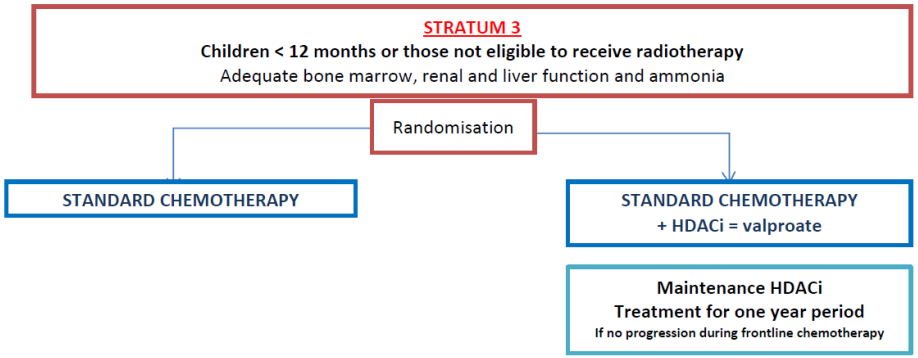


	CHEMO +/- HDACi (**)						
CYCLE N°	1	2	3	4	5	6	7
Vincristine - Carboplatin	D1	D 57	D113	D169	D225	D281	D337
Vincristine - Methotrexate	D15	D 71	D127	D183	D239	D295	D351
Vincristine - Cyclophosphamide	D29	D 85	D141	D197	D253	D309	D365
Cisplatin 2-day Continuous infusion	D43 44	D99 100	D154 155	D211 212	D267 268	D323 324	D379 380
+/- Valproate (*)	Initial dose: 30 mg /kg/day for two weeks in 2 divided doses (BID 15mg/Kg) Increasing weekly up to 40->50->60 mg /kg/day in 2 divided doses until serum target level of 100-150 µg/ml achieved.						

Dosing schedule (***)	Dose over 1 year Or > 10 kg	Dose for infants 6 to 12 months Or ≤ 10Kg	Dose for infants less than 6 months
Vincristine (Maximum dose: 2mg)	1.5 mg/m² x 1	1.125 mg/m² x 1	0.75 mg/m² x 1
Carboplatin	550 mg/m²x 1	412.5 mg/m² x 1	275 mg/m² x 1
Methotrexate	8000 mg/m² x 1	6000 mg/m² x 1	4000 mg/m² x 1
Cyclophosphamide	1500 mg/m² x 1	1125 mg/m² x 1	750 mg/m² x 1
Cisplatin	40 mg/m² x 2	30 mg/m² x 2	20 mg/m² x 2
Valproate * (BID)	30 mg/kg/day*	30 mg/kg/day*	30 mg/kg/day*

* Initial dosing then according to monitoring

**If residual disease please consider for further surgery at each reassessment point.

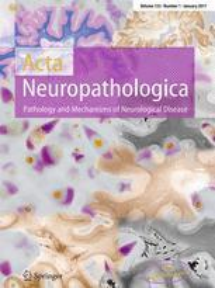
*** for patients in stratum III:

- Those aged 12 months and over receive the full surface area based dose of chemotherapy.
- Those ages 6-11 months receive 75% of the surface-area-based dose if chemotherapy
- Those under 6 month receive 50% of the surface-area –based dose of chemotherapy

CHILDREN'S ONCOLOGY GROUP

COG ACNS-0831 STUDY

- Phase III trial in young children with newly diagnosed ependymoma
- **No residual disease; no disseminated disease-research questions:**
  - whether adding chemotherapy after RT results in improved survival over RT alone
  - whether children with supratentorial nonanaplastic ependymoma who receive a complete resection or who achieve a complete remission after being treated with chemotherapy can be successfully treated without RT
- **Residual disease; no disseminated disease-research question:**
  - whether adding chemotherapy before and after RT results in improved survival compared with previous studies of children who did not receive additional chemotherapy after RT



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CrossMark

CONSENSUS PAPER

The current consensus on the clinical management of intracranial ependymoma and its distinct molecular variants

Kristian W. Pajtler[1,2,3] · Stephen C. Mack[4,5] · Vijay Ramaswamy[6,7] · Christian A. Smith[6] · Hendrik Witt[1,2,3] · Amy Smith[8] · Jordan R. Hansford[9] · Katja von Hoff[10] · Karen D. Wright[11] · Eugene Hwang[12] · Didier Frappaz[13] · Yonehiro Kanemura[14] · Maura Massimino[15] · Cécile Faure-Conter[13] · Piergiorgio Modena[16] · Uri Tabori[7] · Katherine E. Warren[17] · Eric C. Holland[18] · Koichi Ichimura[19] · Felice Giangaspero[20] · David Castel[21,22] · Andreas von Deimling[23,24] · Marcel Kool[1,3] · Peter B. Dirks[6] · Richard G. Grundy[25] · Nicholas K. Foreman[26] · Amar Gajjar[11] · Andrey Korshunov[23,24] · Jonathan Finlay[27] · Richard J. Gilbertson[28] · David W. Ellison[29] · Kenneth D. Aldape[30] · Thomas E. Merchant[31] · Eric Bouffet[7] · Stefan M. Pfister[1,2,3] · Michael D. Taylor[6]

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General Consensus Statements

1. Outside of clinical trials, treatment decisions should not be based on grading (II vs III)
2. ST and PF ependymomas are different diseases although the impact on therapy is still evolving
3. Central radiological and histological review should be a principal component of future clinical trials
4. Molecular subgrouping should be part of all clinical trials henceforth
5. Submission of fresh-frozen tumor samples as well as of blood samples will be mandatory in future clinical trials

Subgroup Consensus Statements

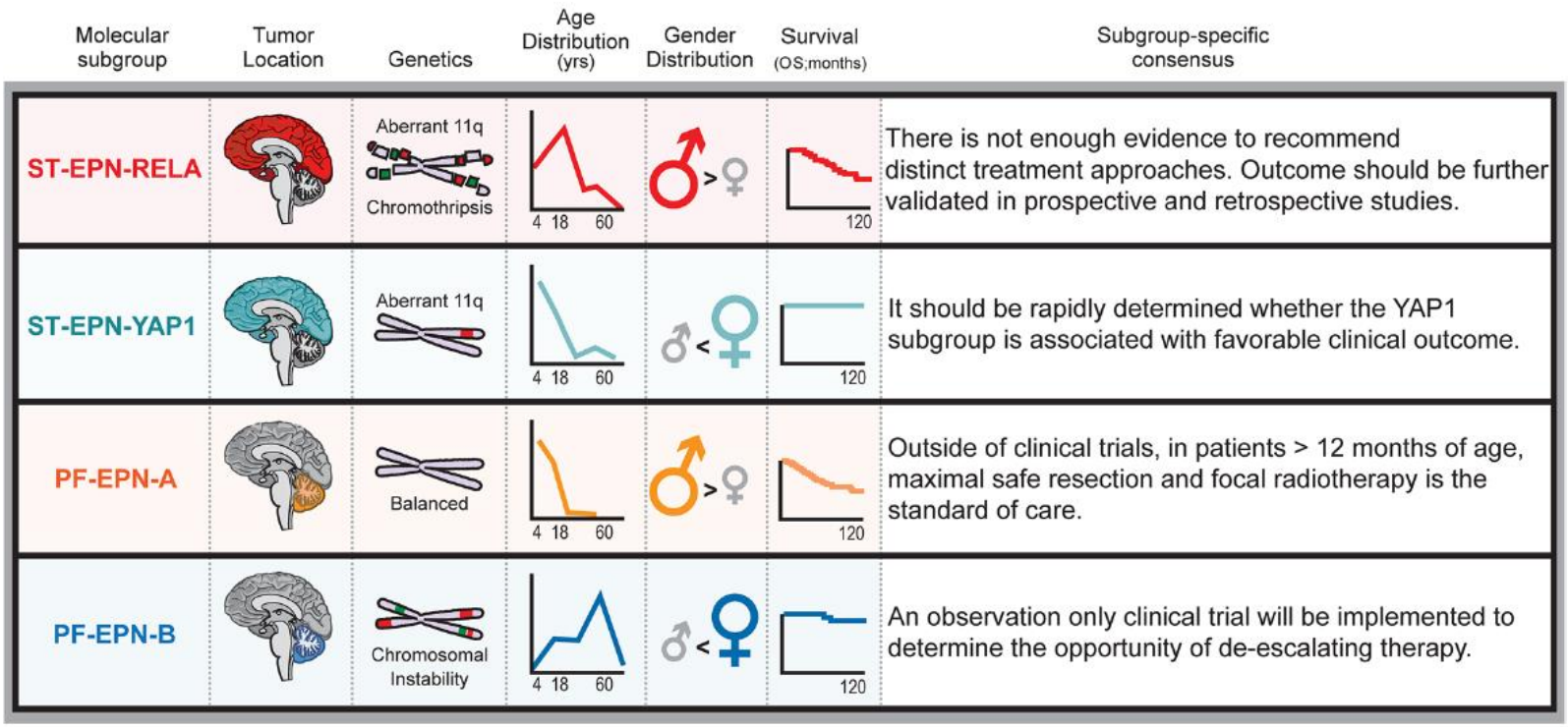

Fig. 1 General and molecular subgroup specific consensus statements on the clinical management of intracranial ependymoma

CONCLUSIONS

- Surgery-mainstay of management, complete resection should be attempted whenever feasible
- Post-operative RT improves local control & PFS
- For localised disease-local conformal RT
- For leptomeningeal dissemination- CSI →boost
- The role of chemotherapy evolving
- The future holds promise for risk adapted therapy as per the molecular classification of ependymoma

THANK YOU