Childhood Low Grade Glioma

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Honoured to be here!!

In 150 BC Attalos King Attalos II king of Pergamom, founded the city of **Attalia** …to base his powerful naval fleet, and the city grew and prospered in the Ancient Roman and Byzantin… The city, along with the whole region, was conquered by the Seliuk Turks in the early 13th century….

Childhood Low Grade Glioma

The talk, “in brief”

- ✓ Semantic & epidemiologic considerations
- ✓ Etiopatogenesis
- ✓ General clinical and biological considerations
- ✓ The therapeutic problems
- ✓ The therapeutic approach
- ✓ Where to go

Semantic & epidemiologic considerations

Childhood LGG - a hetherogeneous groups of tumours

Classification of primary paediatric CNS tumours

I. NEUROEPITHELIAL TUMORS

A. GLIOMAS

1. Astrocytoma
2. Oligodendroglioma
3. Ependymoma
4. Mixed “pure glioma”
5. Neuronal and mixed glial-neuronal tumours
6. Mixed glial-mesenchymal tumours

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Classification of primary paediatric CNS tumours

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1. Astrocytoma

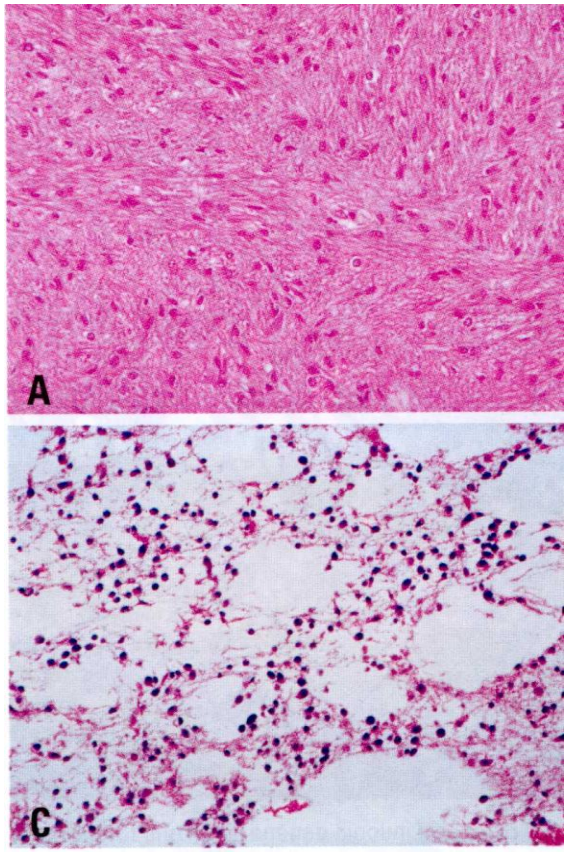
-) diffuse fibrillary astrocytoma

- Astrocytoma (Grade I/II)
- Astrocytoma anaplastico (Grade III)
- Glioblastoma multiforme (Grade IV)
- Protoplasmatic Astrocytoma
- …..

-) Other astrocytic tumours

- pilocytic astrocytoma
- pleomorphic astrocytoma
- Sub-ependymal Giant Cell astrocytoma
- ……

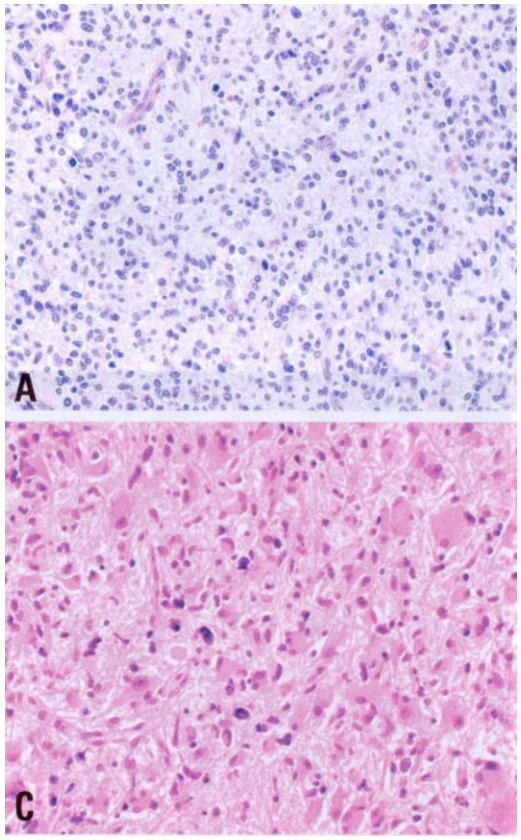
Diffuse astrocytoma, a continuum of lesions



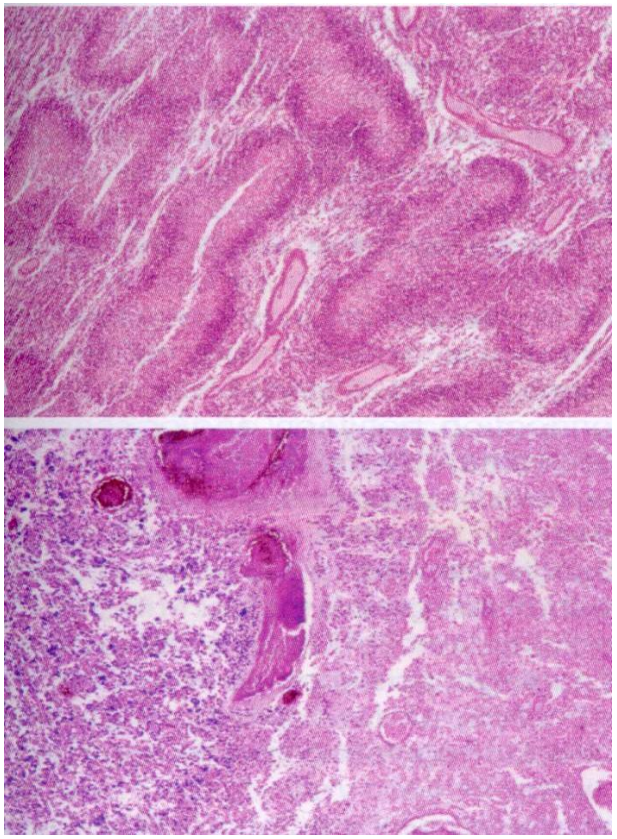
Low grade fibrillary astrocytoma

low cellularity,

no cellular atypia

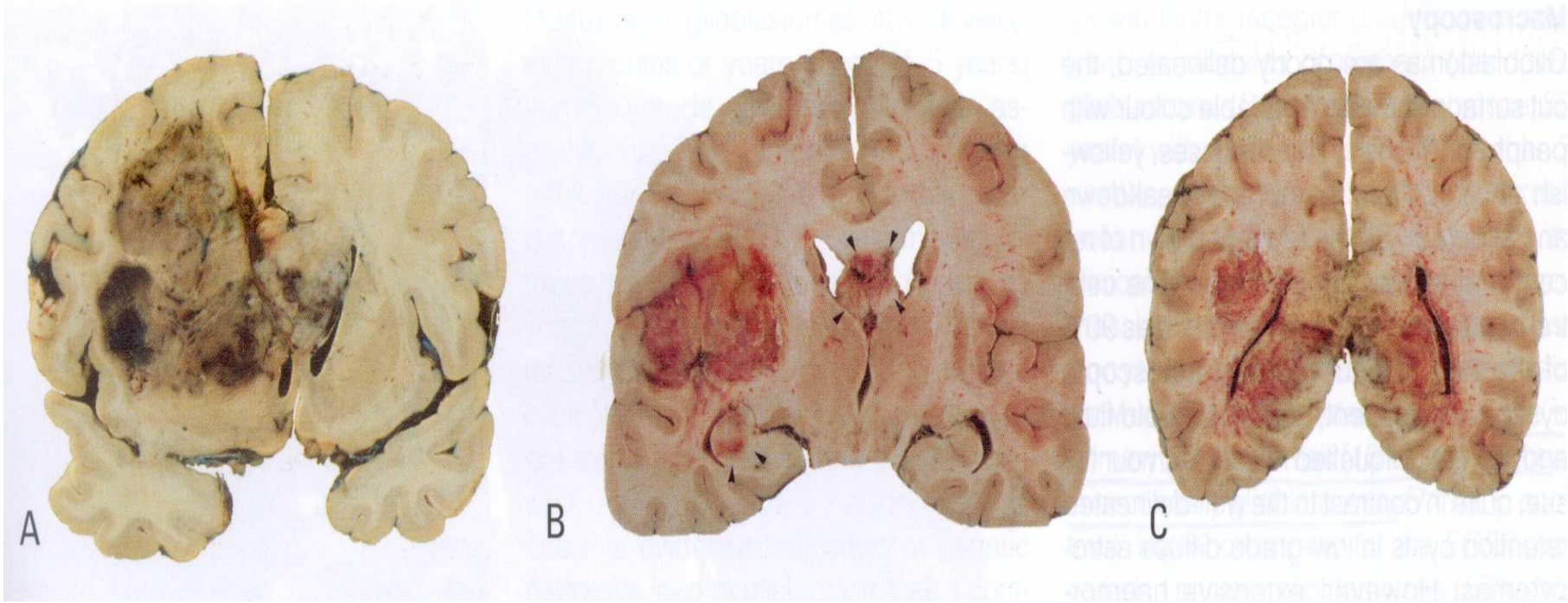


Anaplastic astroctyoma with high cellularity



GBM with pseudopalisading necrosis, marked cellular atypia

Macroscopic features of anaplastic diffuse astrocytoma



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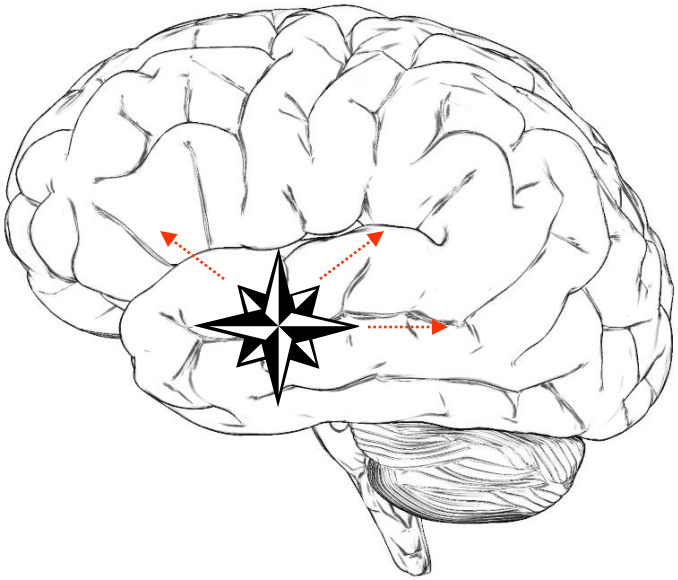
- …..

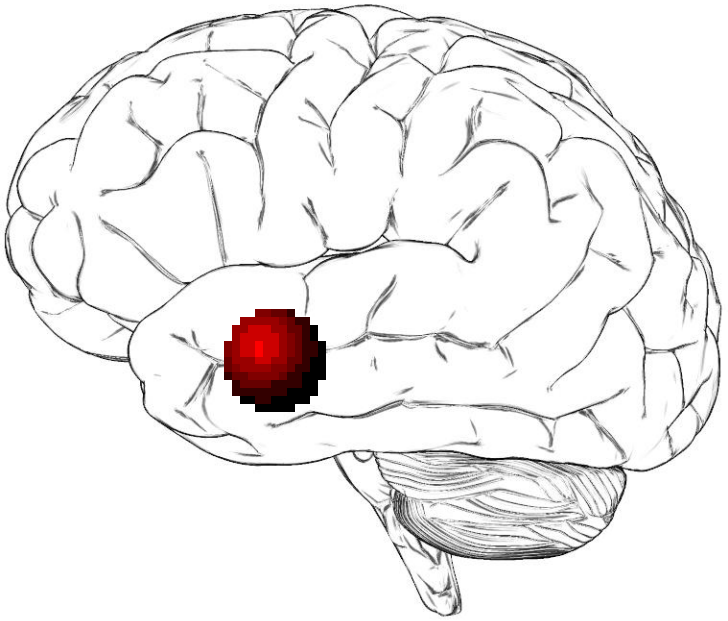
-) Other astrocytic tumours

- **pilocytic astrocytoma**
- pleomorphic astrocytoma
- Sub-ependymal Giant Cell astrocytoma
- ……

Astrocytic tumours – Growth pattern

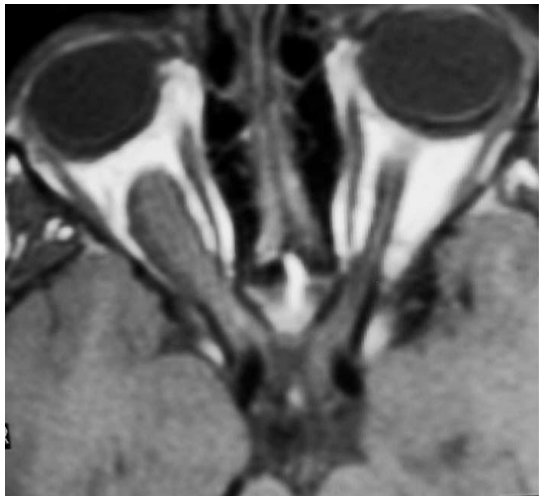


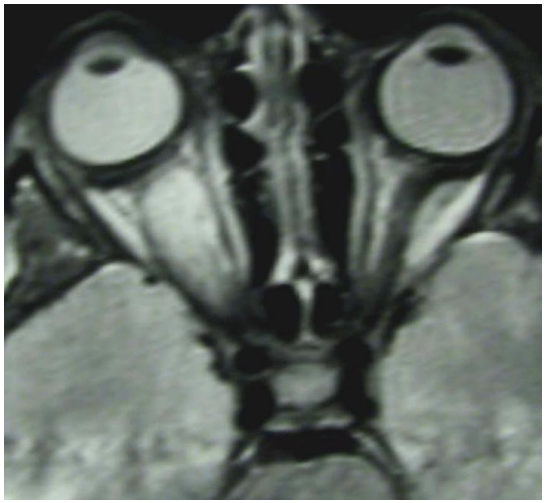
Fibrillary astrocytoma – infiltrative growth pattern

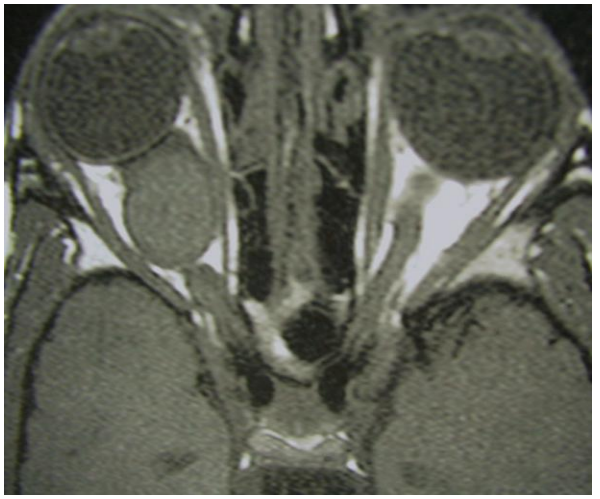


Pilocytic astrocytoma – <u>non</u> infiltrative growth pattern

Pilocytic astrocytoma of the optic pathway

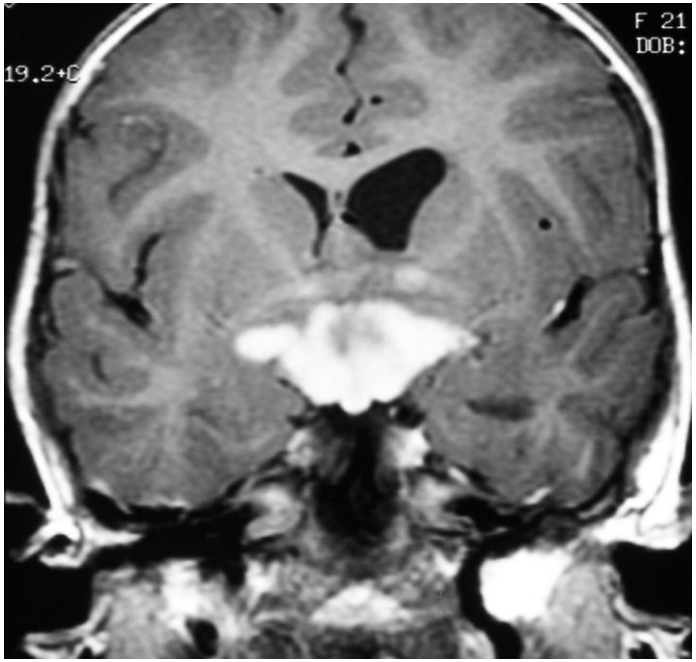


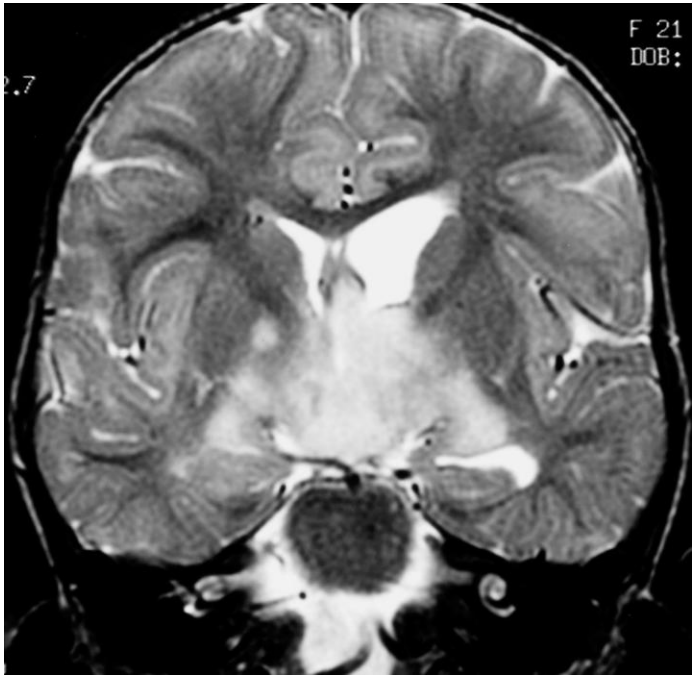




Pure optic nerve glioma: tubular, fusiform excrescent

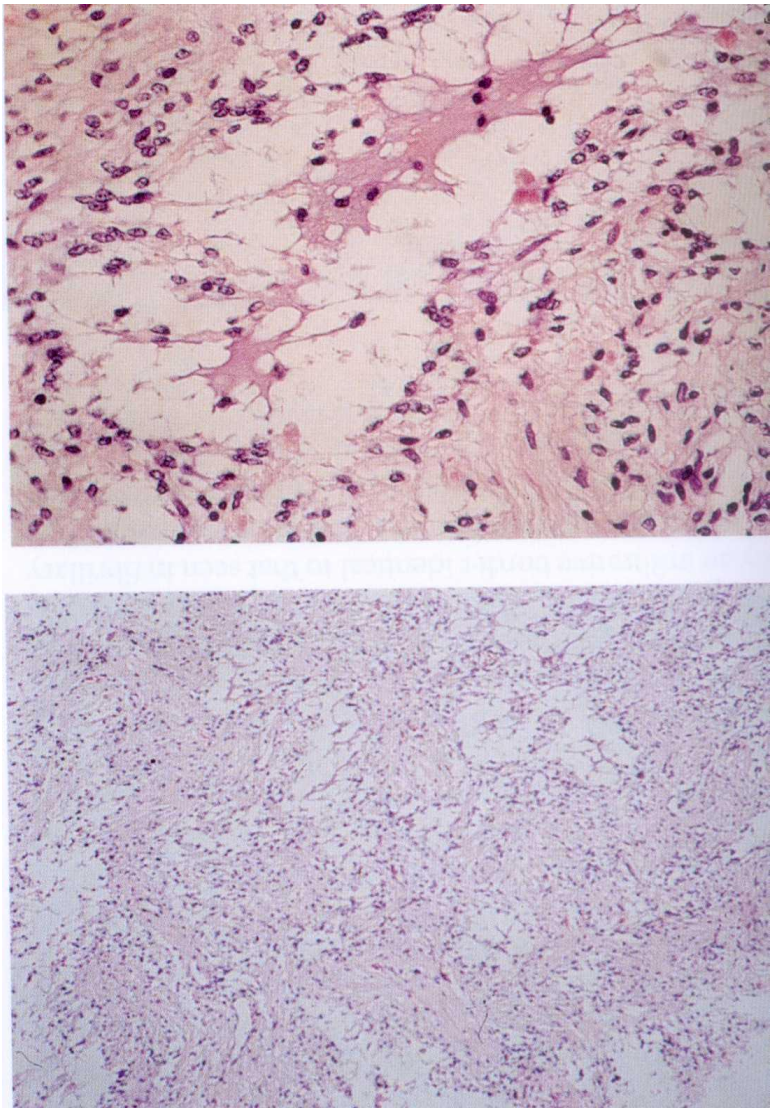
Pilocytic astrocytoma of the optic pathway

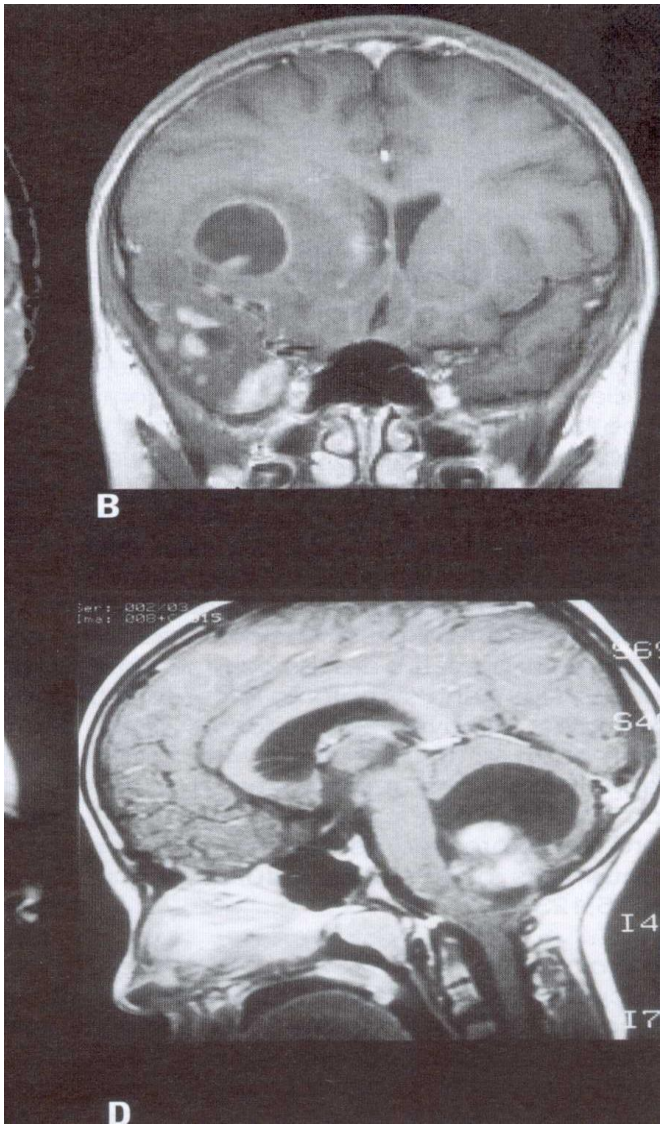




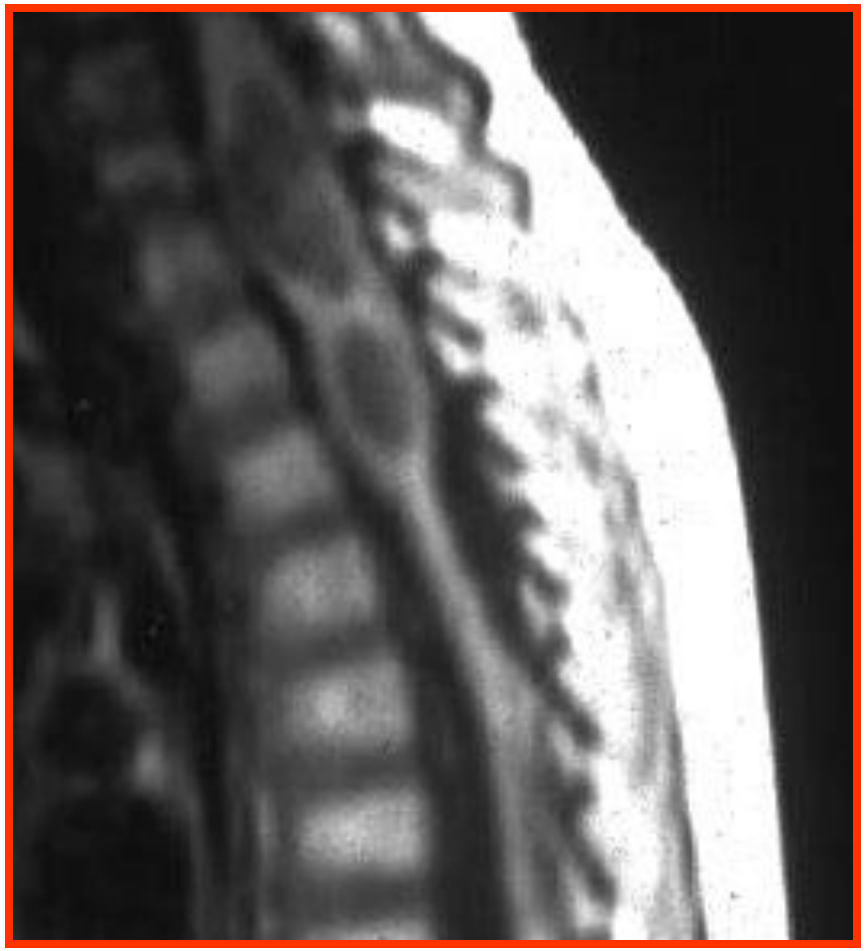
Optic pathway glioma with hypothalamic extension

Micro and macroscopic appearance of pilocytic astrocytoma

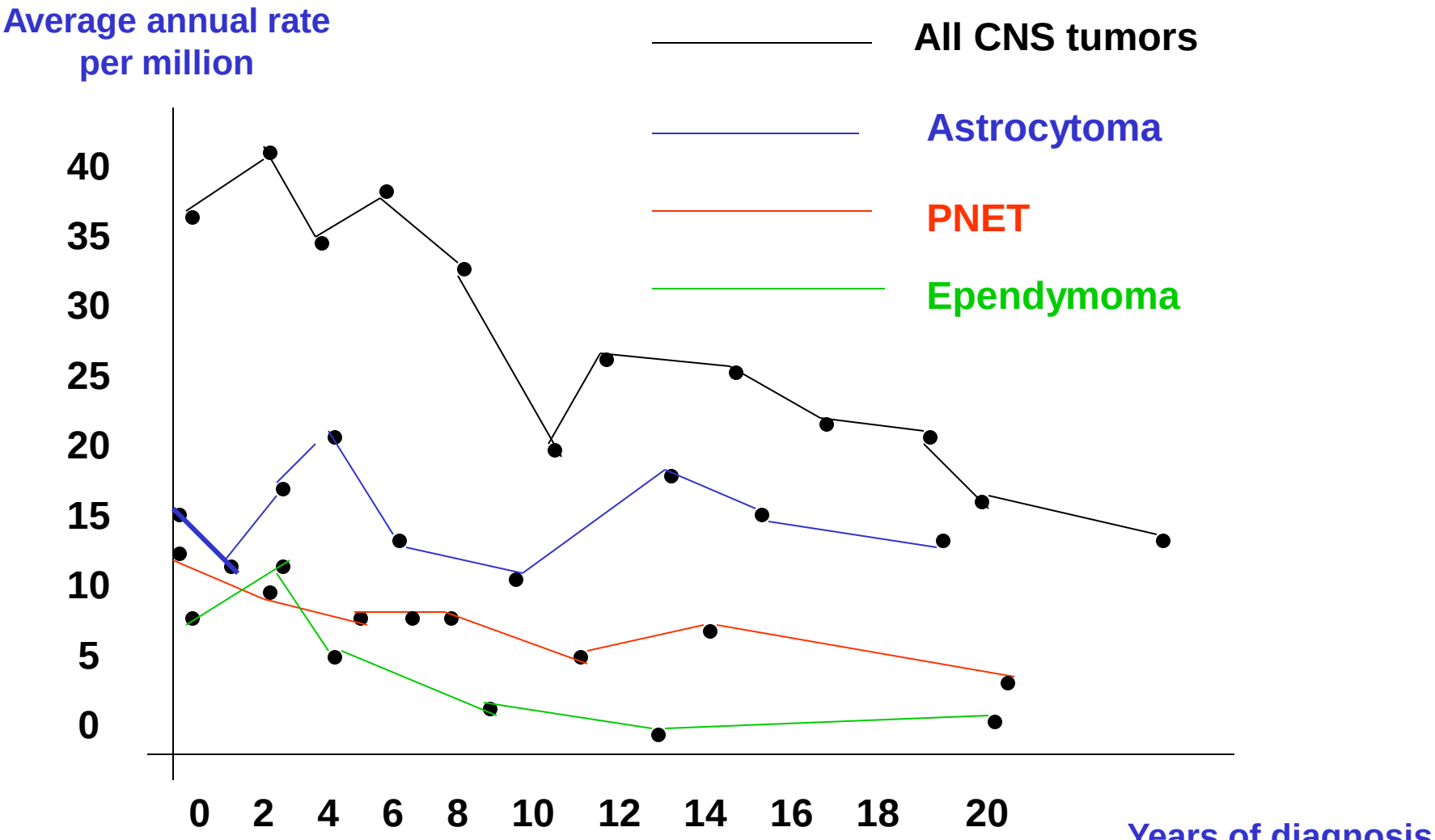




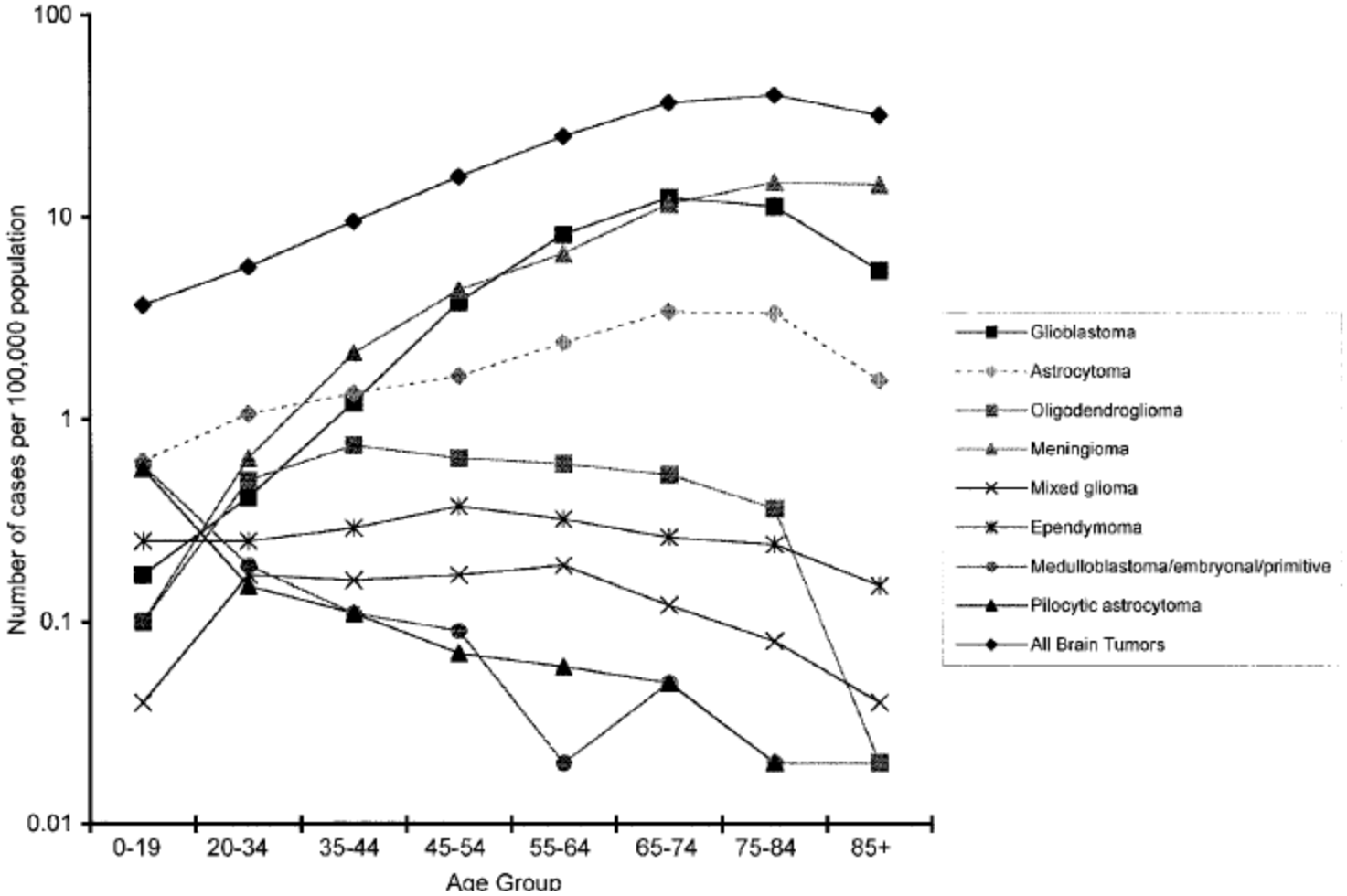
Pilocytic astrocytoma of the spine



SEER - 1975-1995 - Malignant CNS tumours, age specific incidence (all races,both sexes)



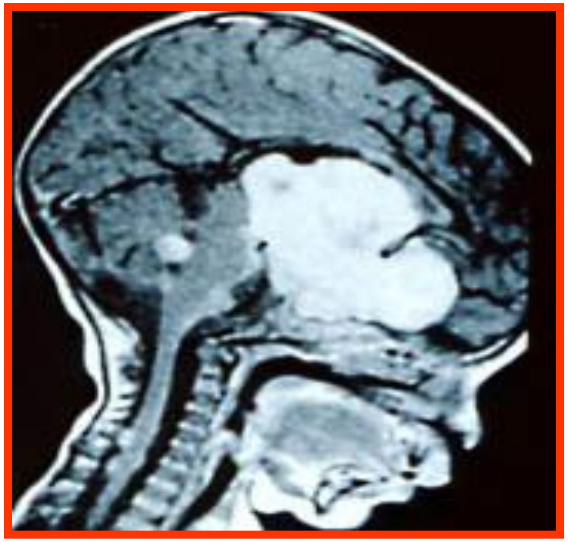
Epidemiology of primary brain tumors: Current concepts and review of the literature[1]

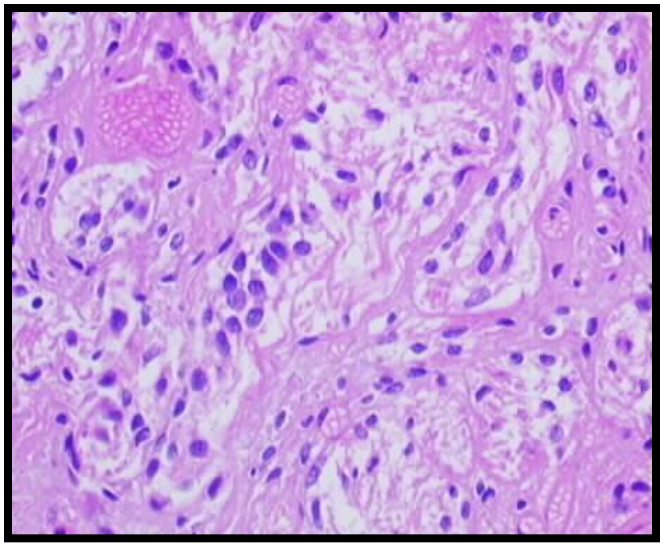


Ethiopathogenesis?

Childhood LGG - Where do they come from?

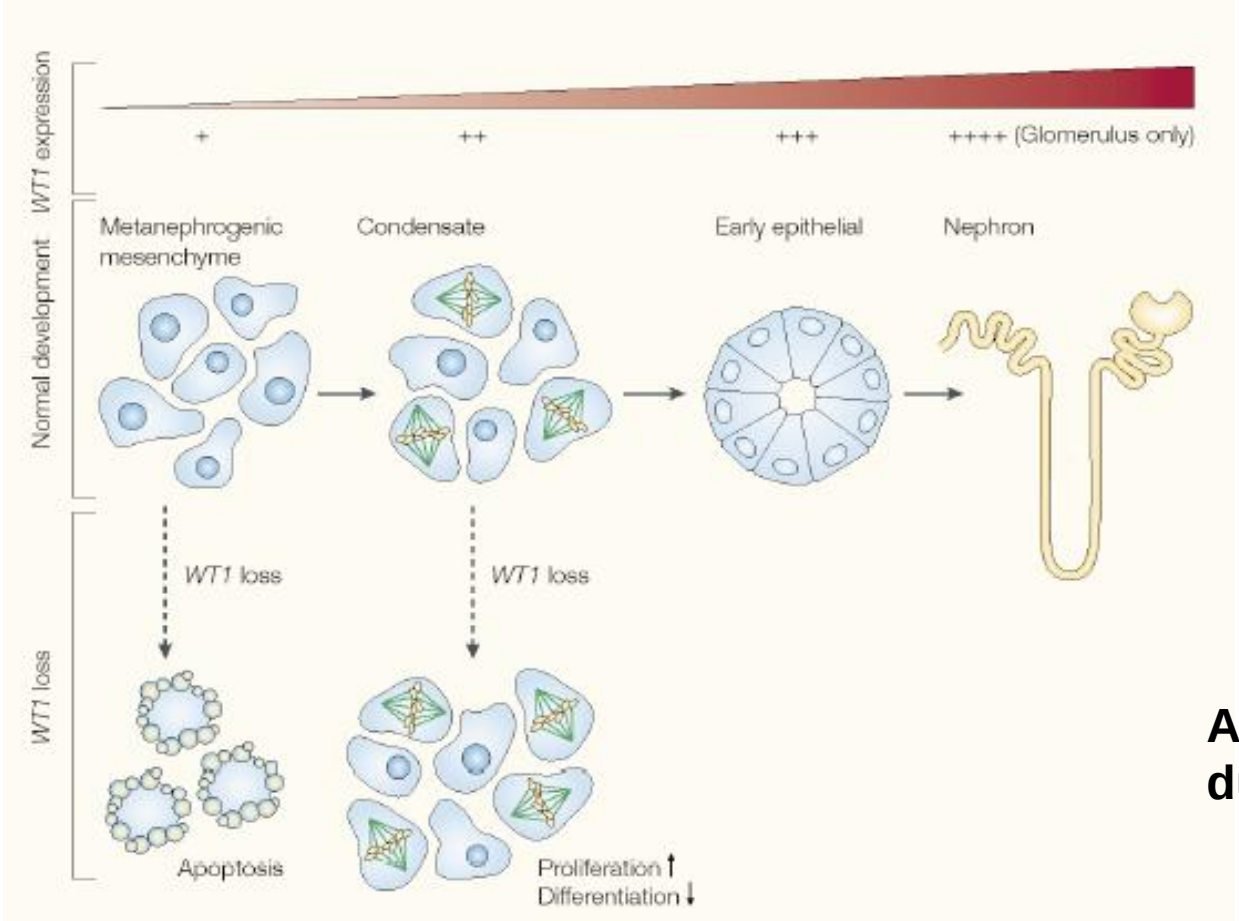
PA; developmental disorder?





…from defects in the mechanism that control normal development, arresting the normal pathway of maturation….and favouring proliferation, plasticity and invasiveness…

The WT1 gene in metanephrons and Wilms tumour development

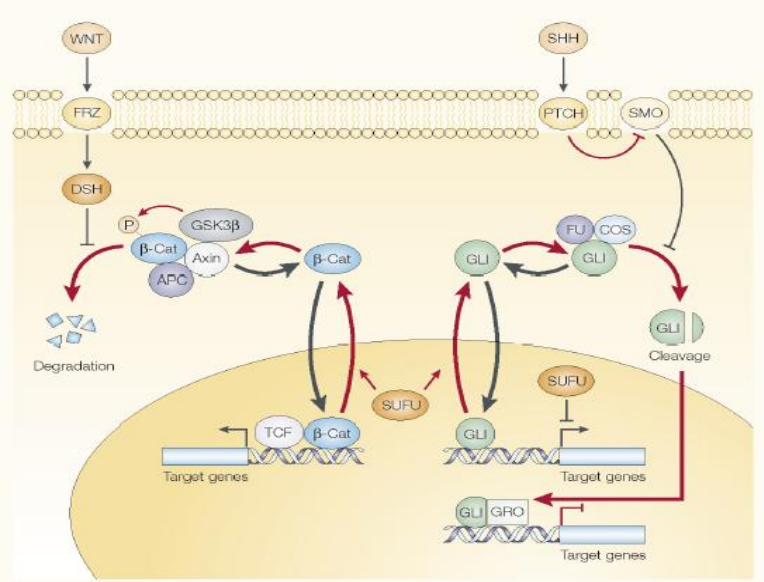


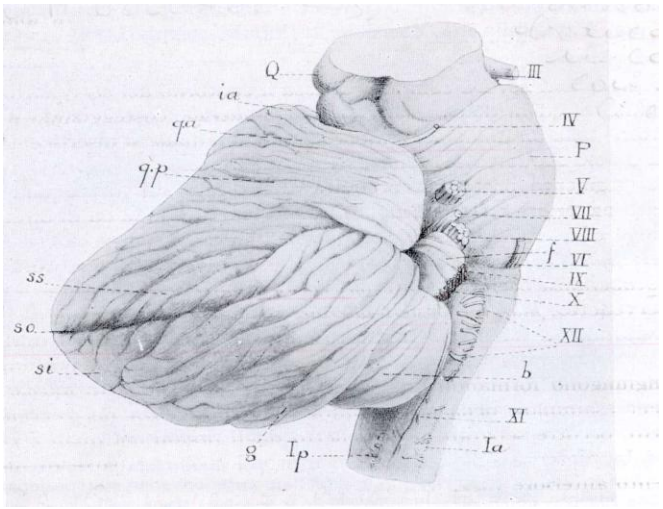
Normal development

Abnormal development due to WT1 gene loss

Nature Review, Cancer June 2005

Cerebellar development & Medulloblastoma

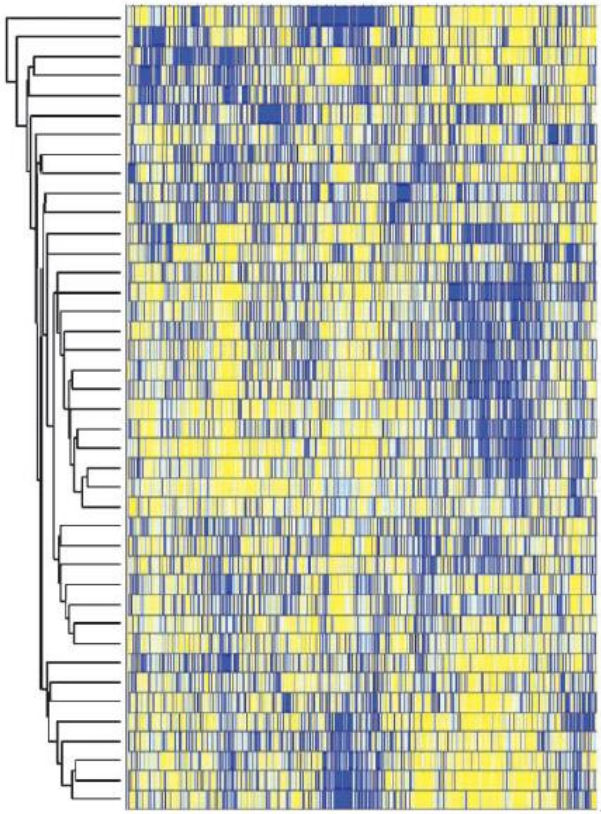




Mutation of the PTHC gene results in a constitutive activation of this pathway, leading to increase proliferation of the granule-cell precursors

PA: a developmental disorder?

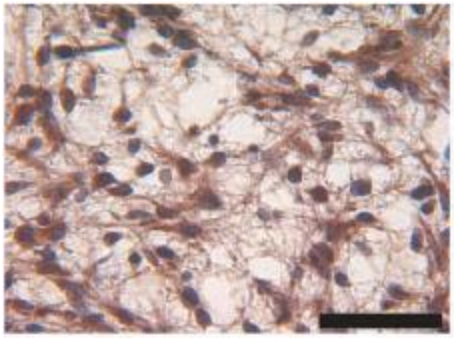
PA arising in the supratentorial compartment Vs posterior fossa: different gene expression pattern

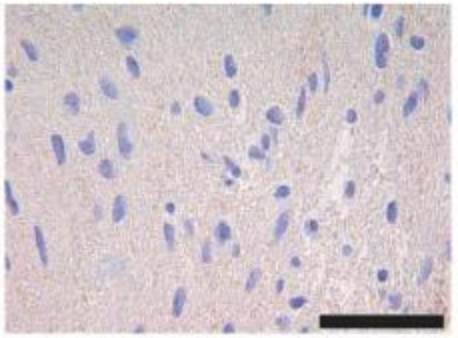


Age	Gender	Location	Comment	NF1
03	F	posterior fossa		N
12	F	posterior fossa		N
37	F	posterior fossa	pleomorphic	N
14	M	posterior fossa		N
24	F	posterior fossa		N
06	F	posterior fossa		Y
13	M	cerebral hemisphere		N
47	M	posterior fossa		N
16	M	ventricular		N
29	F	cerebral hemisphere		Y
12	M	posterior fossa		N
14	M	hypothalamus	aggressive	Y
40	M	cerebral hemisphere	recurrent	N
13	M	posterior fossa	recurrent	Y
04	F	optic nerve		N
16	M	posterior fossa		N
14	M	brainstem		N
13	M	posterior fossa		N
07	F	posterior fossa		N
09	M	posterior fossa		N
14	F	cerebral hemisphere		N
08	F	optic nerve	aggressive	Y
08	M	optic nerve		N
09	F	posterior fossa		N
09	M	posterior fossa		N
11	F	posterior fossa		N
04	M	posterior fossa		N
01	F	posterior fossa		N
53	M	posterior fossa	anaplastic	N
13	M	posterior fossa	recurrent	N
14	F	posterior fossa		N
12	F	brain stem		N
09	M	posterior fossa		N
09	M	posterior fossa	pleiomorphic	N
34	F	posterior fossa		N
03	M	posterior fossa		N
11	M	cerebral hemisphere		N
13	M	brain stem	aggressive	N
09	F	posterior fossa		N
08	F	posterior fossa		N
15	M	cerebral hemisphere		N

PA: developmental disorder?

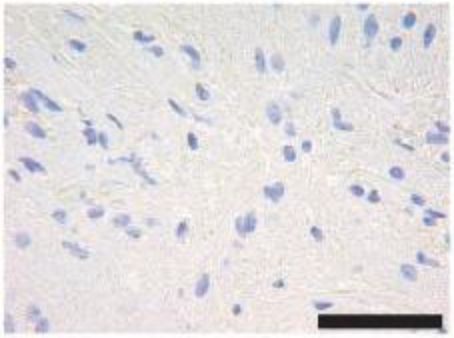
PAX 3 critical gene for proper hindbrain differentiation

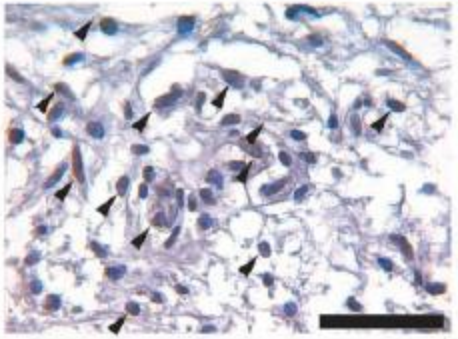




	PAX3 postive	PAX3 negative	Total
Posterior fossa PA	7	3	10
Supratentorial PA	1	9	10

LHX2 is expressed in developing forebrain during embryogenesis

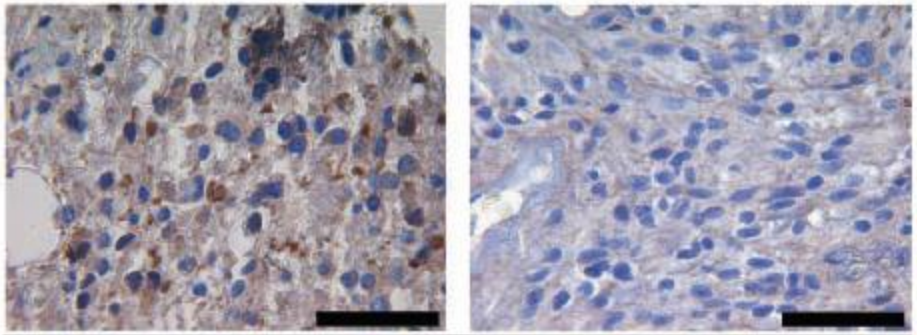




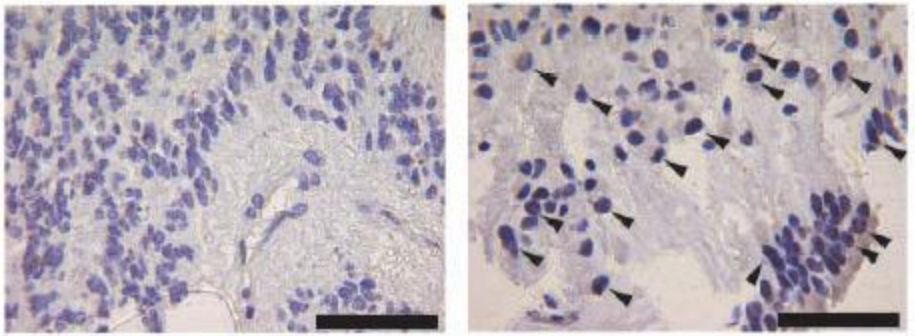
	LHX2 positive	LHX2 negative	Total
Posterior fossa PA	2	8	10
Supratentorial PA	9	1	10

Ependymoma share for same extend the same patter of gene expression: thus….

Brain region specific gene expression pattern exists for glial cell tumours

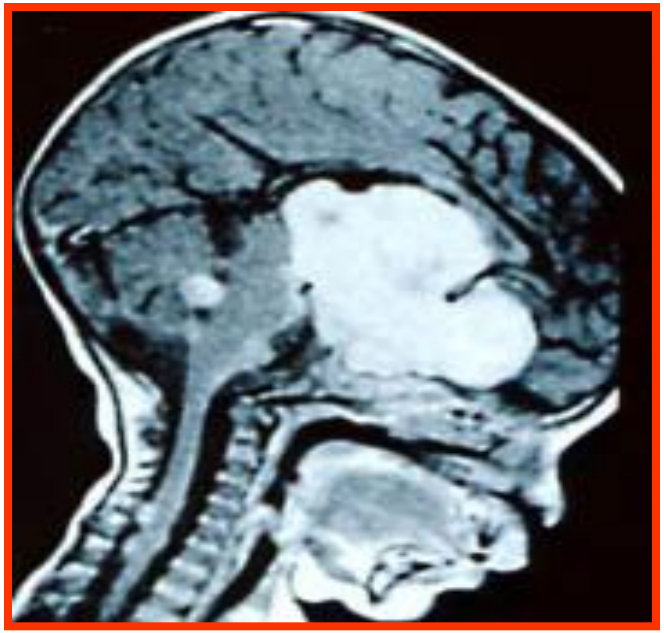


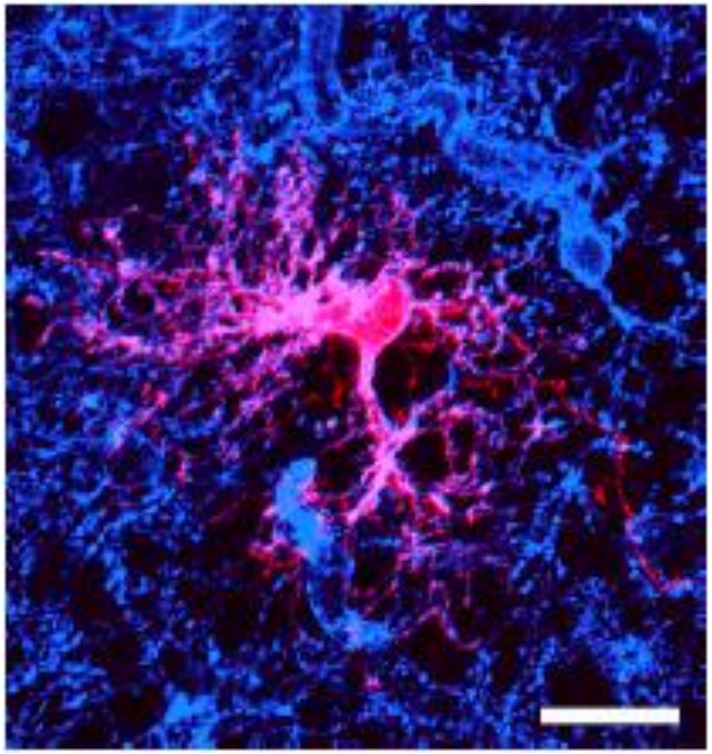
	PAX3 positive	PAX3 negative	Total
Posterior fossa	28	2	30
Supratentorial	0	7	7



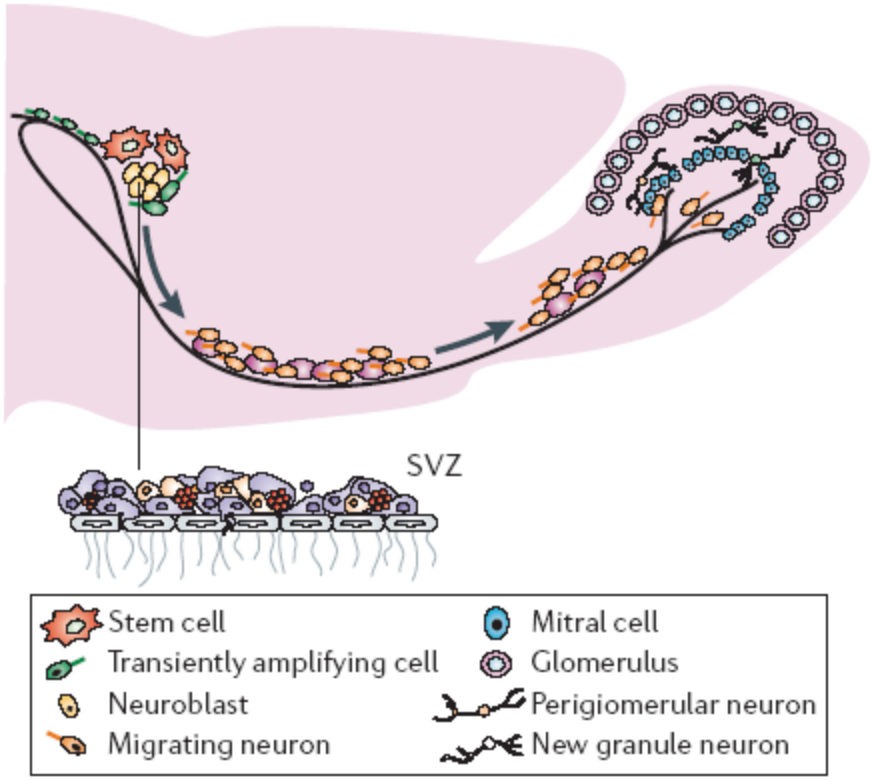
	LHX2 positive	LHX2 negative	Total
Posterior fossa	3	28	31
Supratentorial	8	0	8

PA: brain/cancer stem cell disorder?





Brain tumour stem cells theory

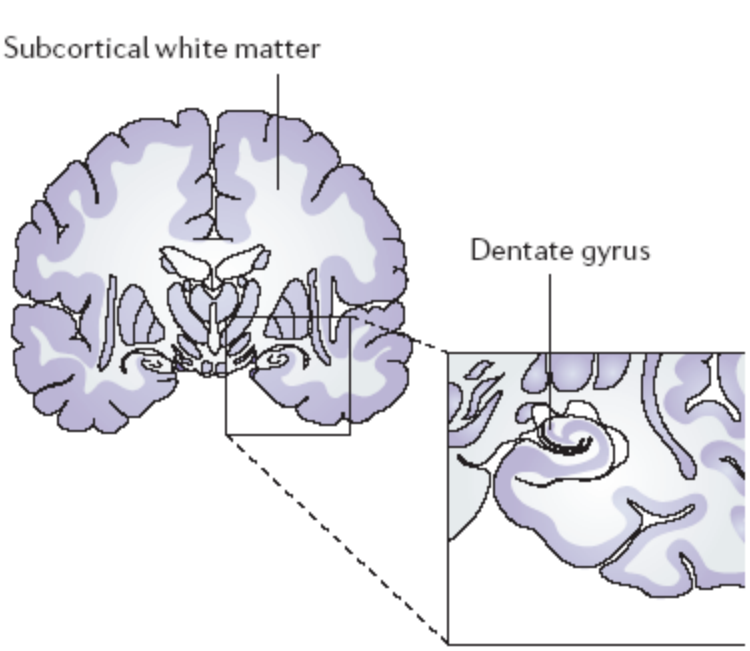


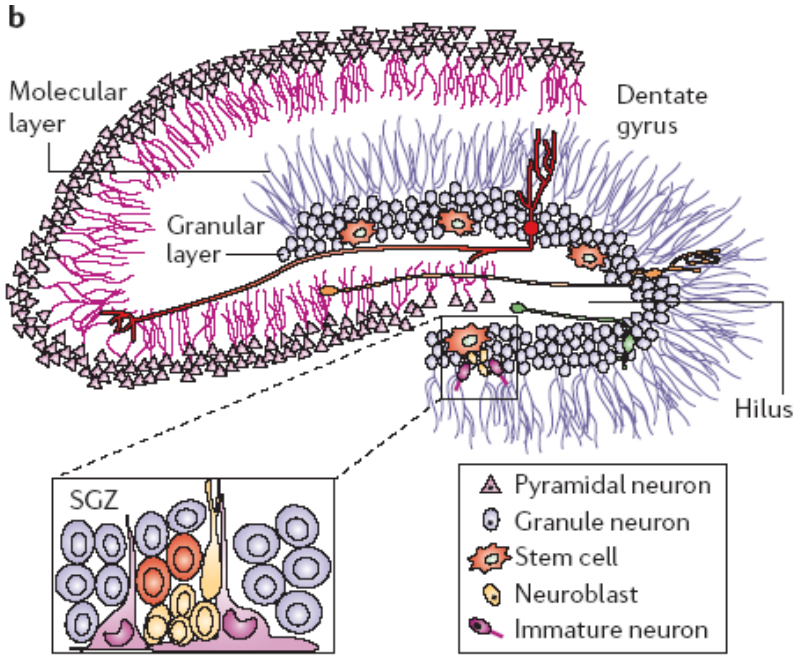
Sagitall section through the lateral ventricle; the larger area of adult neurogenesis; sub-ventricular zone

Neogenesis of mature cells persists throughout adult life within discrete brain regions, primarily in the dentate gyrus of the hippocampus and in the subventricular zone of the forebrain lateral ventricles

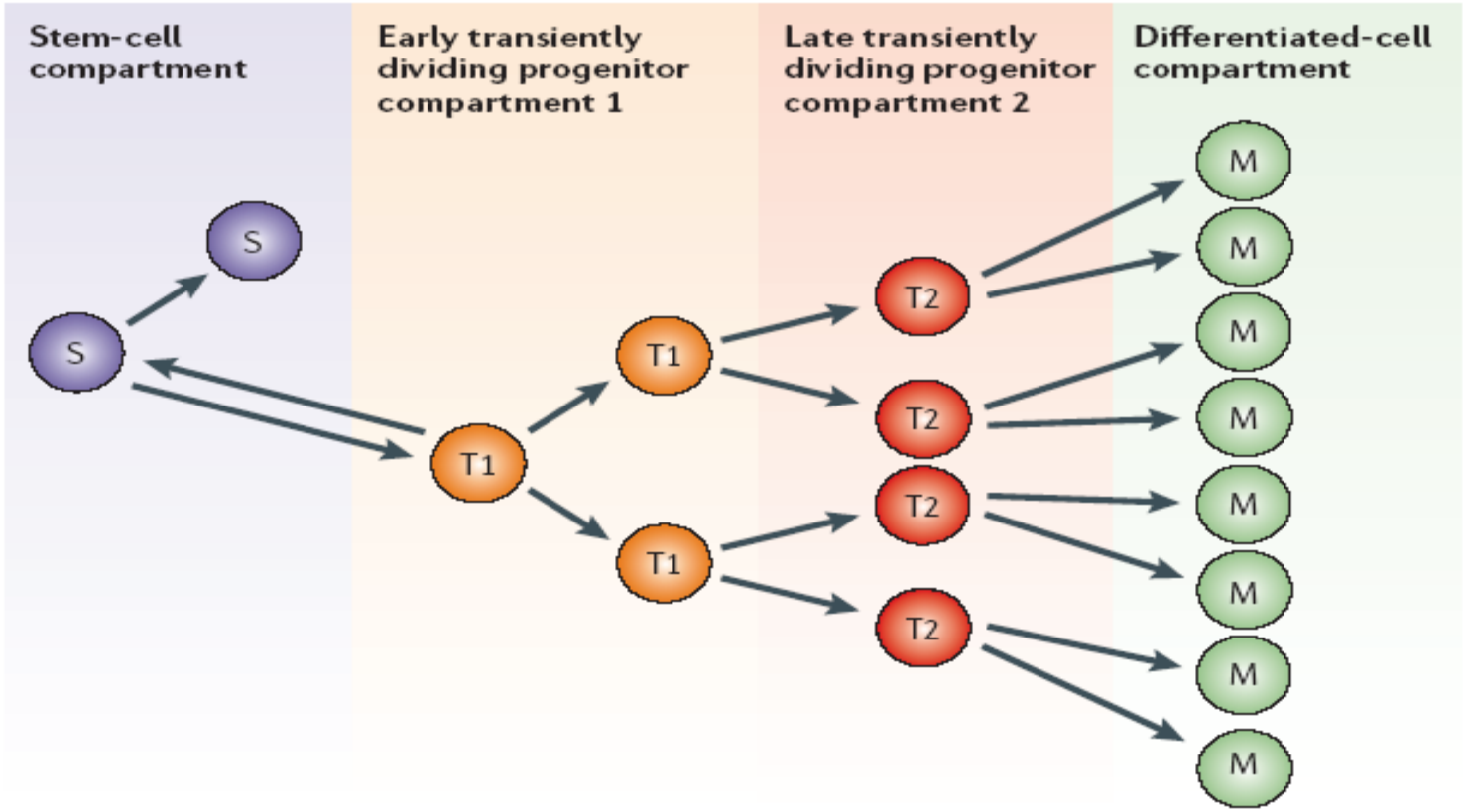
This process is central to the generation and integration of new neurons and.. for the maintenance of brain integrity, plasticity and optimal function.

Brain tumour stem cells theory





An additional adult neurogenetic region is found in the subgranular zone (SGZ), which is located within the dentate gyrus of the hippocampus.

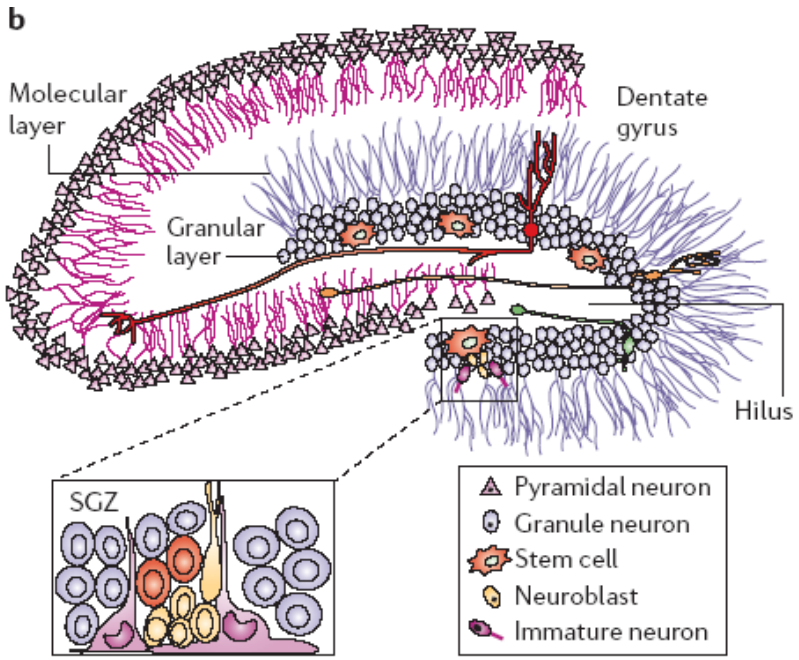


b

Type B (1 and 2) Astrocyte	Type C Putative precursor	Type A Migrating neuroblast	Mature cell Neuron
GFAP positive Vimentin positive Nestin positive Mitotically active (B2)	Nestin positive Mitotically active Excluded from the RMS	PSA-NCAM positive Type III β-tubulin positive HSA positive at RMS start	Neurofilament positive MAP2 positive Tyrosine hydroxylase positive GABA positive

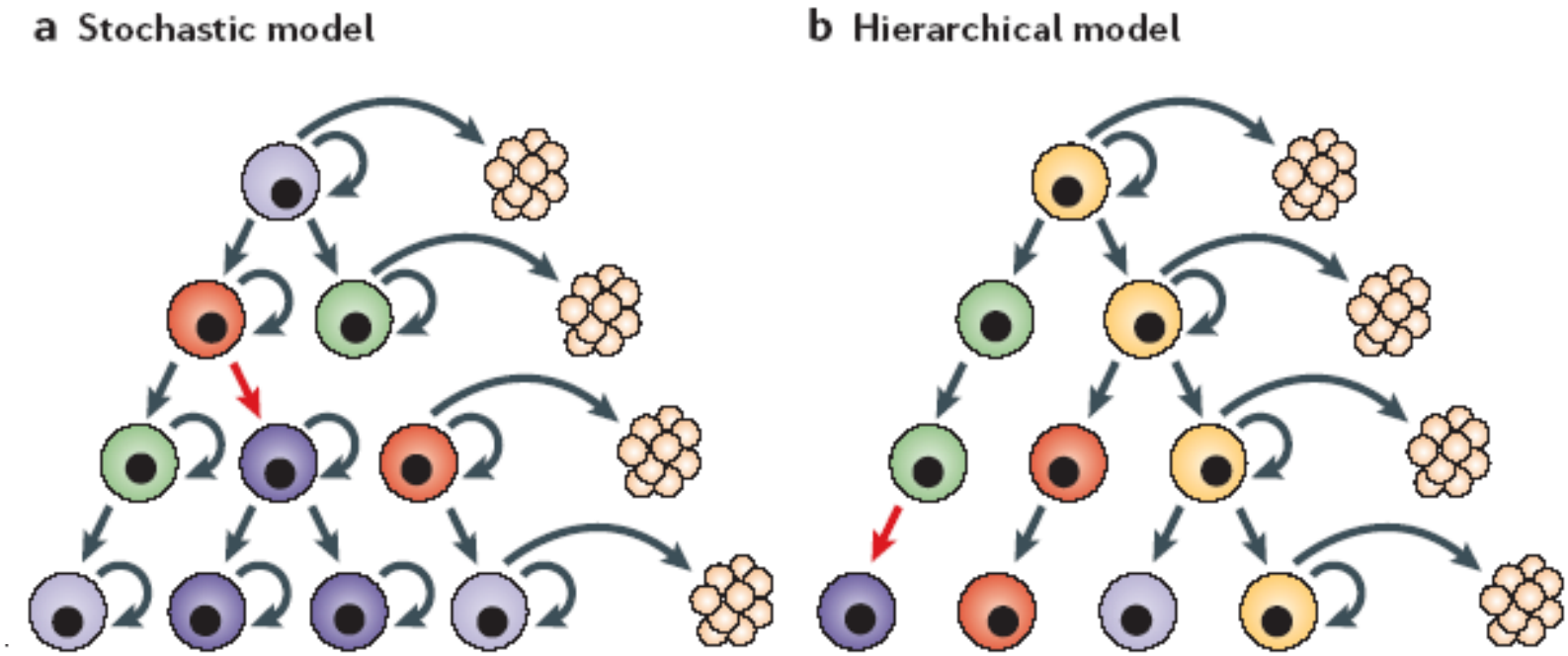
c

Brain tumour stem cells theory



Hypothesis - Brain tumour may originate by transformation of undifferentiated precursors cells found in areas of the mature brain, in which neurogenesis persist throughout adulthood

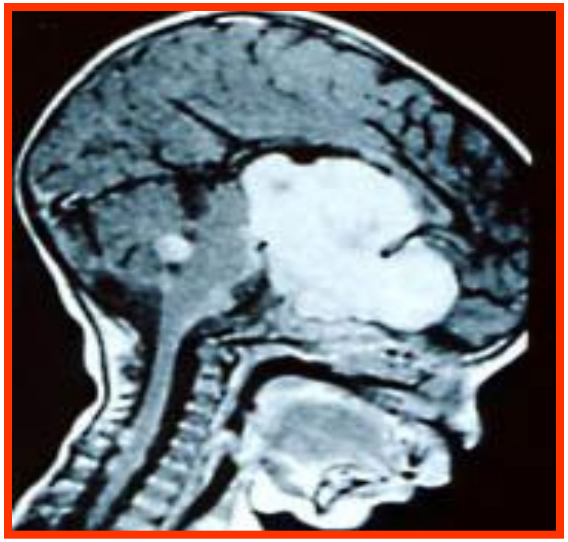
Brain tumour stem cells theory

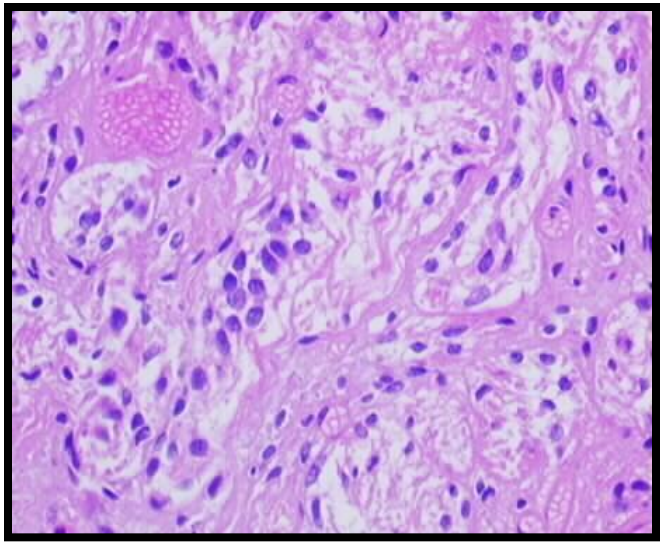


All tumour cells have similar oncogeic potential

Only a rare sub-set of cells have unlimited proliferation potential (the others are terminally differentiated cells)

PA: infectious problems?





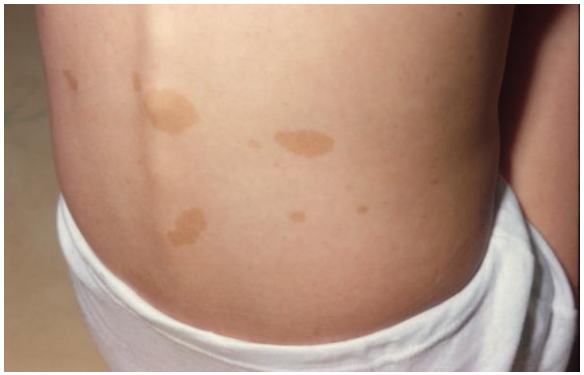
…fascinating case reports of children affected by PA and metachromatic leuko-encephalopathy!

PA & Neurofibromatosis type 1

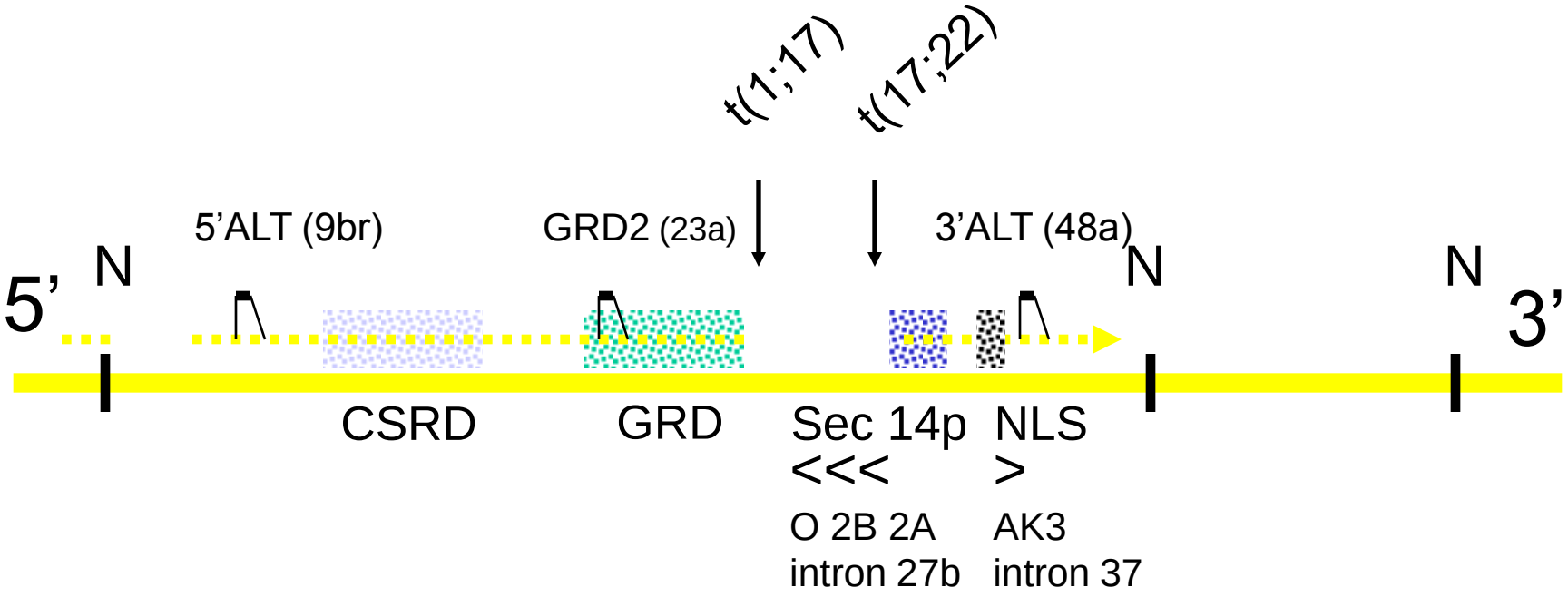
Life time risk in NF1 patients of developing OPG 10-20%

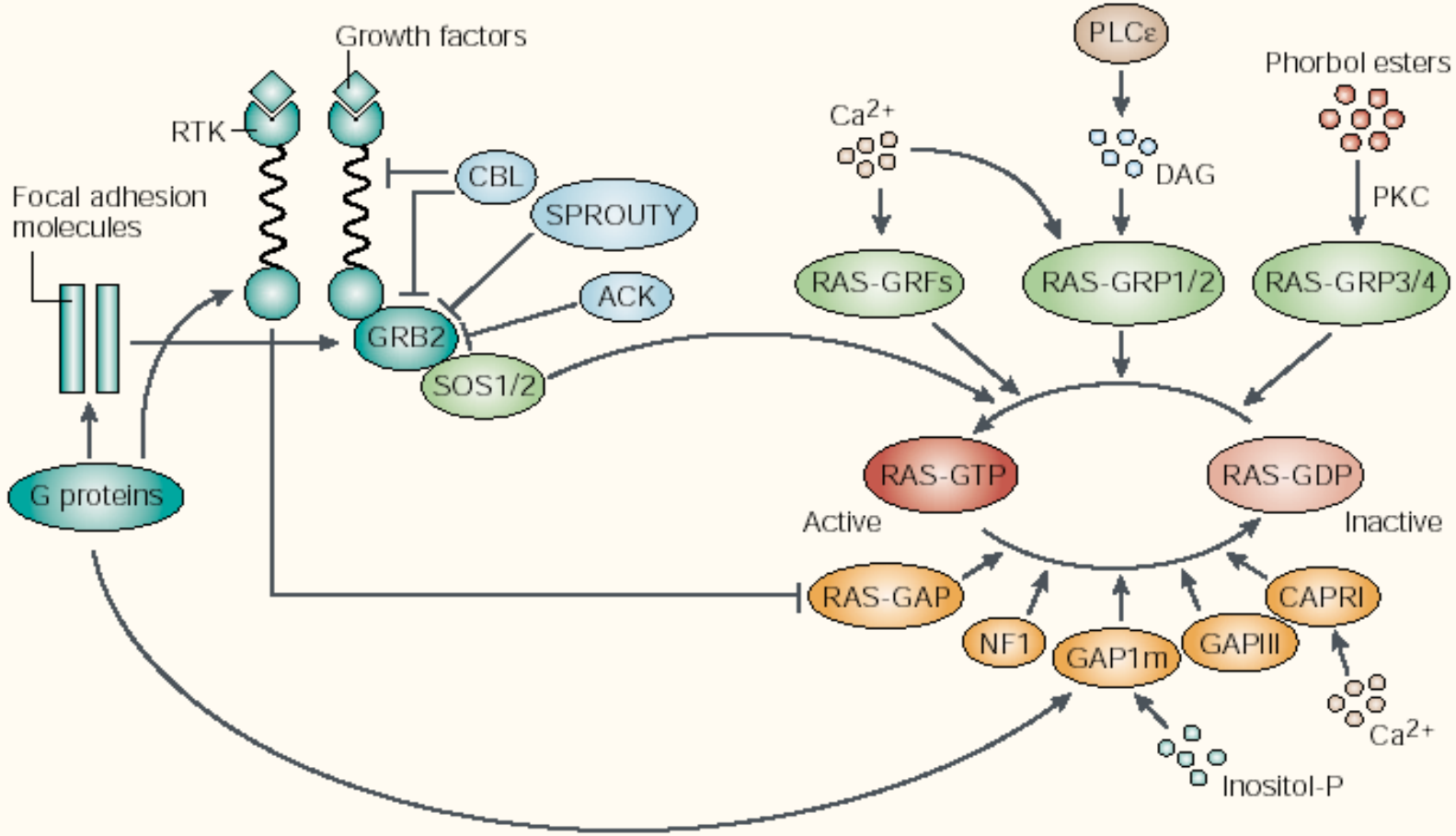
Prevalence of:

- ✓ **OPG in the NF1 population 5%**
- ✓ **NF1 in the OPG population 50%**



Genomic organization of *NF1*



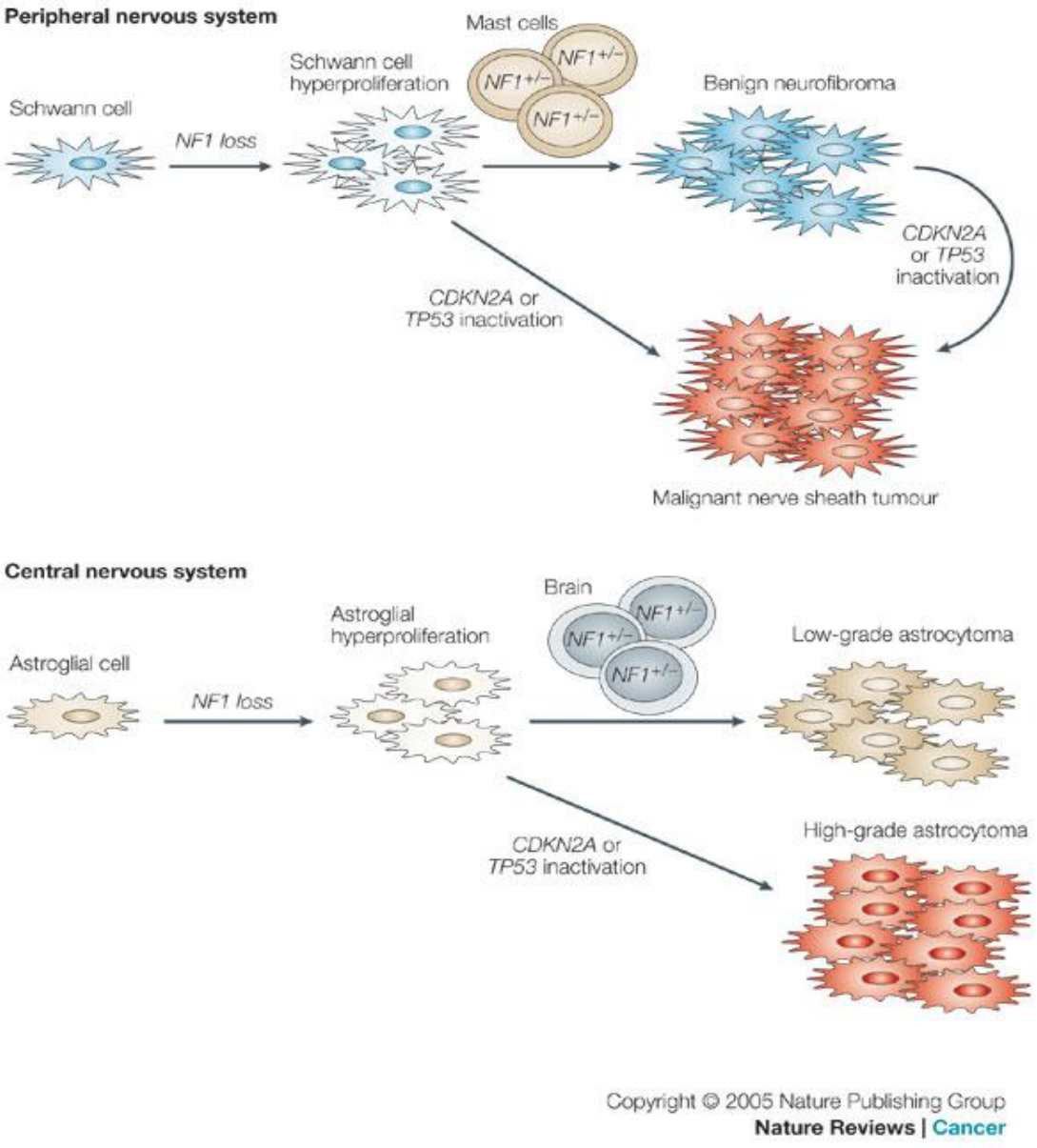


Marcos Malumbres and Mariano Barbacid

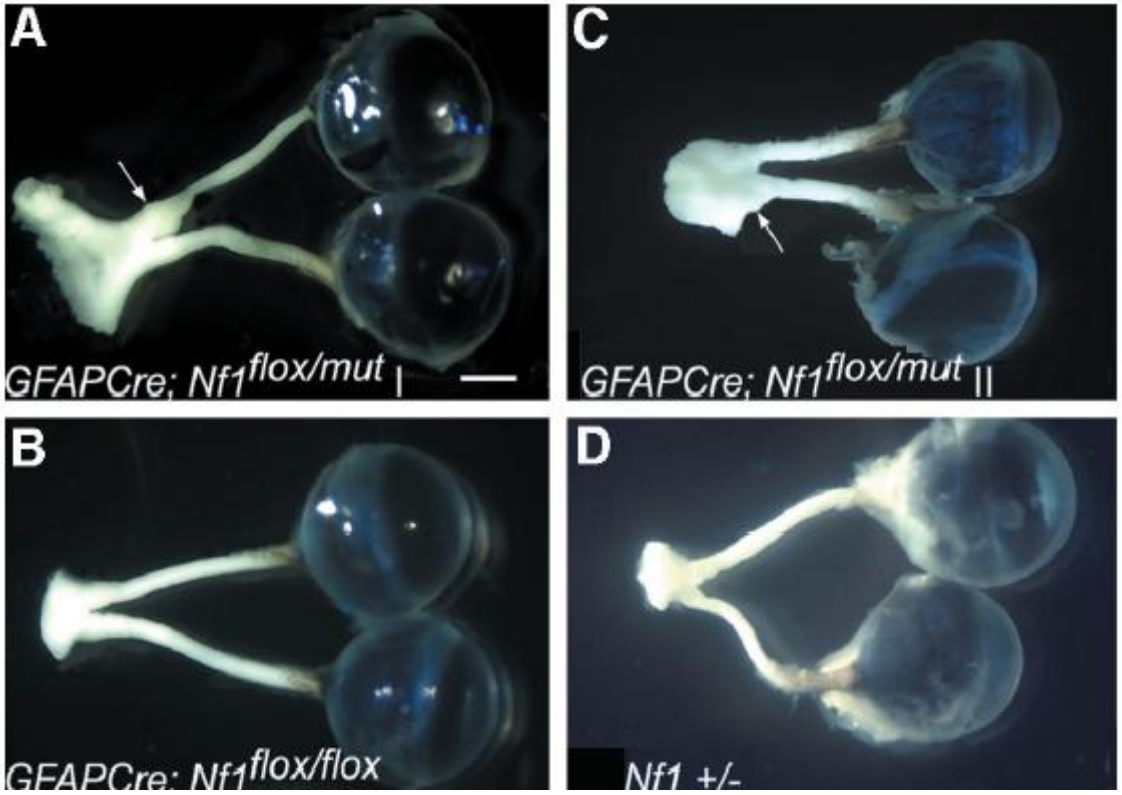
RAS oncogenes: the first 30 years

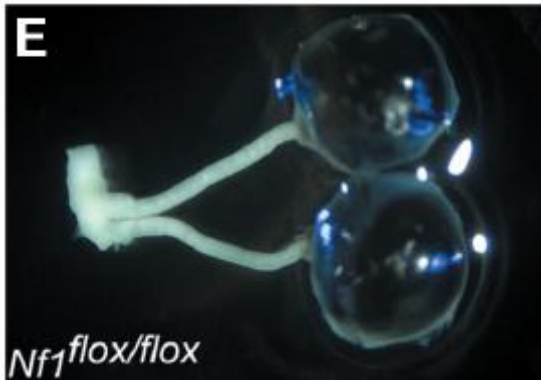
NATURE REVIEWS | CANCER VOLUME 3 | JUNE 2003

Evolution of NF1-associated peripheral and CNS system tumours



Nf1 +/- mice without expression of Nf1 in astrocytes





[**Optic Nerve Glioma in Mice Requires Astrocyte *Nf1* Gene Inactivation and *Nf1* Brain Heterozygosity**

M. Livia Bajenaru, et al Cancer Research 63,8573,2003

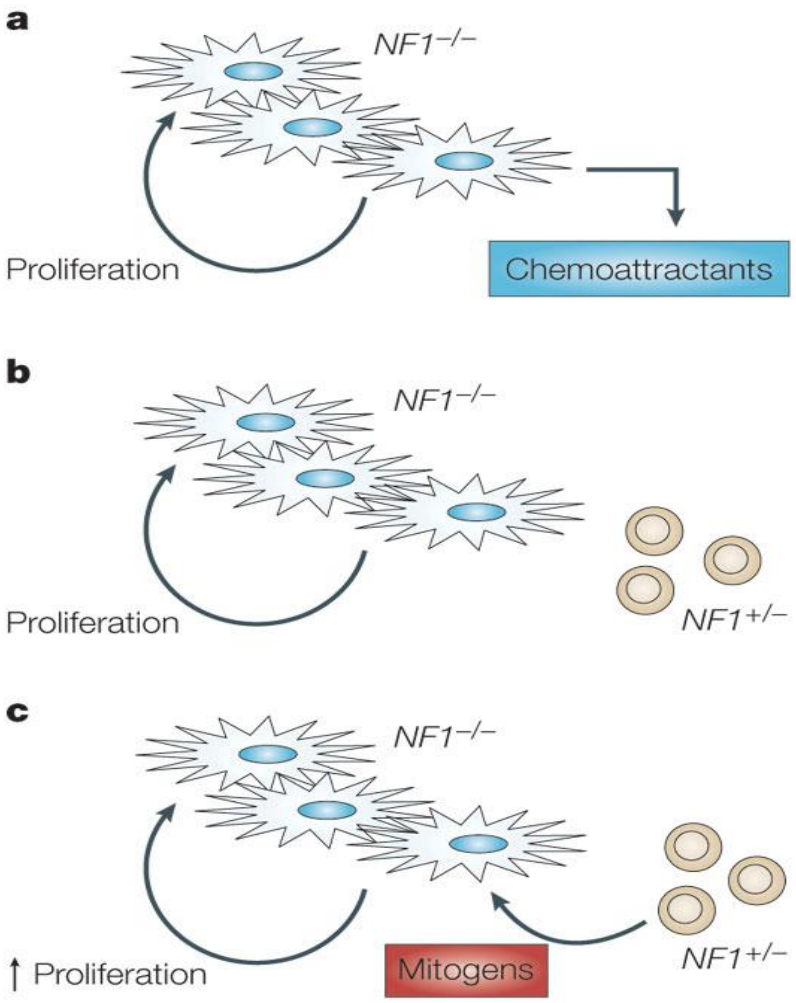
- **No parenchymal tumors**

Inter-action between stronal cells and hyperproliferating pre-neoplastic cells (astrocytes)

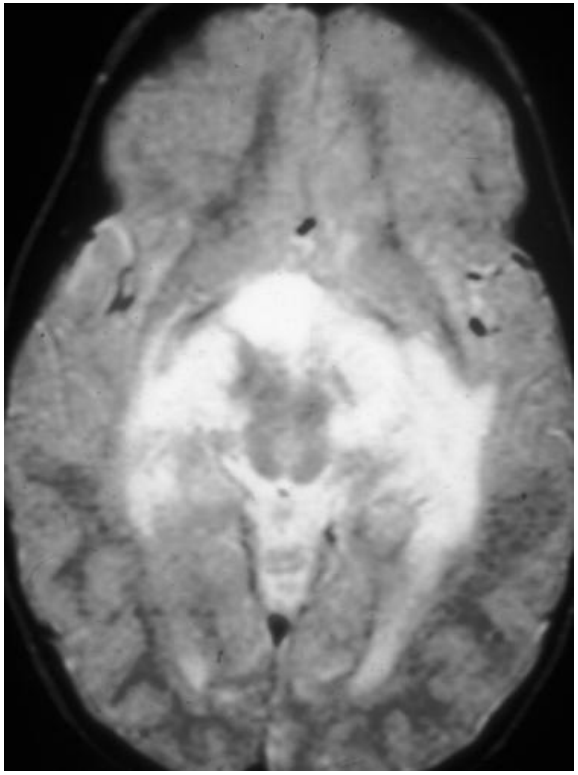
NF1 gene loss not sufficient for "transformation"

Hyper-proliferating Nf1 -/- cell secrete chemoattracting agents - angiogenic factors; Nf -/+ microglia are attracted altering the micro-environment

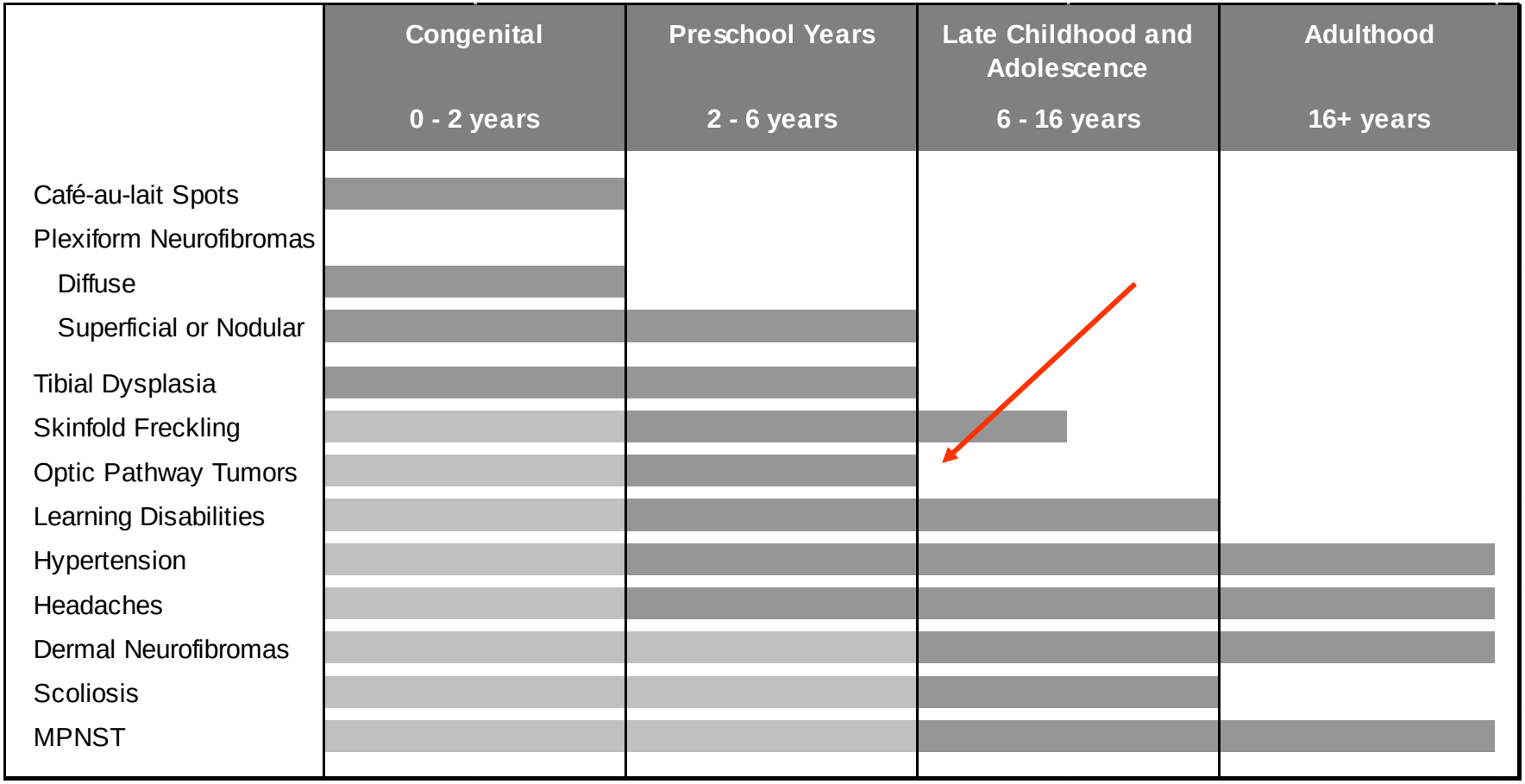
Factors produced by the NF1-/+ microglia + localized mitogens promote "transformation"



Optic pathway glioma (PA) in children with NF1



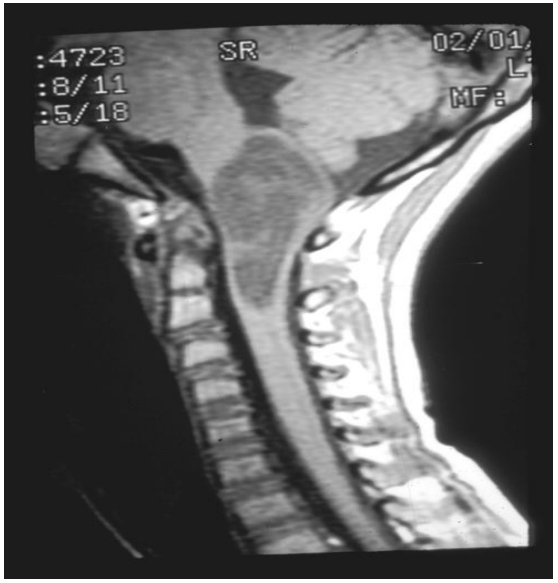
“Time line” of NF1 clinical features

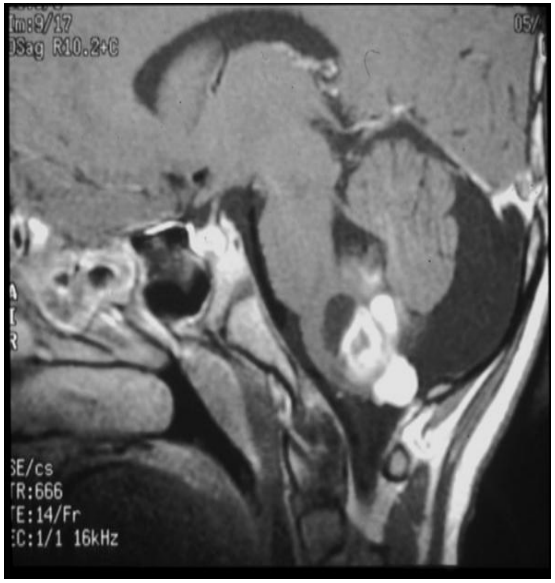


PA - Clinical biological considerations

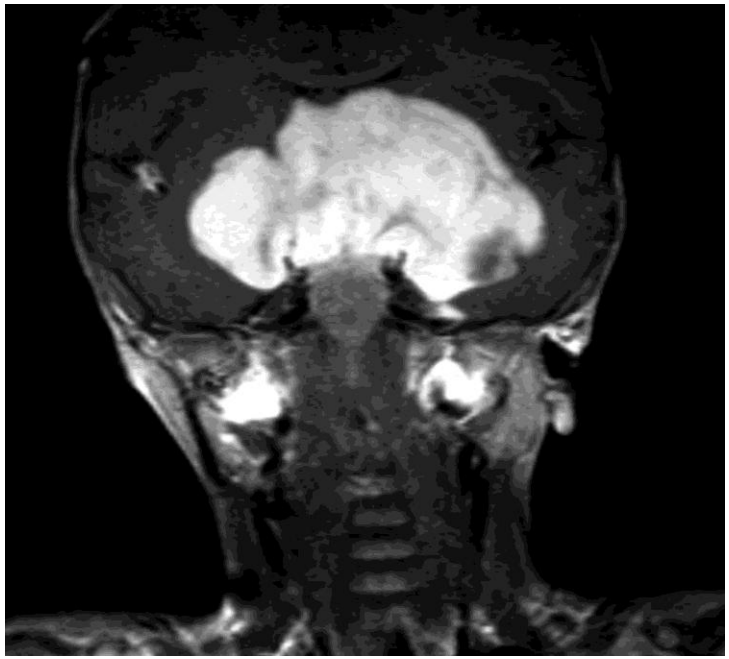
- ✓ PA are not benign tumours; “most” of them are slow growing tumours (“chronic disease”)
- ✓ The biological behaviour of these tumours is unpredictable

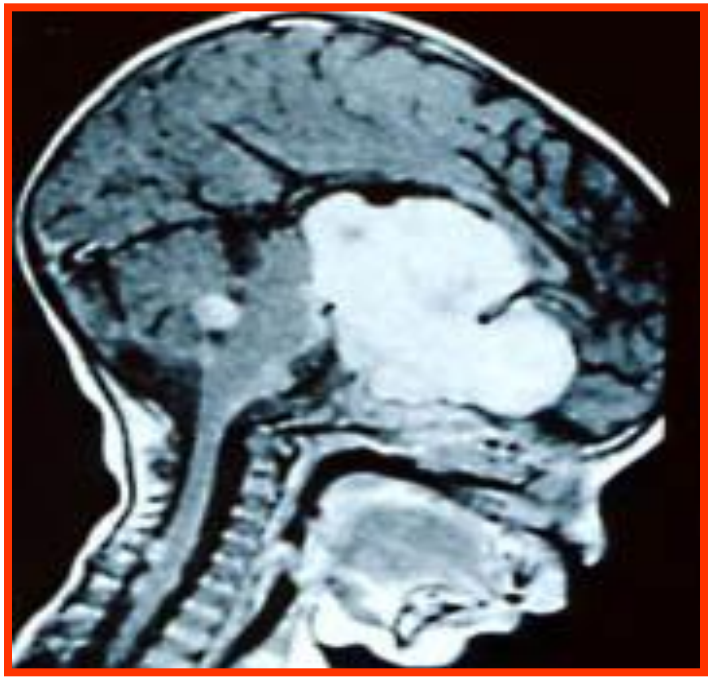
PA may growth in potentially "malignant" site



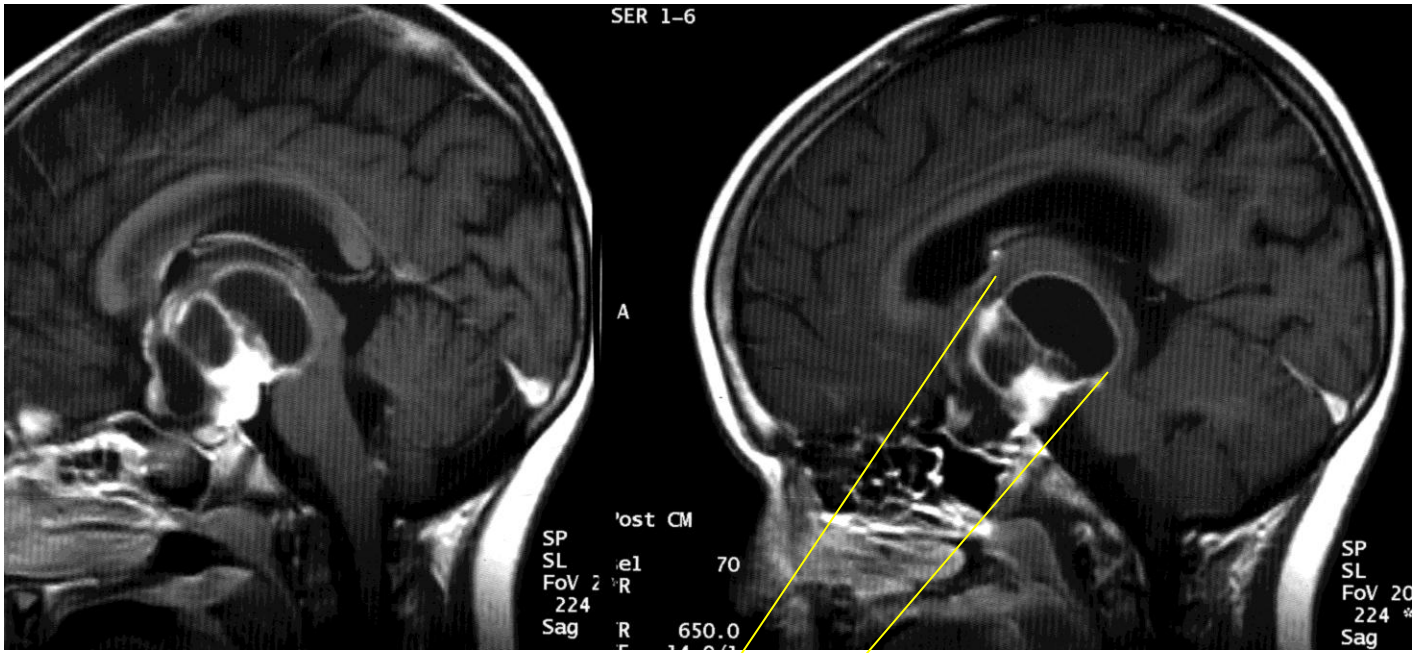


PA may reach huge dimension

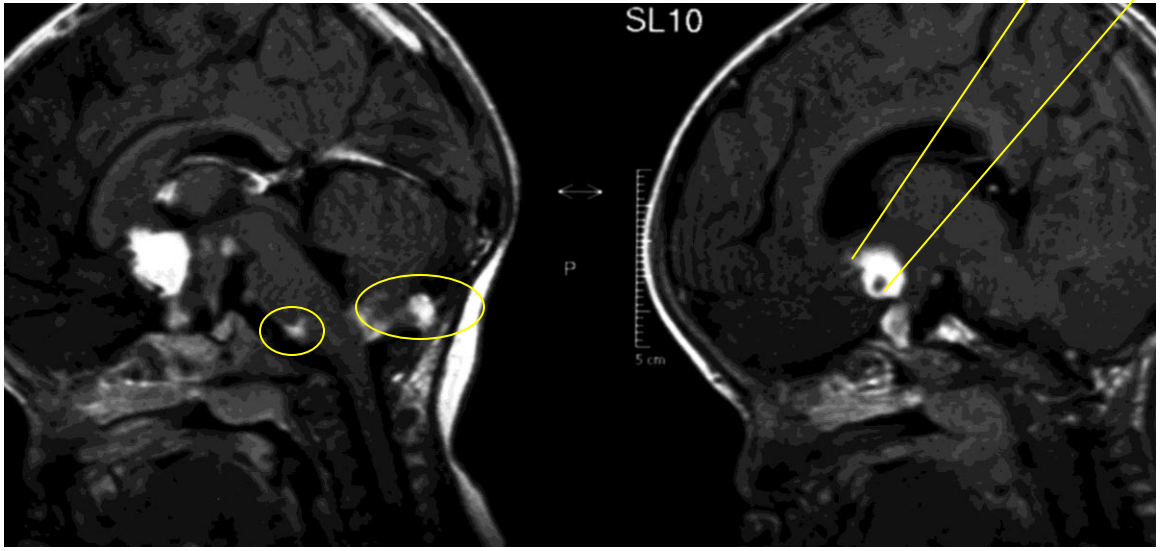




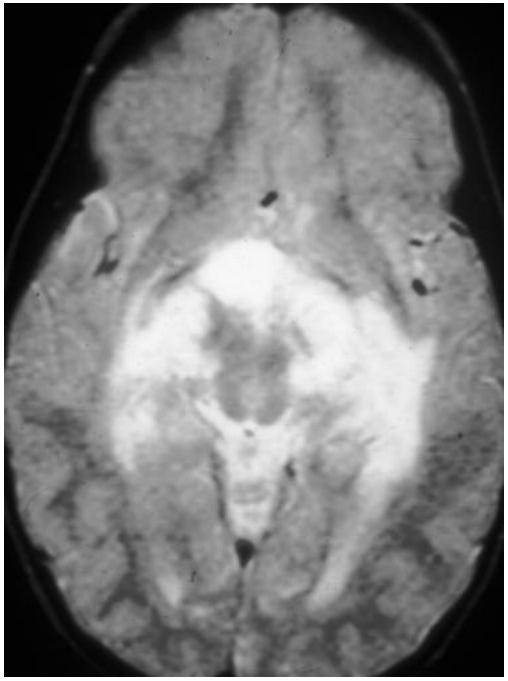
PA may create cysts

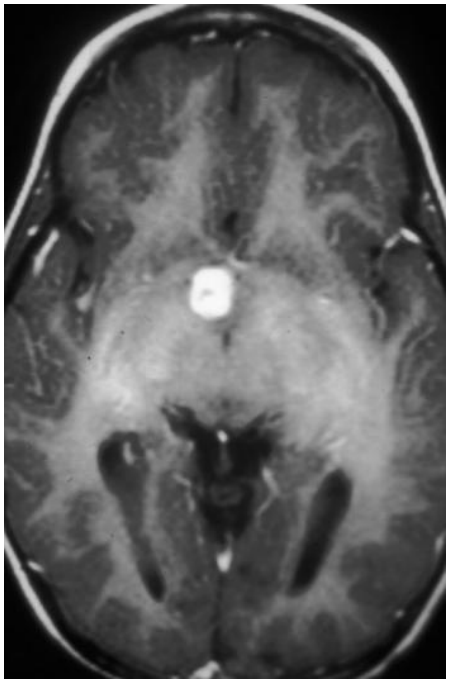


At the time of death



At diagnosis

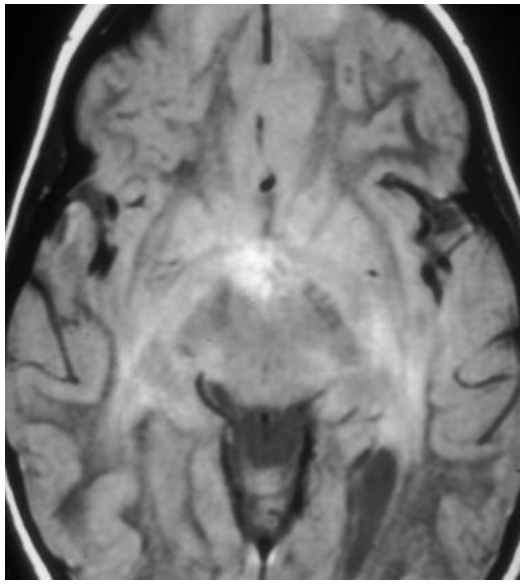


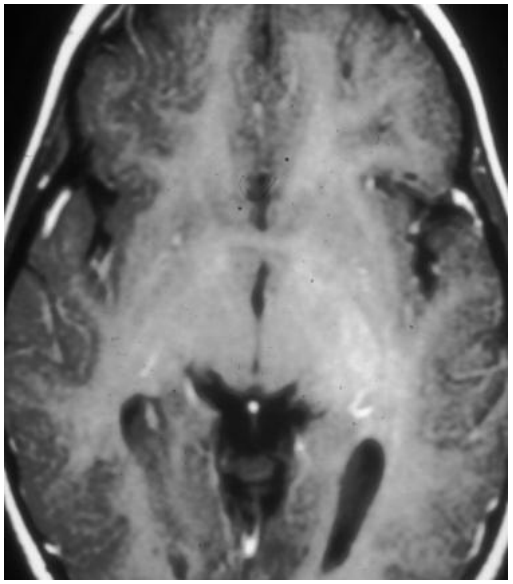


1989

Optic pathway glioma (=PA) in NF1 patients

Evolution over time: spontaneous resolution





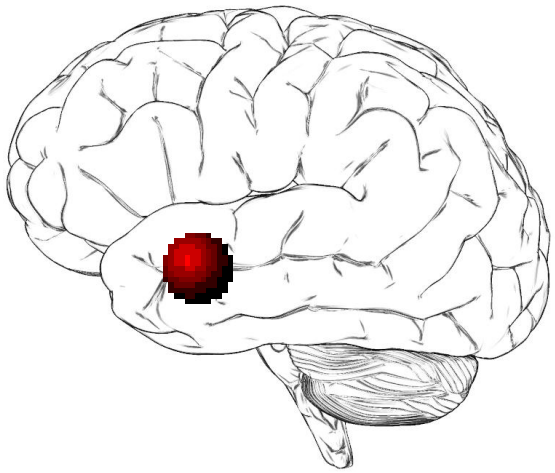
1992

PA - The clinical and therapeutic problem

- ✓ **The clinical and biological behaviour is unpredictable**
- ✓ **The growth rate (if they have a growth rate) is low**
- ✓ **In general the life expectancy of these patients is very long**
- ✓ **Quality of life is very important in planning any therapeutic act**

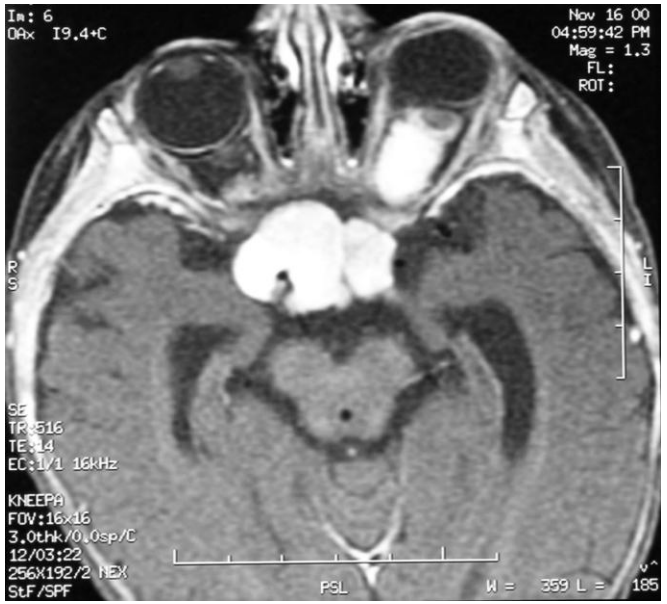
The therapeutic approach

✓ **The complete surgical resection (usually) is always what is needed for PA**

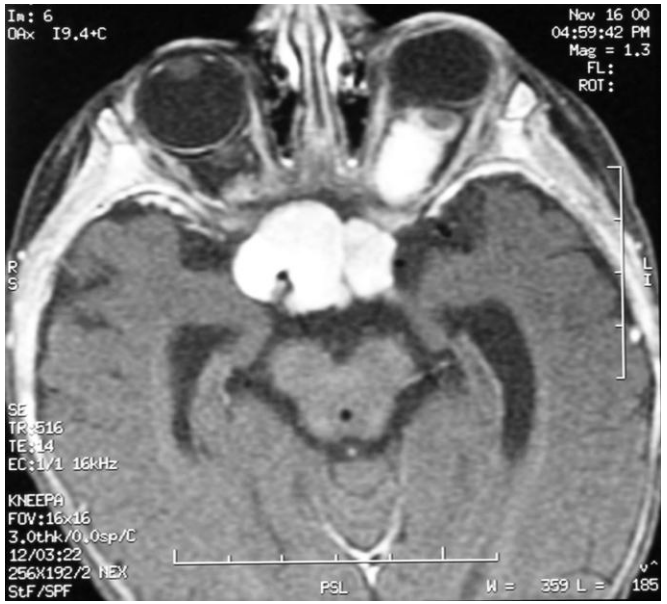


The therapeutic approach

✓ **The clinical dilemma arises when the complete surgical resection is not an option**



PA - The therapeutic approach



The clinical dilemma

1. **Considering the unpredictable clinical behaviour of PA, who and when one should be treated?**
2. **How to treat, if treatment is needed?**
3. **Which is the "purpose (=why to treat) of the treatment?**

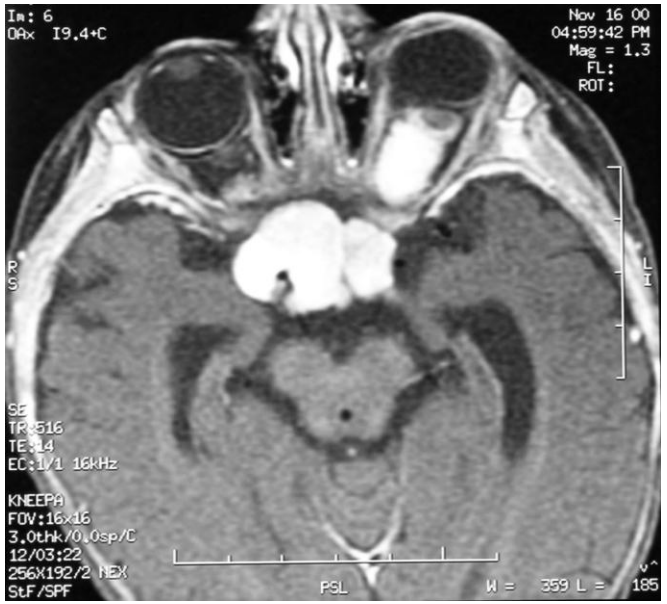
The therapeutic approach

The clinical dilemma

1. … who and when one should be treated?

The answer:

1. The ones with severe tumour related symptoms (e.g. compromised vision; diencephalic syndr,) or with unquestionable evidences of tumour progression



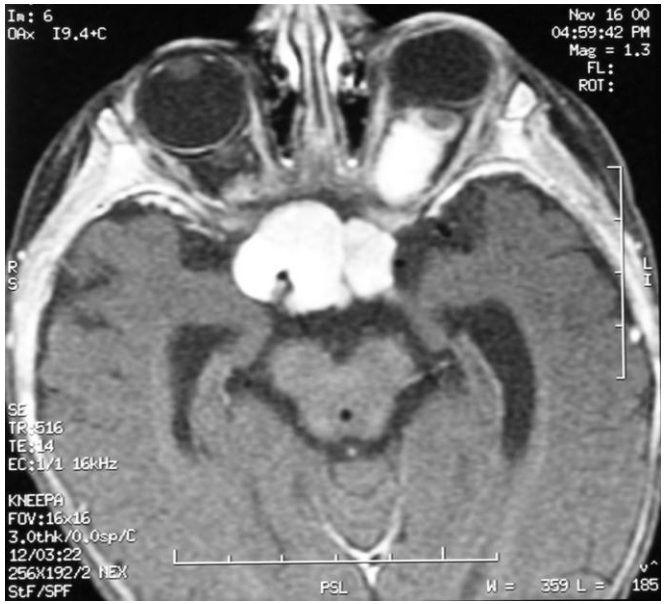
The therapeutic approach

The clinical dilemma

2. How to treat, if treatment is needed?

The answer:

2. ….



The therapeutic approach

✓**Radiotherapy (RT) has/is been considered the "gold standard" for the treatment of PA/LGG**

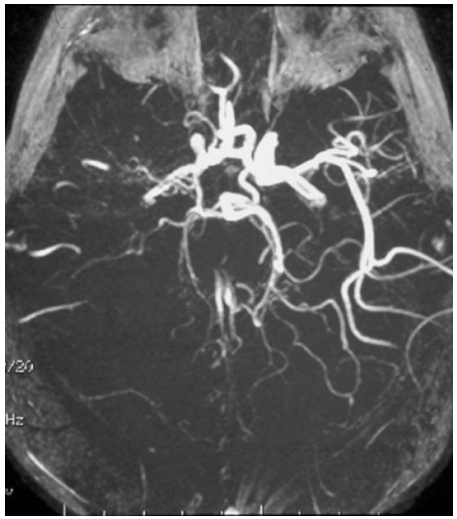
✓ **The use of RT on a growing brain is aggravated by severe side effects**

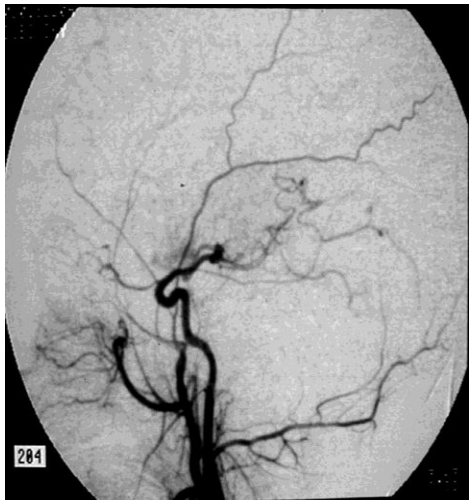
Side effects of RT on a developing brain

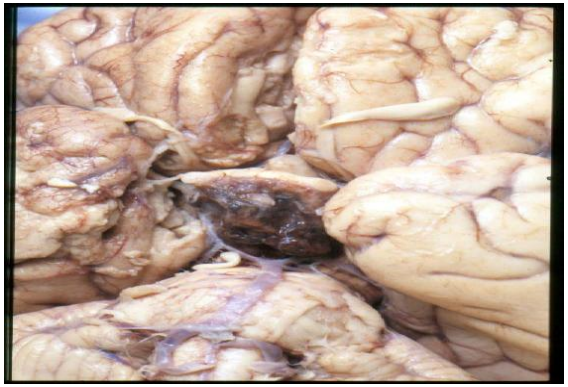
- ✓ **Endocrinological deficits…**
- ✓ **Vascular damages**
- ✓ **Skeletal deformities….**
- ✓ **Neuro-cognitive deficits**
- ✓ **Risk of secondary neoplasm**

Radiotherapy and Neurofibromatosis

Cerebro-vasculopathy and malignancy: catastrophic complications of RT for optic pathway glioma in NF1 patients







Moya Moya disease

NF1 and optic pathway gliomas (OPG) - Epidemiologic data from the North West of England NF1 data and Cancer Registry (Singhal & Birch 2002)

- ✓ **NF1 + OPG - 52 patients**
- ✓ **5/52 (10%) developed a second intracranial tumour (ST)**
- ✓ **Time interval between treated and ST 7-32 years**
- ✓ **2/5 were previously irradiated**
- ✓ **1/5 appeared to survive of ST**

Long term outcome of hypothalamic/chiasmatic astrocytoma in children treated with conservative surgery - *Sutton 1995*

Age at beginning RT for patient attending special education classes and for patients in or completing regular classes

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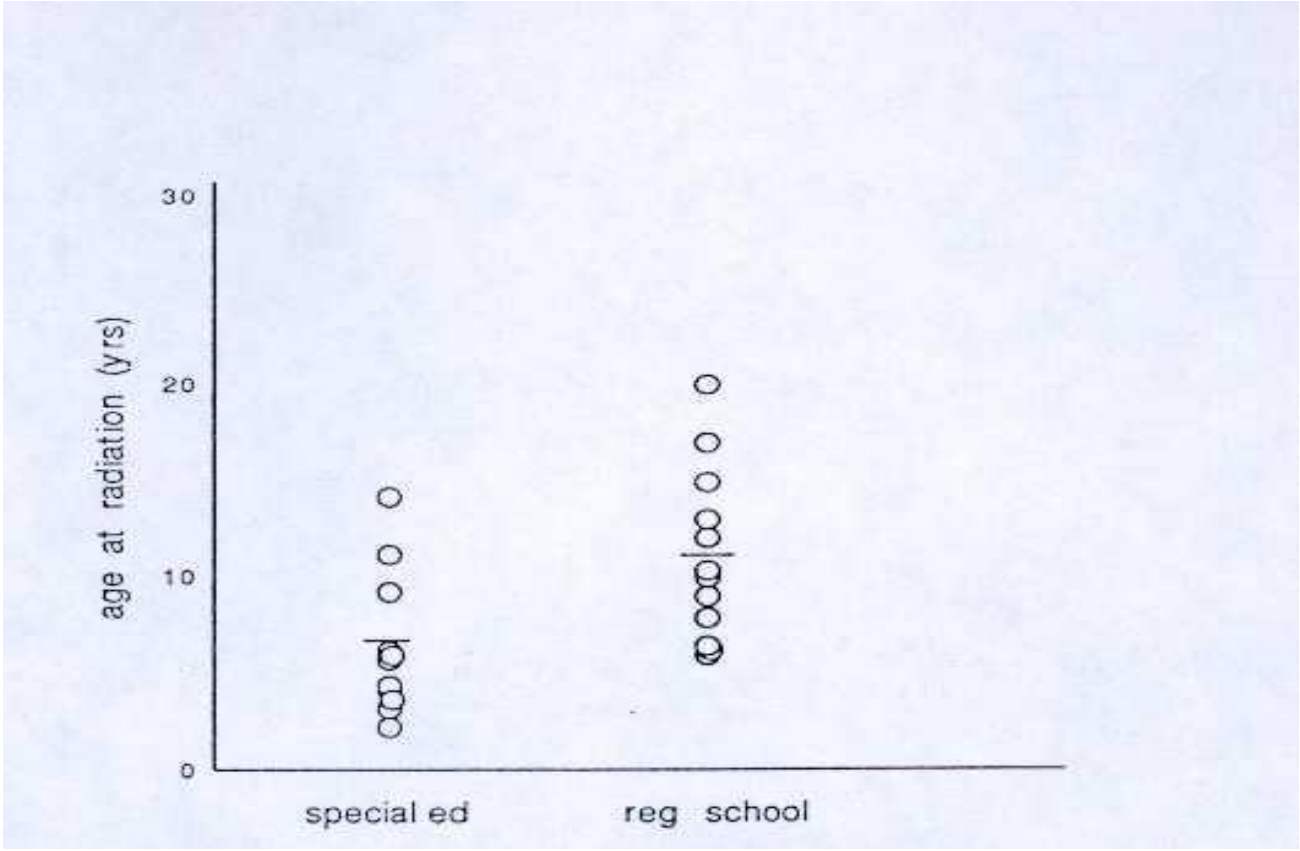
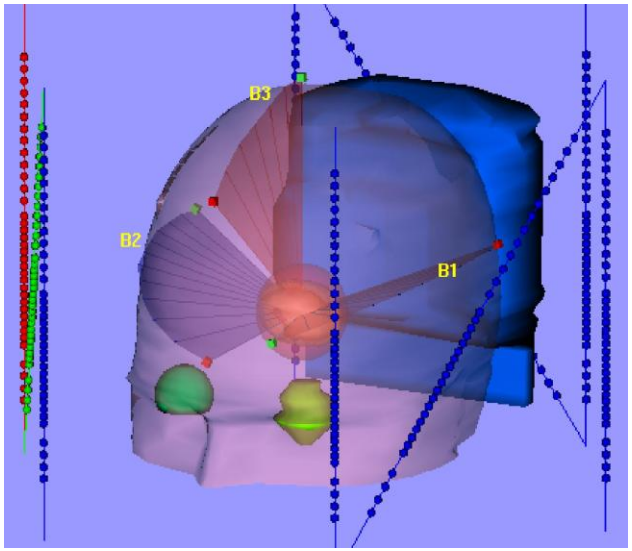


Survival and function outcome of children with hypothalamic-chiasmatic tumors - Fouladi 2003

Patients < 5 years had a lower IQ score at diagnosis (79.1) than older patients

Radiotherapy and brain tumours

The new RT techniques minimize the side effects of RT



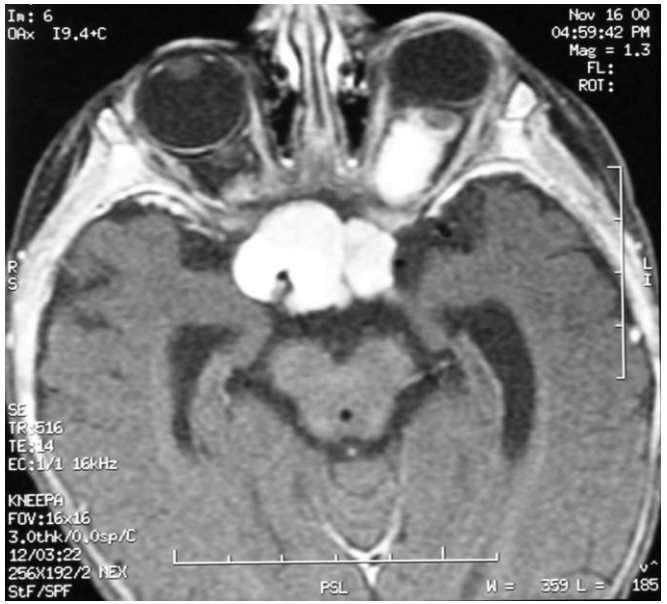
The therapeutic approach

The clinical dilemma

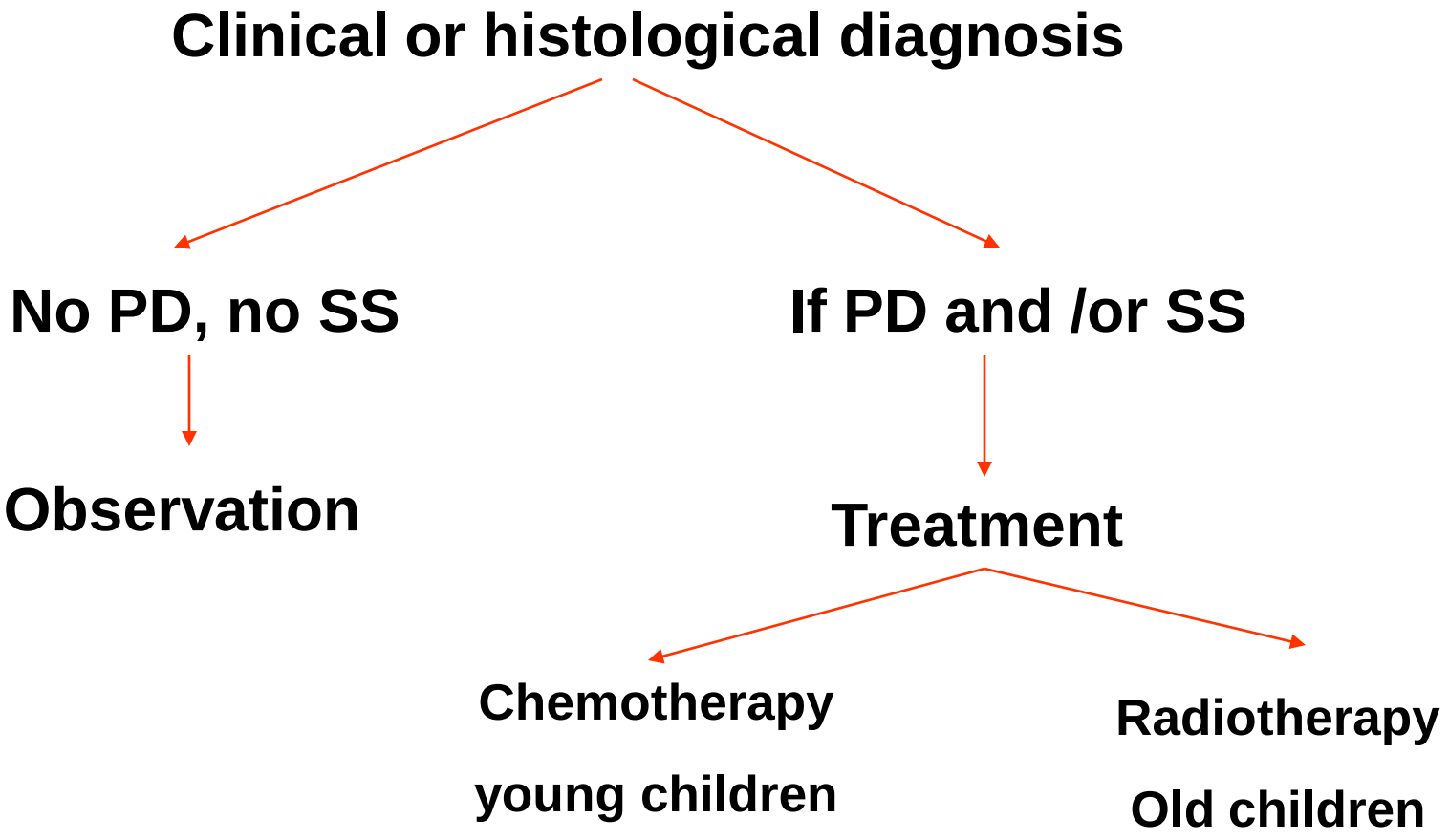
2. **How to treat, if treatment is needed?**

The answer:

2. **With RT but why not, in alternative, with conventional CT at least in young children!?**



Treatment approach to children with pilocytic astrocytoma



The therapeutic approach

The clinical dilemma

3. Why to treat?

The answer:

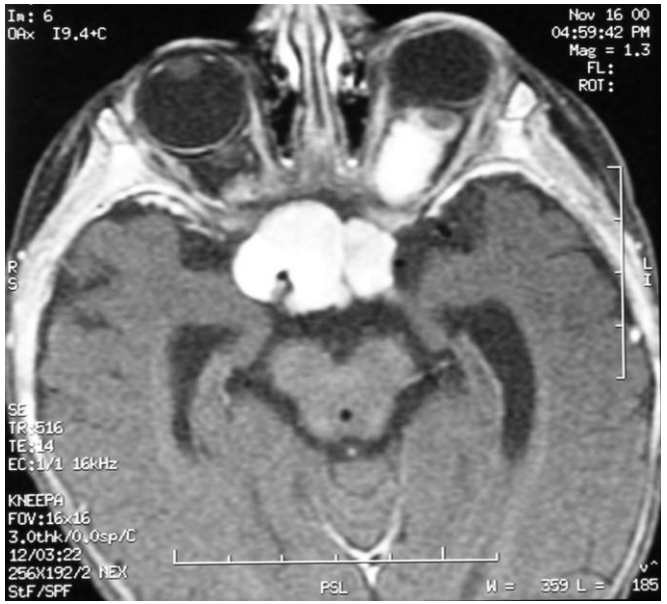
3. To save life???

To stop the tumour from growing!

To make the tumour smaller!?

To relieve symptoms/sings!

To delay RT!



LGG/PA - Radiotherapy survival data

Montgomery 1977	optic tumours	80% mean F-U 6.3m
Danoff 1980	optic glioma	73% - 10 years OS
Horwich 1985	optic glioma	93% - 10 years OS
Wong 1987	optic glioma	87% - 10 years OS
Flickinger 1988	optic gl.+ chiasma	94% - 5 years OS 31% - 10 years OS
Kovalic1990	optic gl.+ chiasma	94% - 5 years OS 81% - 10 years OS

LGG/PA - Radiotherapy survival data

		10 years PFS	10 years 0S
Baitani 1991	chiasma	83.5%	83.5%
Jenkin 1993	optic glioma	73 %	79%
Erkal 1997	optic gl.+hyp	77%	79%
Cappelli 1997	optic glioma	-	74%
Grabenbaurer 2000	optic gl.+ thal.	69%	94%
Kortmann 2000	optic gl.+hyp	87.1*%	95.7*%

Chemotherapy (CT) for LGG/PA

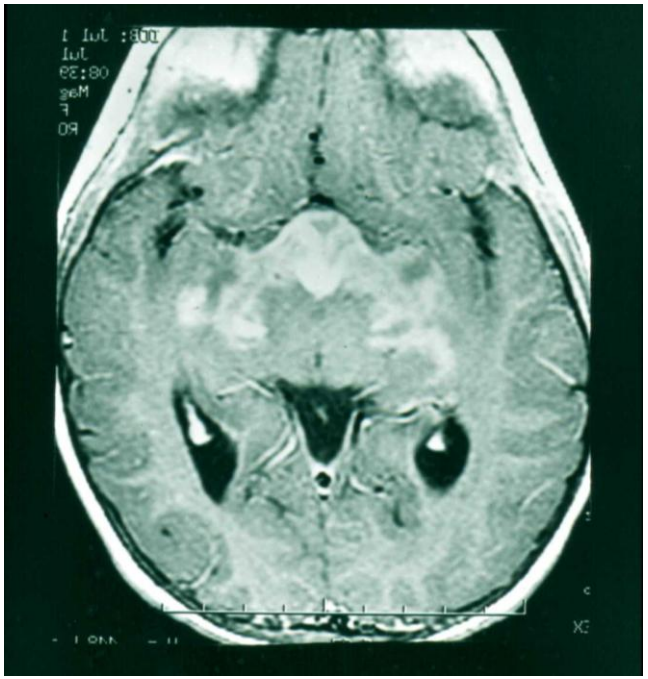
Preliminary considerations : Since the late ’80s, 92 full papers have addressed (primarily or as part of the overall report) the issue of the role of CT for LGG, almost uniformly saying that “it does work”…

… however, despite this huge amount of data, many issues remain unsolved….

Chemotherapy for LGG/PA

Systematic (literature) review on the issue of the impact of chemotherapy on optic pathway glioma (OPG)

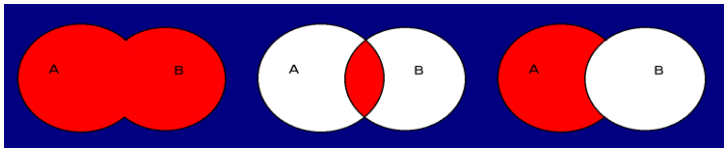
OPG were chosen as prototype of unresectable LGG



Chemotherapy for LGG/PA – Systematic literature review; search strategy based on P.I.C.O. selected

- **Find key words, synonyms, text words, truncate**
- **Search PubMed**

  words were combined using Boolean operator OR, AND, NOT and save your searches



- **Translate search for other database (Embase)**
- **Search for additional studies (references, experts)**

Chemotherapy for LGG/PA – Systematic literature review; search strategy based on P.I.C.O. selected

Define inclusion criteria

…and select studies fulfilling inclusion criteria

Type of …

- Studies
- Patients
- Intervention
- Outcome

(…think at P.I.C.O.)

•Selection independently made by two authors;

• Calculated inter-observer agreement;

• Clearly stated reasons for exclusion of the studies

Chemotherapy for LGG/PA – Systematic literature review; search strategy based on P.I.C.O. selected

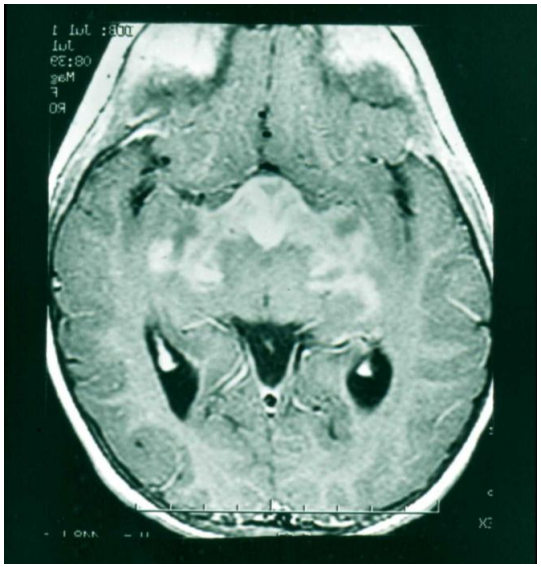
Inclusion criteria

- Type of studies: all design original studies with prognostic analysis, published in english, italian, french, dutch languages
- Type of patients : 20 or more children with OPG, or with mean age < 18yr, or series of LGG or PA where OPG patients are more than 50% of the entire group
- Type of intervention: no intervention; surgery (less than 50% resected); chemotherapy, radiotherapy, combined treatments
- **Type of outcome progression-free-survival, PFS,**

Chemotherapy for optic pathway glioma /PA

Systematic (literature) review

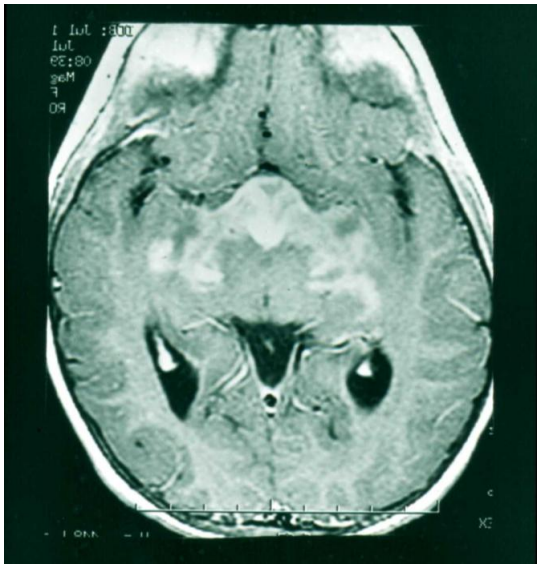
Papers reviewed	**95**
Papers selected	**9**
Inter-observer agreement	**98%**
Reasons for exclusion	
non prospective trials	**75**
less than 20 patients	**11**



Chemotherapy for optic pathway gliomas /PA

Systematic (literature) review – 9 Selected papers

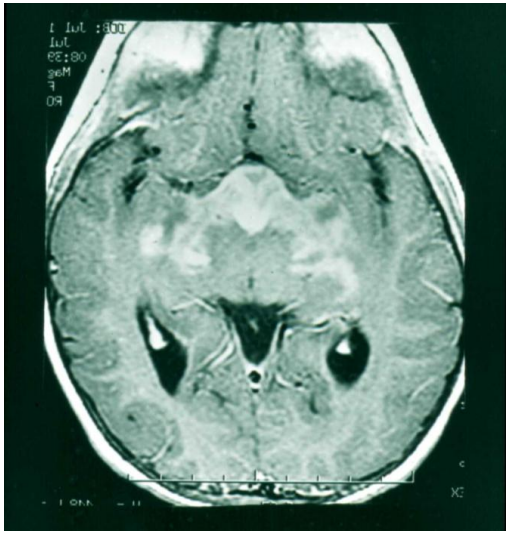
Randomised/controlled trials	**0**
Only progressive tumours	**9**
Multicentric studies	**6**
Exclusively OPG	**4**
NF1 patients	**15-45%**
Median follow-up time	**30m-6.5yrs**



Chemotherapy for optic pathway gliomas/PA

Systematic (literature) review – 9 Selected papers

Numbers of patients	**24-210**
Median age at diagnosis	**17m-5yrs**
NF1 patients	**15-45%**
Median follow-up time	**30m-6.5yrs**
No pure optic nerve glioma	**7**
Definition of progression	
RM only	**2**
RM + clinic	**6**



Chemotherapy for optic pathway gliomas/PA

Systematic (literature) review – 9 Selected papers

 # 1 3 yrs PFS 68% +/- 7%

 # 2 3 yrs PFS 73%

 # 3 3 yrs PFS 64% (95%CI 54-76%)

 # 4 5 yrs PFS < 50%

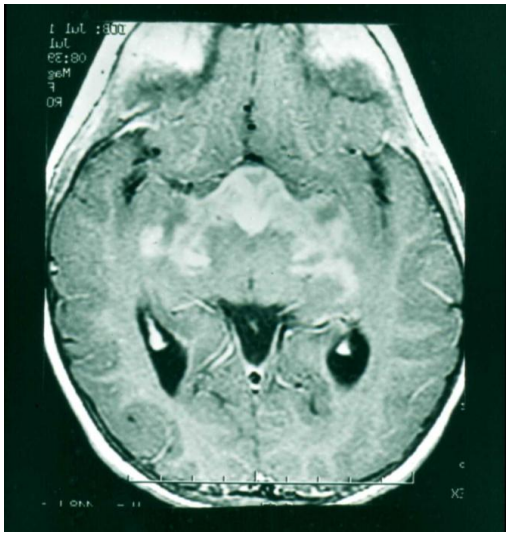
 # 5 5 yrs PFS 55.8%

 # 6 5 yrs PFS 34%

 # 7 5 yrs PFS 61% +/- 5%

 # 8 5 yrs PFS 45.2% (95%CI 35-54%)

 # 9 time to progression: median 132 wks



Chemotherapy for optic pathway gliomas/PA

Systematic (literature) review – 9 Selected papers

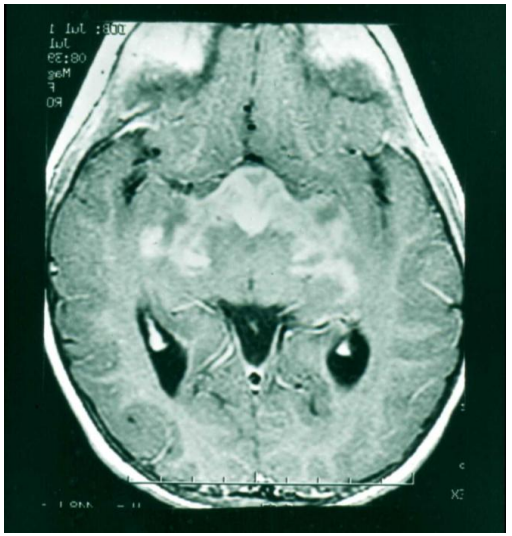
# 1	3 yrs PFS 68% +/- 7%	VCR/CARBO
# 2	3 yrs PFS 73%	CARBO/VP16
# 3	3 yrs PFS 64% (95%CI 54-76%)	CDDP/VP16
# 4	5 yrs PFS < 50%	VCR/ACT-D
# 5	5 yrs PFS 55.8%	CARBO
# 6	5 yrs PFS 34%	BB-SFOP
# 7	5 yrs PFS 61% +/- 5%	VCR/CARBO
# 8	5 yrs PFS 45.2% (95%CI 35-54%)	VCR/CARBO
# 9	time to progression: median 132 wks	TPDCV

Chemotherapy for optic pathway gliomas /PA

Systematic (literature) review – 9 Selected papers

Relevant conclusions:

- **no randomized/control trials**
- **most of the trials have shown some "efficacy" in term of PFS**
- **difficult to compare results**
- **all trials methodological limitations (e.g. selection bias)**
- **difficult to give a clear-cut "take home" message**



Chemotherapy for optic pathway gliomas/PA

Systematic (literature) review – 9 Selected papers

# 1	3 yrs PFS 68% +/- 7%	VCR/CARBO
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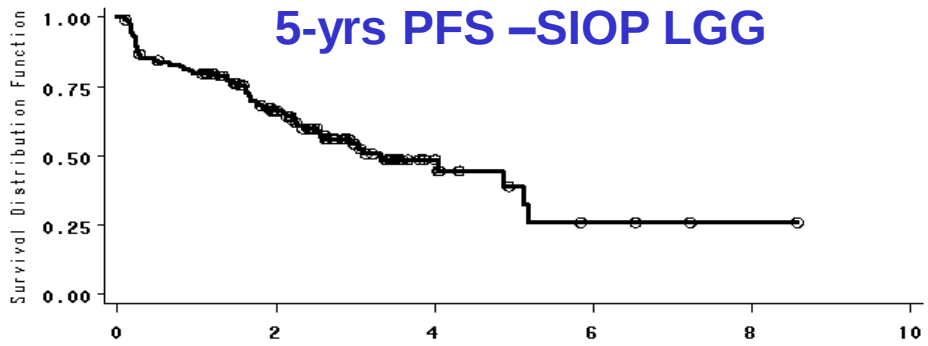
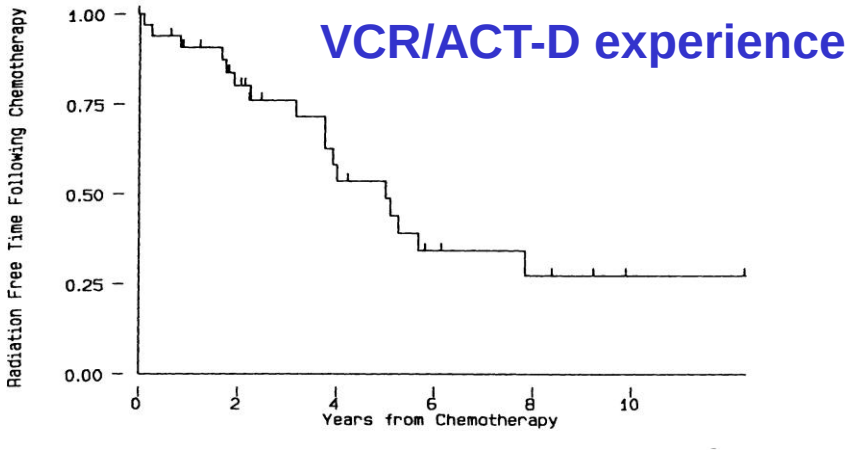
# 8	5 yrs PFS 45.2% (95%CI 35-54%)	VCR/CARBO
# 9	time to progression: median 132 wks	TPDCV

Chemotherapy for optic pathway gliomas/PA

Systematic (literature) review – 9 Selected papers

These curves don't seem to plateau at least for the first 6 years

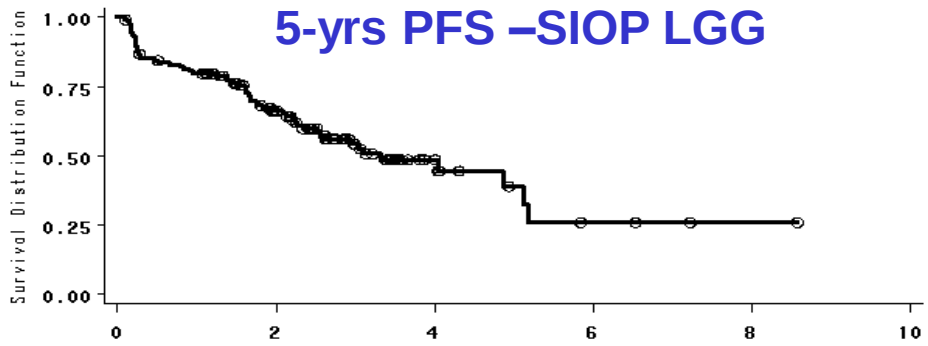


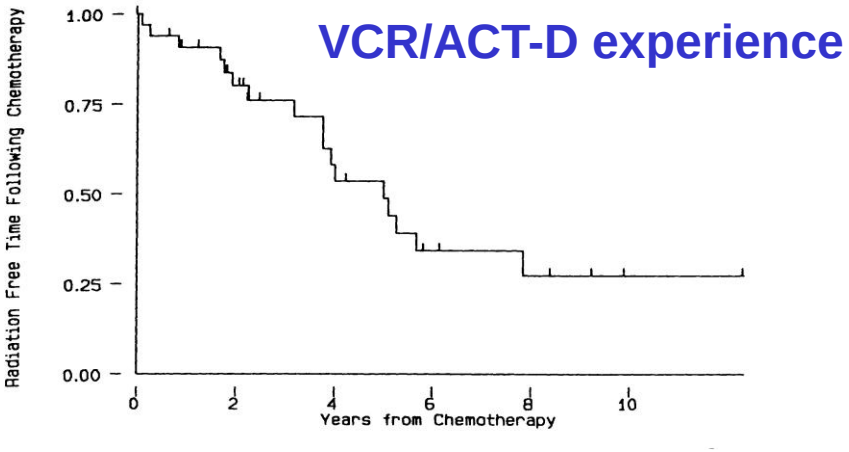


Chemotherapy for optic pathway gliomas/PA

Systematic (literature) review – 9 Selected papers

Thus, what is the actual role of CT on childhood LGG?

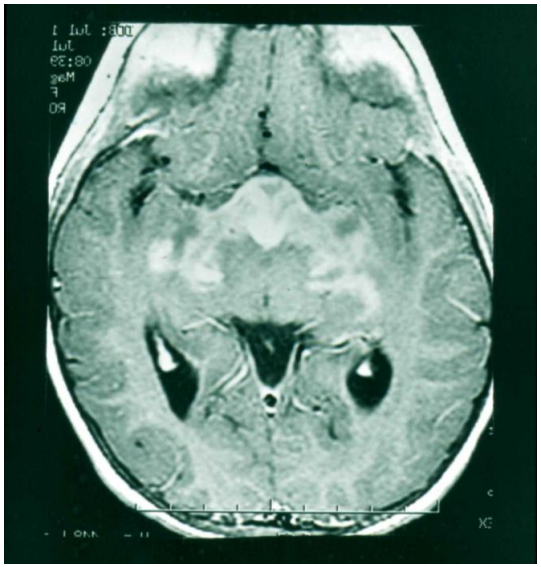




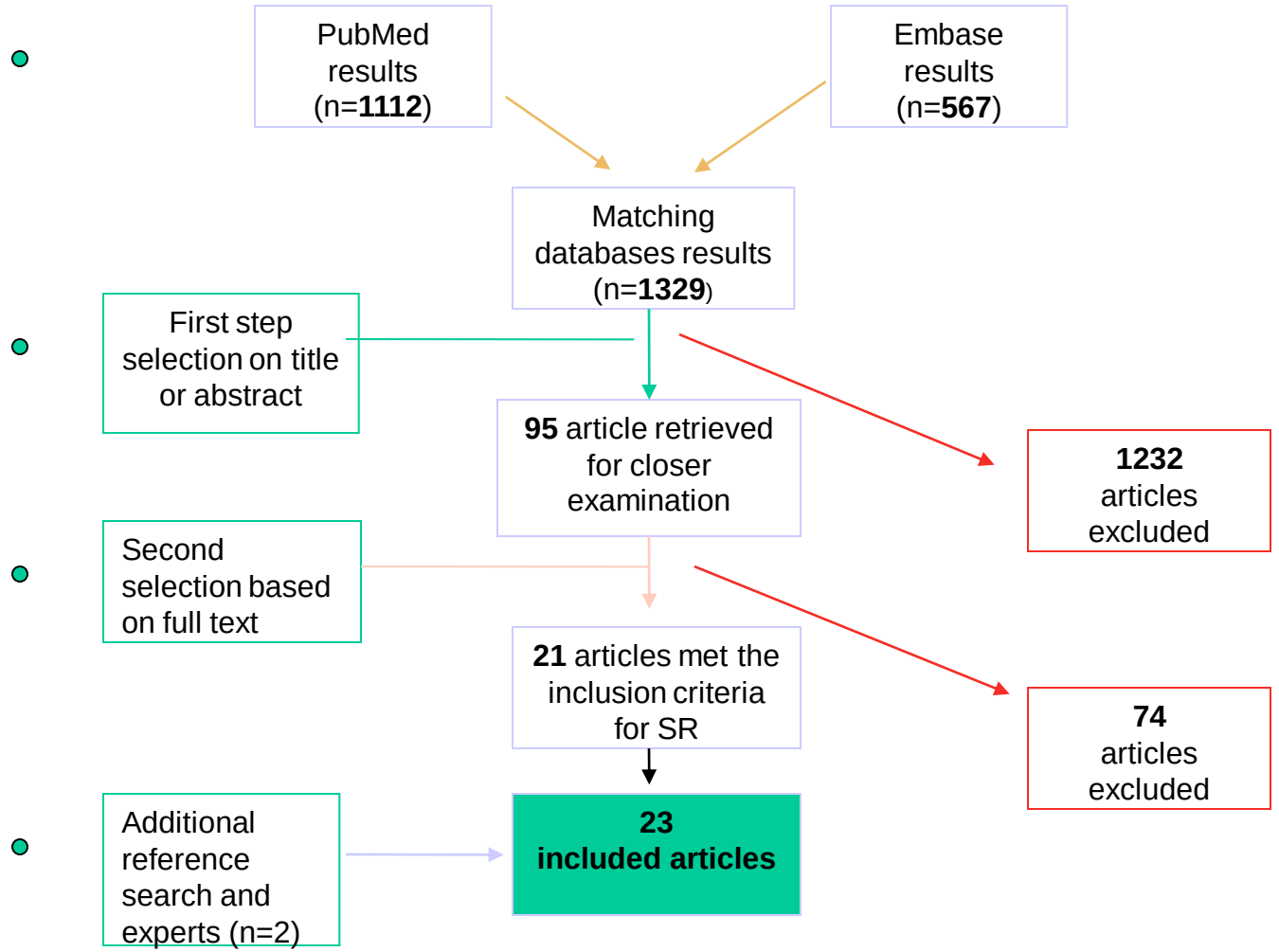
Optic pathway gliomas/PA – Which prognostic factors

Systematic (literature) review –

Randomised/controlled trials	**0**
Only progressive tumours	**9**
Multicentric studies	**6**
Exclusively OPG	**4**
NF1 patients	**15-45%**
Median follow-up time	**30m-6.5yrs**

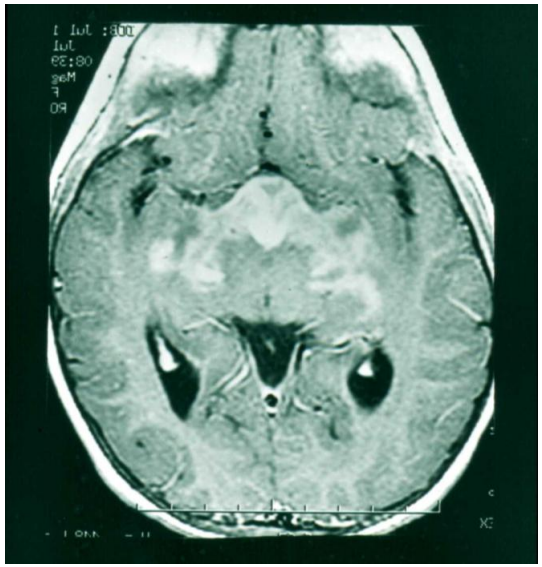


OPG systematic review – Which prognostic factors?



OPG/PA literature review - Which prognostic factors?

Papers reviewed	**23**
prospective	**16**
retrospective	**7**
Inter-observer agreement	**98%**
Reasons for exclusion	
review	**4**
mean age < 18 yrs	**1**
no PF analysis	**30**
< than 20 patients	**19**
others reasons	**20**



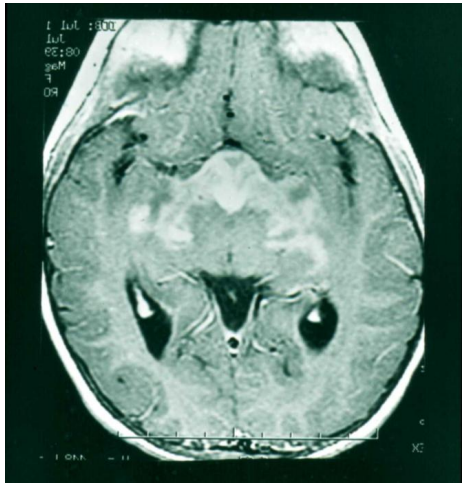
OPG/PA literature review - Which prognostic factors for Progression Free Survival?

Age < 1 year - Three very good quality prospective studies; by multivariate analysis.

1 RR (<1yr vs >1yr)= 1.8 (95% CI 1.02-3.02);

2 HR (1-4yr vs <1yr)= 0.51 (95% CI 0.26-1.02);

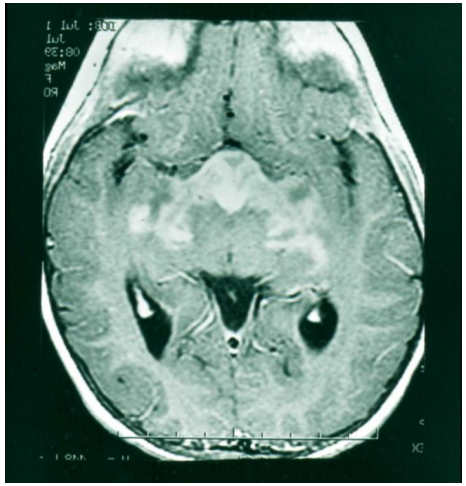
3 HR (1-5yr vs <1yr)= 0.44 (95% CI 0.27-0.72)



OPG/PA literature review - Which prognostic factors for Progression Free Survival?

NF1 status: one study without methodological limitation reported by multivariate analysis: RR (NF1+ vs NF1-) = 0.47 (95% C.I.=0.22-0.99) for PFS

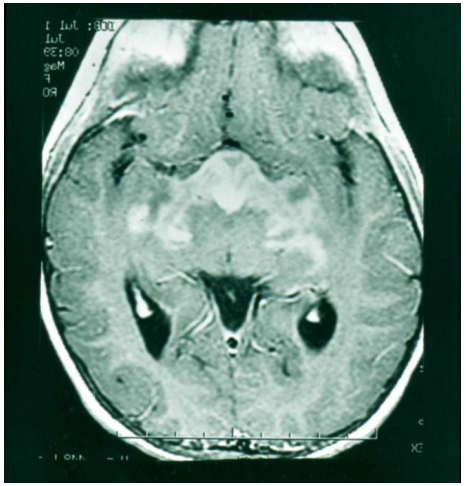
Hypothalamic/chiasmatic tumor (Dodge III) was a significant prognostic factor for PFS or visual loss by multivariate analysis in 2/8 studies; not reported RR or HR



OPG/PA literature review - Which prognostic factors for Progression Free Survival?

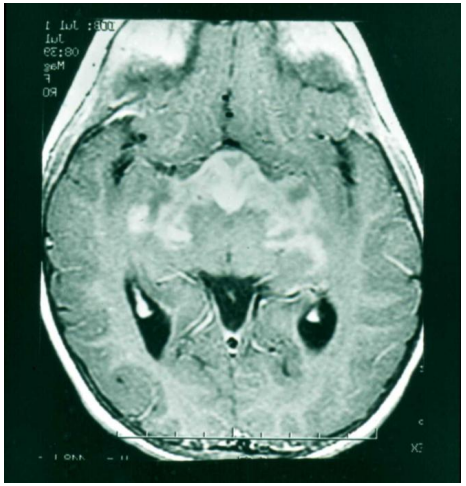
Age is a clear and independent prognostic factor for PFS, with children **less than one year** old having a higher risk for progression

Absence of NF1 and posterior tumor site may have significant prognostic value for progression, but no clear evidences support their clinical relevance,



OPG/PA literature review - Which prognostic factors for Progression Free Survival?

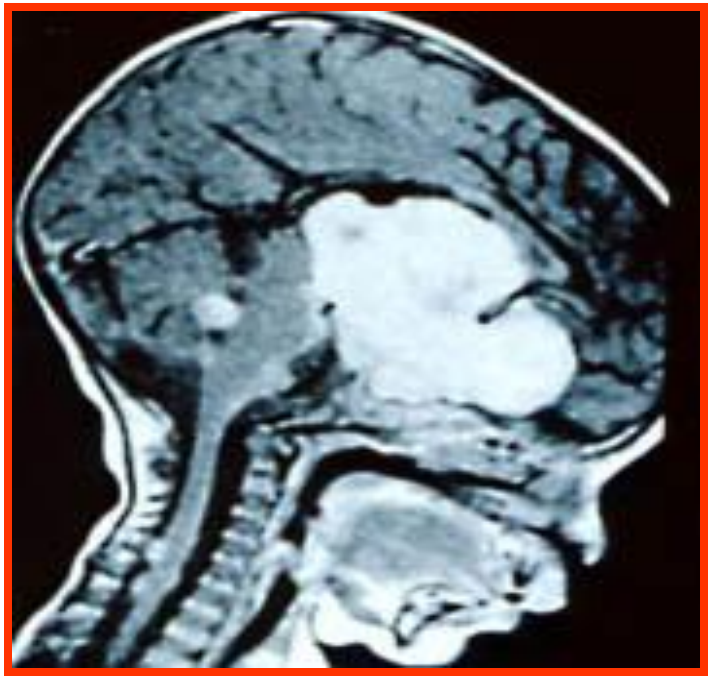
Age < 1 year as a major prognostic factor!….Who are those young children?



The answer to this question is still not entirely clear; no series so far published of children with LGG younger than 1 year

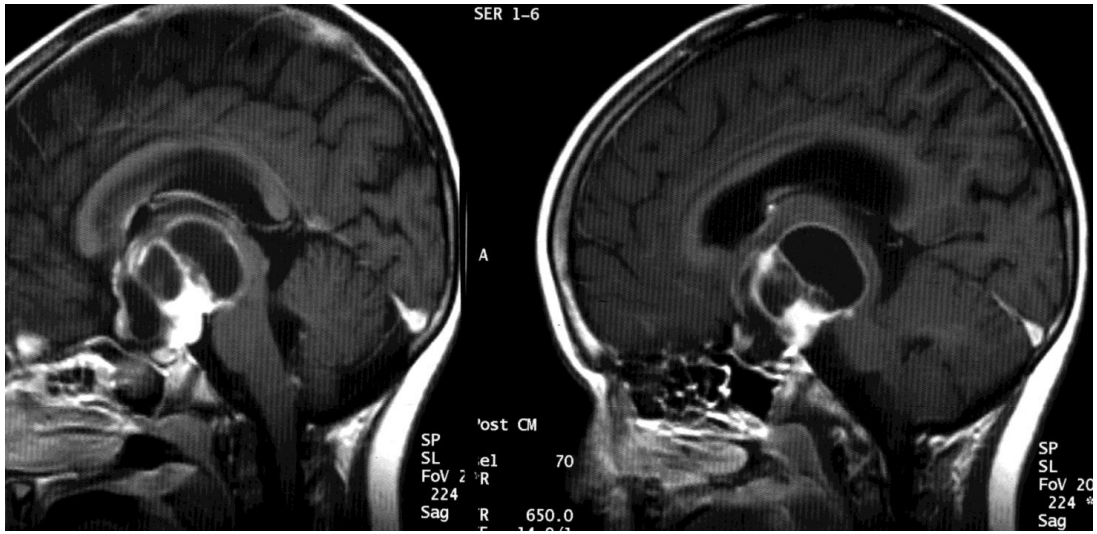
OPG/PA in children less than one year of age

Some of them have huge neoplasm



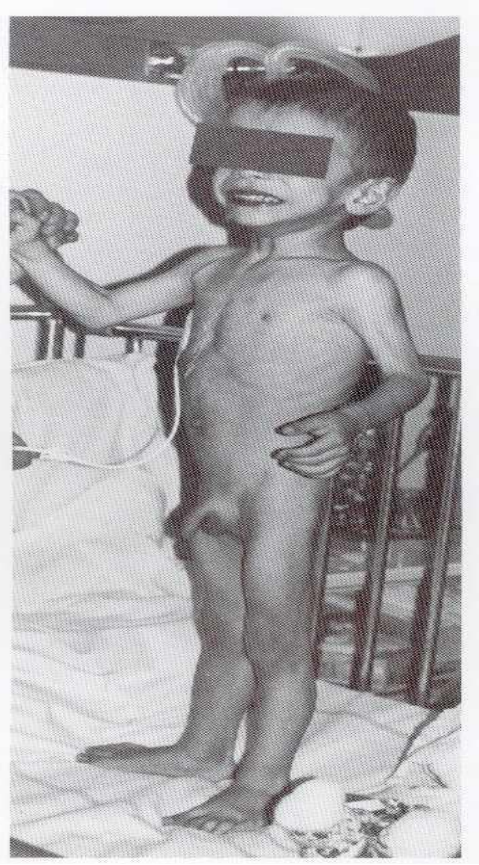
OPG/PA in children less than one year of age

Some of them have huge neoplasm associated with potentially lethal cystic lesions and….



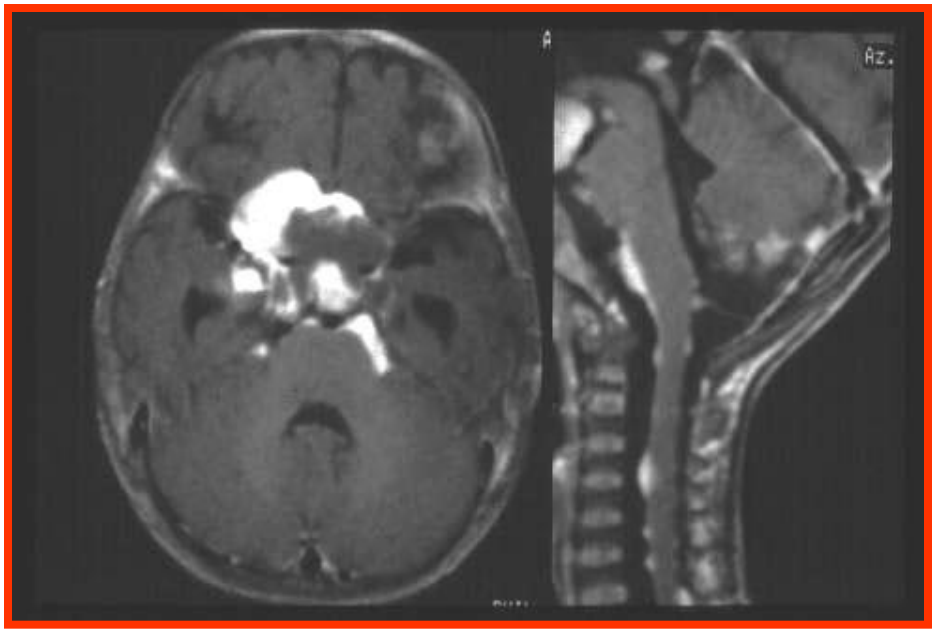
OPG/PA in children less than one year of age

…and diencephalic syndrome
(which by itself it doesn't seem to count)



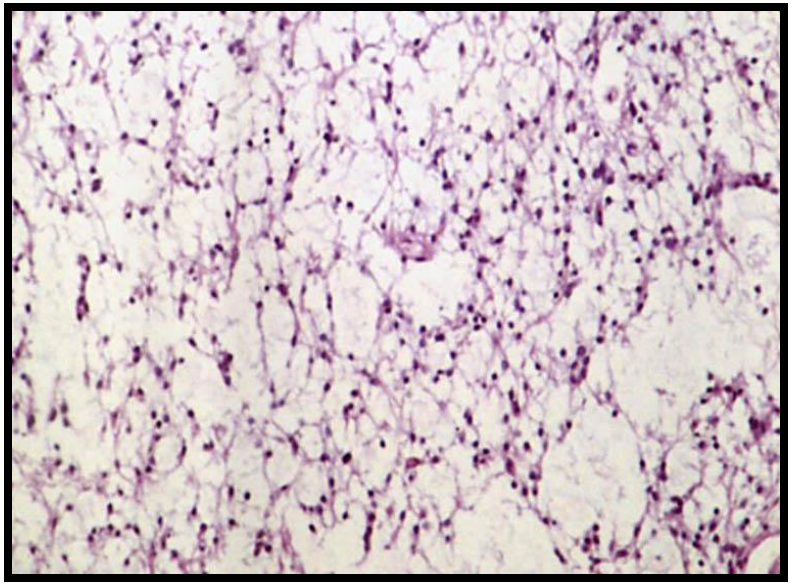
OPG/PA in children less than one year of age

Some of them have disseminated disease, but also this doesn't seem to count that much



OPG/PA in children less than one year of age

Some of them have a monomorphous pilomixoid tumor (a different entity from the classic pilocytic astrocytoma)

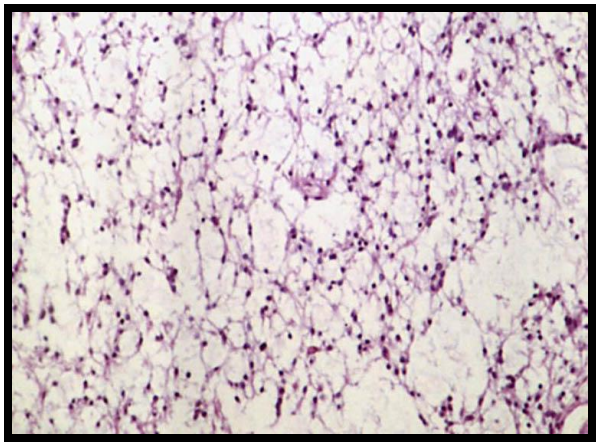


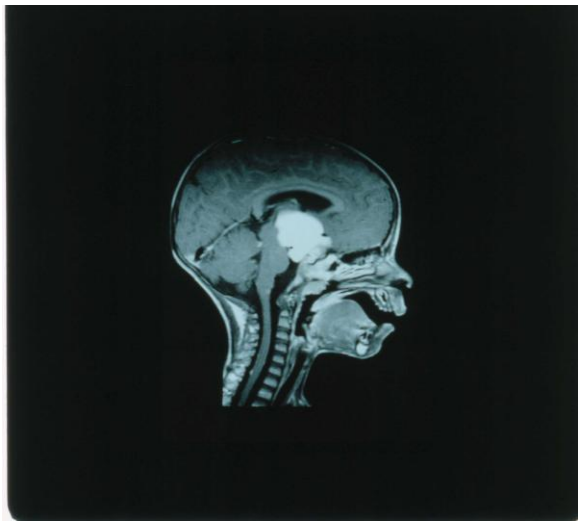
OPG/PA in children less than one year of age

Pediatric Astrocytomas with Monomorphous Pilomyxoid Features have a less Favorable Outcome.

From a neuroradiologic point of view they are undistiguishable from classic pilocytic astrocytoma

Tihan et al. J Neuropath Exp Neurol 58: 1061-1068, 1999





Pilocytic and pilomyxoid hypothalamic / chiasmatic astrocytomas.

Komotar RJ et al Neurosurgery. 2004

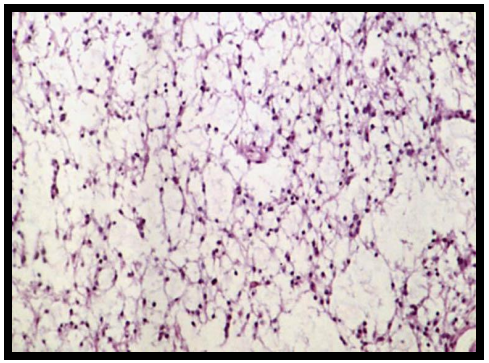
“Within the follow-up period, 7/21 patients with PMAs (33%) and 7/42 patients with PAs (17%) died as a result of their disease”

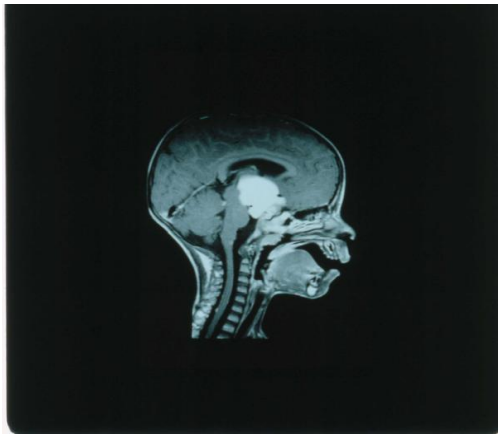
PMA = pilomyxoid astrocytoma; PA = Pilocytic astrocytoma

Pilocytic and pilomyxoid hypothalamic / chiasmatic astrocytomas.

Komotar RJ et al Neurosurgery. 2004 Jan;54(1):72-9;

Conclusions:
Hypothalamic/chiasmatic PMAs occurred in a significantly younger population and were associated with substantially shorter PFS and OS times than were typical PAs…..





The therapeutic approach

The clinical dilemma

3. Why to treat?

The answer:

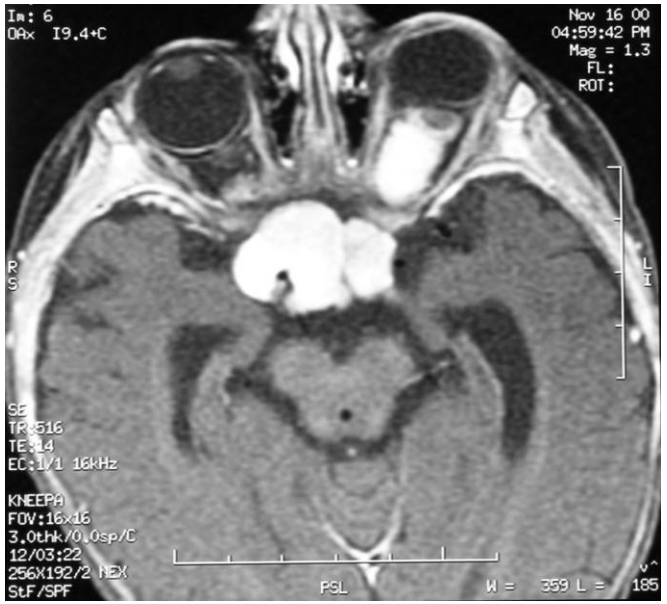
3. To save life???

To stop the tumour from growing!

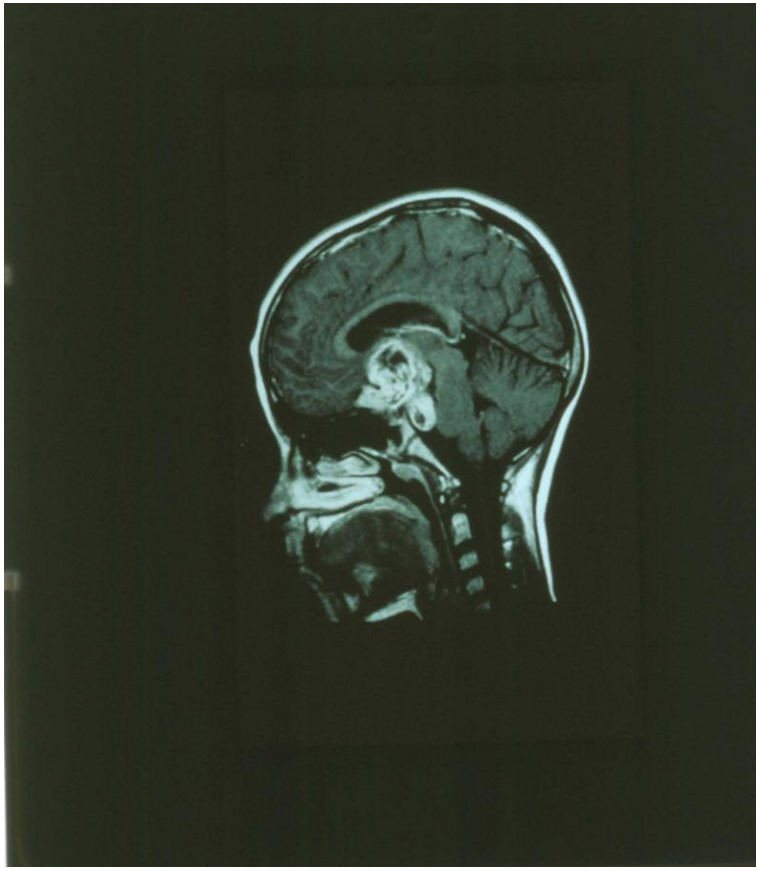
To make the tumour smaller!?

To relieve symptoms/sings!

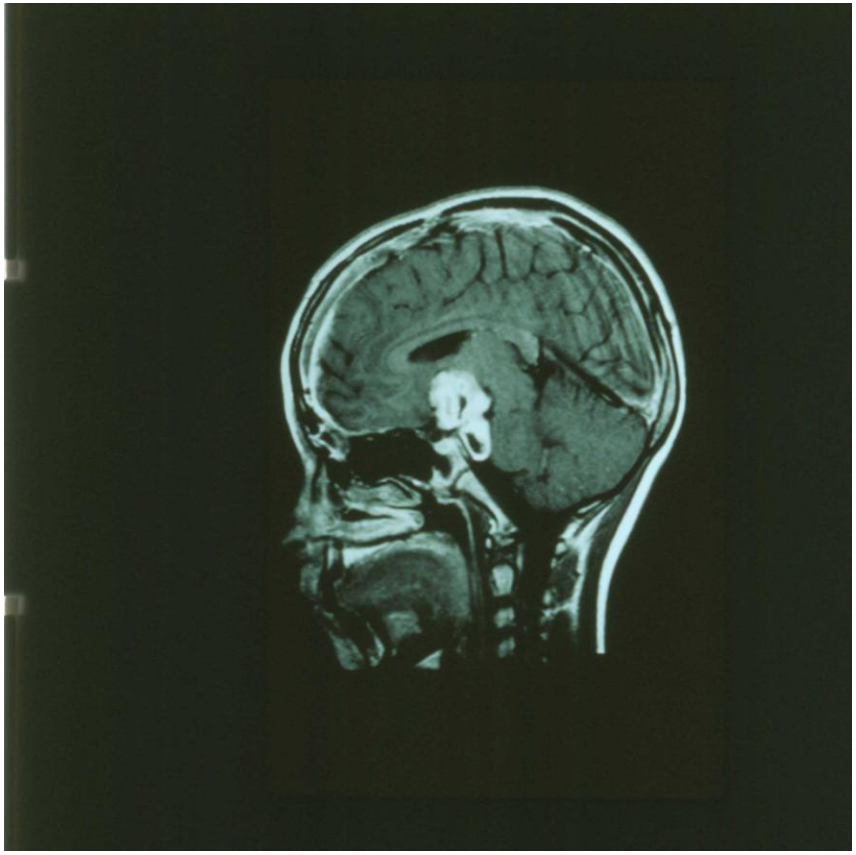
To delay RT!



Before CT

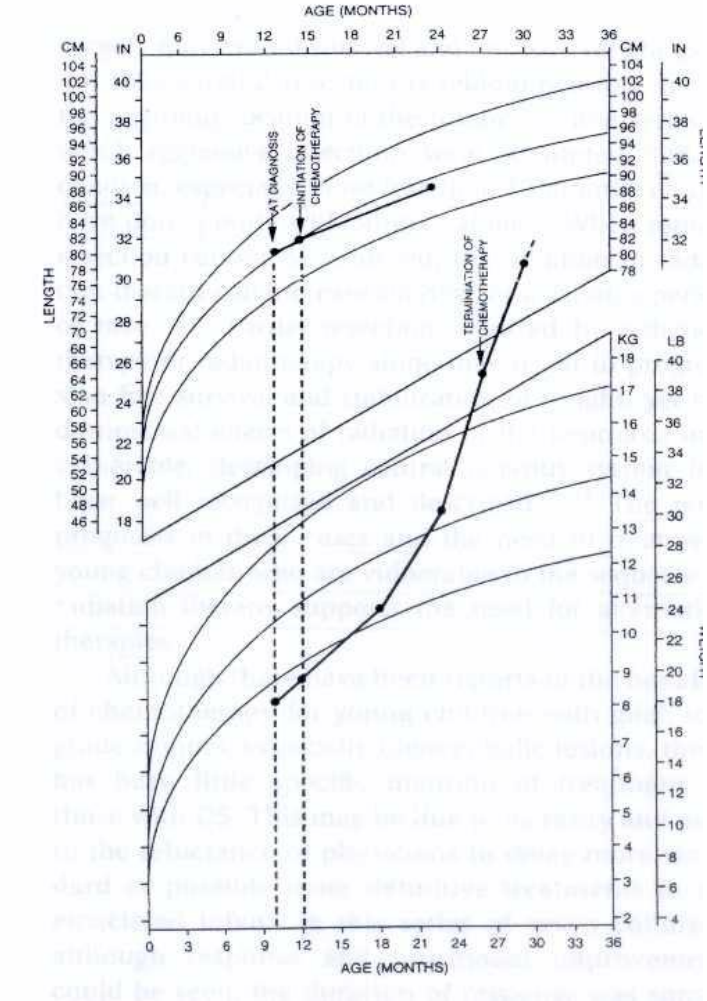


After CT

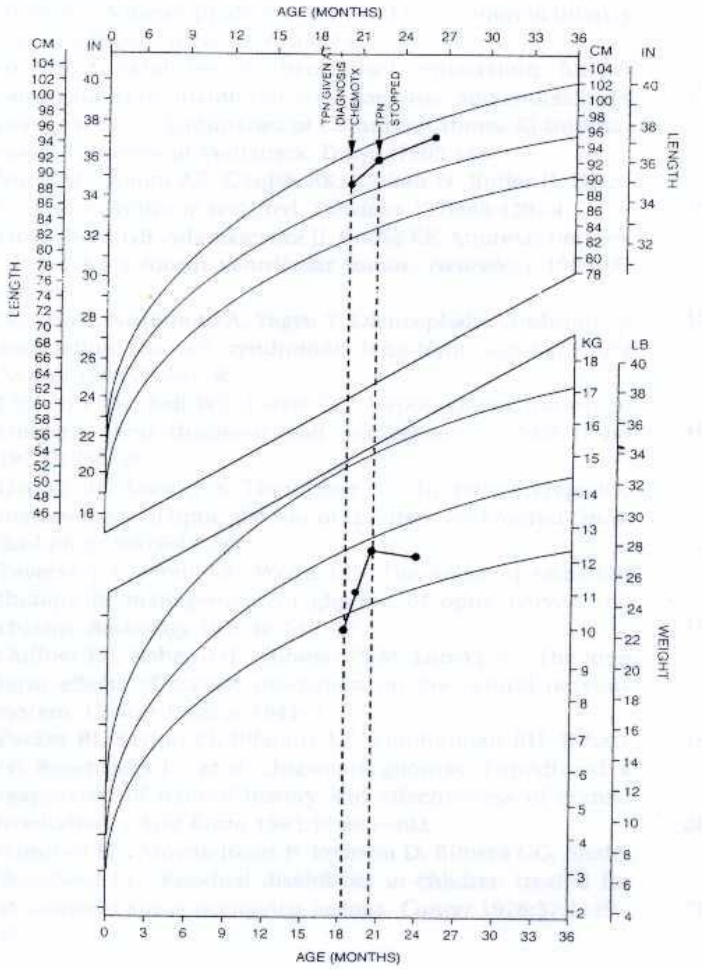


Treatment of diencephalic syndrome with chemotherapy

Gropam AL. Cancer 1998

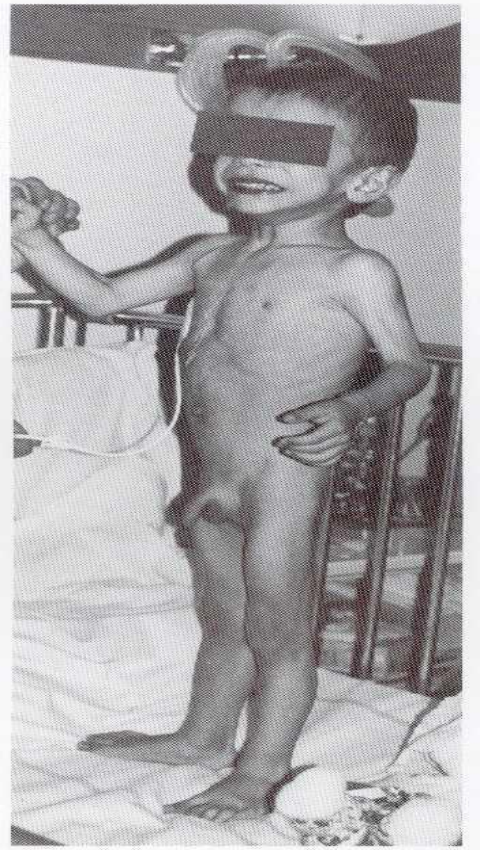


Growth curve in patient "responding to CT

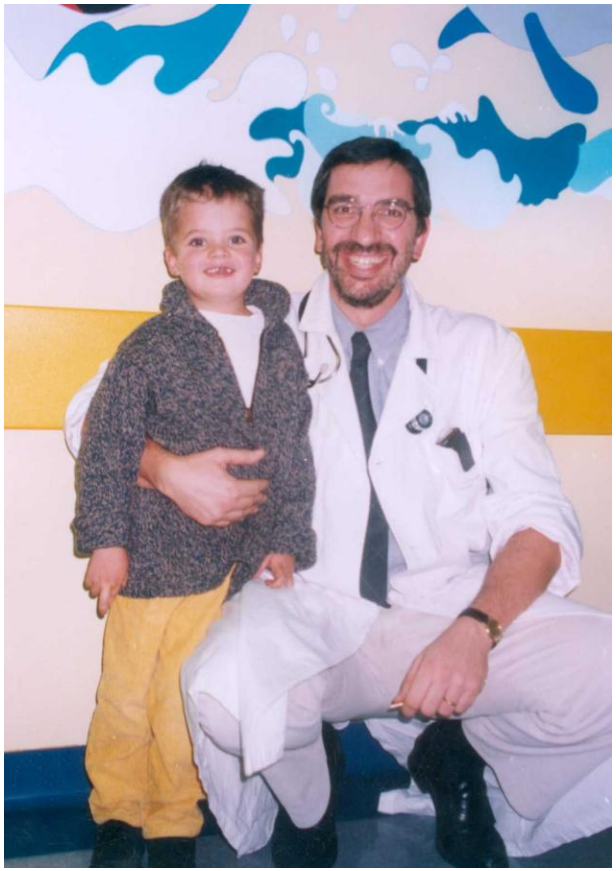


Growth curve in patient non"responding to CT

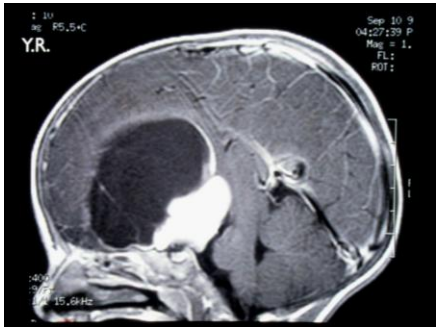
Before therapy

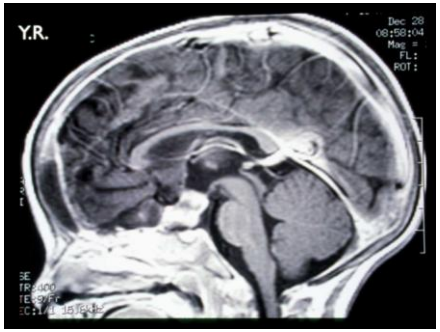


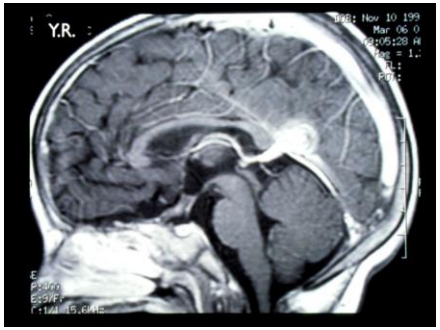
After chemotherapy only



Which is the functional outcome of these children, particularly in term of visual function?







Chemotherapy for OPG/PA in NF1 patients.

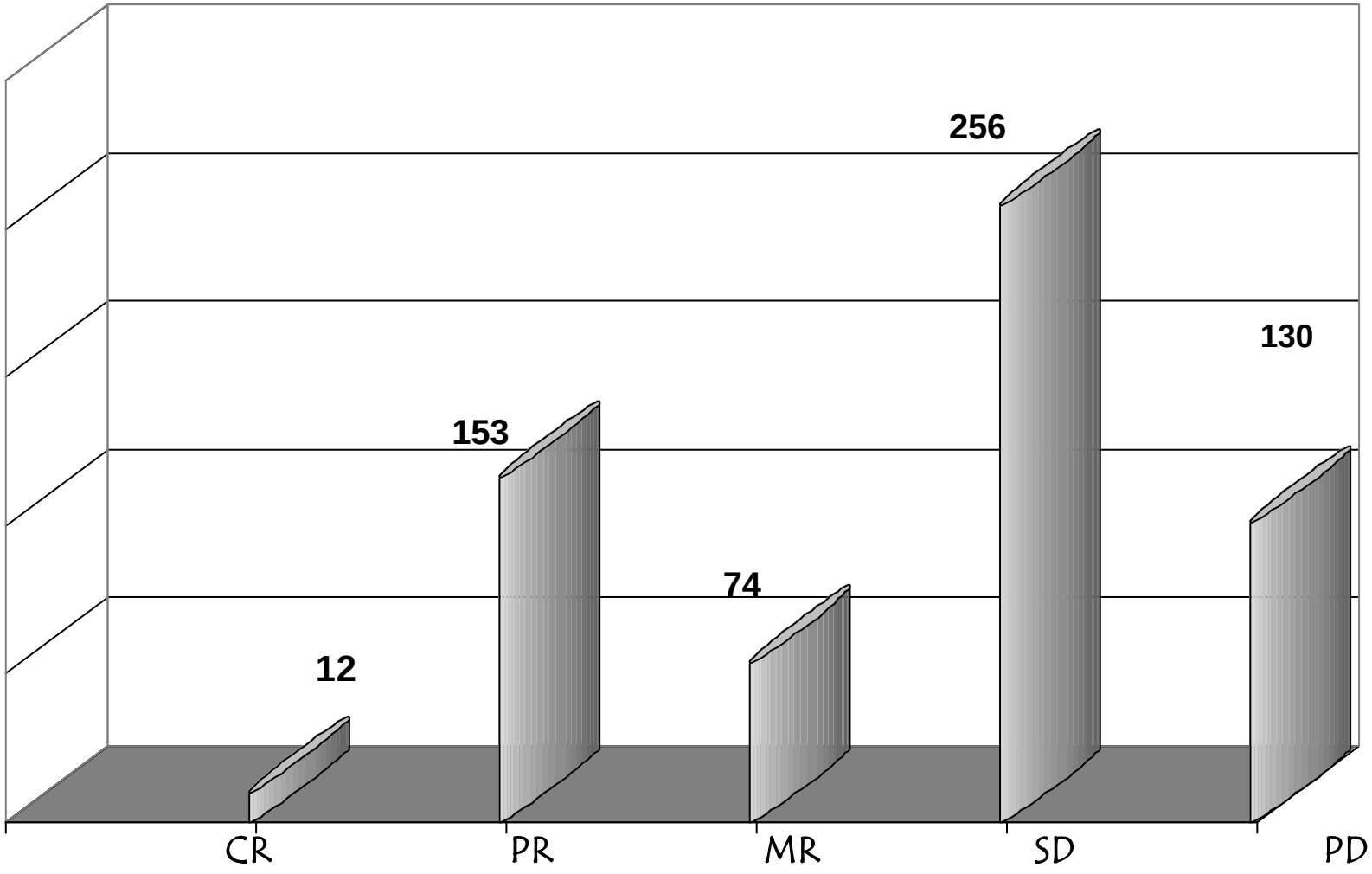
Have we ameliorated vision and, in general, the neurological and endocrionological functions of these children

Table 1 Presentation at progression and NF1. (*NS* not significant)

	With NF1 (n = 51)	Without NF1 (n = 55)	P
Clinical signs			
Severe visual loss	30	19	
Moderate visual loss	10	11	NS
Visual loss not measurable	11	25	
Nystagmus	4	13	0.03
Proptosis	11	3	0.03
Oculomotor palsy	6	12	NS
Seizures	2	6	NS
Ataxia	2	4	NS
Motor deficit	4	7	NS
Increased intracranial pressure	6	18	0.005
Diencephalic cachexia	2	7	NS
Diabetes insipidus	1	1	NS
Precocious puberty	5	2	NS
Radiological signs			
Dodge type I	5	1	
Dodge type II	11	6	NS
Dodge type III	35	48	
Infiltrating lesion	15	5	0.007
Tumoural lesion	36	50	NS

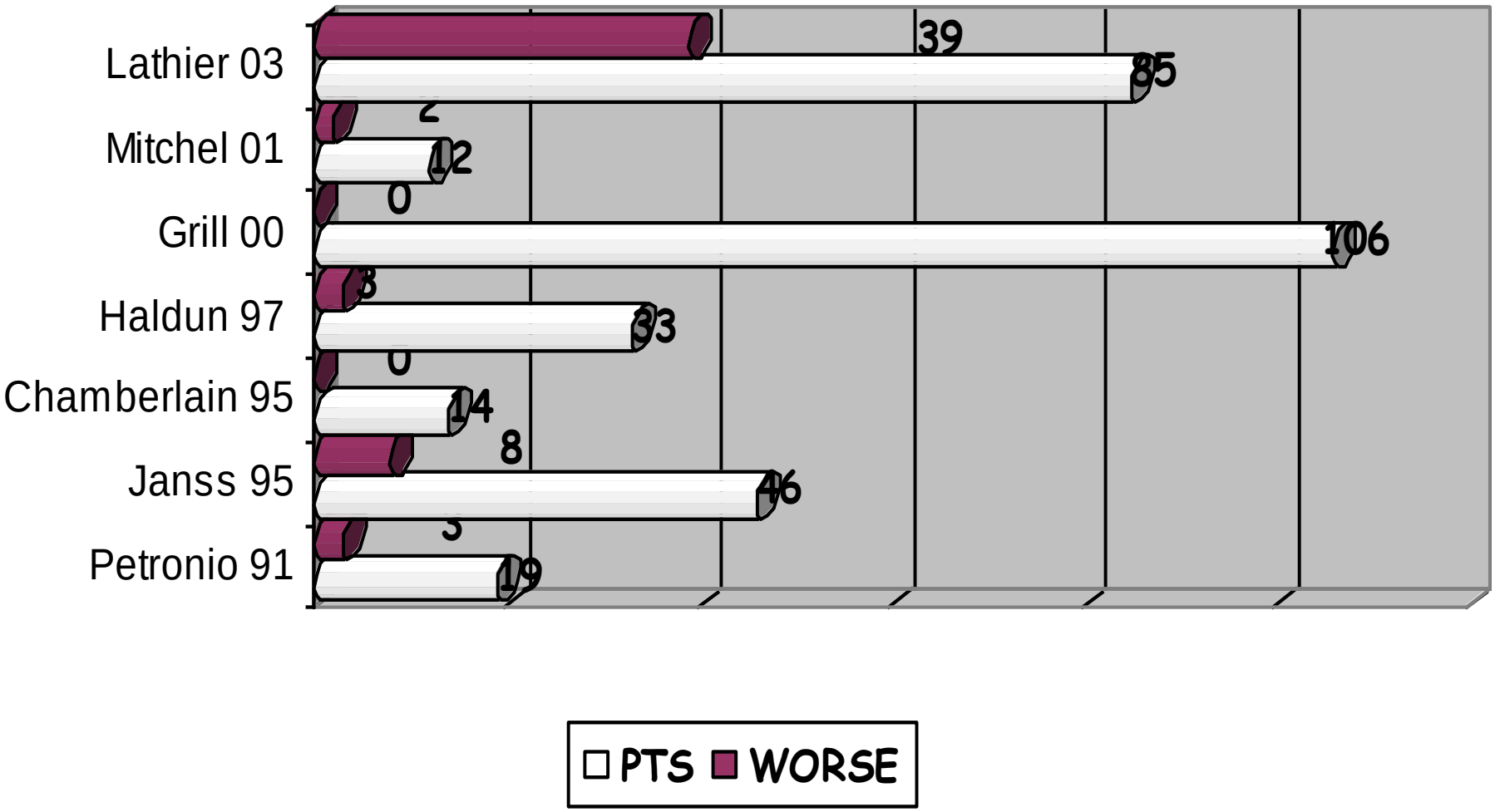
Chemotherapy for optic pathway gliomas/PA

Systematic (literature) review: visual function outcome



Chemotherapy for optic pathway gliomas/PA

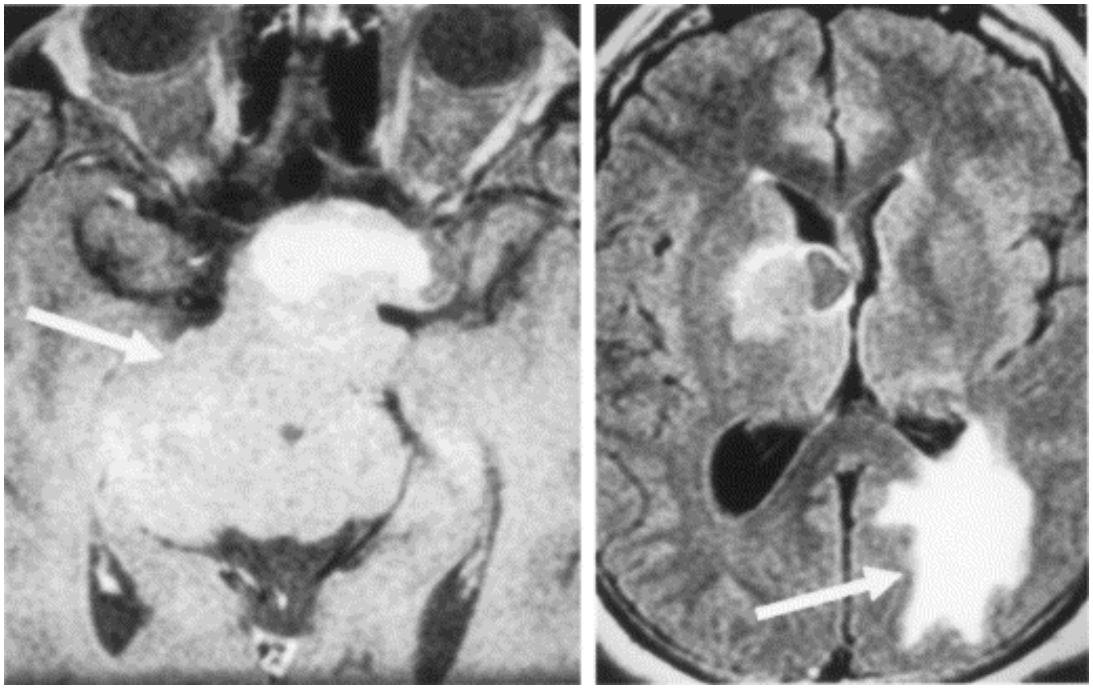
Systematic (literature) review: visual function outcome



OPG/PA in NF1 patients

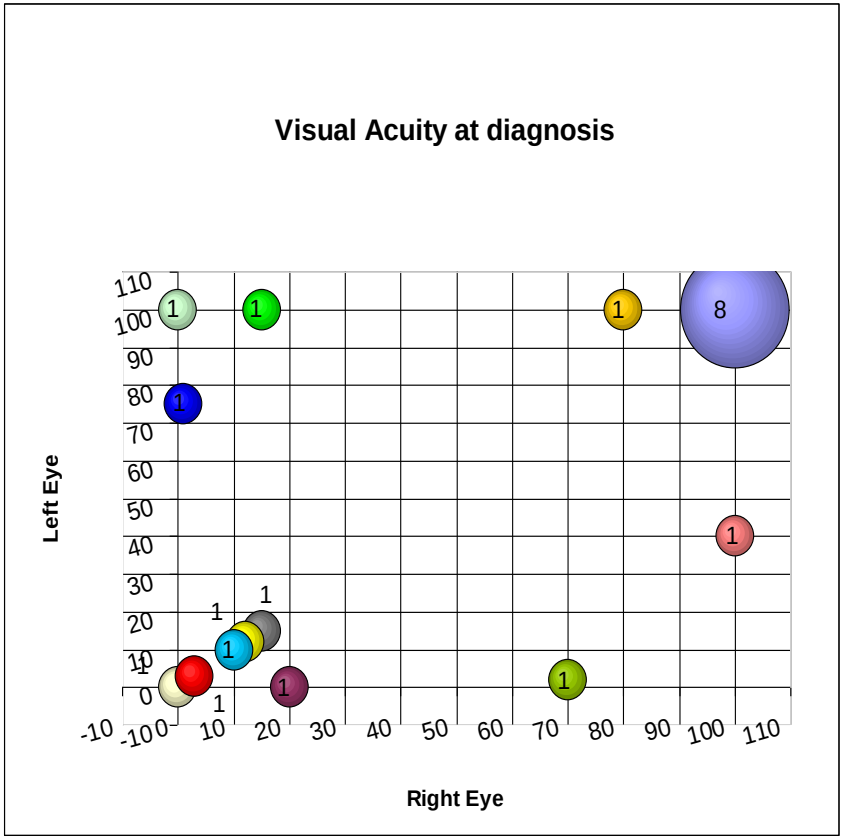
Involvement of the optic tracts and other post-chiasmal structures seem to be associated with a significantly higher probability of visual loss (*P* = .048)

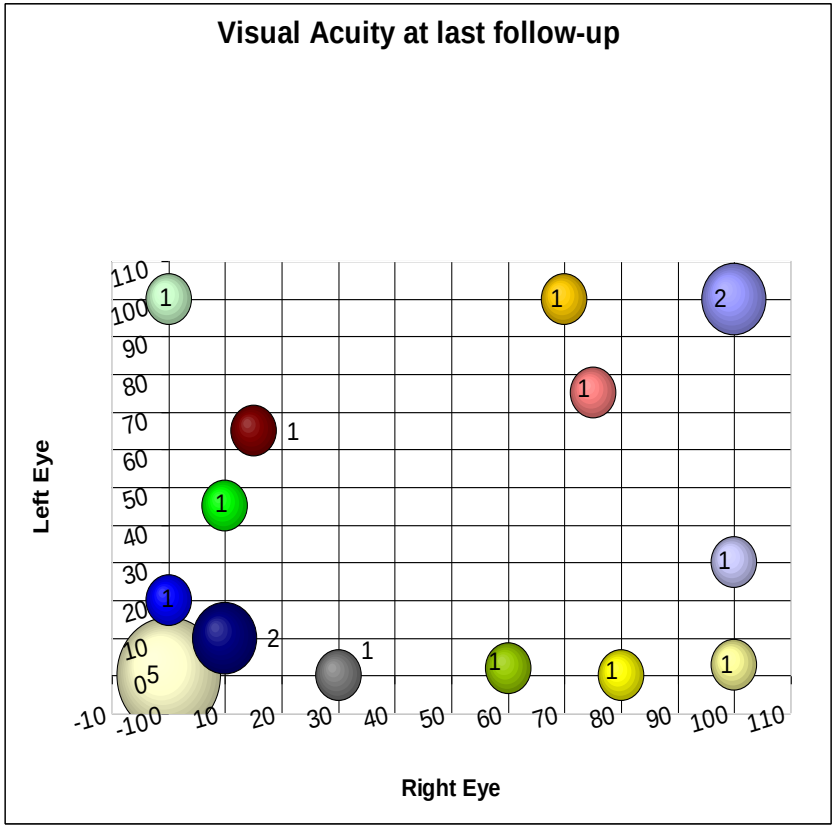
Grant T. Liu Am J Ophthalmol. 2004 Mar;137(3):407-14.



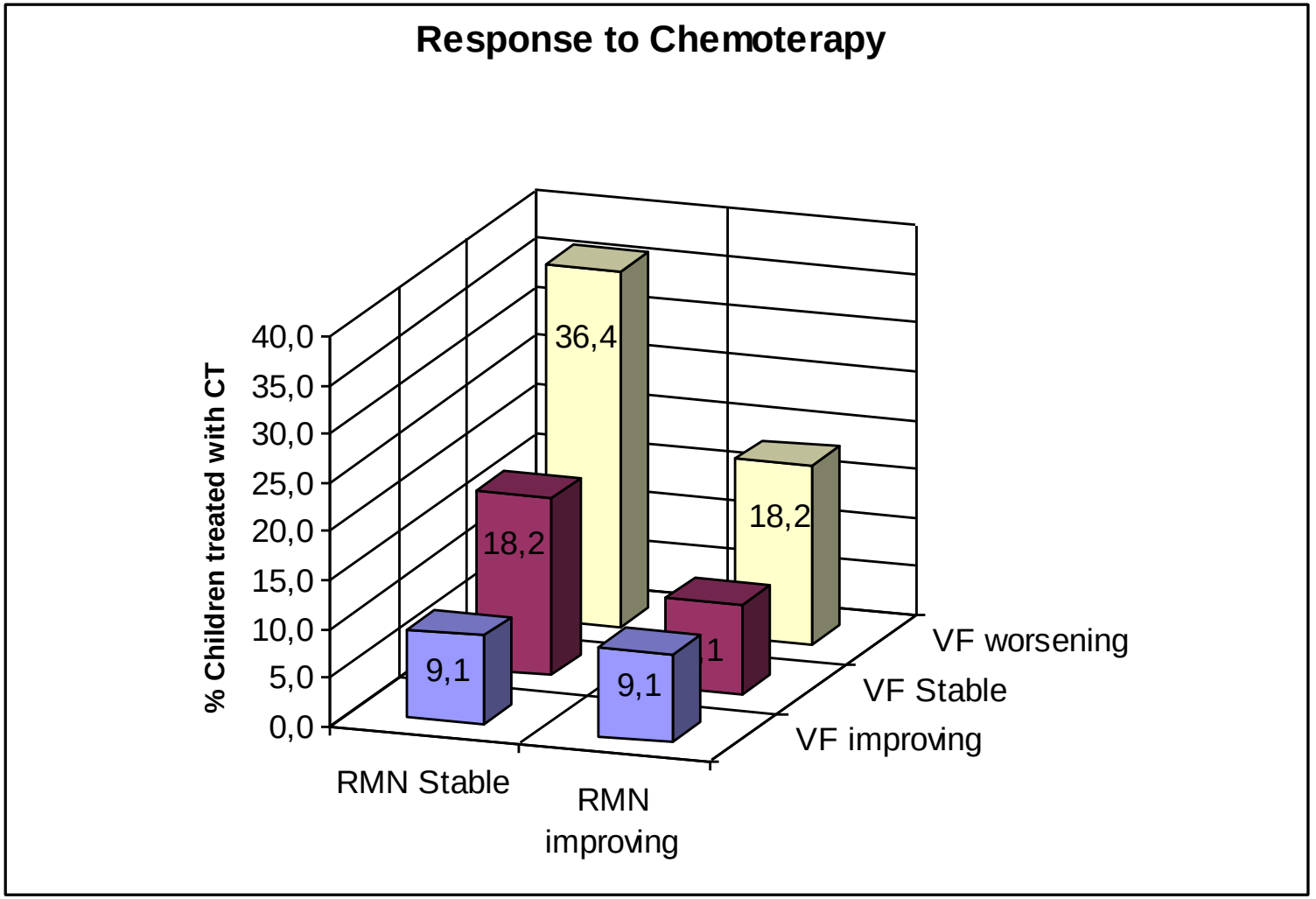
Contrast-enhanced T1-weighted axial MRI. (Left) Hypothalmic/chiasmal glioma (arrow). (Right) New lesion (arrow) involving the left optic radiation at age 14.

Optic pathway glioma in NF1 patients treated with Chemotherapy – Functional outcome





Optic pathway glioma in NF1 patients treated with Chemotherapy – Functional outcome



Optic pathway glioma in NF1 patients treated with Chemotherapy – Functional outcome

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Reason for treatment:

Progressive visual loss	8 (> 50%)
Increasing tumor volume	5
Both	2

Visual outcome of the 8 children treated for visual loss

Further deterioration	5 (visual acuity)
Stable vision	3
Improvement	none

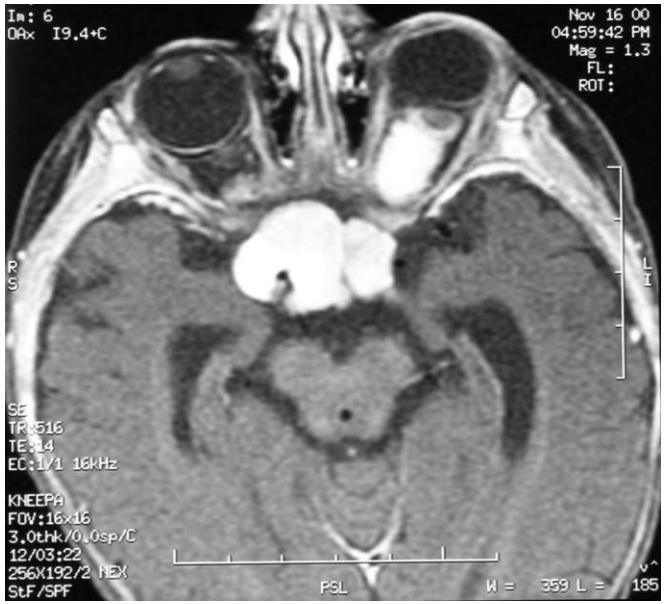
The therapeutic approach

The clinical dilemma

2. **How to treat, if treatment is needed?**

The answer:

2. **With an expert multidisciplinary team approach**

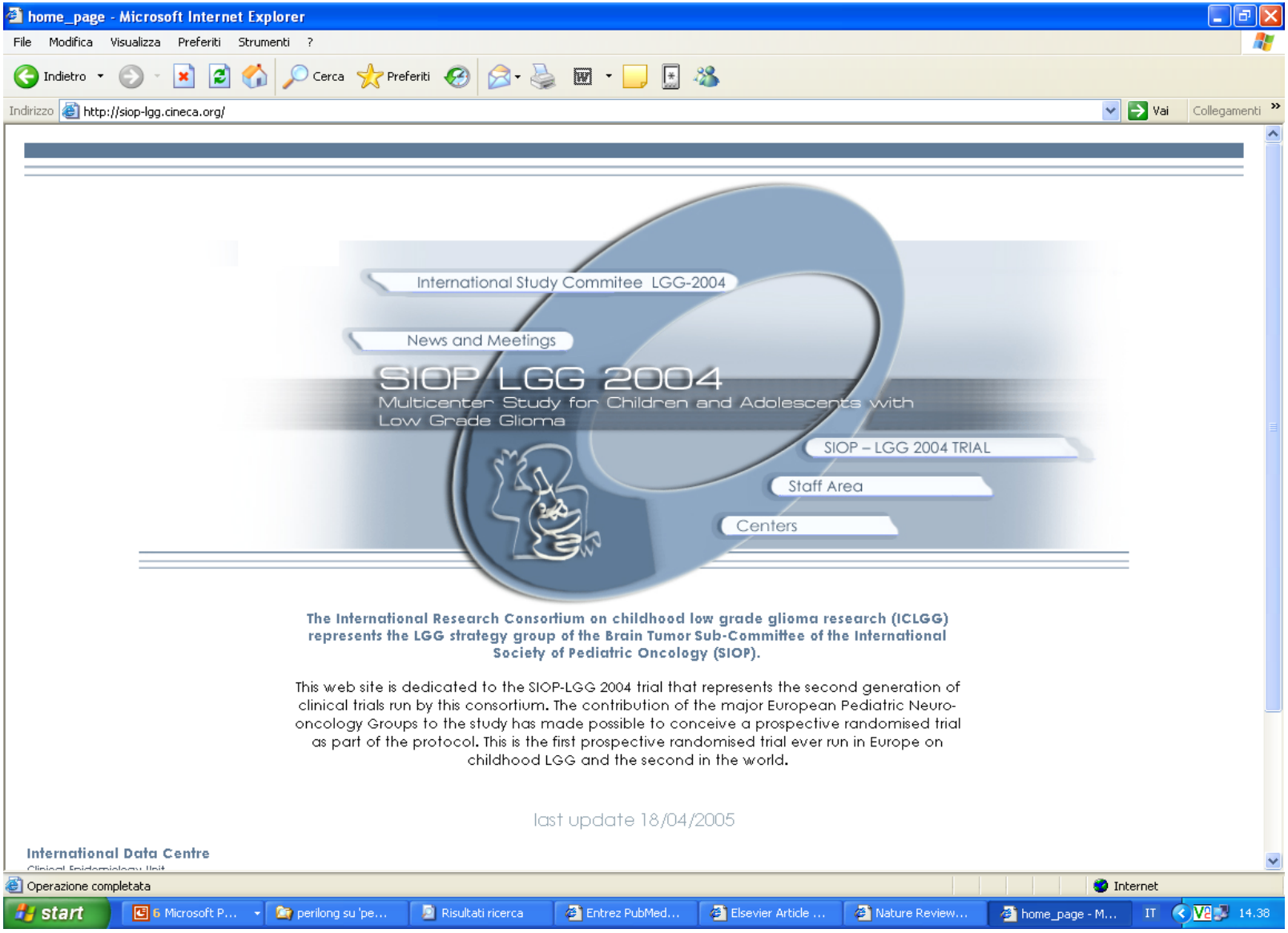


Childhood PA

The talk, “in brief”

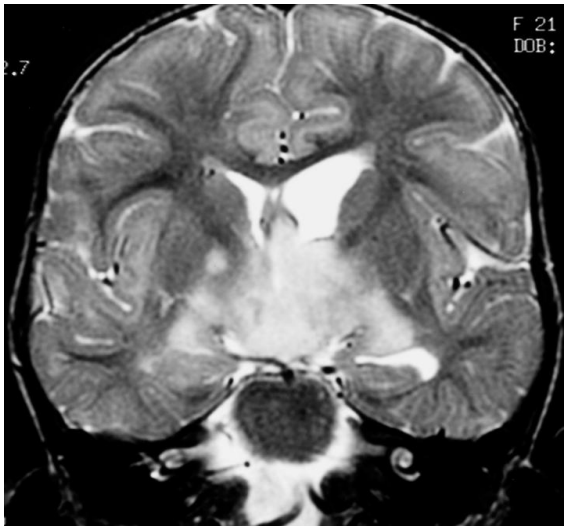
- ✓ Semantic & epidemiologic considerations
- ✓ Etiopatogenesis
- ✓ General clinical and biological considerations
- ✓ The therapeutic problems
- ✓ The therapeutic approach
- ✓ **Where to go**

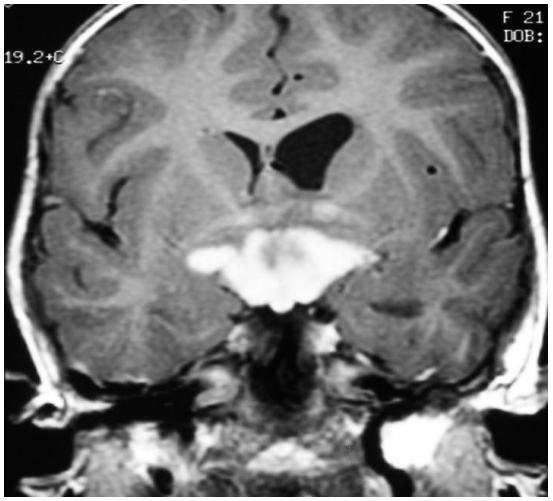
Clinical research response to all these open questions

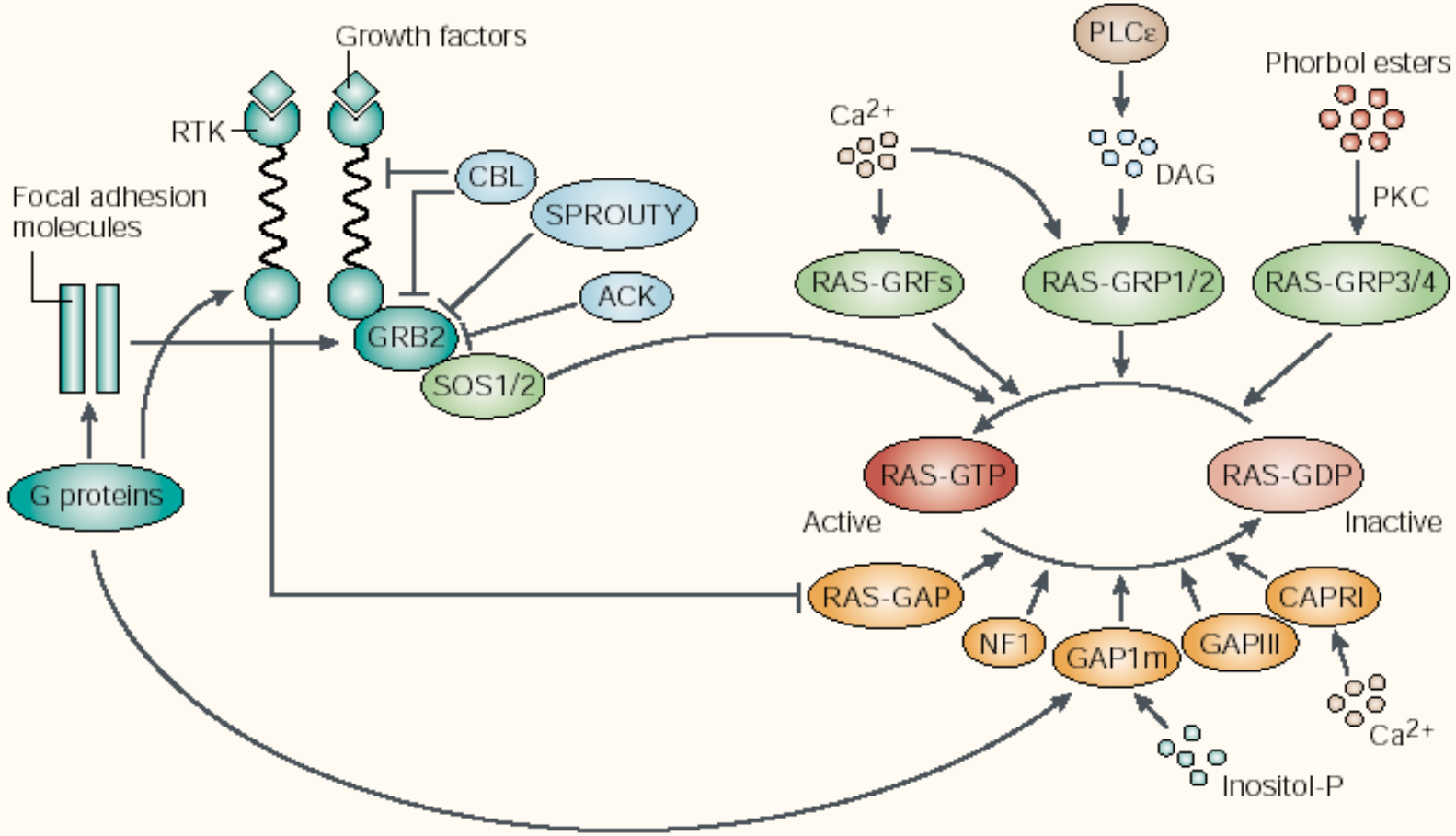


OPG/PA in NF1 patients

OPG/PA in NF1 children - A biological and clinical situation that forces us to think that there must bee something better than CT for treating these tumours







Marcos Malumbres and Mariano Barbacid

RAS oncogenes: the first 30 years

NATURE REVIEWS | CANCER VOLUME 3 | JUNE 2003

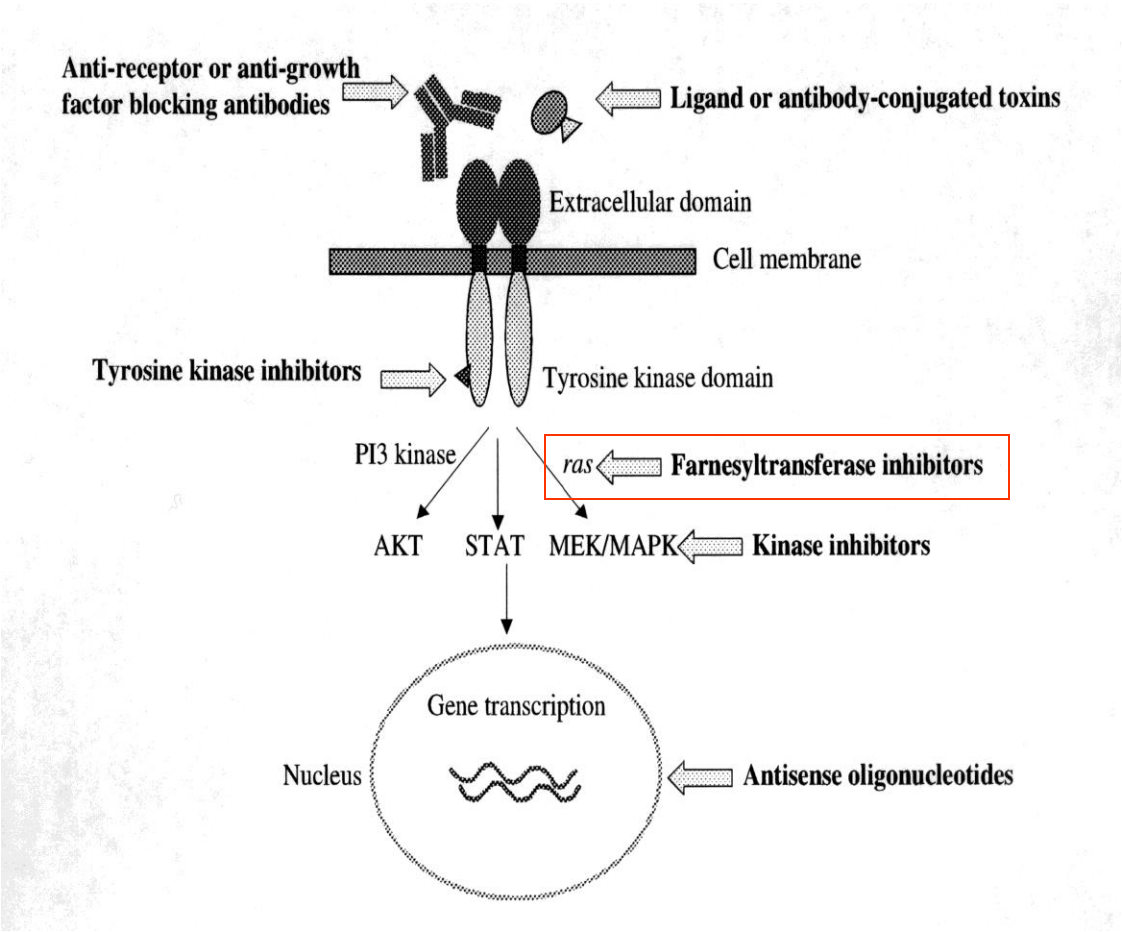
OPG in NF1 patients

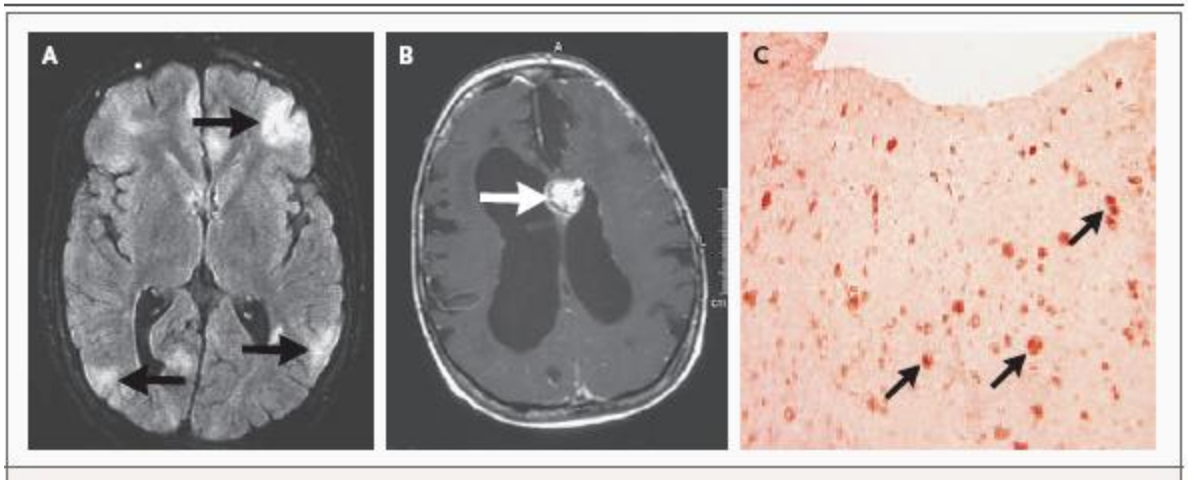
Farneysl transferase inhibitors

R115777

PD169451

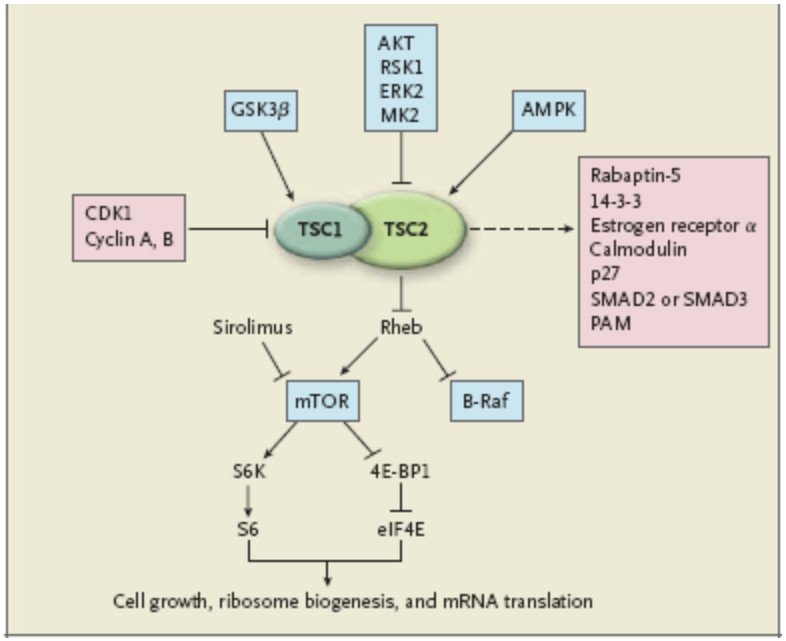
BMS-186511





Sub-ependymal giant cell astrocytoma (SEGA)

Can the lessons on the use mTOR inhibitors on the treatment of SEGA in Tuberous Sclerosis Complex, been used also to treat also LGG (ripamycin)?



PNAS
Proceedings of the National Academy of Sciences of the United States of America www.pnas.org

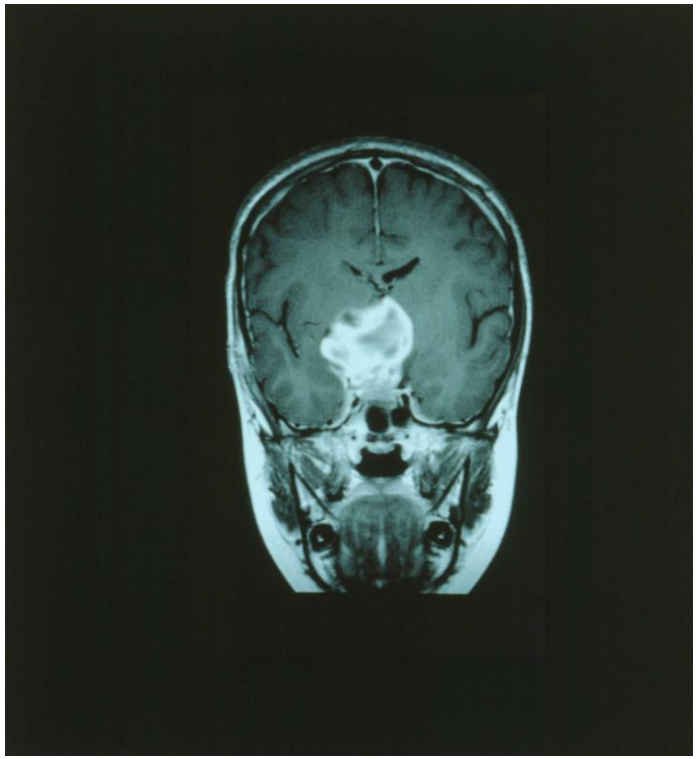
The NF1 tumor suppressor critically regulates TSC2 and mTOR

Cory M. Johannessen, Elizabeth E. Reczek, Marianne F. James, Hilde Brems, Eric Legius, and Karen Cichowski

The mTOR pathway is tightly regulated by neurofibromin. mTOR is constitutively activated in both *NF1*-deficient primary cells and human tumors in the absence of growth factors.

Tumor cell lines derived from NF1 patients, and a genetically engineered cell system that requires *Nf1*-deficiency for transformation, are highly sensitive to the mTOR inhibitor rapamycin.

Should we also consider to use Tyrosine Kinase Inhibitors (e.g. imatinib) for treating PA? Or anti-angiogenic factors?



Childhood Low Grade Glioma

The talk, “in summary”

✓ Semantic & epidemiologic considerations	PA
✓ Etiopatogenesis	not known
✓ General clinical and biological considerations	slow growing tumours
✓ The therapeutic problems	Who? When? Why?
✓ The therapeutic approach	Expert multidisciplinary approach
✓ Where to go	still difficult to say