Bone & soft tissue sarcoma
Central nervous sytem tumors

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ORSZÁGOS ONKOLÓGIAI INTÉZET

Bone tumors

- Very **rare** (0,8 / 100 000)
- Etiology
  - Metaphysis
  - Radiation
  - Chemicals?
  - Rare genetic syndroms
- Histology
  - **60** different entitites
- **Specialized centres**
- International collaboration

- Osteogenic tumors
  - Benign: osteoma, malignant osteosarcoma
- Chondrogenic tumors
  - Chondroma, chondrosarcoma.
- Giant cell tumor, intermediate malignancy
- Bone-marrow origin
  - Ewing-sarcoma
- Angiogenic tumors
  - haemangioma, haemangioendothelioma, angiosarcoma
- Other tumors of connective tissue origin
  - desmoplastic fibroma, fibrosarcoma.
- Other tumors
  - Chordoma, Schwannoma

Bone tumors staging

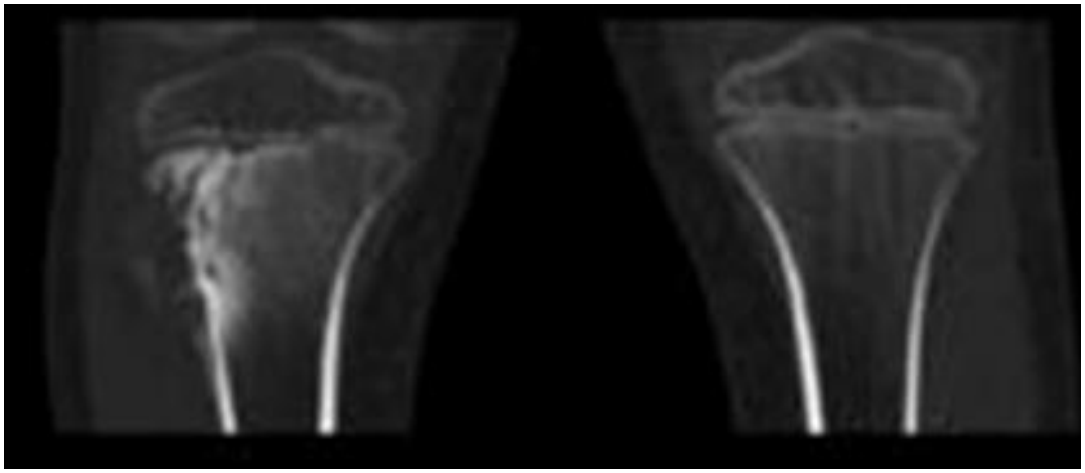
The Enneking staging system of bone tumours			
Stage	**Grade**	**Site**	**Metastasis**
IA	G1	intracompartmental	not present
IB	G1	extracompartmental	not present
IIA	G2-3	intracompartmental	not present
IIB	G2-3	extracompartmental	not present
III	G2-3	any	present

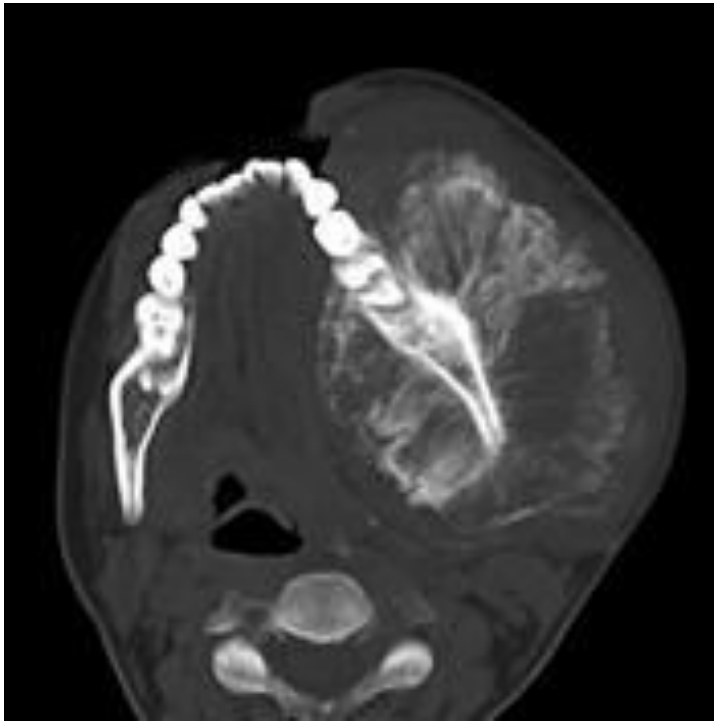
Bone tumors - treatment

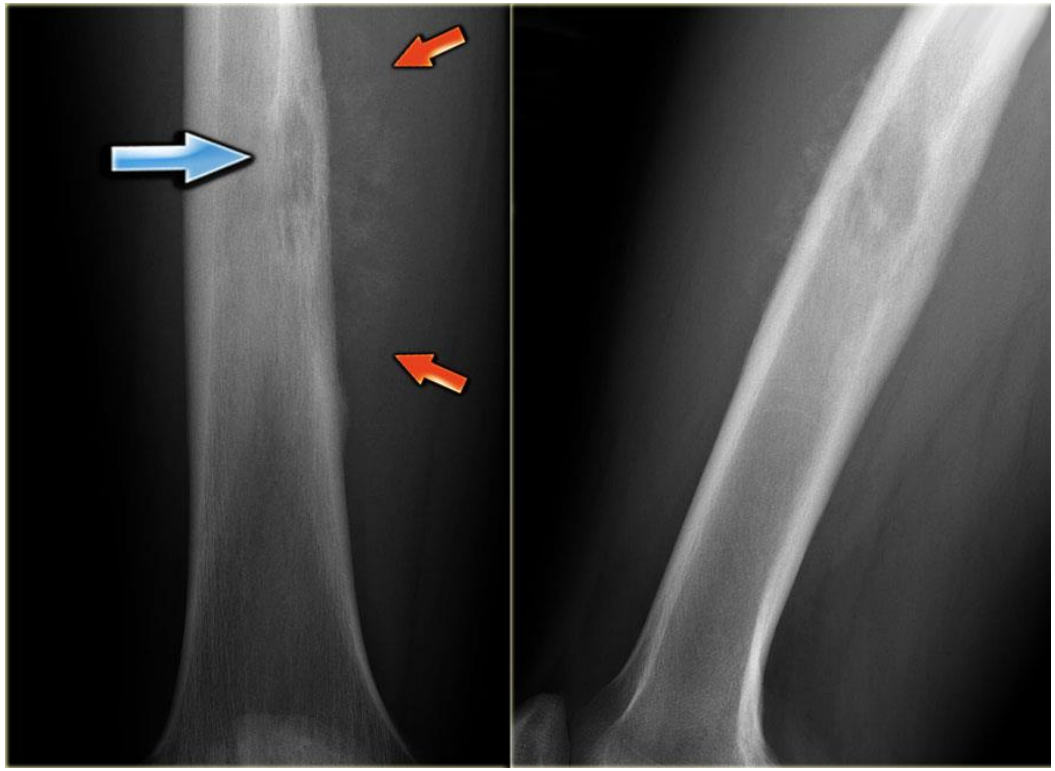
- **Benign**
  - Excochleation – spongioplastics
  - Radical removal („agressive” benign tumors)
- **Low grade** malignant
  - Radical surgery with good margin
- **Osteosarcoma**
  - Function preservation (70%) (radiation resistant)
    - Neoadjuvant chemo-surgery –adjuvant chemotherapy
  - Extra-radical surgery (e.g. hemipelvectomy)
  - Metastatectomy

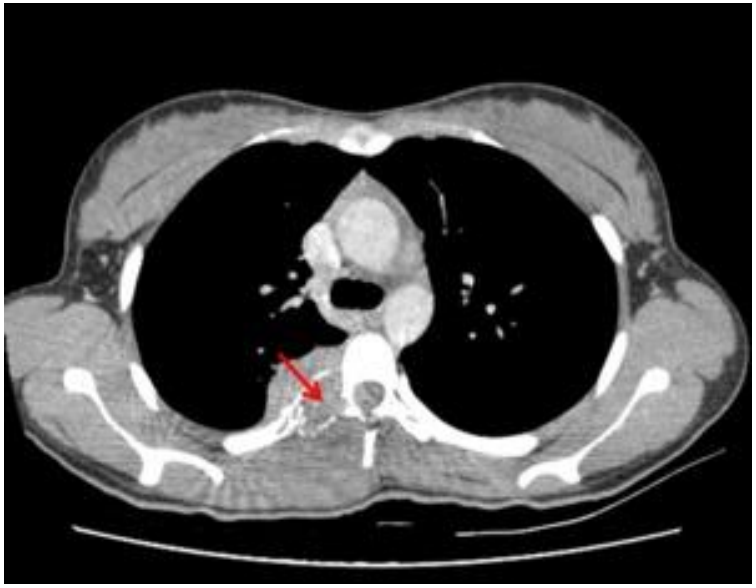
Bone tumors - treatment

- **Ewing-sarcoma**
  - Radio and chemotherapy sensitive
  - Neoadjuvant chemotherapy
  - Surgery (or radiotherayp if surgery not possible)
  - Consolidation chemotherapy
- **Chordoma, chondorsarcoma**
  - Surgery
  - Axial (e.g skull base): adjuvant radiotherapy
  - Radiotherapy alone (proton, heavy ion)
- **Pharmaceuticals**
  - MTX, doxorubicin, ciszplain, ifoszfamid
  - Vincristin, ifosfamid, MESNA, doxorubicin cyclphosphamid, actinomycin D
  - ASCT









- **Incid**
- **Mort**
- Etiolc
  - Ge
- Heter
  - fat
  - fib
  - my
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  - un

Kis kereksejtes desmoplasticus tumor	t(11;22)(p13;q12), EWS–WT1 fúzió
Extrasceletalis Ewing/PNET	t(11;22)(q23;q12), EWS/FLI1 fúzió t(21;22)(q22;q12), EWS/ERG fúzió t(7;22)(p22;q12),EWS/ETV1 fúzió t(2;22)(q33;q12),EWS/FEV fúzió t(17;22)(q12;q12), EWS/E1AF fúzió inv(22)(q12q12),EWS/ZSG fúzió
Extrasceletalis myxoid chondrosarcoma	t(9;22) (q22;q11), EWS/NR4A3 fúzió t(9;17)(q22;q11) RBP56–NR4A3 fúzió t(9;15)(q22;q21) TCF12–NR4A3 fúzió
Malignus rhabdoid tumor	22q SMARCB1(INI1) biallélikus károsodás
Alveolaris rhabdomyosarcoma	t(2;13)(q35;q14), PAX3/FKHR fúzió t(1;13)(p36;q14), PAX7/FKHR fúzió
Synovialis sarcoma	t(X;18)(p11;q11), SYT–SSX fúzió
Dermatofibrosarcoma protuberans	t(17;22)(q21;q13), COL1A1/PDGFB fúzió
Infantilis fibrosarcoma	t(12;15) (p13;q25), ETV6/NTRK3 fúzió
Inflammatoricus myofibroblastos tumor	2p23 génátrendeződés ALK/ –TPM3, –TPM4, –clathrin és más gének fúziójával
Alveolaris lágyrészsarcoma	der (17)t(X;17)(p11;q25), ASPL–TFE3 fúzió
Epithelioid sarcoma	SMARCB1 (INI1) down-reguláció miR 206, 381 és 671–5p miatt
Clear-cell sarcoma	t(12;22)(q13;q12), EWS/ATF1 fúzió
Myxoid liposarcoma	t(12;16)(q13:p11) & DDIT2(CHOP)/FUS t(12;22)(q13:q12) & DDIT3/EWS fúzió
Low-grade fibromyxoid sarcoma	t(7;16)(q34;p11) & FUS/BBF2H7 fúzió
Atípusos lipomatosus tumor	MDM2- és CDK4-amplifikáció
GIST	1p-, 9p-,14q- és 22q-deléció, c-kit- és PDGFRA- mutáció

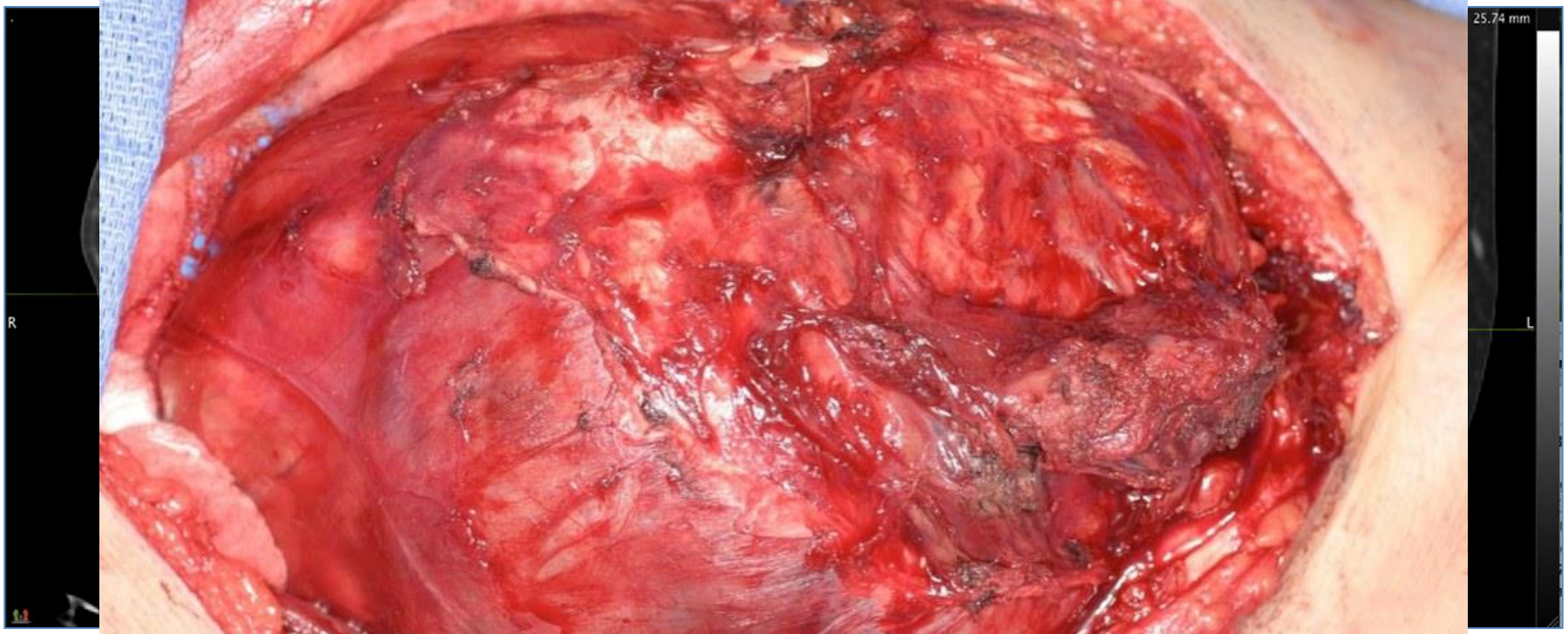
Soft tissue sarcoma staging

Extremity and superficial trunk	
T1	Tumour 5 cm or less in greatest dimension
T2	Tumour more than 5 cm but no more than 10 cm in greatest dimension
T3	Tumour more than 10 cm but no more than 15 cm in greatest dimension
T4	Tumour more than 15 cm in greatest dimension
Retroperitoneum	
T1	Tumour 5 cm or less in greatest dimension
T2	Tumour more than 5 cm but no more than 10 cm in greatest dimension
T3	Tumour more than 10 cm but no more than 15 cm in greatest dimension
T4	Tumour more than 15 cm in greatest dimension

Head and neck	
T1	Tumour 2 cm or less in greatest dimension
T2	Tumour more than 2 cm but no more than 4 cm in greatest dimension
T3	Tumour more than 4 cm in greatest dimension
T4a	Tumour invades the orbit, skull base or dura, central compartment viscera, facial skeleton, and or pterygoid muscles
T4b	Tumour invades the brain parenchyma, encases the carotid artery, invades prevertebral muscle or involves the central nervous system by perineural spread
Thoracic and abdominal viscera	
T1	Tumour confined to a single organ
T2a	Tumour invades serosa or visceral peritoneum
T2b	Tumour with microscopic extension beyond the serosa
T3	Tumour invades another organ or macroscopic extension beyond the serosa
T4a	Multifocal tumour involving no more than two sites in one organ
T4b	Multifocal tumour involving more than two sites but not more than five sites
T4c	Multifocal tumour involving more than five sites

Sof tissue sarcomas - treatment

- Exclusively in high-volume centers (survival)
- Histology before treatment
- Complete resection if feasible with good margins
- Neoadjuvant chemo / radiotherapy
- Postoperative high risk (grade, centrality)
  - adjuvant chemotherapy
- Small margin, R1, R2, G3
  - Adjuvant radiotherapy
- Irresectable – locally advanced
  - Chemotherapy + radiotherapy
- Metastatic
  - chemo or targeted therapy, metastatectomy


R
25.74 mm
L

CNS tumors

Epidemiology, etiology

- **Incidence**: 3160 female, 3880 mae
- **Mortality**: 2765 female, 3340 male
- Etiology
  - Inherited (<5%) v Hippel-Lindau, Li-Fraumeni, neurofibromatosis, sclerosis tuberosa
  - Radiaton
  - Lower in allergic / atopic people
  - Mobile phone: not proven

Histology

- NE HELIAL
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- Em urs (eg. Me e of the
- Pir
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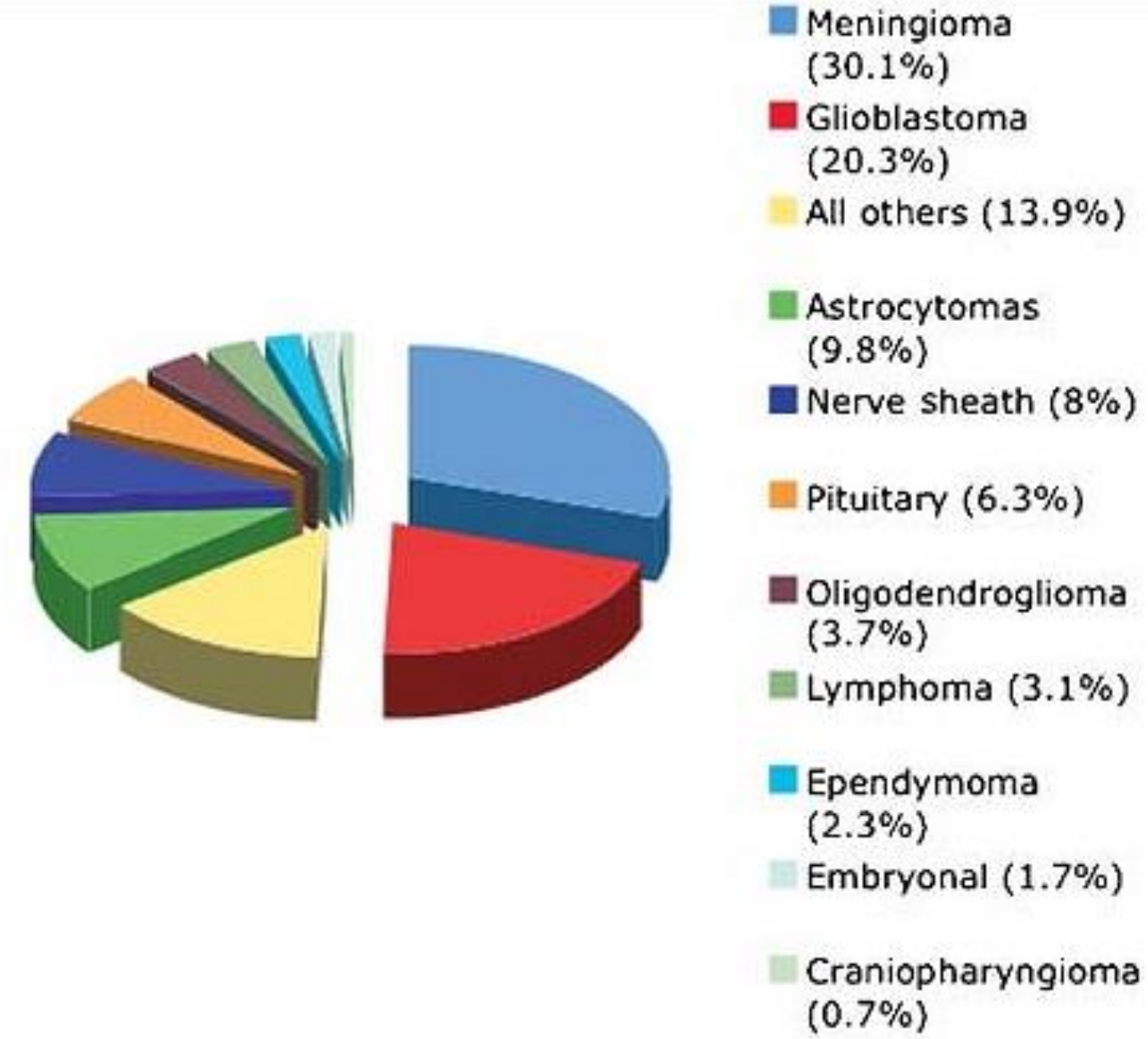
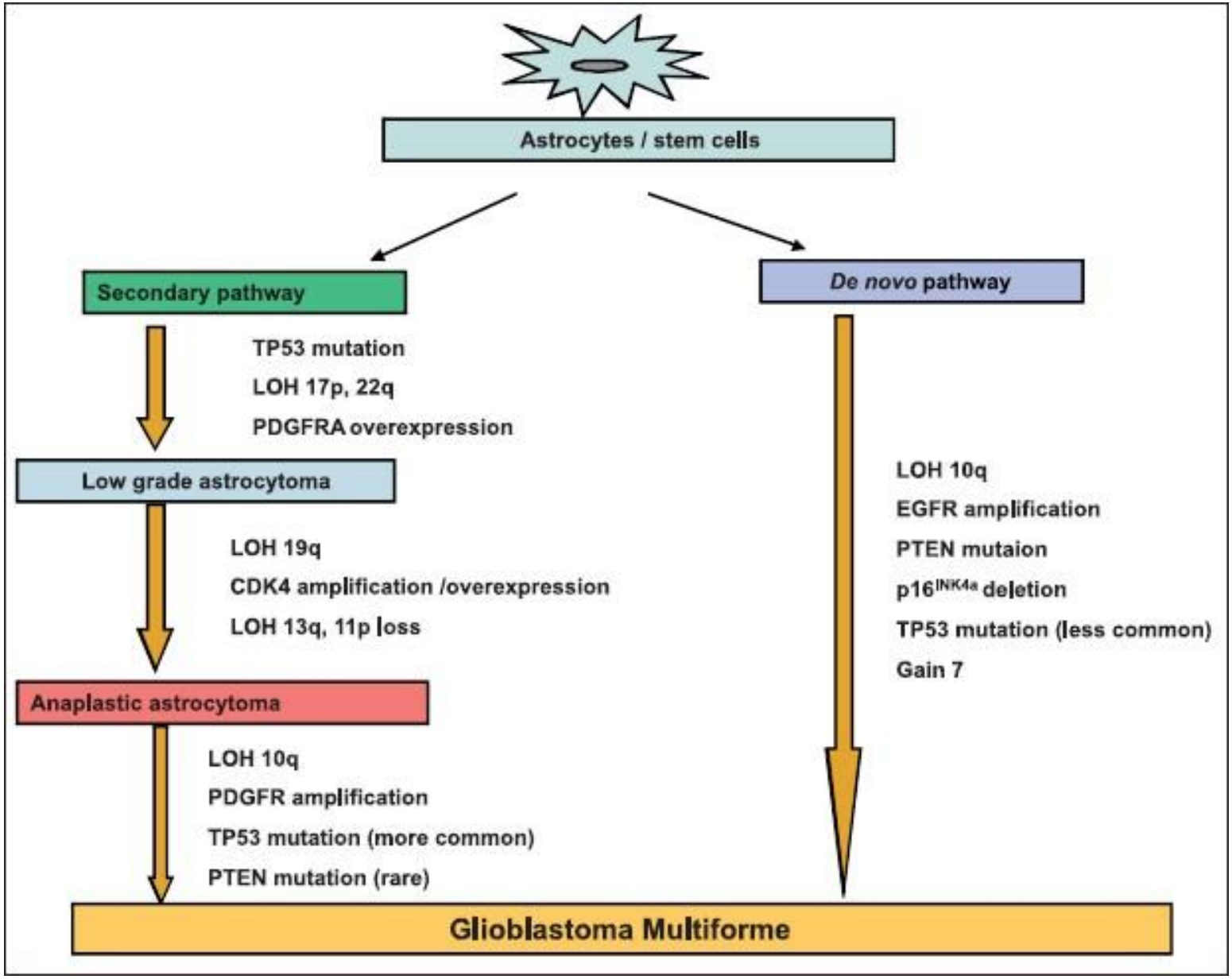
  -




Astrocytes / stem cells
Secondary pathway
De novo pathway
TP53 mutation
LOH 17p, 22q
PDGFRA overexpression
Low grade astrocytoma
LOH 19q
CDK4 amplification /overexpression
LOH 13q, 11p loss
Anaplastic astrocytoma
LOH 10q
PDGFR amplification
TP53 mutation (more common)
PTEN mutation (rare)
LOH 10q
EGFR amplification
PTEN mutaion
p16INK4a deletion
TP53 mutation (less common)
Gain 7
Glioblastoma Multiforme

Molecular pathology-Haarlem consensus

- Molecular pathology is obligatory part of diagnostics
- Morphology and molecular pathology should be blended
- „Layers” should be used
- E.g. High-grade glioma (Gr III.) under microscopy but IDH wild type therefore glioblastoma by molecular fenotype

Louis DN, Brain Pathol. 2014;24(5):429-35.

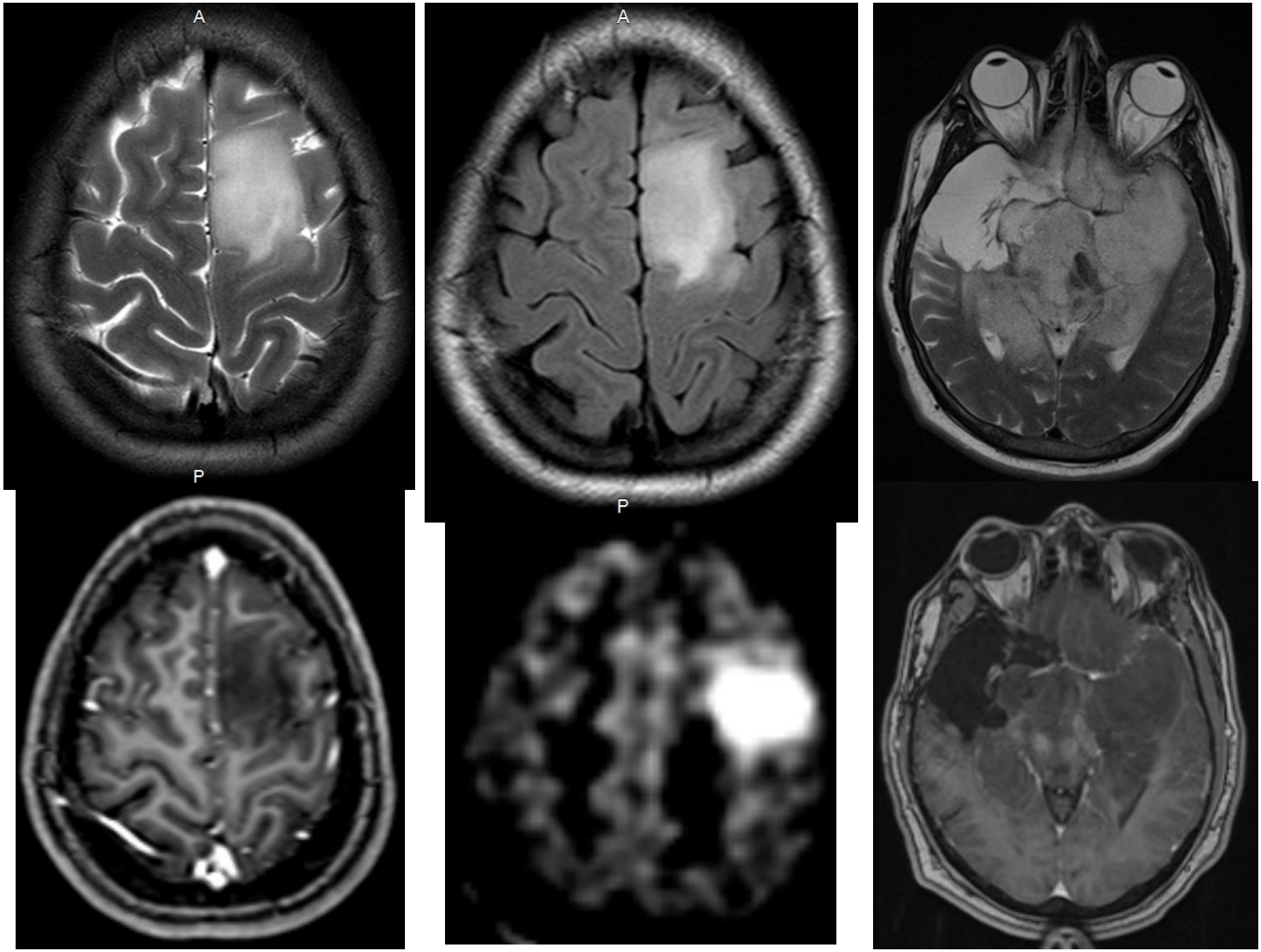
Gliomas

- **Cell type**
  - Astrocyte
  - Oligodendroglia
  - Ependymoma
- **Grade**
  - I. Pl. pylocytic
  - astrocytoma
  - II. Diffuse glioma, low-grade glioma
  - III. Anapalstic glioma
  - IV. Glioblastoma multiforme

- **Molecular markers**
  - IDH 1-2 mutation (prog)
  - 1p19q kodel (prog/pred)
  - MGMT promoter metilation status (pred, prog?)
  - ATRX loss (diag/prog)
  - H3-K27M mutátion (diag)
  - TERT mutation (diag/prog)

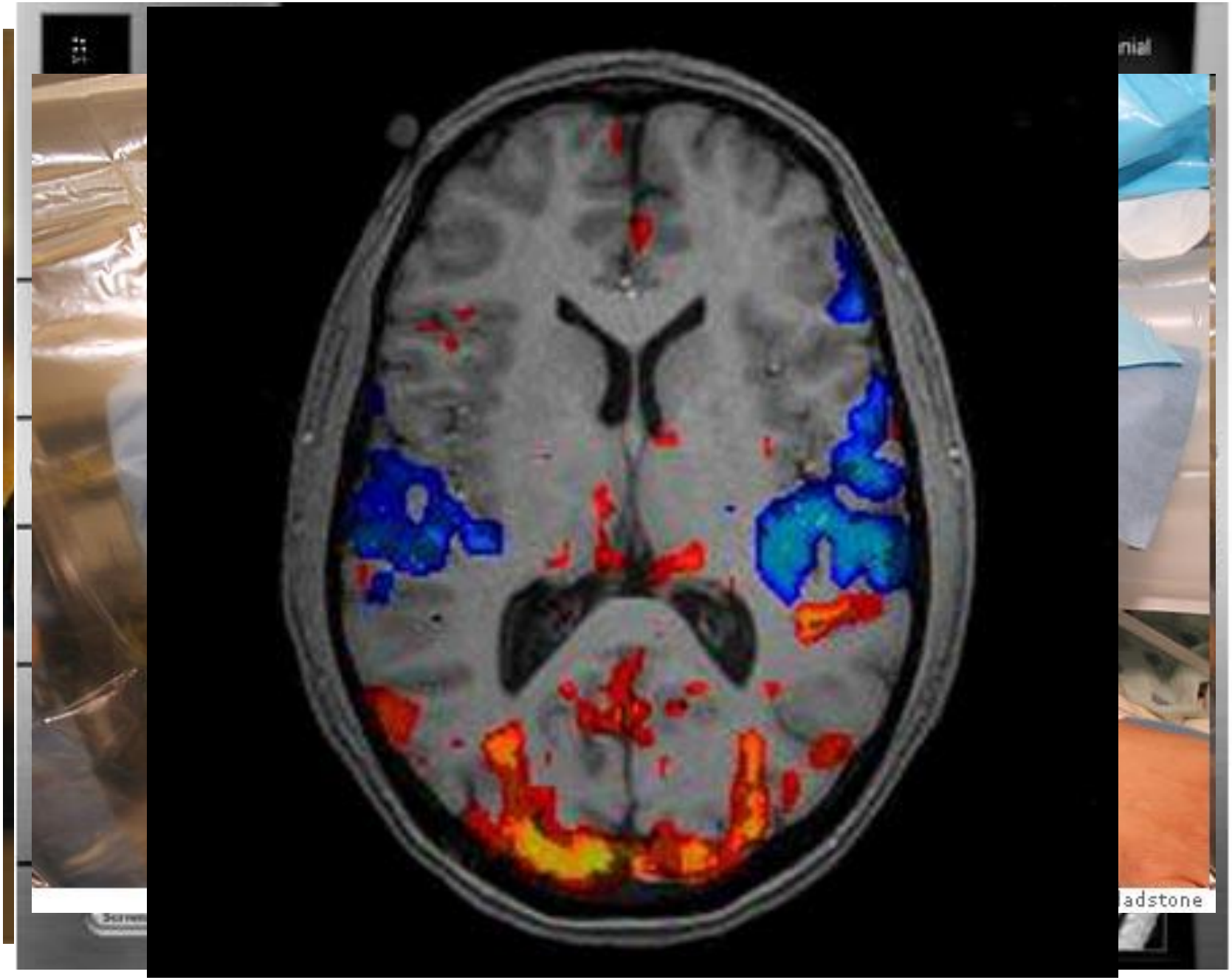
Low-grade glioma

- Slow growth
- Median survival 10-15 years
- Young age population
- Diffuse infiltration
- Complete resection is rare
- Treatment vs. Quality of life


A
A
P
P

Low-grade glioma- treatment

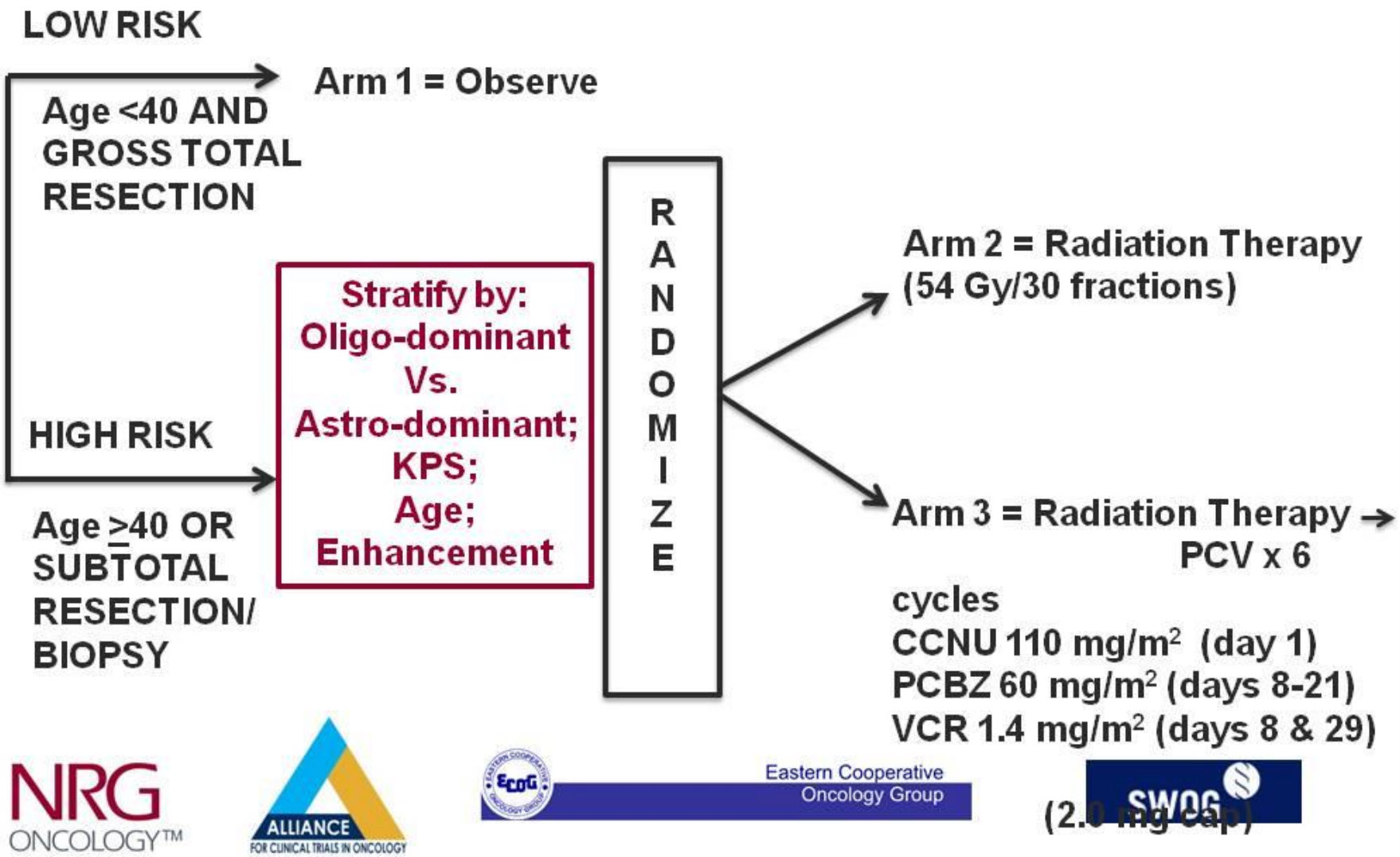
- Active surveillance
  - But surgery improved a lot
- **Maximal safe** resection
  - Neuronavigation
  - Awake surgery
  - fMRI
  - Diffusion tenzor imaging (DTI)



Low-grade glioma- adjuvant treatment

- **Prognostic factors**
  - Resection
  - Oligodendroglioma vs. astrocytoma szövettan
  - Age under/over 40
  - KPS under/over 70
  - Neurology deficit
  - 1p19q kodeletion
  - IDH 1, 2 mutation.

R9802 SCHEMA



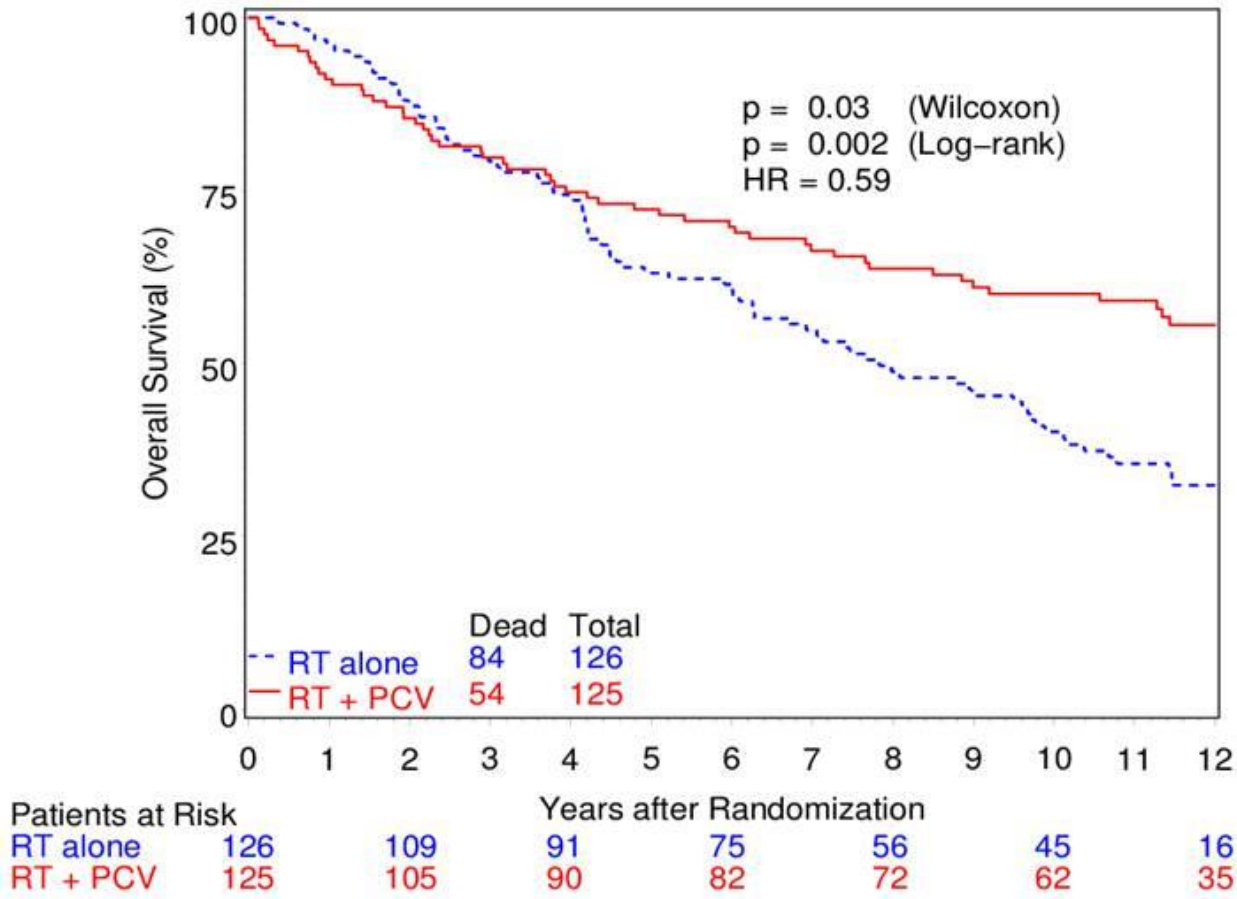
NRG ONCOLOGY™

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

Eastern Cooperative Oncology Group

SWOG

ASCO 2014: Overall Survival



NRG ONCOLOGY™

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

Eastern Cooperative Oncology Group

SWOG

Presented By Jan Buckner at 2014 ASCO Annual Meeting

Overall Survival
ASCO 2014

	RT Alone Estimate (%)	RT + PCV Estimate (%)
Median	7.8 years	13.3 years
5-year	63.1 %	72.3%
10-year	40.1%	60.1%

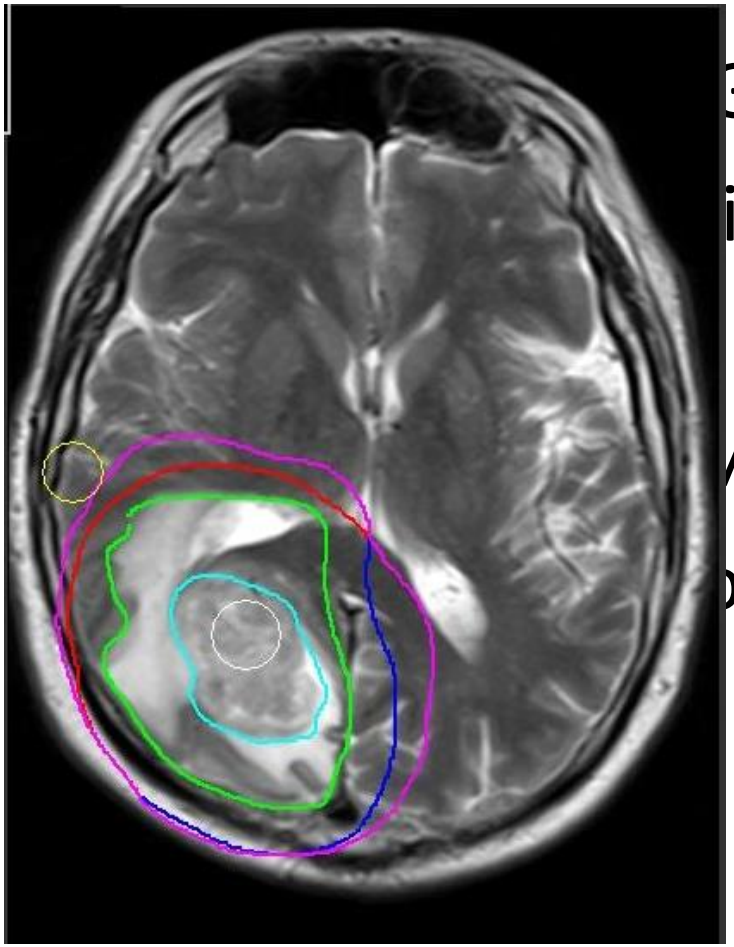
NRG ONCOLOGY™ ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY ECOG Eastern Cooperative Oncology Group SWOG

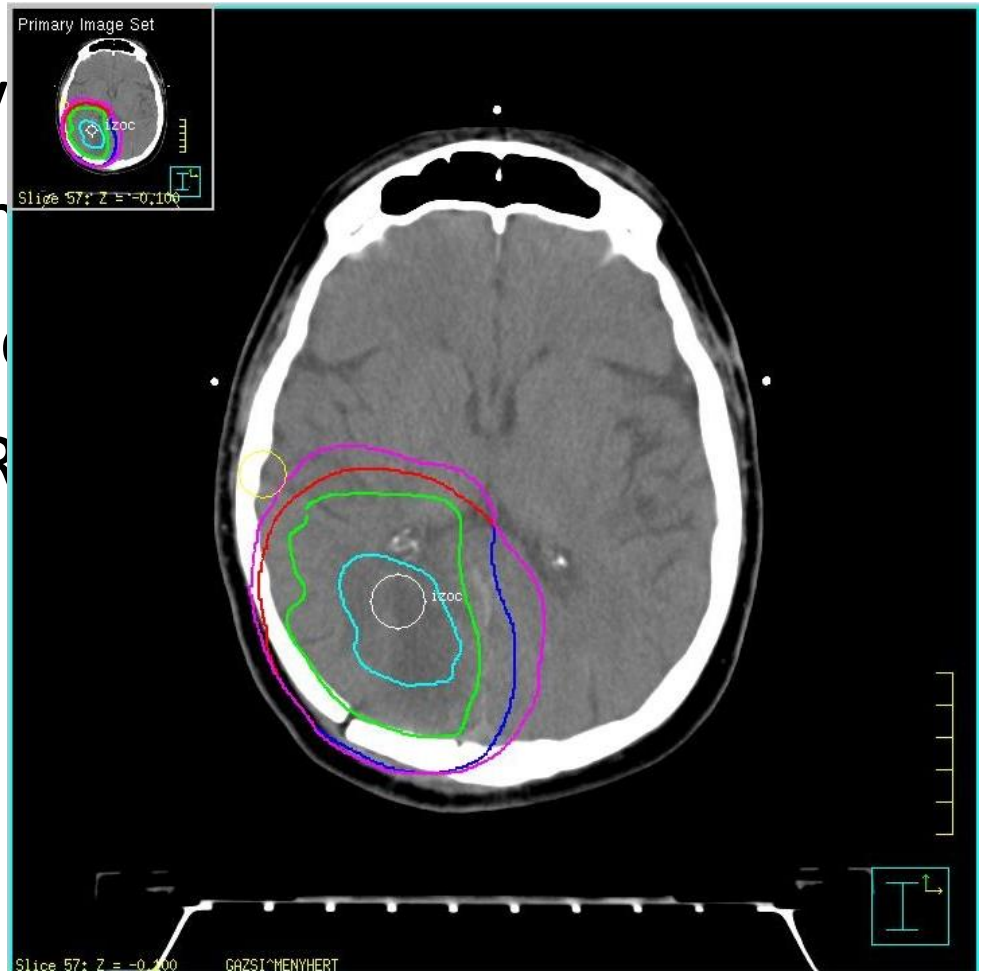
Categorical Change in MMSE Score by Treatment Arm

MMSE Score Change	RT Alone		RT + PCV		
	No.	%	No.	%	P
Year 3	n=48		n=43		.5
Decline	1	2	0	0	
No change	45	94	38	88	
Gain	2	4	5	12	
Year 5	n=22		n=25		.99
Decline	0	0	2	8	
No change	21	96	20	80	
Gain	1	5	3	12	

NRG ONCOLOGY™ ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY ECOG Eastern Cooperative Oncology Group SWOG

Grade II. radiotherapy





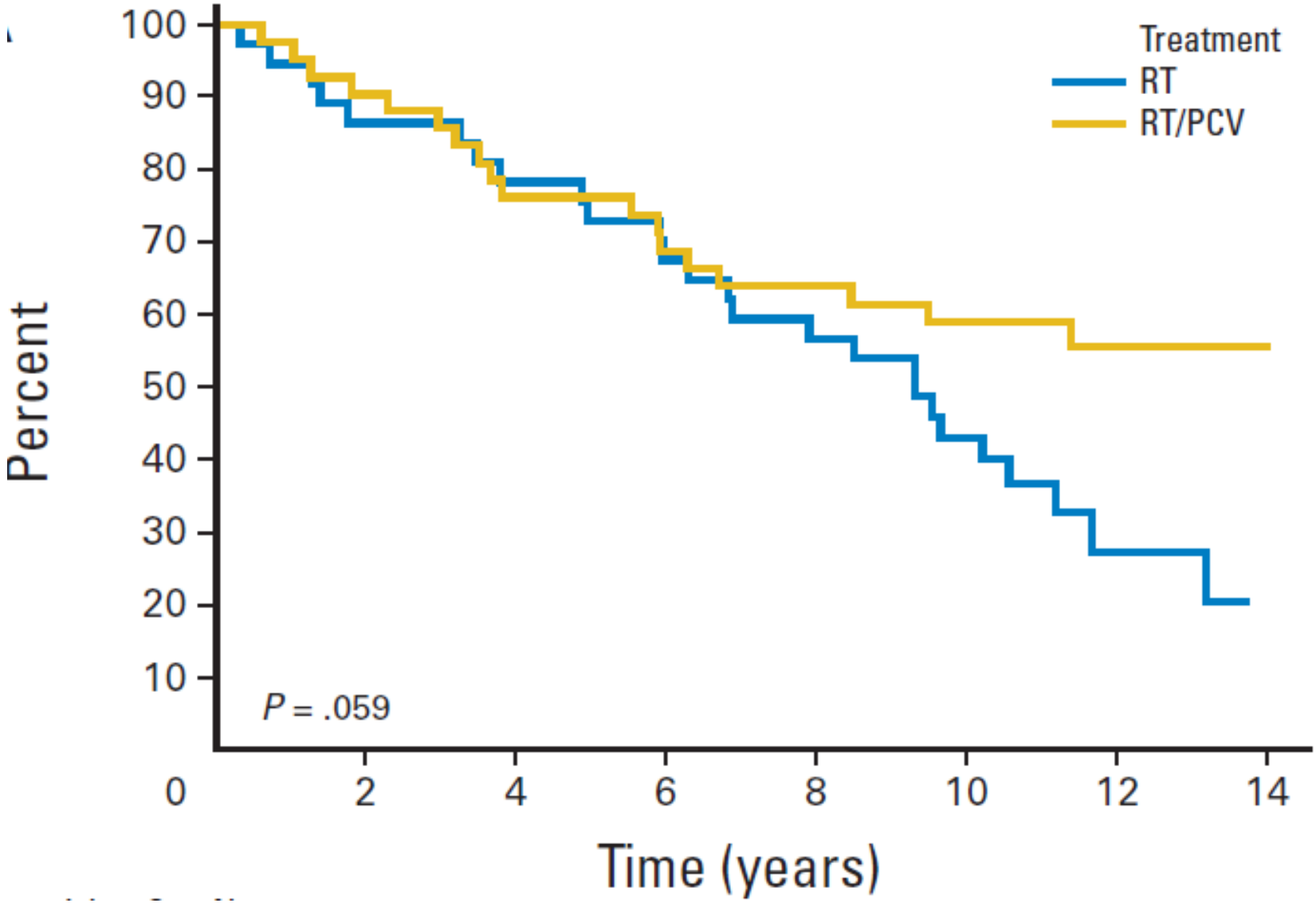
Fused MR image

Treatment planning CT

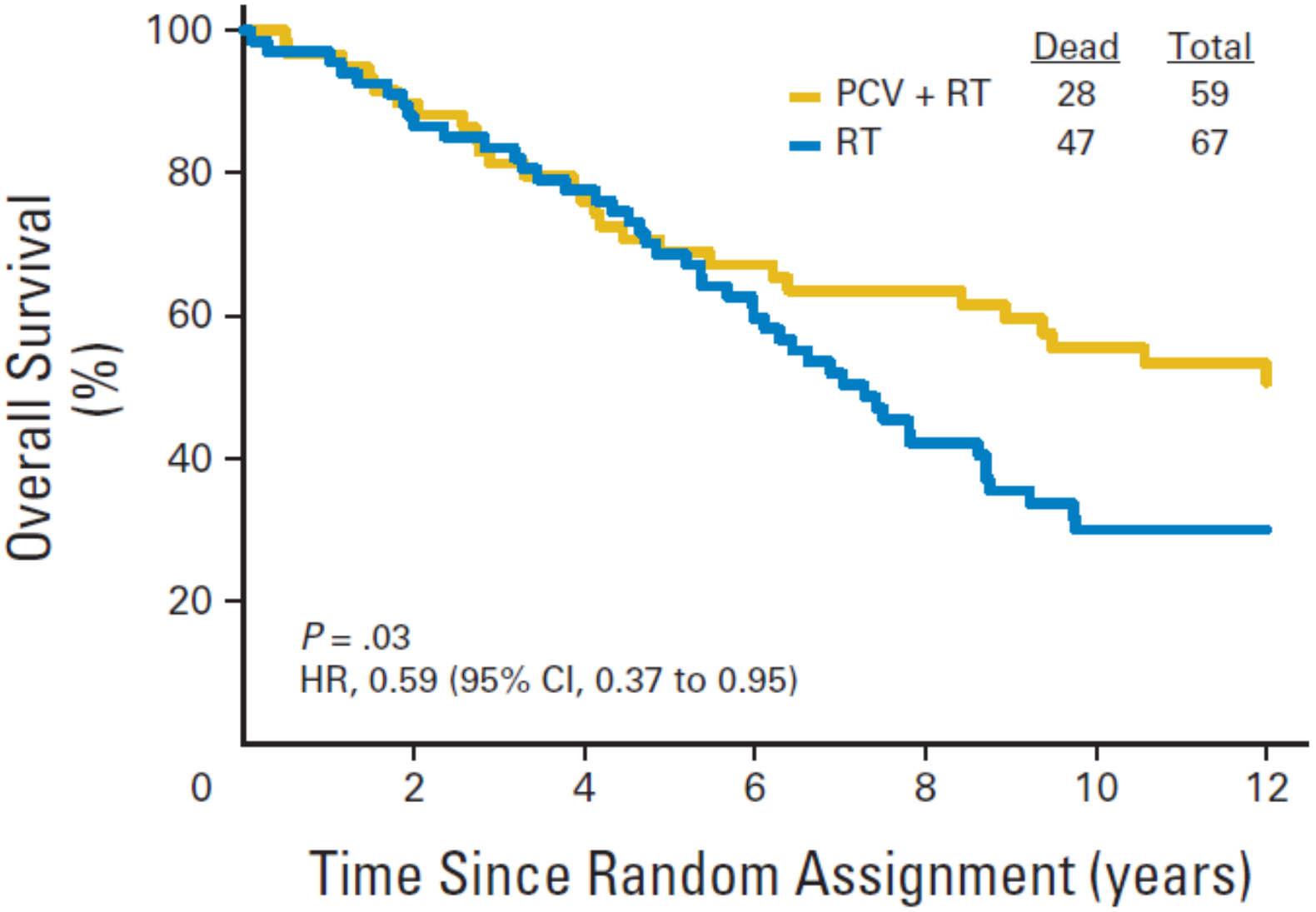
Anaplastic (Gr III.) gliomas

Grade III. glioma	**IDH wt (GBL like)**	**1p19q non kodel**	**MGMT methylated**	**RT or TMZ/PCV**
			MGMT non methylated	RT + TMZ?
		1p19q kodel		RT +6x PCV (TMZ) TMZ / PCV
	IDH mutant	ATRX loss (astrocytoma)		RT TMZ
		1p19q kodel (oligodenroglioma)		RT +6x PCV (TMZ)

EORTC 26951


Percent
100
90
80
70
60
50
40
30
20
10
0
2
4
6
8
10
12
14
Time (years)
Treatment
RT
RT/PCV
P = .059

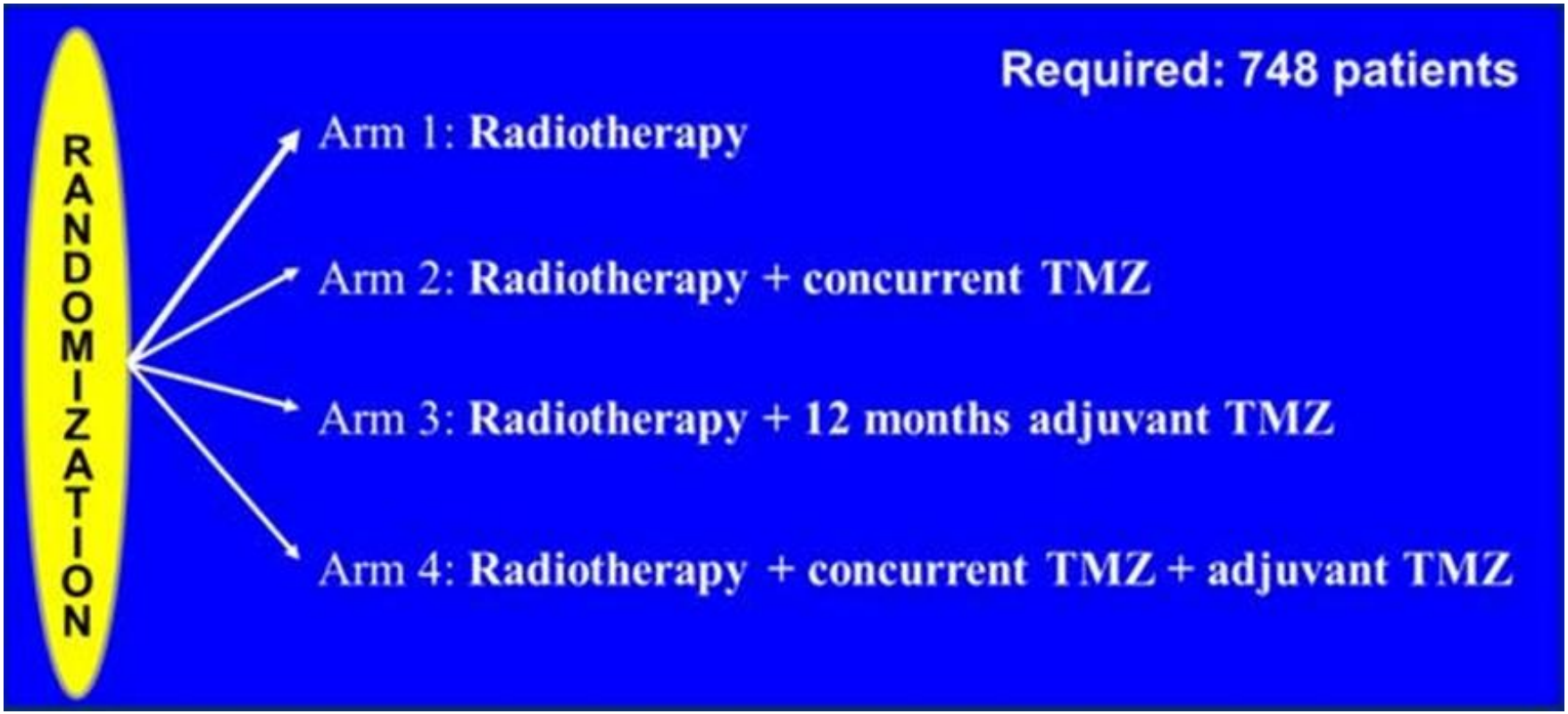
RTOG9402


Dead
Total
PCV + RT
28
59
RT
47
67
100
80
60
40
20
0
2
4
6
8
10
12
Overall Survival (%)
P = .03
HR, 0.59 (95% CI, 0.37 to 0.95)
Time Since Random Assignment (years)

Anaplastic (Gr III.) gliomas

Grade III. glioma	**IDH wt (GBL like)**	**1p19q non kodel**	CATNON
		1p19q kodel	RT +6x PCV (TMZ) TMZ / PCV
	IDH mutant	CATNON	RT TMZ
		1p19q kodel (oligodenroglioma)	RT +6x PCV (TMZ)

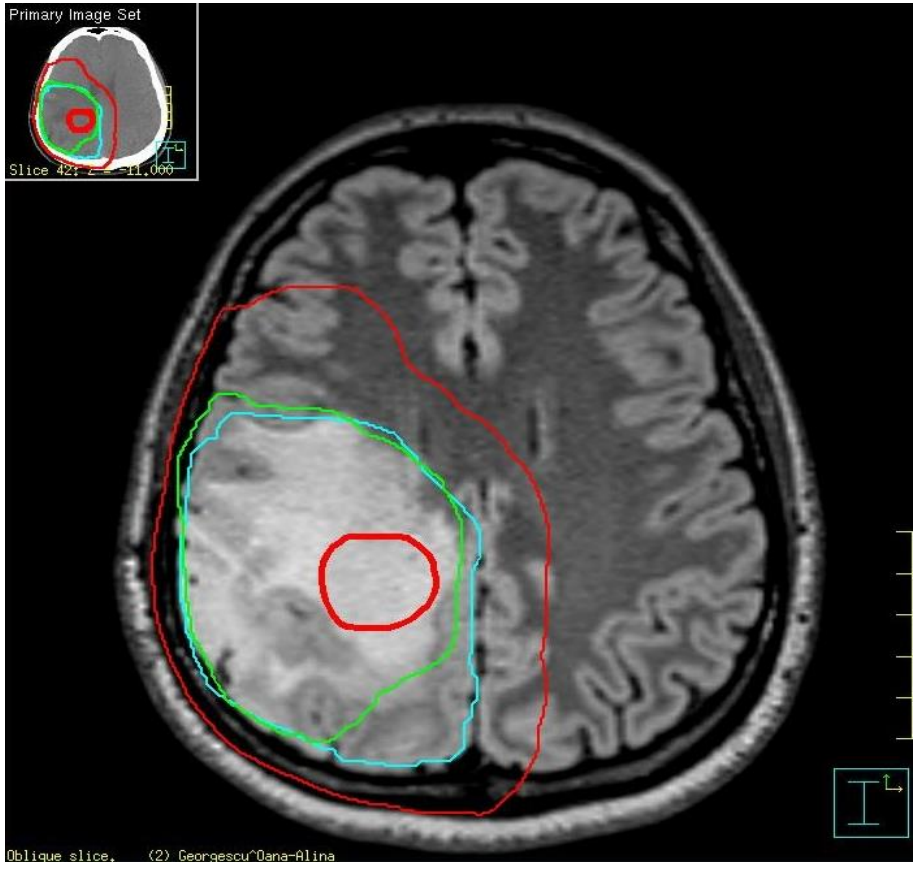
CATNON

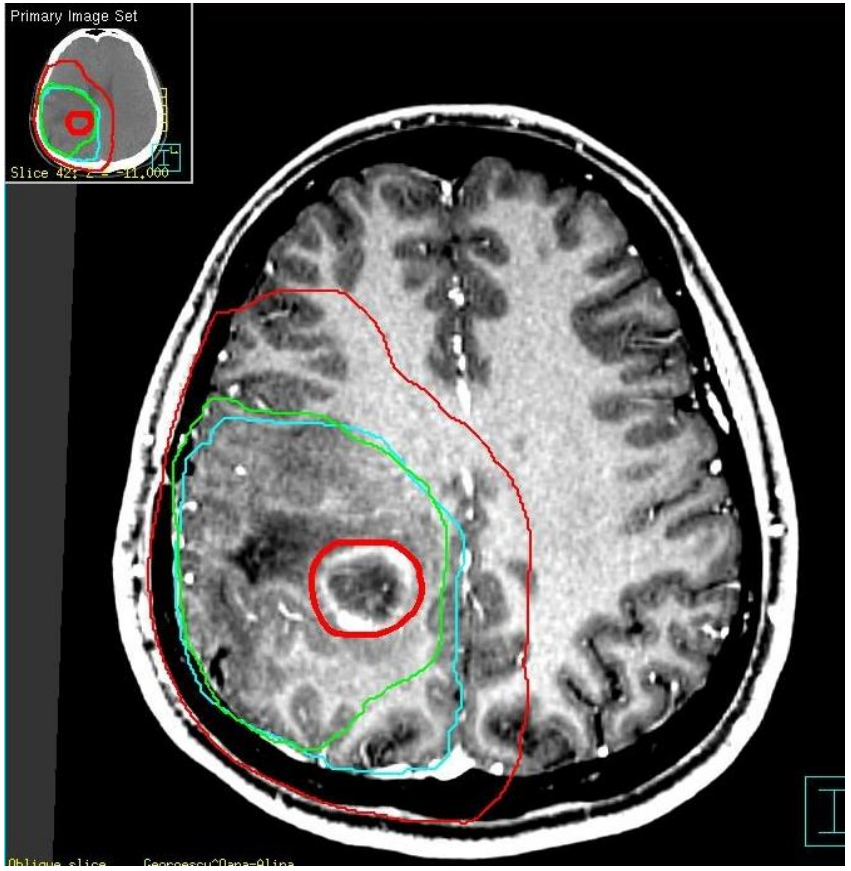


	OS		PFS
Adjuvant TMZ	median	5 -year (%)	median
No (372)	41,1 month	44,1%	19 month
Yes (373)	NR	55,9%	42,8 month

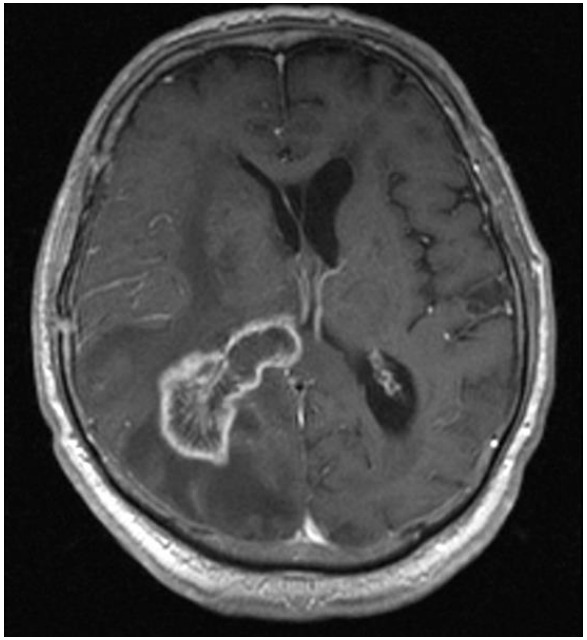
Grade III. radiotherapy

- 60 Gy (50-54 Gy to low grade part)
- Conformal, MR / PET-CT fusion
- GTV-CTV : 1,5- 2 cm



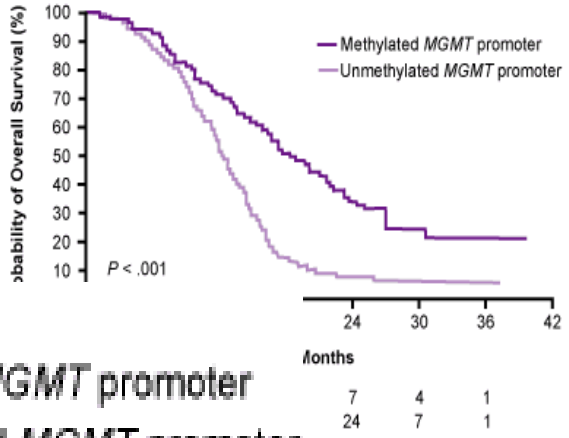


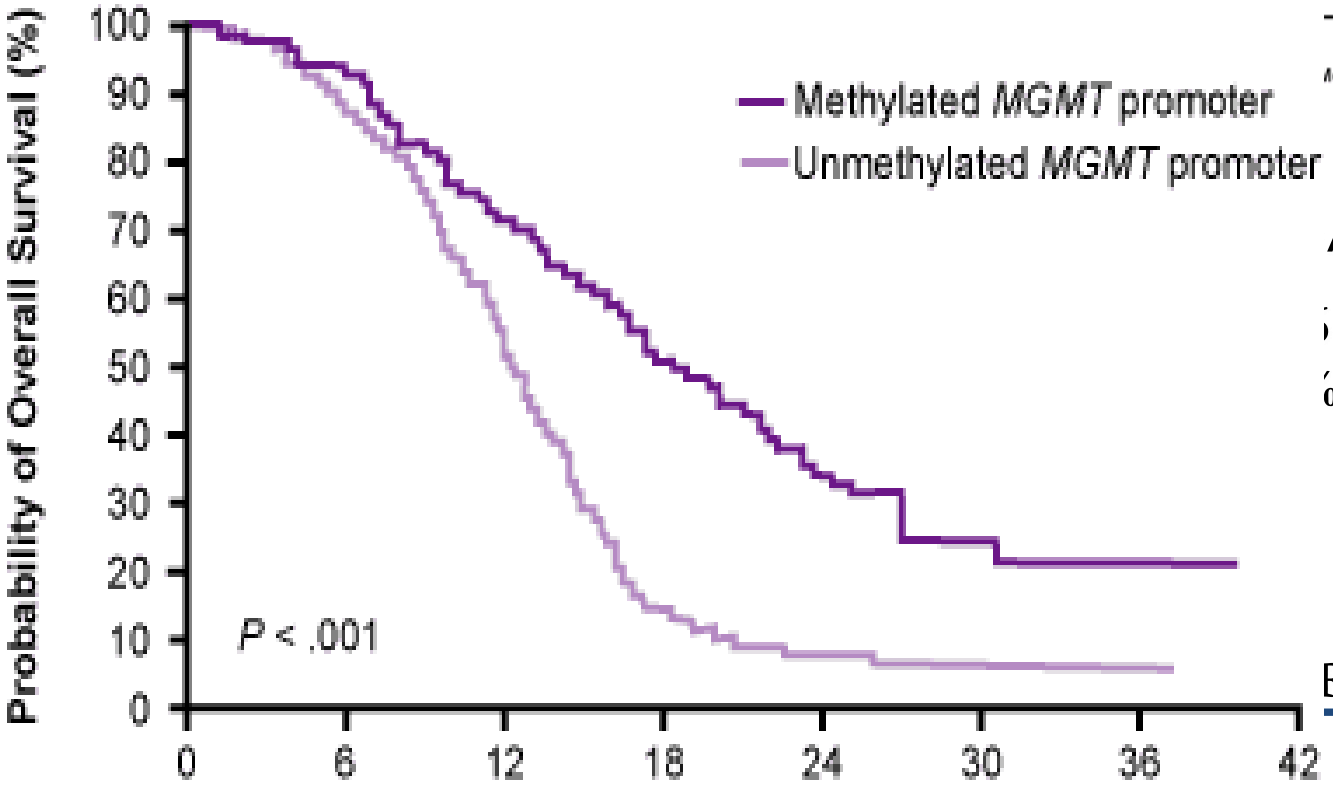
Glioblastoma



- Most ferquent glioma
- Primary / secondary
- Very bad prognosis
- Surgery / biopsy only alone
  - Survival 4-7 months
- Adjuvant radiotherapy (from the 70s)
  - 8-10 months
- Adjuvant chemoradiation + maintenance chemotherapy (60 Gy + 75mg/m2 temozolomide + 6x temozolomide (since 2005)
  - 14,6 months

TMZ and RT in Newly Diagnosed GBM
Overall Survival





/RT

%

RT

(months)

42

No. at Risk							
Unmethylated	114	100	59	16	7	4	1
Methylated	92	84	64	46	24	7	1

RT

TMZ/RT

R Stupp, et al. *Proc ASCO* 2004; abs #2.

RPA (recursive partition analyzis)

- RPA III: < 50 y, PS 0, MMSE >27, complete resection
- RPA IV: <50 év, PS 1-2, / > 50 y, MMSE >27, complete / partial resection
- RPA V: >50, MMSE <27, csak biopisza

	Deaths/ patients	Hazard ratio (95% CI)	Median (months; 95% CI)	2 years (%)	3 years (%)	4 years (%)	5 years (%)
RPA class III							
Radiotherapy	36/39	1·0	14·8 (11·1–17·0)	20·5 (9·6–34·2)	10·3 (3·3–22·0)	6·8 (1·5–18·3)	6·8 (1·4–18·3)
Combined	31/42	0·5 (0·3–0·9)	18·7 (16·4–36·0)	40·5 (25·7–54·7)	31·5 (17·8–46·2)	28·0 (14·8–42·9)	28·0 (14·8–43·0)
RPA class IV							
Radiotherapy	146/150	1·0	13·3 (12·2–15·0)	11·3 (6·9–17·0)	4·1 (1·6–8·4)	3·3 (1·2–7·4)	1·6 (0·2–6·5)
Combined	136/152	0·6 (0·5–0·8)	16·3 (14·1–18·4)	29·1 (22·1–36·5)	15·8 (10·5–22·0)	11·3 (6·8–17·1)	8·9 (4·7–14·7)
RPA class V							
Radiotherapy	96/97	1·0	9·1 (7·9–11·8)	6·3 (2·6–12·3)	2·1 (0·4–6·6)	1·0 (0·1–5·1)	0
Combined	87/93	0·7 (0·5–0·9)	10·7 (9·0–12·6)	18·2 (11·1–26·6)	9·9 (4·8–17·3)	6·8 (2·6–13·9)	3·4 (0·7–9·9)
***MGMT* unmethylated**							
Radiotherapy	54/54	1·0	11·8 (10·0–14·4)	1·8 (0·1–8·6)	0	0	0
Combined	54/60	0·6 (0·4–0·8)	12·6 (11·6–14·4)	14·8 (7·2–25·0)	11·1 (4·7–20·7)	11·1 (4·7–20·7)	8·3 (2·7–18·0)
MGMT* methylated							
Radiotherapy	43/46	0·5 (0·3–0·7)	15·3 (13·0–20·9)	23·9 (12·9–36·9)	7·8 (2·2–18·3)	7·8 (2·2–18·3)	5·2 (1·0–15·0)
Combined	37/46	0·3 (0·2–0·4)	23·4 (18·6–32·8)	48·9 (33·7–62·4)	27·6 (15·4–41·4)	22·1 (11·0–35·7)	13·8 (4·5–28·2)

Further options is GBL

- Adding **bevacizumab** to standard treatment
  - RTOG 08-25, AVAglio
    - PFS and QoL better, OS same
  - Other targeted therapy
    - No benefit
- **Immunotherapy**
  - Many type of immunotherapy – **no results yet**
- EF-14 trial : **alternating electromagnetic fields**
  - 16,6 – 19,6 hónap

EF-14: Stupp + TTF (JAMA 2015)

P = .03

36

28

8

No. at
TTF
Tem

Elderly – poor performance and GBL

- 5 randomized trial
  - BSC worse than active treatment
  - High- dose chemoradiation rarely useful
  - 60 Gy / 2 Gy worse than accelerated RT (13x3)
  - Accelerated RT + TMZ better than RT alone
  - MGMT promoter methylated: temozolomide as good as radiotherapy (NOA-08)

Malmström et al Lancet Oncol 2012, Wick W et al Lancet Oncol 2012, Roa W et al JCO 2015, Guedes de Castro et al IJROBP 20125, Perry JR et al NEJM 2017

Recurrent GBL

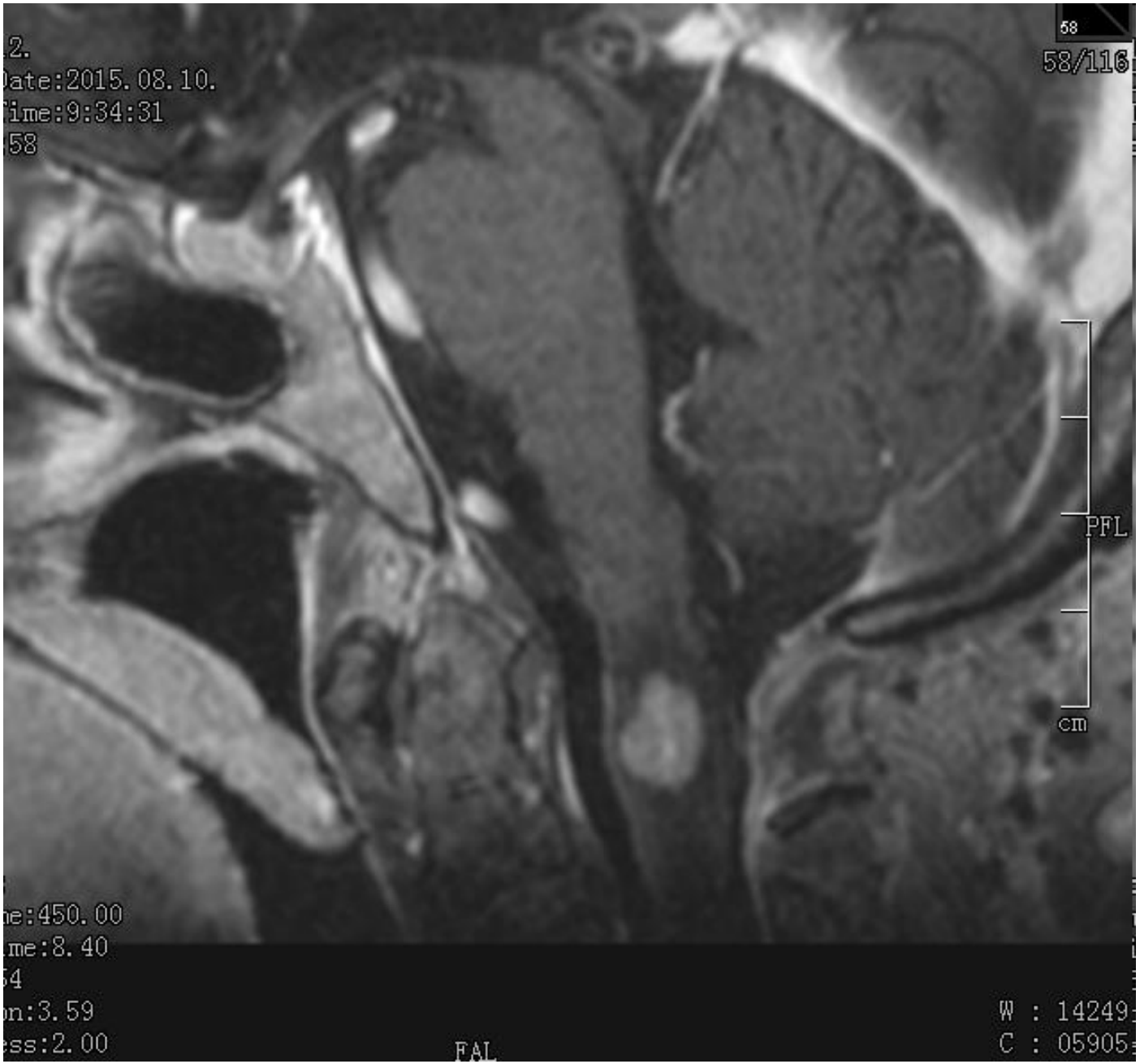
- Reoperation
- Reirradiation
  - After 2 years
- Bevacizumab (Avastin)
  - Off label, median survival ~ 9 months
- Lomustin /CCNU
  - median survival ~9 months

Survival

Glioma type	Treatment	Median survival
Grade II glioma good prognosis	obszervation / RT/ TMZ	>15 y
Grade II. glioma poor prognosis	RT	7,8 y
	RT + PCV	13,3 y
Grade III. oligo 1p19q kodel	RT	7-8 y
	RT + PCV	14,7y
Grade III. glioma non 1p19q kodel	RT / TMZ	2-3 y
	RT + PCV/TMZ	2-3 y
Grade IV. glioblastoma	RT-TMZ + TMZ	14-16 month

Ependymoma

- Rare tumor
- Surgery first
- Molecular pathology (RELA fusion gene)
- Low risk (Grade II, complete resection)
  - Observation
- Medium risk (grade III., one focus, resected)
  - Local radiotherapy
- High risk (multifocal disease, tumor in liquor)
  - CNS axis irradiation + boost to primary site(s)
- Recurrence: platinum based chemo, temozolomide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58/116
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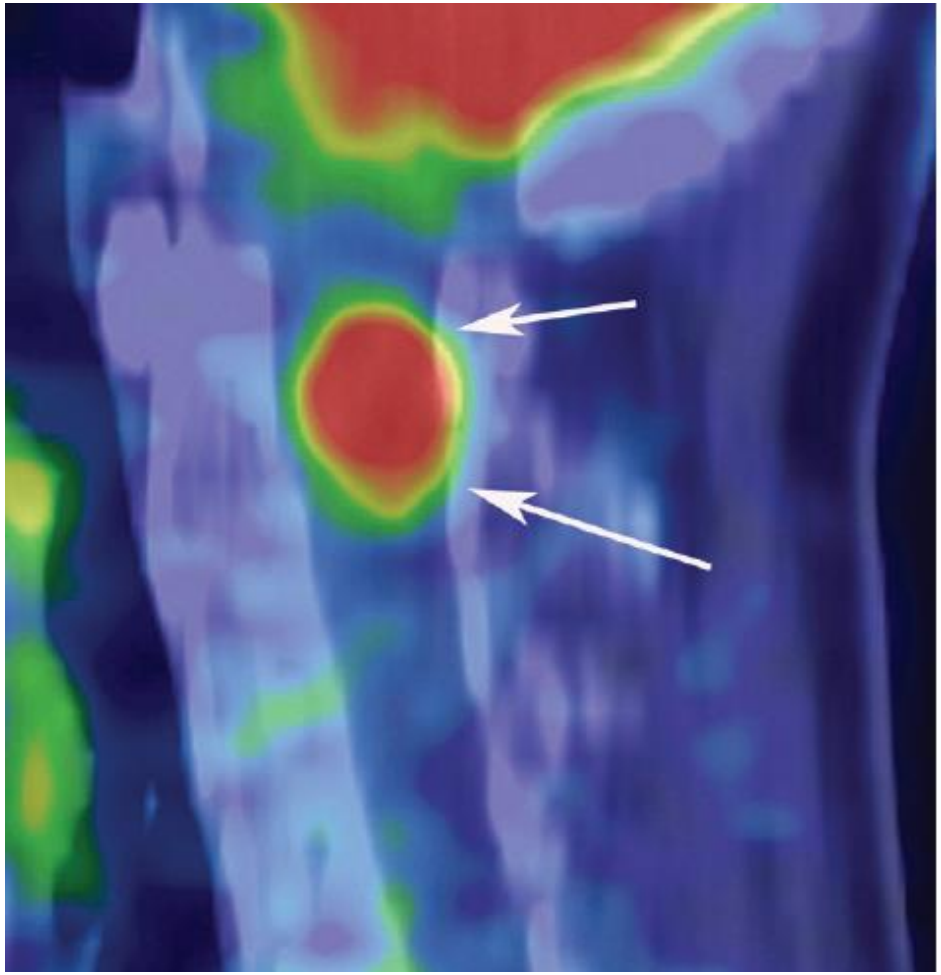
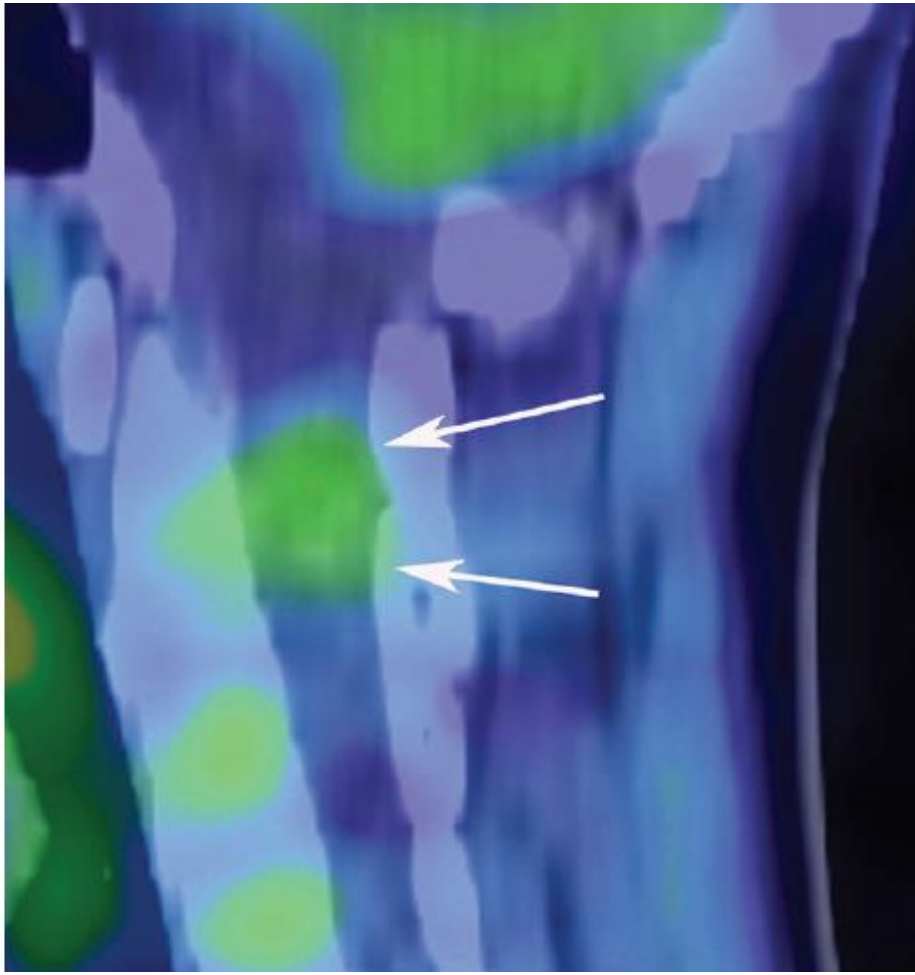
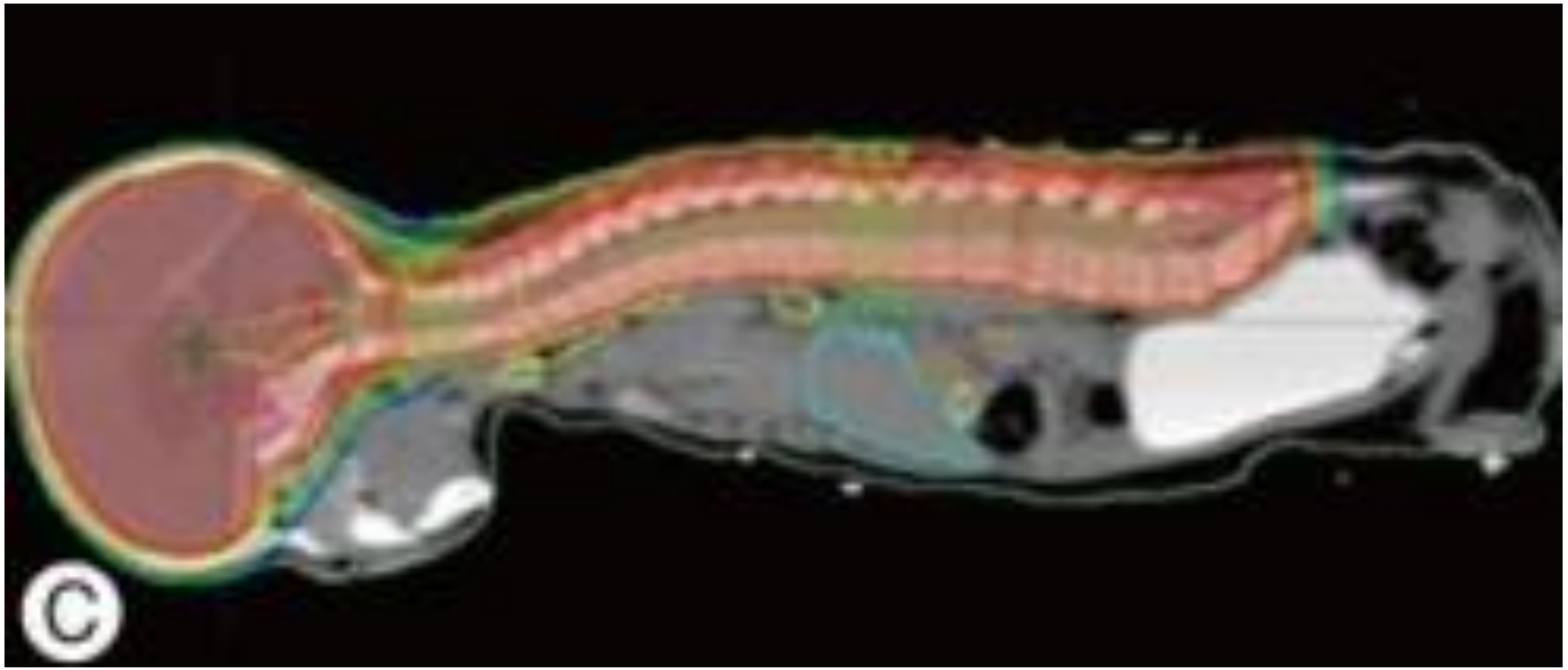
FAL





Tomura et al. AJNR 2013

Craniospinal irradiation



Medulloblastoma / PNET

- Rare in adults, typically in posterior fossa
- Resection
- High risk (>1,5ccm residual tumor, anaplastic / large cell, supratentorial primary, tumor in liquor)
  - CNS axis irradiation + boost + chemotherapy (36 + 24)
  - Chemo based on pediatric trials (VCR)
- Low risk
  - CNS axis irrad + boost +- chemotherapy
- Molecular subtyping already established in children
  - WNT-activated, SHH-activated, non-WNT/SHH-activated groups: types 3 and 4

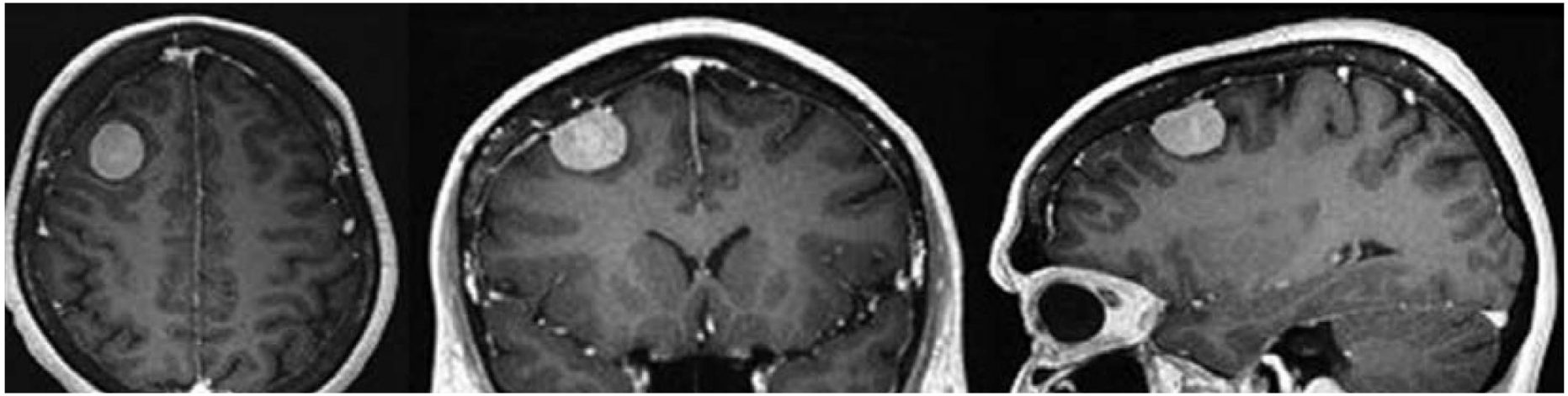
Meningioma

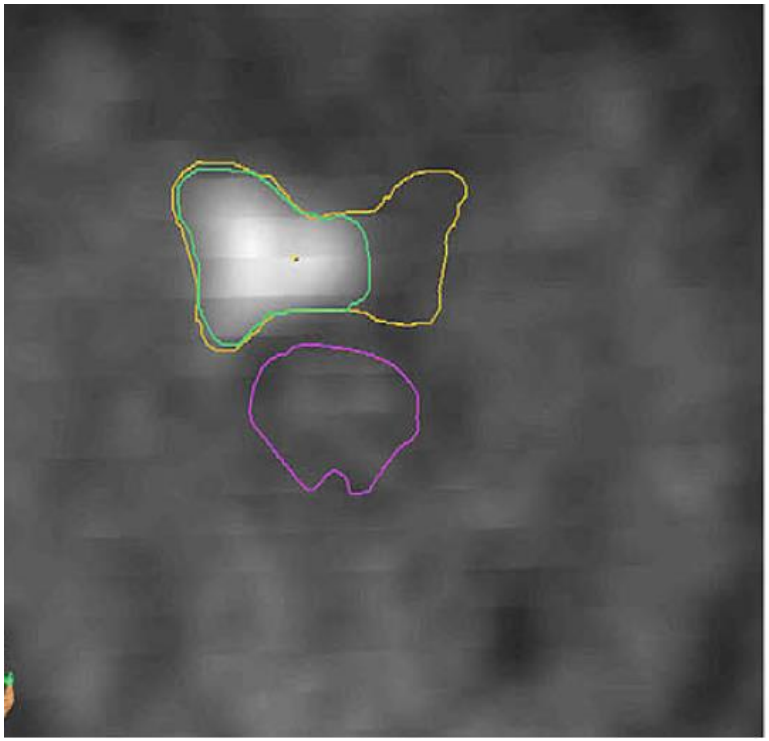
- Treated by **size** and **symptoms**
- Small tumor without symptoms
  - Observation
  - If grows: surgery +- RT (grade III, incomplete resection grade II)
  - RT, if surgery is not feasible
- Large tumor no symptoms
  - Surgery +- RT (grade III, incomplete resection grade II)
  - RT, if surgery is not feasible
  - Observation

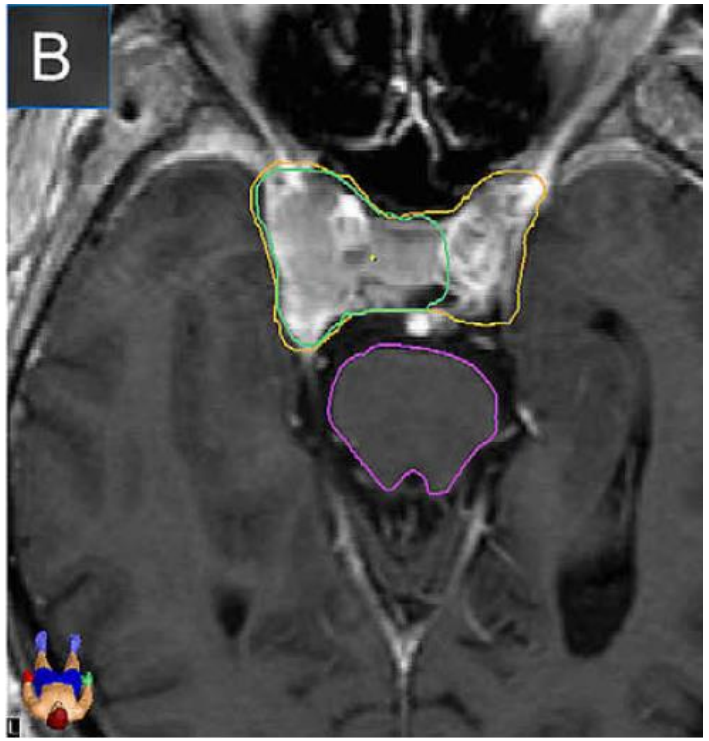
Meningioma

- Small tumor with symptoms
  - Surgery +- RT (grade III)
  - RT, if surgery is not feasible
- Large tumor with symptoms
  - Surgery +- RT (grade III, incomplete resection grade I-II)
  - RT, if surgery is not feasible

Meningioma





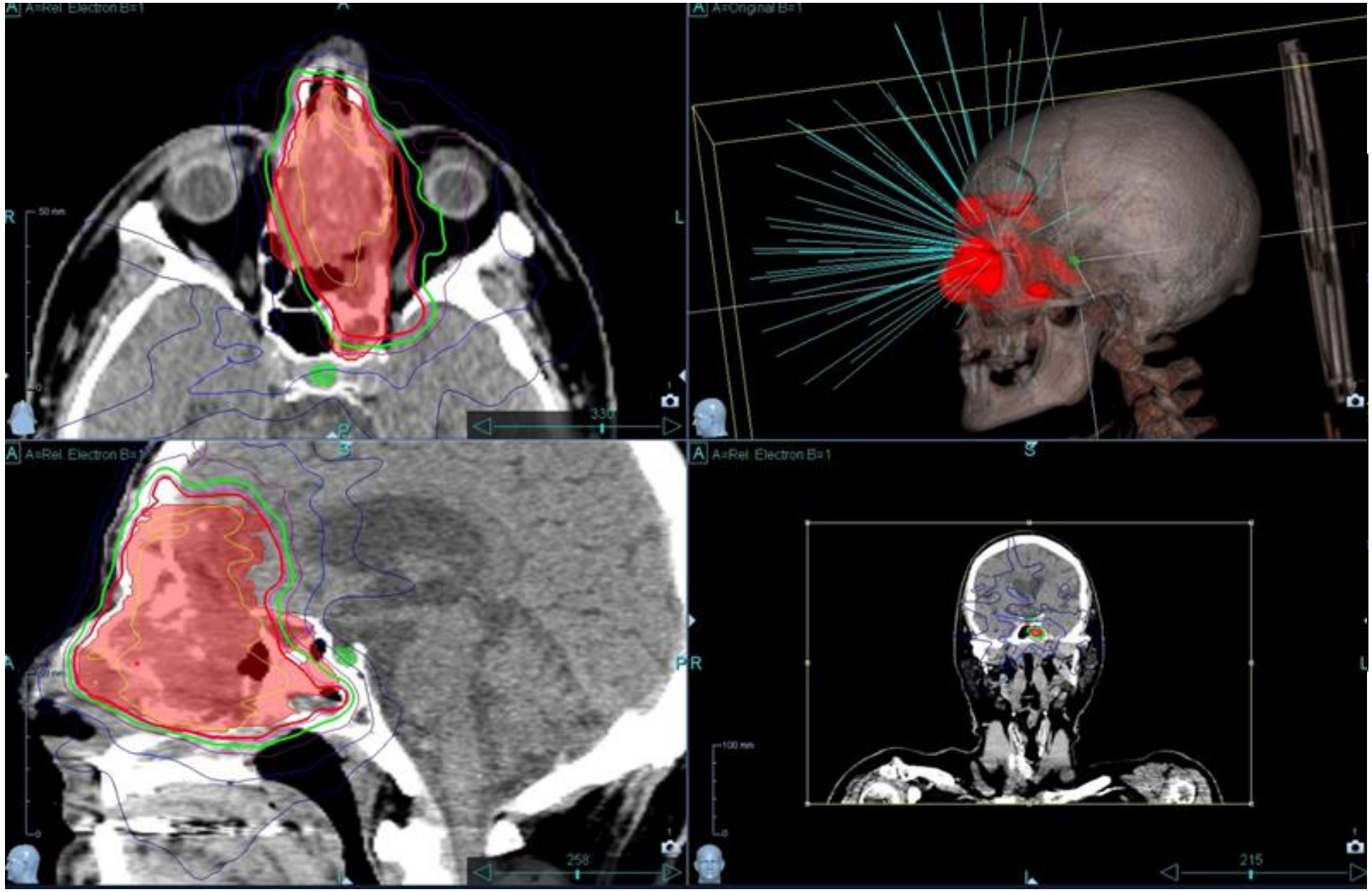


Meningioma radiotherapy

- Grade I
  - 45-54 Gy fractionated
- Grade II
  - 54-60 Gy fractionated
- Grade III
  - 60 Gy frakcionated
- Grade I
  - Streotactic radiosurgery 1x12-16 Gy
- All grade
  - Fractionated stereotactic radiotherapy (e.g. 6x6 Gy)

Recurrent meningioma

- Re-resection
- Reirradiation (stereotactic)
- Pharmaceutical therapy
  - IF-alfa
  - Somatostatin analogue / isotope therapy
  - Sunitinib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A=Original B=1
A=Rel. Electron B=1
A=Rel. Electron B=1
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258
215