Pediatric Low Grade Gliomas

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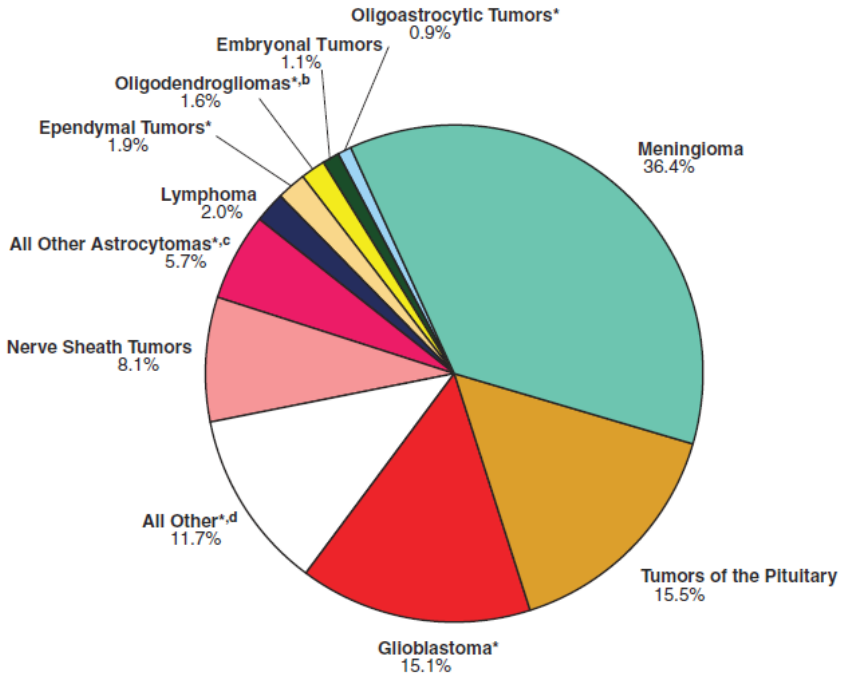
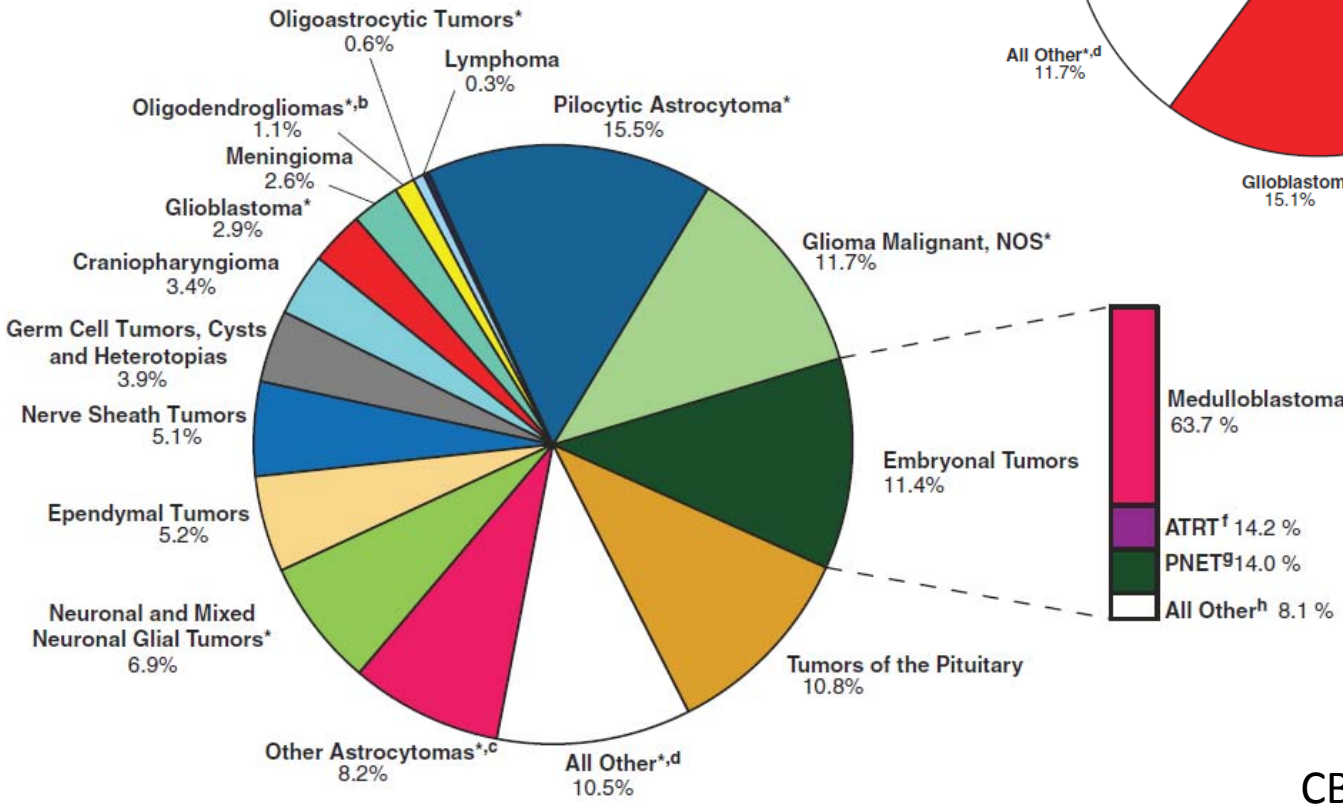
Adult Brain Tumors

LGG are proportionately more common in children



Pediatric Brain Tumors

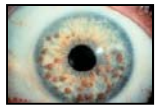


CBTRUS Neuro-Oncol 2015

Predisposing Syndromes

- Tuberous Sclerosis, von Hippel Lindau, Gorlin
- Neurofibromatosis “NF”
  - A group of syndromes with neuro-cutaneous manifestations
  - Autosomal Dominant
  - Multiple Café au Lait spots
  - Neurofibromas
  - Brain Tumors

Neurofibromatosis

- ***Type 1*** (von Recklinghausen)
  - 1:3000
  - Optic pathway gliomas
  - Lisch Nodules 
  - Axillary/inguinal freckles
  - Mental delay
  - Sphenoid dysplasia
  - Pheochromocytoma
  - Renal artery stenosis

- ***Type 2***
  - 1:50,000
  - Bilateral acoustic neuroma
  - Meningioma
  - Spinal cord ependymoma
  - Childhood cataracts

For NF-1 patients, keep in mind:

- Tumors tend to be low grade and slowly growing
- RT complication risk is higher
  - 3x risk of vasculopathy and occlusion of the Circle of Willis: *"moyamoya" syndrome*
  - 3x increase risk of radiation-induced second malignancies

Surgery

Children's Cancer Group 9891
Pediatric Oncology Group 9130

- Largest Prospective study of surgery for all low grade gliomas in children
- n=660
- Post op RT allowed (if $\geq$ 1.5 cc residual)
  - (RT not detailed)

CCG 9891 / POG 9130

PFS based on surgery extent:

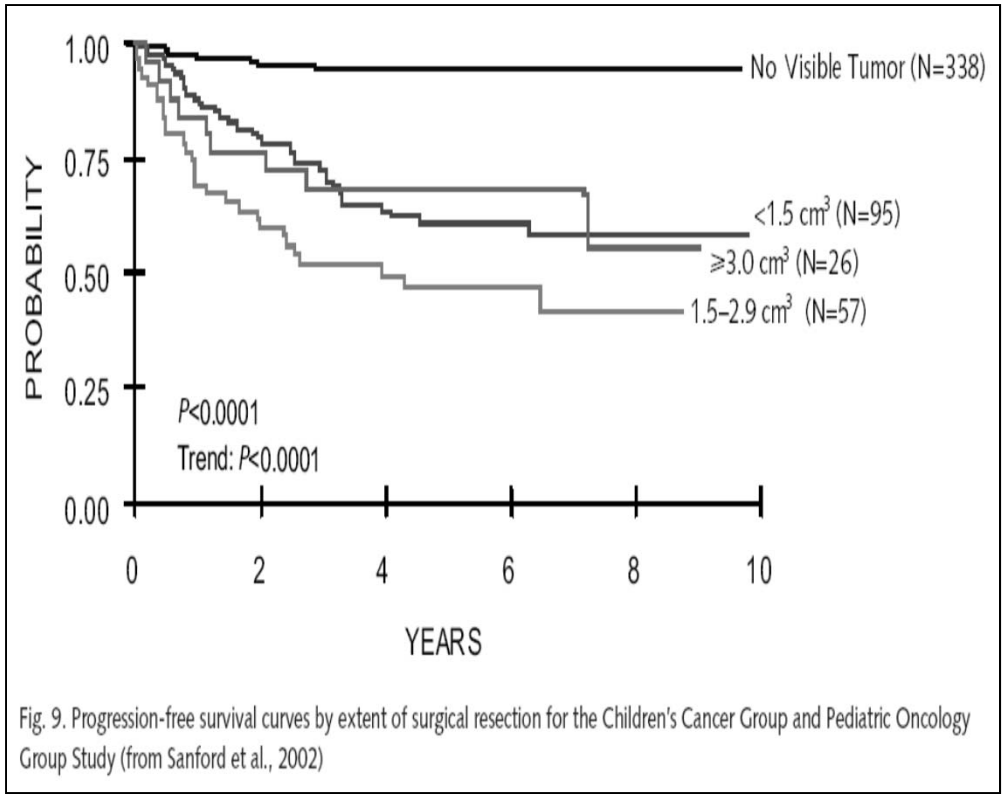


Fig. 9. Progression-free survival curves by extent of surgical resection for the Children's Cancer Group and Pediatric Oncology Group Study (from Sanford et al., 2002)

Shaw Neuro-Oncol 5:153, 2003

Sanford et al (Abstr), 2002

Surgery

- Gross Total Resection is curative usually
- Subtotal resection has an increased risk of progression, though substantial numbers of patients will be progression-free.

Chemotherapy

Treatment of Chiasmatic/Hypothalamic Gliomas of Childhood with Chemotherapy: An Update

Roger J. Packer, MD,*†‡ Leslie N. Sutton, MD,*§ Larissa T. Bilaniuk, MD,*‖ Jerilynn Radcliffe, PhD,¶
Jeffrey G. Rosenstock, MD,*†† Kathy R. Siegel, PA,* Greta R. Bunin, MD,* Peter J. Savino, MD,*†**
Derek A. Bruce, MD,*‡‡ and Luis Schut, MD*§

- 24 Children – median age 1.6 yrs
- 3 patients with Neurofibromatosis
- *Progressive* Hypothalamic or Optic pathway tumors
- Biopsy not mandatory
- Accrual 1977 – 1987
- ***Actinomycin D and vincristine x 6 cycles***

Packer et al Ann Neurology 23:79, 1988

- Median f/u 4.3 years
- Of those getting RT salvage, median age was 4.5 years
- Neuropsych testing in 15 patients:

  1 pt severely impaired

  14 had mean IQ of 103
- Chemo Toxicity: 2 pts required admission, some mild paresthesias

Approx 50% PFS at 5 years

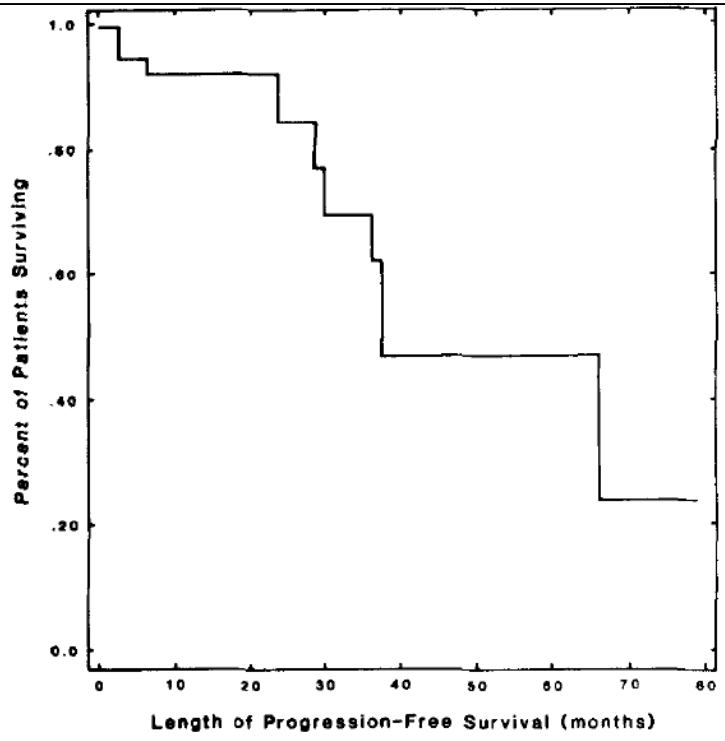


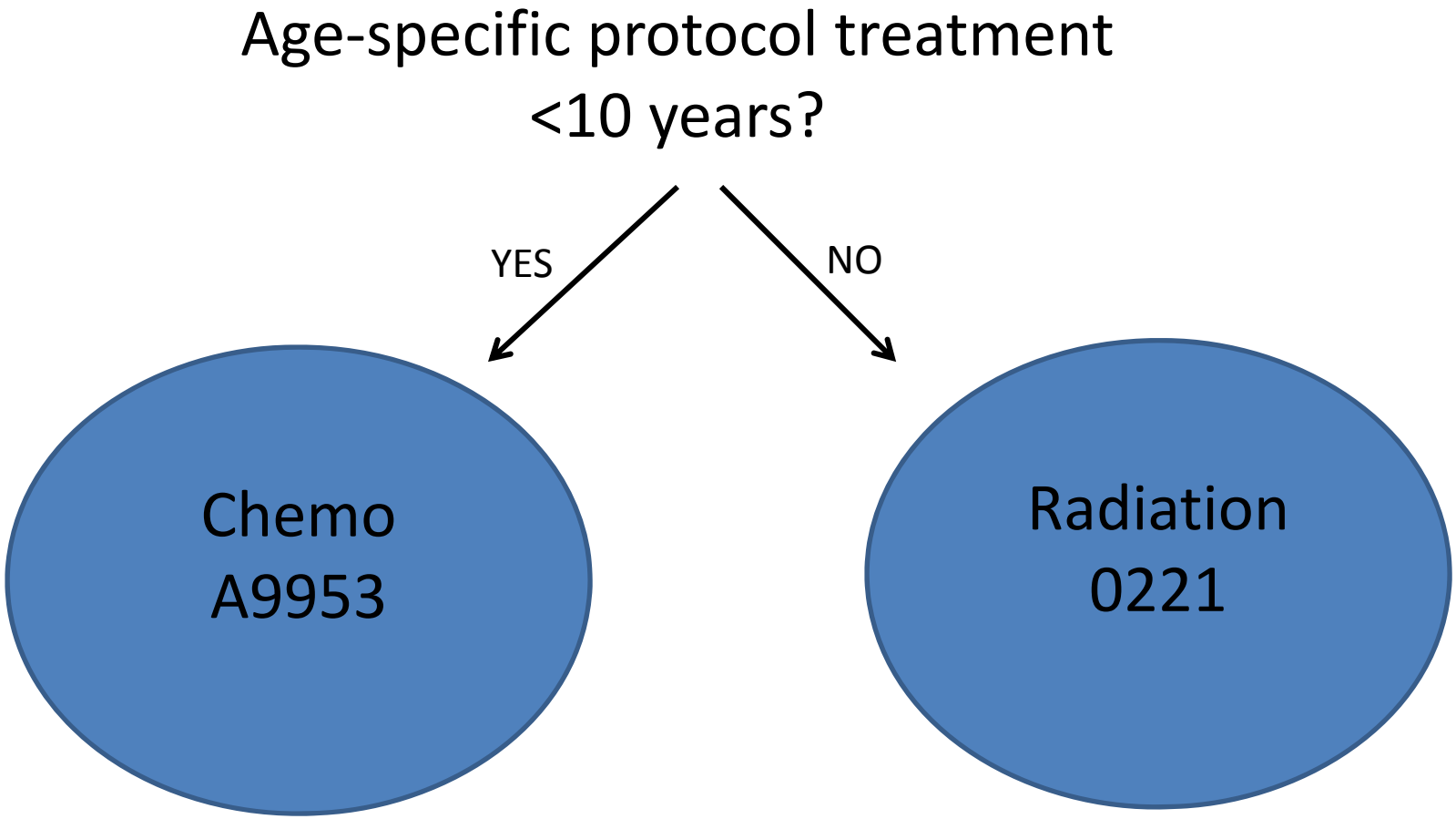
Fig 2. Progression-free survival curve for patients in this study (N = 24).

Chemotherapy has reasonable activity

Potential to delay the RT with chemotherapy

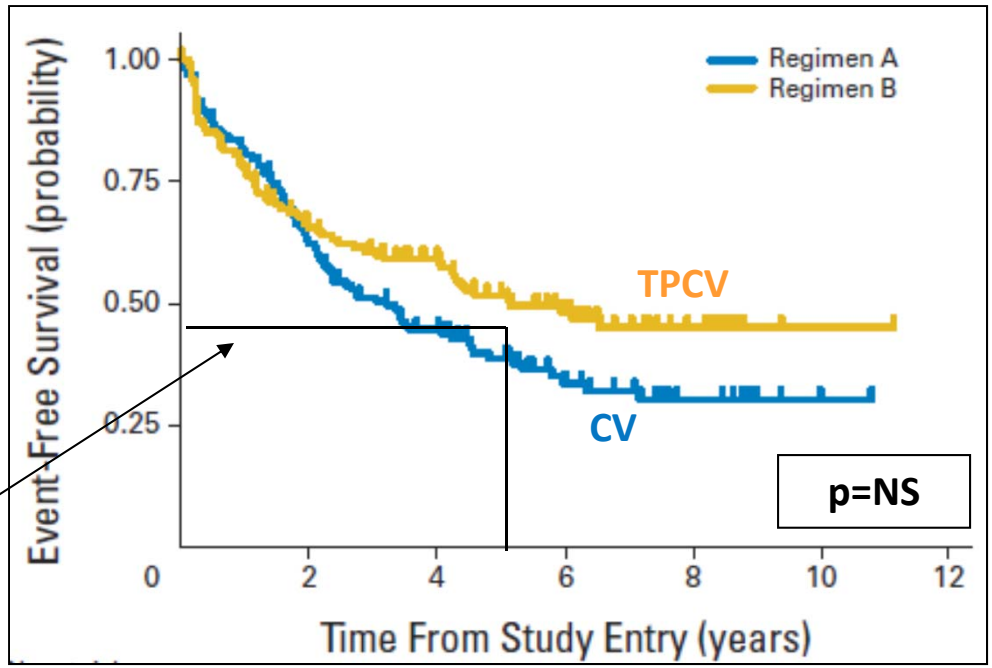
Packer et al Ann Neurology 23:79, 1988

Children's Oncology Group Approach



COG A9952

- Initial Chemotherapy for patients < 10 yr old
- CV vs TPCV
- All low grade gliomas
- n=274
- No NF patients
- Median f/u 5 yrs
- ***PFS 39 vs 52%***



TPCV = Thioguanine, Procarbazine, CCNU, Vincristine TPCV

*Patients with neurofibromatosis (NF) will be non-randomly assigned to Regimen A

CBDCA = Carboplatin
VCR = Vincristine CV

Ater JCO 30:2641, 2012

COG ACNS 0223

- A pilot study to test feasibility of
  - Vincristine, Carboplatin, AND Temozolomide (alternating)
- 60 children $\leq$ 10 yrs (median 4.6 yrs) with unresectable and symptomatic or progressive LGG --grade 1(majority) and 2
- NF1 patients excluded

Chintagumpala et al Neuro-Oncology 17:1132, 2015

COG ACNS 0223

- Grade 3 or higher neutropenia in 50%
- Met feasibility endpoints
- 5 yr EFS 46%

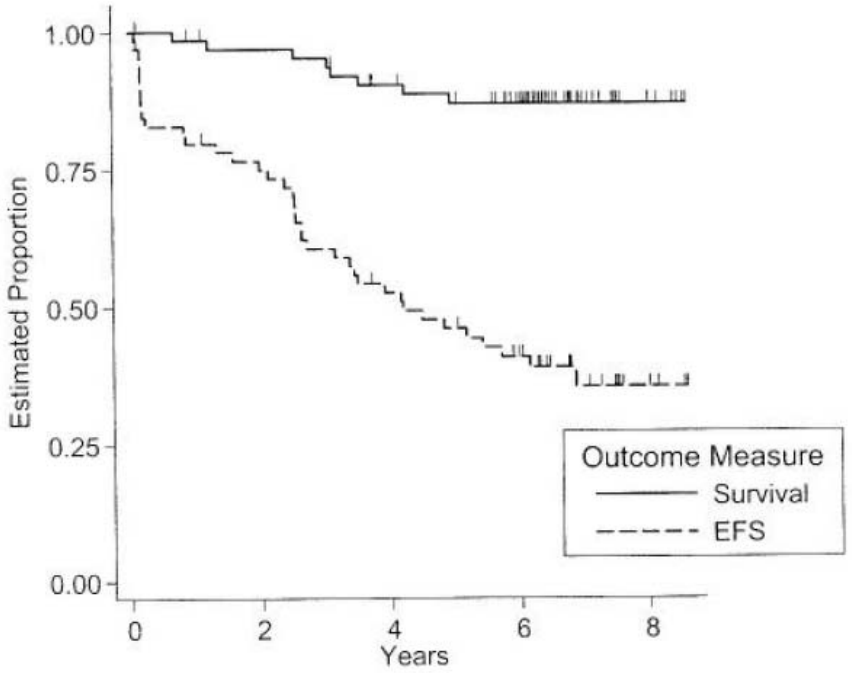


Fig. 1. Event-free and overall survival of all eligible patients on the study.

Radiation Therapy

Washington University
St. Louis Children's Hospital

- 35 children with unresectable pilocytic astrocytoma (Grade 1)
- 1982-2009
- RT alone
- Median dose 54 Gy
- Typically 2 cm margin
- Median f/u 5 years
- No NF patients

Table 1. Patient characteristics

	n
Total patients	35
Gender	
Male	19
Female	16
Race	
Caucasian	31
African-American	4
Central nervous system site	
Supratentorial	20
Optic pathway	3
Infratentorial	11
Spinal cord	1
Surgery extent	
Biopsy only	12
Subtotal	23
Radiotherapy timing	
Immediate	16
Delayed (after progression after observation, or chemotherapy)	19
Radiotherapy modality	
External beam only	29
Radiosurgery only	5
External beam and radiosurgery	1

Mansur *et al,* IJROBP, 79:829, 2011

Washington University
St. Louis Children's Hospital

- Overall survival 100%
- **5 year PFS 68%**
- 8/9 patients who progressed did within the irradiated volume

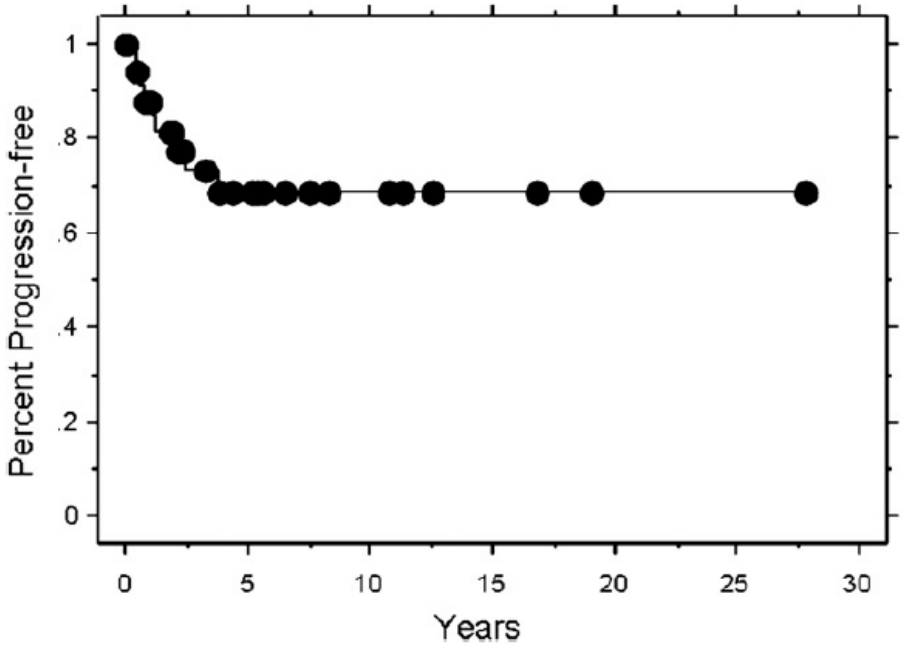


Fig. 1. Progression-free survival for all patients.

Mansur *et al* IJROBP 79:829, 2011

Washington University
St. Louis Children's Hospital

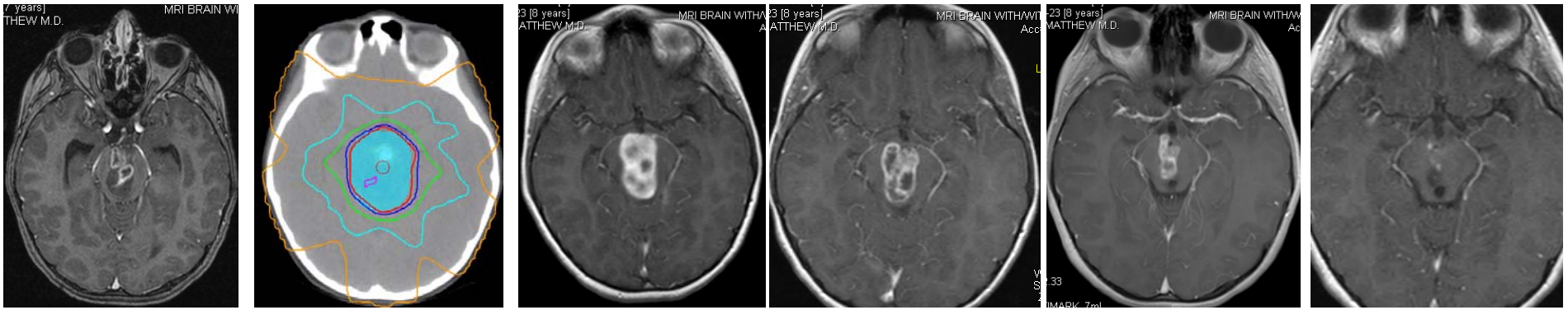
- Pattern of failure

Table 3. Patients with progressive disease

Patient	Gender	Age at RT (y)	Tumor location	Surgery extent	RT timing	RT dose (Gy)	Failure-free interval (y)	Pattern of failure	Comments
14	Female	5	Supra	Sub	Im	54	2.5	Local	Symptomatic increase in size, rebiopsy (+)
16	Female	15	Supra	Sub	Del	54	0.7	Local	Symptomatic increase in size, repeat surgery (+)
18	Male	20	Supra	Sub	Im	15 (RS)	1.3	Local	Symptomatic increase in size, repeat surgery (+)
20	Female	18	Spine	Biopsy	Im	50.4	0.6	Local	Symptomatic increase in size, repeat surgery (+)
24	Male	12	Supra	Biopsy	Im	54	0.5	Local	Symptomatic increase in size, repeat surgery (+)
25	Female	9	Supra	Sub	Del	54	3.8	Local	Symptomatic increase in size, repeat surgery (+)
27	Male	7	Optic	Sub	Del	54	2.0	Distant	Disseminated disease after conformal RT
29	Female	15	Optic	Biopsy	Del	52.2	1.1	Vision	Progressive vision loss despite RT
39	Male	8	Supra	Sub	Del	52.2	0.4	Local	Symptomatic increase in size, repeat surgery (+)

Abbreviations: supra = supratentorial; sub = subtotal resection; im = immediate; del = delayed; RS = radiosurgery; RT = radiotherapy.

Pseudoprogression occurs in a minority of patients



Pre RT

1 month

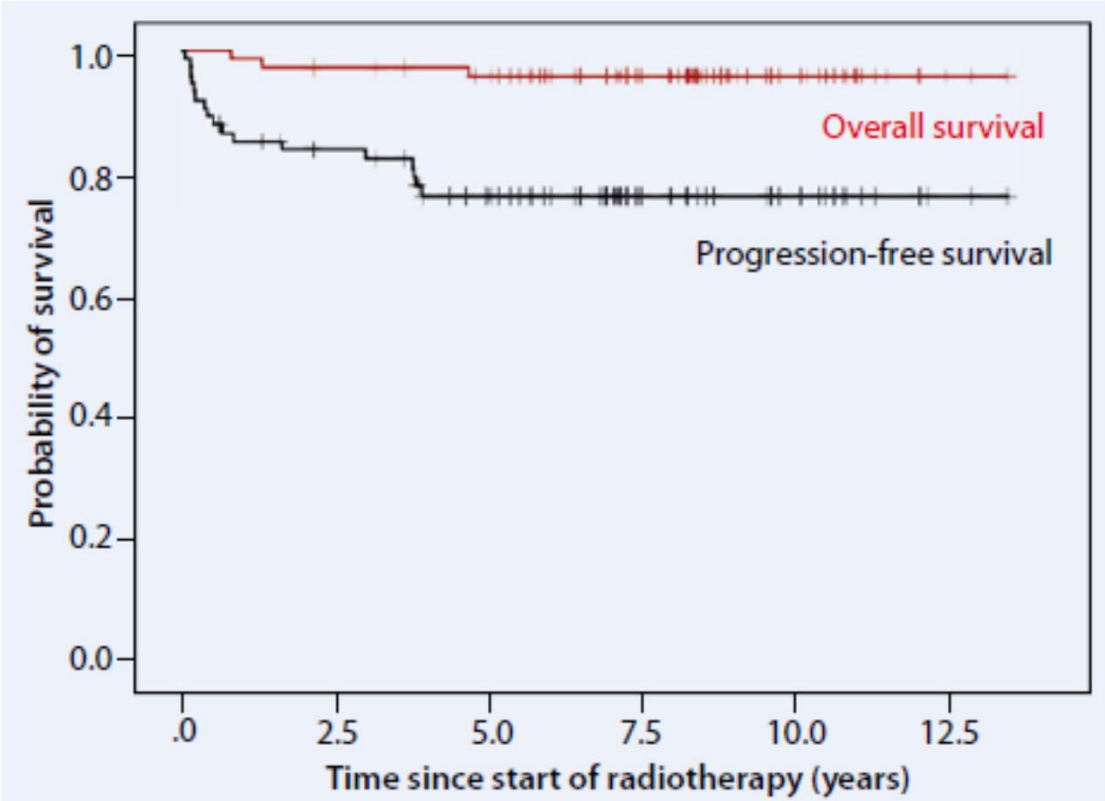
4 month

7 month

10 month

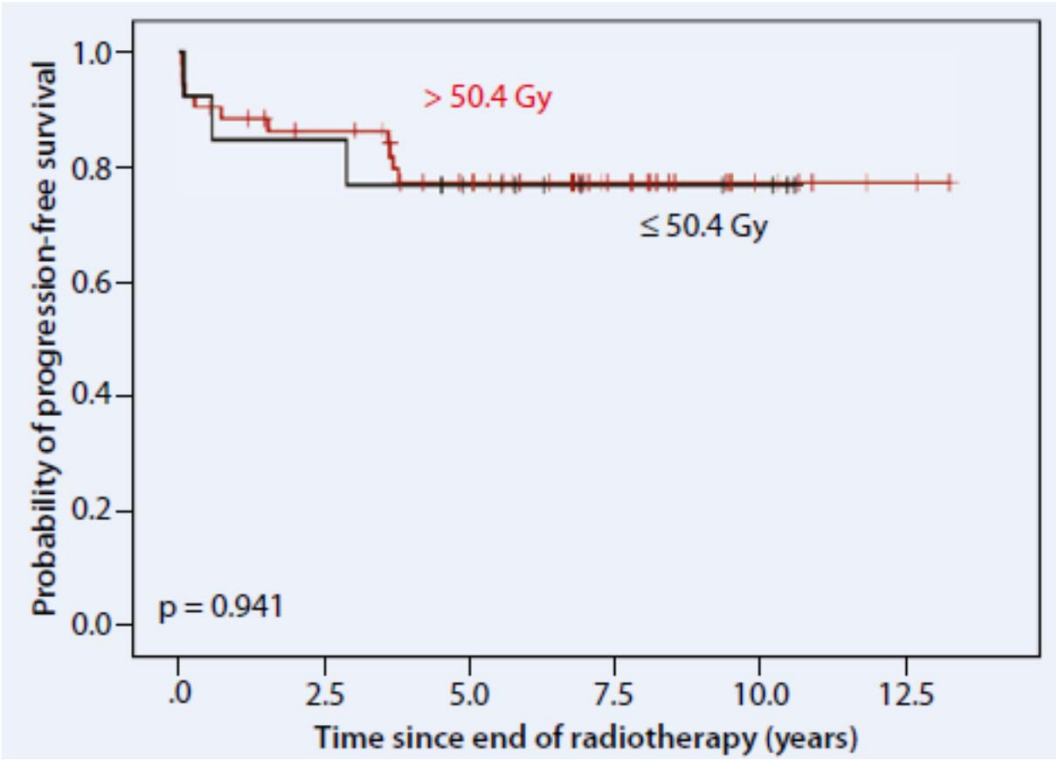
German (GPOH)

- German (GPOH) HIT-LGG 1996)
- 117 children
- 10 had NF
- Median age 9 yrs
- Pilocytic astrocytoma
- RT as first or 2nd line treatment
- Median dose 54Gy
- 1-2 cm margins
- Median f/u 8 yrs
- ***5 yr PFS 77%***



Muller *et al*, Strahlenther Onkol 189:647, 2013

Radiation Therapy Dose



Muller *et al*, Strahlenther Onkol 189:647, 2013

St. Jude Children's – 1 cm margin to CTV

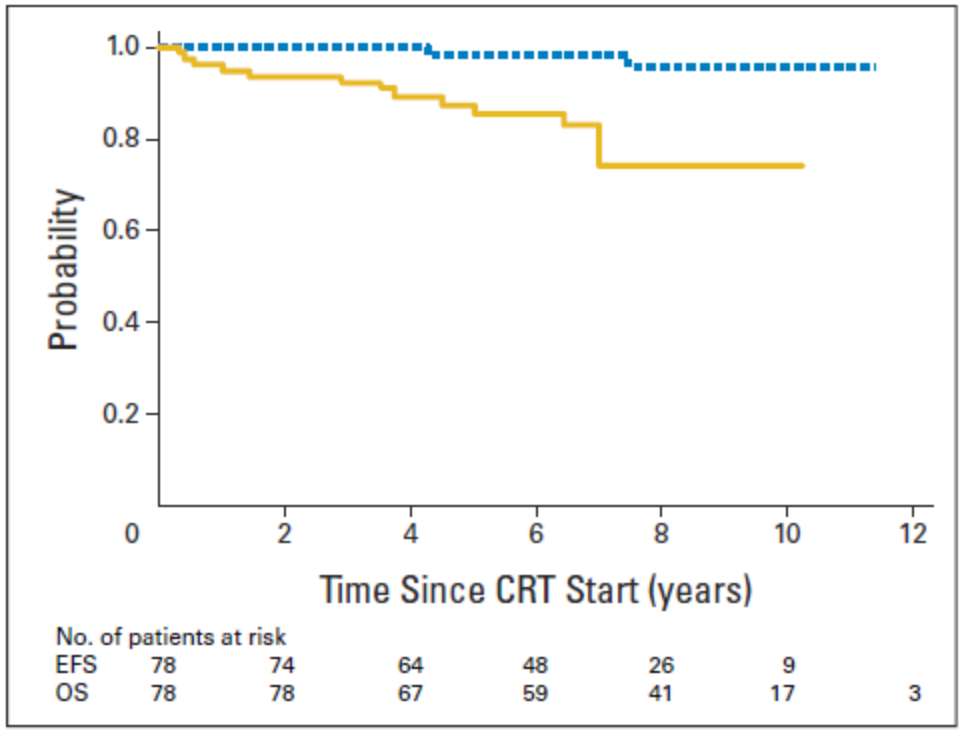


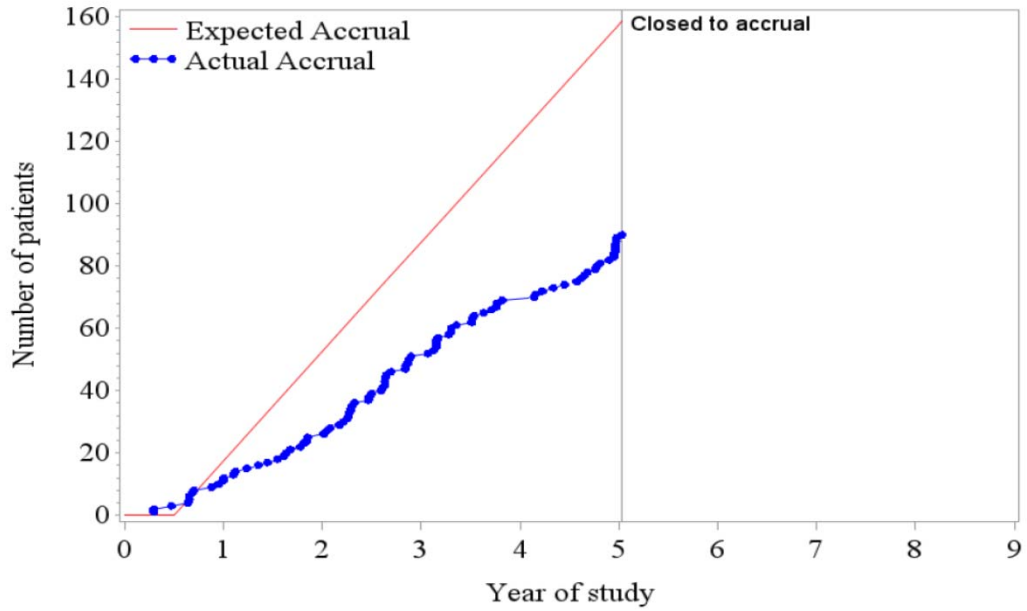
Fig 1. Event-free survival (EFS; gold line) and overall survival (OS; blue line) for pediatric patients with low-grade glioma. Numbers indicate patients at risk. CRT, conformal radiation therapy.

Merchant et al JCO 27:3589, 2009

COG ACNS 0221

- Conformal RT for all unresectable LGG
- Children 10 yrs and over or younger if progressive after chemotherapy
- 3DCRT, IMRT, protons
- MRI (3 mm) co-registration required
- Pre-treatment central review
- CTV = GTV + 5 mm
- 54 Gy

COG ACNS 0221



- Opened in 2005
- Study amended to decrease target accrual to 75
- Closed to accrual 2010……

Chemo-RT?

Children's Cancer Group - 945

- 70 patients with LGG:
  - 44 Grade II
  - 19 pilocytic,
  - 2 ganglioglioma
  - 7 unspecified low grade
- Originally diagnosed as high grade

Median f/u 10 years

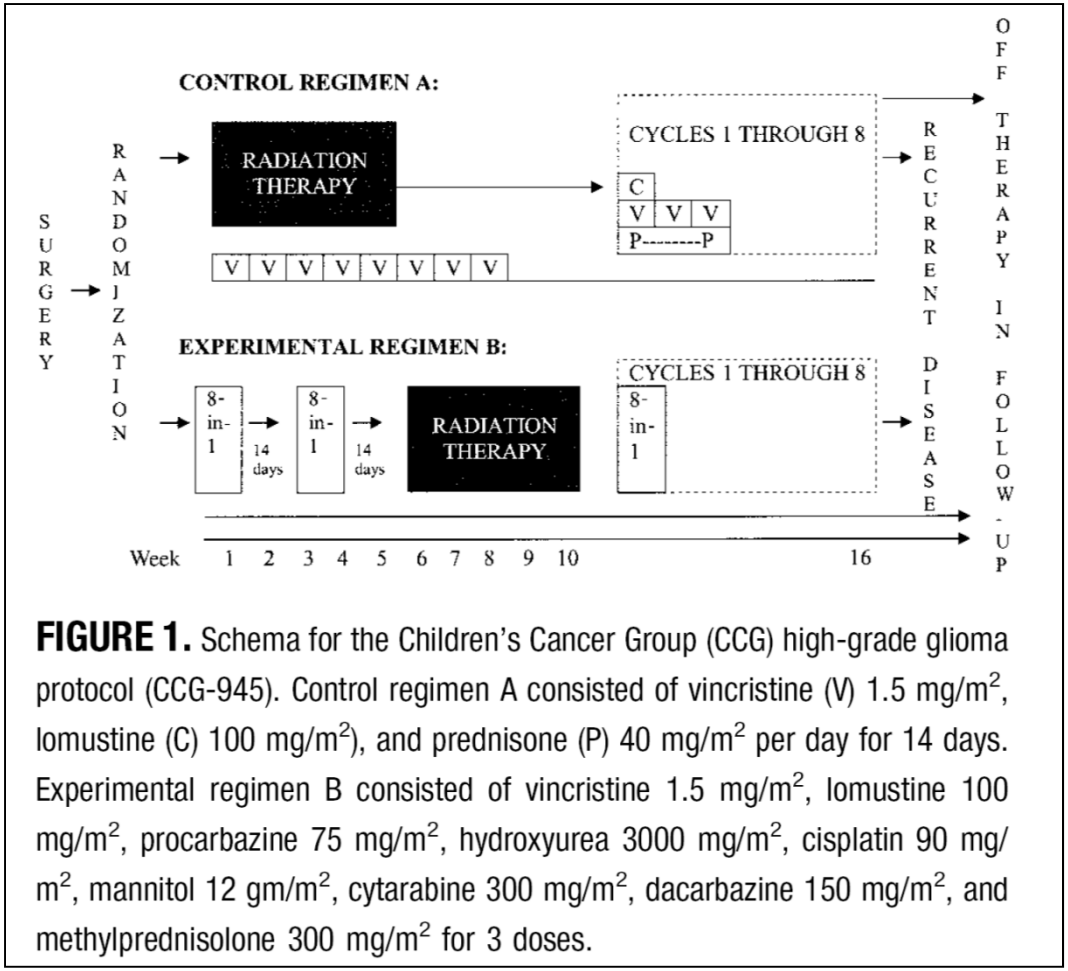
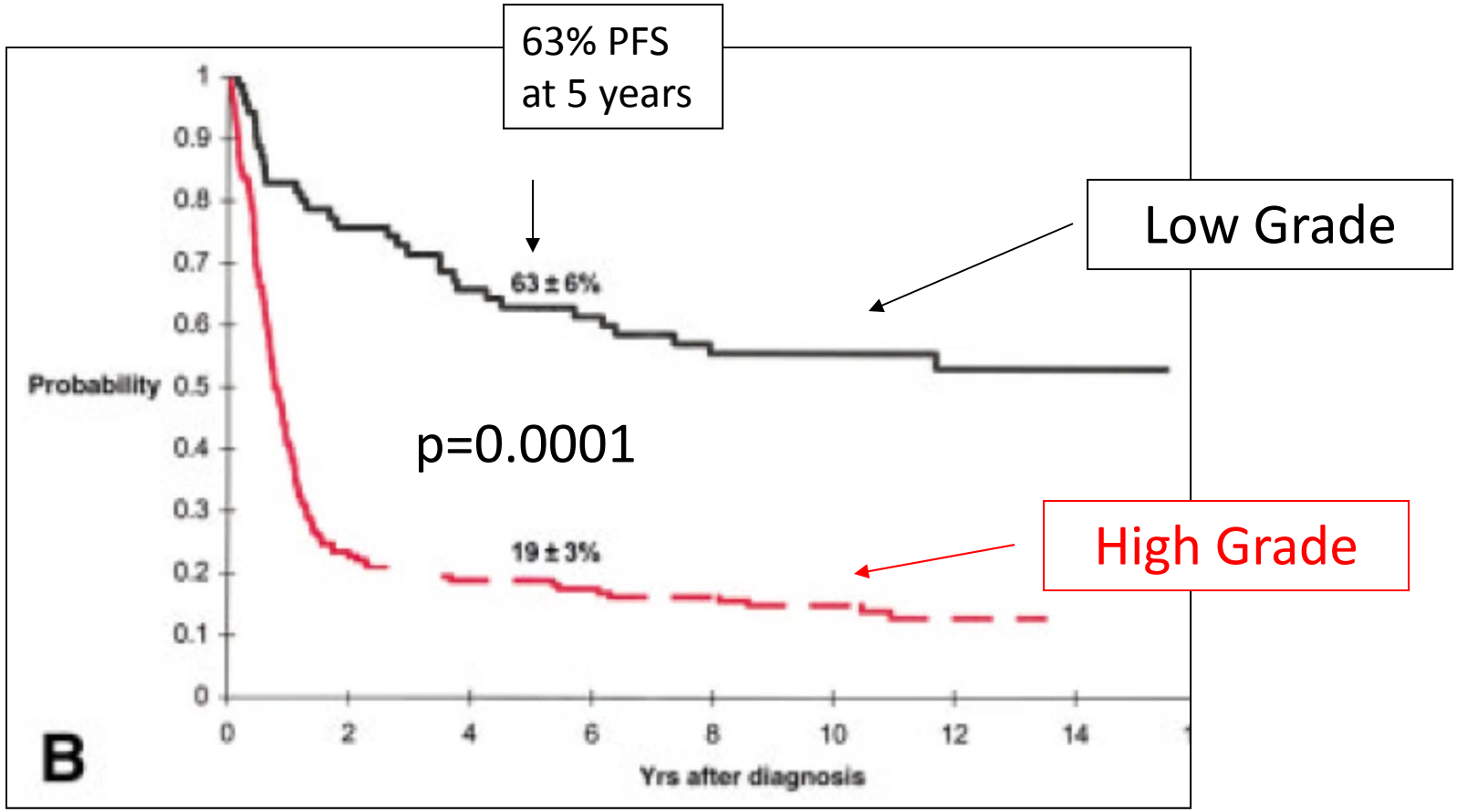


FIGURE 1. Schema for the Children's Cancer Group (CCG) high-grade glioma protocol (CCG-945). Control regimen A consisted of vincristine (V) 1.5 mg/m^2, lomustine (C) 100 mg/m^2), and prednisone (P) 40 mg/m^2 per day for 14 days. Experimental regimen B consisted of vincristine 1.5 mg/m^2, lomustine 100 mg/m^2, procarbazine 75 mg/m^2, hydroxyurea 3000 mg/m^2, cisplatin 90 mg/m^2, mannitol 12 gm/m^2, cytarabine 300 mg/m^2, dacarbazine 150 mg/m^2, and methylprednisolone 300 mg/m^2 for 3 doses.

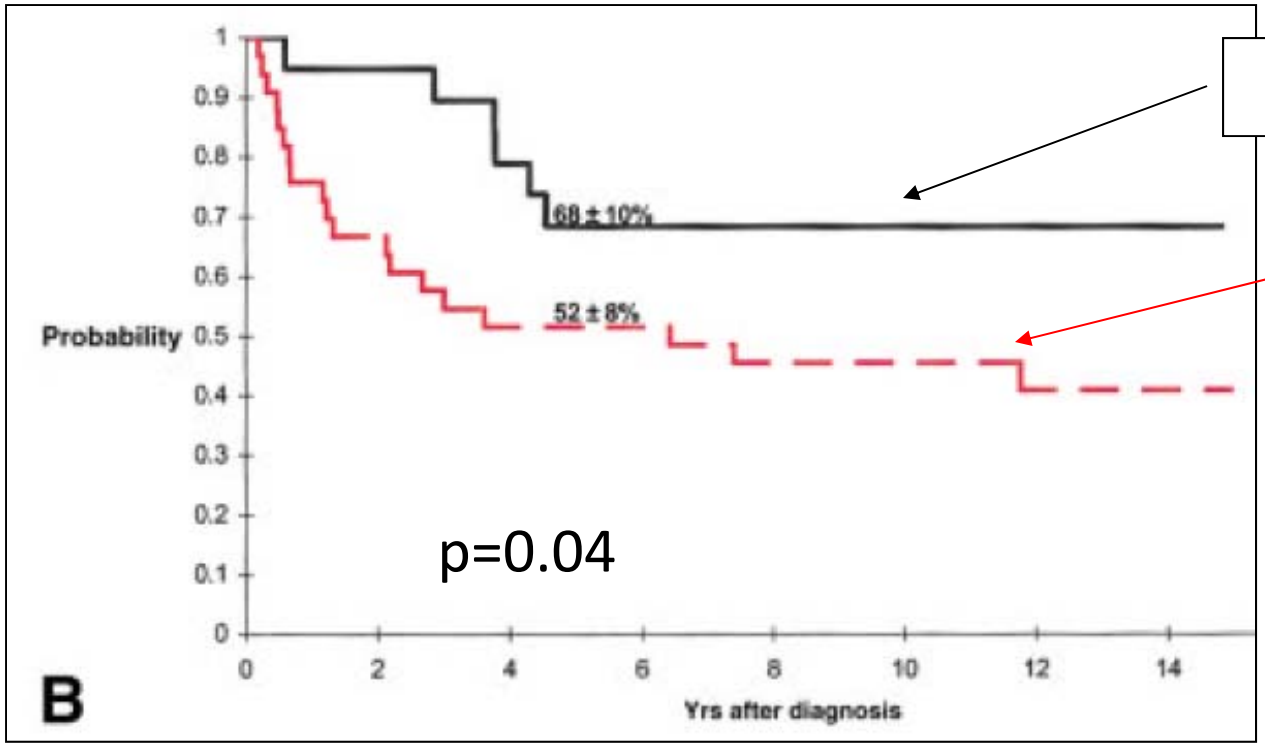
Fouladi Cancer 98:1243, 2003

CCG – 945 progression-free surv



Fouladi Cancer 98:1243, 2003

CCG – 945 progression-free surv



Pilocytics

Fibrillary

Fouladi Cancer 98:1243, 2003

Management Conclusions

- Gross Total Resection is usually curative
- Subtotal resection has an increased risk of progression, though substantial numbers of patients will be progression-free.
- Progressive unresectable disease is an indication for additional treatments
- PFS for chemotherapy is 40-50%, benefit of adding Temodar not clear
- PFS for RT is 70-80%, but this is preferred modality either in older children or those with progression after initial chemotherapy.
- CTV = 1.0 cm expansion (pending 0221 results)
- Pseudoprogression can make interpreting post RT scans difficult
- Combined modality does not appear to improve outcome over RT alone but no randomized data. How to reconcile with recent RTOG 9802 data with PCV is not clear.