Management of Ependymoma: Genetics and Radiation therapy

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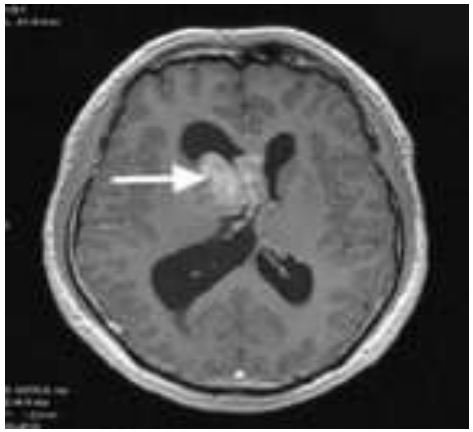
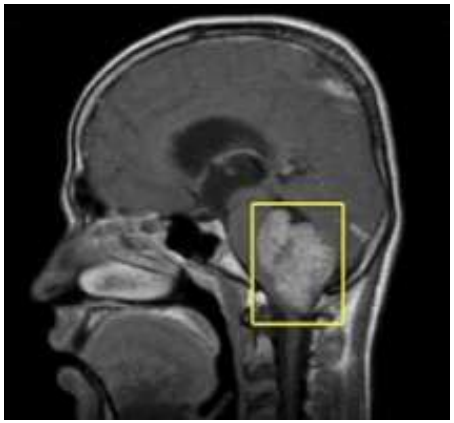
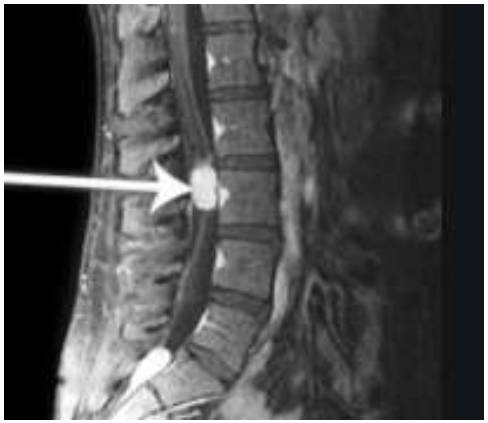
Ependymoma (EPN)

- Glial tumors ,arise within or adjacent to the ependymal lining of the ventricular system, All age groups
- Account for <10% of CNS tumors, more than 20% of primary spinal cord tumors
- Can arise along the entire neuroaxis i.e supratentorial, post fossa, spinal cord







- In children, 90% of ependymomas (EPNs) occur intracranially, 2/3rd in the posterior fossa (PF) and 1/3rd in the supratentorial (ST) compartment (Mol. Cancer Res. 2009; 7:765–786)
- Metastasis at presentation- 10-30% (J Neurooncol.2011 Jul;103(3):693-8)

- Clinical behaviour of EPNs is highly variable
- The 10-year overall survival (OS) is about 64% in pediatric patients and ranges from 70% to 89% in adult patients (Neuro-oncol. 2014; 16)
- Tumors in infancy are associated with a particularly poor survival rate of only 42%–55% at 5 years after diagnosis (Lancet Oncol. 2014; 15:35–47)
- Approximately 40% of patients are incurable because of the paucity of effective treatment options
- Surgery is the mainstay of the treatment with or without radiotherapy
- Role of chemotherapy is controversial

Etiology

- No clear etiology
- Sporadic or genetic, syndromic association
- Increased incidence of spinal intramedullary ependymoma in NF2

  (Cancer Res, 1994, 4(1) : 45- 47)
- NF2 gene, tumor suppressor gene- chromosome 22 q- lost in intramedullary EPN but not in intracranial EPN
- Li-Fraumeni syndrome – germline mutation of p53- Less common
- Rarely: Turcot syndrom- Germline mutation of APC gene: loss of APC gene activates wnt pathway
- Multiple endocrine neoplasia (MEN) I syndrome

Cytogenetic abnormalities

✓ According to age group:

Children:

- Gain of chr 1q: MC, 20% associated with tumors in posterior fossa, anaplastic histology, tumor aggressiveness, poor outcome (Mol Cancer Res , 2009, 7 (6): 765-786)
- Other: loss of 1p, 2, 3, 6q, 9p, 13q, 17,12
- Gain of chr 5, 7, 8, 9,11, 18, 20

Adults:

- Gain of 7 & 9 and loss of 22q, MC, 30% , almost exclusively in spinal ependymoma
- Others: Loss of chr 6, 10, 13q, 14q, 16
- Gain: 2,5 ,12,18 and X

Translocation of chr 1, 11, 22: most frequent in adults

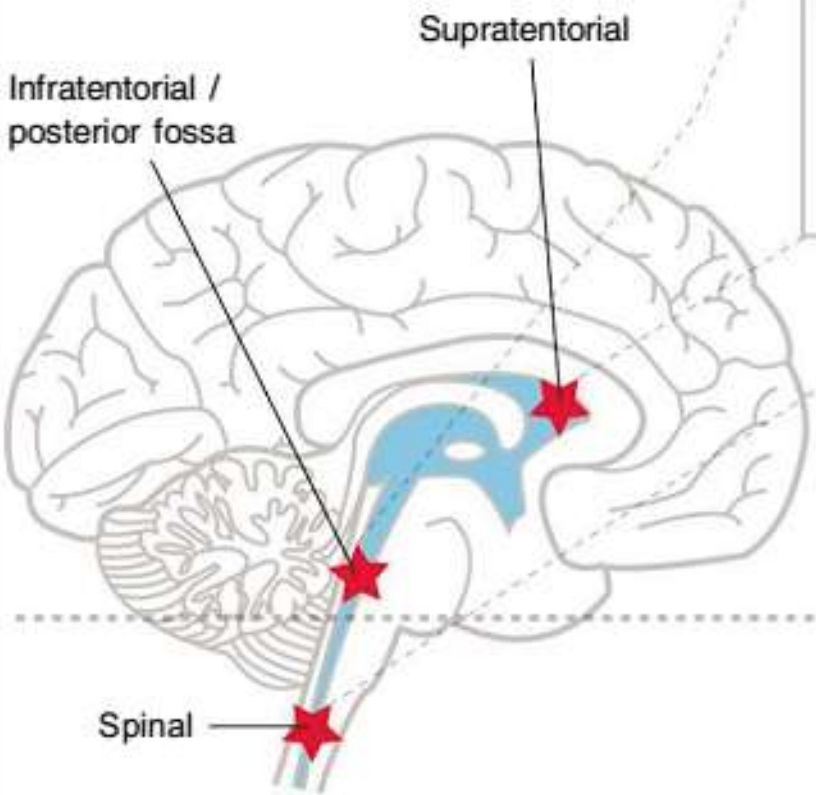
✓ According to location: almost same as above as most of childhood EPN are intracranial while most of the adult EPN are spinal

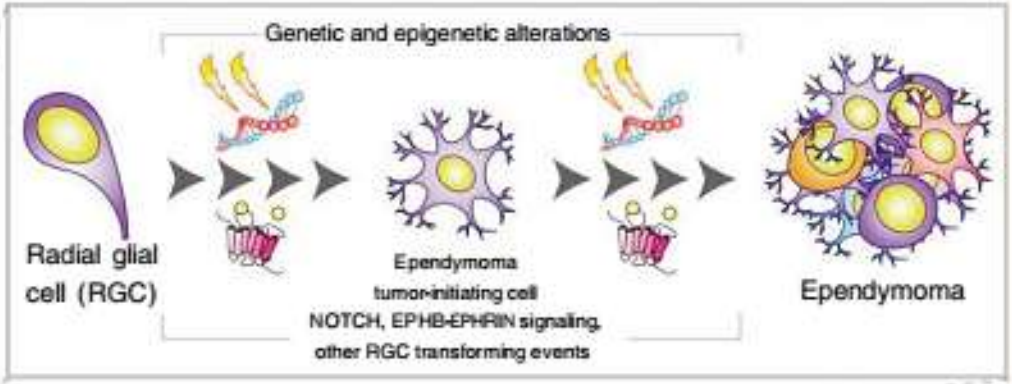
Table 1. Regions of frequent gains and losses in the ependymoma genome

Gains	1p34, 1q, 2p24, 2q23, 3p14, 3q29, 5p15.33, 6p21, 7p21, 7q11.23–22.1, 7q34, 7q35, 8q11.2, 9p24.3–qter, 9q22, 9qter, 10q25.2–26.3, 11q13–q23, 12p, 12q13.13–13. 3, 13q21.1, 14q11.2, 14q32.2, 15q21.3, 16p11.2, 16p13.3, 16pter, 17q21, 18, 19p13.1–13.3, 20p12, Xp21.2, and Xq26.3
Losses	1p36, 3q23–qter, 4q33–qter, 5q31, 6p22–pter, 6q25.3, 6q26, 7q36, 9p21, 9p23, 9p24.31, 10q23–26, 12q13, 13q14.3–qter, 15q21.1, 16p12–13.1, 16q24, 17p13.3, 17q22–24, 18q22.2, 19p13.2, 20q13.2–13.3, 22q12, and 22q13.3

Table 2. Putative oncogenes and tumor suppressor genes in ependymoma

Oncogenes	*DUSP12* (1q23.3), *MYCN* (2p24), *DNASE1L3* (3q25.2), *hTERT* (5p15.33), *NOTCH4* (6p21.32), *EGFR* (7p11.2), *ARHGEF5* (7q34), *EDG3* (9q22), *SHC3* (9q22), *TNC* (9q33.1), *NOTCH1* (9q34.3), *STK32C* (10q26.3), *MDK* (11p11.2), *TYR* (11p13), *YAP1* (11q22), *BIRC2* (11q22), *BIRC3* (11q22), *HOXC4* (12q13.13), *MTA1* (14q32.33), *SLC6A10* (16p11.2), *PRM1* (16q12.2), *CDC6* (17p13.3), *VAV1* (19p13.3), and *JAG1* (20p12.2)
Tumor suppressor genes	*ZNF262* (1p34.3), *AJAP1* (1p36.32), *CDKN2A* (9p21.3), *FOXD4* (9p24.31), *GRID1* (10q23.2), *MINPP1* (10q23.31), *TACC2* (10q26.13), *TUBGCP2* (10q26.3), *PRKCA* (17q24.2), and *SULT4A1* (22q13.3)





Intracranial ependymoma

- Pediatric
- Few partial chromosomal imbalances / balanced profile
- Gain of 1q, loss of 6q
- CDKN2A deletion
- Up-regulation of NOTCH and EPHB-EPHRIN signaling
- Poor prognosis

Spinal ependymoma

- Adult
- Numerous broad chromosomal imbalances
- Gain of 7, loss of 22/22q
- *NF2* mutation
- Up-regulation of HOX family transcription factors
- Good prognosis

Subtypes

- Heterogeneous
- Can be classified as distinct disease subtypes based on age , anatomical tumor location and genetic alterations
- However, No molecular or tumor-specific IHC markers are in routine clinical use
- Historically, histopathologic features have been used to diagnose and risk-stratify EPNs

1. Grade I: myxopapillary EPN: Spine, Subependymoma: Mostly Intracranial (intraventricular)
2. Grade II
3. Grade III (Anaplastic): High mitotic activity, microvascular proliferation and necrosis

- Grading of EPNs according to earlier WHO criteria is of questionable clinical importance
- WHO 2016 classification: one genetically defined EPN subtype has been accepted:

  EPN, RELA fusion–positive

Ependymal tumours
Subependymoma
Myxopapillary ependymoma
Ependymoma
  Papillary ependymoma
  Clear cell ependymoma
  Tanycytic ependymoma
Ependymoma, *RELA* fusion–positive
Anaplastic ependymoma

Why there is a need for molecular classification

- **Only histological criteria is not sufficient because-**
- EPNs from different compartments of the CNS are may have same histology but respond differently to t/t

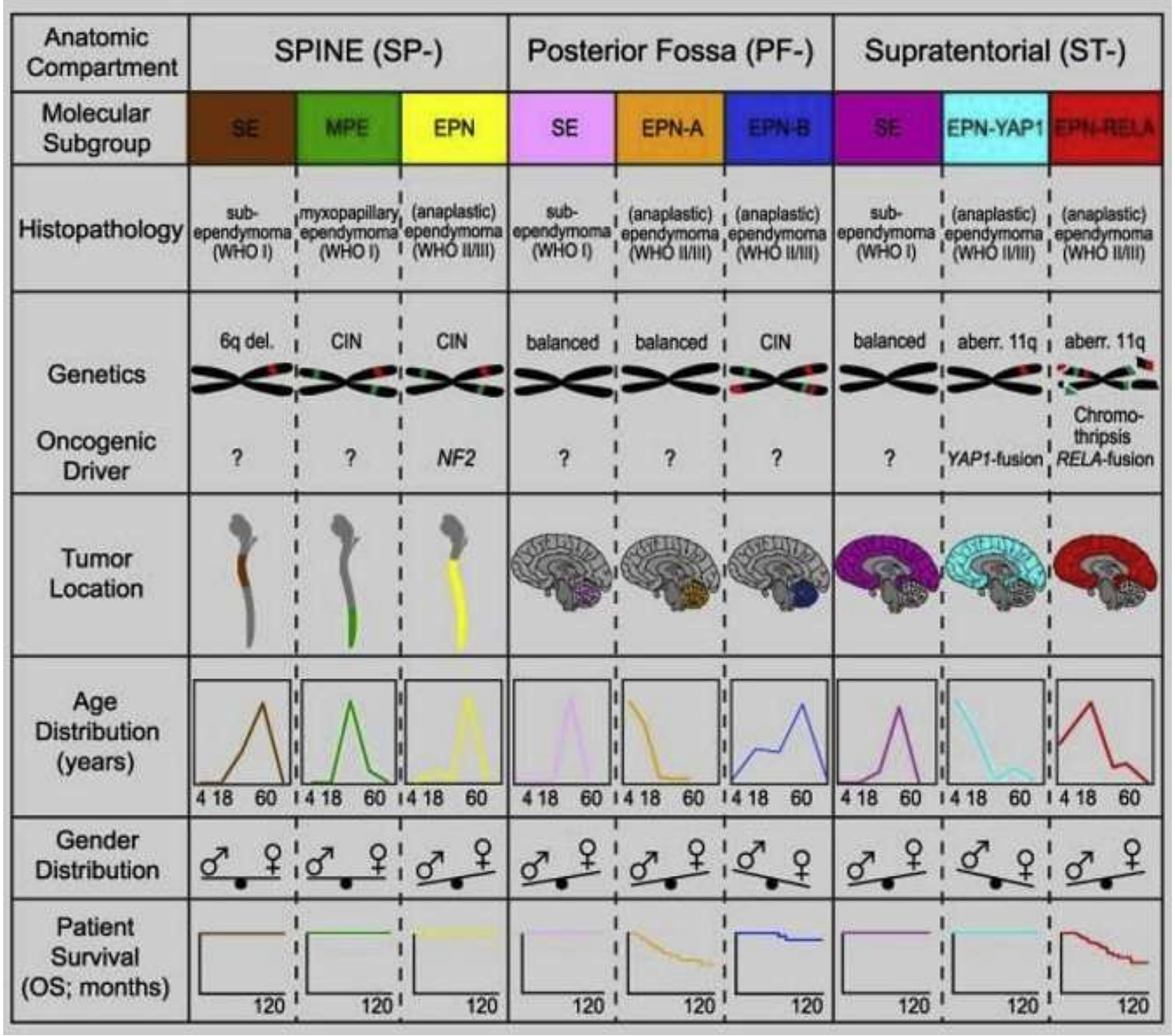
  - biologically distinct

  -diverse genomics, transcriptomics, and epigenomics (omics)
- Other than grade I EPN, histologic grading is of no prognostic utility
- Histopathologic grading of II/III alone should not be used to risk stratify patients (Acta neuropathologica. 2017)

Molecular classification

- A subset of patients with radically resected ST EPNs will not recur even without PORT exemplifying the need for better patient stratification (Pediatr. Blood Cancer. 2012)
- Lack of consistency with histopathologic grading, motivated clinicians to develop reliable prognostic markers
- Molecular stratification may create a precise and reliable platform for better understanding of EPN, May be a potential to alter therapeutic decisions
- A recent international collaborative study identified nine molecular subgroups of ependymal tumors, three in each anatomical compartment of the central nervous system, spine (SP), posterior fossa (PF), and supratentorial region (ST) (Cancer Cell 2015. 27:728–743)
- Each of the 9 molecular subgroups is characterized by distinct DNA methylation profiles and associated genetic alterations

Anatomical compartment	Molecular subtypes	Chracteristics
Supratentoriun (ST)	Subependymoma	Adults only
	ST- EPN -RELA	Gene fusions between C11ORF95-RELA 72% of ST EPN Children and adults, Poor prognosis
	ST- EPN-YAP1	Fusions of the YAP1oncogene with other gene partners Mainly children, Good prognosis, ? Therapy descalation
Postr Fossa (PF)	PF SubEPN	Adults only
	PF EPN A	74% of PF ependymomas Infant and young children High Rate of recurrence Balanced genome and poor outcome PORT for all >12 months
	PF EPN B	Adolescent and young adults Genomic instability and favorable outcome ? Observation after complete surgery
Spine (S)	Subependymoma	Adults only
	Myxopapillary EPN	
	Grade II/III EPN	NF2 mutation is common



Management of Ependymoma in Children, Adolescents and Young Adults. Clin Oncol.2019

RELA (v-rel avian reticuloendotheliosis viral oncogene homolog A) fusion positive ependymoma

- Tumors harboring C11 or F95gene fusions to RELA
- Accounts for > 70% of ST EPN (median age 8 years, range 0–69 years)
- May correspond to WHO grade II or III
- Poor prognosis
- **Molecular classification of ependymal tumors across all CNS compartments, histopathological grades, and age groups** (Cancer Cell. 2015 27:728–743)
- Retrospective analysis, samples collected over a long period of time (>20 years)
- 5-year PFS, 29% and OS, 75
- Interestingly, the level of resection did not significantly affect the outcome

- Ephrin receptor B2 (EPHB2)-driven ST EPN models also highly expressed in ST-EPN-RELA tumors have pinpointed 5-fluorouracil treatment as a potential cytotoxic therapy with efficacy in murine models
- Currently being evaluated in early phase ependymoma clinical trials

Management

- Clinical presentation: site specific
- CEMRI brain
- MRI Spine to r/o leptomeningeal spread
- Lumbar puncture: No less than 14 days after surgery (false positive)

Newly Diagnosed non metastatic Intracranial EPN

- Standard of care - maximal safe resection ± RT
- Extent of sx is the most significant predictors of outcome
- Other factors: Pre-op KPS and tumor location
- 5 years survival is around 70% in case of GTR but much lower with incomplete resection (Lancet Oncol. 2009;10(3):258–266)
- Second look surgery is recommended
- Site of the lesions (eg, posterior fossa tumors involving the ponto-cerebellar region) can limit surgery due to involvement of the lower cranial nerves and brainstem

Definitions for the extent of surgical resection

	Extent of surgical resection
R0	No residual tumour on postoperative MRI in accordance with the neurosurgical report.
R1	No residual tumour on MRI but description of a small residual tumour by the neurosurgeon or if the neurosurgical result is unknown.
R2	Small residual tumour on MRI with the maximum diameter below 5 mm in any direction.
R3	Residual tumour that can be measured in three planes.
R4	Size of the residual tumour not differing from the preoperative status (e.g. after biopsy).
RX	Inadequate imaging or equivocal appearances of the surgical cavity. Every effort should be attempted to clarify the conclusion. Sometimes the presence of blood can be ruled out and distinguished from tumour if the MRI is repeated after some days. Repetition of MRI also may help to distinguish operative changes from residual tumour on T2/FLAIR.

Indications of PORT in intracranial EPNs

- Grade II after incomplete excision (>12 months of age)
- Controversial role after GTE in grade II (J Neurooncol. 2013;115(3):513–520)
- All grade III
- **Intracranial subependymoma**- good prognosis, surgery alone is sufficient. However if poorly defined borders- shorter PFS- may benefit from PORT (J Neurosurg. 2015;122(1):49–60)

Exceptions to PORT for intracranial grade II/III EPN after GTE are

- Very young children (<1 year of age), who are typically offered chemotherapy in an effort to spare potential developmental adverse effects of RT
- Patients who undergo GTE of a ST grade II EPN, who represent a favorable group prognostically, may be considered for observation

Radiotherapy

- Standard postoperative management of intracranial EPN
- Focal conformal radiotherapy
- Excellent tumour outcomes and acceptable morbidity, even in children younger than 3 years (Clin Oncol 2019)

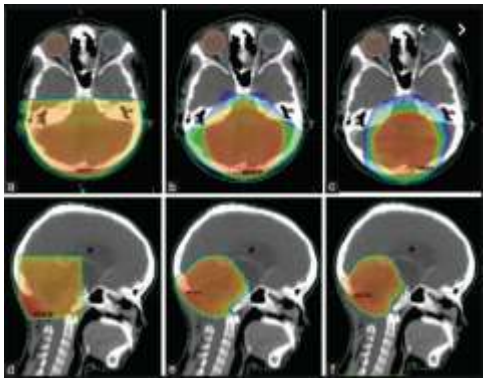
Name of study	*n*	Year of recruitment	Extent of surgery (GTR/NTR/STR)	Radiotherapy (fields/dose)	OS/PFS	Prognostic factors
HIT 88/89/91 IJROBP 2000	55	1988–199?	28/55 - GTR	2/5 – no radiotherapy 40/55 CSI 13/55 focal	3-year OS 75.6% GTR 3-year PFS 83.3% STR 3-year PFS 38.5%	Extent of resection Metastatic disease
St Jude JCO 2004	153	1997–2000	81% GTR	Focal 59.4 Gy 54 Gy	7-year OS 85%	Extent of resection Tumour grade Age Race Pre-irradiation CTX
Second Prospective AIEOP Study Neuro Oncol. 2016	160	2002–2014	75% GTR	Focal 59.4 Gy + 8 Gy/2 fractions for residual	5-year OS 81.1% 5-year EFS 65.4%	Age <3 years (OS) Female gender Tumour grade GTR or NED post-radiotherapy boost
SFCE IJROBP. 2018	202	2000–2014	85% GTR	Variable 62% > 54 Gy	5-year OS 71.4%	Tumour grade Age Extent of resection

Published studies on the treatment of ependymomas in children.

Author, year	Treatment			Number of patients	Efficacy
	Radiotherapy		Chemotherapy		Overall survival
	Proton	Photon			
Timermann et al., 2000 [56]	–	54 Gy at primary site in 13 patients, 1 Gy/fraction 35.2 Gy craniospinal irradiation (1.5 Gy/fraction) + 20 Gy boost (2.0 Gy/fraction) in 40 patients	+	53	3-year: 75.6% (all)
Massimino et al., 2004 [57]	–	Hyperfractionated radiotherapy 70.4 Gy, 1.1 Gy/fraction twice daily	+ in residual tumour (17 patients)	63	5-year: 75 % (all) 5-year: 82 % (complete response) 5-year: 61 % (residual disease)
Merchant et al., 2009 [58]	–	59.4 Gy (131 patients), 1.8 Gy/fraction/d; 54 Gy (22 patients) children < 18 months with complete resection	+ (35 patients)	153	7-year: 81 % 5-year: 93 % (complete resection) 5-year: 52.4 % (R+)
MacDonald et al. [59–61]	55.8 Gy (relative biological efficiency)	–	+ (4 patients)	70	3-year: 95 % 3-year: 97 % (gross total resection) 3-year: 90 % (subtotal resection)

CSI vs focal RT

- In past, craniospinal irradiation (CSI) for all EPN
- However, local site is mc site for failure
- Currently CSI is indicated only if CSF dissemination



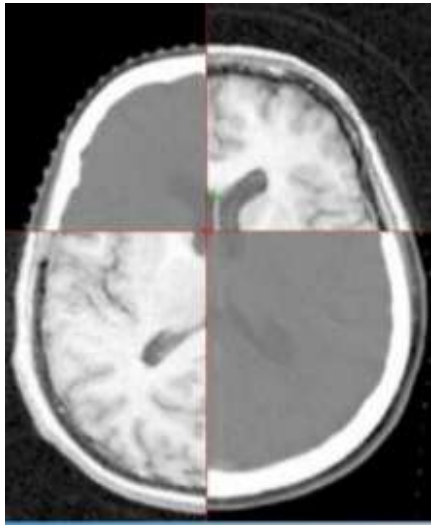
✓ No benefit from routine use of CSI (J Neurosurg 1997)

✓ Local RT achievs good local control with low risk of spinal dissemination (J Neurooncol. 2002;56(1):87–94)

✓ No benefit of CSI in non-metastatic setting (IJROBP 2004)

✓ Limited volume RT achieves high rate of local control with a stable neurocognitive outcome (JCO 2004)

RT planning and target delineation



- 3DCRT or IMRT, Simulation with thermoplastic cast
- GA or sedation may be required
- Fusion MRI with planning CT
- GTV - based on the postop MRI, tumour bed and residual
- Older protocols recommended an expansion of 1 cm from the GTV to the CTV

(Lancet Oncol 2009;10:258-266 & Radiother Oncol2010;96:216-222)

- Newer protocols use a margin of 0.5 cm

  ACNS0831 (0.5 cm)-ongoing
- PTV-0.5 cm, OARS

RT dose

- The current standard doses to the target for intracranial ependymoma are 54 to 59.4 Gy
- Higher doses may be recommended for areas with macroscopic residual
- Dose to the optic chiasm and spinal cord limited to 54 Gy or less
- Very young patients : dose may be reduced to 54 Gy in 30 daily fractions

Lancet Oncol 2009;10: 258-266

Neurooncol2016;18:1451-1460

IJROBP.2018;102:166-173

Is there a need to de-escalate the treatment for a particular group

Therapeutic Impact of Cytoreductive Surgery and Irradiation of Posterior Fossa Ependymoma in the Molecular Era: A Retrospective Multicohort Analysis JCO 2016

Purpose

Posterior fossa ependymoma comprises two distinct molecular variants termed EPN_PFA and EPN_PFB that have a distinct biology and natural history. The therapeutic value of cytoreductive surgery and radiation therapy for posterior fossa ependymoma after accounting for molecular subgroup is not known.

Methods

Four independent nonoverlapping retrospective cohorts of posterior fossa ependymomas (n = 820) were profiled using genome-wide methylation arrays. Risk stratification models were designed based on known clinical and newly described molecular biomarkers identified by multivariable Cox proportional hazards analyses.

Results

Molecular subgroup is a powerful independent predictor of outcome even when accounting for age or treatment regimen. Incompletely resected EPN_PFA ependymomas have a dismal prognosis, with a 5-year progression-free survival ranging from 26.1% to 56.8% across all four cohorts. Although first-line (adjuvant) radiation is clearly beneficial for completely resected EPN_PFA, a substantial proportion of patients with EPN_PFB can be cured with surgery alone, and patients with relapsed EPN_PFB can often be treated successfully with delayed external-beam irradiation.

Conclusion

The most impactful biomarker for posterior fossa ependymoma is molecular subgroup affiliation, independent of other demographic or treatment variables. However, both EPN_PFA and EPN_PFB still benefit from increased extent of resection, with the survival rates being particularly poor for subtotally resected EPN_PFA, even with adjuvant radiation therapy. Patients with EPN_PFB who undergo gross total resection are at lower risk for relapse and should be considered for inclusion in a randomized clinical trial of observation alone with radiation reserved for those who experience recurrence.

This raises a possibility of future clinical efforts to study therapy de-escalation for PF-EPNB pts

Role of radiation dose escalation?

- A recent retrospective study reported that the main pattern of relapse was within the radiation fields even at 59.4 Gy

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Intracranial ependymoma

Patterns of failure after radiotherapy for pediatric patients with intracranial ependymoma

- Is there a role of dose escalation?

Final results of the second prospective AIEOP protocol for pediatric intracranial ependymoma

Neuro-oncology 2016

Background. This prospective study stratified patients by surgical resection (complete = NED vs incomplete = ED) and centrally

Feasibility of Dose Escalation in Patients With Intracranial Pediatric Ependymoma

frontiers in Oncology

June 2019 | Volume 9 | Article 531

Material and methods: The cohort included 101 patients. The dose to planning target volume (PTV59.4) was 59.4/1.8 Gy, and the dose to SIB volume (PTV67.6) was 67.6/2.05 Gy. Gross tumor volume (GTV) was defined as the tumor bed plus residual tumor, clinical target volume (CTV59.4) was GTV + 5 mm, and PTV59.4 was CTV59.4 + 3 mm. PTV67.6 was GTV+ 3 mm. After treatment plan optimization, quality indices and doses to target volume and organs at risk (OARs) were extracted and compared with the standard radiation doses that were actually delivered (median = 59.4 Gy [50.4 59.4]).

Conclusion: Dose escalation with intensity-modulated proton or photon SIB is feasible in some patients. This approach could be considered for children with unresectable residue or post-operative FLAIR abnormalities, particularly if they have supratentorial tumors. It should not be considered for infratentorial tumors encasing the brainstem or extending to the medulla.

Neuro-Oncology

20(4), 445–456, 2017 | doi:10.1093/neuonc/nox166 | Advance Access date 29 November 2017

EANO guidelines for the diagnosis and treatment of ependymal tumors

Table 2 Key recommendations for the treatment of newly diagnosed intracranial WHO grades II and III ependymomas in children

	Class of Evidence	Level of Recommendation
Resection is recommended to obtain a histological diagnosis and should be a gross total resection whenever feasible. As the morbidity can be significant, detailed informed pre-operative counseling by a surgeon experienced in performing such surgery is important.	II	B
Postoperative MRI should be performed to evaluate the extent of resection.	n.a.	Good Practice Point
A second-look surgery should be considered when residual tumor is demonstrated on postoperative MRI and gross total resection is a realistic goal.	II	B
Because a risk of CSF dissemination exists for all patients with newly diagnosed ependymoma, a disease staging, including both craniospinal MRI and CSF cytology, is mandatory following surgery (not earlier than 2–3 wk)	n.a.	Good Practice Point
Postoperative conformal radiotherapy with doses up to 59.4 Gy is recommended in children older than 18 months.	II	B
Postoperative conformal radiotherapy with doses of 54 Gy is recommended in children between 12 months and 18 months or in older children with poor neurological status.	II	B
Chemotherapy alone is an option in children less than 18 months old, while it is recommended in children aged less than 12 months.	III	C
Craniospinal irradiation (CSI) is recommended in case of CSF or spinal dissemination with a boost on focal lesions with doses adapted to patient age.	IV	Good Practice Point
Because of the risk of asymptomatic and/or late relapses, patients should be followed long term with an enhanced MRI.	n.a.	Good Practice Point
Serial monitoring of cognitive and endocrine functions with specific batteries following radiotherapy is recommended whenever feasible.	n.a.	Good Practice Point

EPN with CSF dissemination

- Not common at diagnosis
- More frequently encountered in relapsed disease
- Paucity of evidence
- Resection of the primary tumour and any other areas of bulk disease should be attempted if possible
- Adjuvant therapies depend on the age of the child
- CSI should be considered, depending on the age of the child (generally avoided in <3 years)
- RT dose of 36 Gy in 1.8 Gy fractions with a boost to the primary tumour bed of 59.4 Gy and metastases

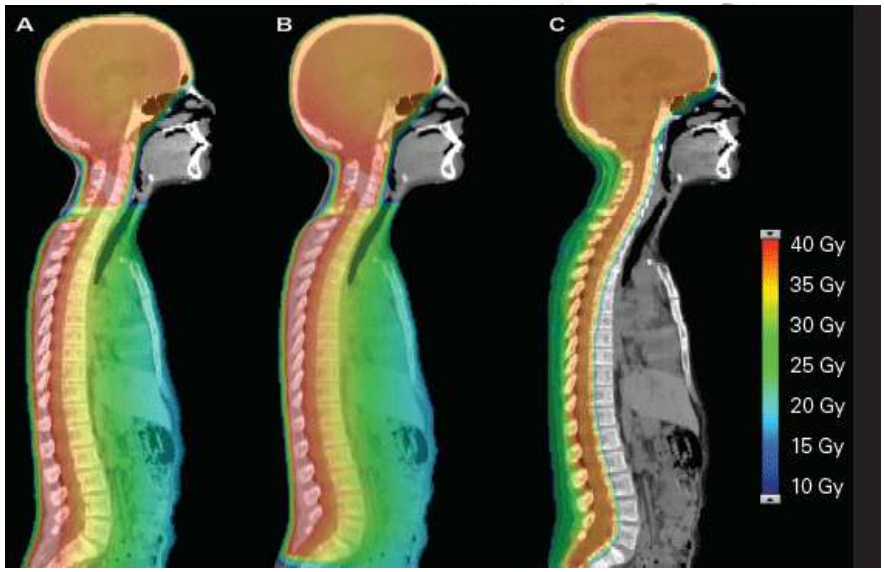
Craniospinal irradiation (CSI)

OARS

- Brain stem, optic pathway, pituitary
- Cochlea / Inner ear
- Parotid, oral cavity, mandible
- Thyroid, larynx
- Heart, lungs, oesophagus
- Liver, kidneys ,gonads

Target volume

- Entire brain, spinal cord and its meningeal coverings



Spinal ependymoma

Adjuvant radiotherapy delays recurrence following subtotal resection of spinal cord ependymomas

Neuro-Oncology 15(2):208–215, 2013

Results. A total of 348 patients underwent surgical resection of spinal cord ependymomas, where GTR was obtained in 77.0% (268/348) of patients. Among those who received STR, 58.8% (47/80) received adjuvant radiotherapy. PFS was significantly prolonged among those who received adjuvant radiotherapy after STR (log rank; $P < .001$). This prolonged PFS with adjuvant radiotherapy remained significant in multivariate Cox regression analysis (STR versus STR + RT group; hazard ratio (HR) = 2.26, $P = .047$). By contrast, improved OS was only associated with GTR (GTR versus STR + RT group; HR = 0.07, $P = .001$) and benign ependymomas (HR = 0.16, $P = .001$).

Radiation dose in spinal ependymoma

Table 5 Key recommendations for the treatment of WHO grades II and III spinal cord ependymomas

	Class of Evidence	Level of Recommendation
Gross total resection is the goal of spinal ependymoma surgery.	II	B
Postoperative MRI should be performed to evaluate the extent of resection.	n.a.	Good Practice Point
Because a risk of CSF dissemination exists for all patients with newly diagnosed ependymoma, disease staging, including both craniospinal MRI and CSF cytology, is recommended following surgery (not earlier than 2–3 wk).	n.a.	Good Practice Point
In case of WHO grade III (anaplastic) ependymomas, postoperative radiotherapy with doses of 45–54 Gy is recommended regardless of the extent of resection.	III	C
In case of WHO grade II ependymomas following gross total resection, a watch-and-wait strategy is recommended.	III	C
In case of incomplete resection of a WHO grade II ependymoma, postoperative local radiotherapy is recommended with doses of 45–54 Gy.	II	B
Because of the risk of asymptomatic and/or late relapses, patients should be followed long term with an enhanced MRI.	n.a.	Good Practice Point

Infantile EPN
Should we avoid RT in young children

- Duffner et al (1993): postop chemomay be used to delay or even avoid RT in children aged < 3 years with malignant brain tumours
- In an attempt to delay RT in very young children, several groups used post-op chemo in children <3 years with 42% being the highest rate of 5-year PFS
- Infant ependymoma in a 10-year AIEOP (Associazione Italiana Ematologia Oncologia Pediatrica) experience with omitted or deferred radiotherapy*
- Median age 22 months
- Poor rates of EFS and OS for up-front chemo in infant ependymoma
- No better neurocognitive outcome was demonstrated in the few survivors who never received RT *(IJROBP. 2011 Jul 1;80(3):807-14)

- ✓ In contrast, immediate PORT in < 3 years led to 7-year PFS of 77%, However, long-term follow-up for toxic effects on development are still pending (Lancet Oncol. 2009 Mar;10(3):258-66)
- 3-year OS was 81% for those undergoing PORT compared with 56% with no RT in younger than 3 years (P-0.005) J Neurooncol 2011;105:583-590

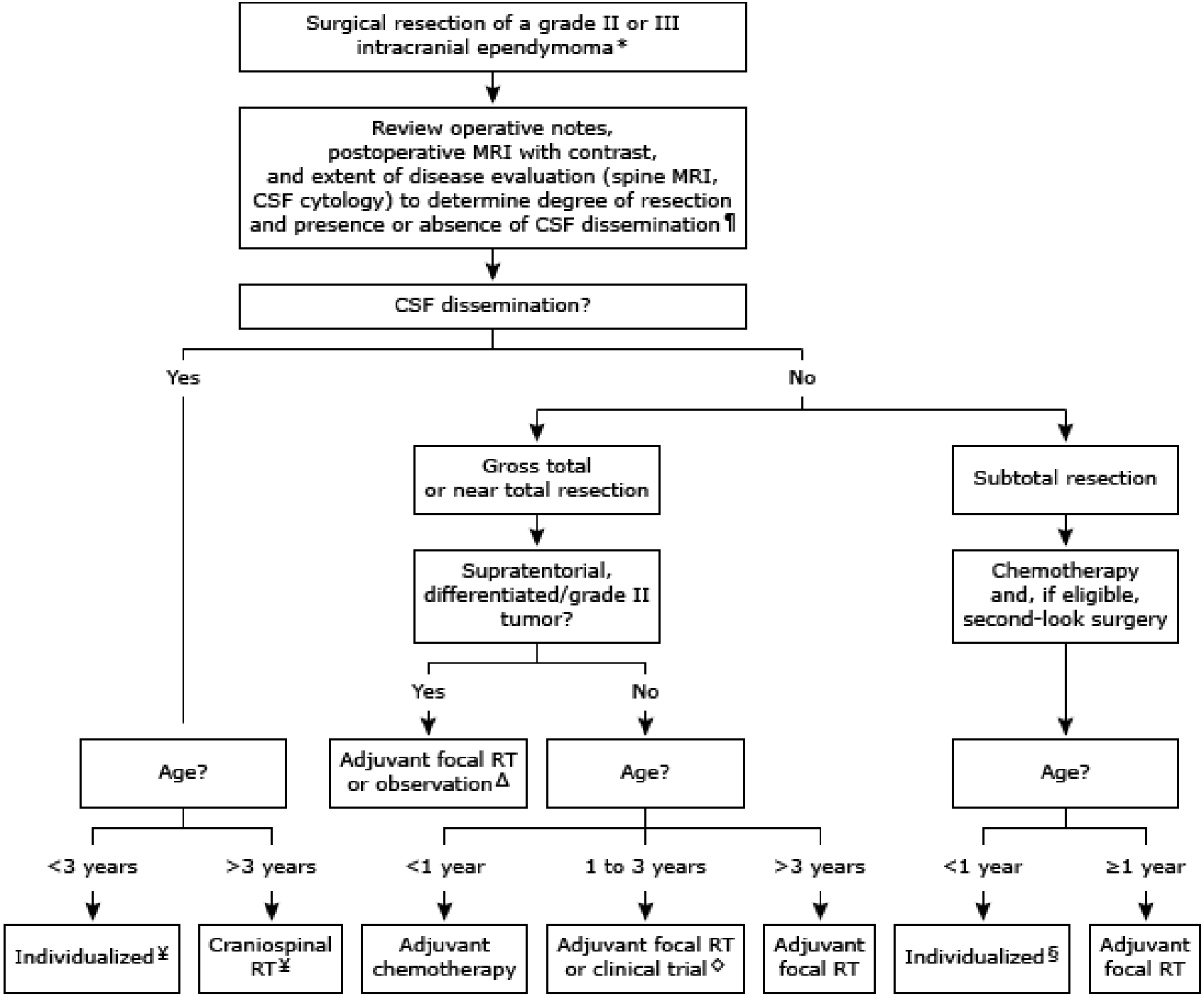
- Thus radiotherapy deferral strategies that use chemotherapy have been abandoned in most institutions for children >12 months of age

EANO guidelines for post surgery treatment

Table 4 Key recommendations regarding nonsurgical treatment of WHO grades II and III ependymomas in children

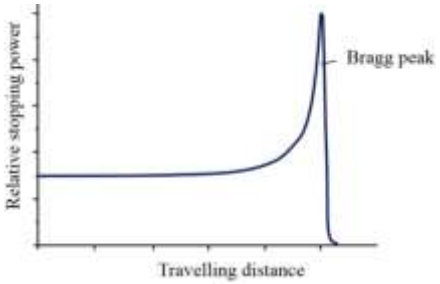
	CT Indication	CT Regimen	CT Timing	RT Indication	RT Timing	GTV (defined with MRI)	CTV	Total Dose, Gy	Dose/fraction, Gy	Technique
Localized tumor, age >18 mo	Debatable	VEC ± cisplatin	Maintenance	Systematically	Postoperatively	Tumor bed and 3D identifiable residual disease	5–10 mm around GTV	59.4	1.8	3DCRT or IMRT or proton
Localized tumor, age >18 mo with visible residual tumor after surgery	Recommended	VEC ± cisplatin ± high-dose methotrexate	Postoperatively	Stereotactic additional boost recommended within a prospective clinical trial with residue after chemotherapy	Postoperatively and post-chemotherapy	Tumor bed and 3D identifiable residual disease		59.4+8	4	3DCRT or IMRT or proton
Localized tumor, age 12–18 mo	Recommended	Baby UK	Maintenance	To be discussed	Postoperatively	Tumor bed and 3D identifiable residual disease		54	1.6–1.8	
Localized tumor, age <12 mo	Recommended	Baby UK	Postoperatively	NORT	NORT	–	–	–	–	
Metastatic tumor	Debatable	VEC ± cisplatin	Before RT	Salvage treatment	Postoperatively or postchemotherapy	Tumors and 3D identifiable residual disease	CSI + boost 5–10 mm around GTV	24 or 36 depending on age + boost up to 59	1.8	
Local relapse	None outside clinical trial	–	–	Recommended	Postoperatively	3D identifiable disease	GTV+2 mm	59 or in a prospective trial 25 Gy/5 fractions or 24 Gy/3 fractions	1.8 or hypofractionation (5–8)	3DCRT or IMRT or proton or hypofractionated stereotactic irradiation

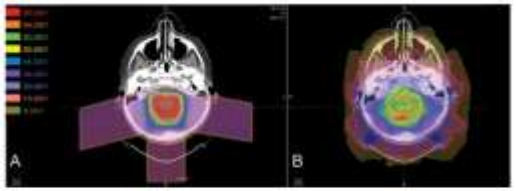
CT, chemotherapy; RT, radiotherapy; VEC, vincristine/etoposide/ cyclophosphamide regimen; GTV, growth tumor volume; CTV, clinical target volume; 3DCRT, 3D conformal radiotherapy; IMRT, intensity modulated radiotherapy;


Surgical resection of a grade II or III intracranial ependymoma*
Review operative notes, postoperative MRI with contrast, and extent of disease evaluation (spine MRI, CSF cytology) to determine degree of resection and presence or absence of CSF dissemination¶
CSF dissemination?
Yes
No
Gross total or near total resection
Subtotal resection
Supratentorial, differentiated/grade II tumor?
Chemotherapy and, if eligible, second-look surgery
Yes
No
Age?
Adjuvant focal RT or observation△
Age?
Age?
<3 years
>3 years
<1 year
1 to 3 years
>3 years
<1 year
≥1 year
Individualized¥
Craniospinal RT¥
Adjuvant chemotherapy
Adjuvant focal RT or clinical trial◇
Adjuvant focal RT
Individualized§
Adjuvant focal RT

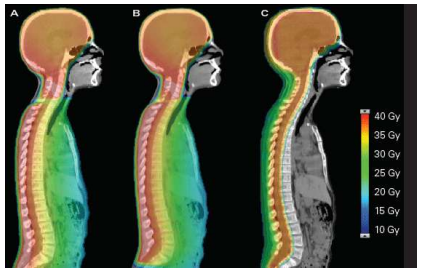
Proton therapy

- Higher radiation dose can probably compensate for the incomplete sx
- Proton dose distribution is particularly pertinent in infantile posterior fossa tumors





Representative (A) proton RT plan and (B) intensity-modulated RT plan for infratentorial ependymoma.



Control rates are predicted to be equivalent

- ✓ Proton radiotherapy for paediatric central nervous system ependymoma: clinical outcomes for 70 patients (Neuro Oncol 2013)
- ✓ Outcomes following proton therapy for pediatric ependymoma. 179 children (≤21 years old) with nonmetastatic grade II/III intracranial ependymoma. (Acta Oncol.2018)
- **Results:** Median FU- 3 years, comparable disease control without unexpected toxicities, late toxicity data is awaited

- Proton Radiotherapy for Pediatric Brain Tumors Requiring Partial Brain Irradiation (Age between 1-25 years): Ongoing study
- Massachusetts General Hospital
- Primary outcome: Endocrine and neurological sequel at 5 years

✓ Low Grade Glioma

✓ Astrocytoma

✓ Ependymoma

✓ Ganglioglioma

- Study completion date : September 2022
  http://clinicaltrials.gov/show/NCT01288235

Radiation toxicity

Acute

- Fatigue
- Mild headache
- Nausea
- Feeling sick

Late

- Neurocognitive deficits
- Focal neurologic deficits
- Sensorineural hearing loss
- Growth abnormalities
- Endocrine abnormalities
- Secondary malignancies

Conclusion

- EPN continues to present clinicians with challenges in terms of outcomes
- Ependymal tumors from different compartments of the central nervous system are biologically distinct
- Molecular sub-classification is expected to significantly support treatment decisions and simplify risk stratification processes
- Surgery remains the mainstay
- Radiotherapy improves outcome in subtotal resection and grade III tumors
- Molecular subgrouping should be a part of all clinical trials

Thank you