



Amino-acid PET imaging in neuro-oncology

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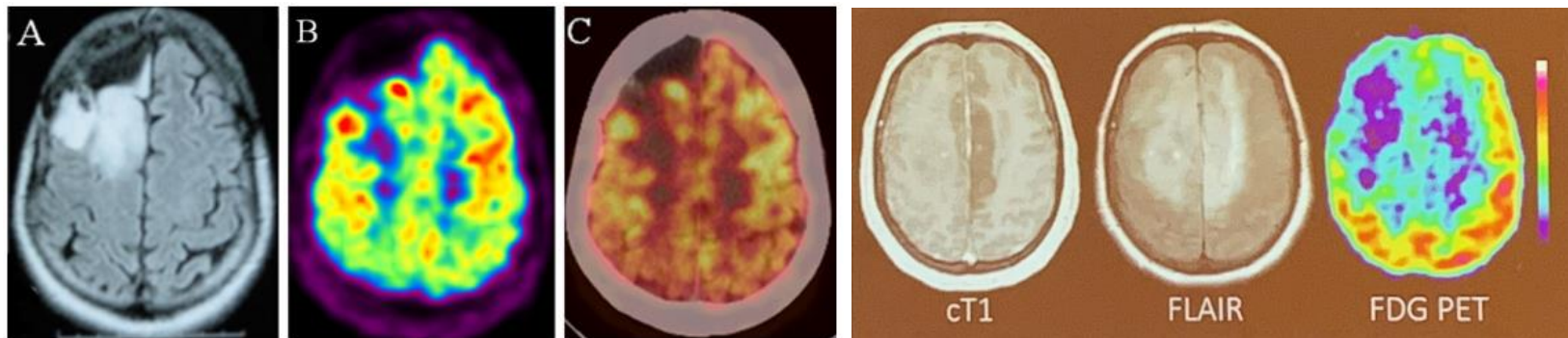
Nuclear Medicine & Molecular Imaging
UZ – KU Leuven

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Centre Hospitalier de Mouscron



PET imaging with FDG

- Among PET tracers, FDG is most widely studied and validated tracer to date
- BUT in brain tumors, FDG PET has limitations
- Disadvantage: tumor delineation in brain is difficult due to physiological high FDG uptake in normal brain tissue



Diffuse oligoastrocytoma (WHO grade II)

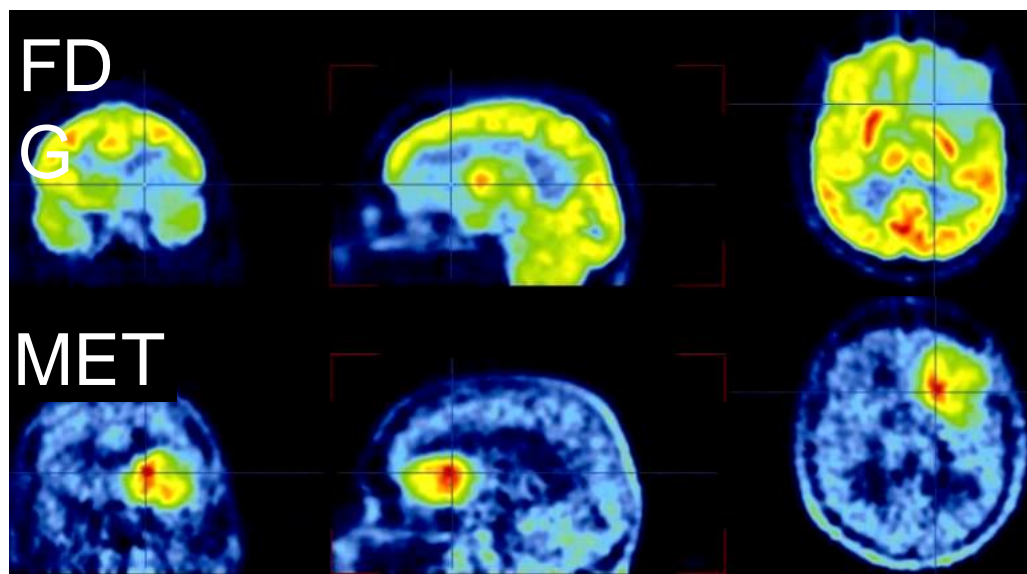
Anaplastic astrocytoma (WHO grade III)

- **Metabolism:** ^{18}F -FDG
- **Synthesis:**
 - Amino acids (/analogues) : ^{11}C -methionine / ^{18}F -FET / ^{18}F -FDOPA
 - Membrane biosynthesis : $^{11}\text{C}/^{18}\text{F}$ -choline
 - DNA/nucleosides (proliferation markers) : ^{18}F -FLT (thymidine)
- **Hypoxia** : ^{18}F -FMISO
- **Specific receptor targeting** :
 - ^{68}Ga -DOTATOC/TATE (somatostatine-2)
- **BBB rupture markers** :
 - ^{201}Tl , $^{99\text{m}}\text{Tc}$ -MIBI, $^{99\text{m}}\text{Tc}$ -TF

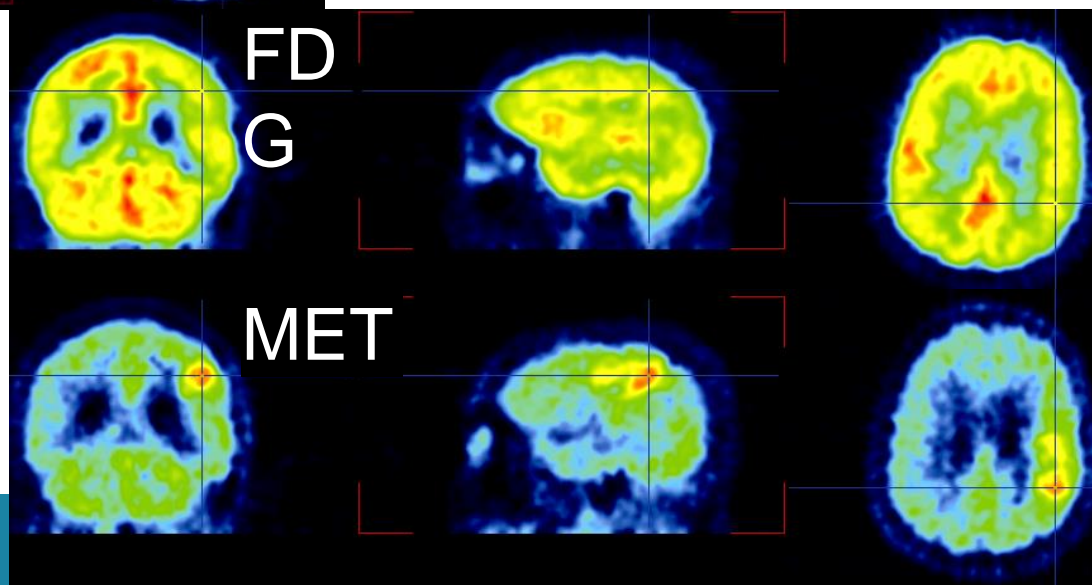
Why?

1. *No uptake in normal brain*
2. *More specific tumor pathophysiology*
3. *More sensitive to the effect of treatment*

Better tumor delineation using AA tracers



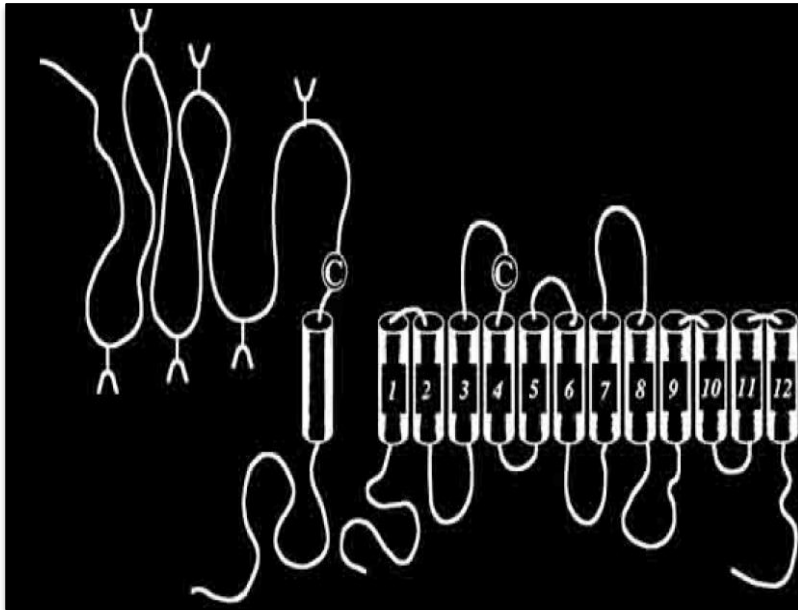
Oligodendroglioma



Glioblastoma

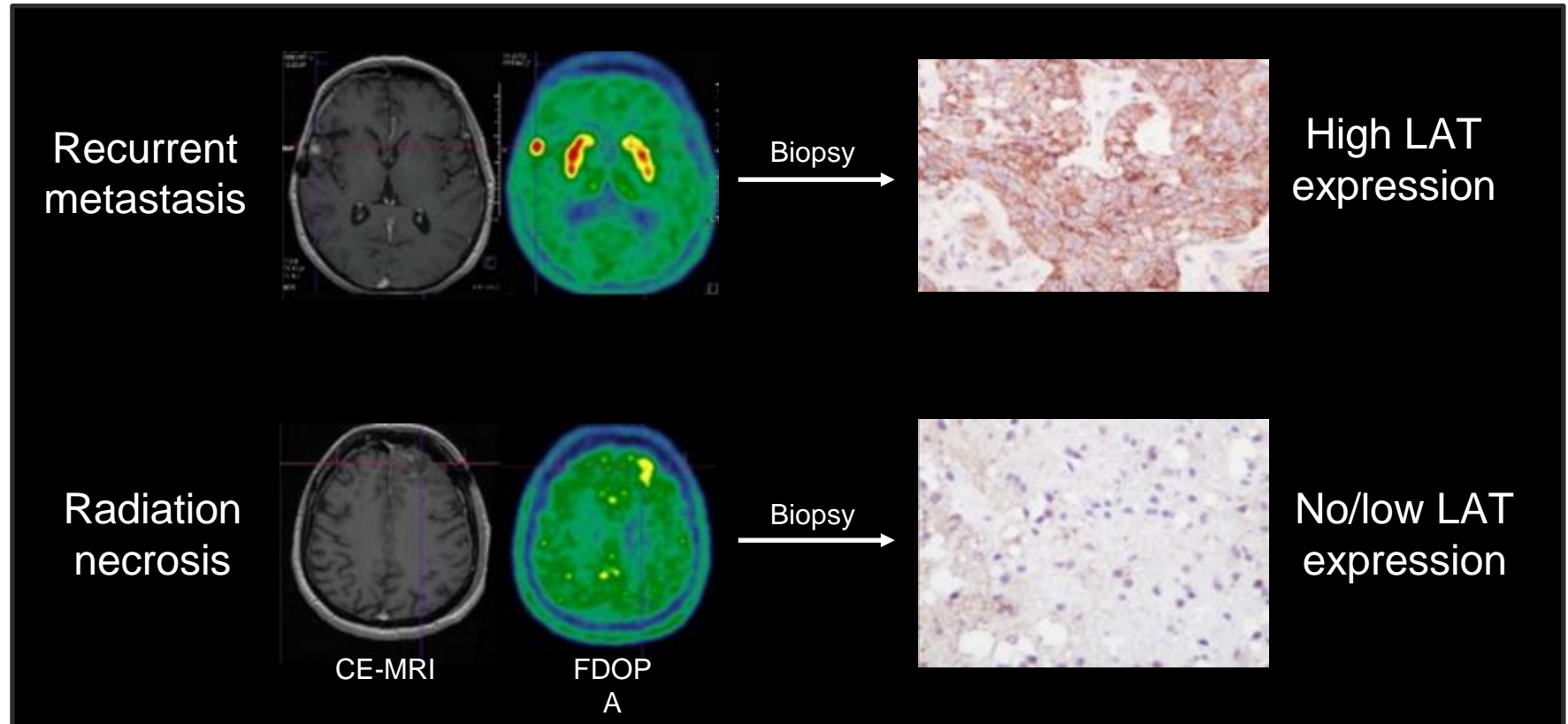
Labelled amino acids (analogues)

L-Type AA transporter



- Overexpression of L-type transporter is likely the most important factor for increased AA uptake in tumors
- Can penetrate intact BBB => also non-MR-contrast enhancing lesions can be visualized (uptake is independent of BBB disruption)
- Marker of
 - Active tumor proliferation (cell proliferation, Ki-67 expression)
 - Number of tumor cells
 - Angiogenesis (density of microvessels)
- AA uptake is not well correlated to protein synthesis (*Ishiwata, JNM 1993*)

Amino acid PET uptake correlates with LAT expression



Advances in neuro-oncology imaging

Karl-Josef Langen ✉, Norbert Galldiks, Elke Hattingen & Nadim Jon Shah

Neuro-oncology

Amino acid PET for brain tumours – ready for the clinic?

Karl-Josef Langen ✉ & Colin Watts ✉

- Amino acid PET has additional clinical value compared to standard MRI in gliomas
 - Better differentiation of equivocal lesions detected with MRI
 - Prevention of nondiagnostic biopsies
 - Improved targeting of surgery and radiotherapy to the true extent of the tumor so that healthy tissue is spared
 - Differentiation between tumor progression and treatment-related changes so that overtreatment can be avoided
 - Early identification of tumor responses to therapy so that unnecessary adverse effects are avoided
- ⇒ Response assessment in neuro-oncology working group (RANO) recommends its use at every stage of management



1. PRIMARY DIAGNOSIS

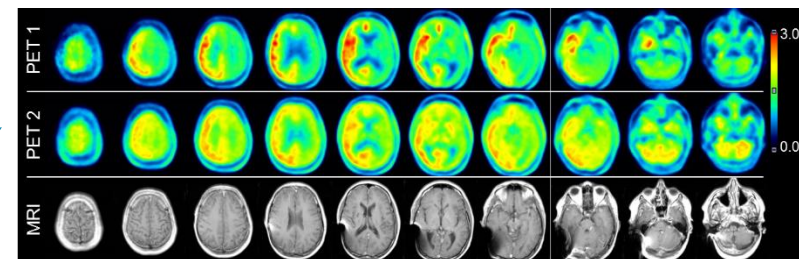
Identification of lesions

Non-invasive tumor grading

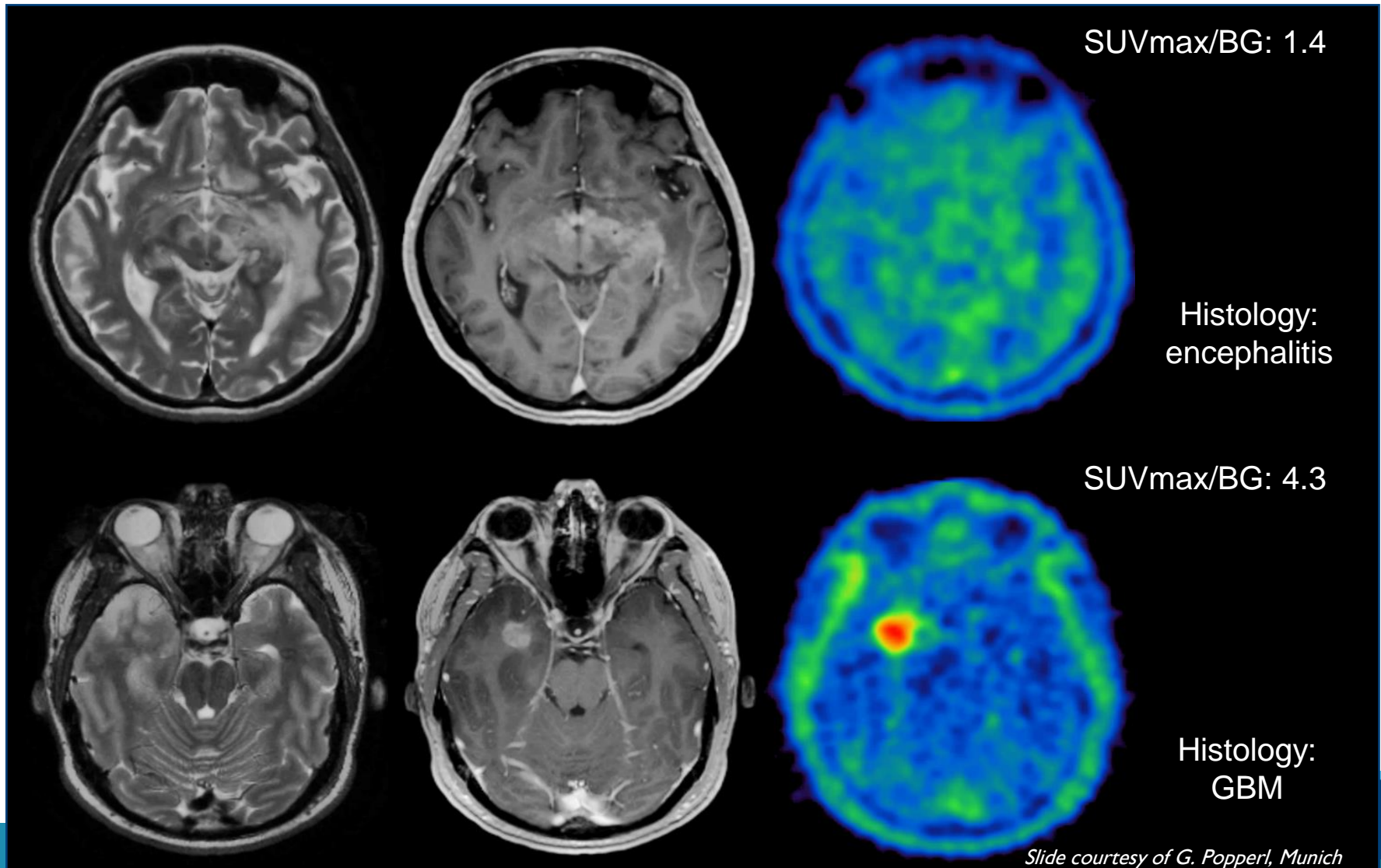
Biopsy planning

Identification of lesions

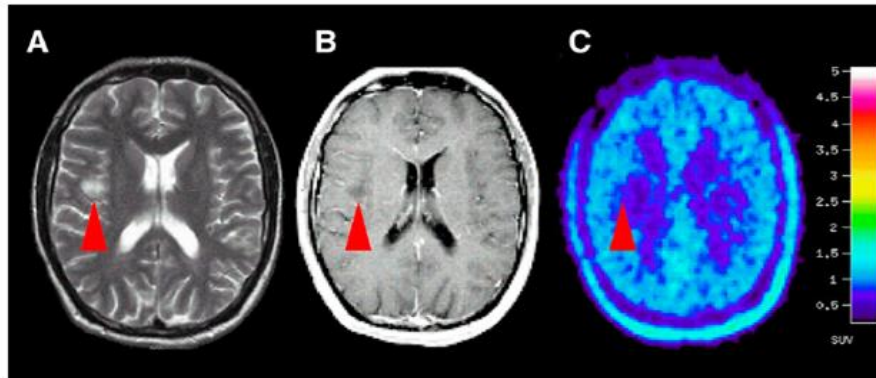
- Almost all high grade gliomas, brain metastases and oligodendrogliomas express high FET uptake
 - A number of *other* brain tumors also show moderate to high tracer uptake
- High negative predictive value for malignancy
 - ~ 80-90 % (cutoff 1.5 TBR) (e.g. *Herholz, Neurology 1998*)
- Low number of false positives:
 - Less effect of inflammation than FDG
 - Possible false positives
 - Hematoma
 - Acute ischemic stroke with reperfusion
 - Brain abscess
 - Focal cortical dysplasia
 - Recent significant epileptic activity



Inflammatory lesion vs HGG



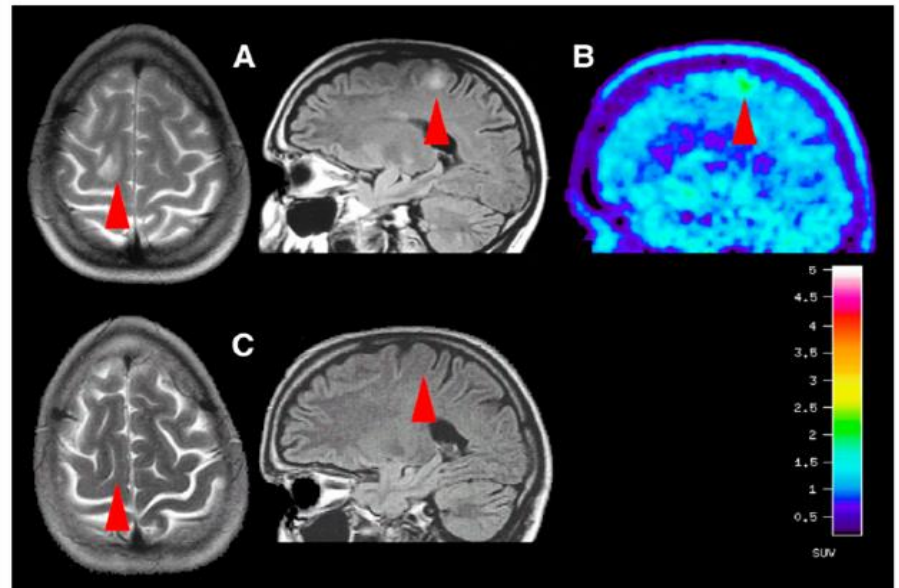
Lesion identification



- Young healthy volunteer in clinical trial
- Lesion frontoinsular right, no CE on MRI
- Lesion stable after 5 years

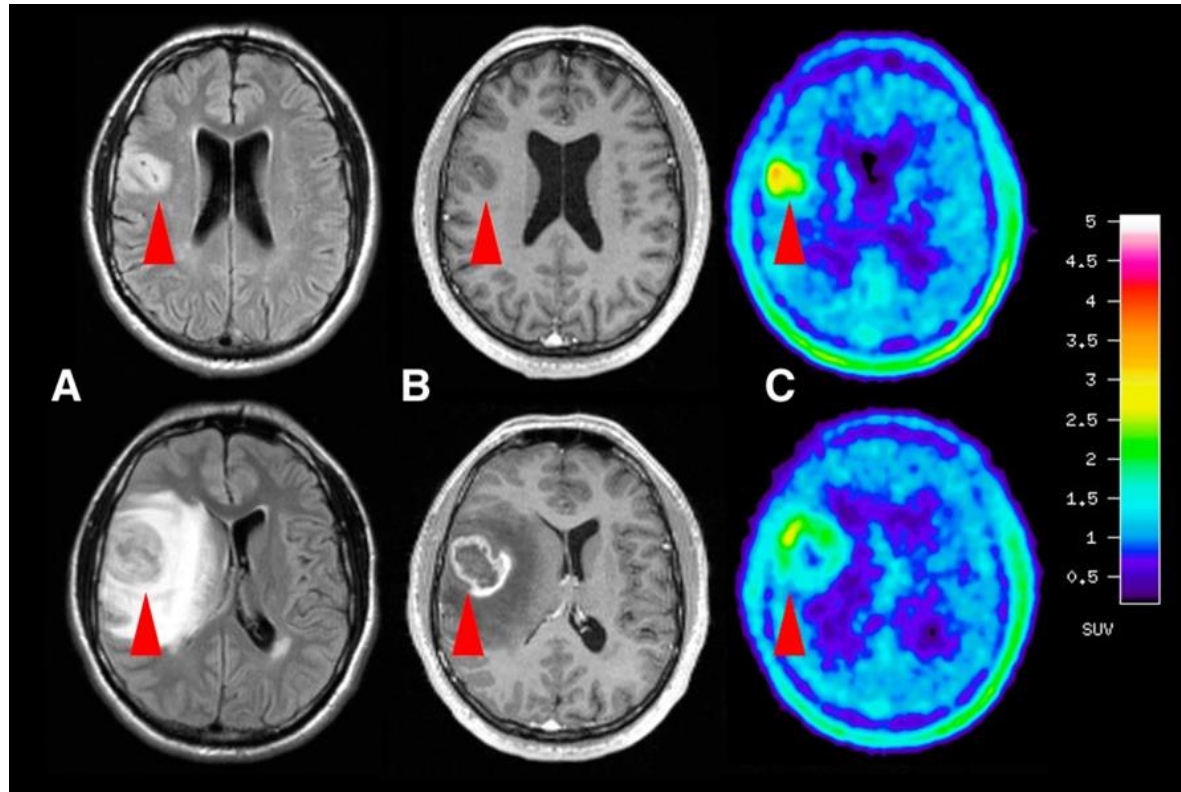
- Chronic dizziness, MRI screening
- Lesion right parietal
- TBR FET = 1.4
- Lesion disappeared at follow-up after 10 months
- Long time follow-up: negative

=> High negative predictive value



Lesion identification

Young man, chronic headache



Initial imaging

- FET ratio: 2.4
- non CE lesion frontal right

Follow-up after 2 md

- FET ratio: 2.5
- growth on MRI, CE rim, necrosis, oedema

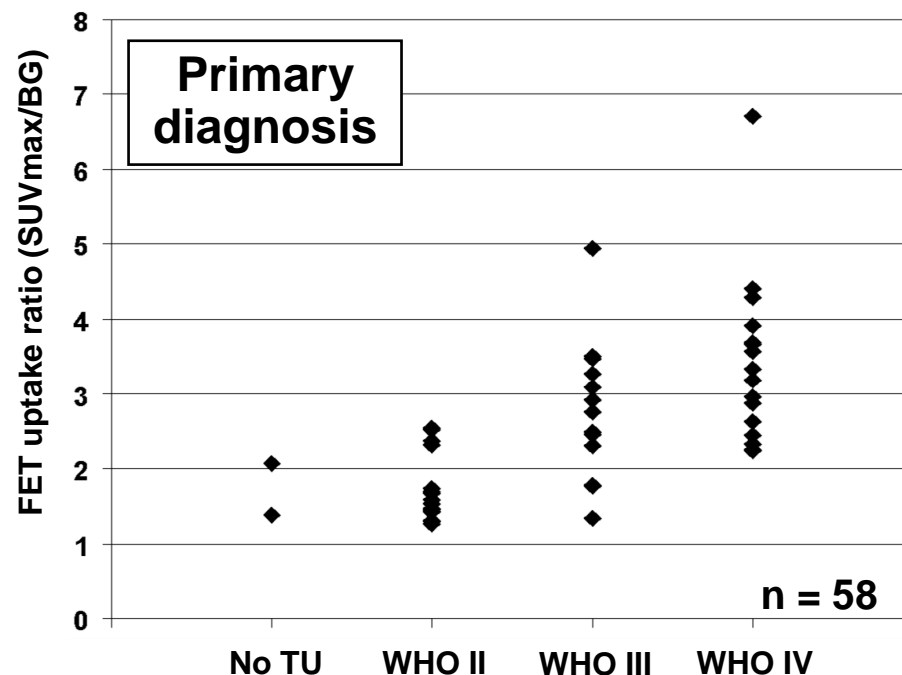
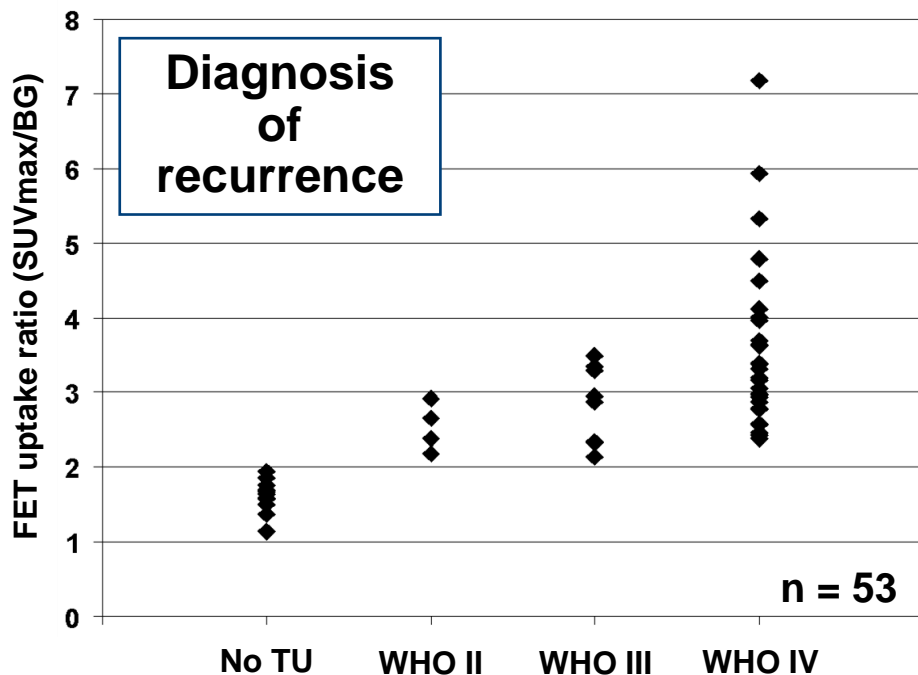
Resection: glioblastoma gr IV

Tumor grading: 18F-FET - TBR

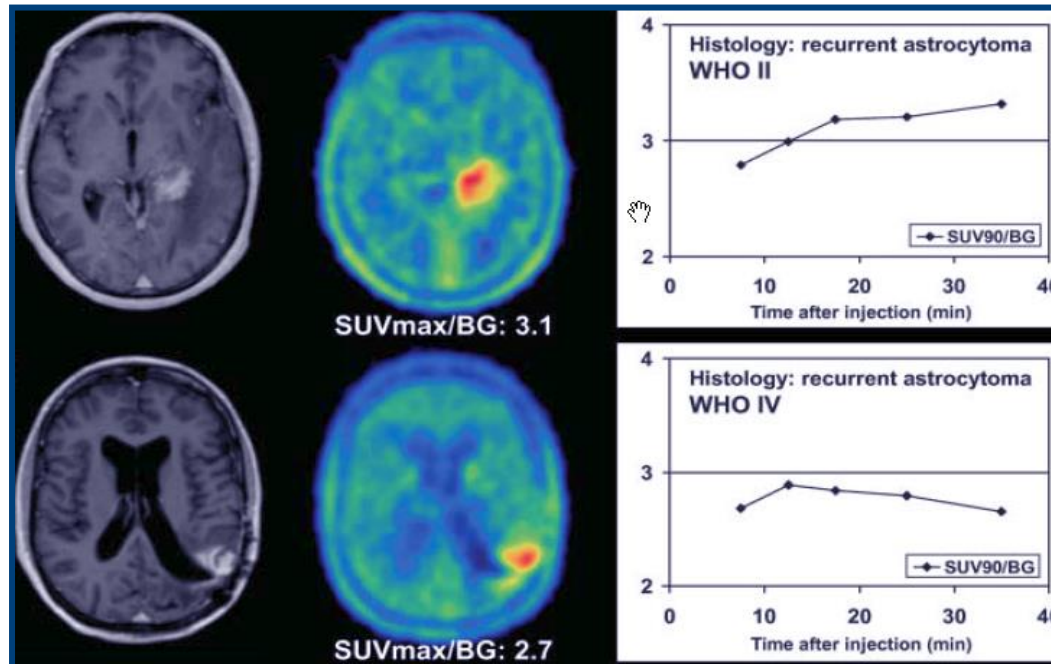
... limited increase in TBR between WHO II and WHO IV

... with important overlap between grades

=> No differentiation possible between LGG and HGG in individual patients



Tumor grading: FET dynamic



Differentiation low – high grade (2007 WHO classification) with sens/spec 92% (n=45)

Glioma diagnosis according to revised glioma WHO classification 2016

- Revised glioma WHO classification 2016

WHO grades of select CNS tumours

Diffuse astrocytic and oligodendroglial tumours

Diffuse astrocytoma, IDH-mutant	II
Anaplastic astrocytoma, IDH-mutant	III
Glioblastoma, IDH-wildtype	IV
Glioblastoma, IDH-mutant	IV
Diffuse midline glioma, H3 K27M-mutant	IV
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	II
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	III

Other astrocytic tumours

Pilocytic astrocytoma	I
Subependymal giant cell astrocytoma	I
Pleomorphic xanthoastrocytoma	II
Anaplastic pleomorphic xanthoastrocytoma	III

Ependymal tumours

Subependymoma	I
Myxopapillary ependymoma	I
Ependymoma	II
Ependymoma, <i>RELA</i> fusion-positive	II or III
Anaplastic ependymoma	III

Other gliomas

Angiocentric glioma	I
Chordoid glioma of third ventricle	II

Choroid plexus tumours

Choroid plexus papilloma	I
Atypical choroid plexus papilloma	II
Choroid plexus carcinoma	III

Neuronal and mixed neuronal-glial tumours

Dysembryoplastic neuroepithelial tumour	I
Gangliocytoma	I
Ganglioglioma	I
Anaplastic ganglioglioma	III
Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos)	I

Desmoplastic infantile astrocytoma and ganglioglioma

Papillary glioneuronal tumour	I
Rosette-forming glioneuronal tumour	I
Central neurocytoma	II
Extraventricular neurocytoma	II
Cerebellar liponeurocytoma	II

Tumours of the pineal region

Pineocytoma	I
Pineal parenchymal tumour of intermediate differentiation	II or III
Pineoblastoma	IV
Papillary tumour of the pineal region	II or III

Embryonal tumours

Medulloblastoma (all subtypes)	IV
Embryonal tumour with multilayered rosettes, C19MC-altered	IV
Medulloepithelioma	IV
CNS embryonal tumour, NOS	IV
Atypical teratoid/rhabdoid tumour	IV
CNS embryonal tumour with rhabdoid features	IV

Tumours of the cranial and paraspinal nerves

Schwannoma	I
Neurofibroma	I
Perineurioma	I
Malignant peripheral nerve sheath tumour (MPNST)	II, III or IV

Meningiomas

Meningioma	I
Atypical meningioma	II
Anaplastic (malignant) meningioma	III

Mesenchymal, non-meningothelial tumours

Solitary fibrous tumour / haemangiopericytoma	I, II or III
Haemangioblastoma	I

Tumours of the sellar region

Craniopharyngioma	I
Granular cell tumour	I
Pituitaryoma	I
Spindle cell oncocytoma	I

Diffuse astrocytic and oligodendroglial tumours

Diffuse astrocytoma, IDH-mutant	9400/3
Gemistocytic astrocytoma, IDH-mutant	9411/3
Diffuse astrocytoma, IDH-wildtype	9400/3
Diffuse astrocytoma, NOS	9400/3
Anaplastic astrocytoma, IDH-mutant	9401/3
Anaplastic astrocytoma, IDH-wildtype	9401/3
Anaplastic astrocytoma, NOS	9401/3

Neuronal and mixed neuronal-glial tumours

Dysembryoplastic neuroepithelial tumour	9413/0
Gangliocytoma	9492/0
Ganglioglioma	9505/1
Anaplastic ganglioglioma	9505/3
Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease)	9493/0
Desmoplastic infantile astrocytoma and ganglioglioma	9412/1
Papillary glioneuronal tumour	9509/1
Rosette-forming glioneuronal tumour	9509/1
Diffuse leptomeningeal glioneuronal tumour	
Central neurocytoma	9506/1
Extraventricular neurocytoma	9506/1
Cerebellar liponeurocytoma	9506/1
Paraganglioma	8693/1

Tumours of the pineal region

Pineocytoma	9361/1
Pineal parenchymal tumour of intermediate differentiation	9362/3
Pineoblastoma	9362/3
Papillary tumour of the pineal region	9395/3

Embryonal tumours

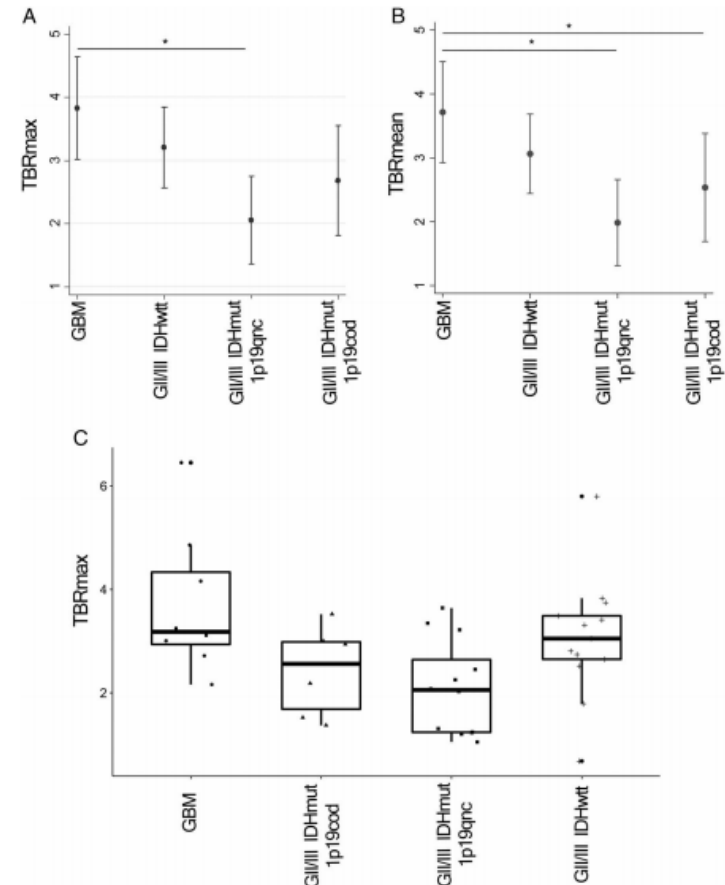
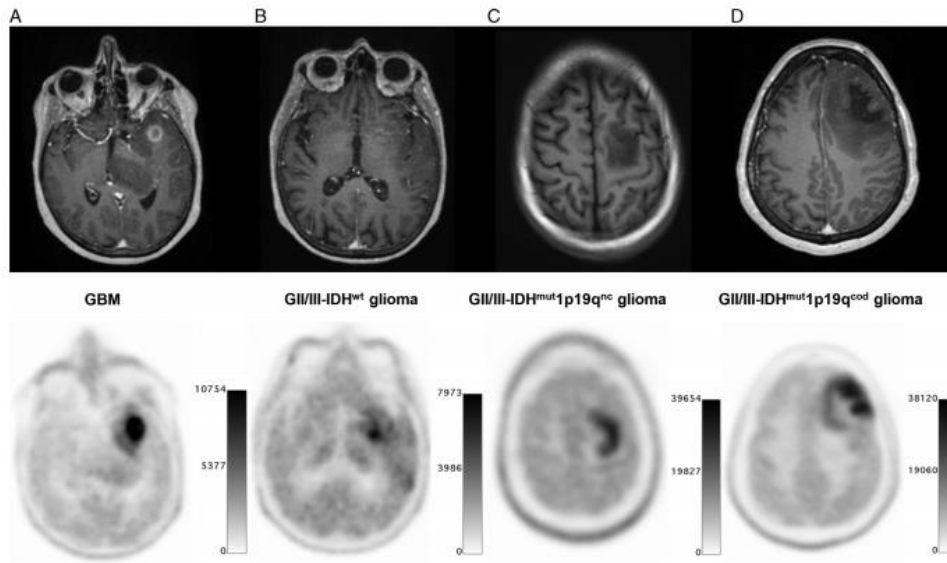
Medulloblastomas, genetically defined	
Medulloblastoma, WNT-activated	9475/3*
Medulloblastoma, SHH-activated and TP53-mutant	9476/3*
Medulloblastoma, SHH-activated and TP53-wildtype	9471/3
Medulloblastoma, non-WNT/non-SHH	9477/3*
Medulloblastoma, group 3	
Medulloblastoma, group 4	
Medulloblastomas, histologically defined	
Medulloblastoma, classic	9470/3
Medulloblastoma, desmoplastic/nodular	9471/3
Medulloblastoma with extensive nodularity	9471/3
Medulloblastoma, large cell / anaplastic	9474/3
Medulloblastoma, NOS	9470/3

Embryonal tumour with multilayered rosettes, C19MC-altered	9478/3*
Embryonal tumour with multilayered rosettes, NOS	9478/3
Medulloepithelioma	9501/3
CNS neuroblastoma	9500/3
CNS ganglioblastoma	9490/3
CNS embryonal tumour, NOS	9473/3
Atypical teratoid/rhabdoid tumour	9508/3
CNS embryonal tumour with rhabdoid features	9508/3

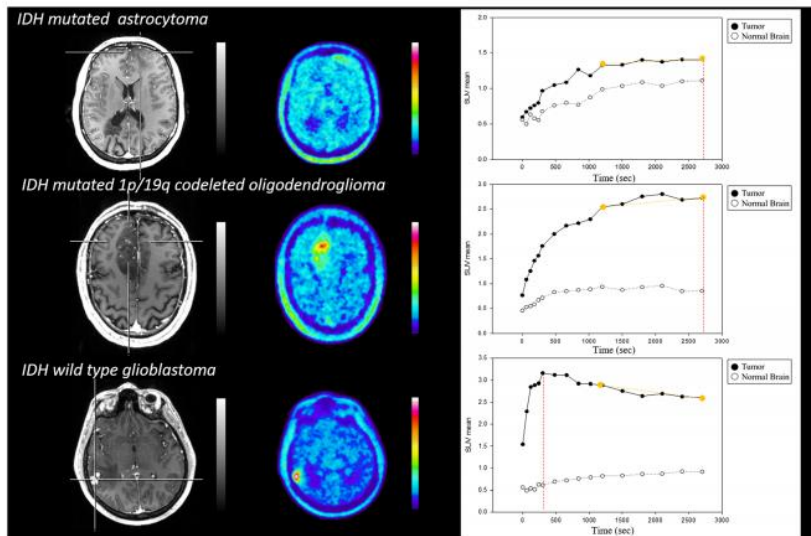
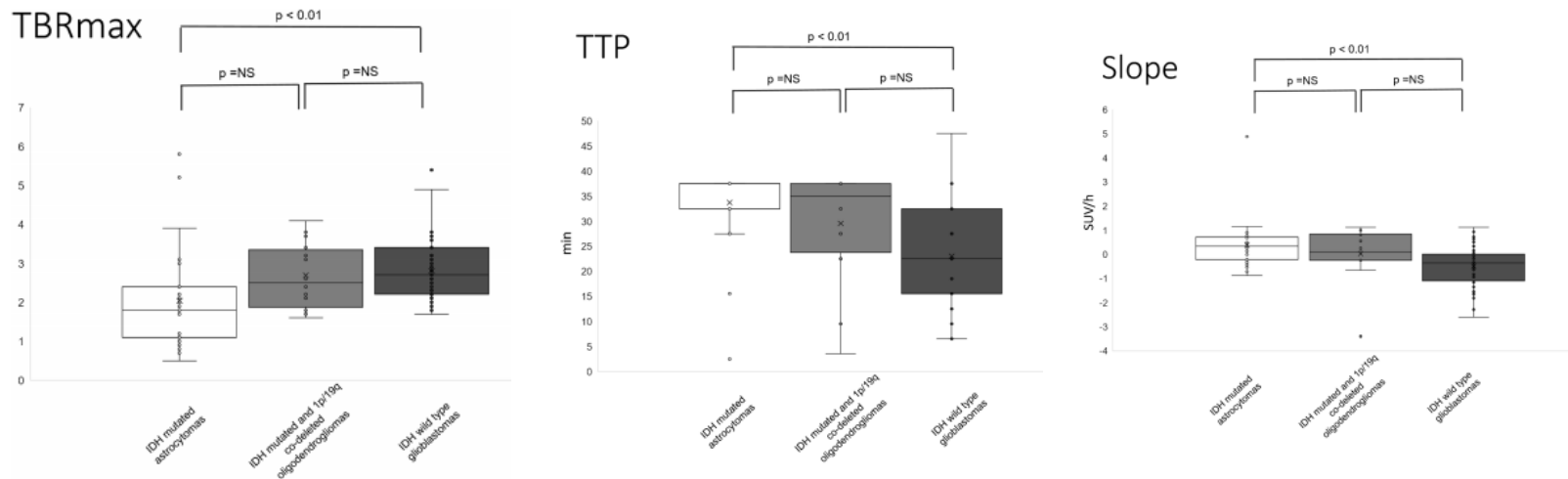
Tumours of the cranial and paraspinal nerves

Schwannoma	9560/0
Cellular schwannoma	9560/0
Plexiform schwannoma	9560/0

Glioma diagnosis according to revised glioma WHO classification 2016



Glioma diagnosis according to revised glioma WHO classification 2016



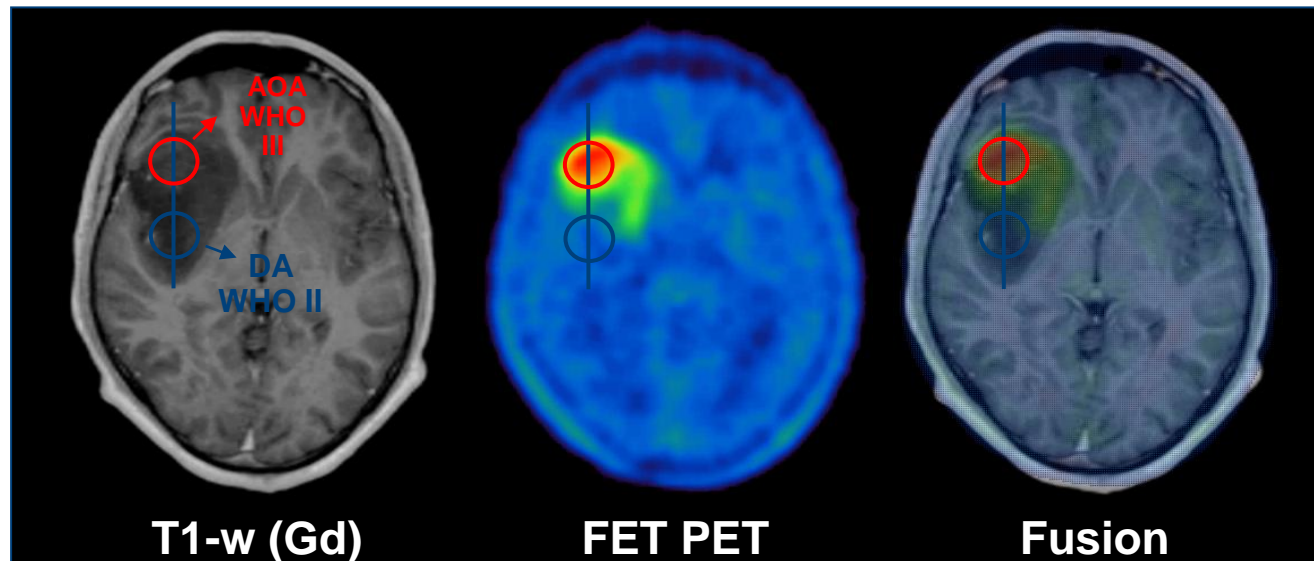
	AUC	p-value	Cut-off	Accuracy	Sensitivity	Specificity
TBR _{mean}	0.73	<0.01	1.85	69%	44%	92%
TBR _{max}	0.68	<0.01	2.15	67%	56%	77%
TTP	0.75	<0.01	25 min	72%	86%	60%
Slope	0.75	<0.01	-0.26 SUV/h	70%	81%	60%
TBR _{mean} + TBR _{max}	—	<0.01	1.85 and 2.15	69%	44%	91%
TTP + Slope	—	<0.01	25 min and -0.26 SUV/h	73%	77%	70%
TBR _{mean} + TTP	—	<0.01	1.85 and 25 min	69%	40%	96%
TBR _{max} + TTP	—	<0.01	2.15 and 25 min	73%	51%	94%
TBR _{mean} + Slope	—	<0.01	1.85 and 2.15	68%	40%	94%
TBR _{max} + Slope	—	<0.01	2.15 and -0.26 SUV/h	70%	47%	91%

AUC, area under the curve; SUV, standardized uptake value; TBR, tumor-to-brain ratio; TTP, time-to-peak

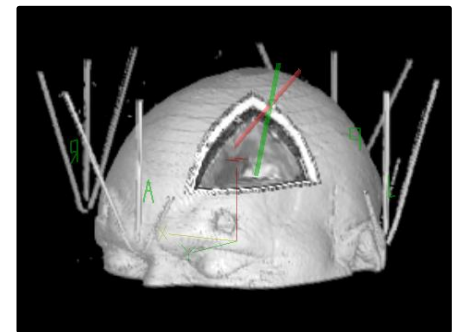
90 patients, suspected primary glioma, FET PET

Biopsy planning

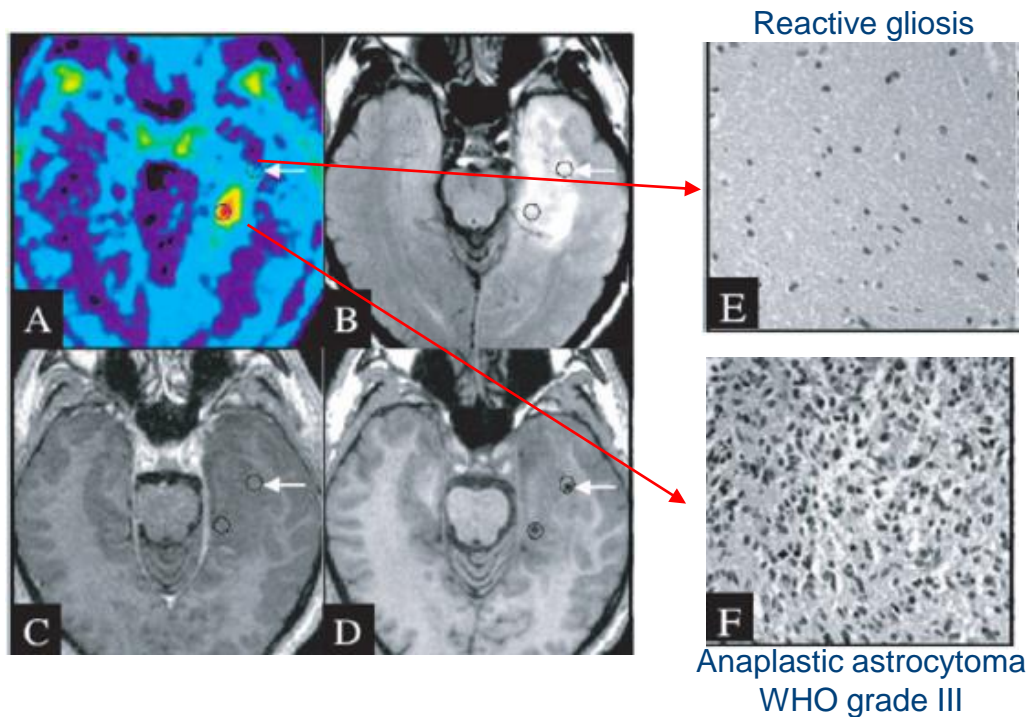
- Gliomas are often heterogeneous tumors
- Biopsy should be taken at the location of the most metabolically active site
- AA PET can indicate this location for stereotactic biopsy and increase the number of effective biopsies



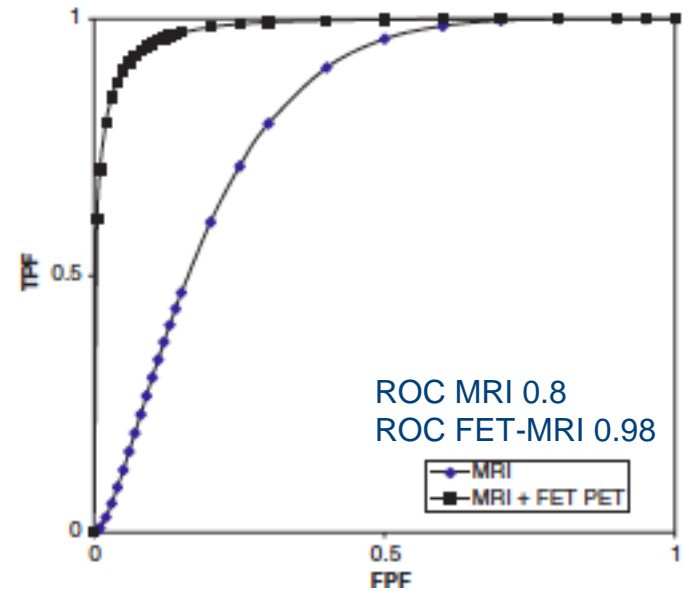
Fusion is mandatory!!
Direct input in stereotactic
Planning system



Biopsy planning



Only biopsy of the FET PET hot spot
yielded tumor tissue



	Sens	Spec
MRI alone	96%	53%
MRI + FET	93%	94%

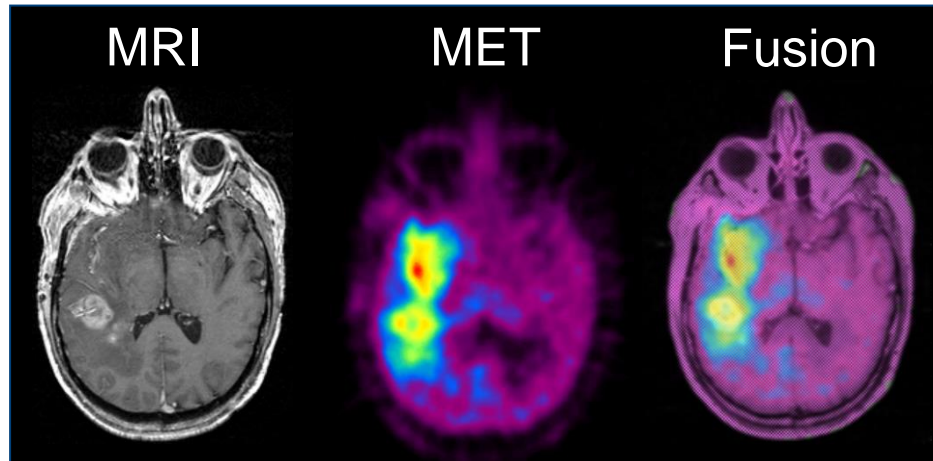


2. DEFINING THE EXTENT OF THE TUMOR TO PLAN SURGERY AND RADIOTHERAPY

Tumor extent

- Spatial distribution of contrast enhancement on MRI is frequently used to define the tumor extent
- However at initial diagnosis, a significant number of gliomas show no contrast enhancement and tumors often extent beyond CE region
- AA PET can help in correct delineation of tumor volume

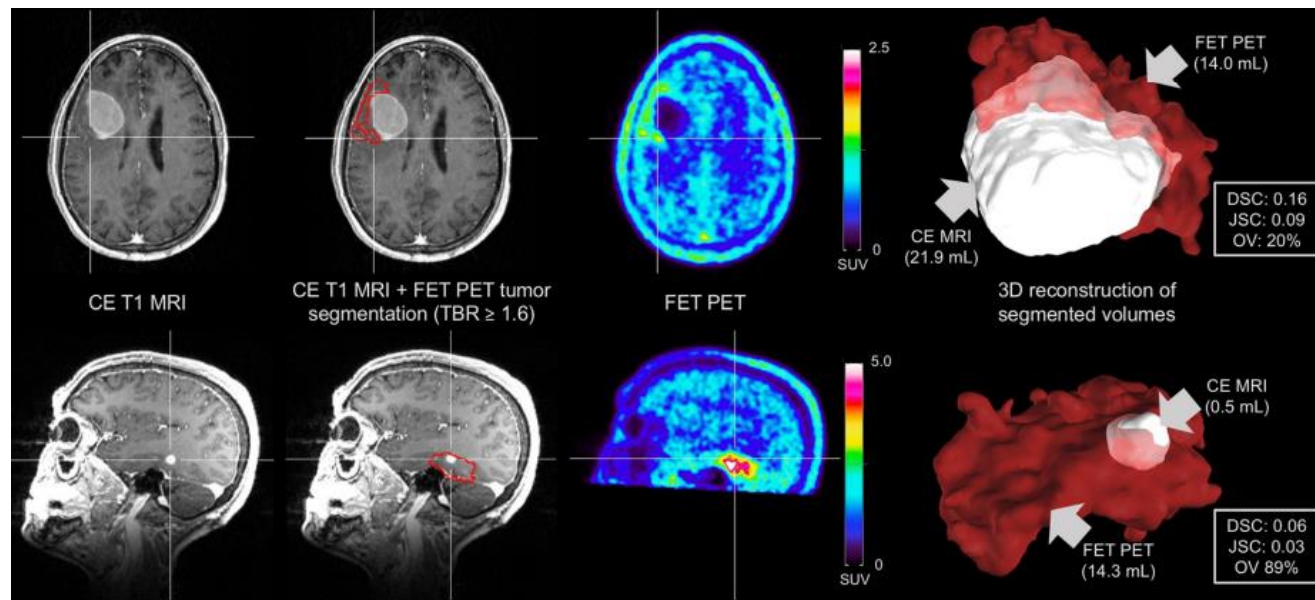
Tumor vol MRI
approx. 5 ml



Tumor vol PET
approx. 70 ml

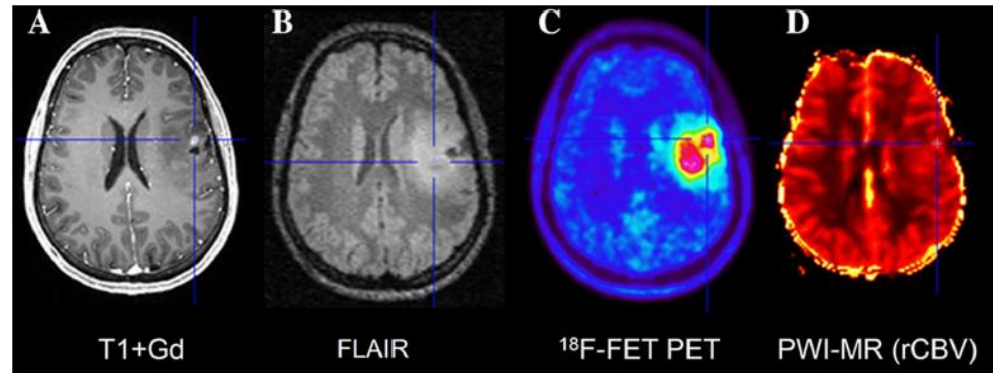
Tumor delineation

- 50 patients with newly diagnosed GBM
- Pre-operative FET PET and standard MRI
- In 83% (n=43) of patients, FET tumor volume significantly larger than CE MRI volume (22 ± 11 ml vs 9 ± 11 ml, $p < 0.001$)
- Low spatial similarity between FET PET and CE MRI

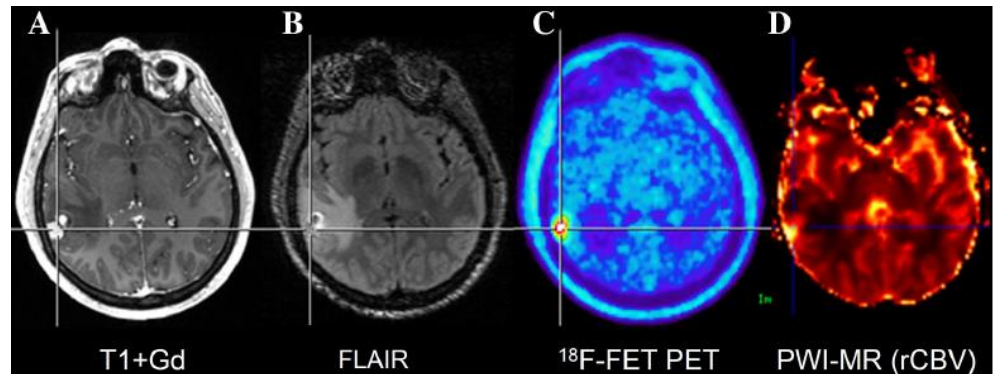


Perfusion-weighted MRI vs FET-PET for glioma delineation

- Spatial overlap between both imaging modalities was only 11%
- Considerably different tumor volumes
 - PET tumor volumes 2.7 fold larger
- Similar findings from other groups (overlap of 10%)



Astrocytoma WHO grade II - discordant



Glioblastoma WHO grade IV - concordant

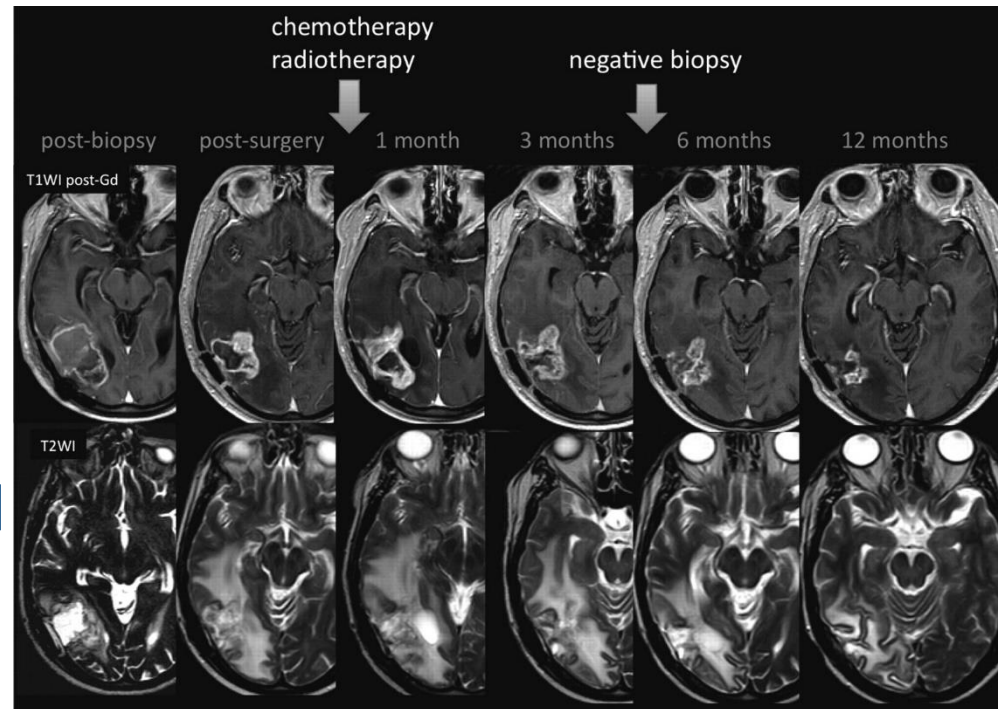
Perfusion MRI likely provides completely different biological information than AA PET



3. IN EARLY TREATMENT TO DIFFERENTIATE BETWEEN PSEUDOPROGRESSION AND EARLY TUMOR PROGRESSION

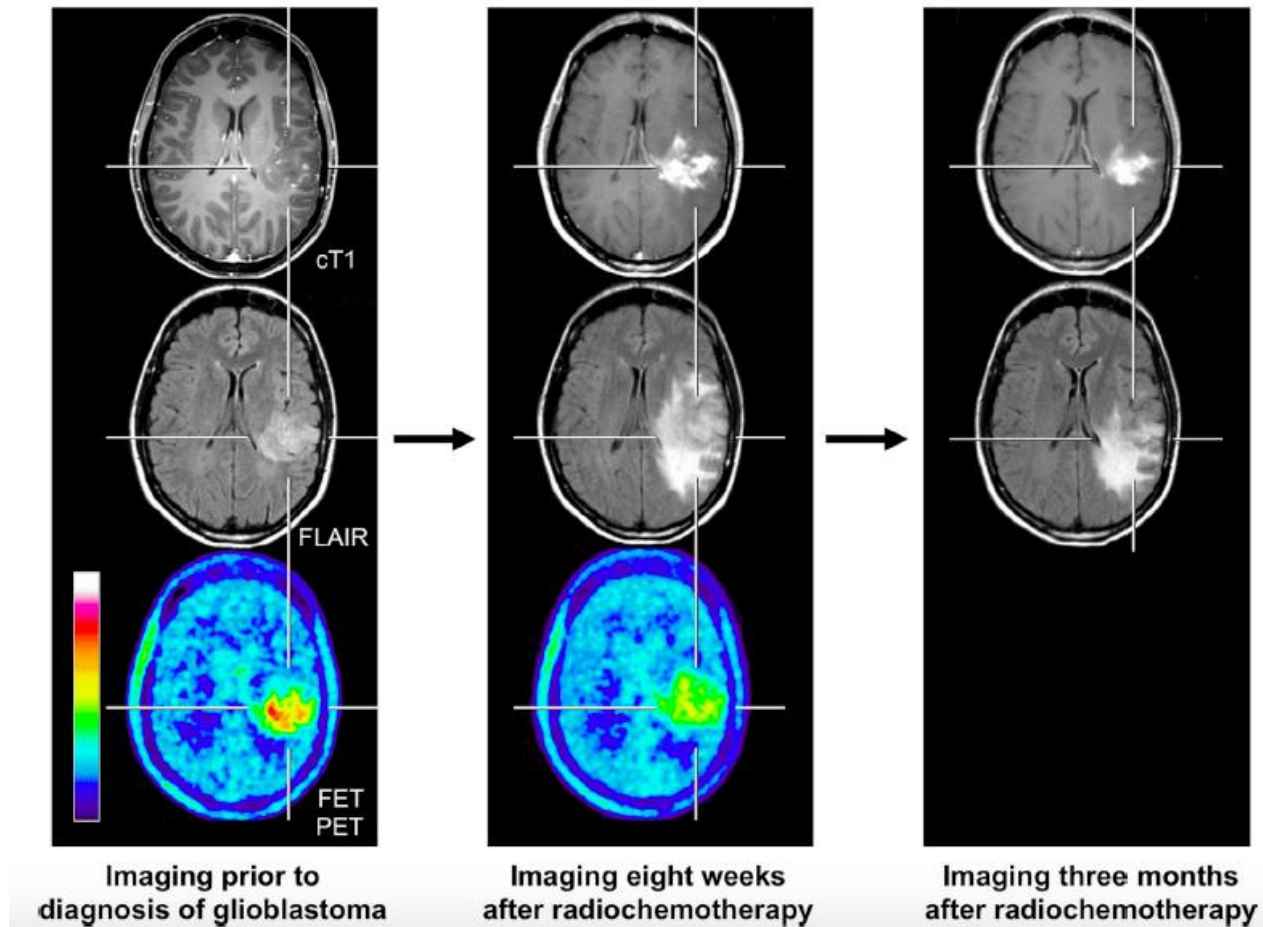
Pseudoprogression

- Transient increase of contrast enhancement after treatment which resolves without any changes of treatment
- Occurs typically within the first 12 weeks after the end of radio(chemo)therapy
- Rate is between 10–30 %
- Often asymptomatic



Differential diagnosis with real progression can be difficult using anatomical MRI

Pseudoprogression



Pseudoproggression vs true progression

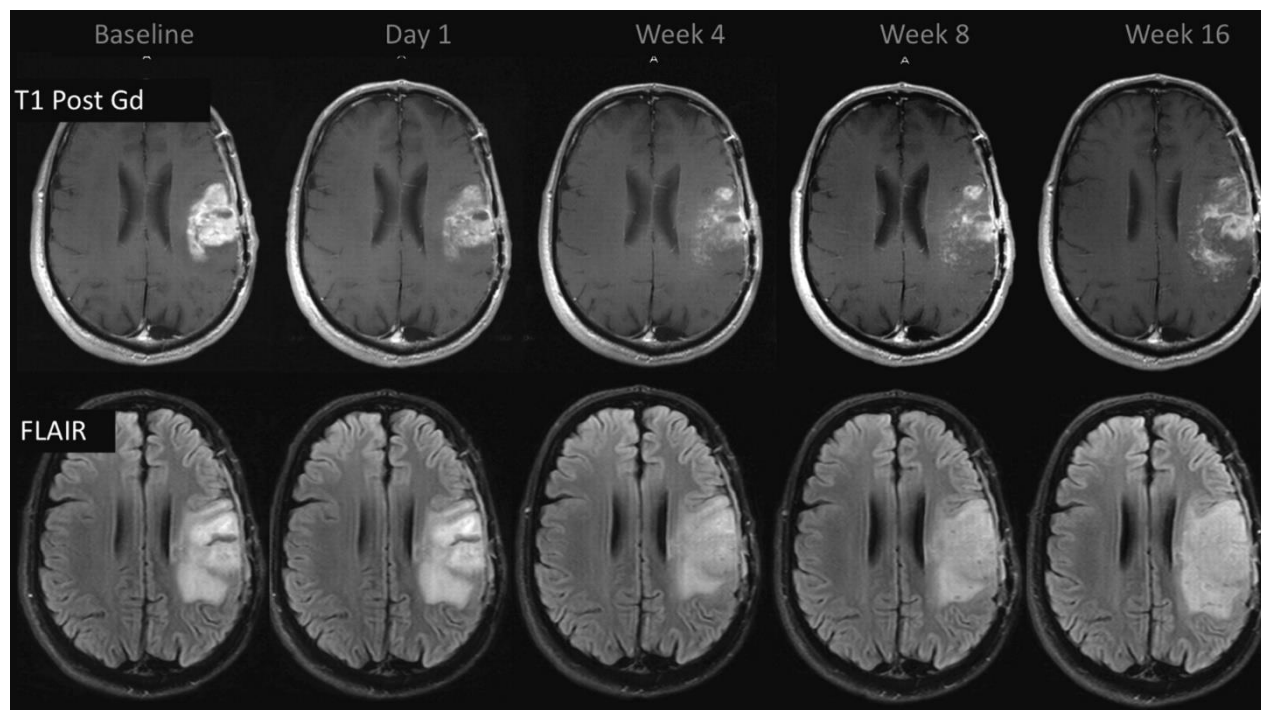
Pseudoproggression

Paper	n (pat)	Sens	Spec	Acc	Sens	Spec	Acc
Galldiks 2015	22	91%	100%	96%			
Kebir 2016	16	84%	86%	85%			
Mihovilovic 2018	36	89%	75%	86%			
Pöpperl 2004	53				n.a.	n.a.	100%
Rachinger 2005	45				100%	93%	n.a.
Mehrkens 2008	31				n.a.	n.a.	83%
Galldiks 2015	132				93%	100%	93%
Jena 2016	26				88%	86%	87%
Pyka 2018	47				80%	85%	n.a.

True progression

Pseudoresponse

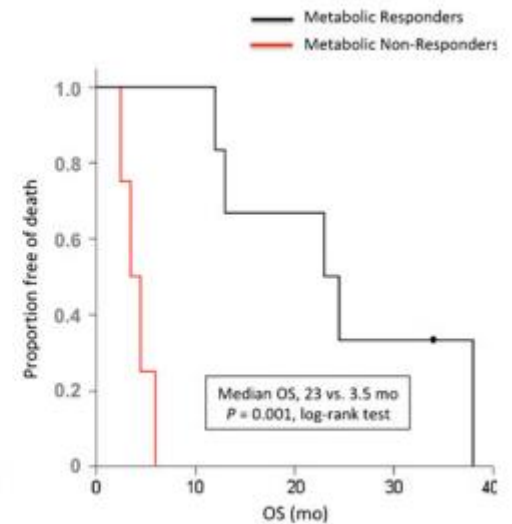
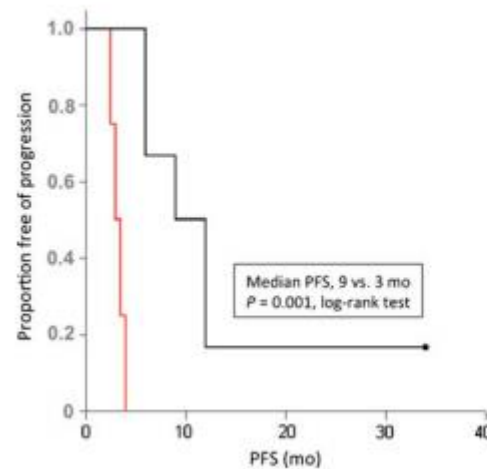
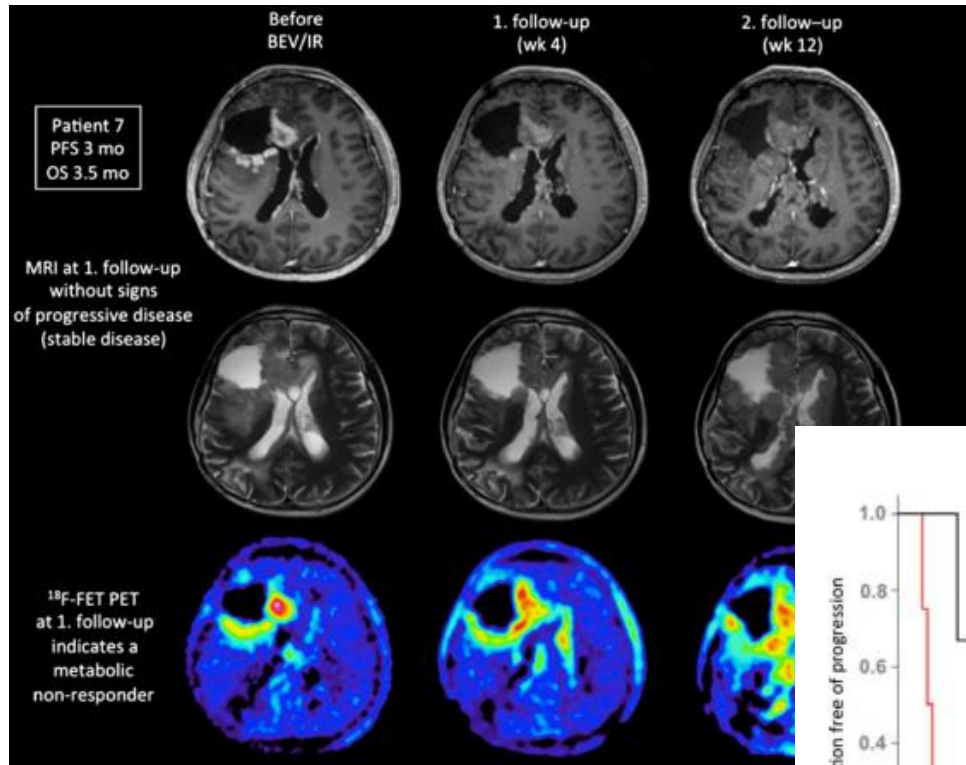
- Rapid decrease in contrast enhancement after start of antiangiogenic agents such as bevacizumab, an anti-VEGF antibody, and cediranib, a VEGF receptor tyrosine kinase inhibitor



Pseudoresponse

- FET PET detects failure of antiangiogenic therapy earlier than standard MRI
- Treatment response based on RANO criteria is discordant in approx. 50% of patients to FET PET findings, indicating pseudoresponse on MRI
- Favorable outcome of responders to bevacizumab observed when decrease of metabolically active tumor volume of 45% or more
- Responders based on FDOPA PET data survive 3.5 times longer than non-responders (<-> only 1.5 times longer survival with RANO criteria for response)

Pseudoresponse



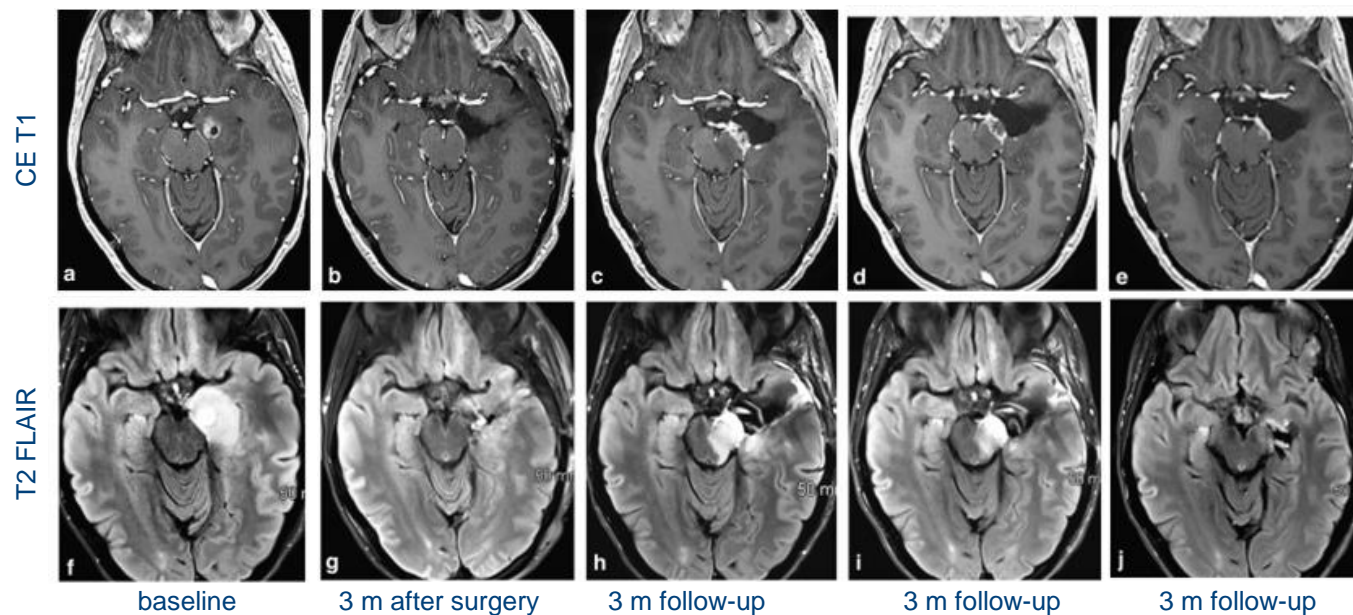
10 patients with recurrent HGG with biweekly treatment with bevacizumab/irinotecan



4. AT LATER STAGES OF TREATMENT FOR THE IDENTIFICATION OF RADIONECCROSIS AND TREATMENT- RELATED CHANGES

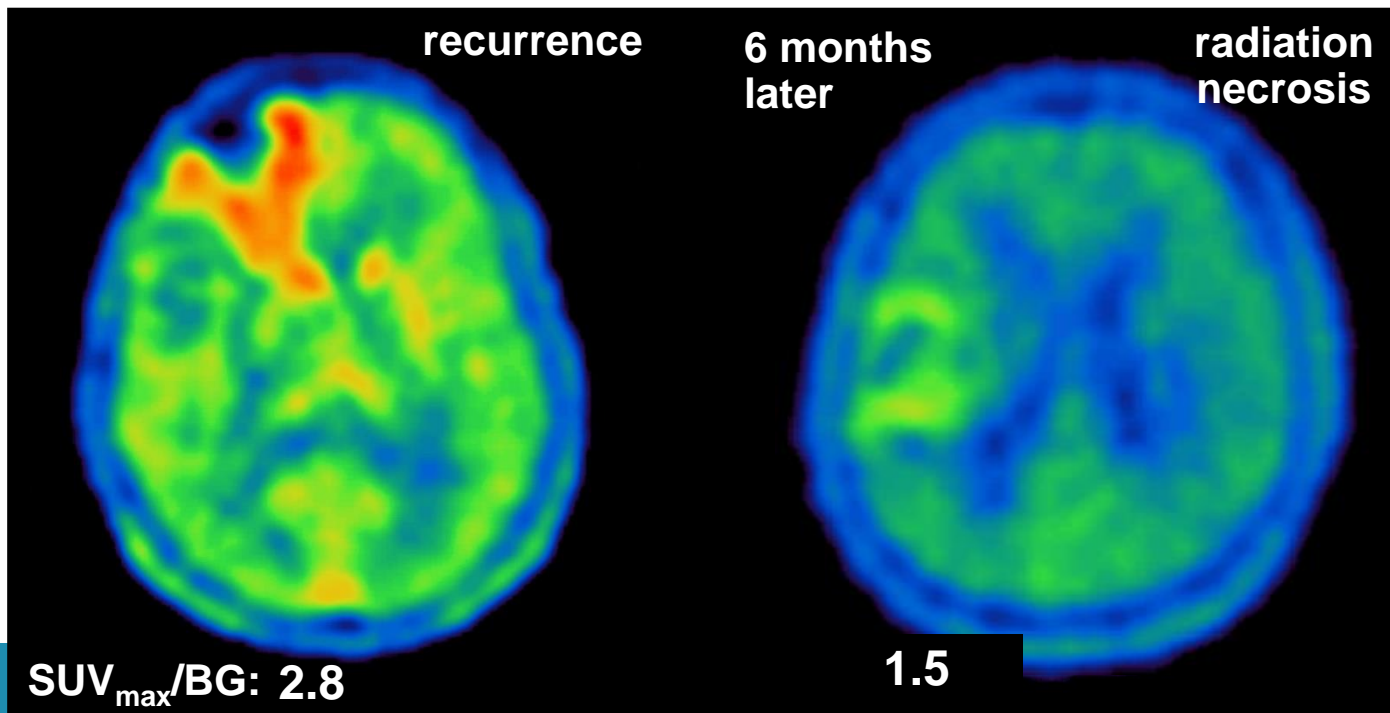
Treatment-related changes after RT

- After fractionated RT and radiosurgery
- Radiation necrosis / radiation injury is difficult to differentiate from recurrent tumor using standard MRI



Differentiation of radiation injury from recurrent glioma

	Ogawa 1991	Sonoda 1998	Tsuyukushi 2003	Tsuyukushi 2004	Pöpperl 2004	Van Laere 2005	Rachinger 2005	Mehrkens 2007	Terakawa 2008
n pat	10	12	21	11	53	30	45	31	26
Tracer	MET	MET	MET	MET	FET	MET	FET	FET	MET
Sens	100%	100%	78%	100%	100%	75%	94%	PPV 84%	75%
Spec	100%	86%	100%	60%	100%	70%	93%	n.a.	75%



Optimal threshold?

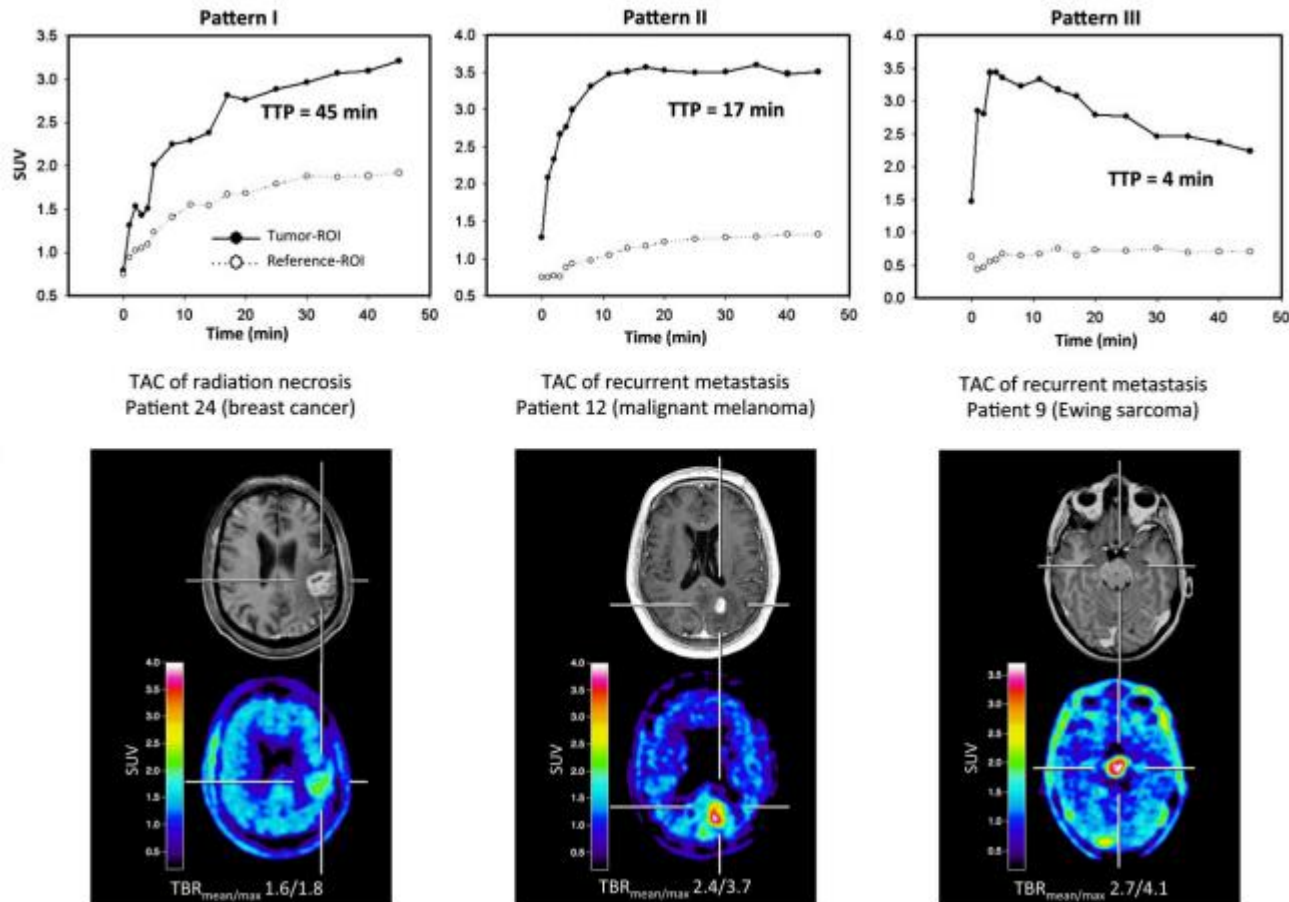
- Variable between studies
- ~ TBR 1.8 - 2.1

Differentiation of radiation injury from recurrent brain metastases

	Tsuyuguchi 2003	Terakawa 2008	Galldiks 2012	Lirezzaga 2014	Cicone 2015	Minamimoto 2015	Romagna 2016	Ceccon 2017	Tomura 2017	Yomo 2017
n pat	21	51	31	32	43	39	22	76	15	32
n lesions	21	56	40	83	50	42	34	62	18	37
Tracer	MET	MET	FET	FDOPA	FDOPA	MET	FET	FET	MET	MET
Sens	78%	79%	74%	81%	90%	82%	86%	86%	90%	82%
Spec	100%	75%	90%	73%	92%	86%	79%	88%	75%	75%
Acc	89%	77%	82%	77%	90%	83%	83%	87%	84%	79%
TBR threshold	1.4	1.4	2.0	1.7	1.7	1.3	2.0	2.0	1.4	1.4
Kinetic analysis	No	No	Yes	No	No	No	Yes	Yes	No	No

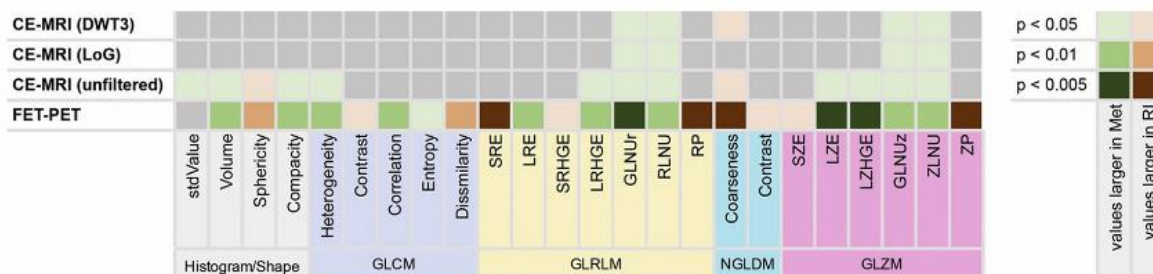
Does kinetic analysis provide additional diagnostic information?

Kinetic analysis in differential diagnosis of radiation injury <-> recurrent brain metastasis



- Texture analysis describing heterogeneity of a lesion
 - 42 textural features analysed

	Accuracy	Sensitivity	Specificity
CE-MRI features	81%	67%	90%
FET-PET features	83%	88%	75%
Combined features	89%	85%	96%



Heat map for textural features with a significant different distribution in patients with recurrent metastasis (Met) compared to those with radiation injury (RI)

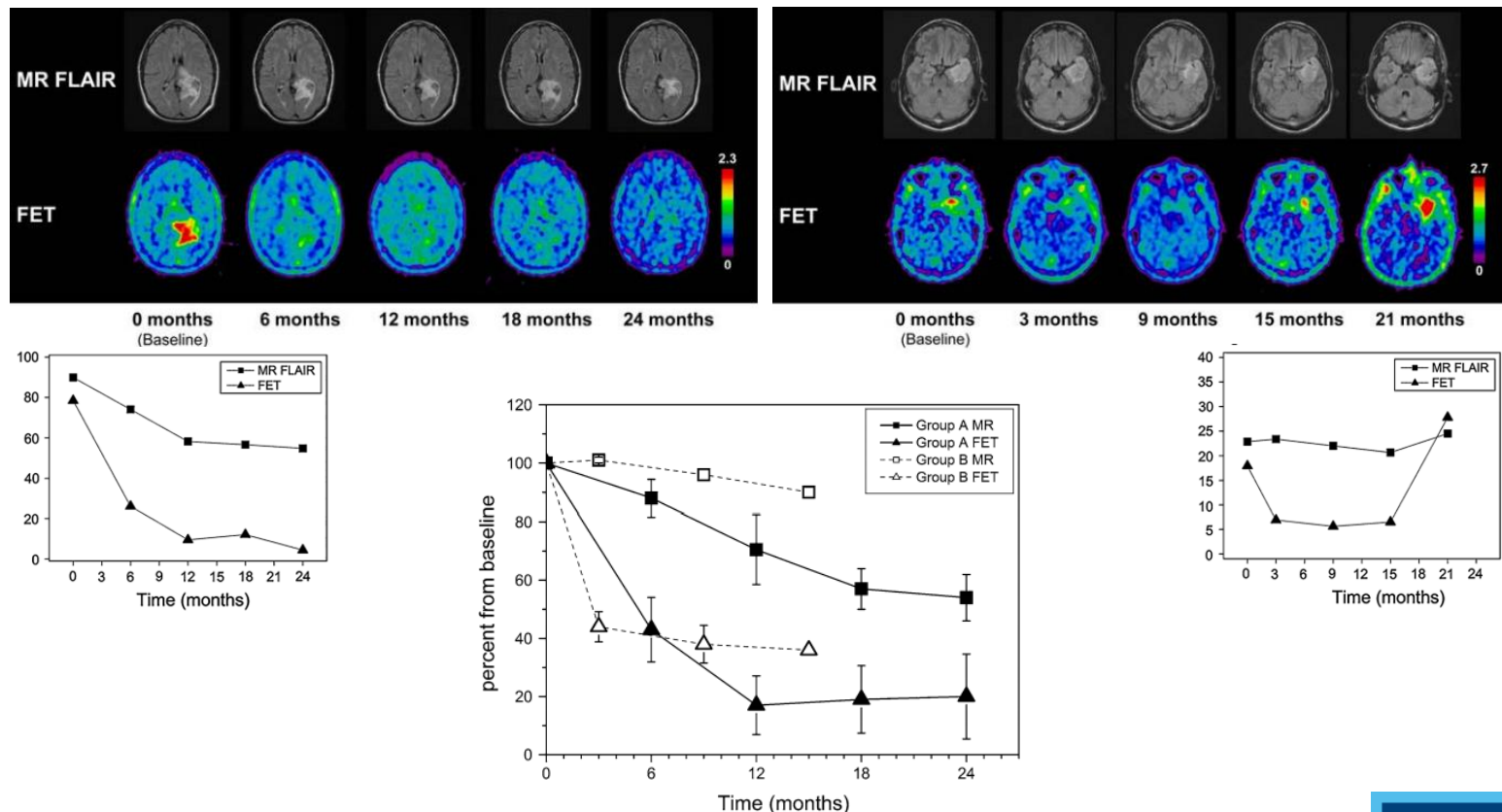


5. FOR MONITORING OF THERAPY

- CE-MRI is method of choice for treatment response assessment
 - But evaluation may be hampered by treatment-related changes
- Newer systemic treatment options such as targeted therapy and immunotherapy have other requirements on neuroimaging
 - Imaging tools which provide additional information on tumor metabolism or proliferation become increasingly important (f.e. using ¹⁸F-FLT in therapy follow-up of BRAF/MEK inhibitors or checkpoint inhibitors in melanoma metastases)

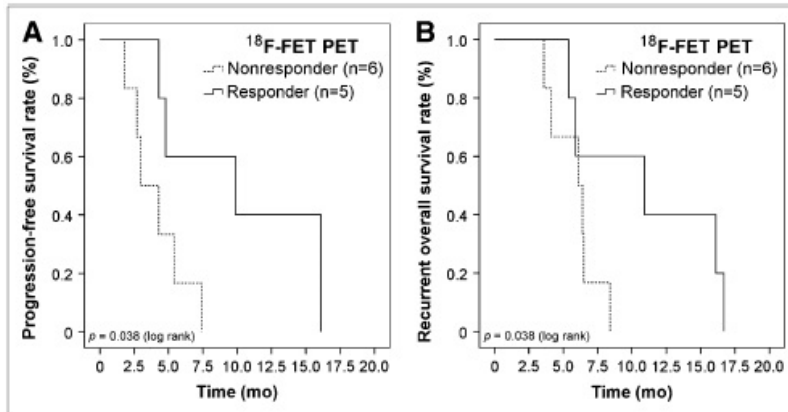
Response assessment during alkylating chemotherapy

- In comparison to FLAIR MRI, an earlier detection of tumor volume changes was possible with FET PET



11 patients with LGG during temozolomide treatment, MRI, FET

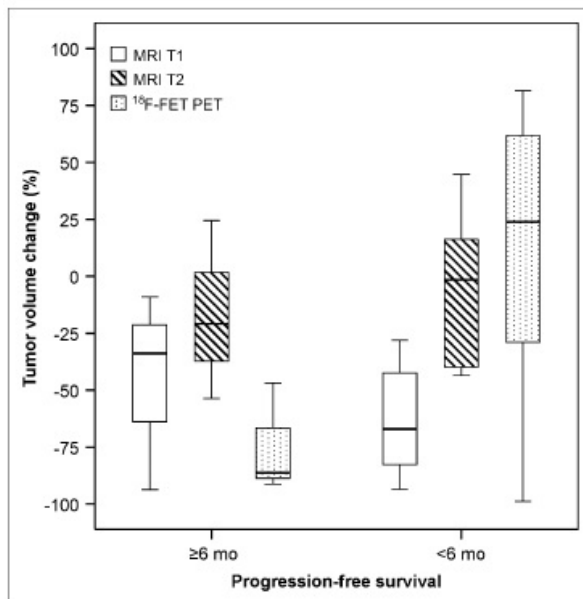
Prognosis during/after therapy



N = 11; recurrent HGG

Treatment with bevacizumab-irinotecan

MR and FET-PET at baseline, after 8-12 weeks



FET-PET response = 45% reduction SUV
 => langere PFS en OS

Which statement concerning MRI of brain tumors is correct?

1. Contrast enhancement in MRI in CT is a specific sign for a brain tumor
2. Brain tumors can always be clearly delineated in T1/T2-weighted MRI
3. MRI is superior to CT in displaying of bony structures and calcifications
4. T1-/T2-weighted MRI has a high sensitivity to detect brain tumors

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Which statement concerning amino acid PET of brain tumors is correct?

1. The increased uptake of ^{18}F -FET in cerebral gliomas is caused by incorporation into protein.
2. ^{11}C -L-methionine is an ideal amino acid tracer since it is available in most PET facilities
3. Radiolabeled amino acids can also accumulate in tumor areas with intact blood-brain barrier, i.e., non-enhancing areas in MRI
4. Amino acids offer no advantages compared with FDG, since there is high uptake of amino acids in the normal brain tissue

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Which statement concerning the differentiation of recurrent brain tumour and unspecific post-therapeutic changes is correct?

1. FDG PET has a higher diagnostic accuracy for differentiating recurrent glioma and radio necrosis than FET and FDOPA PET
2. Conventional MRI achieves high specificity for differentiating recurrent glioma and radio necrosis
3. Pseudo progression of gliomas occurs typically 2 years after completion of radiotherapy
4. FET PET is helpful to differentiate recurrent metastasis and radio necrosis

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Which statement concerning monitoring of brain tumour therapy is correct?

1. Decreasing contrast enhancement in MRI during antiangiogenic therapy of malignant glioma is a specific sign of tumor response
2. Amino acid PET is very sensitive to monitor therapy and to predict response to treatment at an early stage in the course of disease
3. Pseudo response of gliomas during antiangiogenic therapy is accompanied by reduced FET uptake
4. Increasing contrast enhancement in MRI after chemo radiotherapy of gliomas is always a specific sign of progressive tumor

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Take home messages

- AA PET imaging is a valuable clinical tool in diagnosis and follow-up of patients with primary brain tumors and brain metastases
 - Primary staging
 - Equivocal lesions on MRI
 - Biopsy planning
 - Non-invasive grading: role in 2016 WHO classification?
 - Extent of tumoral invasion for treatment planning
 - Differentiation of treatment-related changes from real progression / response at early and late time points
 - Treatment follow-up
- Also check-out *Brain tumor imaging webinar* at ESMIT eLearning EANM

KU LEUVEN