102-1-26 S.P.C

小兒神經外科

劉惠如醫師/黃棣棟主任

Case summary

- Date of admission: 2012-11-28
- 14 y/o boy
- Past medical history:

  Allergic rhinitis
- Chief complain:

  Progressive headache, blur vision and unsteady gait for one month

Case summary

- Clinical course:

  This 14 y/o boy suffered from headache since one month ago. There was no fever but some nasal congestion at that time. He went to local ENT clinic for help and sinusitis was told so he took some medication and the symptom subsided. However, he suffered from intermittent headache attack last Tuesday. Except nasal congestion and ***headache, progressive lethargy and general weakness*** was also noted. Besides, he had ***vomiting for severe times. Poor appetite, poor activity***, and ever ***blur vision and behavior changed*** were found. He was brought to Taipei Mackay memory hospital for help. Under the impression of possible brain lesion, he received brain MRI study and left F-T-P large cystic lesion with midline shift and perifocal swelling was noted. The patient was transferred to Professor Wong's clinic for help.

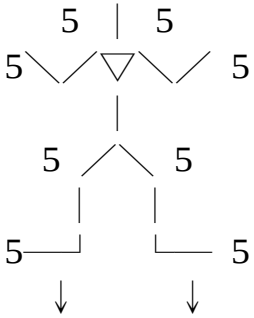
PE and NE

Neurological Examination:

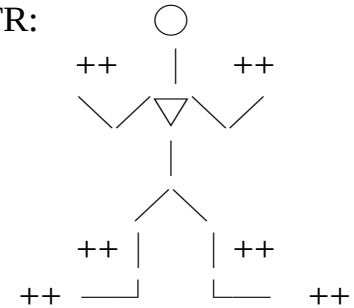
- GCS: E4V5M6, relative lethargy and general weakness
- JOMAC: ok
- CRANIAL NERVE
- CN II: Visual field: Intact
- Direct LR: R(+)/L(+), Consensual LR: R(+)/L(+)
- Pupil size: 2mm/2mm
- CN III, IV & VI:
  - Ptosis: nil, Proptosis: nil
  - EOM- full EOM
- CN V: Corneal reflex: intact, Jaw jerk: nil
- No sensory deficit
- CN VII: right facial palsy peripheral type
- CN VIII: No nystagmus
- CN IX & X: Gag reflex-R(+)/L(+), No uvula deviation
- Dysphagia: nil Dysarthria: nil Dysphonia: nil
- CN XI: Turning head: full
- CN XII: Tongue: no deviation, no fasciculation

MOTOR

MP:



DTR:



Barbinski sign : Negative
Both SLRT test : Negative

COORDINATION (Cerebellar sign)
Finger-nose-finger: no dysmetria
Heel-knee-shin: no dysmetria on Bil lower limbs
Rapid alternating movement: no dysdiadochokinesia
No rebound phenomenon

BALANCE & GAIT
Gait: normal gait
Romberg's test: negative
Extrapyramidal sign: Absent

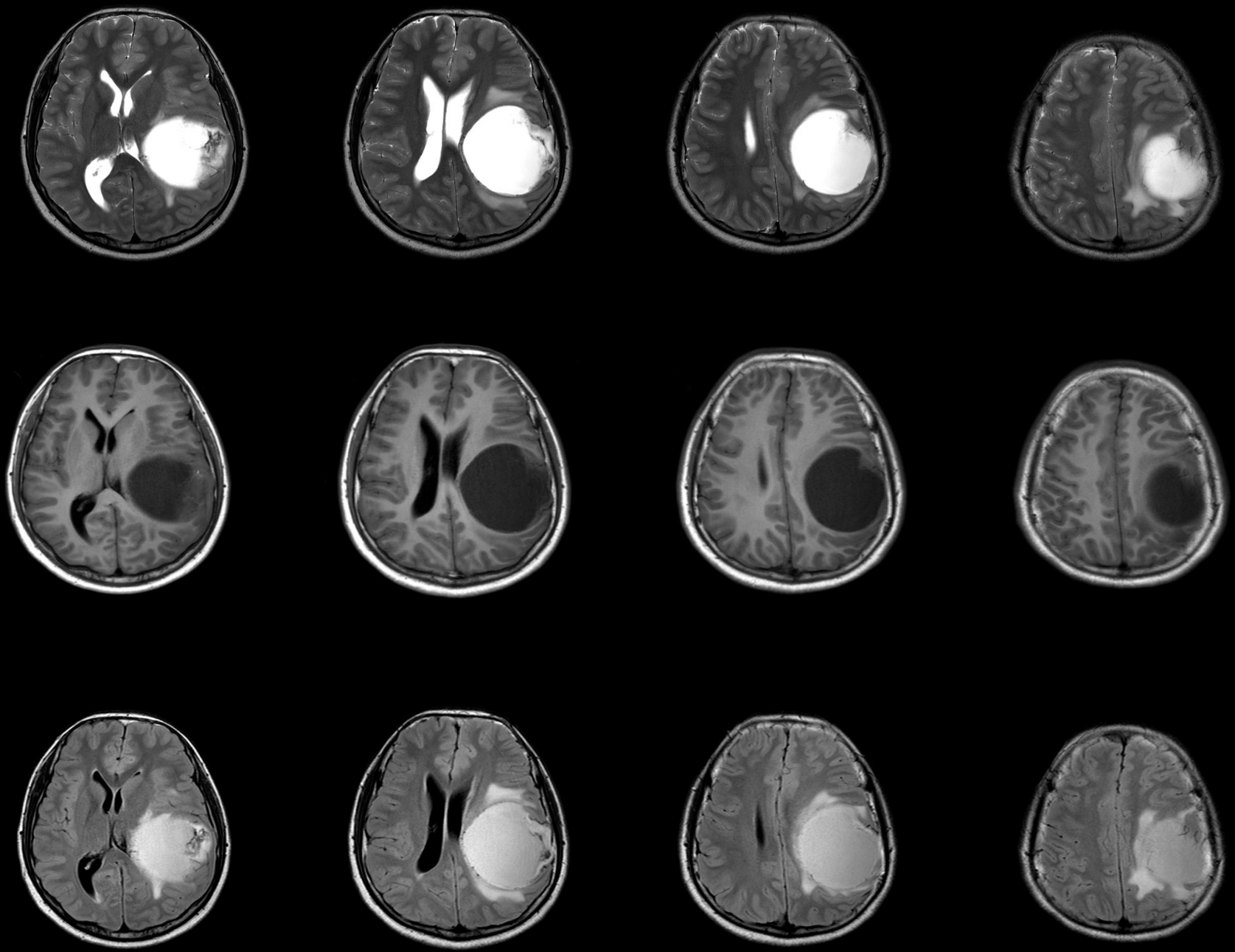
- Lab data: among normal range
- Imaging study brain MRI
  - A 6.78x6.44x5.06cm in size well-defined cystic mass with surrounding edematous change ,mass effect ,and peripheral contrast enhancement over left T-P lobes

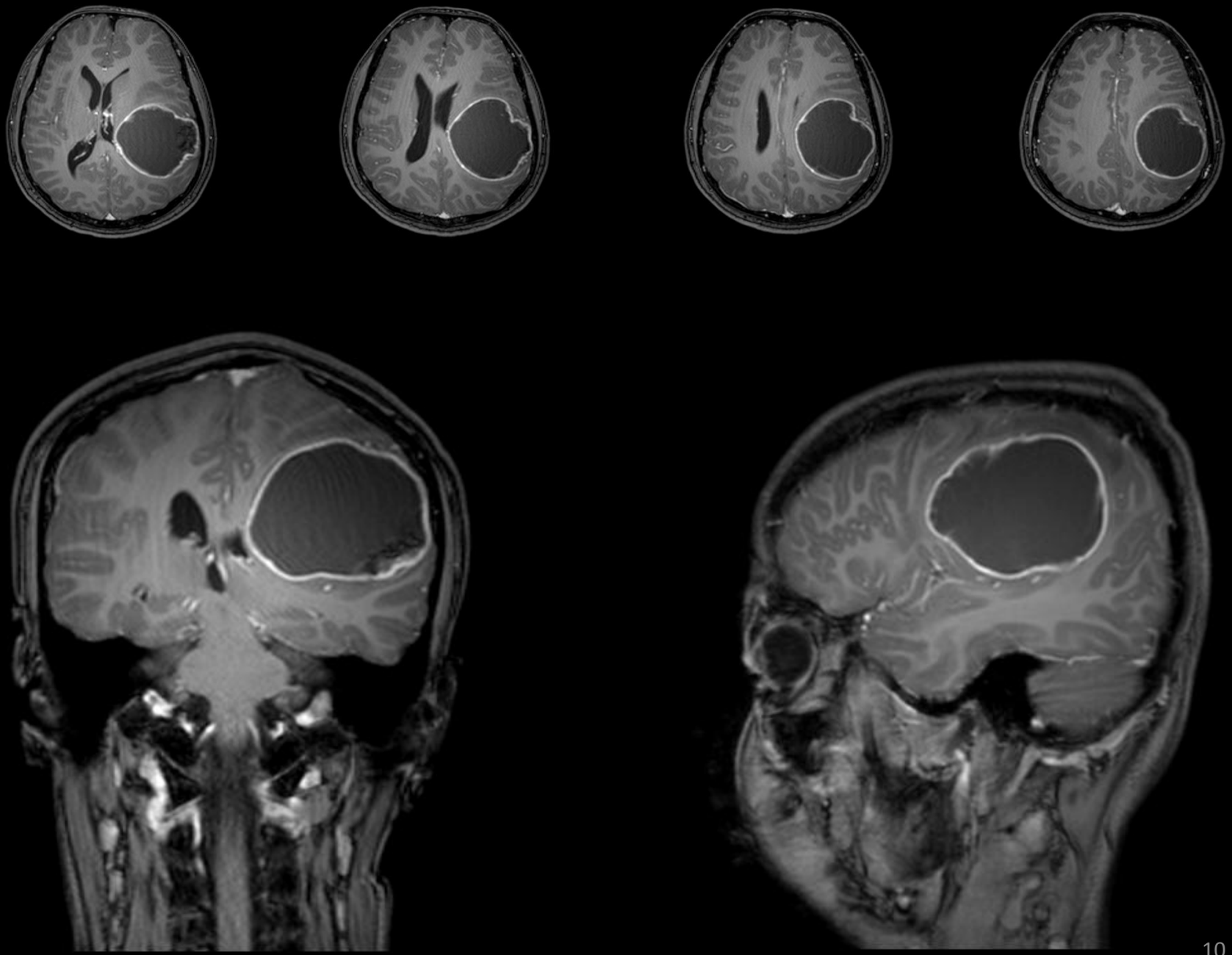
- Ophthamologist consultation:
  - Iris & Pupil: round in center, L/R sluggish ou,
  - Fundus: papilloedema OU, macula OK, EOM: full and free OU
  - Confrontation test: enlarged blind spot, no obvious peripheral VF defect OU
  - Impression:
    - Papilloedema, IICP related OU,
    - Myopia OU

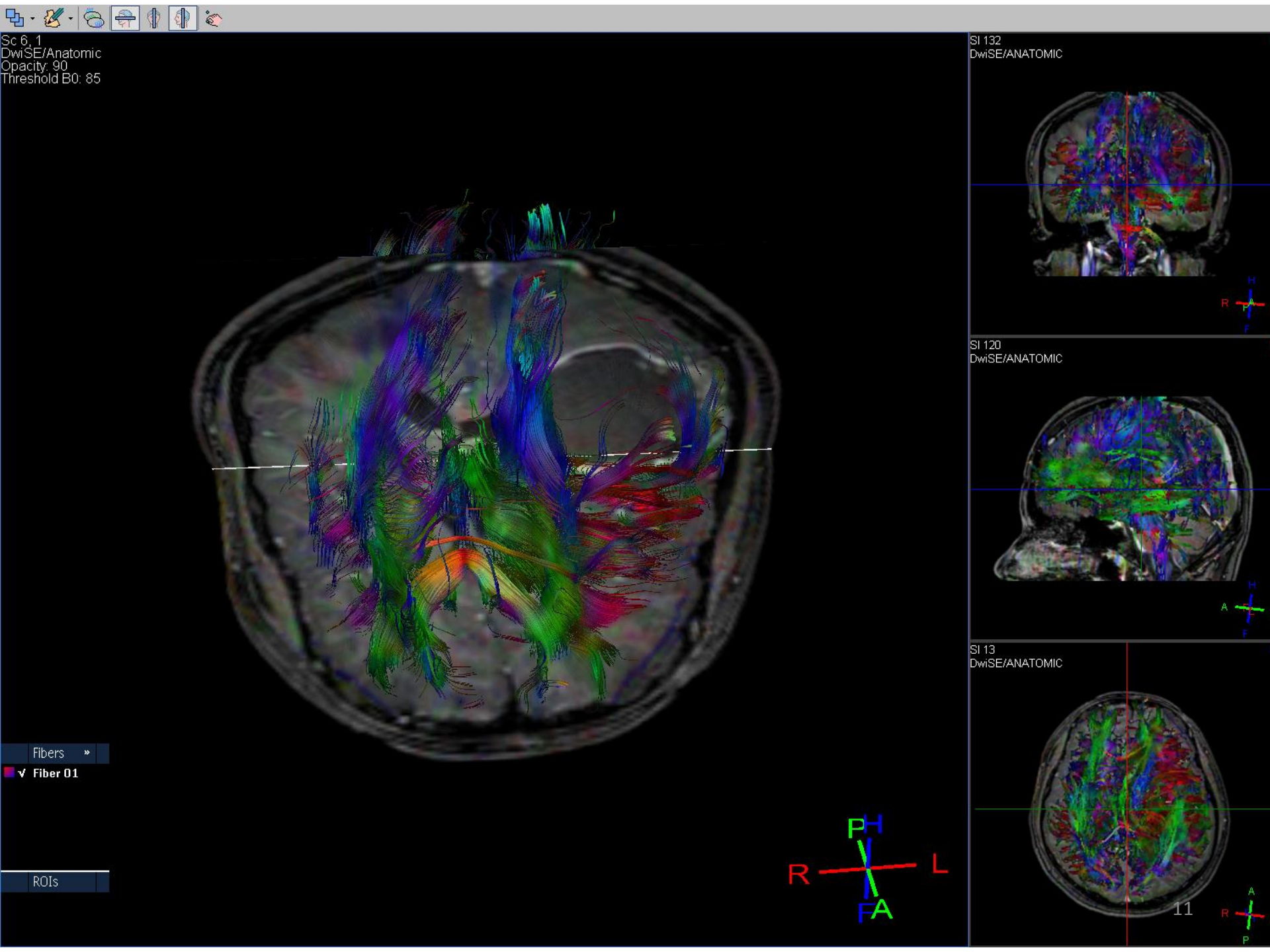
- Impression:
  - left F-T-P large cystic lesion with enhancement and IICP

  D.D: pilocystic, high grade astrocytoma, or brain abscess

Pre op MRI



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DwiSE/Anatomic
Opacity: 90
Threshold B0: 85
SI 132
DwiSE/ANATOMIC
SI 120
DwiSE/ANATOMIC
SI 13
DwiSE/ANATOMIC
Fibers
Fiber 01
ROIs
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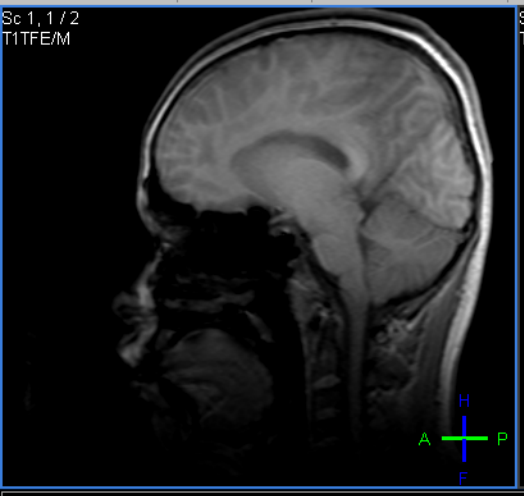
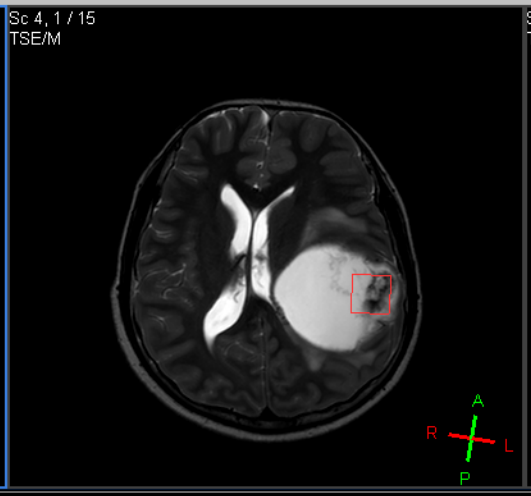
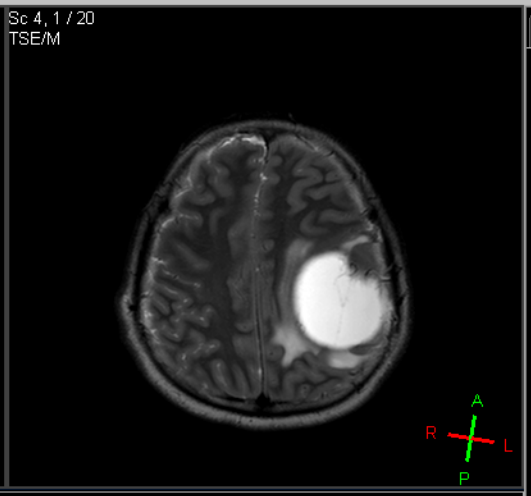
Current Script: LongTeBrain_sv







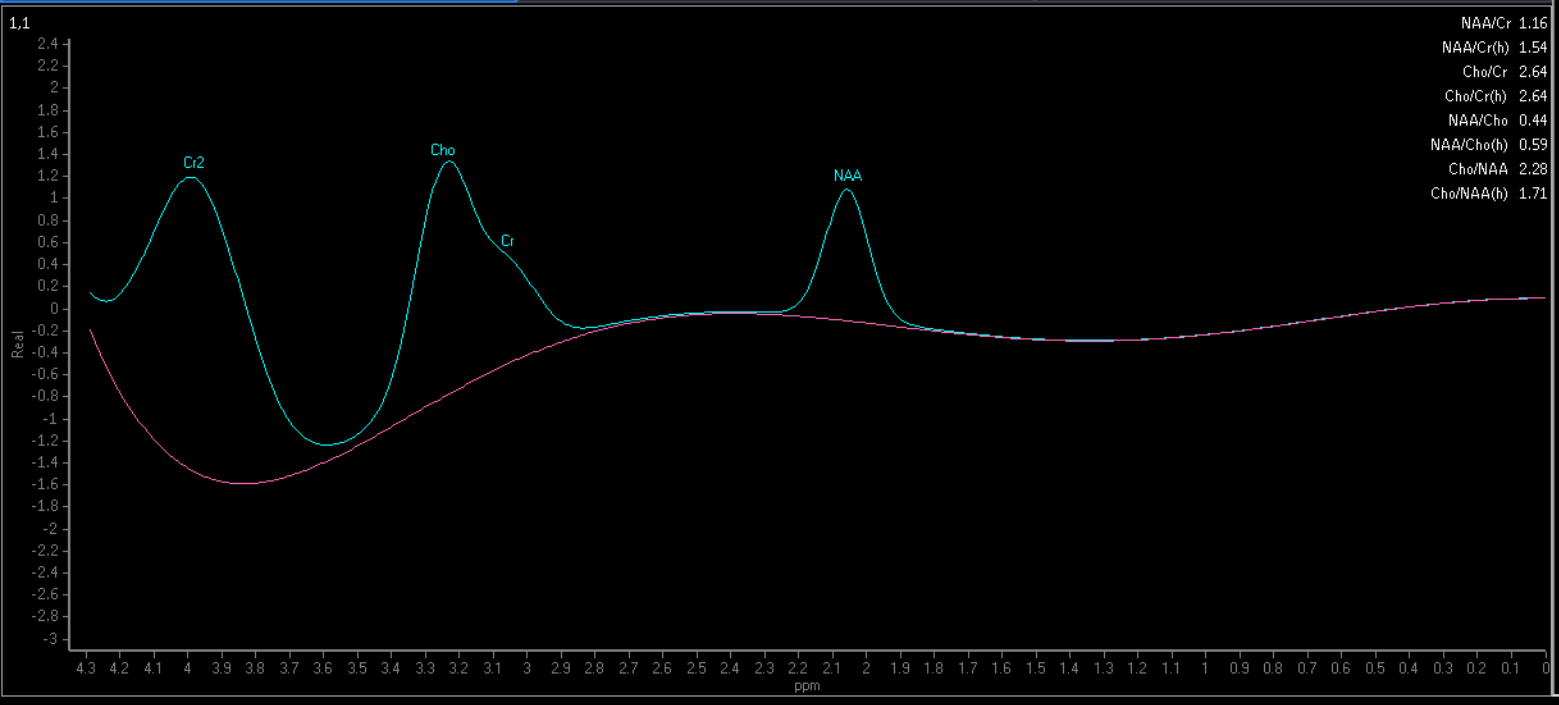
Acquisition | Script

Script Parameters

LongTeBrain_sv
Long-TE Brain (1H SV)
Data: SV Nucleus: 1H
Anatomy: Brain TE: long
Field: 1.0T, 1.5T, 3.0T, 7.0T

* Initial Baseline Subtraction
  Baseline Terms: 7
* Select Peaks
  Metabolites: NAA, Cr, Cr2, Cho
* Peak Fitting
  Gaussian Character: 90
  Baseline terms: 7
  Peak fit phase: Real
  Lock relative frequencies: Yes
  Lock widths: No
  Analysis limits: 4.35 to -1 ppm
  Display limits: 4.35 to 0 ppm
* Results Table
  Ratio Denominator: Cr(3.03)
* Graph Display

Scan Nr: 10,1
Scan Name: SV_PRESS_144



Spectro Results

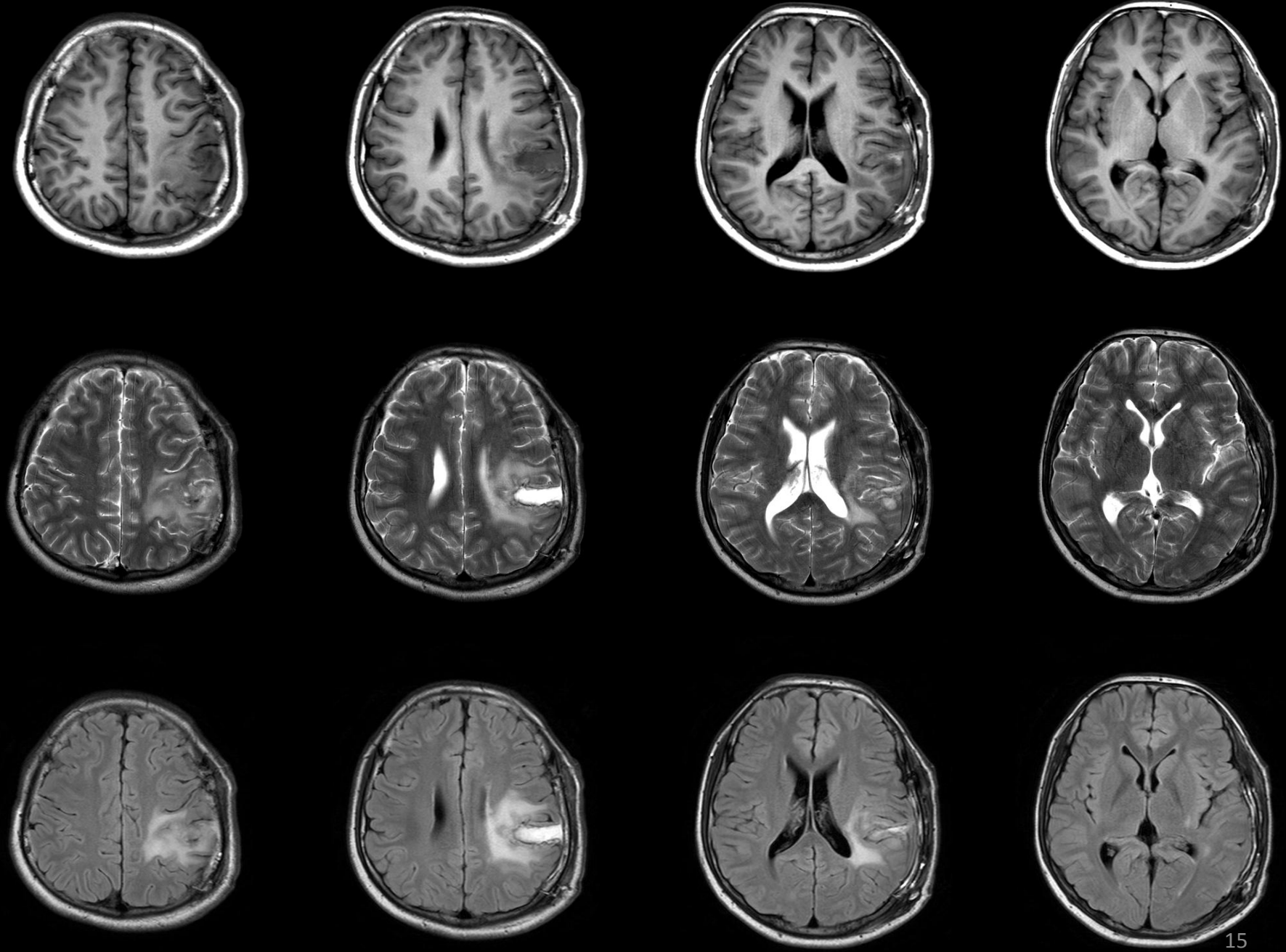
Metab	Position	SNR	Width	Height	Ht/Cr	Area	Ar/Cr
NAA	2.059	3.4	0.150	1.188	1.545	0.199	1.157
Cho	3.245	5.8	0.200	2.028	2.637	0.454	2.637
Cr	3.055	2.2	0.200	0.769	1.000	0.172	1.000
Cr2	3.979	7.6	0.349	2.664	3.463	1.043	6.056

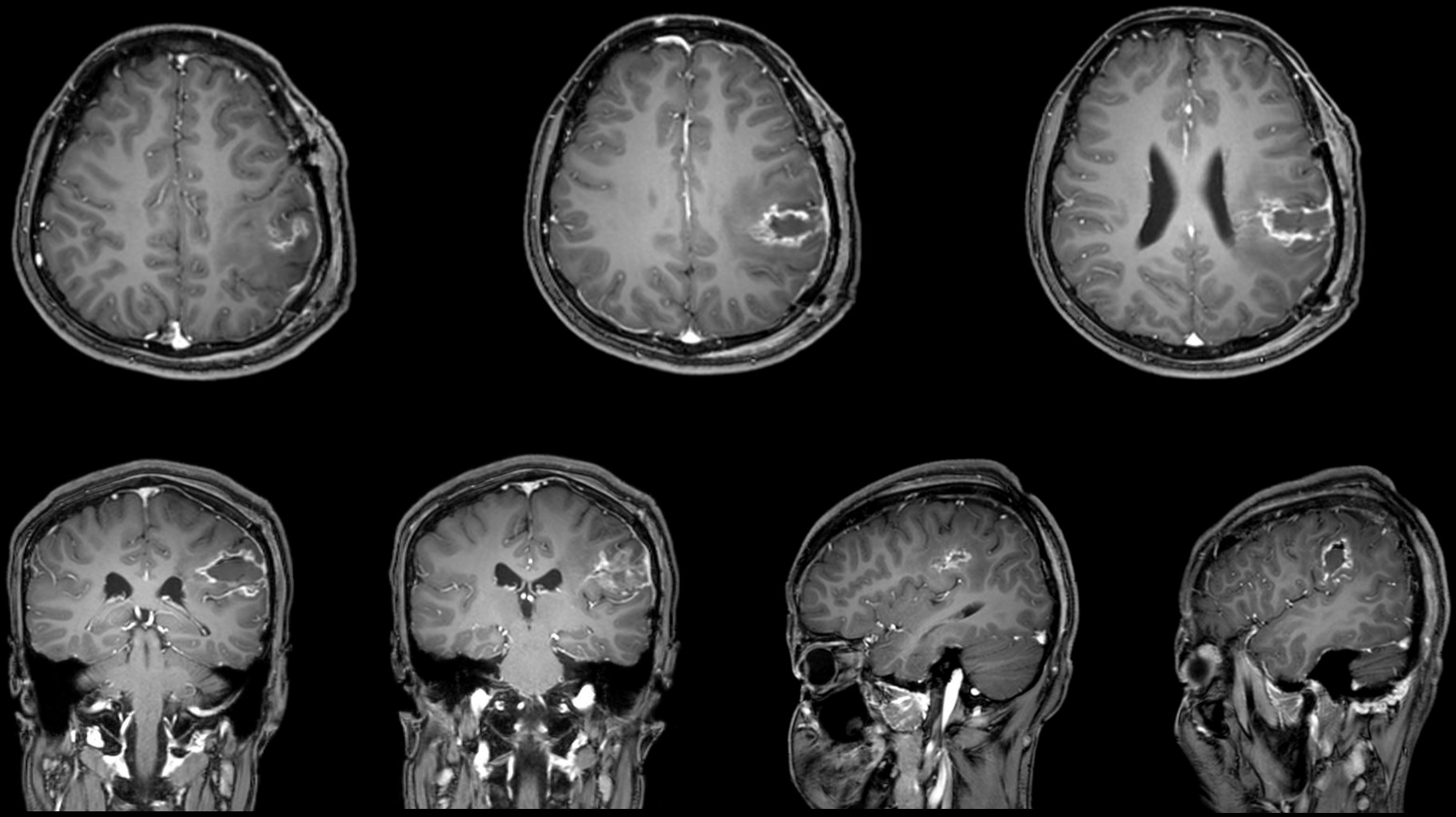
Clinical course

- 2012/11/29
  - left parietal craniotomy and removal of brain tumor
  - Op finding:
    - 1.intact cortical surface with significant brain swelling; relative slack after aspiration of fluid content(brown color,thick fluid about 10cc)
    - 2.gray,soft & jelly like tumor, hypervascularity with infiltration into brain parechymal without clear margin

- Pathologic report:
  - **Anaplastic astrocytoma**

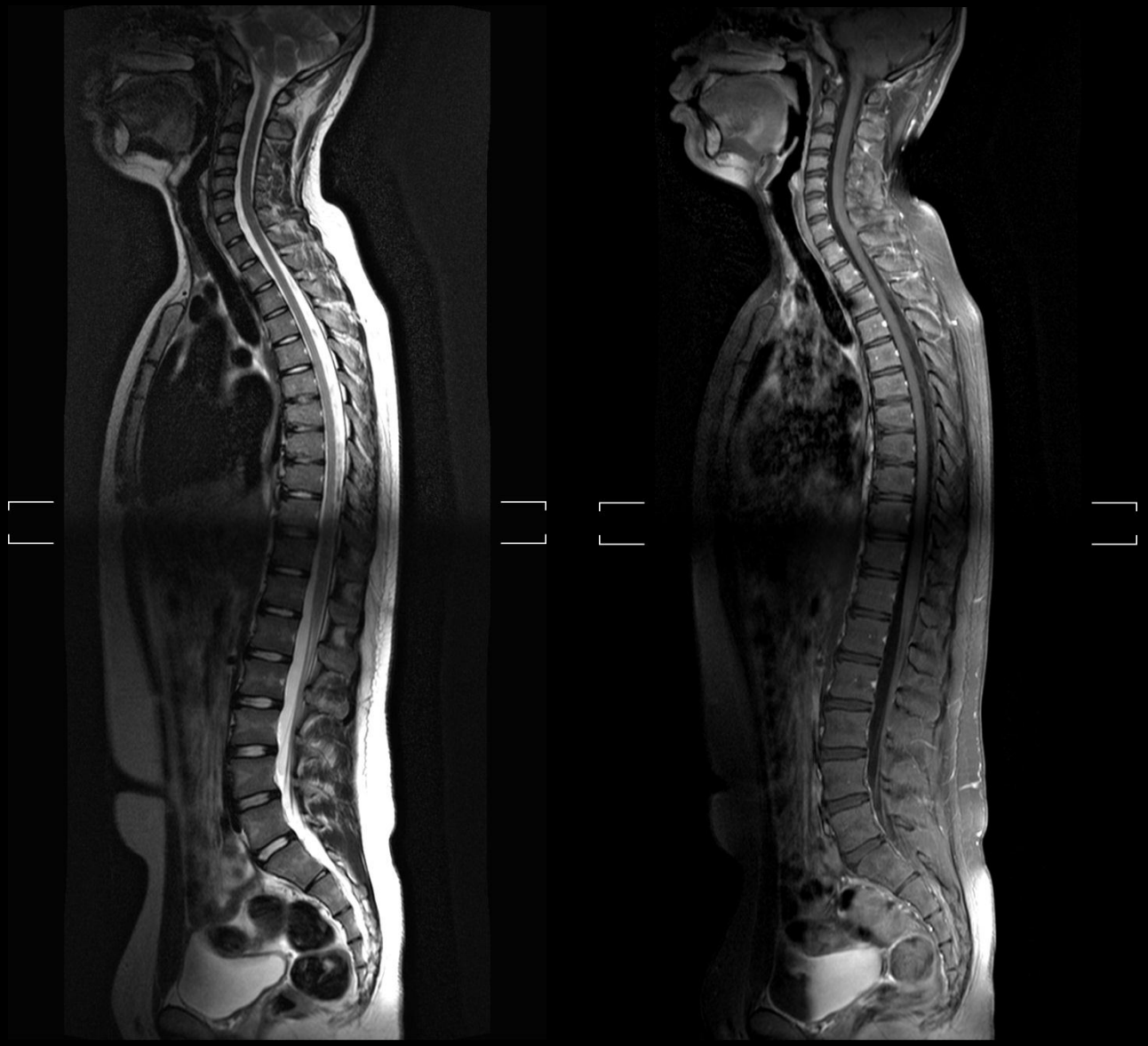
Post op day 12, 12/11





Post op day 12, 12/11

Whole spine MRI
12/17



Clinical course

- 12/13 whole brain radiotherapy+ Temozolomide (75mg m2/day)

Target Volume	Dose(cGy)	Fraction Number	Anatomical Description of Clinical Target Volume and Mamo
CTV	6000	30	Left T-P tumor bed

Discussion:

High grade astrocytoma

Classification of astrocytomas by cell type

Ordinary astrocytomas	Special astrocytomas
Fibrillary Gemistocytic protoplasmic	Pilocytic Microcystic cerebellar Subependymal giant cell

WHO Classification of (ordinary) Astrocytic Tumors

Designation	Criteria
II: diffuse astrocytoma	Cytological atypia alone
III: anaplastic astrocytoma	Anaplasia and mitotic activity
IV: GBM	Also show microvascular proliferation and necrosis

Anaplastic astrocytoma

- Epidemiology: mean age is 45-50y/o
- Localization: similar locations to other diffuse infiltrating astrocytomas, with a preference for all the cerebral hemisphere
- Microscopically: AAs are characterized by diffusely infiltrating astrocytes with increased cellularity, nuclear atypia and mitotic activity. By definition, microvascular proliferation and necrosis are absent.

Anaplastic astrocytoma

- Grading- WHO grade III
- Imaging:
  - MRI:
    - hyperintense central core with an isointense rim and peripheral finger-like extensions of vasogenic **edema** on T2WI
    - Marked **irregular peripheral ring-like enhancement** if typical
    - MRS**: increase choline, decrease NAA**
      - **Cho/Cr and Cho/NAA ratios correlate with histological grade of tumors**

Anaplastic astrocytoma

- Surgery: a safe radical resection
- Radiotherapy
  - Up to 60Gy is delivered to the tumor plus a margin of ≈2cm
- Chemotherapy
  - AAs are treated with temozolomide with radiation followed by adjuvant temozolomide, based on the survival advantage seen in GBM patients treated with this regimen. It seems less toxic than and at least as effective as the PCV(procarbazine, CCNU, vincristine)
- Prognosis
  - Median survival is in the range 2.5-3 years.

Glioblastoma multiforme(GBM)

- Epidemiology: the most frequent intrinsic brain tumor(12-15% of all intracranial tumors and 60-75% of astrocytic tumors)
- Localization:
  - **Subcortical white matter of the cerebral hemispheres**; tumour infiltration often extends into the adjacent cortex and through the corpus callosum into the contralateral hemisphere

Glioblastoma multiforme(GBM)

- Microscopically:
  - Prominent microvascular proliferation and necrosis are essential diagnostic features
- Treatment
  - Standard of care involves surgical resection followed by conformal external beam radiation and concurrent temozolomide chemotherapy followed by adjuvant temozolomide
- Prognosis:
  - Median life expectancy with treatment is 12-15 month with <5% of patients living 5 years

Table 2. Ratios of Low Grade and High Grade Astrocytoma Arising in Different Locations in 440 Cases of Histologically verified Pediatric Astrocytic Tumors in Taipei VGH collected from 1971-2011

Location	Pilocytic A	Diffuse A	LGA	Anaplastic A	GBM	HGA
Cerebral Hemisphere (123/277) Basal ganglia (10/57)	13 (10.6%) 4 (40%)	50 (40.7%) 3 (30%)	63 (51.2%) 7 (70%)	20 (16.3%) 1 (10%)	30 (24.4%) 2 (20%)	50 (40.7%) 3 (30%)
Cerebellum (113/332) Vermis (50/230) Hemipshere (57/87)	86 (76.1%) 41 (82%) 40 (70.2%)	17 (15.0%) 5 (10%) 11 (19.3%)	103 (91.2%) 46 (92%) 51 (89.5%)	6 (5.3%) 2 (4%) 4 (7%)	4 (3.5%) 2 (4%) 2 (3.5%)	10 (8.8%) 4 (8%) 6 (10.5%)
Thalamus (50/71)	12 (24%)	14 (28%)	26 (52%)	15 (30%)	9 (18%)	24 (48%)
Brain Stem (55/175) Midbrain (6/16) Pons (33/137) Diffuse (21/111) Unilateral/Focal (10/23) PM exophytic – MC (16/21)	14 (25.5%) 1 (16.7%) 4 (12.1%) 3 (11.3%) 1 (10%) 9 (52.3%)	17 (30.9%) 4 (66.7%) 8 (24.2%) 6 (21.6%) 2 (20%) 5 (31.3%)	31 (56.4%) 5 (83.3%) 12 (36.4%) 9 (42.9%) 3 (30%) 14 (87.5%)	15 (27.3%) 1 (16.7%) 12 (36.4%) 7 (33.3%) 5 (50%) 2 (12.5%)	9 (16.4%) 0 9 (27.3%) 5 (23.8%) 2 (20%) 0	24 (43.6%) 1 (16.7%) 21 (63.6%) 12 (57.1%) 7 (70%) 2 (12.5%)
Sellar Optic pathway (49/53) Hypothalamic (6/20)	 40 (81.6%) 2 (33.3%)	 2 (4.1%) 3 (50%)	 42 (85.7%) 5 (83.3%)	 6 (12.2%) 1 (16.7%)	 1 (2%) 0	 7 (14.3%) 1 (16.7%)
Pineal (2/108)	0	2 (100%)	2 (100%)	0	0	0
Ventricle (26/128)	22 SEGA (84.6%)	3 (11.5%) 1 Piliomyxoid (3.9%)	26 (100%)	0	0	0
Spinal Cord (15/24)	3 (20%)	9 (60%)	12 (80%)	2 (13.3%)	1 (6.7%)	3 (20%)

Distribution of Anaplastic Astrocytomas

Cerebral hem.	***20***	***31.5%***
Basal Ganglia	***1***	***1.6%***
Cerebellum	***6***	***9.4%***
Vermis	***2***	***3.1%***
Hem.	***4***	***6.3%***
Thalamus	***15***	***23.4%***
Brain stem	***15***	***23.4%***
Midbrain	***1***	***1.6%***
Pons	***13***	***20.3%***
PM dorsal exophytic	***0***	***0%***
MC	***1***	***1.6%***

Sellar -	***6***	***9.4%***
Optic pathway	***6***	***9.4%***
-	***0***	***0%***
Hypothalamus		
Pineal	***0***	***0%***
Ventricle	***0***	***0%***
Spinal cord	***2***	***3.1%***

Pediatric high grade astrocytoma

- High grade gliomas:8-12% of all childhood CNS tumors
- 35-50% are located within the cerebral hemisphere
- Median age:9 y/o
- Tumor grade was the most significant independent prognostic factor where the extent of resection was the most significant indicator of survival

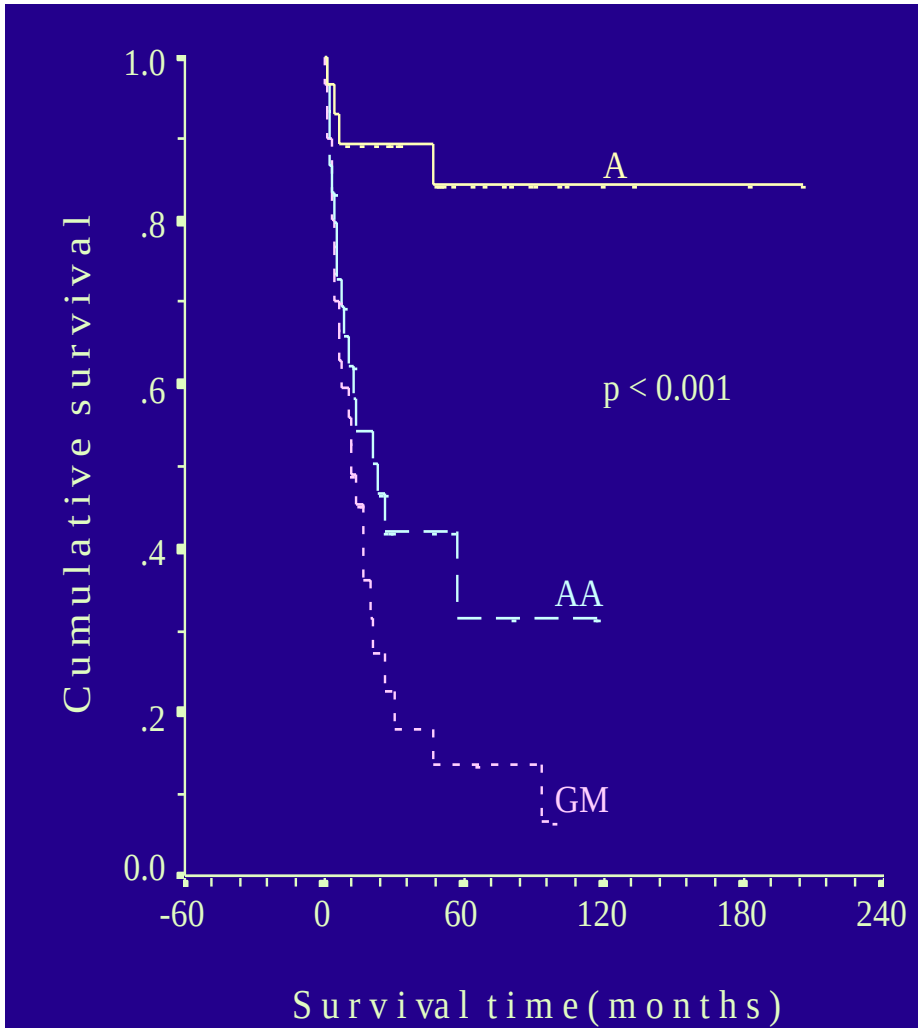
Immunohistochemical study

- Ki-67 antigen is expressed in all phases of the cell cycle except G0 (only used in fresh-frozen specimens)
- MIB-1 monoclonal antibody using recombinant parts of the Ki-67 as an immunogen and can be used on paraffin-embedded sections of fixed tissue
  - Cell leaving G0/G1 phase and entering the S phase stain positive

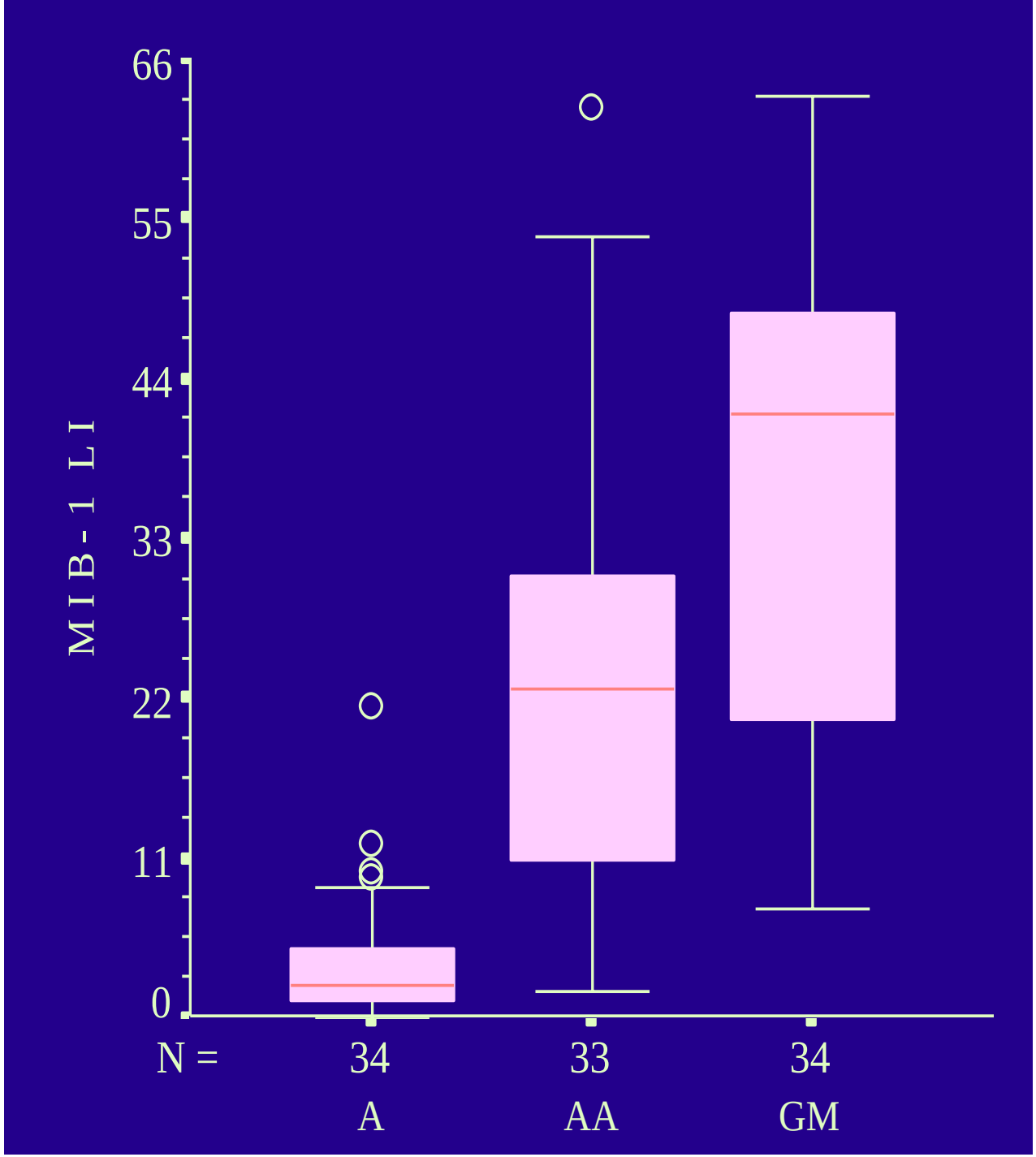
MIB-1 Labeling Index in Nonpilocytic Astrocytoma of Childhood

A Study of 101 Cases

***Cancer* 1998;82:2459–66.**

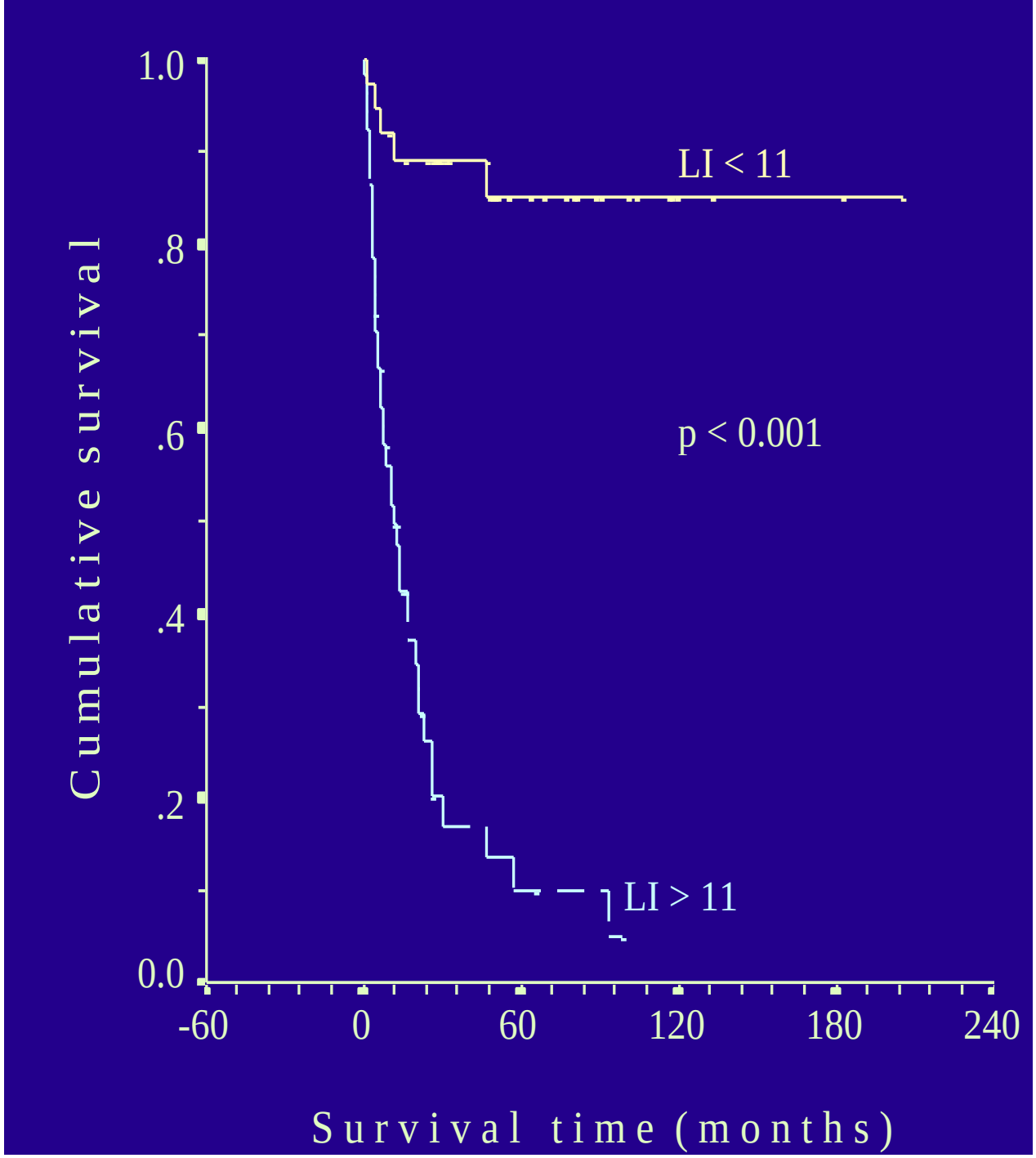


Survival Time (mo.)	n	mean ± S.E.
A	34	165.2 ± 14.9
AA	33	46.1 ± 9.9
GM	34	21.8 ± 5.6



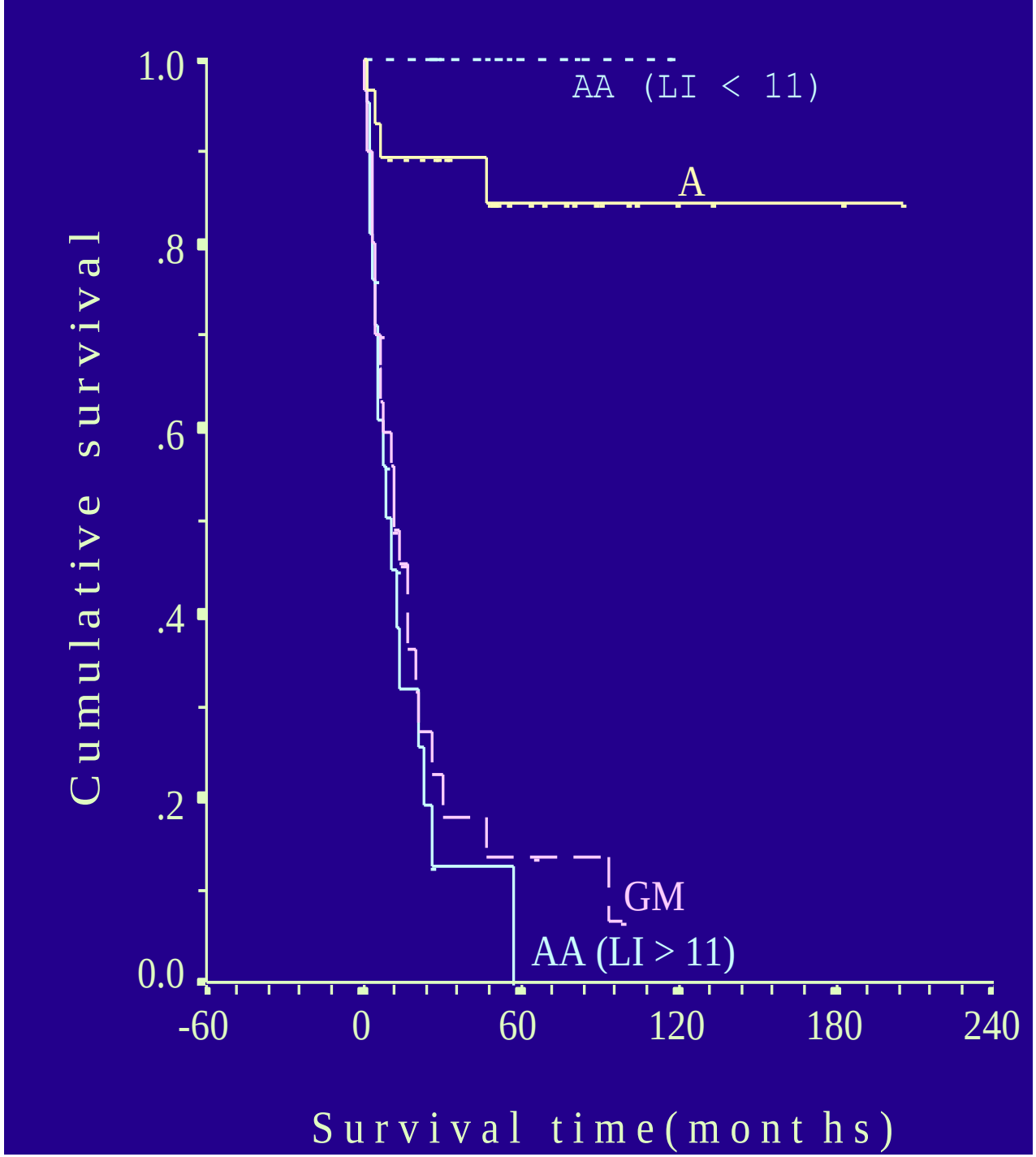
MIB-1 LI

	mean ± S.D. (range)
A	3.9 ± 4.3 (0.0-21.6)
AA	24.3 ± 15.6 (1.7-62.8)
GM	35.9 ± 16.4 (7.36-63.3)
A	2 LI > 11
AA	9 LI ≤ 11
	24 LI > 11
GM	1 LI ≤ 11



Survival (mo.)

LIs	mean ± S.E.
≤ 11	173.2 ± 12.2
> 11	20.3 ± 4.1


1.0
.8
.6
.4
.2
0.0
Cumulative survival
AA (LI < 11)
A
GM
AA (LI > 11)
-60
0
60
120
180
240
Survival time(months)

Pathophysiology and biology of pediatric high grade glioma

- While the histology of HGGs between adults and children appears identical, the biology of the tumors may vary significantly

Molecular marker	adult	children	Prognostic factor
EGFR	amplification	infrequent	
Akt and PTEN	PTEN mutation→ Akt↑	infrequent	
PDGFR		overexpressed	
TP53/P53	Often mutated	Older child 40% <3y/o 12%	P53: prognostic markers
MGMT	Reduce the efficacy of alkylating chemotherapy		Poor overall survival
IDH1	Common in secondary GBM	rare	

Indicators of prognosis in pediatric HGGs

Extent of resection	**Completely resection : all= 63%: 19%**
MGMT promoter methylation	1. Prolonged survival(P=0.005) 2. Better response to Temozolamide(P=0.007)
P53 overexpression	Poor prognosis

EXPRESSION OF p53 AND PROGNOSIS IN CHILDREN WITH MALIGNANT GLIOMAS

IAN F. POLLACK, M.D., SYDNEY D. FINKELSTEIN, M.D., JEFFREY WOODS, B.S., JUDITH BURNHAM, B.A., EMIKO J. HOLMES, M.S., RONALD L. HAMILTON, M.D., ALLAN J. YATES, M.D., PH.D., JAMES M. BOYETT, PH.D., JONATHAN L. FINLAY, M.B., CH.B., AND RICHARD SPOSTO, PH.D., FOR THE CHILDREN'S CANCER GROUP

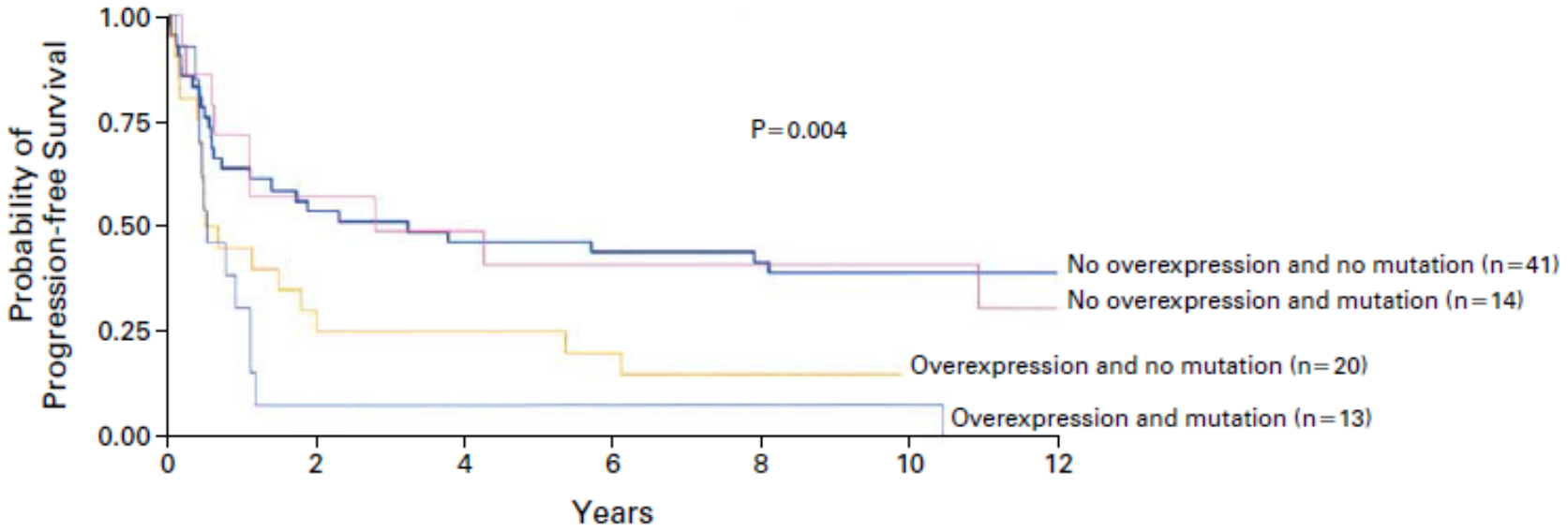


Figure 2. Relation of Mutations in *TP53* and Overexpression of p53 to Outcome in Children with High-Grade Gliomas.

The 41 children who had tumors that exhibited neither overexpression of p53 nor mutations in *TP53* had a mean rate of progression-free survival at five years of 46±8 percent, as compared with 41±14 percent among the 14 with *TP53* mutations but no p53 overexpression, 25±10 percent among the 20 children who had tumors with overexpression of p53 and no mutations, and 8±7 percent among the 13 children who had tumors with both overexpression and mutations ($P=0.004$; P for trend, <0.001).

American Journal of Pathology, Vol. 158, No. 4, April 2001

Pediatric High-Grade Astrocytomas Show Chromosomal Imbalances Distinct from Adult Cases

1. 23 pediatric high-grade astrocytomas by comparative genomic hybridization.
2. A significantly shorter survival was found for anaplastic astrocytomas showing +1q (P <0.05), MIB-1 proliferation index >25% (P < 0.001) and glioblastomas (P < 0.05).
3. The results show that chromosomal aberrations differ between pediatric anaplastic astrocytomas and glioblastomas as well as between pediatric and adult high-grade astrocytomas, **supporting the notion of a different genetic pathway**.

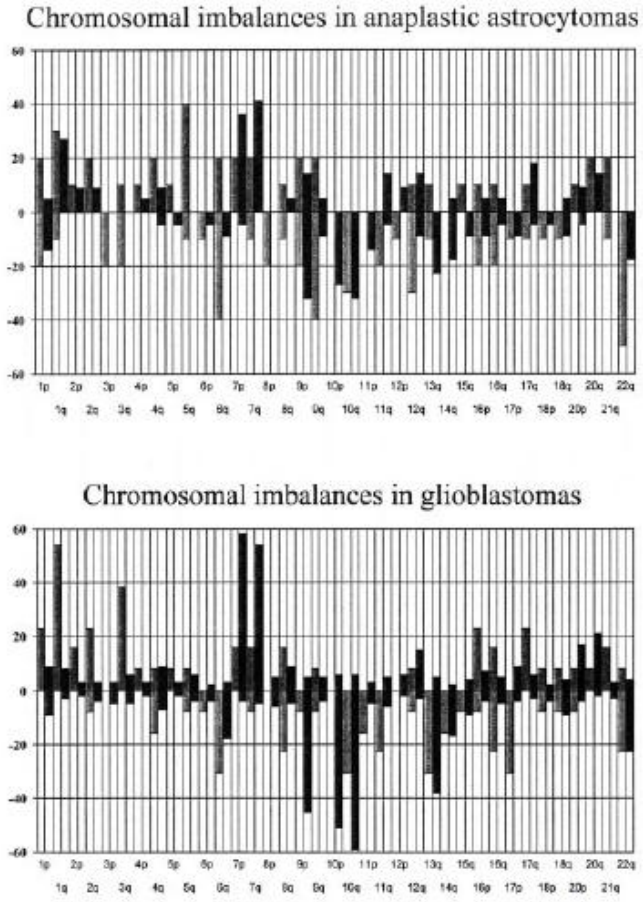


Figure 3. Comparison of CGH data of pediatric (gray) and adult (black) anaplastic astrocytomas (**top**) as well as pediatric (gray) and adult (black) glioblastomas (**bottom**), charted against each affected chromosomal arm. Relative frequency of chromosomal imbalances in percent; gains charted above, losses below the respective midlines. CGH results of primary adult high-grade astrocytomas gained from 22 anaplastic astrocytomas[21–24] and 184 glioblastomas.[21–29]

Treatment options for pediatric HGG

- Multiagent Chemotherapy
  - CCNU, vincristine and prednisone *1989 children cancer study group*
    - 5-year-event-free survival:46% vs 18% in op & RT
  - 8-drug regimen children's cancer group. J clin oncol. 1995;13,112-123
    - No statistical superiority than any regimen
  - Intensive chemotherapy HIT-GBM-C protocol . Cancer 2010,116,705-712
    - No benefit
  - High-dose myeloablative chemotherapy followed by autologous bone marrow transplantation children's cancer group 1998
    - No difference to standard therapy

Treatment options for pediatric HGG

- Temozolomide
  - 85mg/m2 for 42days in recurrent cases Eur J cancer 2006,42
    - Recorded responses in 4/28 cases treated but no benefit in further studies J neuro oncol2006.76.313-319
  - ACNS0126 study children's oncology group, neuro oncol 2011
    - Failed to improve outcome
  - There remains the possibility that temozolomide may have a role in multidrug regimens in children

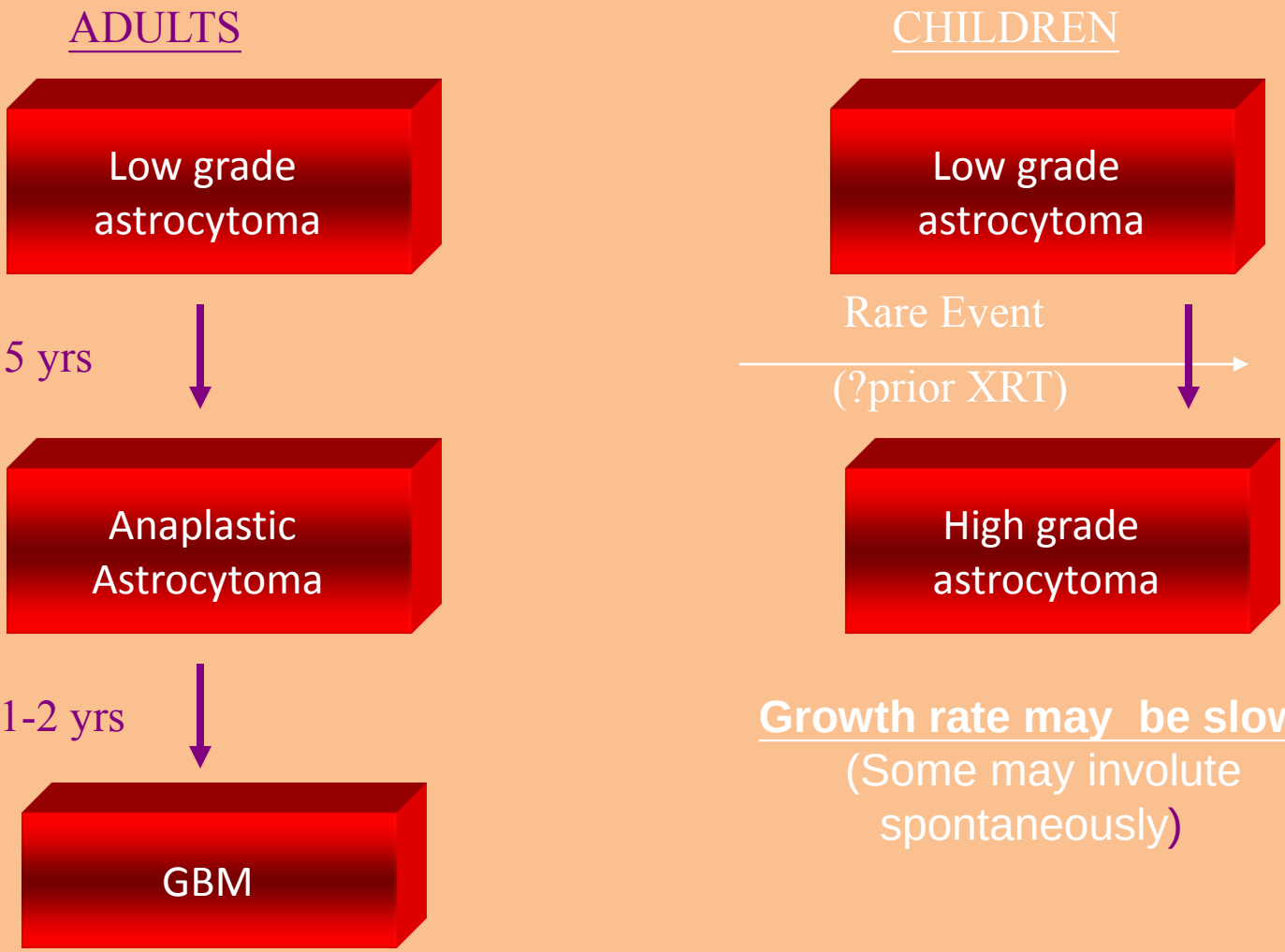
Treatment options for pediatric HGG

- Angiogenesis inhibitor
  - Vascular endothelial growth factor (VEGF) inhibitor bevarizumab: not effective
- Molecular targeted therapy
  - Imatinib (target PDGFR): phase II study
  - EGFR inhibitors gefitinib: phase II trial


The End

“Low-grade” glioma

Adults vs children



Growth rate may be slow
(Some may involute spontaneously)

Anaplastic astrocytoma

- Clinical features
  - Presenting symtpoms include seizures, IICP(headache, nausea, blurred vision, lethargy, and personality change) and neurological deficits depending on the location of the tumors
- Treatment
  - Maximal safe resection followed by radiation and concurrent temozolomide chemotherapy followed by adjuvant temozolomide chemotherpy

Anaplastic astrocytoma

- Surgery
  - A safe radical resection is the surgical procedure of choice, encompassing all of the contrast-enhancing tissue. It should be performed with the aid of intra-operative stimulation mapping with cortical and subcortical motor and sensory pathway in addition to cortical language mapping.
- Prognosis
  - Median survival is in the range 2.5-3 years. Prognostic factors include age, extent of surgical resection and performance status

Glioblastoma multiforme(GBM)

- Imaging:
  - MRI:
    - T1WI and T2WI show a poorly delineated mass of mixed intensity, often with necrosis or cyst formation
    - D.D:
      - anaplastic astrocytoma
      - Abscess
      - Metastasis
      - lymphoma
      - Demyelinating lesions
- Clinical features:s/s correspond to tumor location

Glioblastoma multiforme(GBM)

- Treatment
  - Standard of care involves surgical resection followed by conformal external beam radiation and concurrent temozolomide chemotherapy followed by adjuvant temozolomide
- Prognosis:
  - Median life expectancy with treatment is 12-15 month with <5% of patients living 5 years

Temozolomide(Temodal)

- An oral alkylating agent; rapid conversion to the active monomethyl triazenoimidazole carboxamide(MTIC), which is associated with alkylation of DNA
- FDA approved for use in adults for
  - The initial relapse of anaplastic astrocytoma
  - For newly diagnosed GBM

Table 1. Molecular markers in pediatric HGGs

Marker	Relevance to Pediatric HGGs
ADAM3A	DNA analysis of 38 predominantly pretreatment pediatric HGG samples (including 13 DIPGs) revealed homozygous loss at 8p12 in 16% of cases. This novel deletion includes the *ADAM3A* gene.[32]
Akt	Ras/Akt activation is observed in pediatric HGG and may be associated with poor prognosis[16,17]
BRAF	The $BRAF^{V600E}$ mutation has been found in pediatric high-grade astrocytomas[19]
CDKN2A/B	Approximately 50% of supratentorial tumors expressed CDKN2B and ~75% of infratentorial tumors were positive for CDKN2B expression. Pediatric DIPG samples showed high-frequency loss of 17p and 14q and lack of CDKN2A/CDKN2B deletion.[32]
EGFR	A lesser degree of *EGFR* amplification is observed in children compared with adult HGG.[8,11] Marked overexpression of *EGFR* is observed in pediatric HGG relative to pediatric low-grade glioma.[10]
EGFRvIII	*EGFRvIII* deletion mutations have been observed in pediatric HGG, but no *EGFRvIII* activating mutations.[12]
IDH1	Until recently, most data had shown that *IDH1* mutations were rare or absent in pediatric HGG.[9,34] However, a recent study found *IDH1* mutations in 7 AA/GBM tumors from children ≥14 years old.[20]
MGMT	*MGMT* overexpression is rare in pediatric HGG but is associated with poor prognosis.[26] Methylation of the *MGMT* promoter may be prognostic for survival in pediatric HGG.[26–28]
PDGFRA	*PDGFRA* is overexpressed in the majority of pediatric HGG cases and amplified in ~ 1/3 of pediatric HGG, including DIPG.[9,13,18]
P53	p53 overexpression and mutation correlate independently with adverse outcome and appears to vary with age.[22,23]
VEGF 121 isoform	The VEGF 121 isoform, which promotes mitogenesis and vascular permeability, has been linked with AA and GBM.[33]