Diffuse Intrinsic Pontine Glioma

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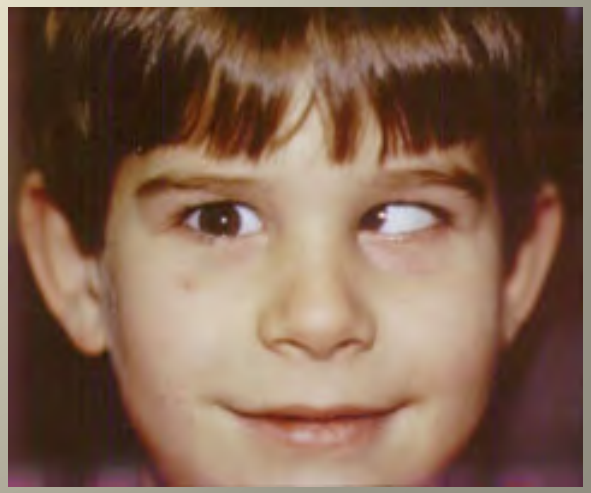
RADT 709A

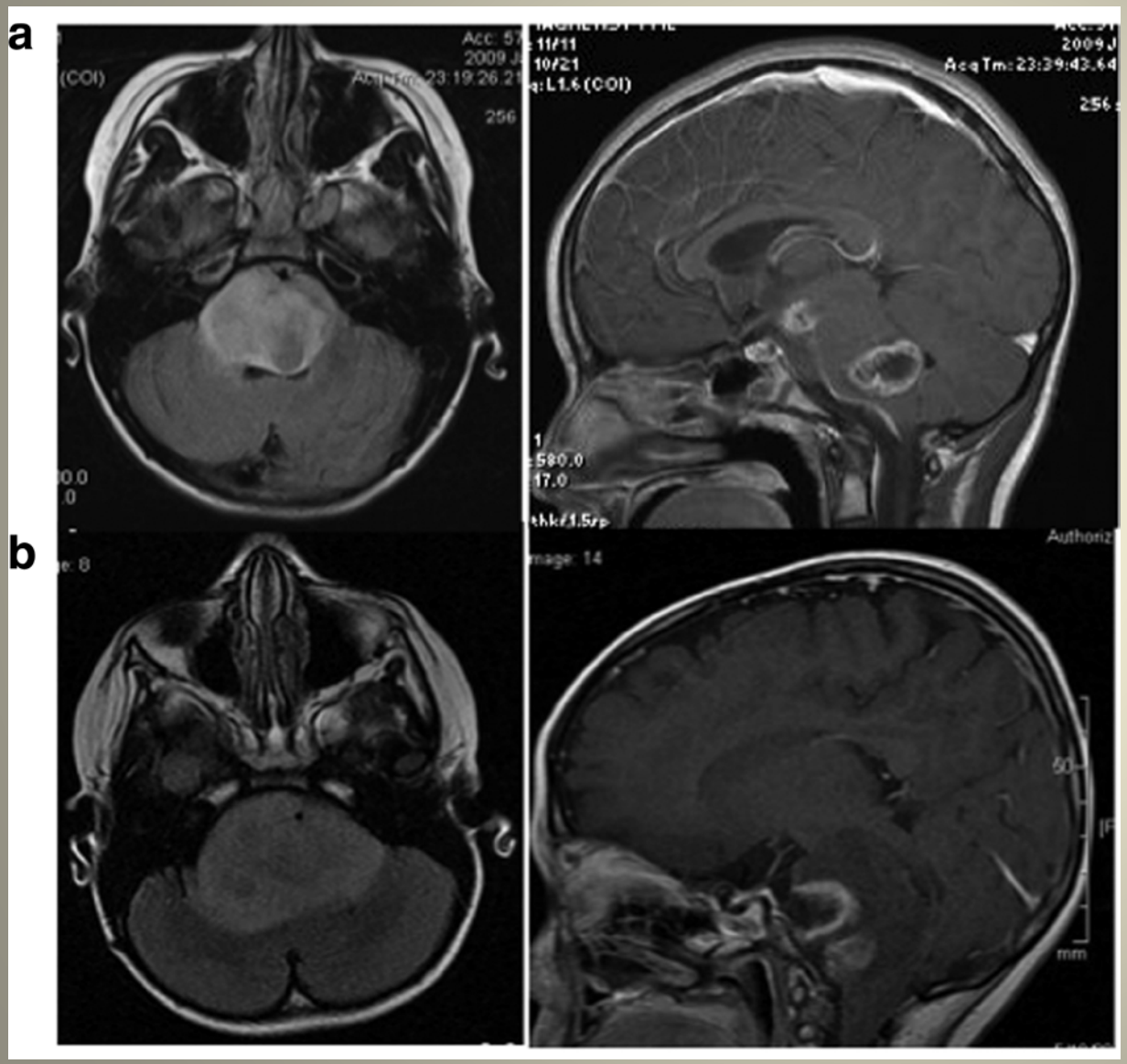
Case Presentation

- 3.5 yo previously healthy boy presents with 2 months of progressing “eye turned in”, clumsiness and drooling/slurred speech
- Physical exam reveals unilateral CN VI, VII palsy, bilateral hyperreflexia
- A brain MRI is ordered…



Imaging

FLAIR T1

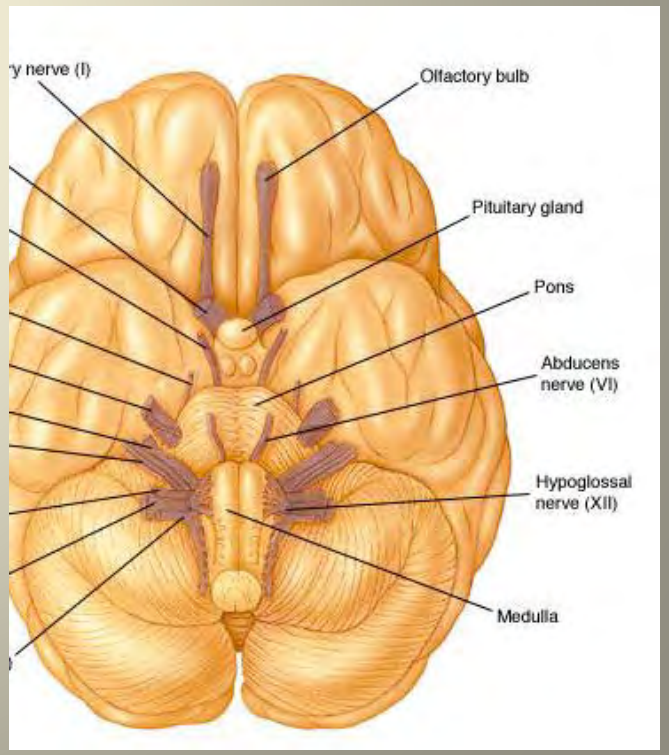


Enlarged pons
Diffuse T2/FLAIR signal
Minimal Gd-enhancement
Engulfed basilar artery

Schroeder *et al*. Pediatric RESEARC (2014) **75**, 205-209.

Diagnosis - DIPG

- Diffuse Intrinsic Pontine Glioma
  - Classic Triad
    - CN deficits (esotropia, facial assymetry)
    - Long tract signs (hyperreflexia, + Babinski)
    - Cerebellar signs (dysmetria, ataxia)
  - 15% of pediatric CNS tumors
  - Primarily Ventral Pons
    - CN VI first symptom
    - rarely hydrocephalus



Prognosis - DIPG

- Most lethal pediatric CNS tumor
- 100-150 in US/year
- median age 6.5 years
- <10% survival at 2 years
- Median PFS 5-6 months
- Median OS 8-11 months

Center, Washington, USA. This work was supported by the Semmy Foundation, KiKa Children Cancer Free, Child Health Research Institute, Lucile Packard Foundation for Children's Health, as well as the Stanford CTSA—award number UL1 TR000093—(V.C.), Stanford University School of Medicine Dean's Fellowship (V.C.), National Institutes of Neurological Disease and Stroke (NINDS grant K08NS070926), Alex's Lemonade Stand Foundation, McKenna Claire Foundation, The Cure Starts Now, Lyla Nsouli Foundation, Connor Johnson Memorial Fund, Dylan Jewett Memorial Fund, Dylan Frick Memorial Fund, Abigail Jensen Memorial Fund, Zoey Ganesh Memorial Fund, Wayland Villars Memorial Fund and Musella Foundation.

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Treatment - DIPG

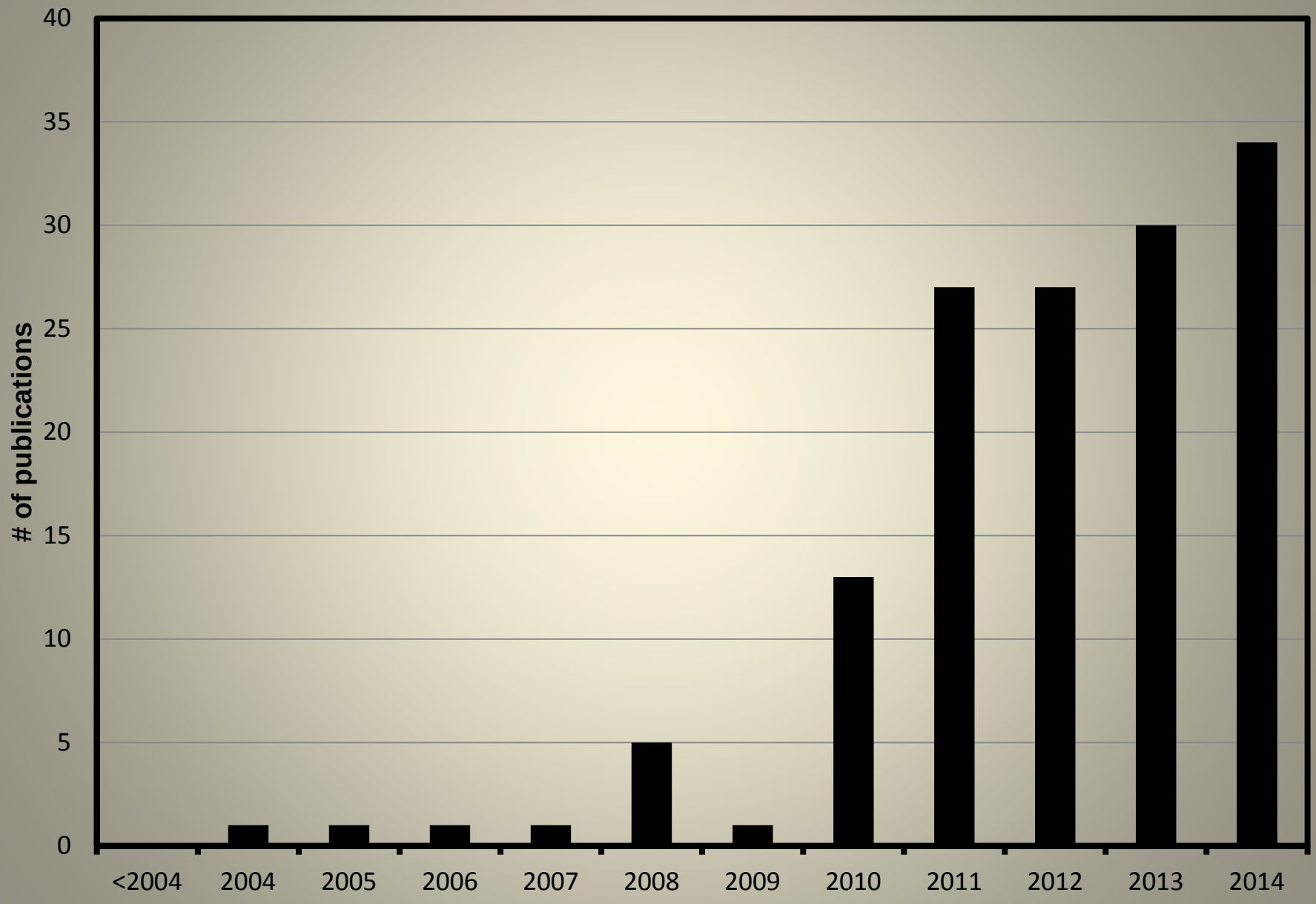
- Dexamethasone
- Radiotherapy is standard of care and only option short of a clinical trial
- 1.8-2 Gy/Fraction X30
- 70% response rate, can be dramatic
- Regrowth in 5-8 months
- Death in 7-14 months
- RT prolongs OS 2 months

Failed Trials - ChemoRT

- Based largely on adapting adult HGG data
- ACNS0126 (RT + temozolamide)
- CCG-9941 3 cycles of carbo/etop/vincristine vs. cis/etop/cyclophos/vincristine before HFEBRT to 72 Gy
- >50 others
  - Jansen *et al*. Cancer Treatment Reviews. 2012; 38: 27-35.
  - Hargrave *et al*. Lancet Oncology. 2006; 7: 241-8.

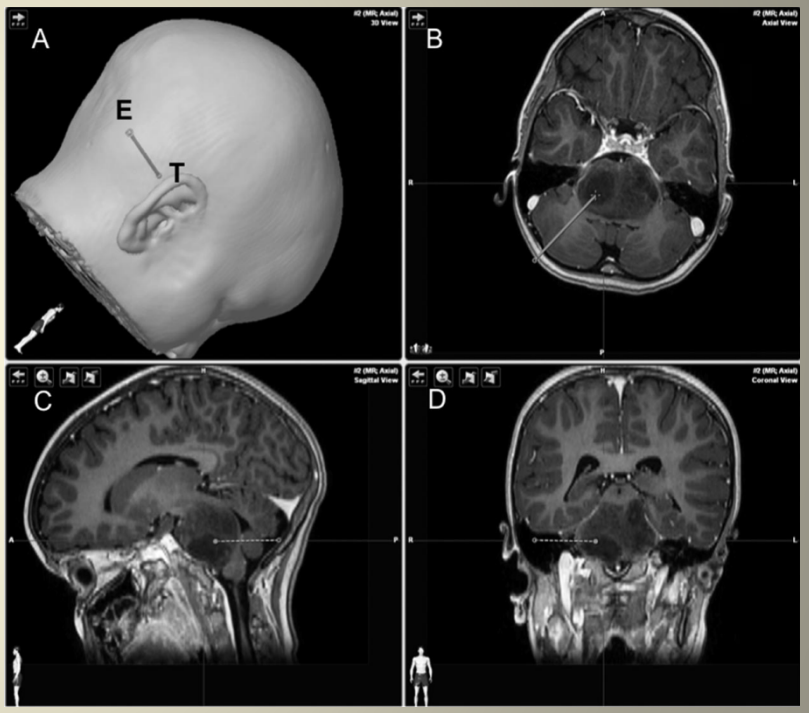
Hypofractionation

- Due to responsiveness, and limited benefit, efforts to optimize efficacy, minimize RT time
- 3 Gy X 13 or 2.8 Gy X 16 were equivalent to historical 1.8 Gy X 30 (OS 9 months)
  - Janssens *et al*. Int J Radiat Oncol Biol Phys. 2013; 85(2): 315-20.
- 3Gy X 15 (OS 7.6 months)
  - Negrettie et al. J Neurooncol. 2011; 104(3): 773-7.
- Convection-enhanced delivery of 124I-8H9
  - MSKCC trial currently recruiting


PubMed Search Results for "diffuse intrinsic pontine glioma"
# of publications
0
5
10
15
20
25
30
35
40
<2004
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014

Recent Developments

- "Paradigm shift" biopsy → targeted approaches
  - Safety
    - French/UK since 2003
    - <1% mortality
  - Mutational Analyses
    - H3F3A.3 K27M mutation in 71%
    - p53 mutation in 40-77%
    - PDGFR amp in 13-36%
    - EGFR amp in 28%
- Establishment of cell lines
    - Monje *et al*. PNAS 2011
- Establishment of genetically engineered mouse models
    - Becher *et al*. Cancer Res. 2010; 70(6): 2548-57.



DIPG Trial at OHSU

- NCT01182350 “Molecularly Determined Treatment of Diffuse Intrinsic Pontine Gliomas”
- DFCI sponsored, Chaired by Mark Kieran MD/PhD
- **Biopsy** for EGFR and MGMT status, then **RT to 59.4 Gy and concurrent bevacizumab**
- Following RT, observation or erlotinib or temodar or both pending bx results
- Planned enrollment: 100
- Outcomes: safety/feasibility of bx and path, path findings, toxicity profiles of treatment arms, PFS, correlation of imaging with outcomes