WHY BIOPSY?
Diagnosis and Research
1. Diagnosis only by Imaging (like no other tumor)

The issue of **Typical** versus **Atypical** DIPG
Magnetic resonance spectroscopic detection of lactate is predictive of a poor prognosis in patients with diffuse intrinsic pontine glioma.
Work-up

• MRI with complete neuraxis
• CSF examination not routinely performed
• Lab studies: not useful for diagnosis
• Extraneural disease extremely rare
  – staging work up seldom indicated
DIPG

NHC:1268450
DN:12/06/2003
008Y
M

Neuroradiologie Purpan
SURVEY
IRM ENCEPHALE APC

T1W_TSE TEST
IRM ENCEPHALE APC
Pathology

• Majority are High-grade astrocytic tumors (WHO III - IV)

• But, some are Low-grade astrocytomas

• Other diagnoses (PNET, AT/RT)

Frequency of high-grade vs. low grade lesions at diagnosis?
<table>
<thead>
<tr>
<th>Procedure</th>
<th>Samples Description</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autopsy</td>
<td>WHO grades 3 and 4 predominate</td>
<td>Packer, 1983</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Silbergeld, 1988</td>
</tr>
<tr>
<td>Stereotactic &amp; open biopsies</td>
<td>36 biopsy specimens 13 LGA 13, 20 AG, 2 GBM</td>
<td>CCG, Albright, 1993</td>
</tr>
<tr>
<td>Biopsy</td>
<td>71 children 75% WHO 2, 25% HGG</td>
<td>Selvapandian, 1999</td>
</tr>
<tr>
<td>Retrospective study</td>
<td>48 specimens, Pons, Diffuse features; predominate Fibrillary A</td>
<td>Fisher PG, 2000</td>
</tr>
<tr>
<td>Stereotactic biopsy</td>
<td>18 DPG patients 5 LGA, 5 AA, 8 GBM</td>
<td>Cartmill M, Punt J, 1999</td>
</tr>
<tr>
<td>Stereotactic biopsy</td>
<td>(CT diagnosis) 20 Pontine gliomas 50% LGG/HGG, other</td>
<td>Chico-Ponce de León, 2003</td>
</tr>
<tr>
<td>18 surgical biopsy 10 postmortem specimens</td>
<td>12 WHO grades II 9 WHO III, 7 WHO IV</td>
<td>Gilbertson, 2003</td>
</tr>
<tr>
<td>Stereotactic biopsy</td>
<td>22 WHO III or IV 1 JPA, 1 WHO II</td>
<td>Roujeau, Sainte-Rose, 2007</td>
</tr>
<tr>
<td>Retrospective study</td>
<td>Fibrillary 2 (5%) AA 6 (15.5%) GBM 1 (2.5%) No histology 30 (77%)</td>
<td>Hargrave, 2007</td>
</tr>
<tr>
<td>Autopsy</td>
<td>WHO III or IV</td>
<td>HSJD</td>
</tr>
</tbody>
</table>
Glioma: High-grade or Low grade?
2. The risk of biopsying the pons
Neurosurgery the Way it Was

[Images of skulls and a historical medical scene]
Advances in Neurosurgery/ Neuroimaging

- **Green** – Tumor
- **Blue** – Ventricles
- **Aqua** – fMRI activation
- **Red** – Blood vessels
- **Yellow** – White matter track
Brain Stem Gliomas in Children

Albright, A. Leland; Price, Robert A.; Guthkelch, A. Norman

Postoperative neurological complications were reported in five children (11%); in two cases, the neurological complications occurred after stereotactic biopsies, and in three, these complications occurred after open biopsies.

Magnetic Resonance Scans Should Replace Biopsies for the Diagnosis of Diffuse Brain Stem Gliomas: A Report from the Children's Cancer Group

Albright, A. Leland; Packer, Roger J.; Zimmerman, Robert; Rorke, Lucy B.; Boyett, James; Hammond, G. Denman
Stereotactic Biopsy

- Pincus 2006-100% (I=25%, II=0, III/IV=50%, other 25%)
  - Morbidity=10%, mortality=0%
- Pirote 2007- 100% (I=14%,II=7% III/IV=65%, other=14%)
  - Morbidity=14%, mortality=0%
- Schumacher 2007- 100% (I=23%, II=37%, III/IV=40%, other=0)
  - Morbidity=3%, mortality=0%
- Roujeau 2007- 100% (I=4%, II=4%, III/IV=82%, other=0)
  - Morbidity=8%, mortality=0%
3. The Biopsy does not benefit the patient

The mould and mother of all the virtues is prudence.
There are a number of human goods to which every human person is naturally inclined: *the knowledge of truth,*

All men by nature desire to know. Knowing is a mode of existing.
Preradiation chemotherapy may improve survival in pediatric diffuse intrinsic brainstem gliomas: Final results of BSG 98 prospective trial

Didier Frappaz, Matthias Schell, Philippe Thiesse, Perrine Marec-Bérard, Carmine Mottolese, David Perol, Christophe Bergeron, Thierry Philip, Anne Claire Ricci, Sophie Galand-Desme, Alexandru Szathmari, and Christian Carrie
Stereotactic biopsy of diffuse pontine lesions in children

THOMAS ROUJEAU, M.D.,1 GUILHERME MACHADO, M.D.,1 MATTHEW R. GARNETT, F.R.C.S.,1,2 CATHERINE MIQUEL, M.D.,3 STEPHANIE PUGET, M.D.,1 BIRGIT GEOERGER, M.D., PH.D.,4 JACQUES GRILLI, M.D., PH.D.,4 NATHALIE BODDAERT, M.D.,5 FEDERICO DI ROCCO, M.D.,1 MICHEL ZERAH, M.D.,1 AND CHRISTIAN SAINTE-ROSE, M.D.1

Departments of 1Pediatric Neurosurgery, 3Neuropathology and 5Radiology, Hôpital Necker–Enfants Malades, Paris, France; 4Department of Pediatric Oncology, Institut Gustave-Roussy, Villejuif, France; and 2Department of Neurosurgery, Addenbrookes Hospital, Cambridge, United Kingdom


Biopsy sampling allowed a histological diagnosis to be confirmed in all patients. High-grade infiltrative astrocytoma (WHO Grade III or IV) was diagnosed in 22 patients. In the remaining two, one had a WHO Grade II astrocytoma and one had a pilocytic astrocytoma.

Fondo Alicia Pueyo
Grade II: Olig2+, p53 negative, IDH1 negative, EGFR negative, PDGFrα
Personalizing therapy?

Phase I Study of Vandetanib During and After Radiotherapy in Children With Diffuse Intrinsic Pontine Glioma

Alberto Bronisler, Justin N. Baker, Michael Tagen, Arzu Onar-Thomas, Richard J. Gilbertson, Andrew M. Davidoff, Atmaram Pai Panandiker, Wing Leung, Thomas K. Chin, Clinton F. Stewart, Mehmet Kocak, Christopher Rowland, Thomas E. Merchant, Sue C. Kaste, and Amar Gajjar
<table>
<thead>
<tr>
<th>Target</th>
<th>Expression/amplification</th>
<th>% of samples</th>
<th>Targeted by drugs⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>Protein expression</td>
<td>27–50%</td>
<td>Erlotinib, gefitinib, nimotuzumab, cetuximab, vandetanib (also VEGFR)</td>
</tr>
<tr>
<td></td>
<td>Amplification</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>PDGFR</td>
<td>Protein expression</td>
<td>63–100%</td>
<td>Imatinib, dasatinib</td>
</tr>
<tr>
<td></td>
<td>Amplification</td>
<td>36%</td>
<td></td>
</tr>
<tr>
<td>VEGF(R)</td>
<td>NA</td>
<td>NA</td>
<td>Vandetanib (also EGFR), bevacizumab</td>
</tr>
<tr>
<td>MTOR</td>
<td>Protein expression</td>
<td>100%</td>
<td>Everolimus, sirolimus</td>
</tr>
<tr>
<td></td>
<td>Amplification</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>PARP</td>
<td>Expression</td>
<td>36%</td>
<td>ABT-888 (study ongoing)</td>
</tr>
<tr>
<td></td>
<td>Amplification</td>
<td>27%</td>
<td></td>
</tr>
<tr>
<td>MGMT</td>
<td>Protein expression</td>
<td>0%</td>
<td>O6-benzylguanine</td>
</tr>
<tr>
<td>RAS</td>
<td>NA</td>
<td>NA</td>
<td>Lonofamib, tipifarnib</td>
</tr>
<tr>
<td>avβ3 and avβ5</td>
<td>NA</td>
<td>NA</td>
<td>Cilengitide (EMD121974)</td>
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<tr>
<td>IL-13</td>
<td>NA</td>
<td>NA</td>
<td>IL13-PE38QQR</td>
</tr>
</tbody>
</table>

⁴: Drugs listed are examples of targeted therapies for the corresponding target. The list is not exhaustive.
Personalizing therapy?

Title: Phase II Trial of Molecularly Determined Treatment of Children and Young Adults with Newly Diagnosed Diffuse Intrinsic Pontine Gliomas

Principal Investigator: Mark W. Kieran MD, PhD

Day -7 to -1
  Diagnosis by clinical and MRI criteria
Day 0
  Image guided pontine biopsy
Day +1 to +7
  Analysis for EGFR, MGMT
Day +8
  Stratify therapy groups
Personalizing therapy?

Should we irradiate Low-grade DIPG??
4. Quality and representativity of the Biopsy sample
Small sample size: Accuracy

• The accuracy of CNS stereotactic biopsy is >85% (Aker FV et al. Neuropathol 2005).
• Heterogeneity: it happens to all tumors!
  And biopsy is not questioned.
Small sample size: Research value

- ? Sufficient material for molecular analysis
- ? Quality of material for RNA/DNA etc.
- ? Heterogeneity of target
Mixed of Biopsy/Autopsy samples
Homozygous loss of ADAM3A revealed by genome-wide analysis of pediatric high-grade glioma and diffuse intrinsic pontine gliomas

Jennifer Barrow, Martyna Adamowicz-Brice, Maria Cartmill, Donald MacArthur, James Lowe, Keith Robson, Marie-Anne Brundler, David A. Walker, Beth Coyle, and Richard Grundy

Children’s Brain Tumour Research Centre, School of Clinical Sciences, Queen’s Medical Centre, University of Nottingham, Nottingham (J.B., M.A-B., M.C., D.M., J.L., K.R., D.A.W., B.C., R.G.); Department of Neurosurgery, Queen’s Medical Centre, Nottingham University Hospital, Nottingham (M.C., D.M.); Department of Neuropathology, Queens Medical Centre, Nottingham University Hospital, Nottingham (J.L., K.R.); Department of Histopathology, Birmingham Children’s Hospital, Birmingham (M-A.B.)


**Critical Oncogenic Mutations in Newly Diagnosed Pediatric Diffuse Intrinsic Pontine Glioma**

Jacques Grill, MD, PhD, Stephanie Puget, MD, PhD, Felipe Andreiuolo, MD, Cathy Philippe, MD, Laura MacConaill, PhD, and Mark W. Kieran, MD, PhD

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<table>
<thead>
<tr>
<th>Patient</th>
<th>Gene</th>
<th>Mutation</th>
<th>p53 CNA</th>
<th>p53 IHC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ATM</td>
<td>P604S</td>
<td>−0.5292</td>
<td>−</td>
</tr>
<tr>
<td>1</td>
<td>MPL</td>
<td>W515L</td>
<td>−0.5292</td>
<td>−</td>
</tr>
<tr>
<td>2</td>
<td>PI3KCA</td>
<td>H1047R</td>
<td>0.0155</td>
<td>−</td>
</tr>
<tr>
<td>3</td>
<td>PI3KCA</td>
<td>H1047L</td>
<td>0.0033</td>
<td>++</td>
</tr>
<tr>
<td>4</td>
<td>PI3KCA</td>
<td>E542K</td>
<td>0.0421</td>
<td>+++</td>
</tr>
<tr>
<td>5</td>
<td>TP53</td>
<td>R248W</td>
<td>−0.4546</td>
<td>++</td>
</tr>
<tr>
<td>6</td>
<td>TP53</td>
<td>R273H</td>
<td>−0.5166</td>
<td>++</td>
</tr>
<tr>
<td>7</td>
<td>TP53</td>
<td>V157F</td>
<td>−0.8058</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>TP53</td>
<td>R273*</td>
<td>−0.1597</td>
<td>NA</td>
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<tr>
<td>9</td>
<td>TP53</td>
<td>R273L</td>
<td>0.0011</td>
<td>+++</td>
</tr>
<tr>
<td>10</td>
<td>TP53</td>
<td>R282W</td>
<td>0.0174</td>
<td>+++</td>
</tr>
<tr>
<td>11</td>
<td>TP53</td>
<td>R273H</td>
<td>−0.3997</td>
<td>+++</td>
</tr>
<tr>
<td>12</td>
<td>TP53</td>
<td>R273L</td>
<td>0.0101</td>
<td>NA</td>
</tr>
</tbody>
</table>
Emerging Technologies: Single-Molecule Sequencing for Cancer Mutation Profiling

- Exceeds 2 Gb per run (250 Mb/lane x 8 lanes)
5. Use of Autopsy samples

Certainly doesn’t help the individual patient
Prospective Collection of Tissue Samples at Autopsy in Children With Diffuse Intrinsic Pontine Glioma

Alberto Broniscer, MD1,2; Justin N. Baker, MD3; Suzanne J. Baker, PhD4; Susan N. Chi, MD5; J. Russell Geyer, MD6; E. Brannon Morris, MD1; and Amar Gajjar, MD1,2

Somatic histone H3 alterations in pediatric diffuse intrinsic pontine gliomas and non-brainstem glioblastomas

Gang Wu1,8, Alberto Broniscer2,8, Troy A McEachron3,8, Charles Lu4, Barbara S Paugh3, Jared Beckfort5, Chunxu Qu5, Li Ding4, Robert Huether1, Matthew Parker1, Junyuan Zhang3, Amar Gajjar2, Michael A Dyer3, Charles G Mullighan6, Richard J Gilbertson3, Elaine R Mardis4, Richard K Wilson4, James R Downing6, David W Ellison6, Jinghui Zhang1 & Suzanne J Baker3 for the St. Jude Children’s Research Hospital–Washington University Pediatric Cancer Genome Project7
9/11 samples from autopsies
DNA repair genes involved

Whole-Genome Profiling of Pediatric Diffuse Intrinsic Pontine Gliomas Highlights Platelet-Derived Growth Factor Receptor α and Poly (ADP-ribose) Polymerase As Potential Therapeutic Targets
Maryam Zarghooni, Ute Bartels, Eric Lee, Pawel Buczkowicz, Andrew Morrison, Annie Huang, Eric Bouffet, and Cynthia Hawkins

March 2010
Genome-Wide Analyses Identify Recurrent Amplifications of Receptor Tyrosine Kinases and Cell-Cycle Regulatory Genes in Diffuse Intrinsic Pontine Glioma


JOURNAL OF CLINICAL ONCOLOGY

September 2011
Autopsy samples: What have we learned?

AMC 2011: 13 yo girl diagnosed of DIPG in July of 2008 (age 10)
Autopsy samples:
What have we learned?

Diffuse infiltrate of tumor glial cells into the normal parenchyma

Courtesy: Dra. Mariona Suñol. Pathology HSJDBCN
Autopsy samples: What have we learned?

- Low grade cellularity
- Calcifications
Autopsy samples:
What have we learned?

Low number of mitosis
Autopsy samples: What have we learned?

Courtesy: Dr. Jordi Muchart

Dra. Mariona Suñol

MRI: June 10, 2011
AMC
Autopsy: June 25, 2010
Autopsy samples:
What have we learned?

Courtesy: Dra. Mariona Suñol

Dr. Jordi Muchart
Autopsy samples:
What have we learned?

Brainstem peduncles
Autopsy samples: What have we learned?

Grade 3 cellularity and mitoses
Autopsy samples: What have we learned?

Courtesy: Dra. Mariona Suñol

Dr. Jordi Muchart
Autopsy samples: 
What have we learned?

Cerebellar dentate nucleus infiltrate
Autopsy samples:
What have we learned?
Autopsy samples:
What have we learned?

KI67

P53
The inherent tendency of glial tumors to widely disseminate

- Single invasive cells can be identified far from the large tumor mass
- Invasive cells migrate along basement membranes of blood vessels and perivascular spaces
- Anaplastic phenotypes invade through CSF or subarachnoid spaces

Recommended reading: Giese A. et al. The cost of migration. JCO 2003
In conclusion:

1. Diagnosis of DIPG can’t be made by imaging
2. The risk of biopsying is low/acceptable
3. Biopsy benefits the patient (and the family)
4. Samples allow diagnosis & high-quality research
5. Autopsies should be performed but not substitute biopsies.
Developmental Tumors of the Nervous System