



Diffuse Pontine Gliomas (Progress and Future Potential)

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Disclosures

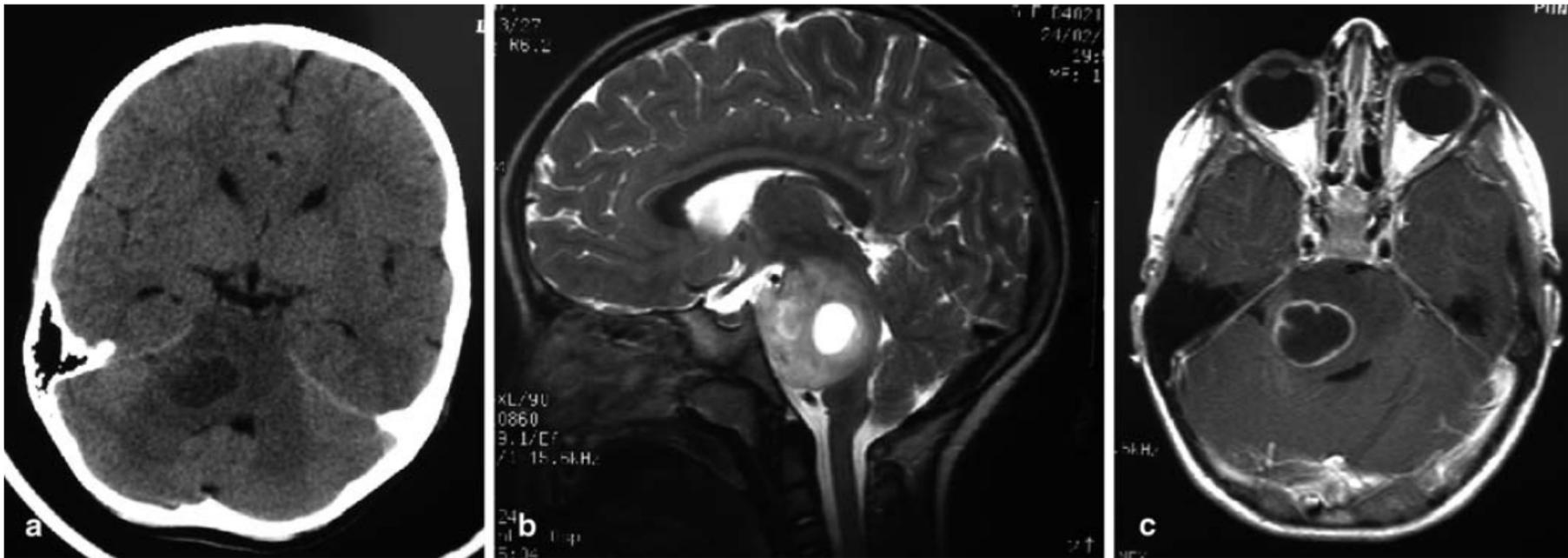
- None

Fast Facts for DIPG

- Without radiation survival approximately 4 months
- Survival is 30% at one year and less than 10% at 2 years.
- Long term survival 2-3 % usually associated with atypical imaging and clinical features
- Multiple studies investigating medical therapy

Diagnosis of DIPG

- Initially describe in 1985



- Bright signal on T2 and hypointense on T1

DIPG: How are we doing?

Most children die within two years

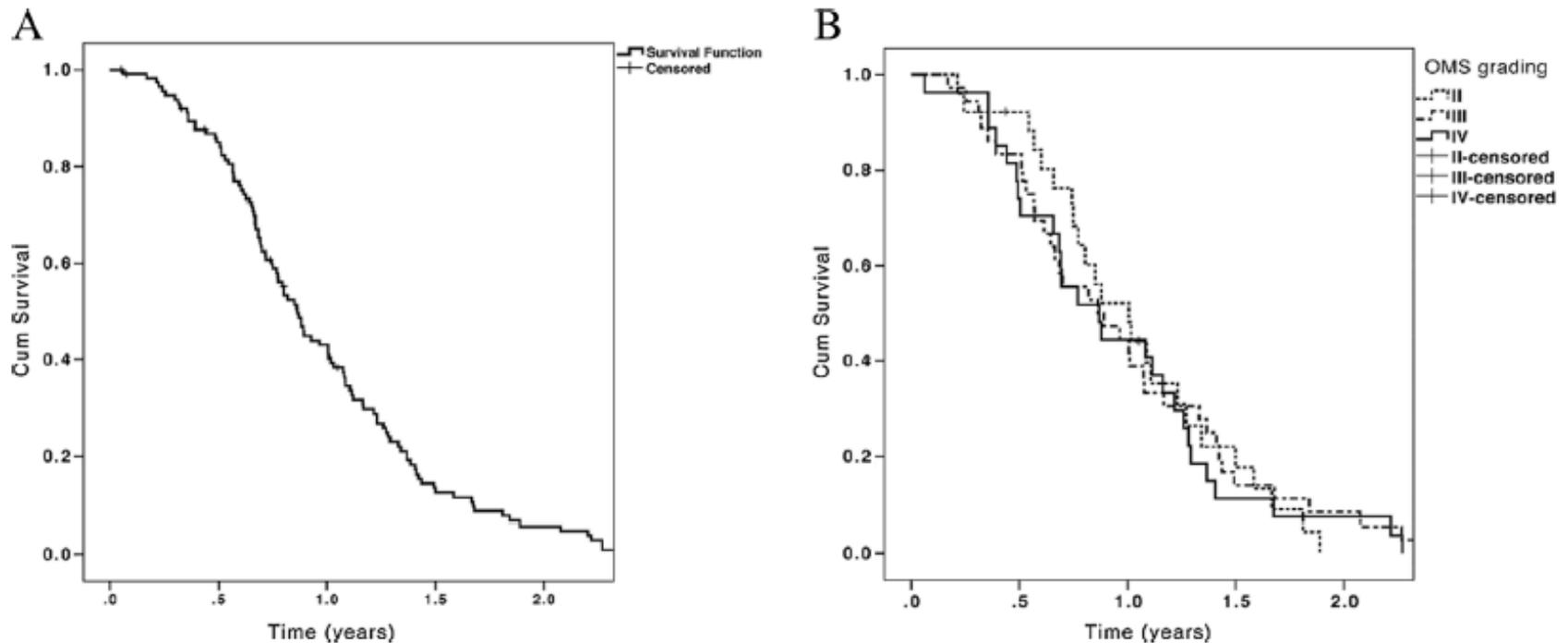


Fig. 3 Whole overall survival of the DIPG biopsy children (a) and according to the WHO grading (b)

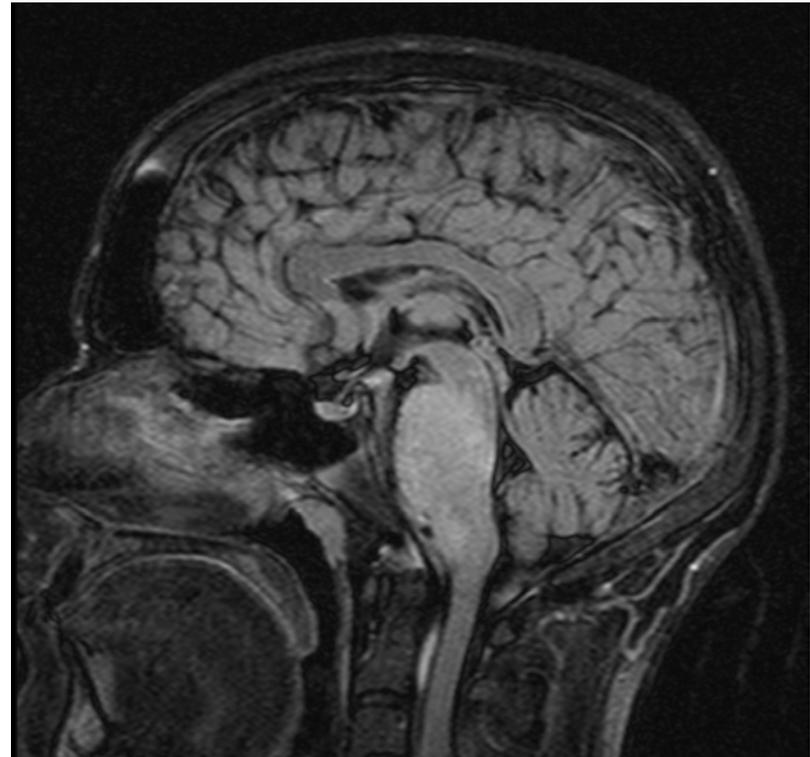
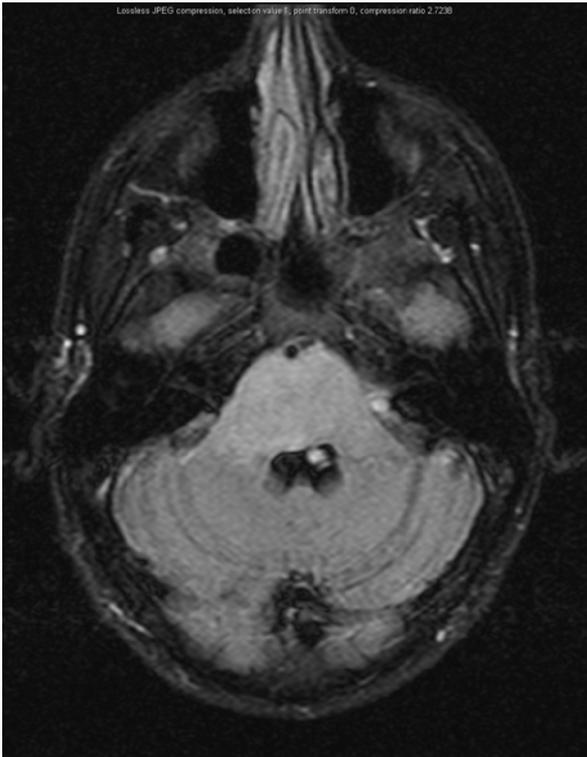
Childs Nerv Syst (2015) 31:1773–1780



NATIONWIDE CHILDREN'S
When your child needs a hospital, everything matters.

23 year old white male that presented with left hemiparesis

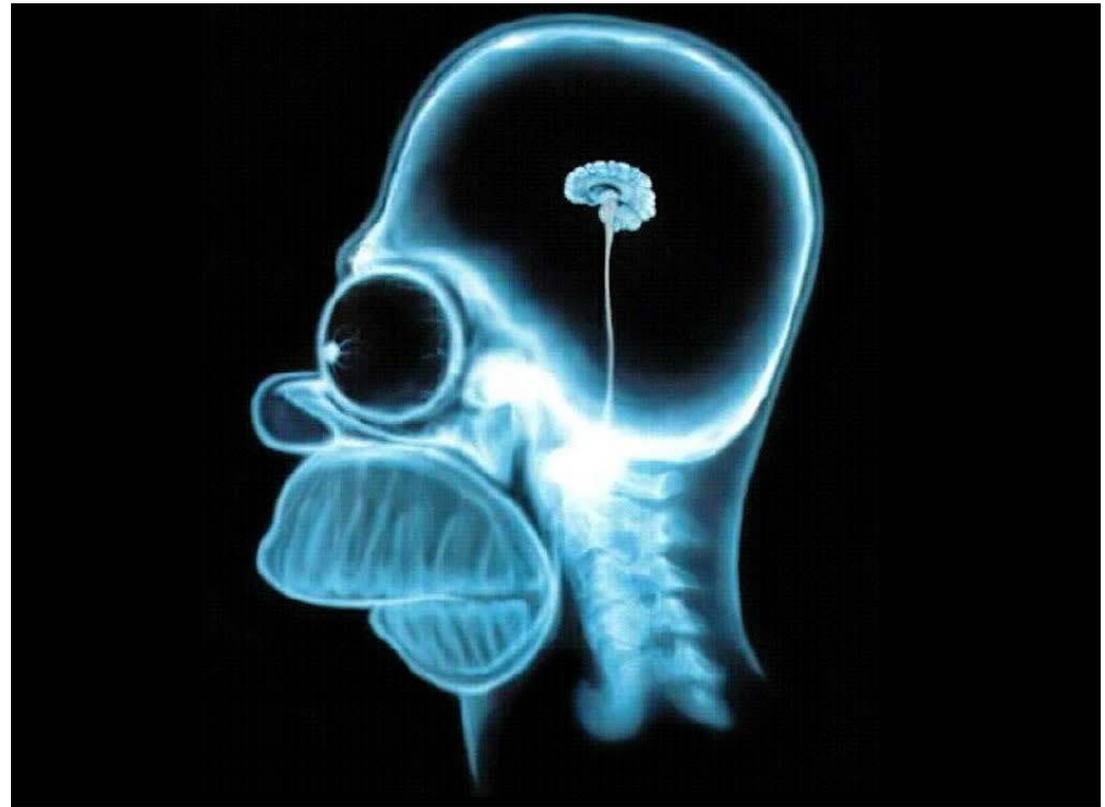
- Multiple chemotherapy regimens
- Radiation
- Symptoms resolve, presents to us to discuss next steps.
- Stereotatic Needle biopsy



Neurosurgeon's Previous Role: Surgery is not the answer!



Old thoughts!



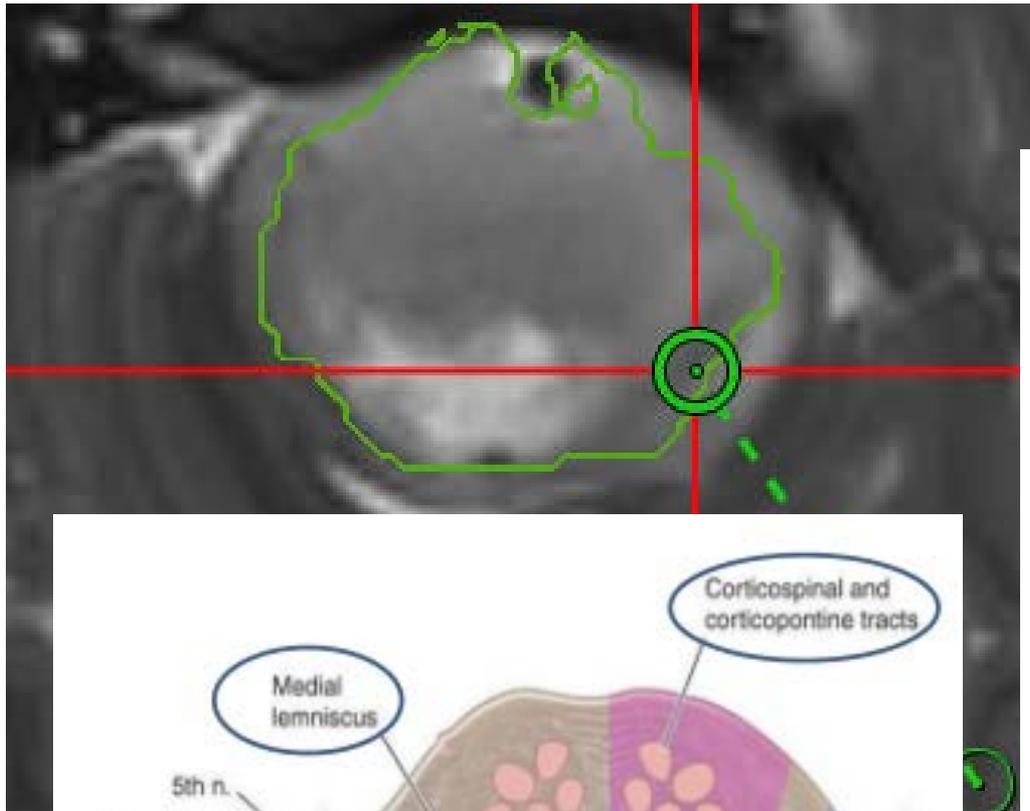
Stereotactic Biopsy of Pontine lesions

- Two routes: transcortical and transcerebellar.
- Transcortical
 - Can sample lesions at all brainstem levels
 - Stereotactic navigation is necessary
- Transcerebellar
 - Fewer eloquent structures at risk
 - Preferred for upper medullary and pontine masses

Complications (series of 130 DIPG patients)

- Morbidity of 3.9%; all deficits temporary
- Worsening of preexisting ataxia
- Ataxia and VI and VII nerve palsy
- Isolated VI nerve palsy
- 4 patients had small clinically insignificant hemorrhage
- Morbidity rates 0-25% with most transient in other series





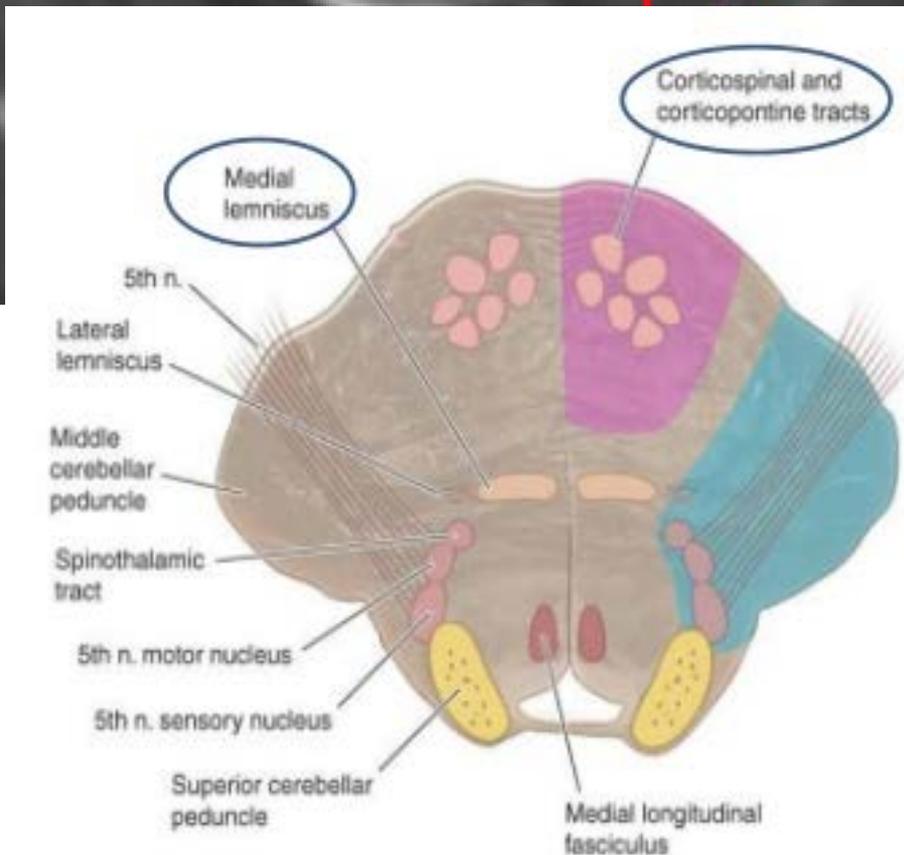
On side of lesion

Ataxia of limbs and gait (more prominent in bilateral involvement): *Pontine nuclei*

On side opposite lesion

Paralysis of face, arm, and leg: *Corticobulbar and corticospinal tract*

Variable impaired touch and proprioception when lesion extends posteriorly: *Medial lemniscus*



Diffusion Tensor Imaging (DTI) fiber tracking AP view (hand)



Dr Jeff Leonard
PROCEDURE:

Coronal

Sagittal

Axial

3D

Plan 1

49.2 Length (mm)

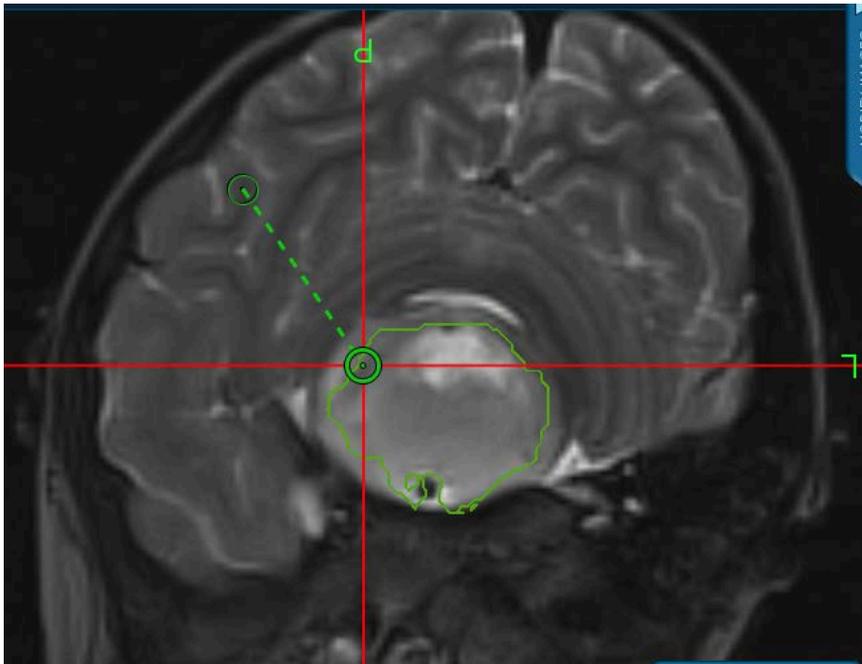
0.0 Depth (mm)

Passive Biopsy Needle
Small Passive Cranial Frame

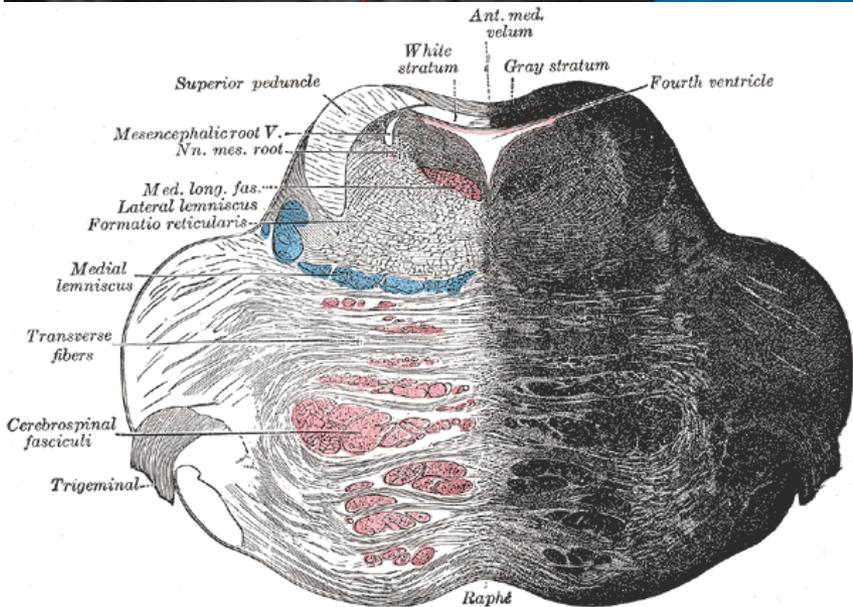
Periodically verify accuracy by navigating on known anatomical landmarks.

Medtronic

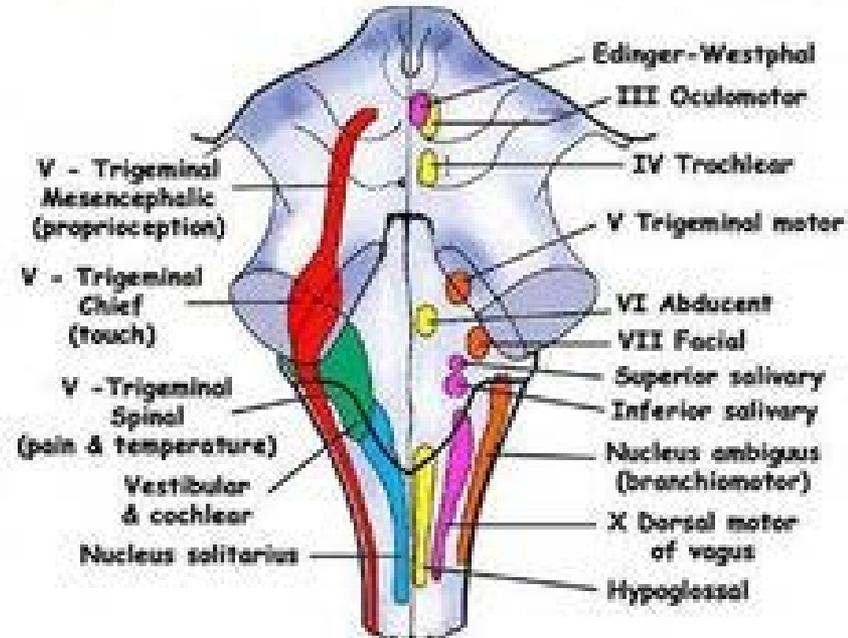
Camera Help Admin Exit



MODIFY IMAGES

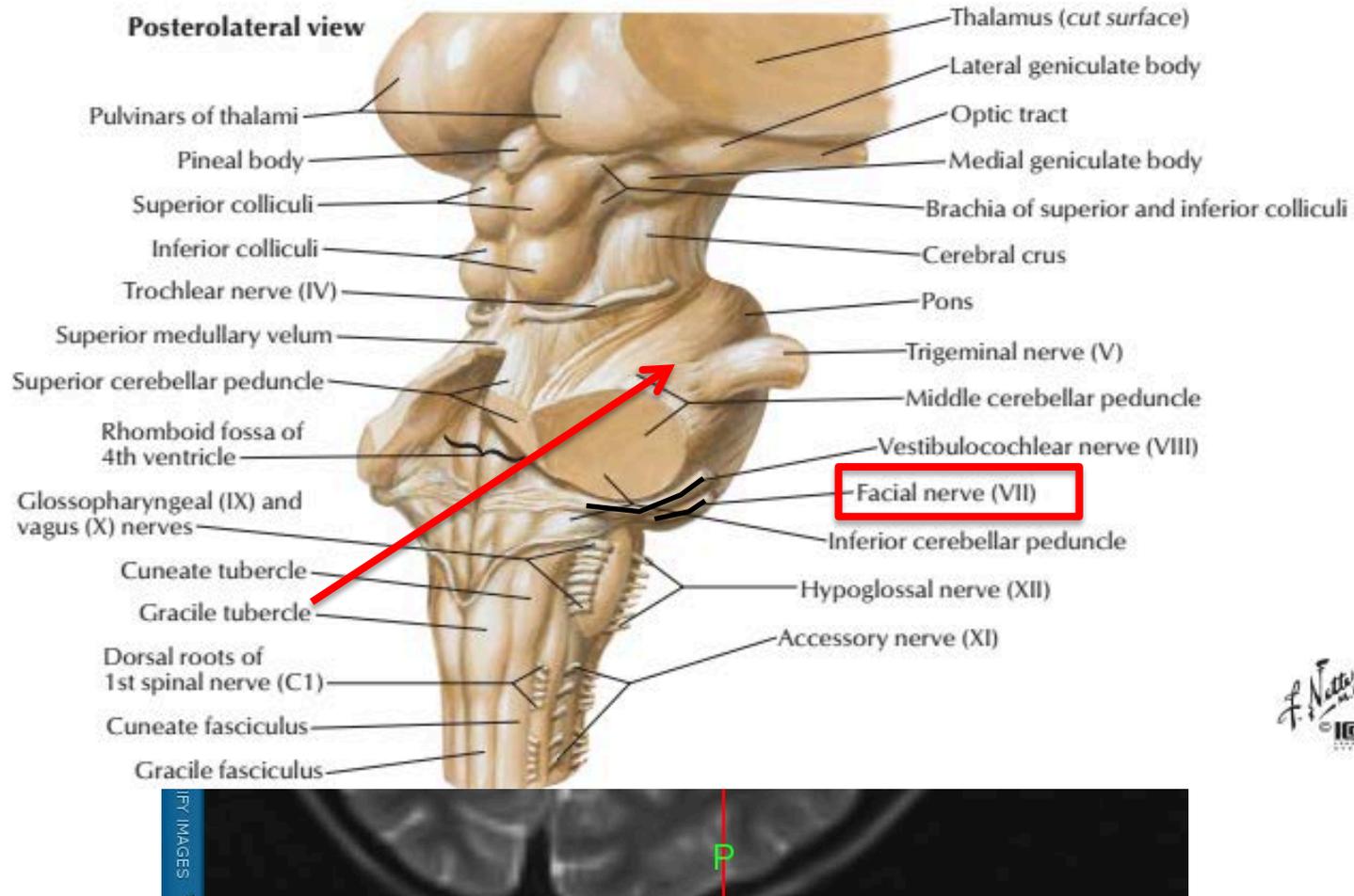


CRANIAL NERVE NUCLEI IN BRAIN STEM



SENSORY		MOTOR	
Somatic	Red	Somatic	Yellow
Taste/baroreceptors	Blue	Parasympathetic	Purple
Special sense	Green	Branchiomotor	Orange

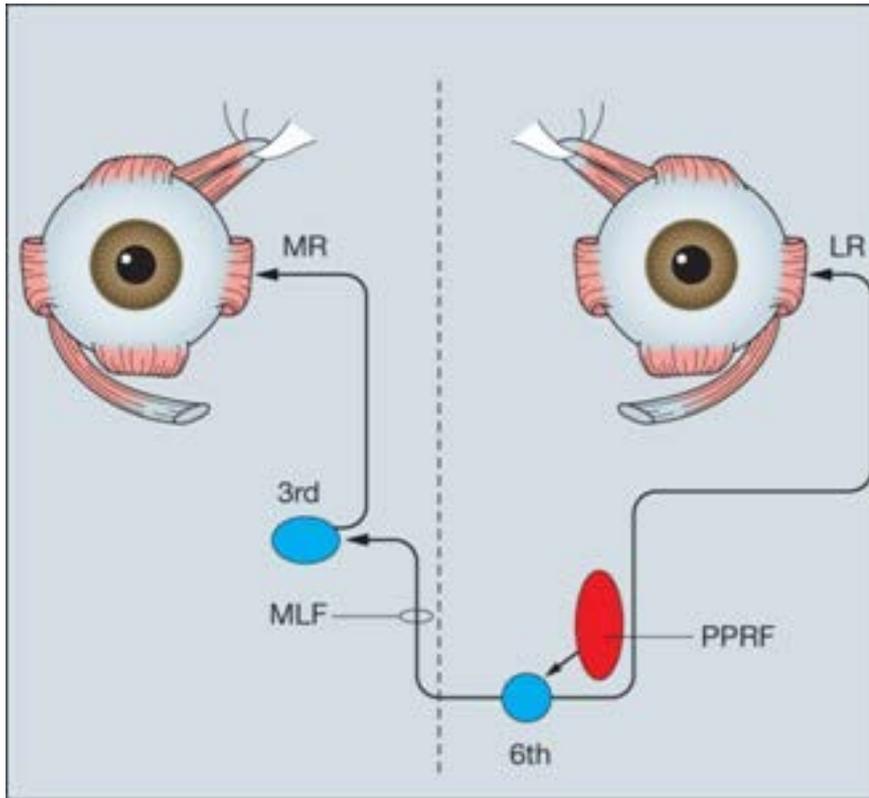




Biopsy Trajectory



Internuclear Ophthalmoplegia

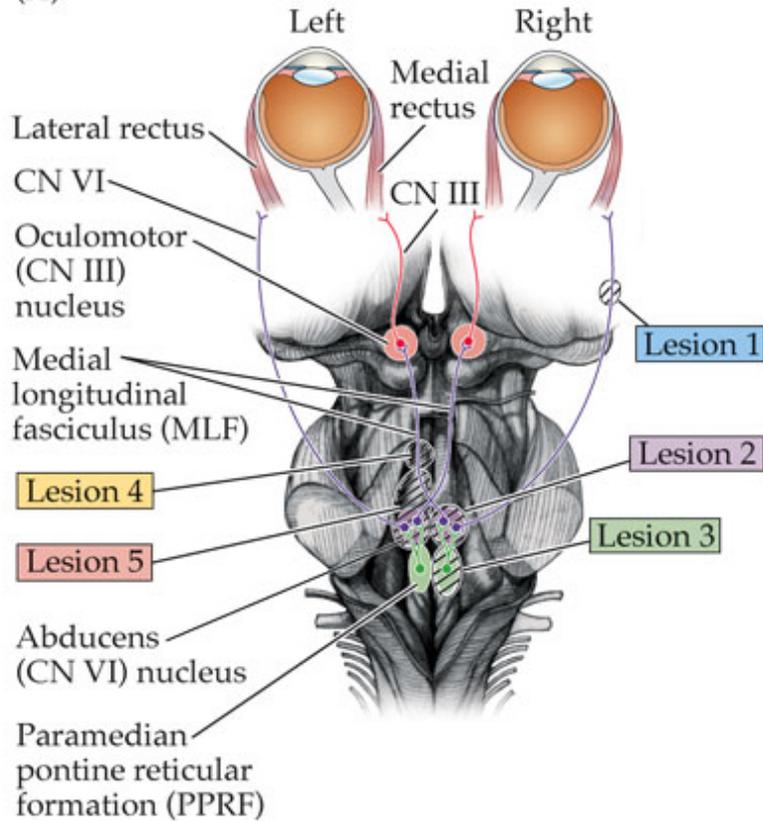


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1. Absence of adduction of the eye on the affected side
2. Convergence is preserved.
3. Nystagmus of the unaffected eye on lateral gaze.

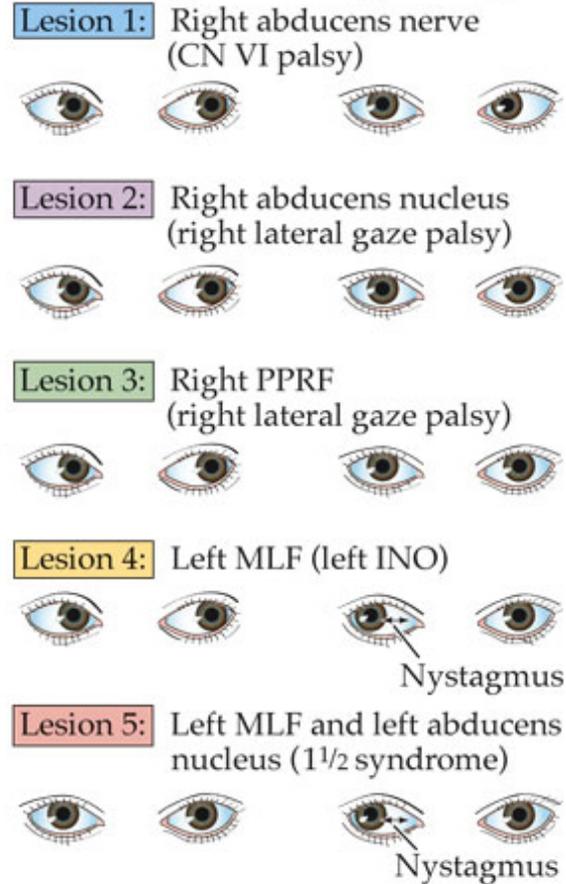
Brainstem syndromes

(A)



(B)

Leftward gaze Rightward gaze



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Conclusions

- Transcerebellar is preferred route for biopsy of DIPGs
- Most complications are temporary and involve eye movements
- Deeper biopsies can affect motor pathways
- New approaches are needed to make progress in treatment of DIPGs because current therapies are failing

Surgical Biopsy for Diffuse Intrinsic Pontine Glioma

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Disclosure

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UCSF

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A Banerjee

K Bankiewicz

MS Berger

D Lim

S Mueller

T Ozawa

T Nicolaidis

JJ Phillips

M Prados

D Rowitch

WA Weiss

PNOC

S Mueller

M Prados

Mayo Clinic

Z Zhang

Northwestern Univ

R Hashizume

CD James

Support

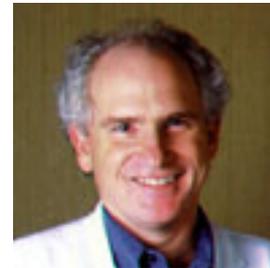
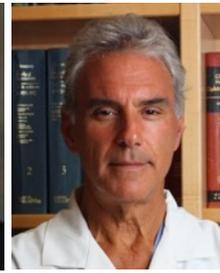
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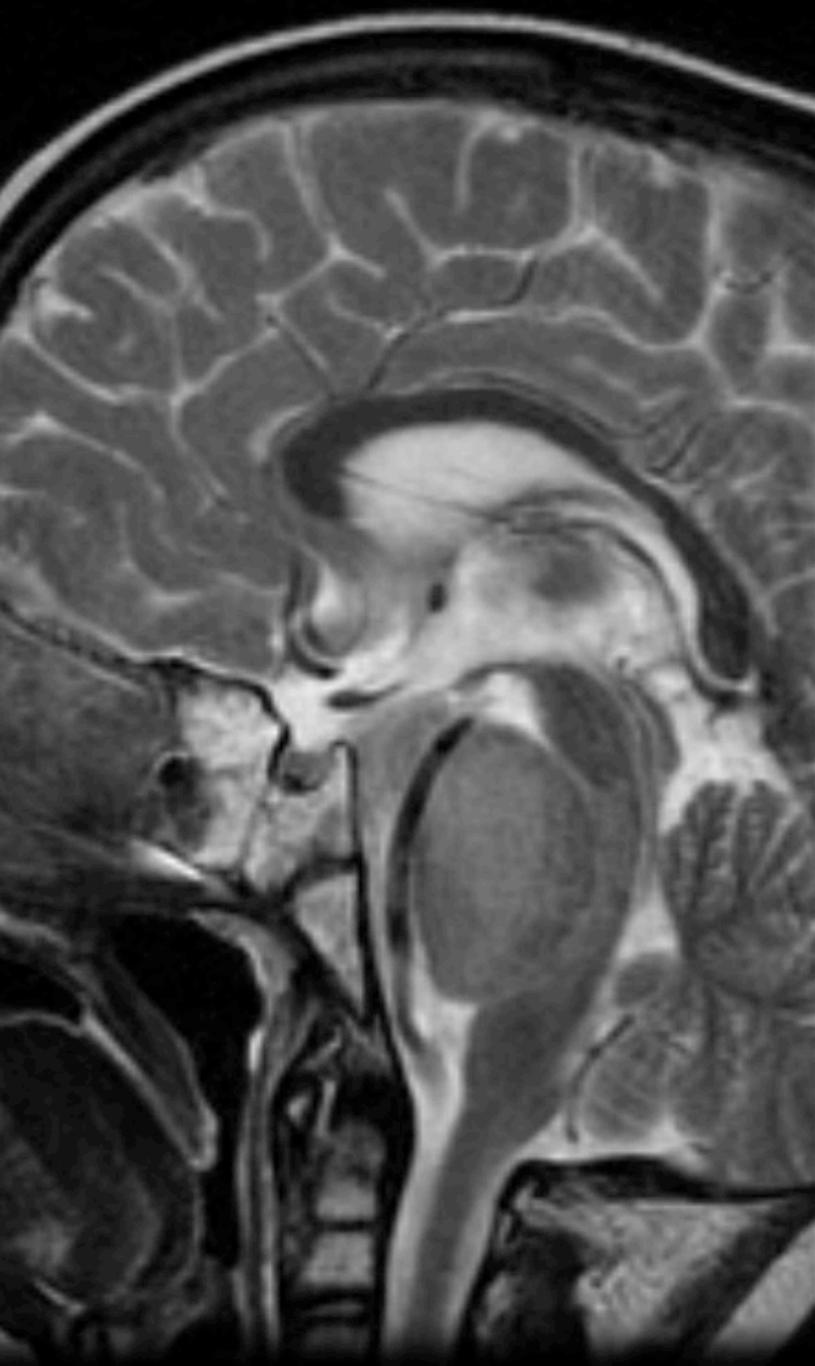
NIH/NCI

SPORE

HHMI

Pfizer





DIPG - 1996

Natural History

“Diffuse tumors have terrible prognosis with most patients dead in 12 months.”

Treatment

“The most common neoplasm is the diffuse variety. These are malignant. Can be diagnosed on basis of MRI (pontine). Biopsy felt unnecessary. Radiation offered as palliation.”

“MR scans should replace biopsies for the diagnosis of diffuse brain stem gliomas: A report from the children's cancer group”
(Albright et al, 1993)

DIPG BATS - Rationale

MGMT promoter methylation correlates with improved PFS and OS

Hegi, et al. MGMT and temozolomide in GBM (NEJM 2005)

EGFR expression in DIPG

Gilbertson (2003): 4/7 demonstrated EGFR +

Pediatric Phase I and II experience

RT+TMZ (II); erlotinib+TMZ (I); XRT+bevacizumab+TMZ (I/II)

Little molecular data is available to guide development of new agents

New strategies are needed; current molecular assays require small amounts of tissue available through stereotactic-guided biopsies

Surgical Biopsy

Roujeau, et al. Stereotactic biopsy of diffuse pontine lesions in children (J Neurosurg 2007)

N = 24; histologic diagnosis made in all (they have now done over 100 cases)

Dx: Malig astrocytoma (22), low grade astro (1), PA (1)

No periop deaths; 2 transient CN deficits (<2 mos), 1 worsening of pre-morbid hemiparesis

Pincus, et al. Brainstem stereotactic biopsy sampling in children (J Neurosurg 2006)

N = 10, high diagnostic yield

1 post-op diplopia; 1 altered therapy

DIPG-BATS Summary

Biopsy



MGMT methylation - EGFR expression



**MGMT +
EGFR -**

*radiation
temozolomide
bevacizumab*

1

**MGMT +
EGFR +**

*radiation
temozolomide
erlotinib
bevacizumab*

2

**MGMT -
EGFR +**

*radiation
erlotinib
bevacizumab*

3

**MGMT -
EGFR -**

*radiation
bevacizumab*

4

Objectives

Phase II

primary objective is to estimate PFS/OS of children with DIPG treated with a molecularly-based treatment strategy, as compared to historical controls; patient survival will be correlated with tissue markers of EGFR expression and angiogenesis

evaluate the safety and feasibility of a surgical biopsy of non-disseminated, diffuse, intrinsic pontine gliomas

assess toxicity of the four treatment strata

molecular analysis of specimens acquired during biopsy

Planned Biologic Studies

MGMT methylation

EGFR/ EGFRvIII

IHC for expression, FISH for gene amplification

Additional IHC

VEGF, p-AKT, PDGFR, PTEN

Gene expression array, SNP array

Whole genome sequencing

Whole exome sequencing

OncoMap: mutational analyses of kinome, tumor suppressor genes, oncogenes and other regulators of cell proliferation

DIPG BATS - Participating Institutions

UCSF

Dana Farber Cancer Institute

Lurie Children's Hospital (Chicago)

Children's Hospital Los Angeles

Seattle Children's Hospital

Children's Hospital Colorado

Johns Hopkins Univ

Miami Children's Hospital

Children's Healthcare Atlanta

Univ of Florida

Weill Cornell Medical College

Washington Univ Children's Hospital

New York Univ Med Center

Doernbecher Children's Hospital
(OHSU)

Children's Hospital Michigan

Children's Hospital of Minnesota

UT Southwestern

Univ of Mississippi

Kosair Children's Hospital (Louisville)

Penn State Hershey Medical Center

Cook Children's Medical Center

Stanford University

Surgical Biopsy

Target selection - *optional adjuncts*

areas of post-gadolinium contrast enhancement, or
abnormal regions determined by 2D MR spectroscopy, or
areas of increased metabolism determined by PET scan, or
areas of increased MR perfusion, or
tumor distinct from major white matter pathways as determined
by DTI

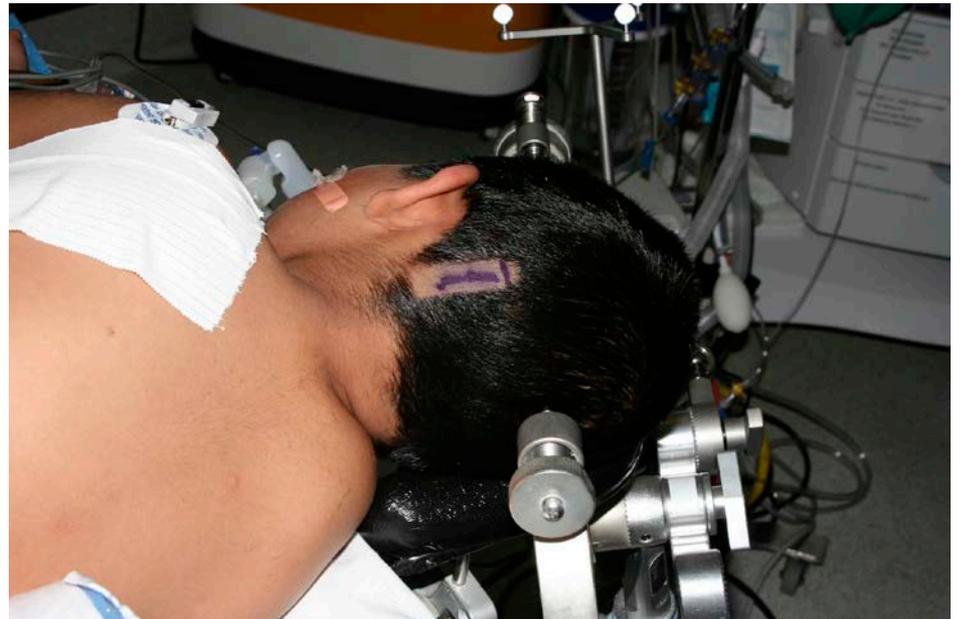
‘Ideal’ tumor features

homogeneous tissue features on MR
necrotic or cystic areas are minor features (do not select
largely necrotic areas)
adjacent to cerebellar peduncle

Entry point generally over midpoint of cerebellar hemisphere, at least 1 cm below transverse sinus

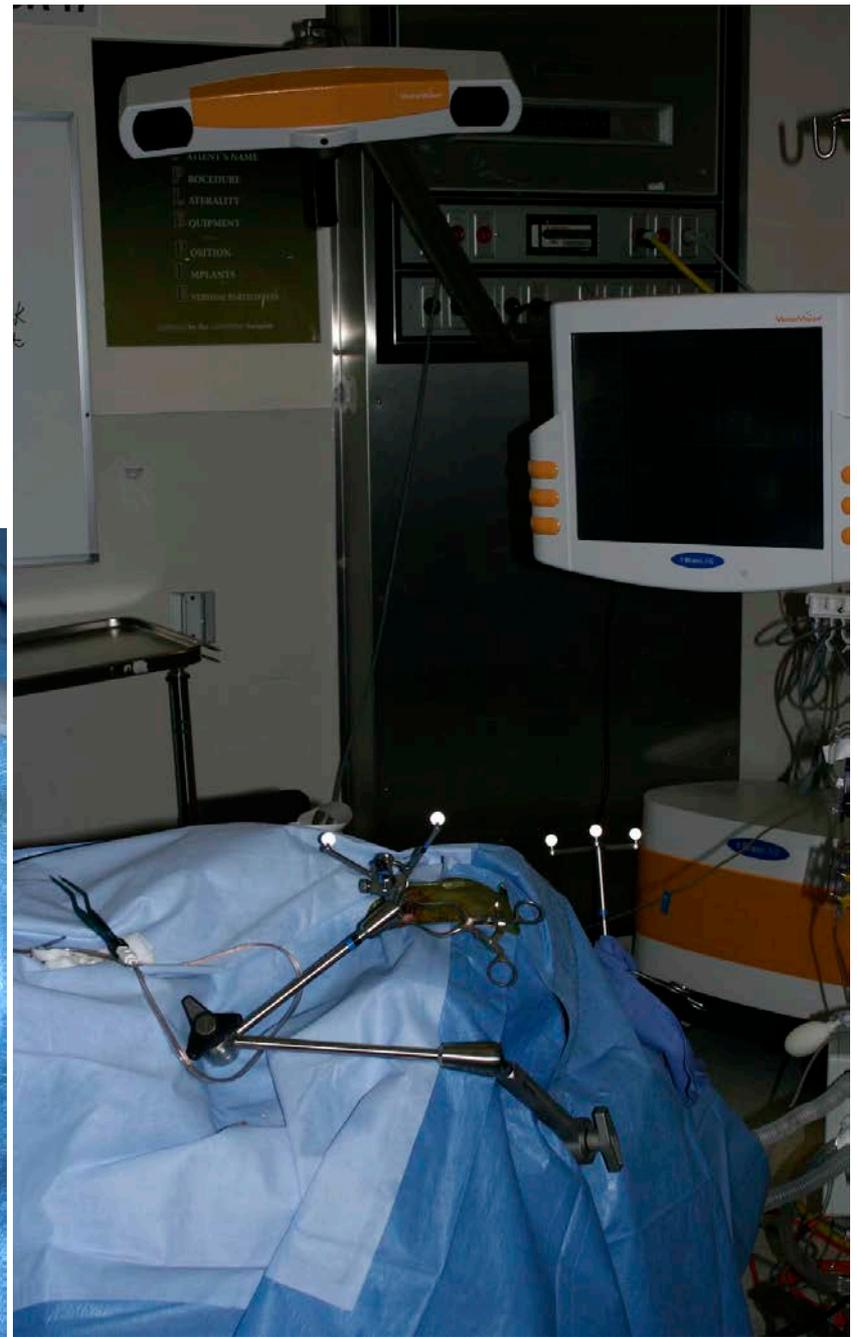
Single burr hole with coagulation of dura and cerebellar surface

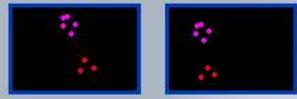
Standard closure, with burr hole closure (plate, cement, or none) according to surgeon preference



Neuronavigation system positioned to allow direct entry and visualization as biopsy needle is advanced

‘Free-hand’ technique avoided





Register

Data

Tools

0 mm

Tooltip

Offset

Acquire

Freeze

Target

130 %

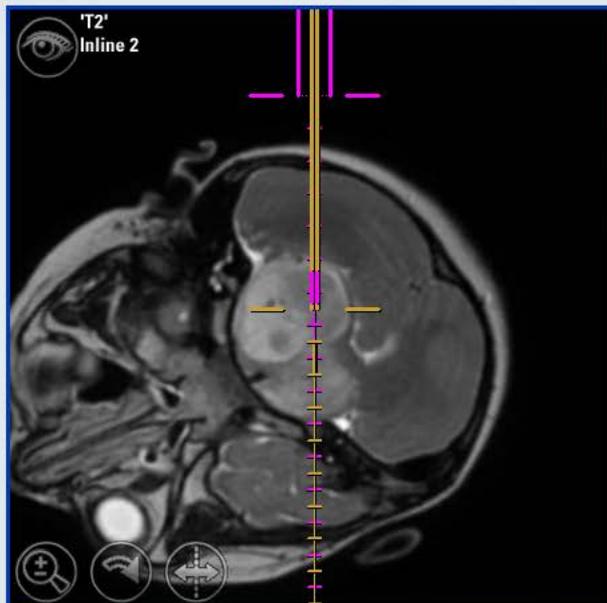
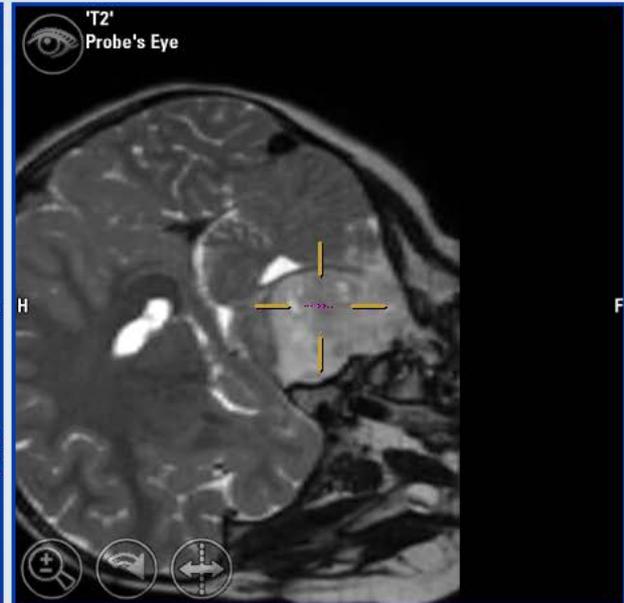
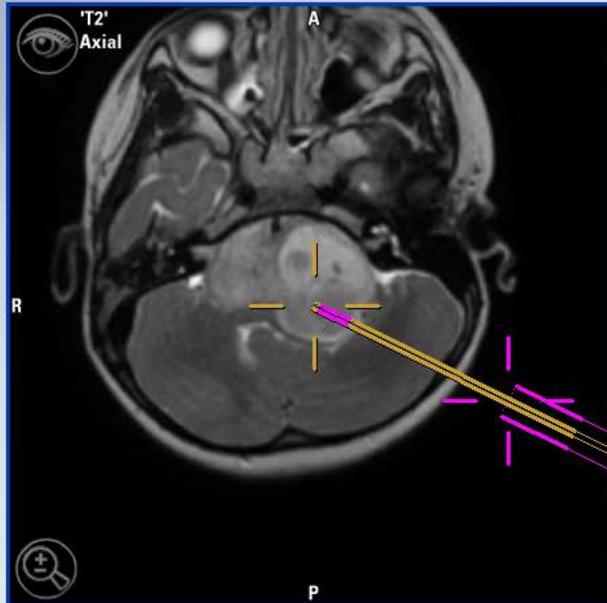
Zoom

Reset

II

Display

Screenshot





Register

Data

Tools

70 mm

Tooltip

Offset

Acquire

Freeze

Target

130 %

Zoom

Reset

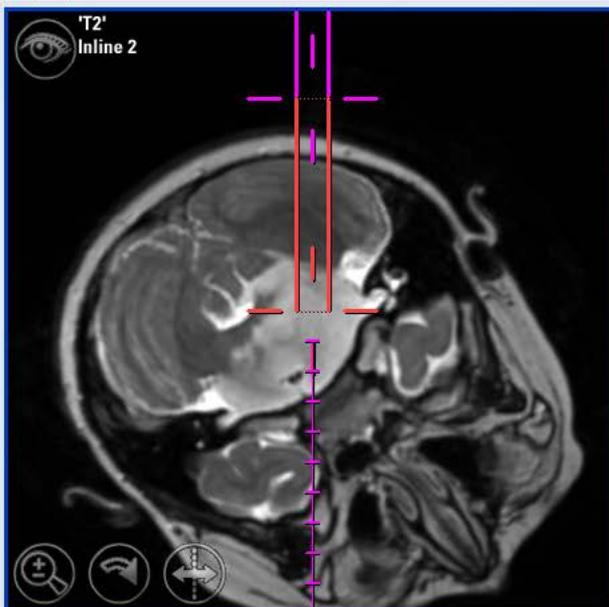
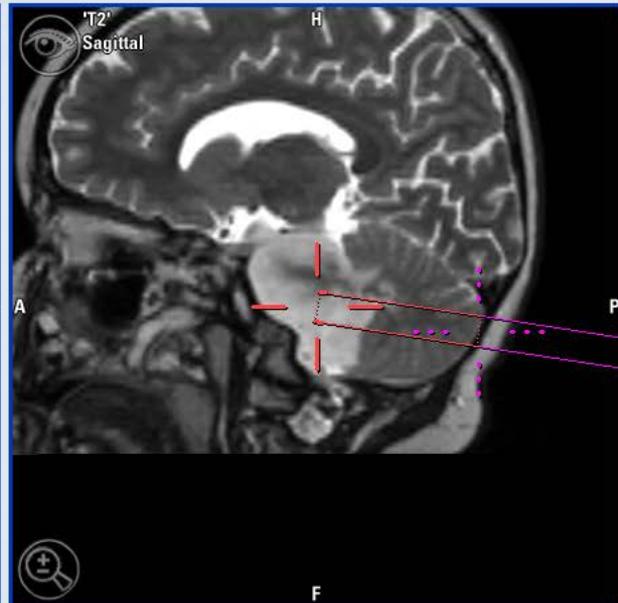
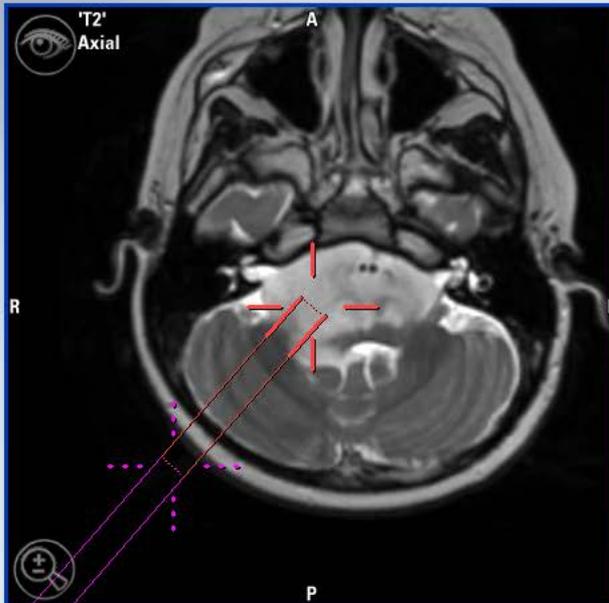
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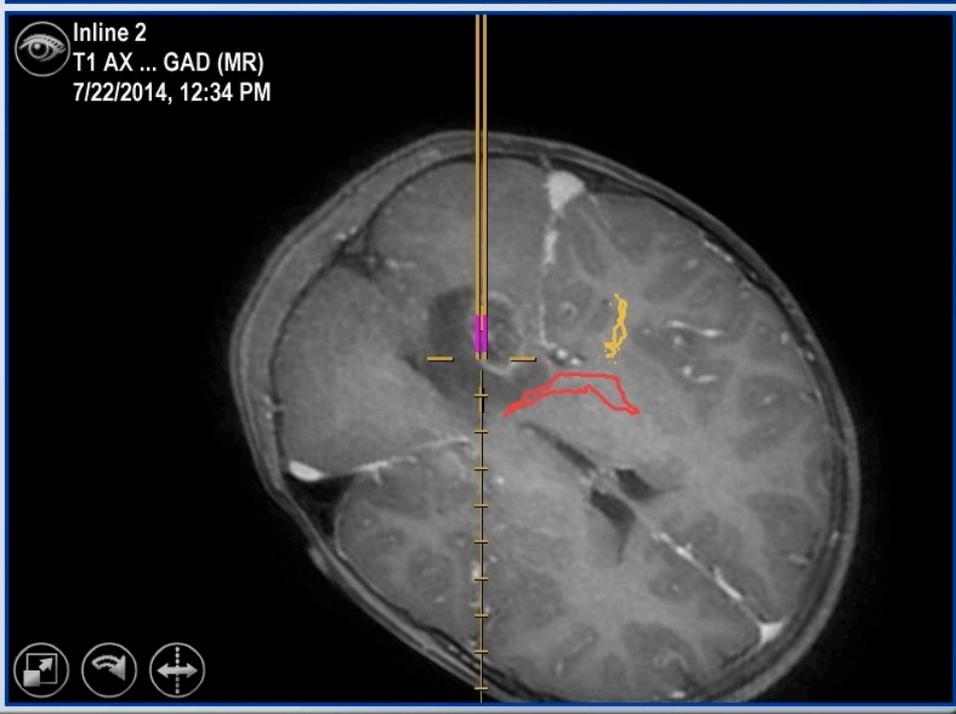
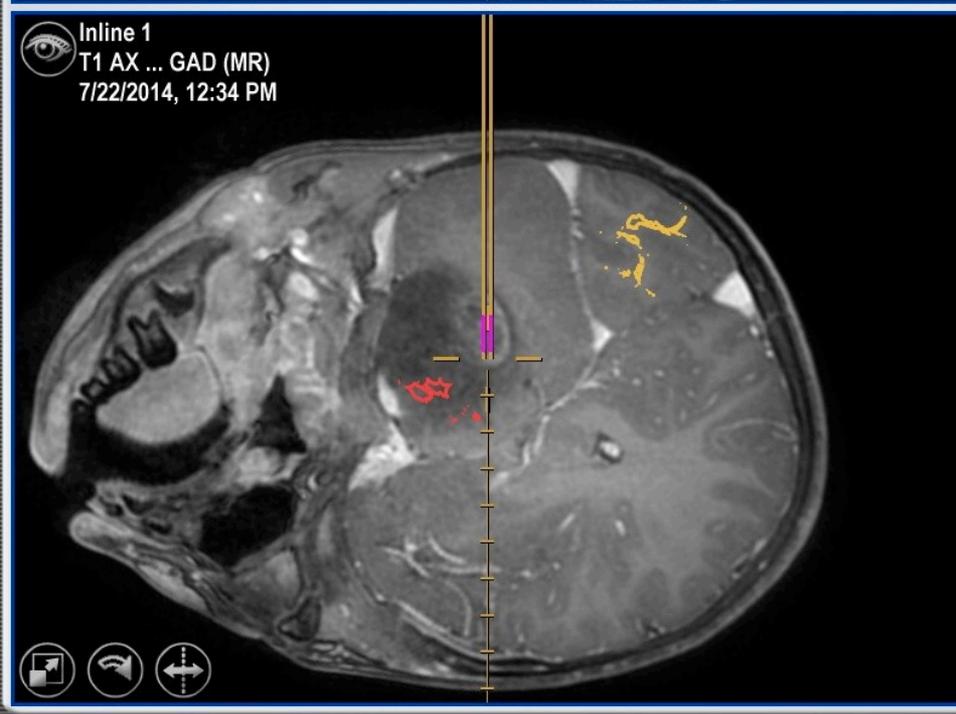
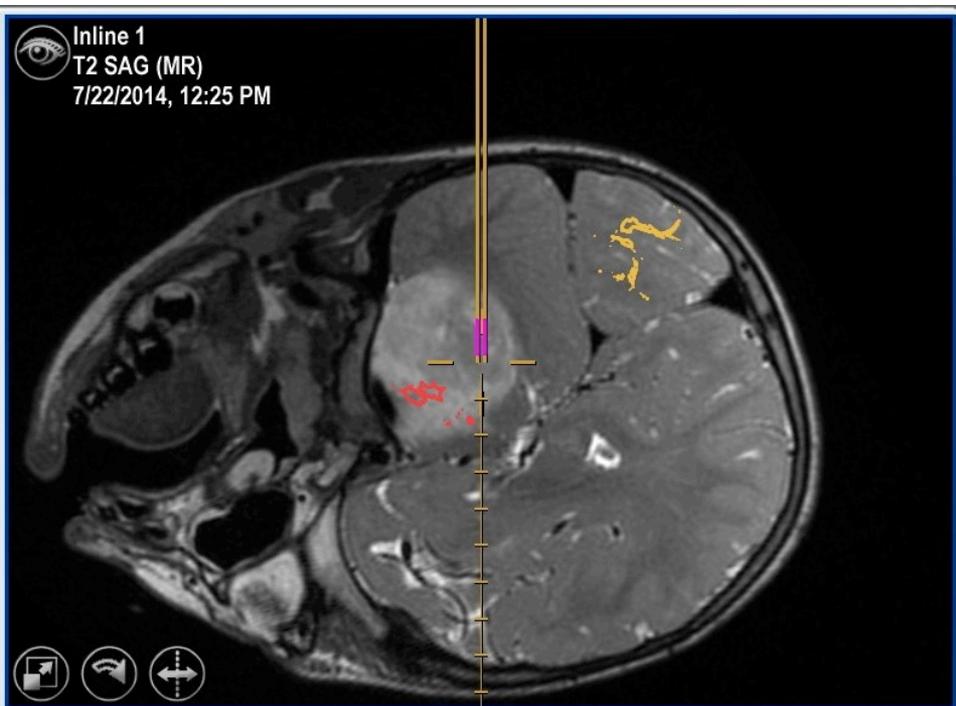
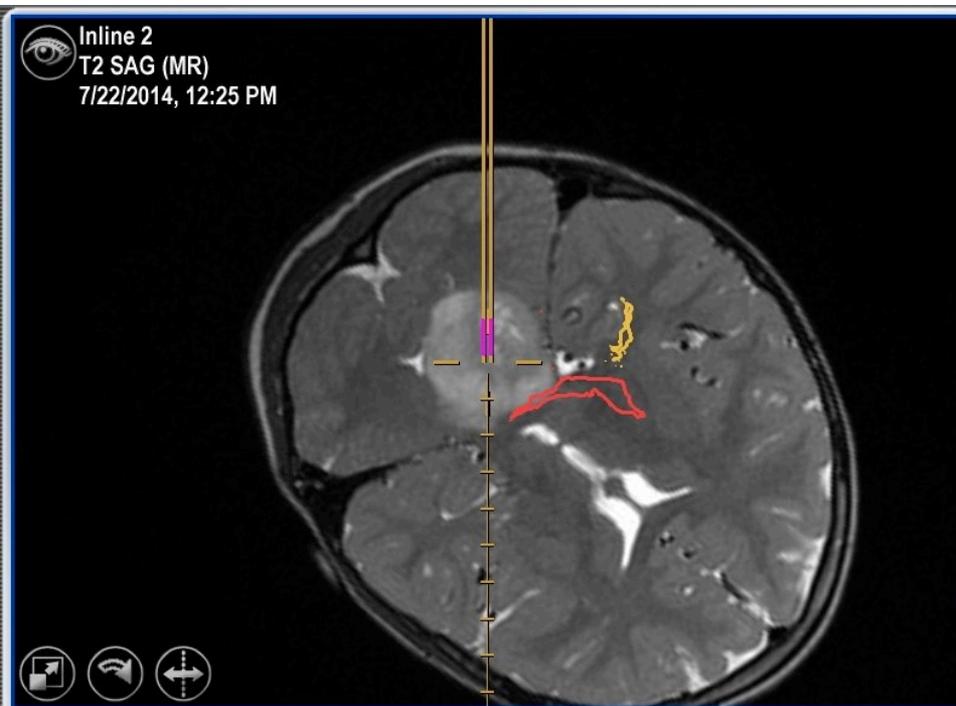
II

III

Display

Screenshot





Tissue Samples

6.2.4 Tissue Handling. **4 specimens** should be obtained. An initial tissue specimen will be used for histologic confirmation of tumor. A second tissue specimen will be used for immunohistochemical evaluation of tumor. Additional specimens (specimens number three and four) will be obtained for molecular analysis (see section 9). These specimens can also be used for immunohistochemical verification if insufficient material is obtained in sample 2.

Tissue handling, storage and shipping, whether performed directly or delegated, is the primary responsibility of the study neurosurgeon

Sample 1 stays at biopsy site, samples 2-4 are sent to Neuropath Core Lab

Results – Adverse Events

Total of >50 patients enrolled

- 1 patient with somnolence, possibly related to biopsy
- 1 patient with grade 2 ICH, possibly related to biopsy
- 1 patient with epidural hematoma, related to biopsy

PNOC - Participating Institutions

UCSF Benioff Children's Hospital San Francisco & Oakland

Children's Hospital Los Angeles

University of Washington - Seattle Children's Hospital

Oregon Health Sciences University

Children's Hospital of Philadelphia

University of California Los Angeles – Mattel Children's Hospital

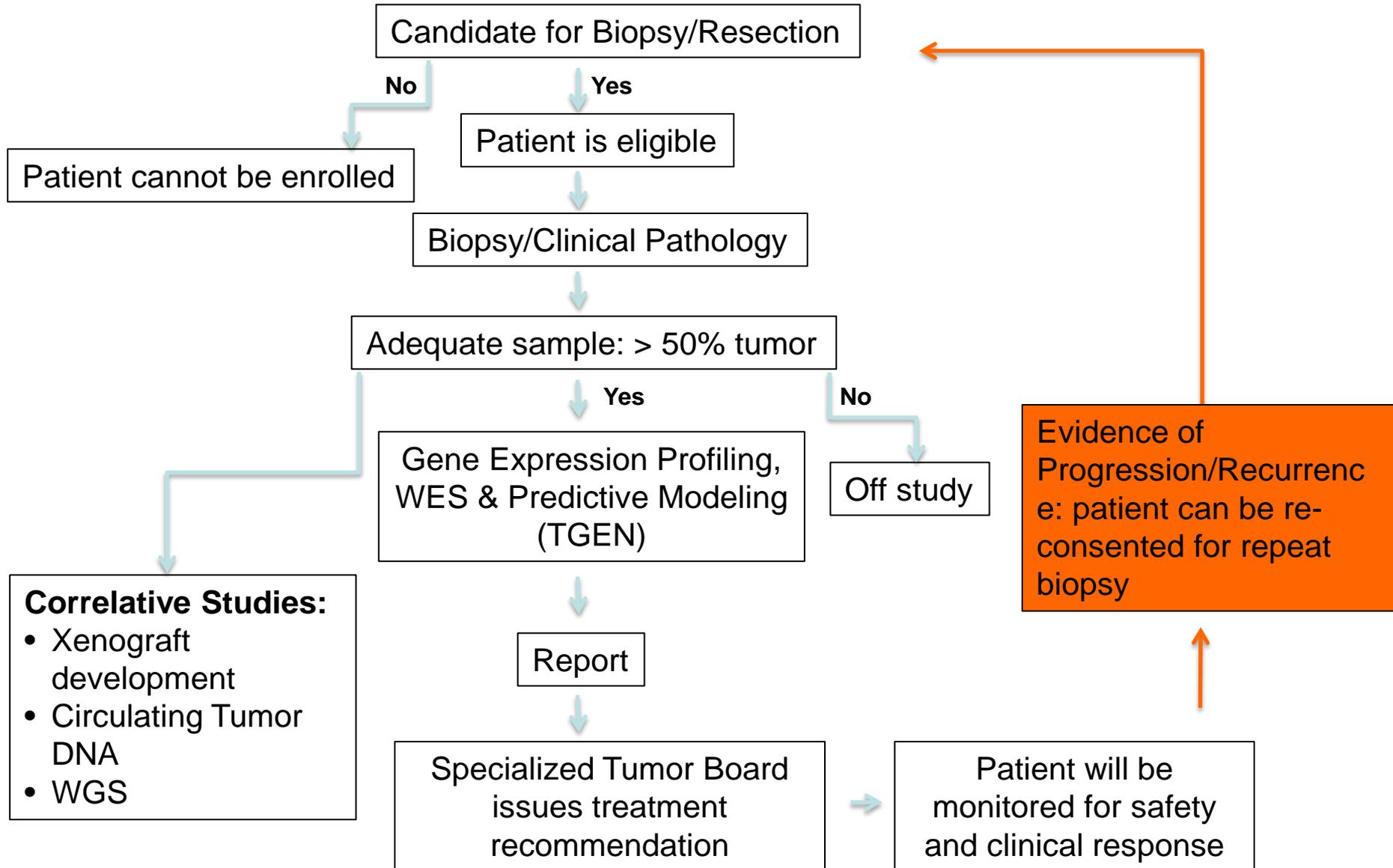
University of Utah – Primary Children's Hospital

University of California San Diego – Rady Children's Hospital

Children's National Medical Center

St. Jude's Children's Research Hospital

Children With Newly Diagnosed DIPG



PNOG 003 - Objectives

Primary Objective

Feasibility: To determine the feasibility of a specialized tumor board making individualized treatment recommendations within 21 business days of tumor tissue collection, using RNA based expression analysis, WES and predictive modeling for children and young adults with newly diagnosed DIPGs.

PNOG 003 - Objectives

Secondary Objectives

To determine the safety and describe the toxicity of using a molecularly based treatment approach and specialized tumor board recommendation in children and young adults with newly diagnosed DIPG.

To determine the safety and describe the toxicity of using a molecularly based treatment approach and specialized tumor board recommendation in children and young adults with progressive/recurrent DIPG.

To evaluate the safety of performing biopsy and obtaining tissue for molecular and genomic profiling in children and young adults with newly diagnosed DIPG.

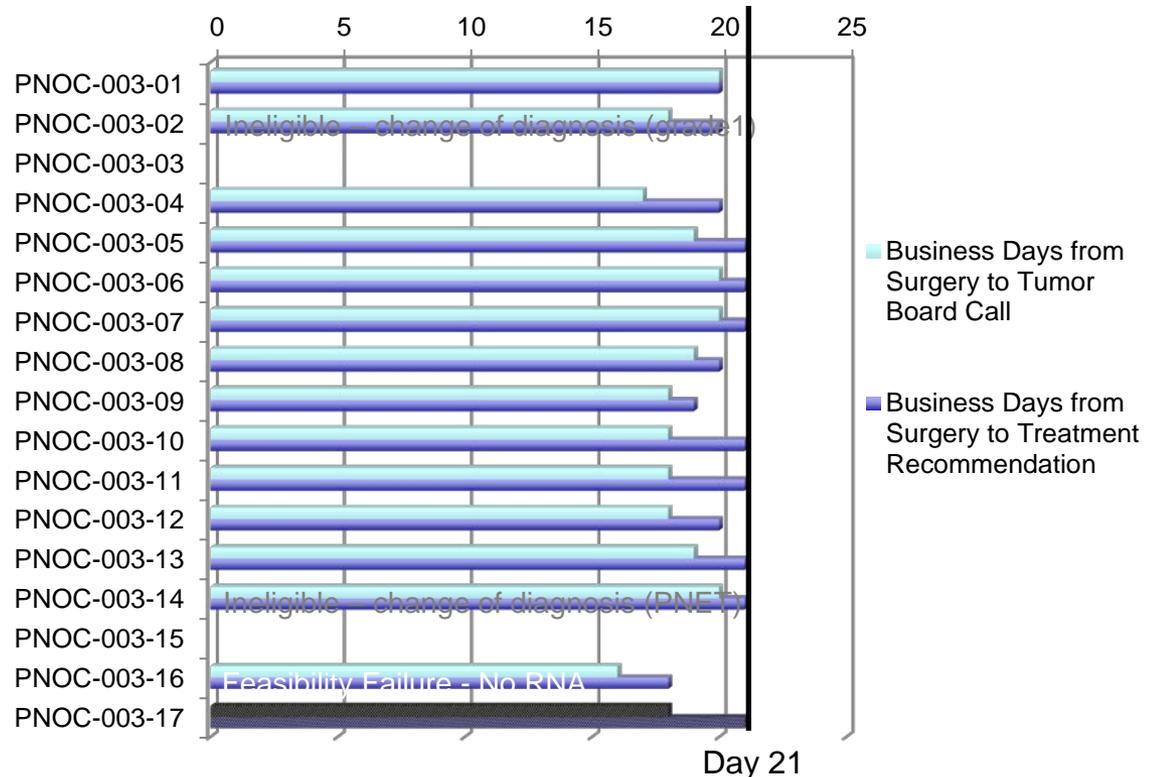
To evaluate the safety of performing biopsy and obtaining tissue for molecular and genomic profiling in children and young adults with progressive/recurrent DIPG.

PNOC 003 - Feasibility

Primary Objective: To determine the feasibility of a specialized tumor board making individualized treatment recommendations within 21 business days of tumor tissue collection, using RNA based expression analysis, WES and predictive modeling for children and young adults with newly diagnosed DIPGs.

Total Enrolled	17
Eligible Patients	15
Patients Completed	14
Feasibility Failures	1
Ineligible Patients	2

Business Days (Surgery to Treatment Recommendation)



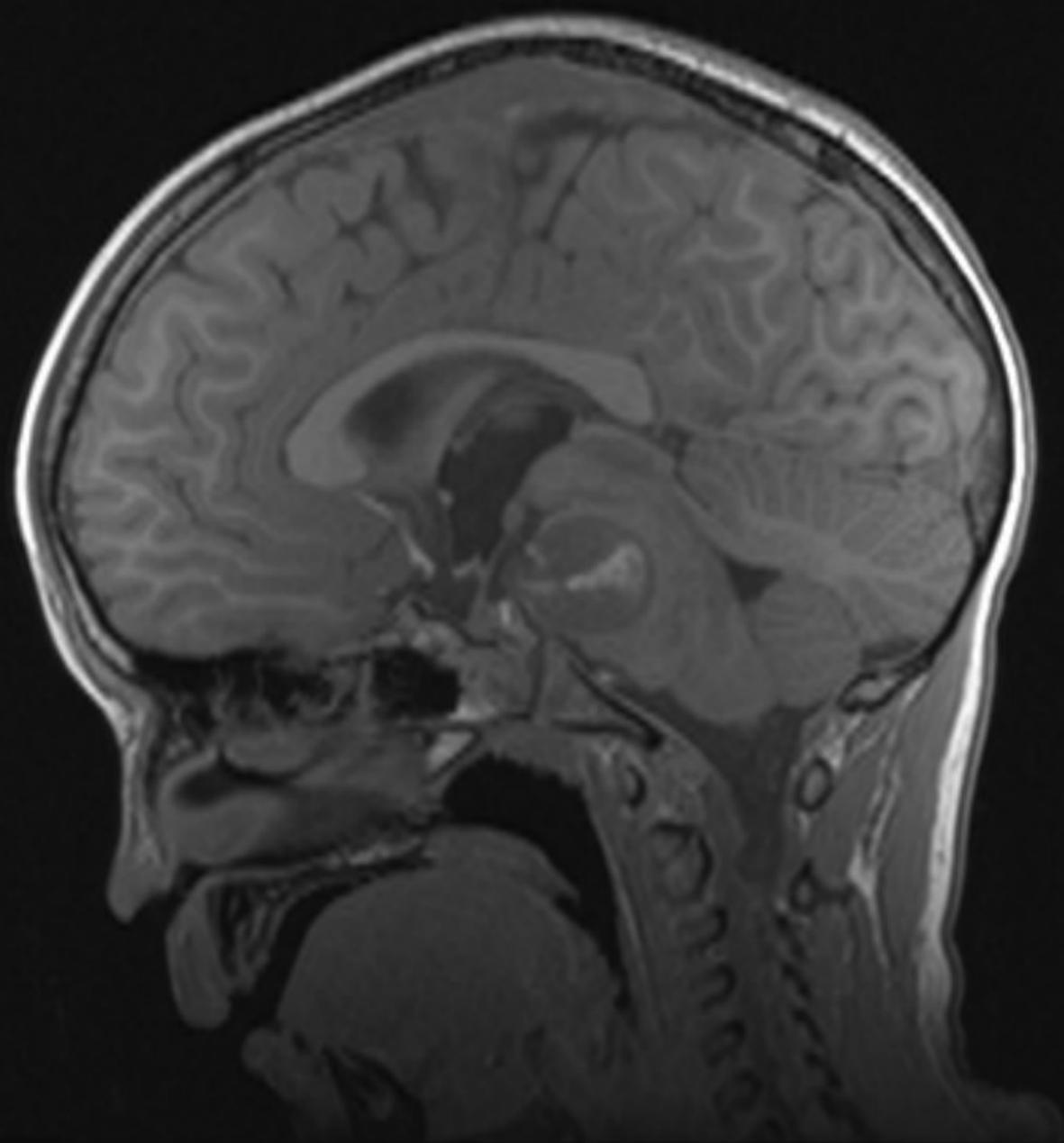
Business days from surgery to tumor board call (average):
18.5 days

Business days from surgery to treatment recommendation (average):
20.3 days

Results – Adverse Events

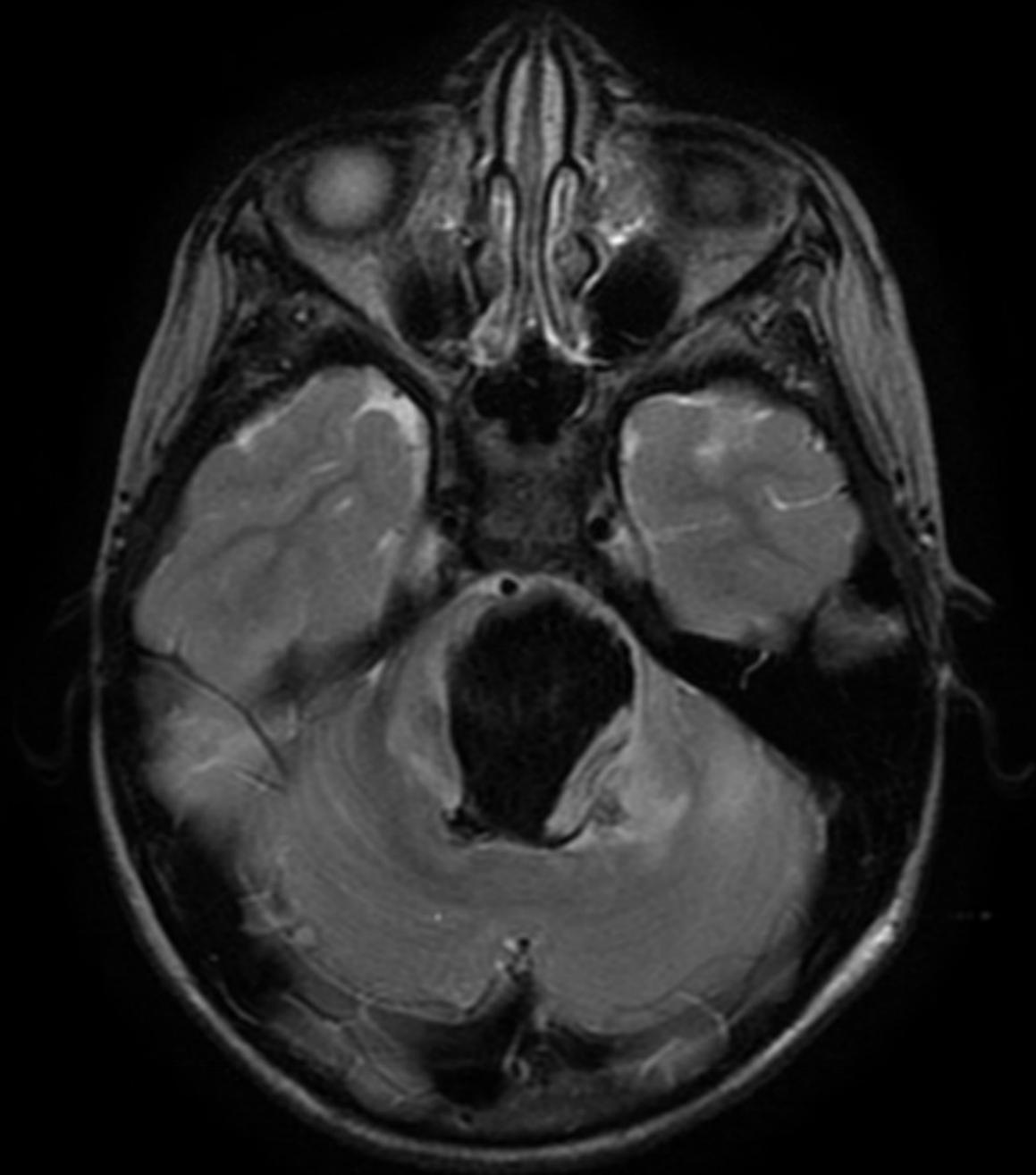
Some patients with transient neurologic deficits

One patient with a delayed intra-tumoral hemorrhage



AFL

Desc: MR BRAIN WITH ANC

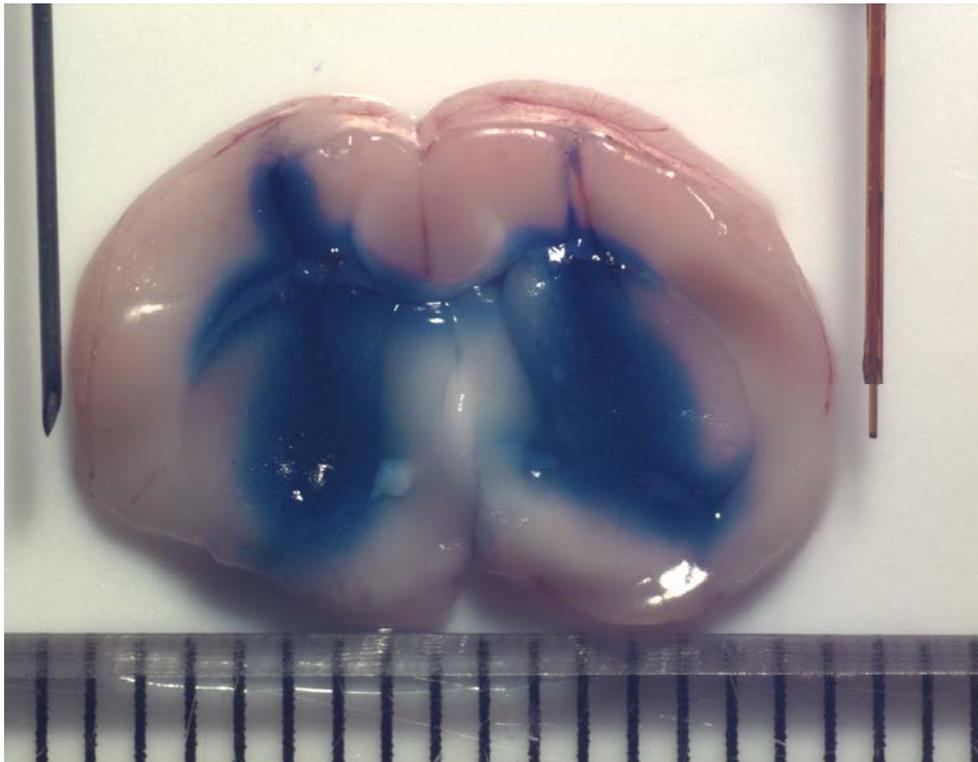


PHR

In

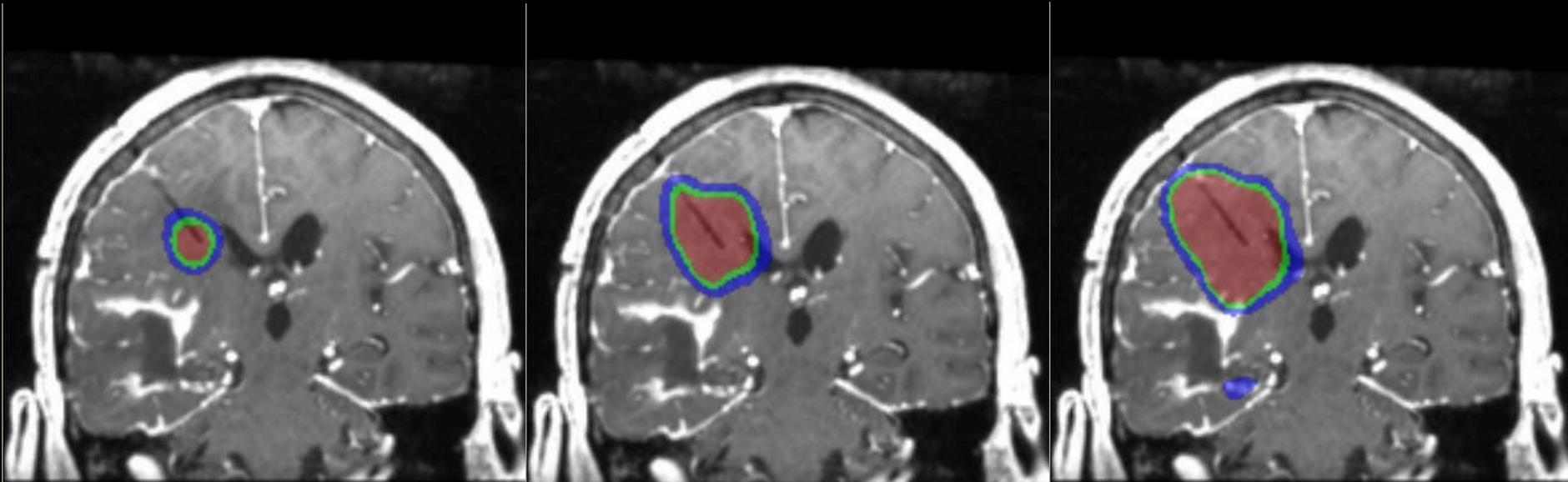
Convection-Enhanced Delivery (CED)

An approach for delivery of small and large molecules to targeted sites in solid tissues, utilizes bulk flow to deliver and distribute macromolecules to clinically significant volumes of tissue ^{1,2}



1. Bobo, R.H. et al. Convection-enhanced delivery of macromolecules in the brain. PNAS 91, 2076, 1994
2. Lieberman, D.M., et al. Convection-enhanced distribution of large molecules in gray matter during interstitial drug infusion. J Neurosurg 82, 1021, 1995

Clinically Significant Vd



6hrs

24hrs

48hrs

Convection-enhanced delivery for diffuse intrinsic pontine glioma

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Childs Nerv Syst (2015) 31:221–226

DOI 10.1007/s00381-014-2568-3

ORIGINAL PAPER

Toxicity evaluation of prolonged convection-enhanced delivery of small-molecule kinase inhibitors in naïve rat brainstem

Sharon L. Ho • Ranjodh Singh • Zhiping Zhou •
Ehud Lavi • Mark M. Souweidane

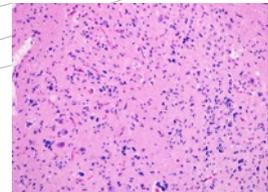
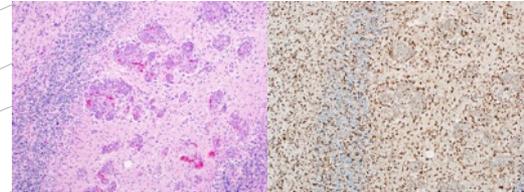
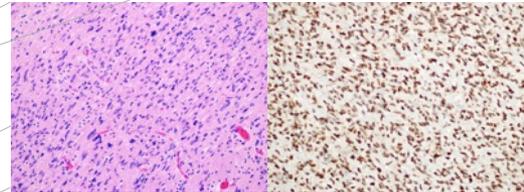
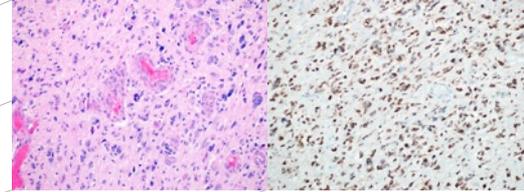
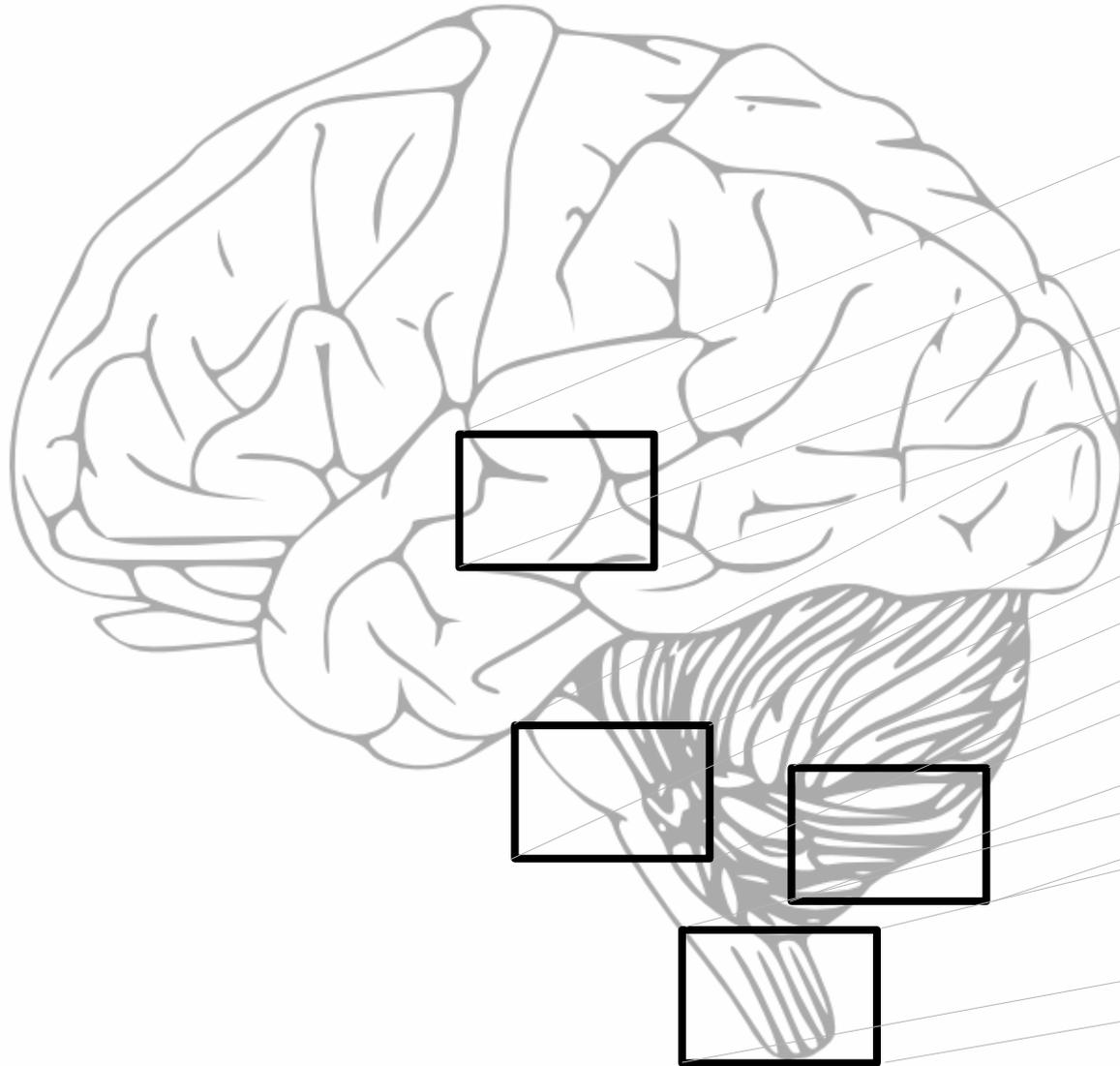
PNOG 009

CED with liposomal irinotecan

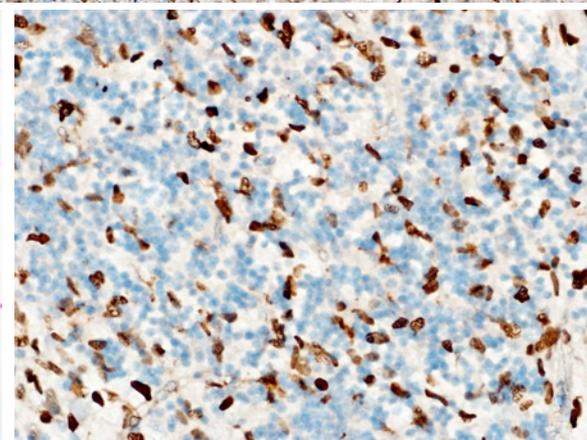
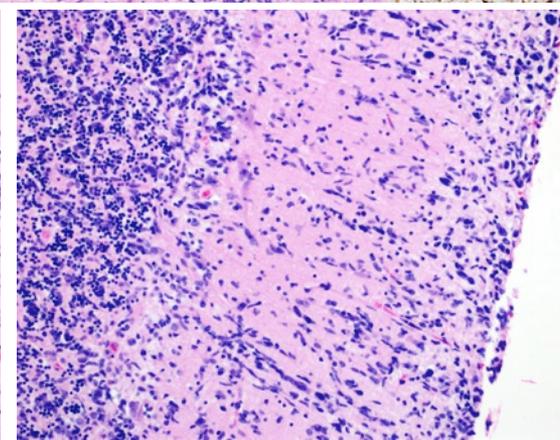
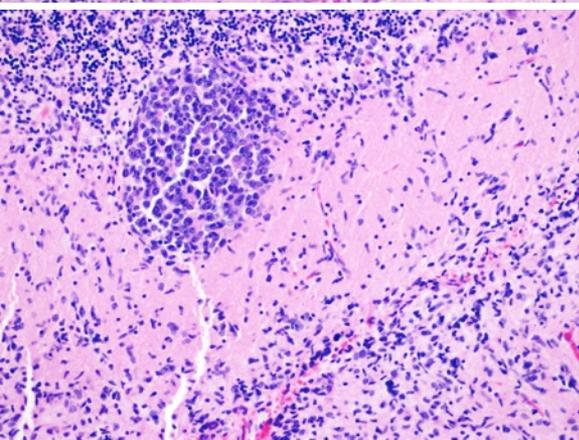
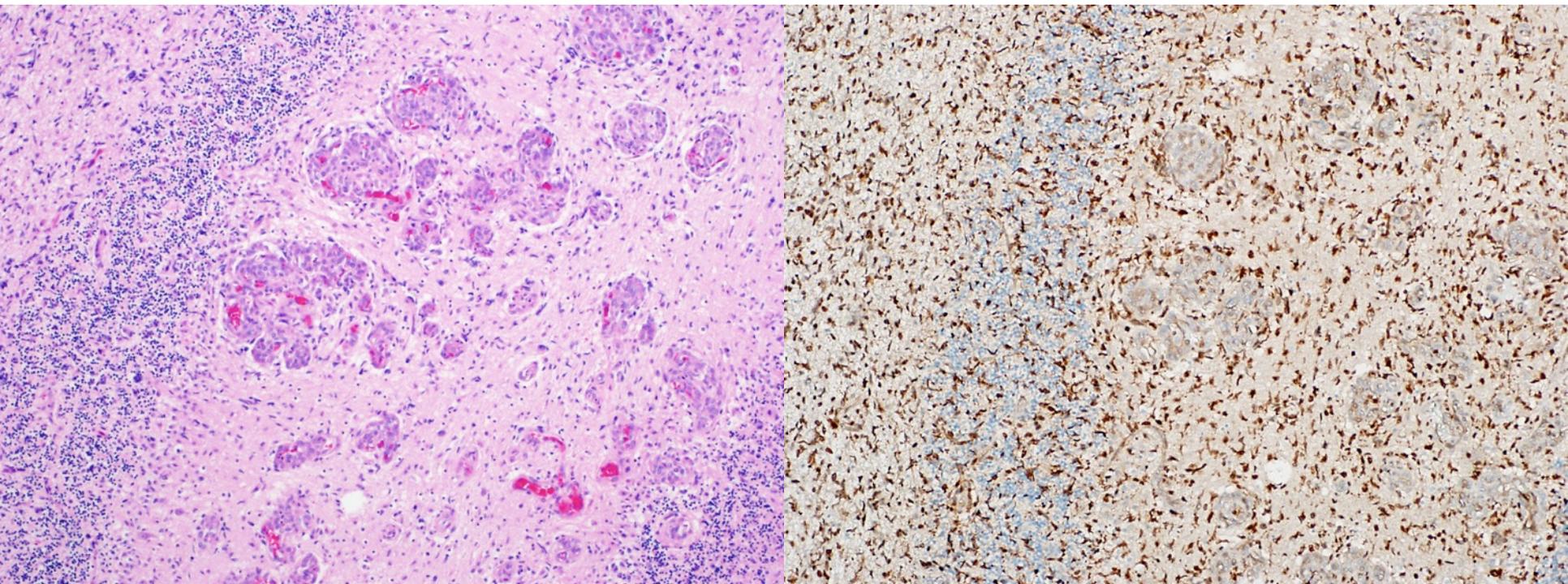
Co-infusion with gadolinium

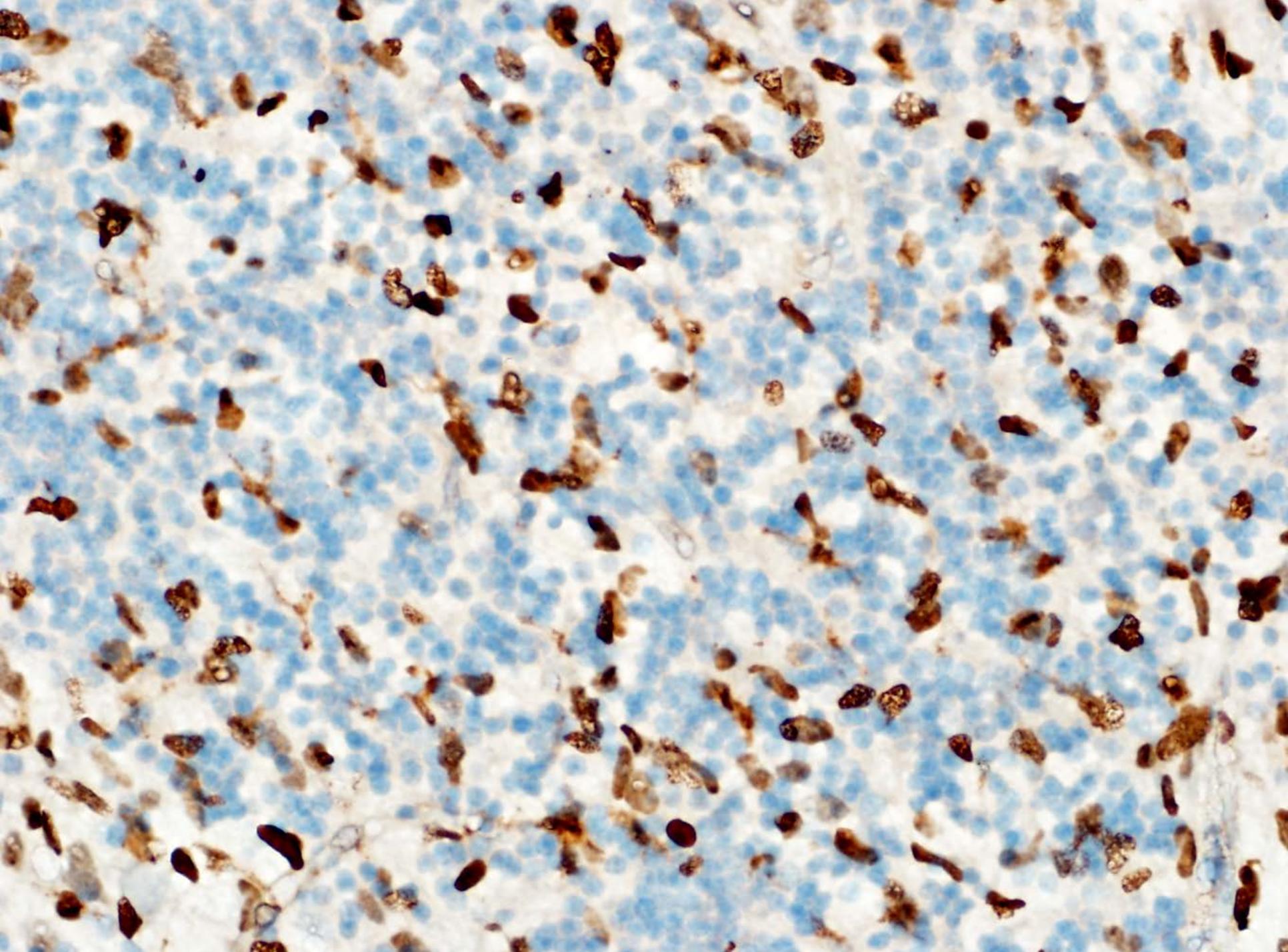
Repeated infusion with the goal of covering the total tumor target

Dissemination



Cerebellum





Summary

Upfront therapy in conjunction with detailed genetic and epigenetic characterization

Multimodality therapy including CED, intra-arterial delivery

- implantable systems
- real-time visualization

Multiple targets to be treated simultaneously