ARRO Case: Pediatric Ependymoma

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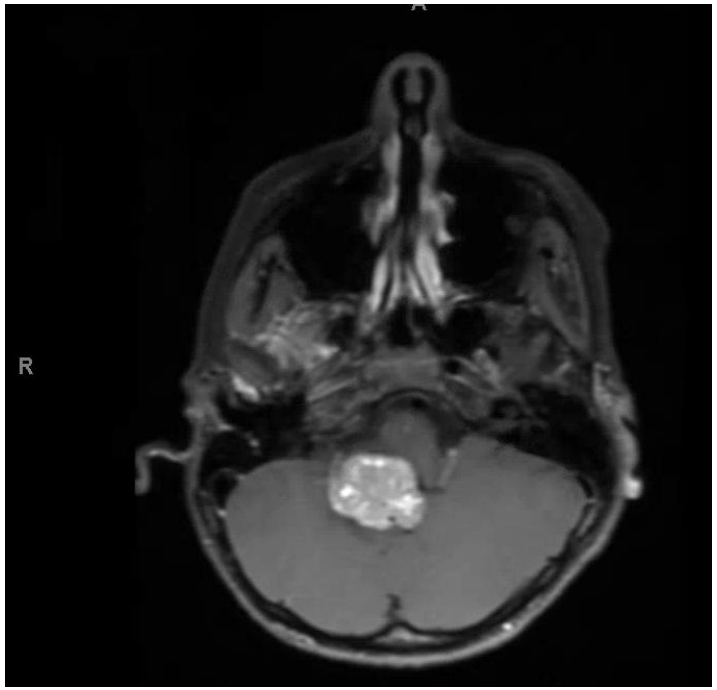
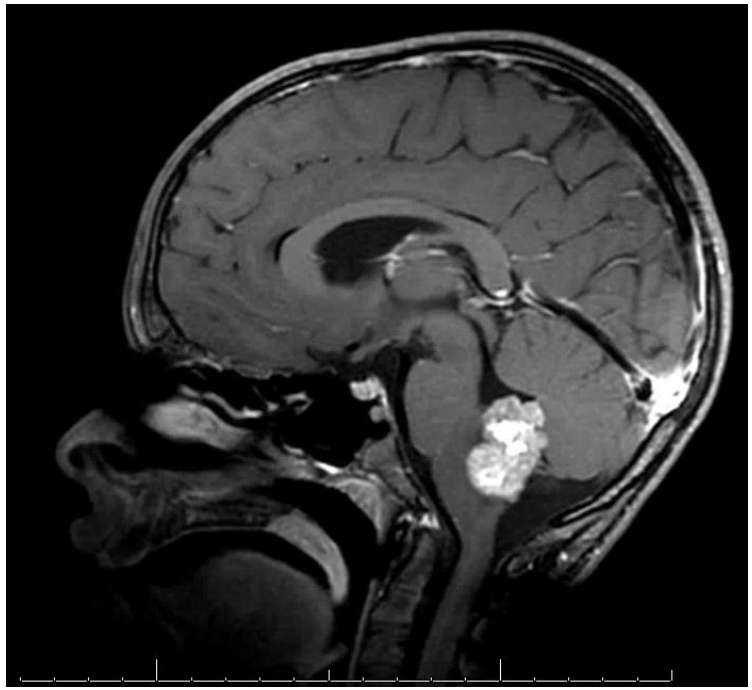
Presentation

- 10 year old boy presents with dizziness and morning nausea x 2.5 months followed by double vision x several weeks
- MRI brain with contrast (T1+ Gad)





Initial Work-Up

- **H & P**
  - History: ask about symptoms of increased ICP: HA, N/V
  - Physical exam:
    - Cranial nerve deficits, ataxia, fundoscopic exam to look for papilledema
    - “Setting sun” sign: downward deviation of gaze from increased ICP (CN III, IV, VI)
  - Family history:
    - Ask about FH history of cancer
      - Gorlin’s (PTCH) or Turcot’s (APC)
- MRI brain

Differential: BEAM HIM Juvenile

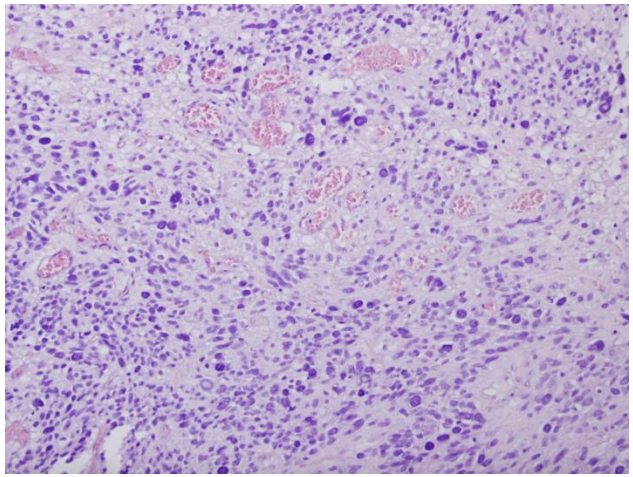
- **B**rainstem Glioma
- **E**pendymoma
- **A**strocytoma/**A**typical teratoid rhabdoid tumor (ATRT)
- **M**edulloblastoma
- **H**emangioblastoma
- **I**nfection
- **M**ets
- **J**uvenile pilocytic astrocytoma

Next steps

No biopsy will be done on a posterior fossa mass prior to resection→ these patients go straight to resection (with the exception of diffuse intrinsic pontine glioma)

Case continued

- Patient goes on to gross total resection
- Pathology shows:
  - Anaplastic ependymoma (focal Ki-67 labeling up to 38%)



http://www.pathologyoutlines.com/topic/cnstumoranaplasticependymoma.html

Case continued

- Next steps in work-up
  - MRI spine→negative for metastases
  - CSF→negative

Overview

- Ependymoma arises from lining of the ventricular system and central spinal canal
- Adults:
  - Tumors primarily arise in the spine
- Pediatrics:
  - 90% are intracranial, 60% arise in the posterior fossa
  - 8-10% of childhood CNS tumors
  - 30% occur in children who are <3 years old
    - Mean age is 5 years old
- NF2: increased incidence of spinal cord tumors

Pathology

- Grade 1: myxopapillary (not seen in brain) and subependymoma
- Grade 2: classic ependymoma
  - Includes cellular, papillary, clear cell, tancytic types
- Grade 3: anaplastic ependymoma
  - High mitotic rate, microvascular proliferation, and pseudopalisading necrosis
- Grade 4: ependymoblastoma: extremely rare, highly malignant primitive embryonal tumors
  - **NOT** considered in classification of ependymoma
  - Renamed embryonal tumor with abundant neuropil and true rosettes (ETANTR)

Risk stratification

- Extent of resection (dominant prognostic factor)
  - Event free survival 50-75% after GTR vs 30-45% with incomplete removal
- Age
  - Inferior likelihood of disease control at age <3 years
- Lower doses of radiation (worse local control)
- Higher expression of Ki67 or MIB-1→greater risk of treatment failure
- Anaplastic histology
- Chromosome 1q25 gain: inferior outcome for both posterior fossa and supratentorial ependymoma
- Expression of hTERT and Nestin (worse prognosis)
- Supratentorial and infratentorial ependymomas have different genomic, gene expression, and IHC signatures

Further risk stratification

- Molecular subtypes

Molecular Subgroups of Ependymoma

Subtype	Location in CNS	Molecular and Clinical Features
Group A/CIMP+	Posterior Fossa	Epigenetic changes, chromosome 1q gain, young children, and intermediate to poor prognosis; CPG island methylator phenotype, WHO grade III (common); 70%+ of PF tumors
Group B/CIMP–	Posterior Fossa	Chromosomal defects; adolescent children, adults, good prognosis; <30% of PF tumors
RELA Fusion positive	Supratentorial	C11orf95-RELA fusion (70% of supratentorial tumors); typically young children, WHO grade II/III
Yap1 fusion positive	Supratentorial	MAMLD1-YAP1 or FAM1188-YAP1 fusions, Children, Who grade II/III; 30% of supratentorial tumors
Myxopapillary	Spinal	WHO grade I, adolescent children/adults; good prognosis (80%+ of spinal tumors)
Classic/Spinal Subependymoma	Spinal All CNS compartments	Adolescent children, adults, who grade II, good prognosis WHO grade I, balanced genome, adults, good prognosis

Data from Gajjar A, Bowers DC, Karajannis MA, Leary S, Witt H, Gottardo NG. Pediatric brain tumors: innovative genomic information is transforming the diagnostic and clinical landscape. *J Clin Oncol.* 2015;33(27):2986–2998.

EPN-PFA: High rates of disease recurrence→33% PFS at 5 years, 68% OS at 5 years

EPN-PFB: 5 year PFS of 73% and OS of 100%

ST-EPN-RELA: gain of ch 1q (poor prognostic factor) in 25% of cases, unfavorable outcome compared to other ependymoma subtypes (5 yr PFS 29% and OS 75%)

YAP1: relatively favorable, 5 year PFS 66% and OS 100%

(Yock, et al. Ch 4: Tumors of the posterior fossa and spinal canal. from Constine, Tarbell et al. 2016)

Treatment

Current treatment paradigm-all patients get surgery

Tumor subtype	Treatment following surgery
Subependymoma	Observation
Spinal cord ependymoma, GTR	Observation
Spinal cord ependymoma, STR	Adjuvant RT to 50.4 Gy (in general, field should include 2 VB above and below)
Myxopapillary ependymoma, GTR	Observation (some evidence that focal RT may improve PFS and reduce dissemination to other parts of neuroaxis-so possible RT)
Myxopapllary ependymoma, STR	Adjuvant RT can improve local control
Grade II/III, GTR, M0	Conformal RT to tumor bed (59.4 Gy for photon, 54 Gy for proton)
Grade II/III, GTR, M1	CSI 30-36 Gy + focal boost (54-60 Gy for local disease, 45 Gy for spine)
Grade II/III, STR, M0	**Second look surgery** then conformal RT to tumor bed (59.4 Gy for photon, 54 Gy for proton)
Grade II/III, STR, M1	**Second look surgery** then CSI 30-36 Gy + focal boost (54-60 Gy for local disease, 45-50 Gy for spine metastases)
<12 months	Chemotherapy with delayed radiation

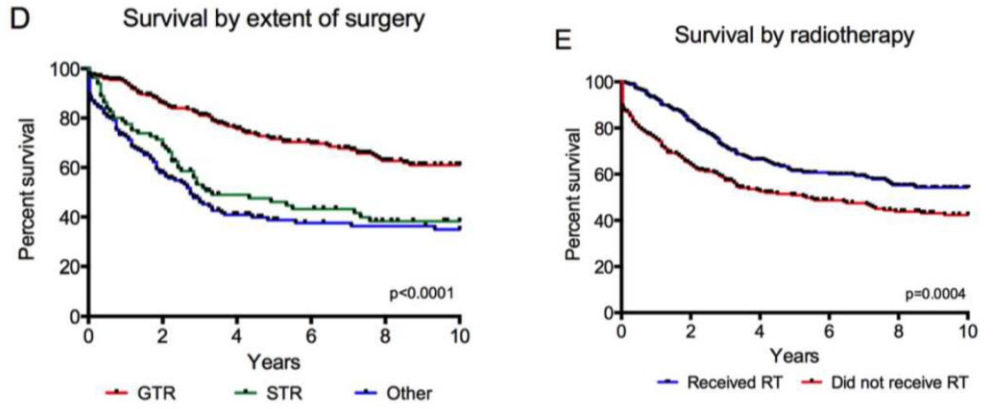
(Modified from Hansen, Roach 2018)

Improved OS with RT

- Pollack, et al. showed 5 year OS of 45% with surgery + RT vs 13% with surgery alone (Pollack, Gerszten et al. 1995)
- Rousseau, et al. showed 63% survival at 5 years with surgery + RT vs 23% with surgery alone (Rousseau, Habrand et al. 1994)

Role of radiation

- Historically, patients <3 years old would be treated with chemotherapy and patients >3 years old would be treated with radiotherapy
- A retrospective SEER analysis by (Snider, Yang et al. 2018)which evaluated 482 patients between 1973 and 2013 showed that:
  - RT significantly benefitted OS for both grade II and grade III ependymoma



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

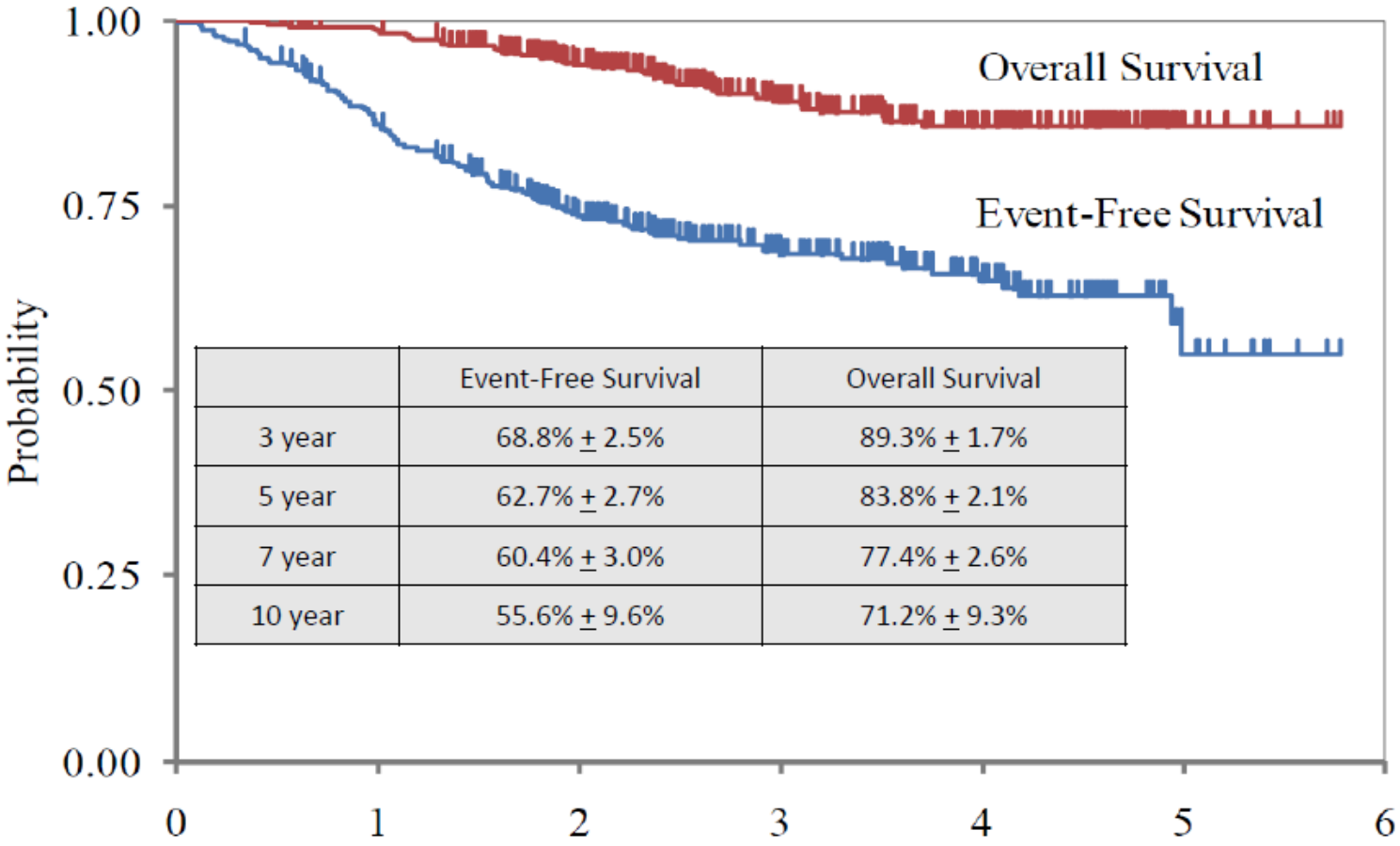
ACNS0121: Phase II trial

Enrolled patients >12 months, intracranial ependymoma

Stratum	1	2	3	4
Surgery	Gross total resection1(no visible tumor under microscope)	Subtotal resection (residual tumor >0.5 cm on post-op imaging)	Near total resection (residual tumor on imaging)or Gross total resection2 (microscopically visible residual tumor, negative imaging)	Gross total resection1(no visible tumor under microscope)
WHO Grade	II	II-III	II-III	II-III
Site	Supratentorial	Any	Any	Supratentorial III Infratentorial II-III
Treatment	Observation	Chemotherapy +/- second surgery + RT	Radiation therapy	Radiation therapy
Treatment Group	1	2	3	3

(Merchant, Bendel et al. 2019)

Event-Free and Overall Survival



	Event-Free Survival	Overall Survival
3 year	68.8% ± 2.5%	89.3% ± 1.7%
5 year	62.7% ± 2.7%	83.8% ± 2.1%
7 year	60.4% ± 3.0%	77.4% ± 2.6%
10 year	55.6% ± 9.6%	71.2% ± 9.3%

(Merchant, Bendel et al. 2019)

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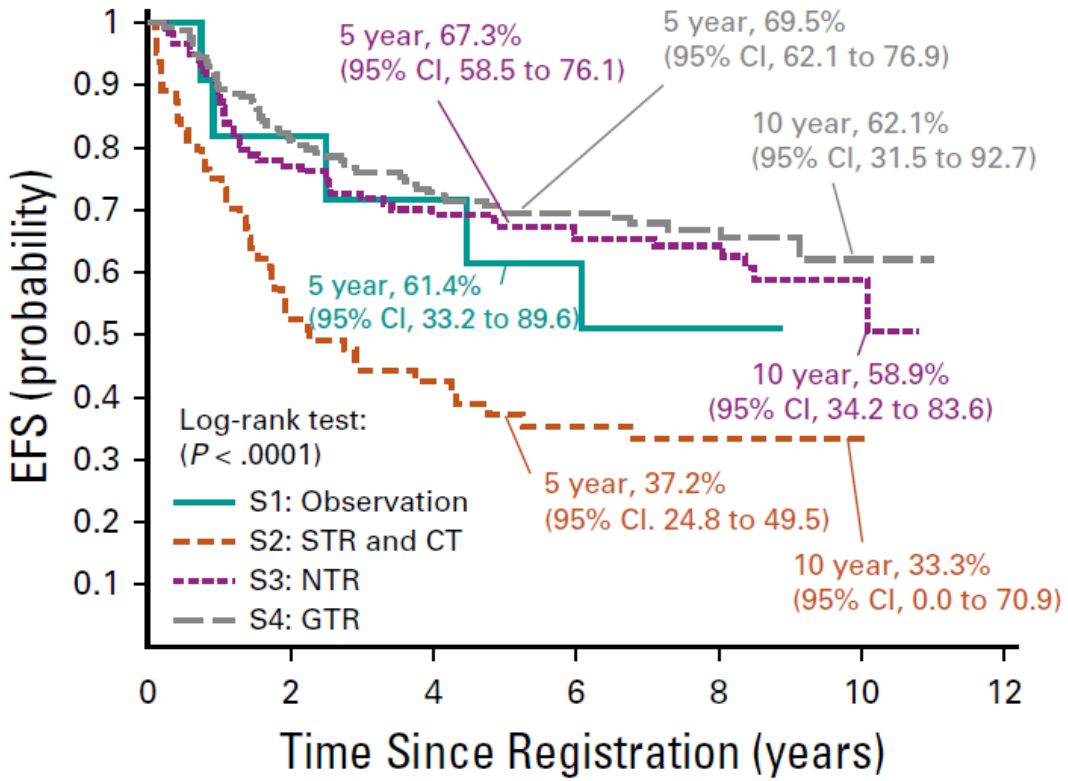


No. at risk

S1: Observation	11	9	7	6	3		
S2: STR and CT	64	48	26	21	13	7	
S3: NTR	118	105	82	71	63	24	
S4: GTR	163	141	120	101	83	25	1

- GTR/nGTR with radiation did best (stratums 3 and 4)
- STR with chemotherapy and adjuvant RT did the worst (statum 2)
- Supratentorial/GTR/WHO grade II only→observation: A priori felt to be best prognosis group (statum 1) – did worse than expected with 5 year EFS (61% +/- 14%)

(Merchant, Bendel et al. 2019)

Neurocognitive outcomes:

- Merchant, et al. evaluated 316 patients who received focal RT for localized ependymoma (Merchant, Mulhern et al. 2004)
- Mean scores on all neurocognitive outcomes were within normal limits (no more than 10 pts from the normative mean for age group)

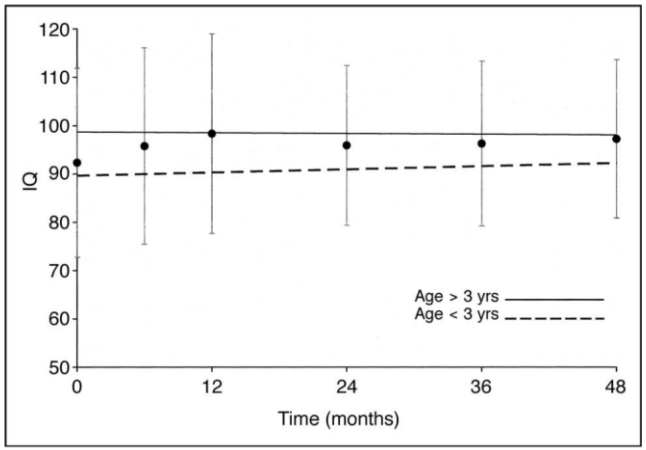


Fig 2. Estimated mean intelligence quotient (IQ) before and after conformal radiation therapy.

- 3 year progression free survival was 74.7% +/- 5.7%
- Studies are in process evaluating whether long-term toxicities are less with proton compared to photon RT(Indelicato, Bradley et al. 2018)

Chemotherapy

- Only prospective randomized trial looked at CCNU, vincristine, and prednisone after surgery and RT in the 1980s (Evans, Anderson et al. 1996)
  - No improved disease control with chemotherapy
- Randomized trial of adjuvant CCNU/vincristine/prednisone vs “8 in 1” regimen (Robertson, Zeltzer et al. 1998)
  - No improvement in either arm of trial

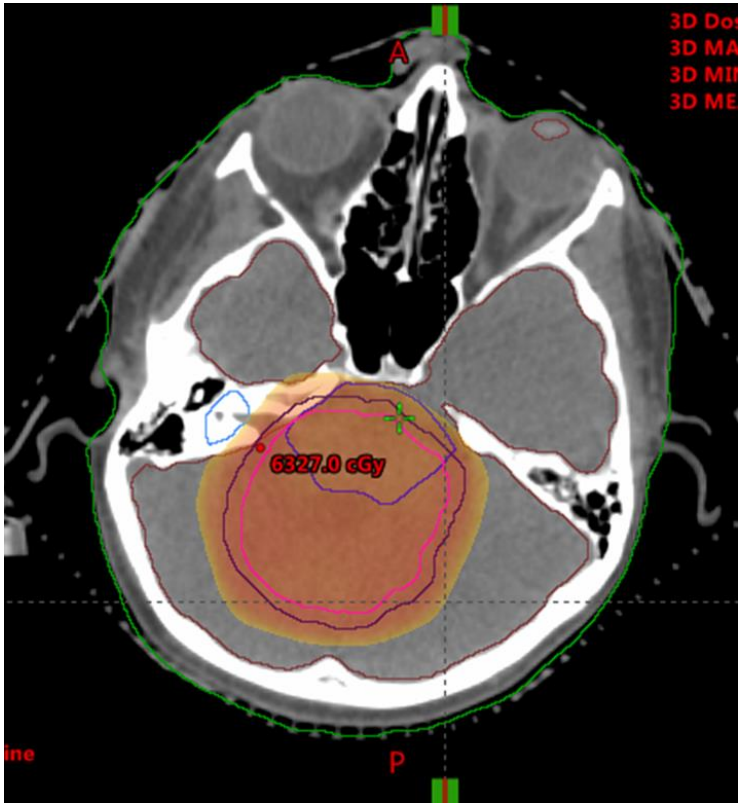
Radiation treatment planning

- **MO patients:**
  - Target volumes have evolved from whole brain to posterior fossa to now tumor bed only
    - Posterior fossa ependymomas tend to adhere to the floor of fourth ventricle and cranial nerves, does not invade brainstem or adjacent normal brain →trend toward smaller margins (CTV margin for ACNS0831 is 5 mm although 1 cm is commonly used)

      (Constine, Tarbell et al. 2016)
  - Recommendations for GTV include tumor bed and residual tumor based on pre and post-operative imaging
  - Common patterns of disease extension such as encasement of basilar artery and extension into foramina of Luschka should be assessed; pay attention to spread along cervical spine (10-30% of 4^{th} ventricle tumors)
  - Recommendation to limit dose to optic chiasm and spinal cord to 54 Gy
  - Standard to limit brainstem to 54 Gy; Merchant suggests limiting brainstem to <60 Gy (no more than 53 Gy to center of brainstem or 64 Gy to surface) is safe (Merchant, Chitti et al. 2010)
  - Dose is 54-59.4 Gy in 1.8 Gy fractions
- **M1 patients:**
  - CSI 30-36 Gy + focal boost (45 Gy for spine metastases, 54-60 Gy for primary site)

Case continued

- Went to resection→GTR
- Treated with adjuvant radiation:
  - VMAT plan
  - 59.4 Gy to primary tumor
  - 5 mm margin for CTV
  - 3 mm margin for PTV
  - Reduced dose to portion of CTV involving brainstem



Ongoing trials

- ACNS0831: evaluating patients with GTR + RT, post-radiation VCEC vs no post-radiation chemotherapy
- SIOP Ependymoma II: Primarily a chemotherapy trial, but patients with tumors that persist despite pre-RT chemo and RT (59.4 Gy/1.8 Gy fractions) will get a boost of 4 Gy x 2 to residual tumor bed

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