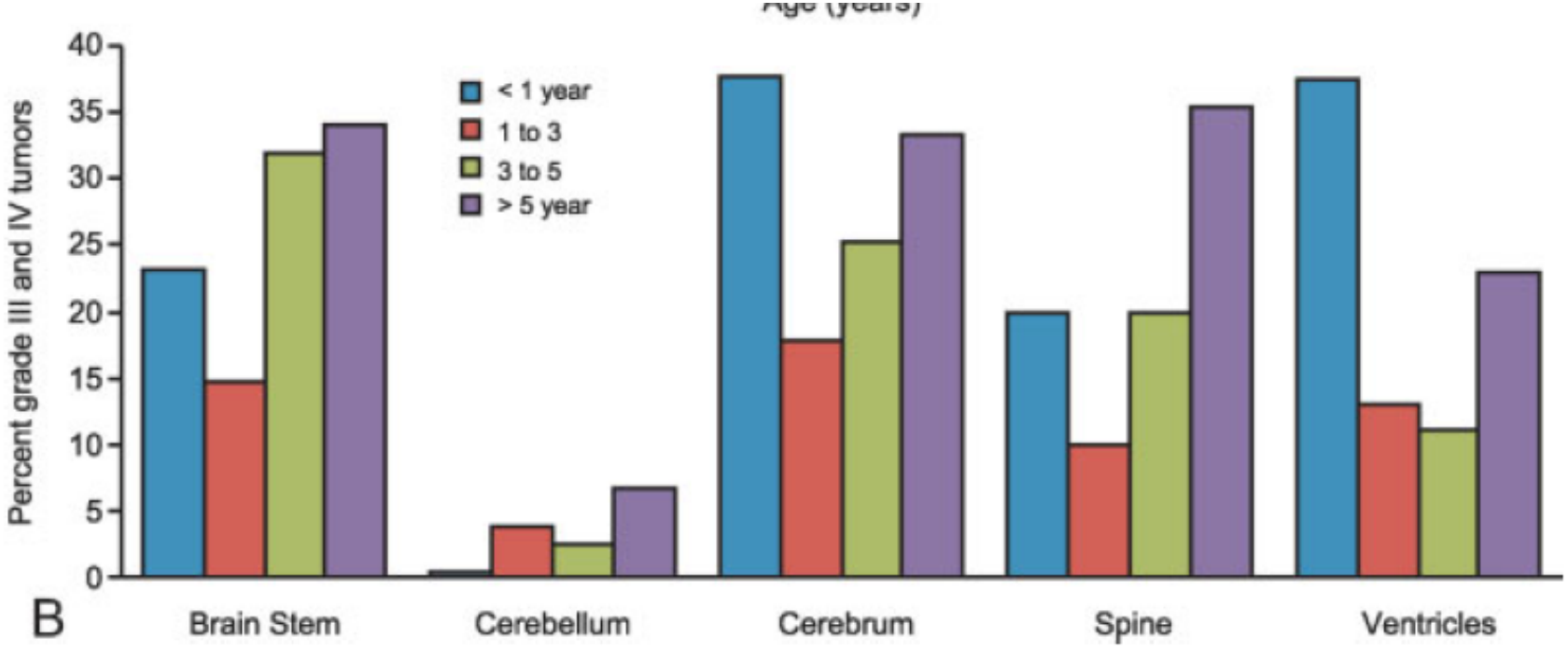
Paediatric HGG- Clinical Background

Darren Hargrave
Royal Marsden Hospital

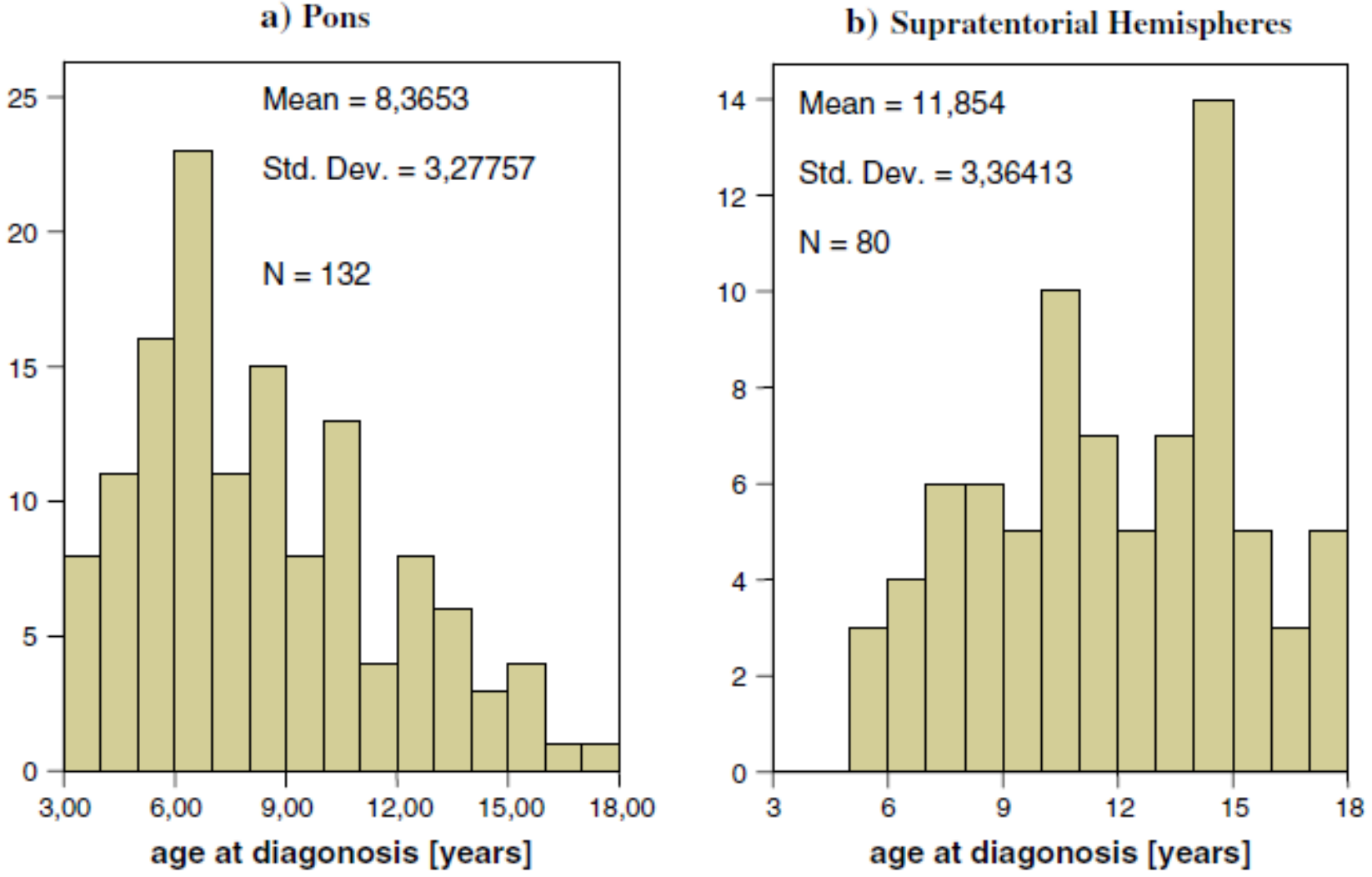
Epidemiology



Cancer December 15, 2009

Ibrahim Qaddoumi, MD, MS[1]; Iyad Sultan, MD[2]; and Amar Gajjar, MD[1]

Epidemiology

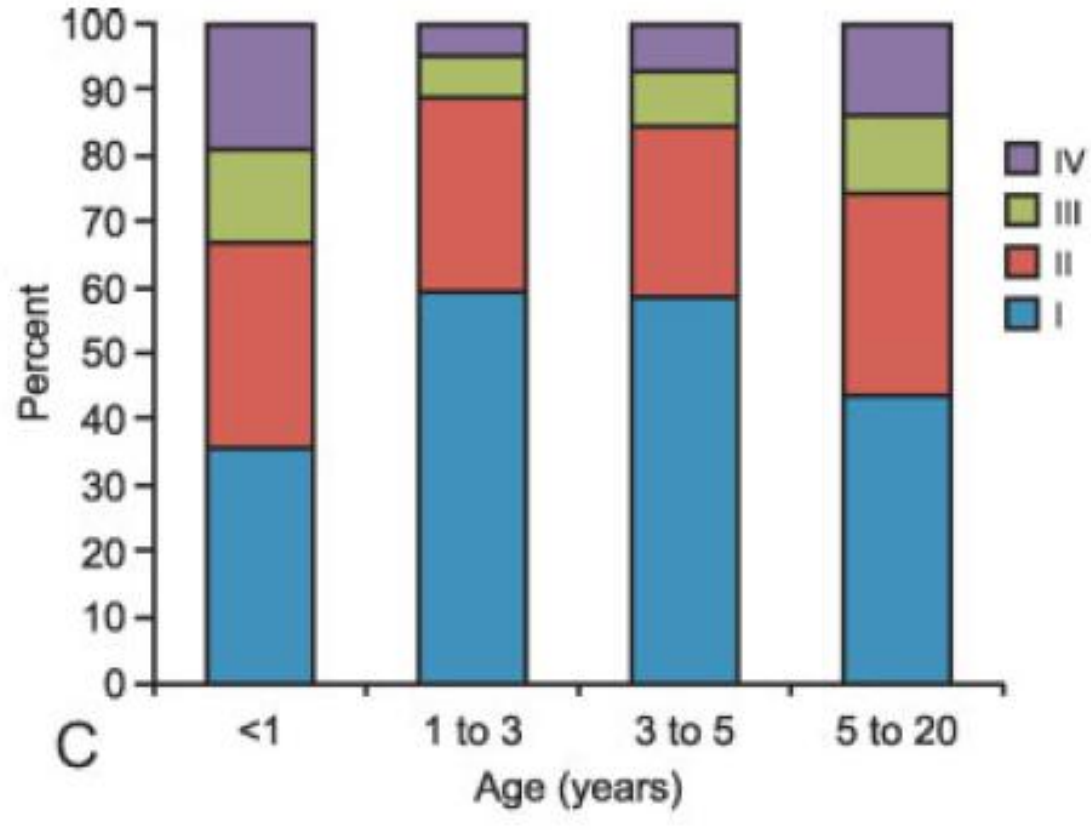


J Neurooncol (2008) 87:155–164

Johannes E. A. Wolff

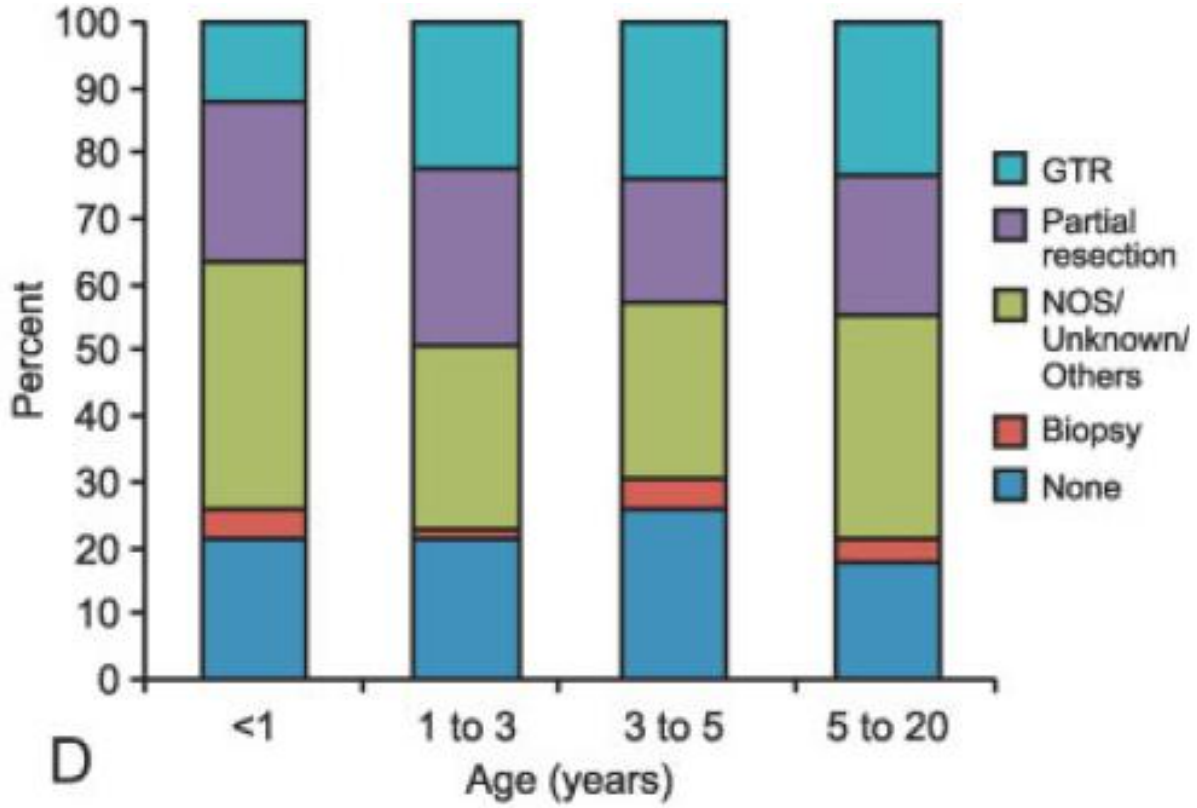
Epidemiology

- Slight M>F
- Metastases presentation 12/290 (0% Pons)
- DIPG
  - III (48%)
  - IV (30%)
- Cerebrum
- IV>III

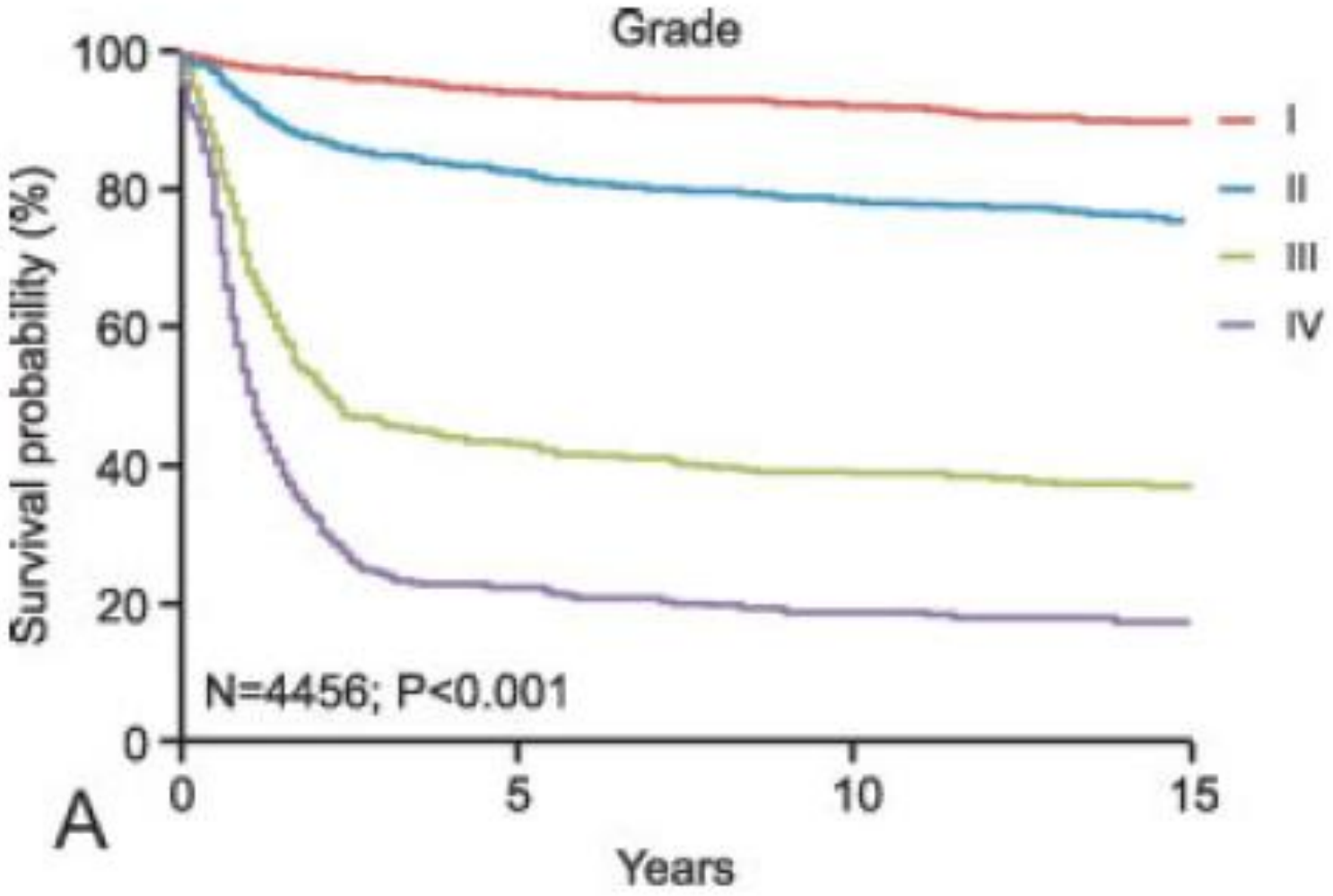


Treatment

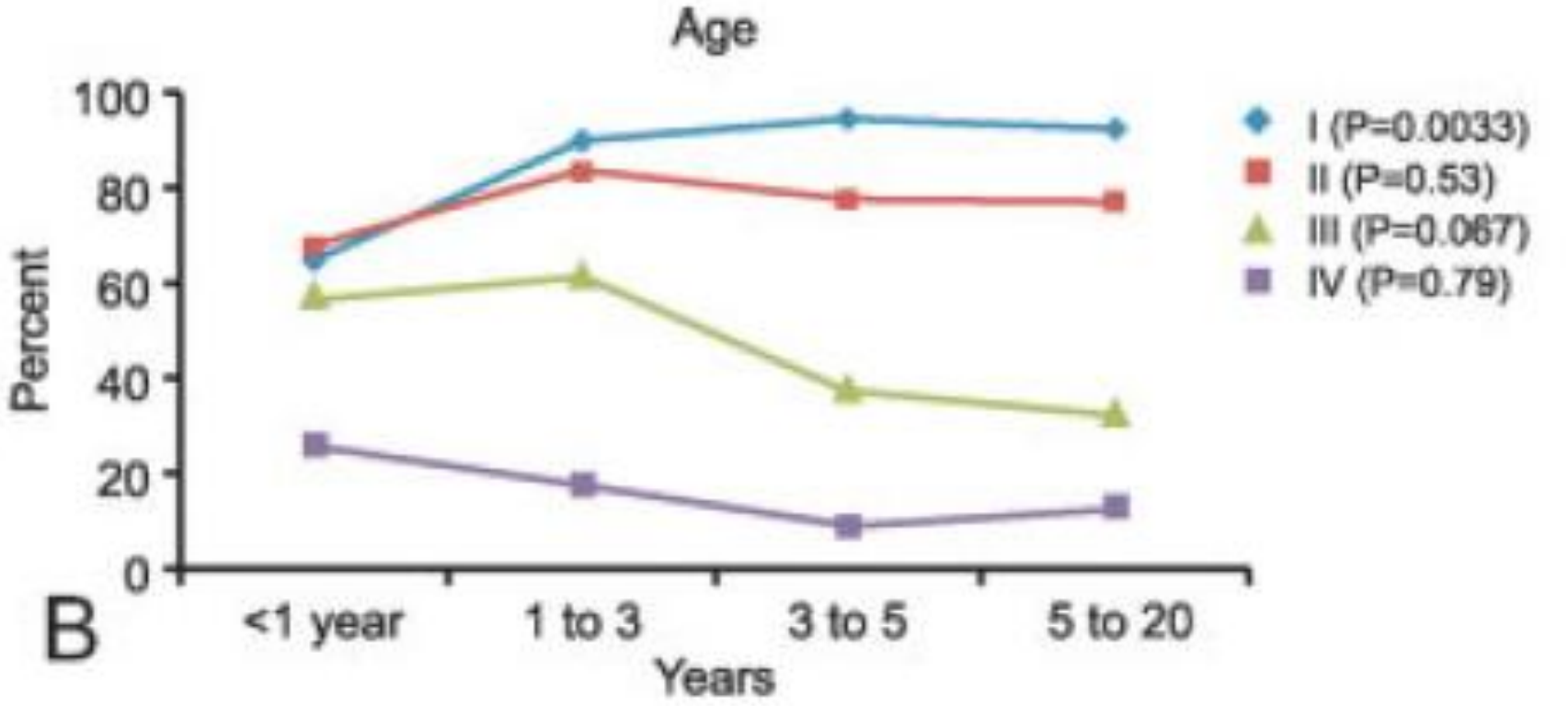
- Surgery
  - Cerebellum /Cerebrum 50% CR



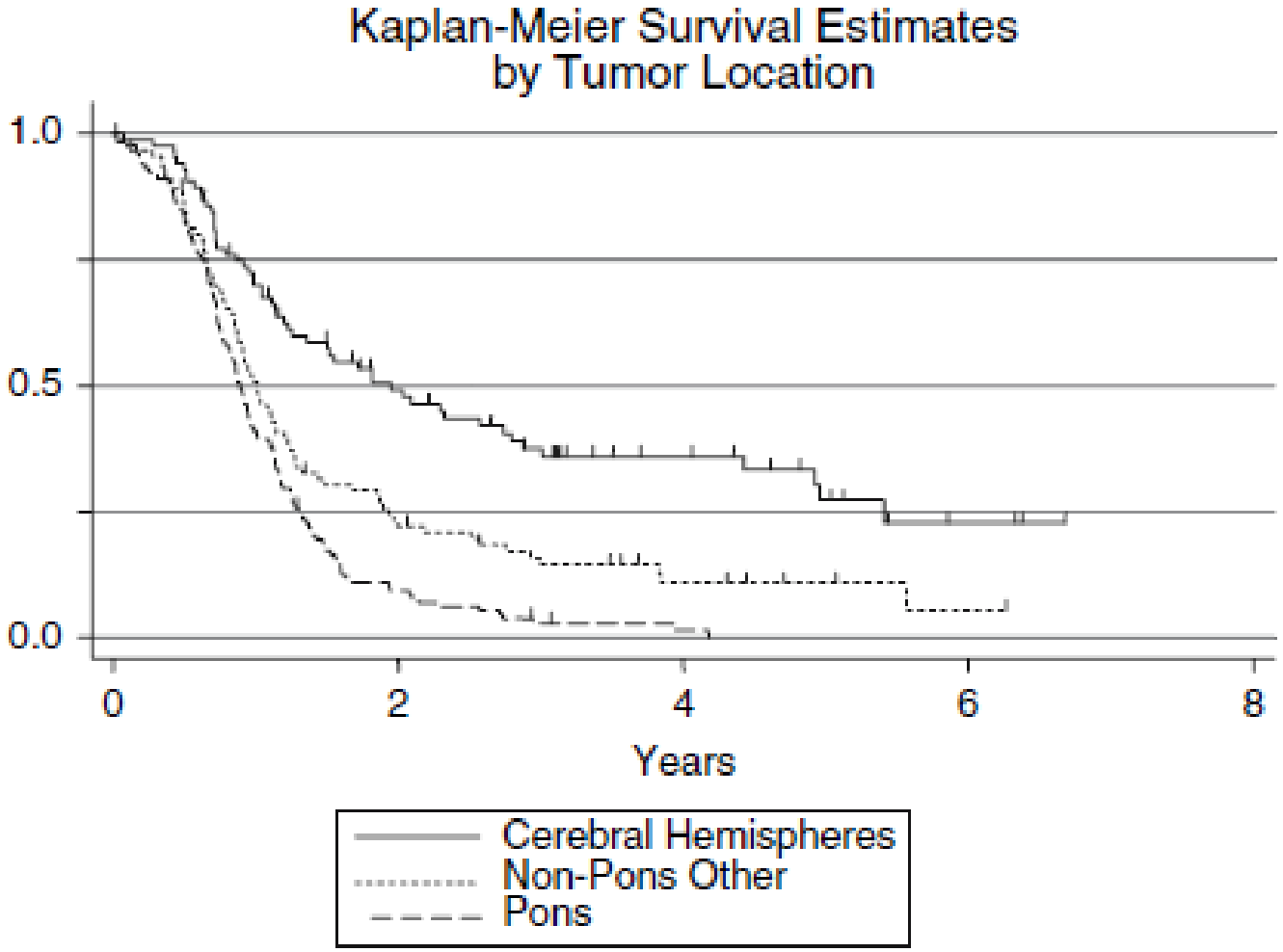
Outcome


Grade
100
80
60
40
20
0
Survival probability (%)
I
II
III
IV
N=4456; P<0.001
A
0
5
10
15
Years

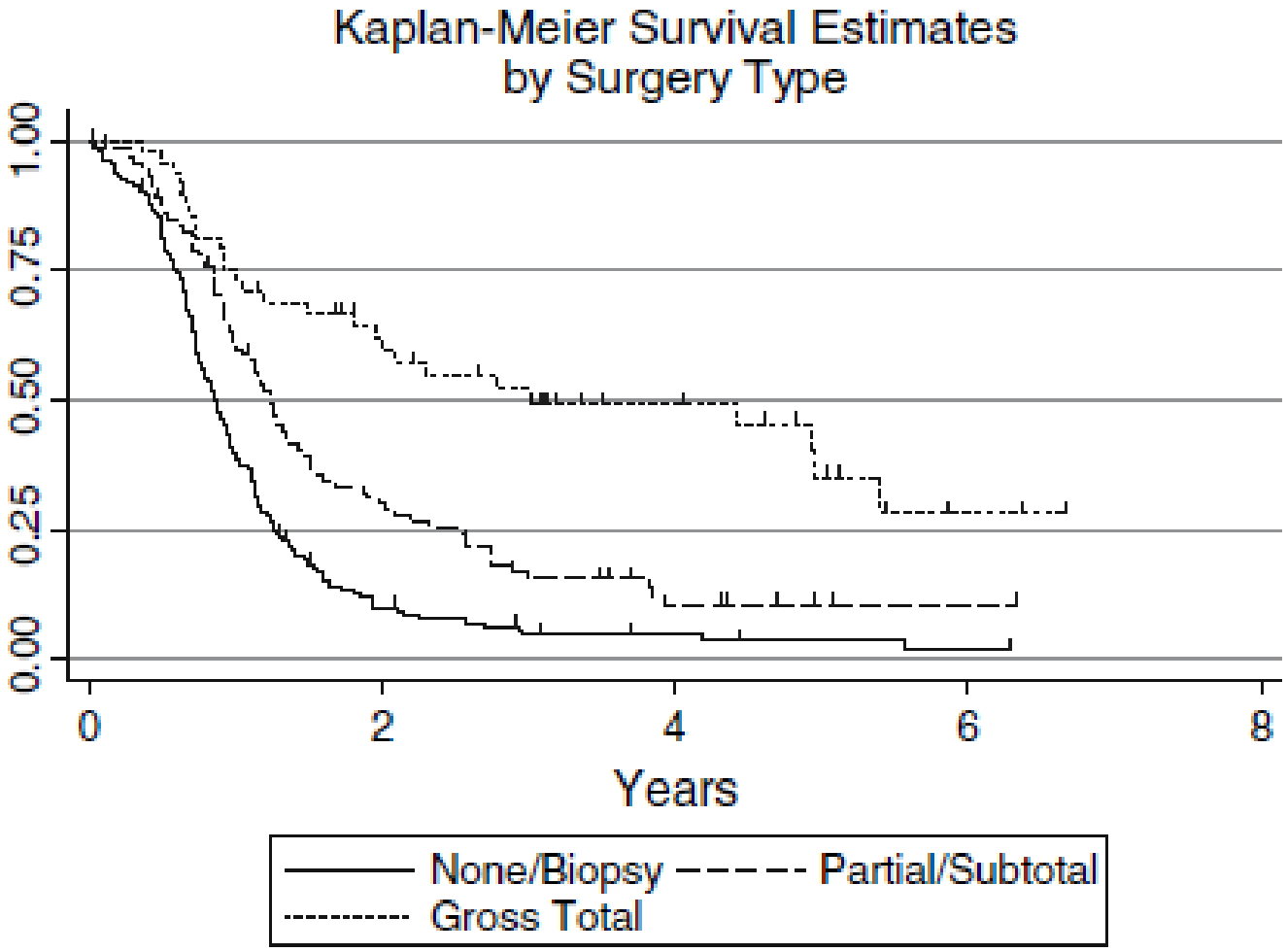
Outcome


Age
Percent
100
80
60
40
20
0
B
<1 year
1 to 3
3 to 5
5 to 20
Years
I (P=0.0033)
II (P=0.53)
III (P=0.067)
IV (P=0.79)

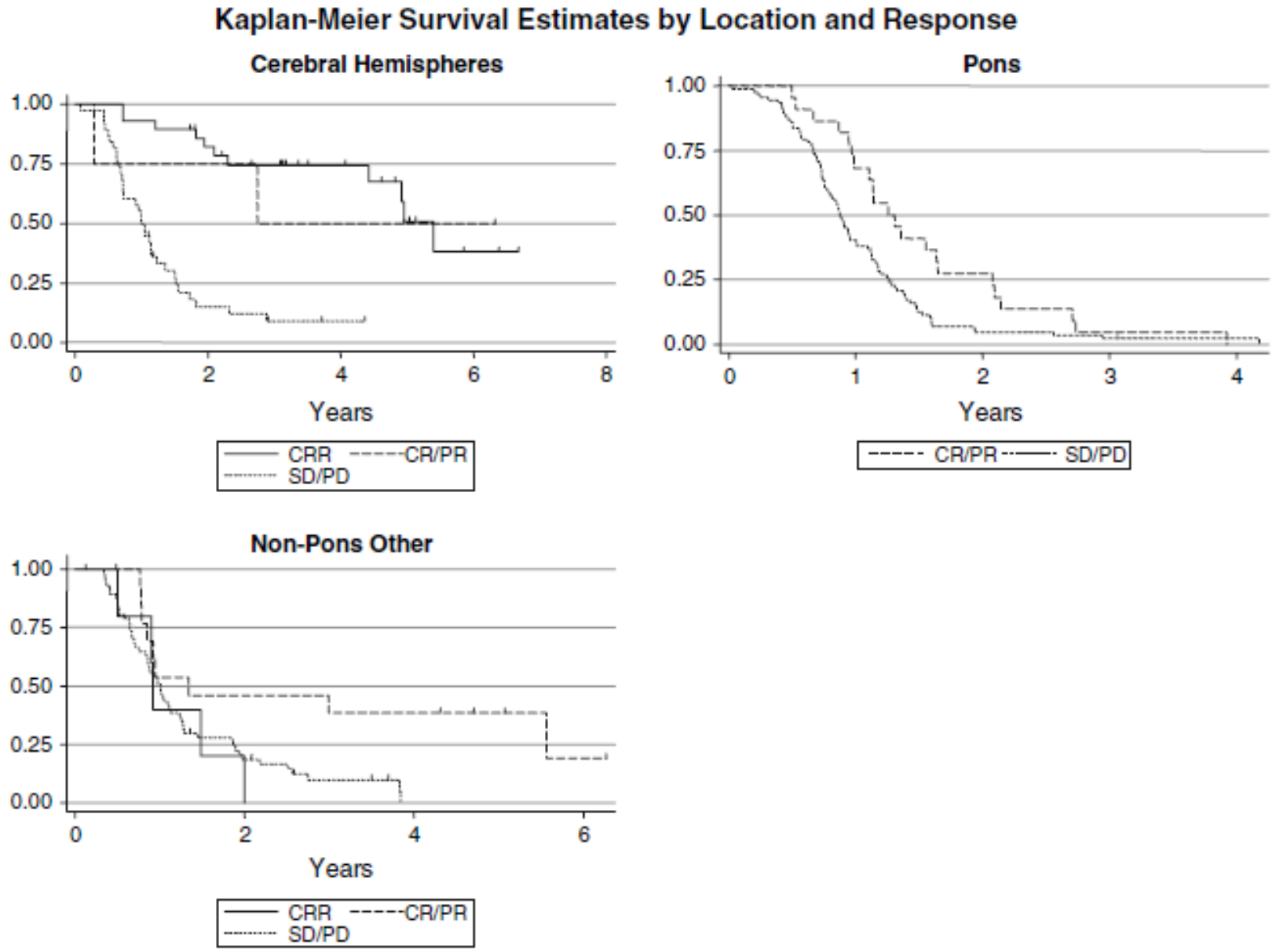
Outcome


Kaplan-Meier Survival Estimates
by Tumor Location
1.0
0.5
0.0
0
2
4
6
8
Years
Cerebral Hemispheres
Non-Pons Other
Pons

Outcome


Kaplan-Meier Survival Estimates
by Surgery Type
1.00
0.75
0.50
0.25
0.00
0
2
4
6
8
Years
None/Biopsy
Partial/Subtotal
Gross Total

Outcome


Kaplan-Meier Survival Estimates by Location and Response
Cerebral Hemispheres
1.00
0.75
0.50
0.25
0.00
0
2
4
6
8
Years
CRR
CR/PR
SD/PD
Pons
1.00
0.75
0.50
0.25
0.00
0
1
2
3
4
Years
CR/PR
SD/PD
Non-Pons Other
1.00
0.75
0.50
0.25
0.00
0
2
4
6
Years
CRR
CR/PR
SD/PD

Trials

- CCG 943 (1989)
  - RT alone vs RT with weekly VCR follwed by CT (PCV*)
  - 58 (40GBM + 18AA)
  - 18% vs 46% (5yr EFS)
- CCG 945 (1998+)
  - 172 (NB disconcordant pathology in 51)
  - RT+ PVC vs local RT and 8-in-1 CT pre & post RT
  - 19% vs 23% (5yr EFS)
  - Pathology & biology very well reported

Trials

- HIT 88/89 - HIT 91
  - N=55
  - Surgery + Ifosfamide, etoposide, MTX, cisplatin, cytarabine --> RT followed by 8 cycles of VCR, CCNU, ciplatin (sandwich CT)
  - (3 yrs EFS) Total resection 83%; partial resection 38%
  - Grade III>grade IV

Trials

- HIT GBM-C
  - N=97 (37 Pons, 35 grade IV)
  - CR (21), PR (29)
  - Cisp, etoposide, VCR; ifosfamide + RT
  - OS 91%(6mo), 56%(12mo) & 19% (60mo)
- HIT GBM-D
  - MTX prior to RT then PEI then PCV
  - Results awaited

Current Treatment

- ? Influence from Adult GBM studies

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

Roger Stupp, M.D., Warren P. Mason, M.D., Martin J. van den Bent, M.D., Michael Weller, M.D., Barbara Fisher, M.D., Martin J.B. Taphoorn, M.D., Karl Belanger, M.D., Alba A. Brandes, M.D., Christine Marosi, M.D., Ulrich Bogdahn, M.D., Jürgen Curschmann, M.D., Robert C. Janzer, M.D., Samuel K. Ludwin, M.D.,Thierry Gorlia, M.Sc., Anouk Allgeier, Ph.D., Denis Lacombe, M.D., J. Gregory Cairncross, M.D., Elizabeth Eisenhauer, M.D., and René O. Mirimanoff, M.D., for the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group*

Glioblastoma- 1st Line therapy

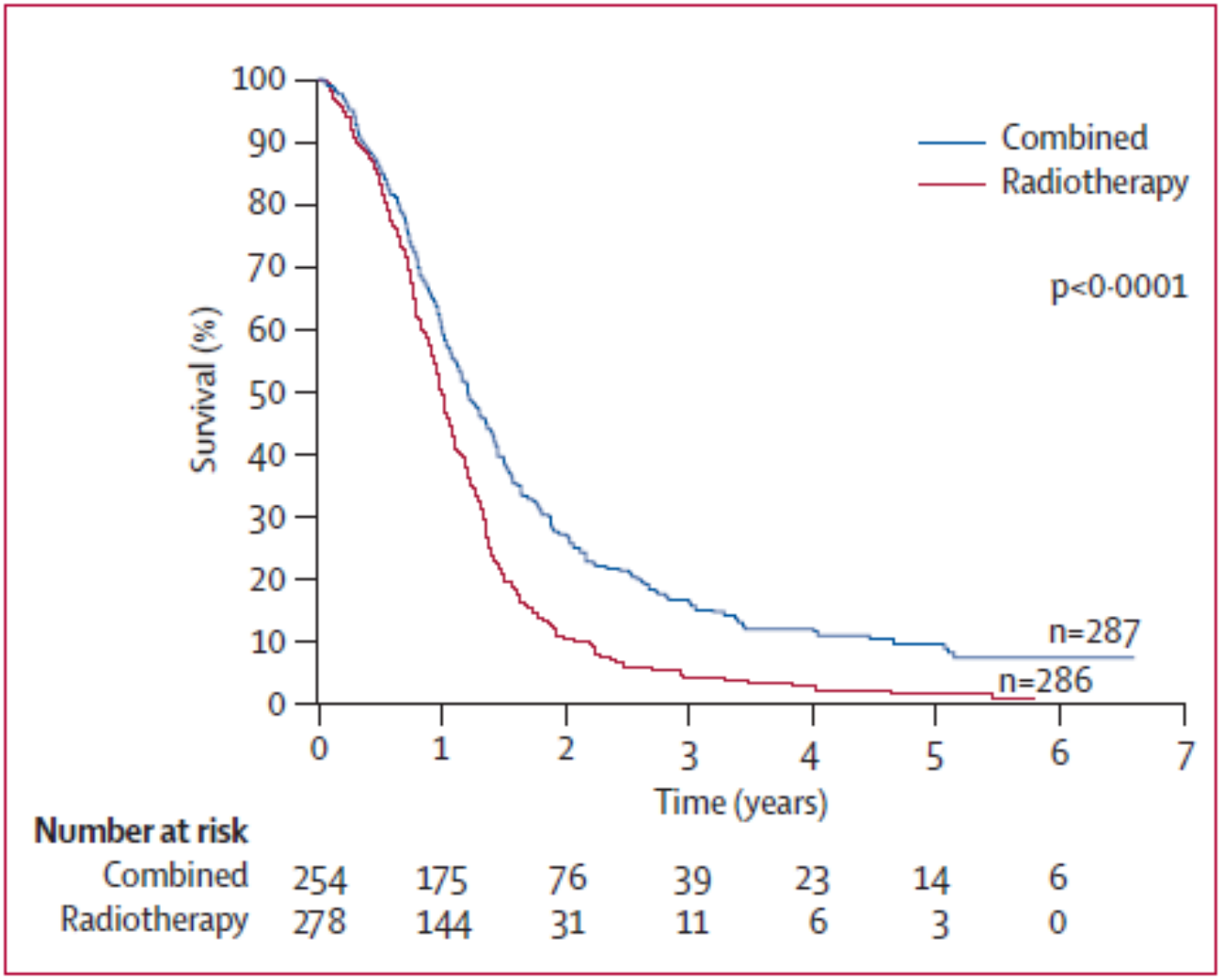


Figure 2: Kaplan-Meier estimates of overall survival by treatment group

- Adult (TMZ)
- PFS (95% CI)
- 26.9% (21.8–32.1) 1 yr
- 11·2% (7·9–15·1) 2 yrs
- 6·0% (3·6–9·2) 3yrs
- 5·6% (3·3–8·7) 4 yrs
- 4·1% (2·1–7·1) 5 yrs

- Paeds (TMZ)
- 36% (± 7) 1yr
- AA
- 31% (± 8) 1yr

HGG- Standard treatment

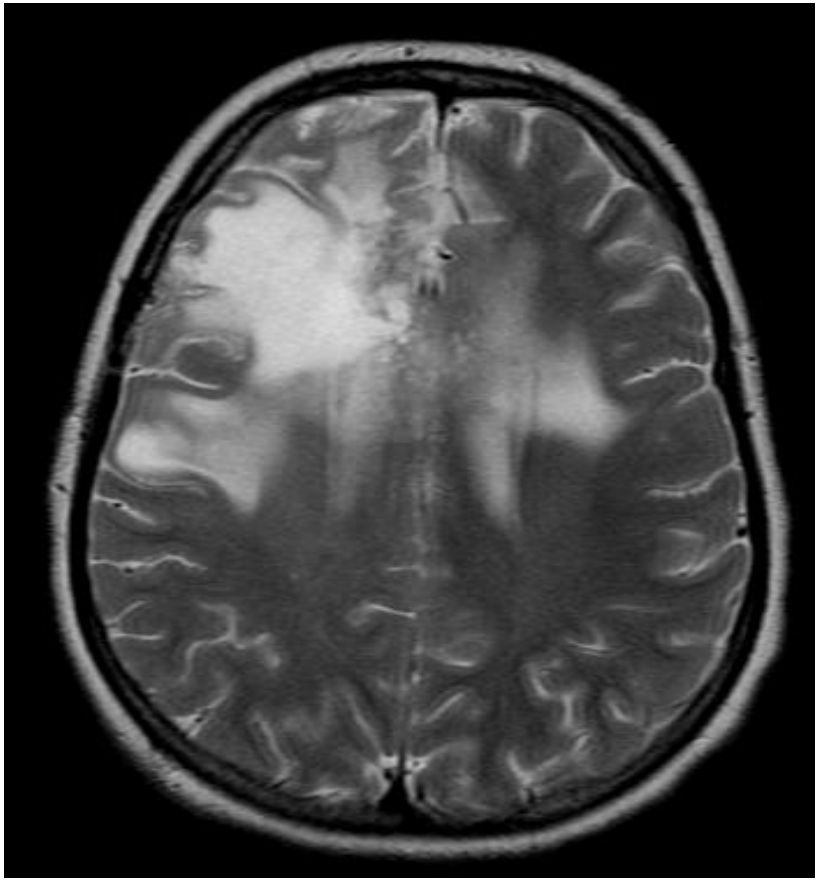
- At present many HGG patients >3years
- Treated with “Stupp Regimen”
  - GBM results
    - Adult- 1-year PFS 26.9 (21.8–32.1), 1 yr OS 61%
    - Paediatric- 1-year EFS 36% ± 7%, 1 yr OS 68%.

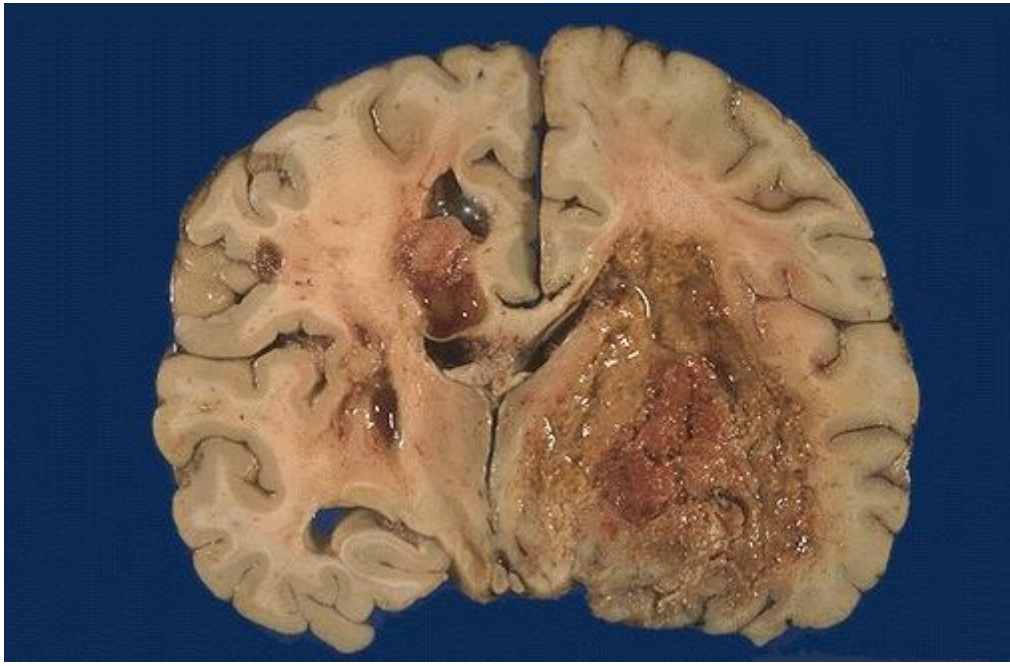
- But is this a standard?

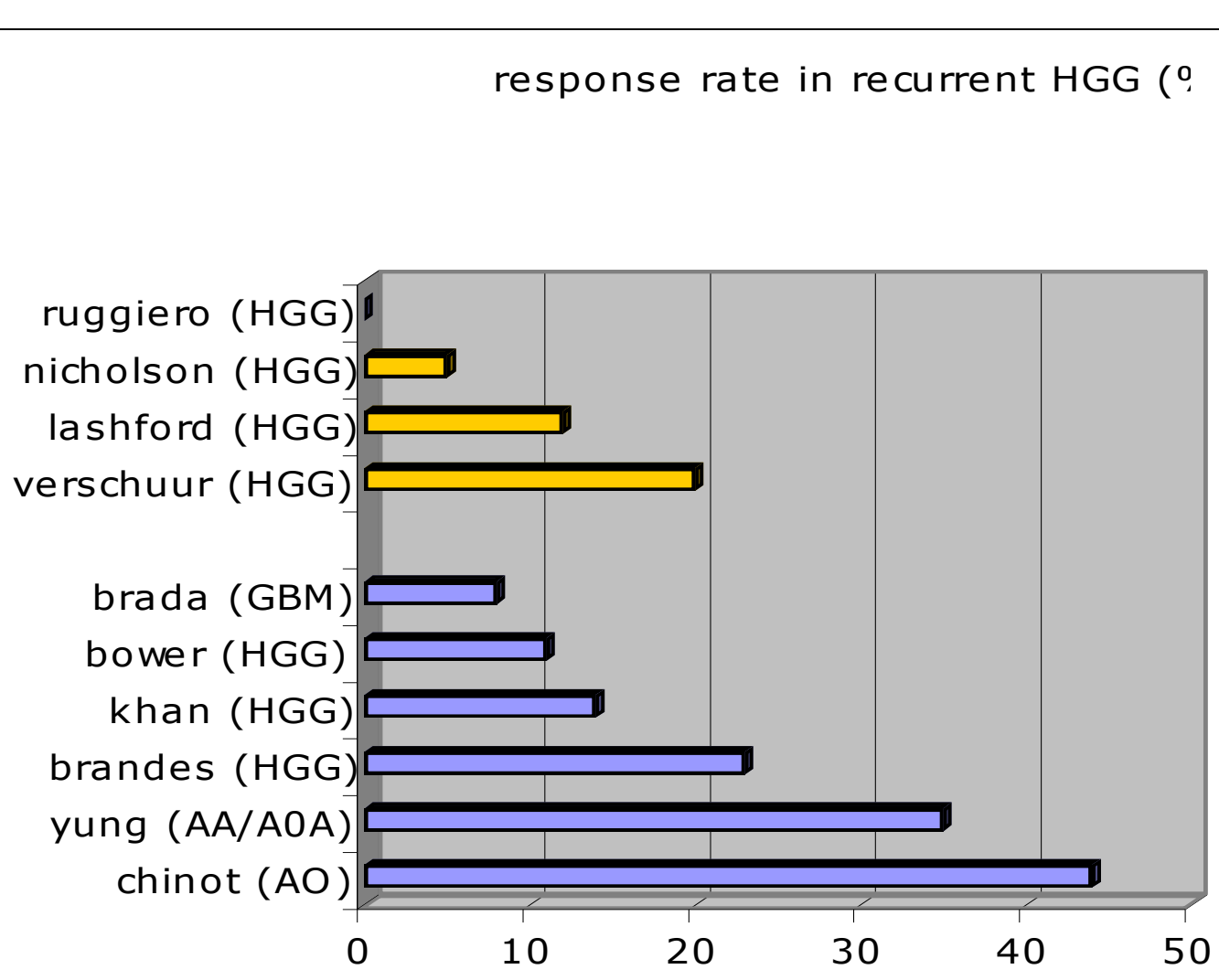
Temozolomide in Relapsed Paediatric HGG

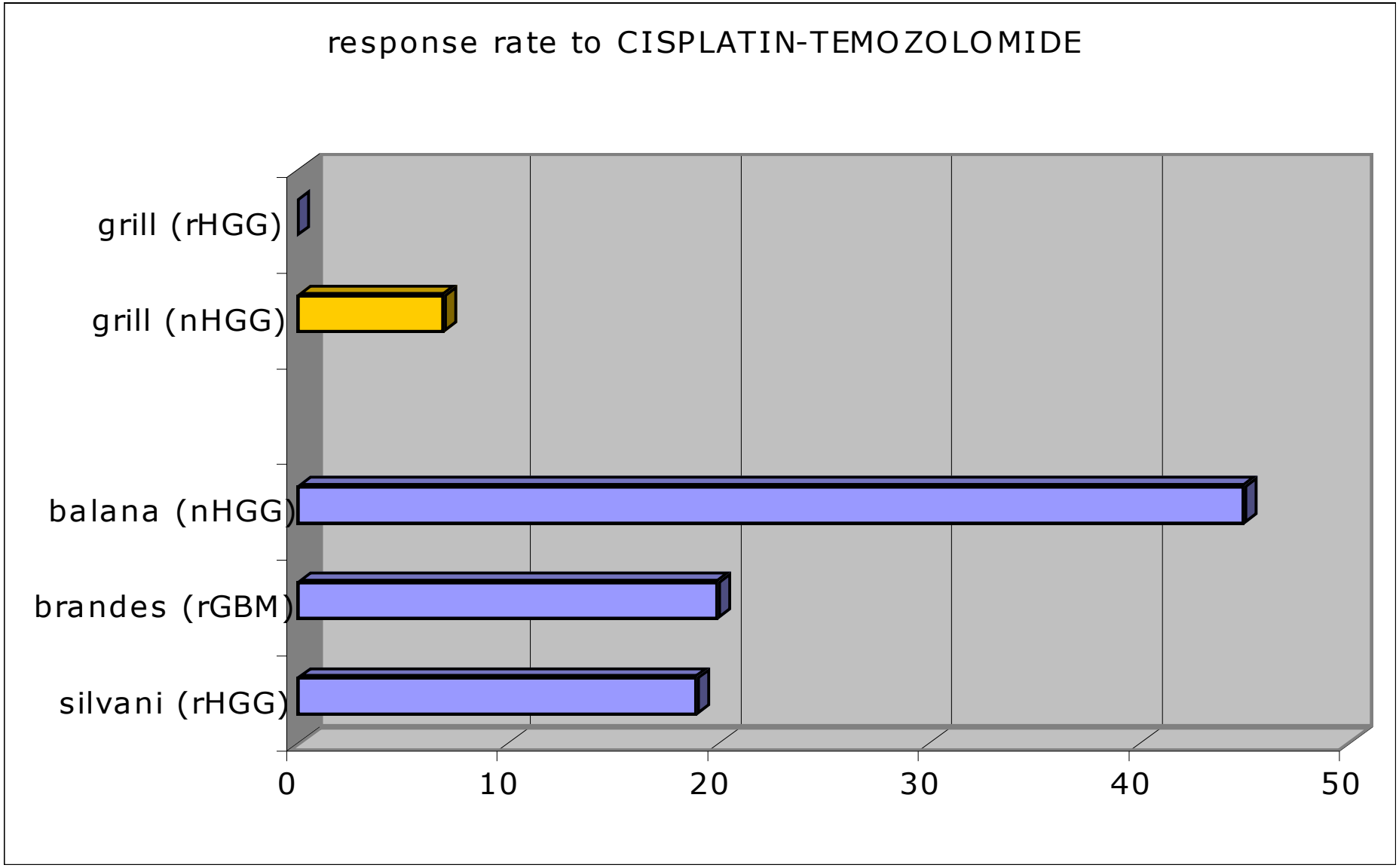
No.	Objective Response rate	Median (6) PFS	Median OS	Study
34	12%		4.7	Lashford et al.
24	0%	3 (33%)	4.0	Ruggerio et al.
23	4%		?	Nicholson et al.
20	20%	2 (20%)	10	Verschuur et al.
11	63%	6		Korones et al.

Are paediatric HGG and adult HGG different?






response rate in recurrent HGG (º
ruggiero (HGG)
nicholson (HGG)
lashford (HGG)
verschuur (HGG)
brada (GBM)
bower (HGG)
khan (HGG)
brandes (HGG)
yung (AA/A0A)
chinot (AO)
0
10
20
30
40
50


response rate to CISPLATIN-TEMOZOLOMIDE
grill (rHGG)
grill (nHGG)
balana (nHGG)
brandes (rGBM)
silvani (rHGG)
0
10
20
30
40
50

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Bevacizumab Plus Irinotecan in Recurrent Glioblastoma Multiforme

James J. Vredenburgh, Annick Desjardins, James E. Herndon II, Jennifer Marcello, David A. Reardon,

Results

The 6-month progression-free survival among all 35 patients was 46% (95% CI, 32% to 66%). The 6-month overall survival was 77% (95% CI, 64% to 92%). Twenty of the 35 patients (57%; 95% CI, 39% to 74%) had at least a partial response. One patient developed a CNS hemorrhage, which occurred in his 10th cycle. Four patients developed thromboembolic complications (deep venous thrombosis and/or pulmonary emboli).

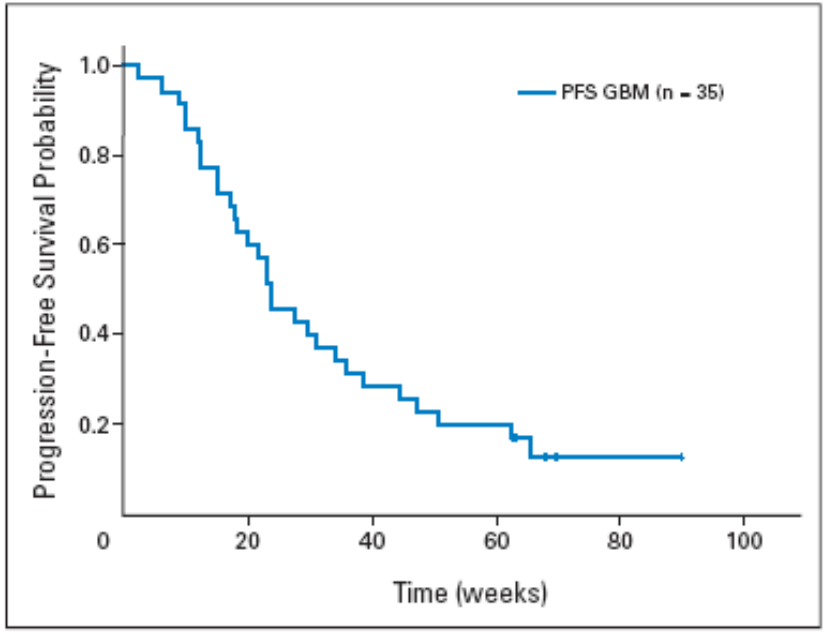
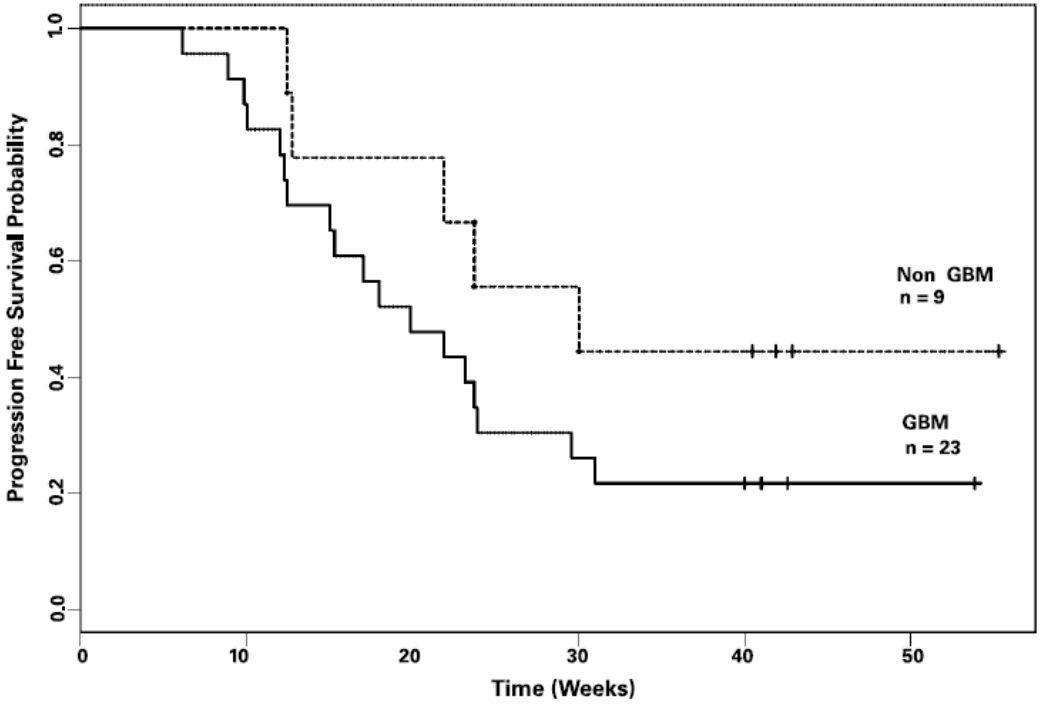


Fig 1. Kaplan-Meier progression-free survival (PFS). GBM, glioblastoma multiforme.



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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Lack of Efficacy of Bevacizumab Plus Irinotecan in Children With Recurrent Malignant Glioma and Diffuse Brainstem Glioma: A Pediatric Brain Tumor Consortium Study

Sridharan Gururangan, Susan N. Chi, Tina Young Poussaint, Arzu Onar-Thomas, Richard J. Gilbertson, Sridhar Vajapeyam, Henry S. Friedman, Roger J. Packer, Brian N. Rood, James M. Boyett, and Larry E. Kun

From the Preston Robert Tisch Brain Tumor Center; Duke University Medical Center, Durham, NC; Dana-Farber Cancer Institute; Children's Hospital Boston, Boston, MA; St Jude Children's Research Hospital; Operations and Biostatistics Center for the Pediatric Brain Tumor Consortium, Memphis, TN; and the Children's National Medical Center, Washington, DC.

Submitted November 9, 2009; accepted March 17, 2010; published online ahead of print at www.jco.org on May 17, 2010.

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Presented in part at the Society for Neuro-Oncology, Las Vegas, NV, November 20-23, 2008, and New Orleans, LA, October 22-24, 2009.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org.

ABSTRACT

Purpose
A phase II study of bevacizumab (BVZ) plus irinotecan (CPT-11) was conducted in children with recurrent malignant glioma (MG) and intrinsic brainstem glioma (BSG).

Patients and Methods
Eligible patients received two doses of BVZ intravenously (10 mg/kg) 2 weeks apart and then BVZ plus CPT-11 every 2 weeks until progressive disease, unacceptable toxicity, or a maximum of 2 years of therapy. Correlative studies included diffusion weighted and T1 dynamic contrast–enhanced permeability imaging, BVZ pharmacokinetics, and estimation of vascular endothelial growth factor receptor 2 (VEGFR-2) phosphorylation in peripheral blood mononuclear cells (PBMC) after single-agent BVZ.

Results
Thirty-one evaluable patients received a median of two courses of BVZ plus CPT-11 (range, 1 to 19). No sustained responses were observed in either stratum. Median time to progression for all 34 eligible patients enrolled was 127 days for MG and 71 days for BSG. Progression-free survival rates at 6 months were 41.8% and 9.7% for MG and BSG, respectively. Toxicities related to BVZ included grade 1 to 3 fatigue in seven patients, grade 1 to 2 hypertension in seven patients, grade 1 CNS hemorrhage in four patients, and grade 4 CNS ischemia in two patients. The mean diffusion ratio decreased after two doses of BVZ in patients with MG only. Vascular permeability parameters did not change significantly after therapy in either stratum. Inhibition of VEGFR-2 phosphorylation in PBMC was detected in eight of 11 patients after BVZ exposure.

Conclusion
BVZ plus CPT-11 was well-tolerated but had minimal efficacy in children with recurrent malignant glioma and brainstem glioma.

Infant HGG-Baby POG

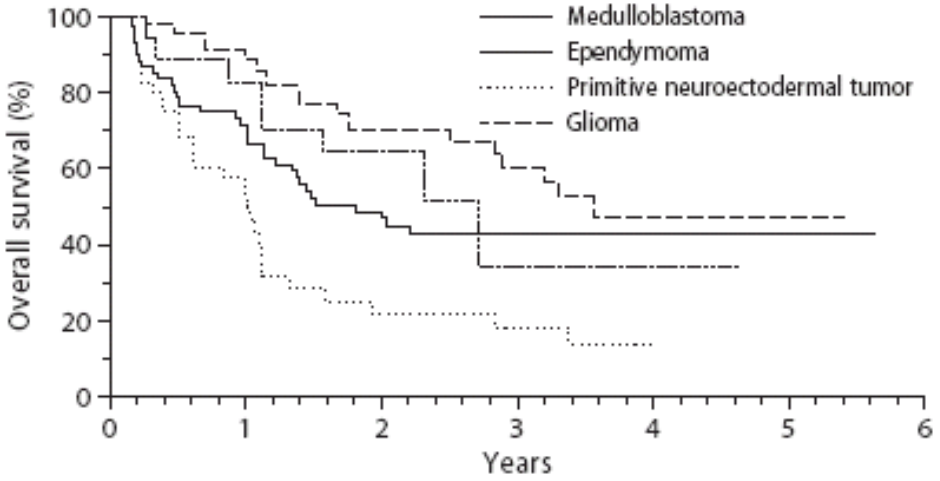
- Under 36m with malignant brain tumour
  - 198 cases of which 18 HGG (9%)
  - 12/18 <6m of age (BSG excluded)
  - 83% cereb hemispheres, 11% midline, 5% PF
  - 4 mestastatic (spine)
  - GBM =6, AA= 3, unclass. = 9
- Max.surgical resection recommended
  - 6 Gross total, 1 debulk (>75%), 8 partial, 2Bx

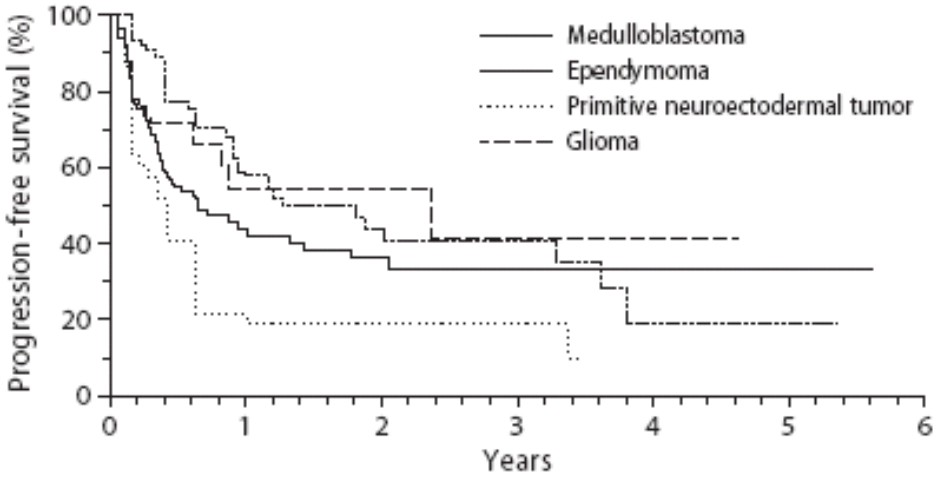
Baby POG

- Chemotherapy
  - AABAAB 28 day cycle, duration 12/24m
    - A= VCR, Cyclo (65mg/kg)
    - B= CDDP (4mg/kg), VP16 (6.5mg/kg x2)
- Radiation for all after last cycle CT 54Gy
- Response
  - 10 evaluable no CR but 6 PR, 3 SD & 1PD
  - 2 with spinal mets 2 had CR of mets
  - 2 developed PD after total resection

Baby POG

- PFS
  - 1+2 yr = 54%
  - 3+5 yr = 43%
- OS
  - 3+5 yr = 50%
- Failures
  - Local and 89% within 1 year
- 4 children no RT and alive at 43-84m





High-grade glioma in children under 5 years of age: A chemotherapy only approach with the BBSFOP protocol

C. Dufour[a,*], J. Grill[a], A. Lellouch-Tubiana[b], S. Puget[c], P. Chastagner[d], D. Frappaz[e], F. Doz[f], F. Pichon[g], D. Plantaz[h], J.C. Gentet[i], M.A. Raquin[a], C. Kalifa[a]

Eur J Cancer. 2006 Nov;42(17):2939-45.

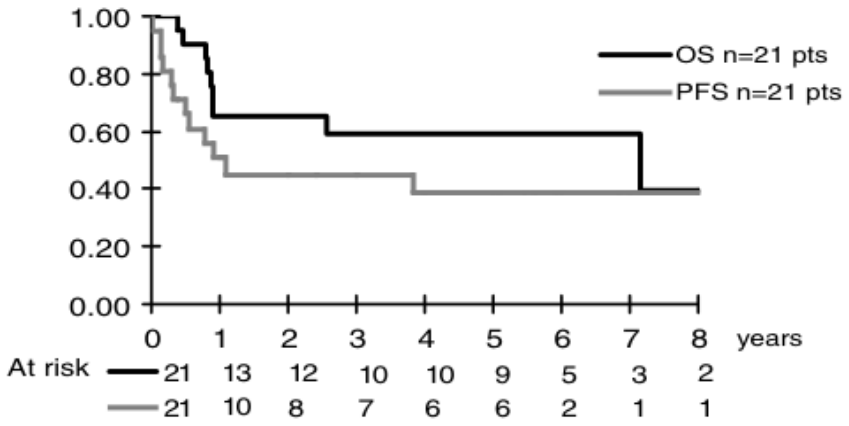
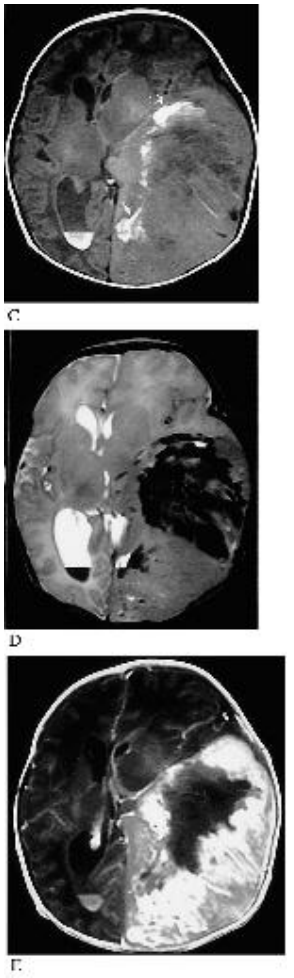


Fig. 1 – Overall survival (OS) and progression-free survival (PFS).



Questions- Gaps

- Grade III vs. IV Rx same?
- DIPG vs. HGG Rx same?
- Paediatric vs. Adult HGG Rx same?
- Infant vs. Older HGG Rx same?
- ? What is standard Rx in new or relapse?
- Which endpoints?