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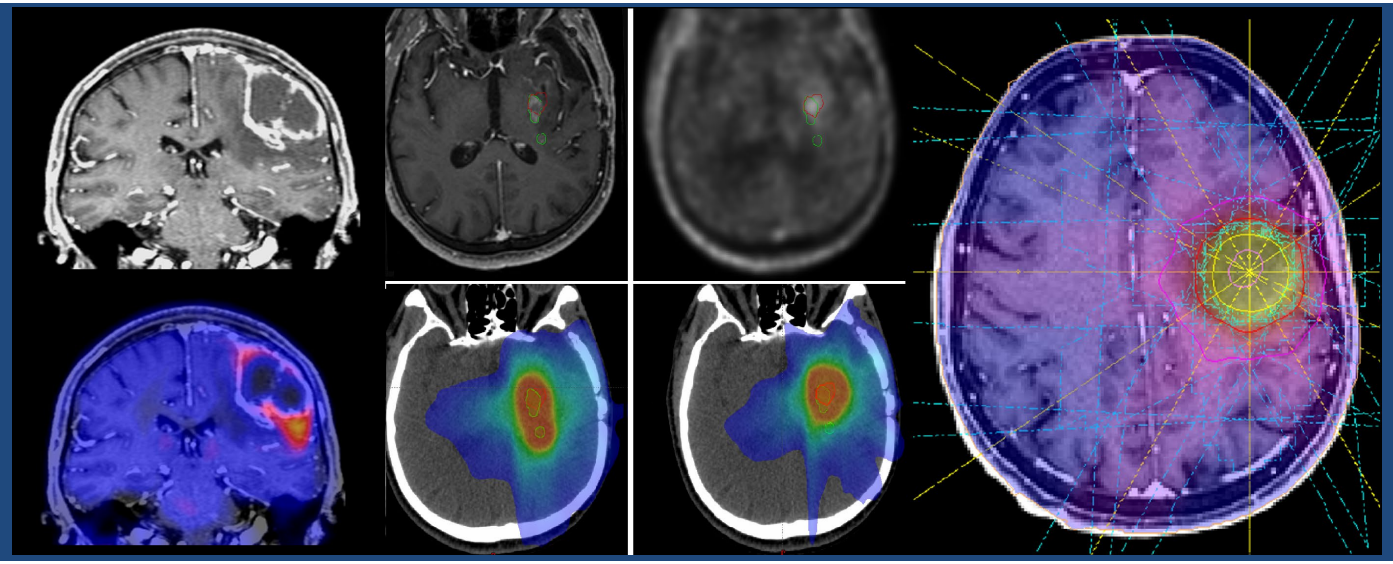

FET-PET versus MRI-based re-irradiation in recurrent glioblastoma: results of the prospective randomized multicentric trial - GLIAA (NOA-10/ARO 2013-1/NUK/RT 2010-1, DKTKa)

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Department of Radiation Oncology, University of Freiburg, Germany

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Disclosure

Research cooperation and support in clinical studies, Department of Radiation Oncology, University Medical Center, Freiburg

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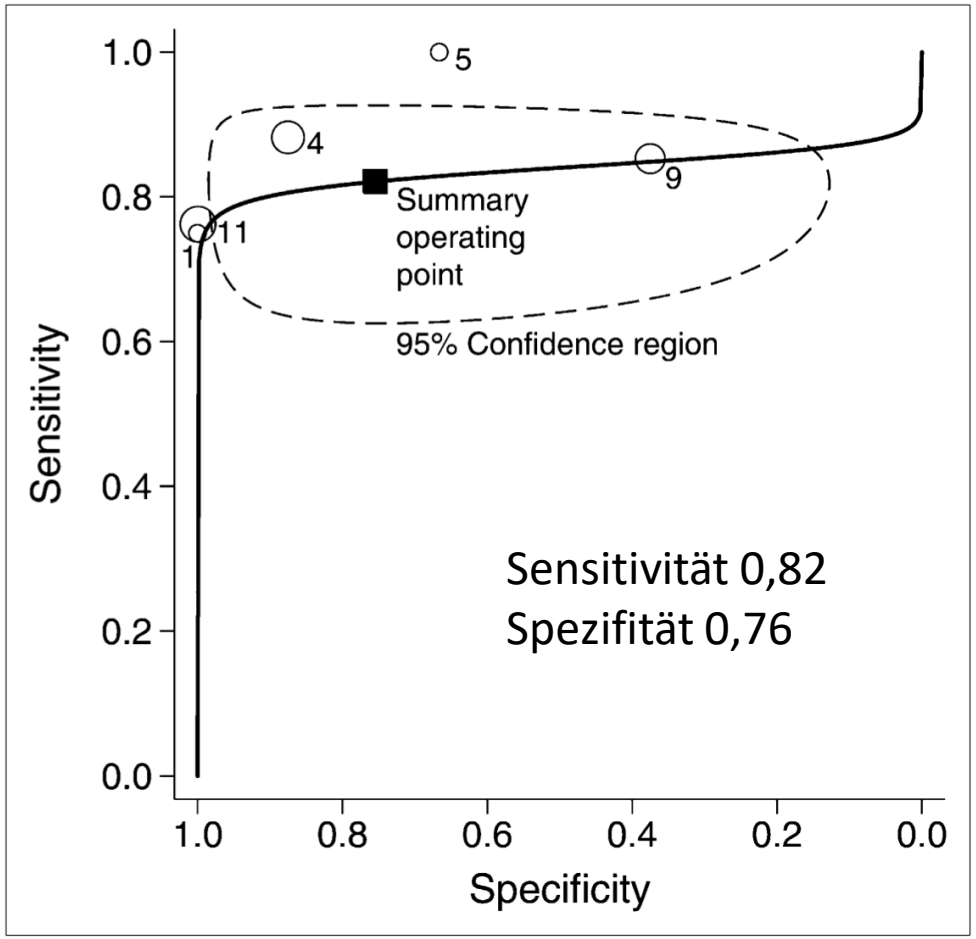
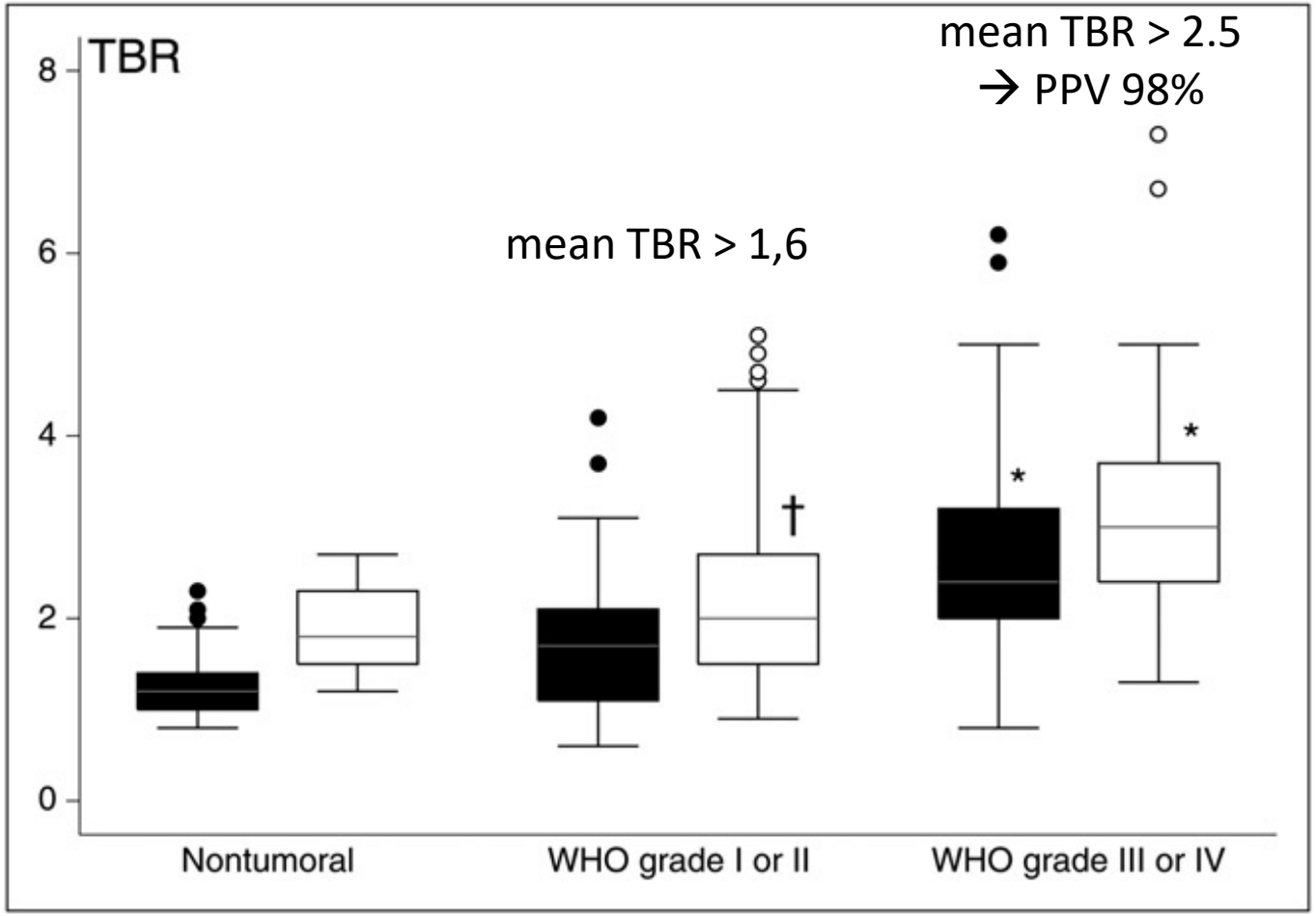
Novocure GmbH
German Cancer Aid (Deutsche Krebshilfe)
German Research Foundation (DFG)
The Federal Ministry of Education and Research (BMBF)

Amino-Acids-PET in Neuro-Oncology

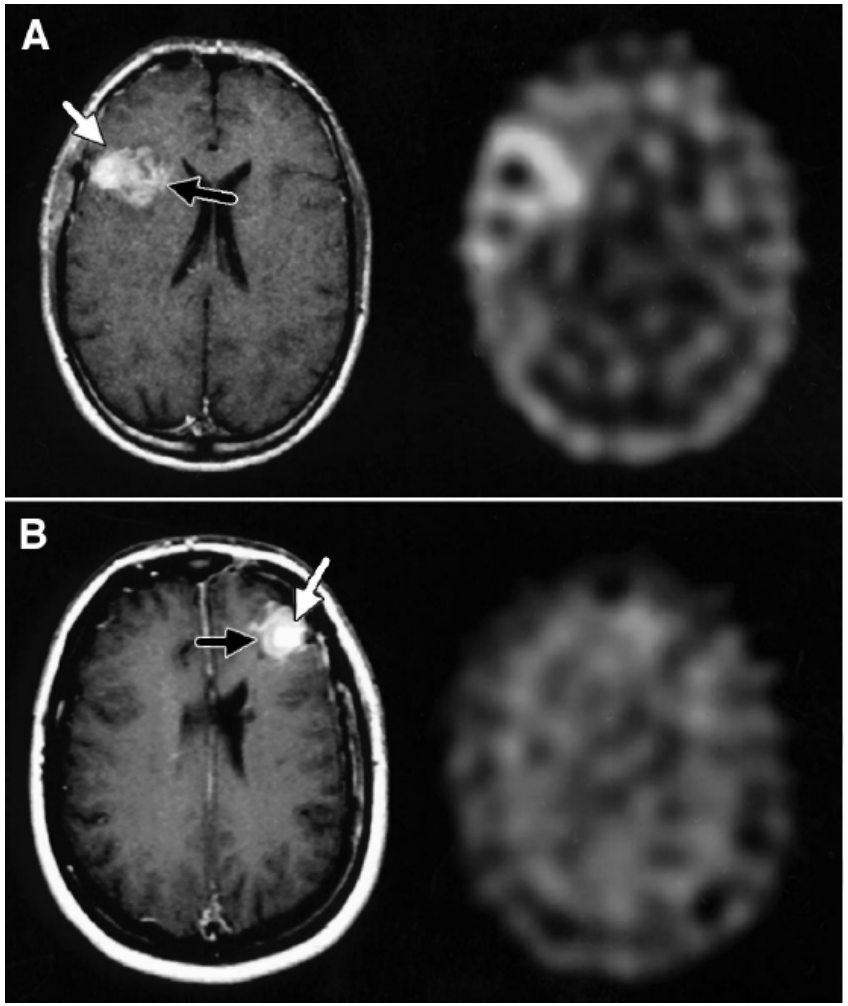




Dunet et al., J Nucl Med 2012; Rapp et al., J Nucl Med. 2013

AA-PET in Neuro-Oncology

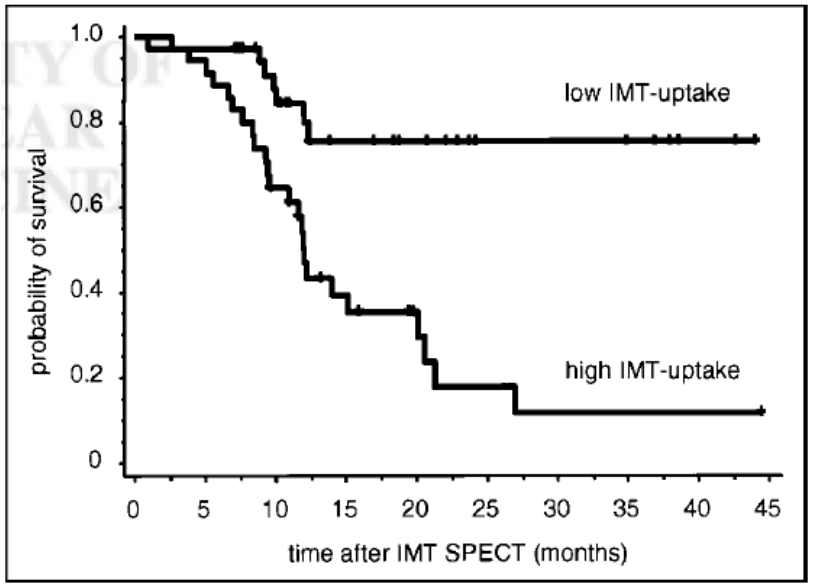
Gliomas



Correlation Between Postoperative 3-[^{123}I]Iodo-L-α-Methyltyrosine Uptake and Survival in Patients with Gliomas

Wolfgang A. Weber, Susanne Dick, Guenther Reidl, Brigitte Dzewas, Raymonde Busch, Horst-Jürgen Feldmann, Michael Molls, Christianto B. Lumenta, Markus Schwaiger, and Anca L. Grosu

Departments of Nuclear Medicine, Radiotherapy, and Medical Statistics, Technische Universitaet Muenchen, Munich; and Department of Neurosurgery, Krankenhaus-Muenchen Bogenhausen, Munich, Germany



retrospektiv, 114 Patienten

FIGURE 3. Kaplan–Meier estimates of overall survival among patients with low and high postoperative IMT uptake ($n = 71$). In patients with IMT uptake ratio > 1.7 (high IMT uptake, $n = 35$), survival is significantly shorter ($P < 0.001$ by log-rank test) than in patients with uptake ratio ≤ 1.7 (low IMT uptake, $n = 36$).

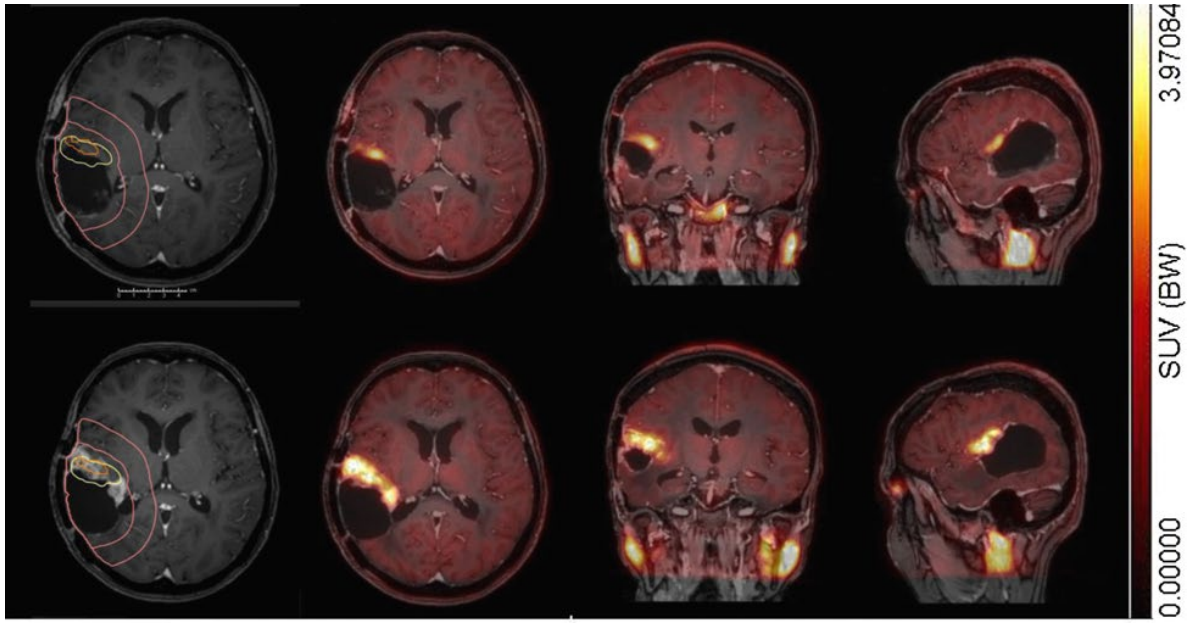
Weber et al. J Nucl Med 2001

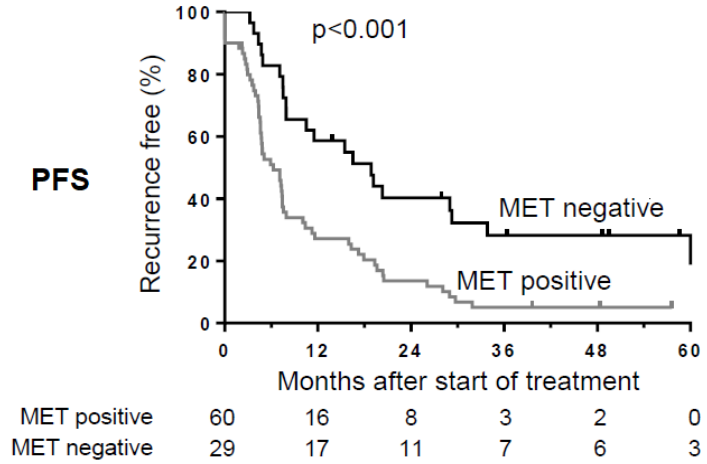
AA-PET in Neuro-Oncology

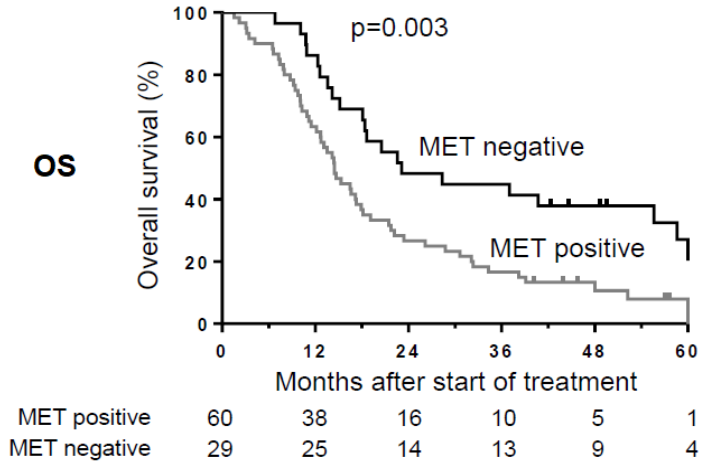
Primary GBM

Final Results of the Prospective Biomarker Trial PETra: [^{11}C]-MET-Accumulation in Postoperative PET/MRI Predicts Outcome after Radiochemotherapy in Glioblastoma

Annekatrin Seidlitz[1,2,3,4], Bettina Beuthien-Baumann[5,6], Steffen Löck[1,3,4], Christina Jentsch[1,2,3], Ivan Platzek[7], Klaus Zöphel[5], Annett Linge[1,2,3,4], Jörg Kotzerke[5], Jan Petr[8,11], Jörg van den Hoff[5,8], Jörg Steinbach[8,12], Dietmar Krex[9], Gabriele Schmitz-Schackert[9], Monique Falk[1,2,4], Michael Baumann[1,3,10,13], and Mechthild Krause[1,2,3,4,10]







prospektiv,
single-center
102 Patienten

Seidlitz et al. Clin Cancer Res 2021

Int. J. Radiation Oncology Biol. Phys., Vol. 73, No. 2, pp. 479–485, 2009
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Printed in the USA.
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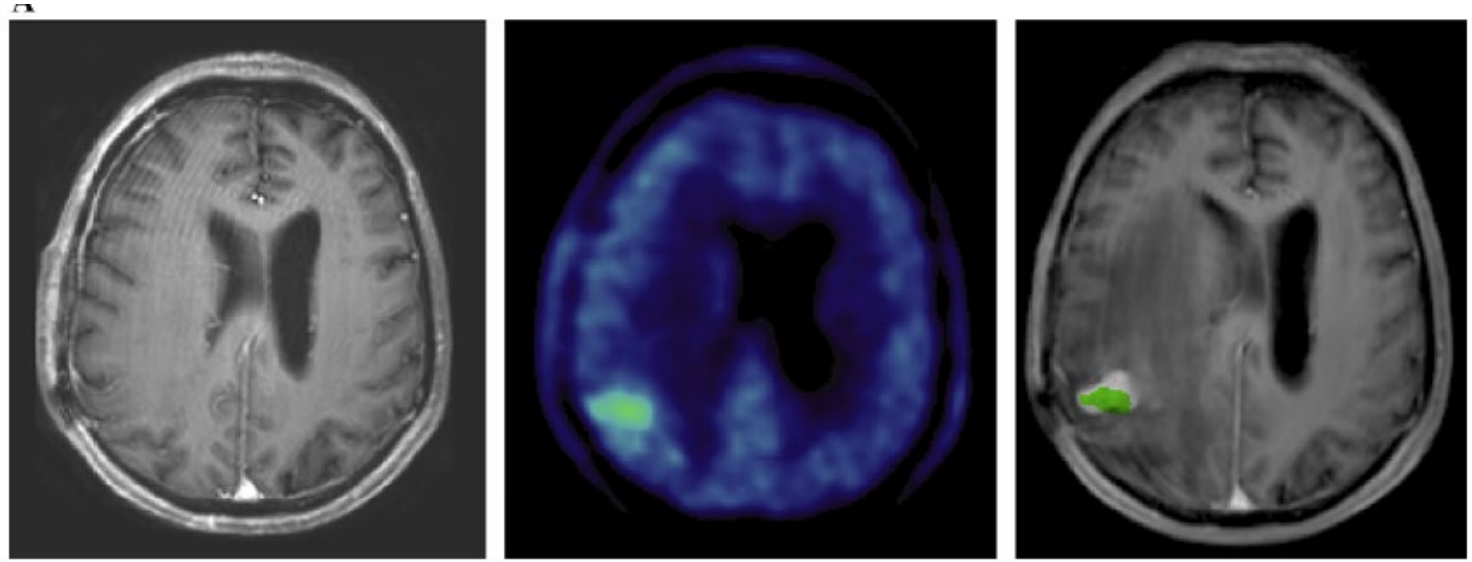
doi:10.1016/j.ijrobp.2008.04.050

CLINICAL INVESTIGATION **Brain**

ASSOCIATION OF ^{11}C-METHIONINE PET UPTAKE WITH SITE OF FAILURE AFTER CONCURRENT TEMOZOLOMIDE AND RADIATION FOR PRIMARY GLIOBLASTOMA MULTIFORME

IRWIN H. LEE, M.D., PH.D.,* MORAND PIERT, M.D.,† DIANA GOMEZ-HASSAN, M.D., PH.D.,‡ LARRY JUNCK, M.D.,§ LISA ROGERS, M.D.,§ JAMES HAYMAN, M.D.,* RANDALL K. TEN HAKEN, PH.D.,* THEODORE S. LAWRENCE, M.D., PH.D.,* YUE CAO, PH.D.,* AND CHRISTINA TSIEN, M.D.*

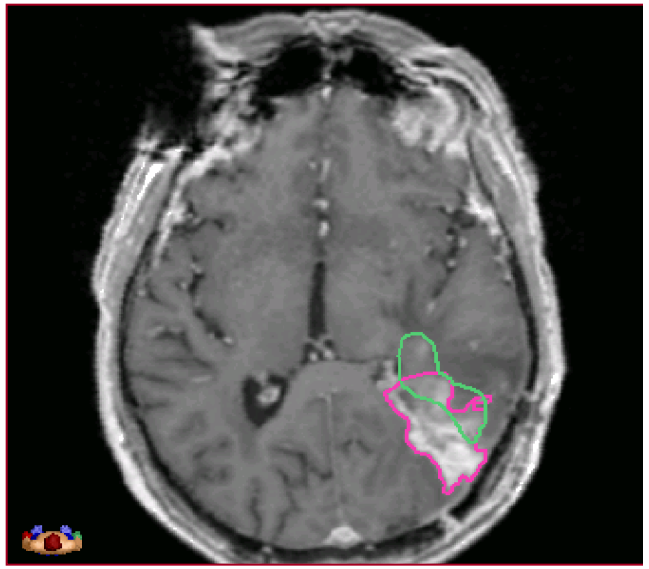
Departments of *Radiation Oncology, †Nuclear Medicine, ‡Radiology, and §Neurology, University of Michigan, Ann Arbor, MI

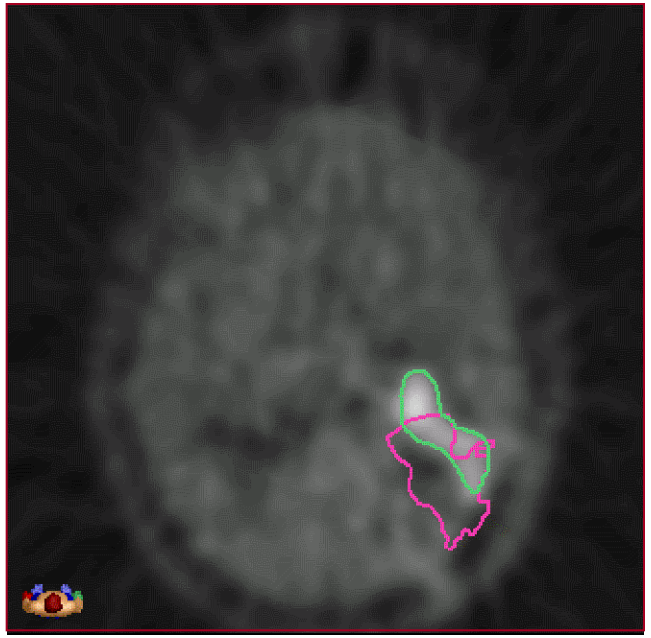


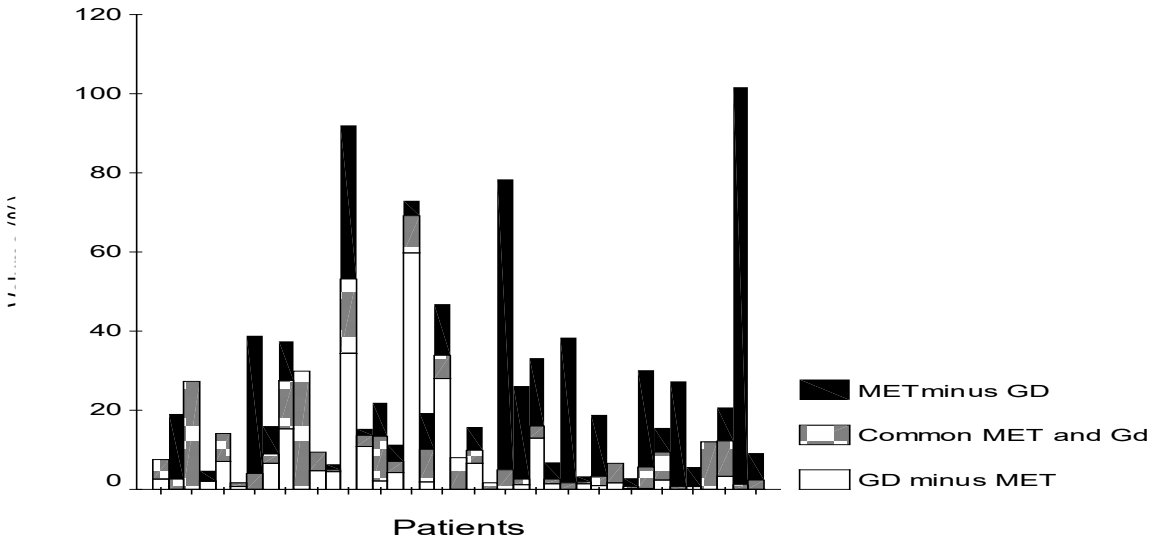
Conclusion: Pretreatment MET-PET appears to identify areas at highest risk for recurrence for patients with GBM. It would be reasonable to test a strategy of incorporating MET-PET into radiation treatment planning, particularly for identifying areas for conformal boost.

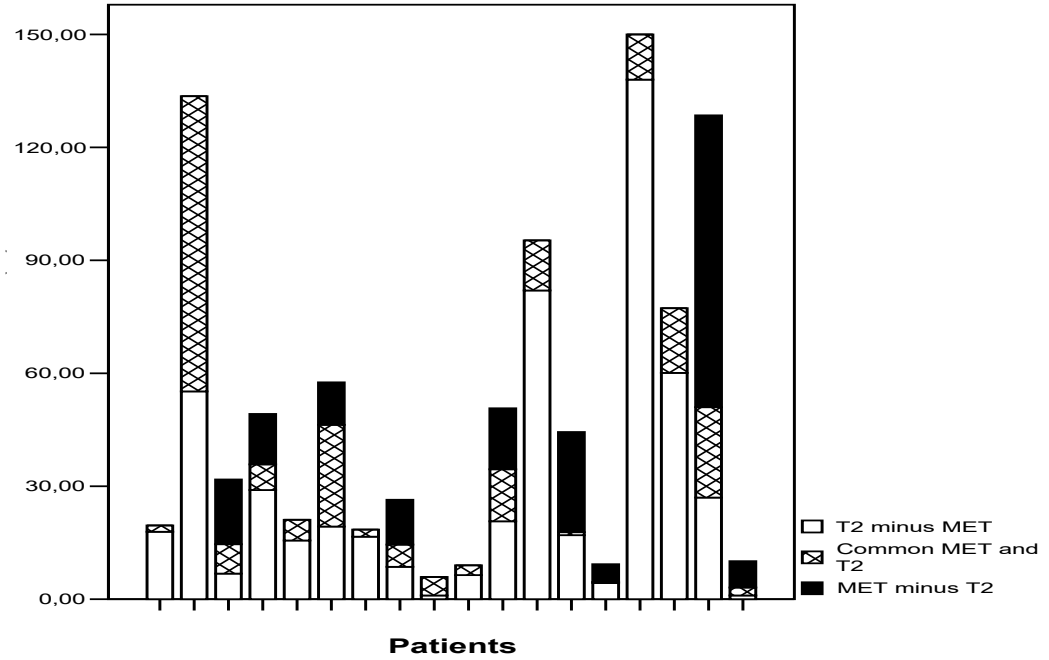
MET-PET / T1Gd-MRI image fusion. Volumetrical evaluation (T/N >1.6) in GBM

(Grosu et al. IJROBP)



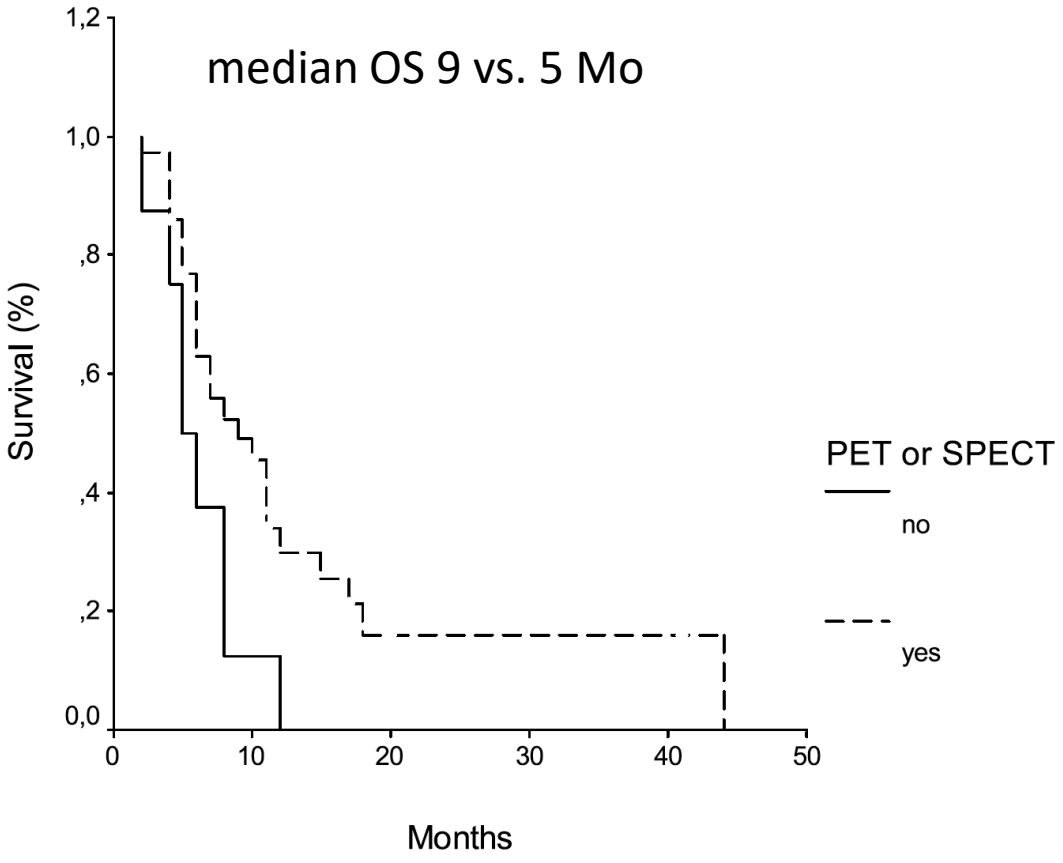


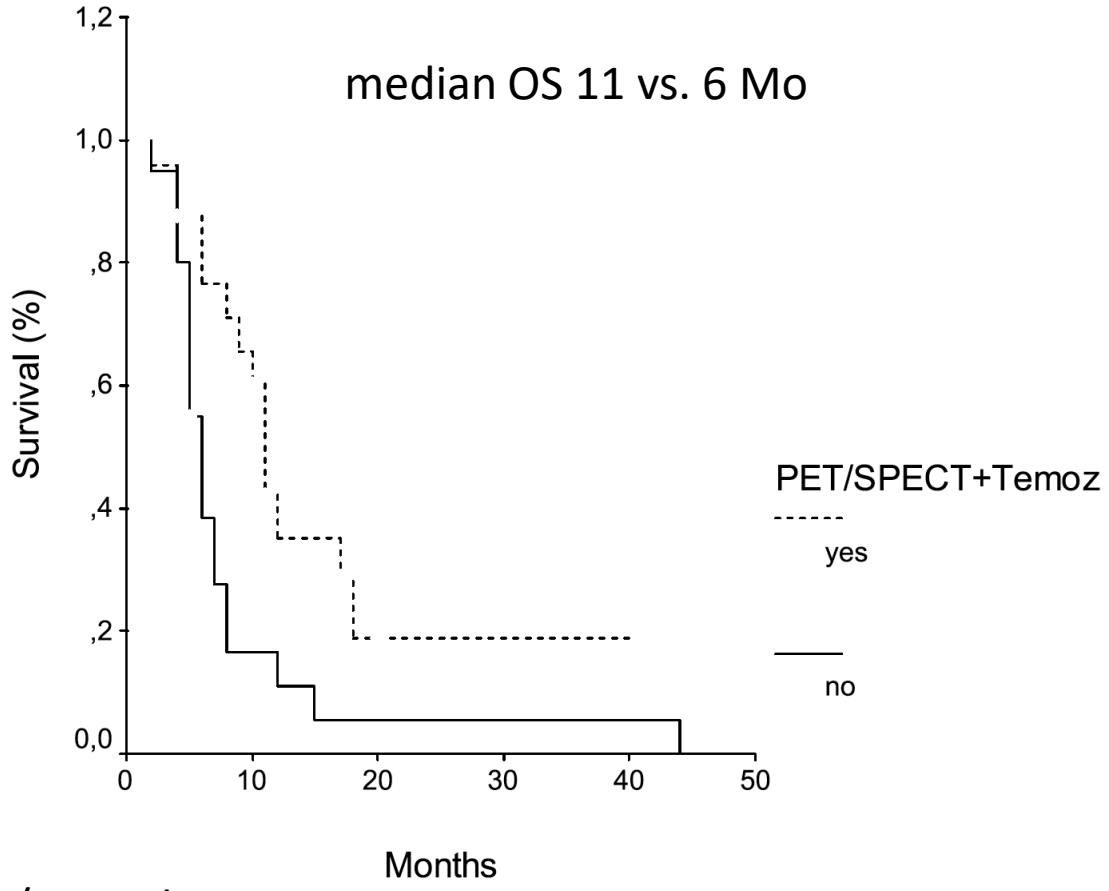




AA-PET and mpMRT in Neuro-Oncology

Impact on re-RTx in GBM



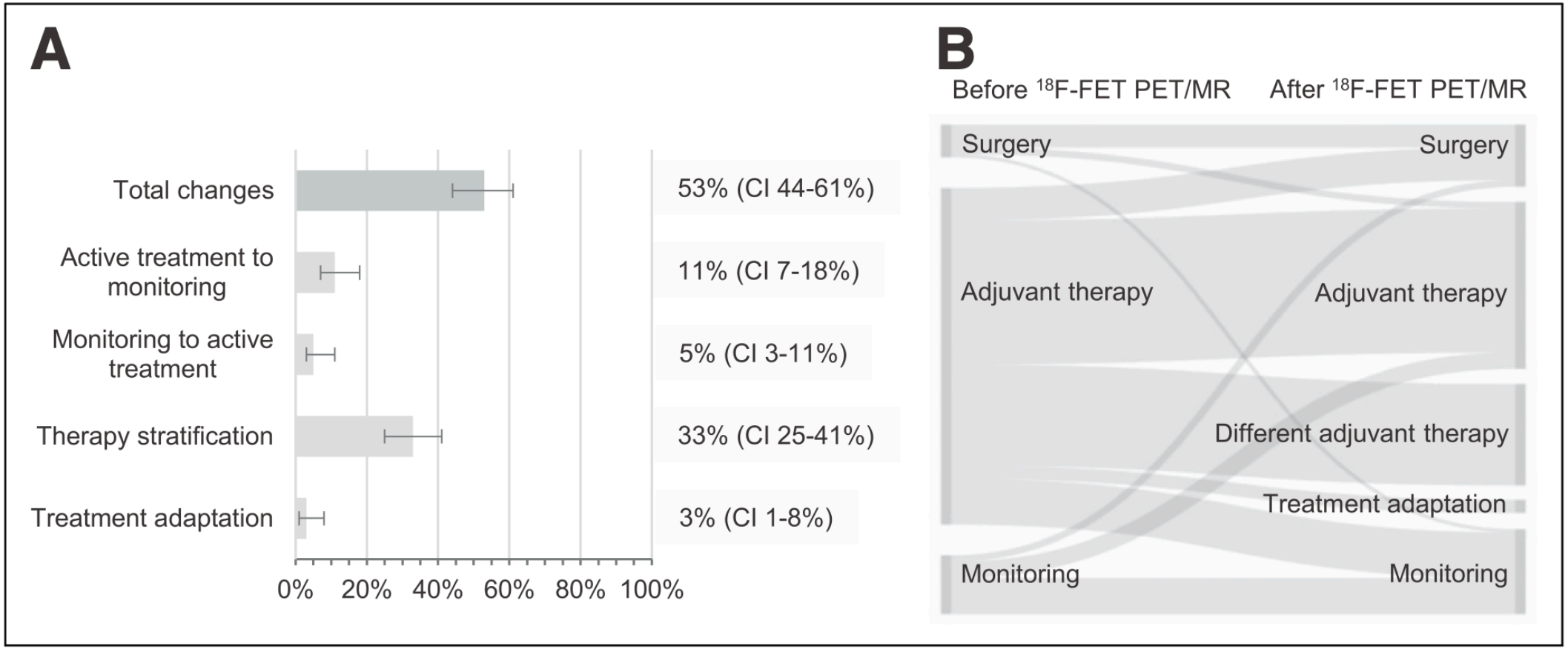


44 Pat., SFRT 30 Gy à 5 Gy + TMZ; AS-PET/CT/MRT versus CT/MRT Planung

Grosu et al. IJROBP 2005

PET and mpMRT in Neuro-Oncology

FET-PET+MRI in recurrent CNS Tumors



Brendle et al., J Nucl Med 2022

Int. J. Radiation Oncology Biol. Phys., Vol. 81, No. 4, pp. 1049–1058, 2011

0360-3016/$ - see front matter

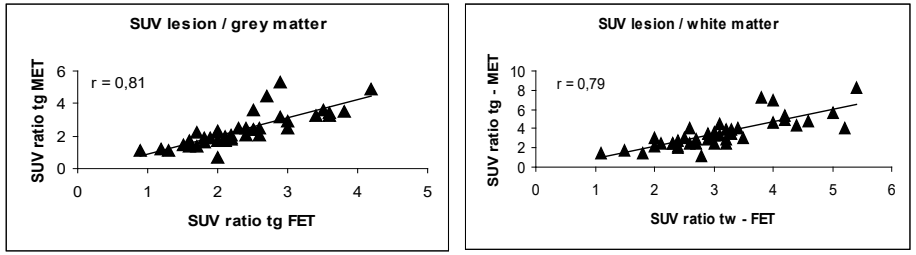
doi:10.1016/j.ijrobp.2010.07.002

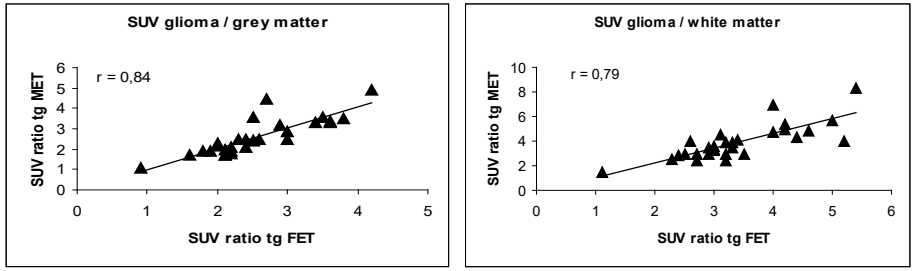
CLINICAL INVESTIGATION **Brain**

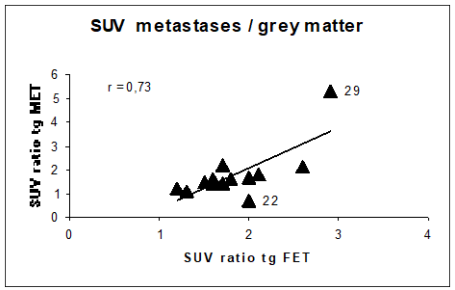
AN INTERINDIVIDUAL COMPARISON OF O-(2- [^{18}F]FLUOROETHYL)-L-TYROSINE (FET)– AND L-[METHYL-^{11}C]METHIONINE (MET)–PET IN PATIENTS WITH BRAIN GLIOMAS AND METASTASES

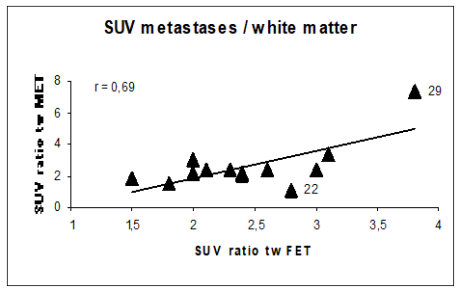
ANCA-LIGIA GROSU, M.D.,*† SABRINA T. ASTNER, M.D.,† EVA RIEDEL, M.D.,‡§ CARSTEN NIEDER, M.D.,†‖ NICOLE WIEDENMANN, M.D.,*† FELIX HEINEMANN, M.D.,* MARKUS SCHWAIGER, M.D.,‡ MICHAEL MOLLS, M.D.,† HANS-JÜRGEN WESTER, PH.D.,‡ AND WOLFGANG A. WEBER, M.D.‡¶

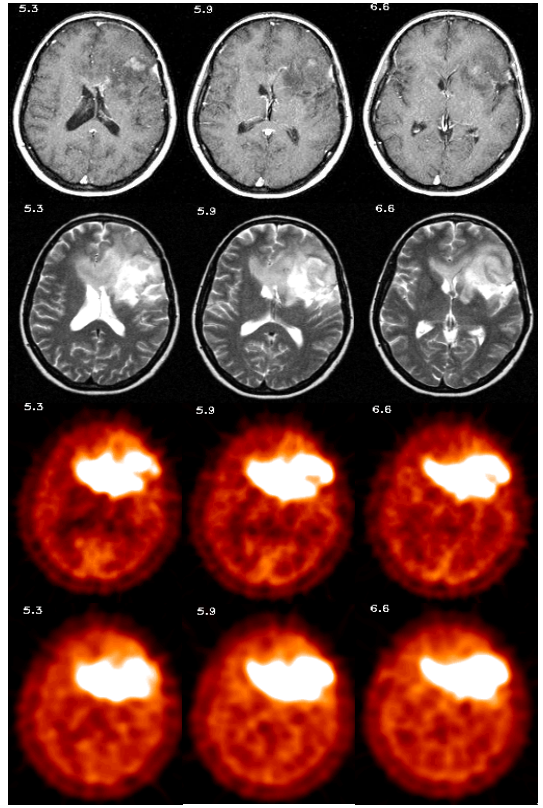
Department of *Radiation Oncology and ¶Nuclear Medicine, Albert Ludwigs Universität Freiburg, Freiburg, Germany; Departments of †Radiation Oncology and ‡Nuclear Medicine, Klinikum Rechts der Isar, Technische Universität München, Munich, Germany; §Department of Neurology, Klinikum Grosshadern, Ludwig Maximilians Universität München, Munich, Germany; and ‖Department of Internal Medicine–Oncology, Nordlandssykehuset HF Hospital, Bodø, Norway











GLIAA

Study Objective

Evaluation of the value of O-(2-[18F]fluoroethyl)-L-Tyrosine (FET-PET) versus contrast enhancement (CE)-T1MRI supported target volume contouring for high-precision/SFRT re-irradiation of recurrent glioblastoma (reGBM)

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Study Design

SFRT in reGBM 39 Gy, 3 Gy/d, 5x/week

200 Patients with reGBM were 1:1 randomized

- GTV max. tumor diameter (PET and MRI) 1-6 cm
- Stratification:
  - time since first radiotherapy
  - MGMT
  - CTx yes/no
  - Max. tumor diameter >/< 3cm

Arm A: 18F-FET-PET (experimental arm)

GTV according to FET-PET:

GTV = FET-PET uptake (TBI > 1.8)

CTV = GTV + 3 mm,

PTV = CTV + 1-2mm

Arm B: CE-T1MRI (control arm)

GTV according to CE-T1MRI:

GTV = CE-T1MRI

CTV = GTV + 3 mm,

PTV = CTV + 1-2mm

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Inclusion and exclusion criteria

- **Inclusion criteria:**

- **Recurrence of GBM (on MRI and PET)** – not operated or with residual tumor after surgery (OP)
- **Histologically confirmed GBM at initial diagnosis or at relapse**
- Pre-irradiation with **59.4 or 60 Gy (ED 1.8-2 Gy)**
- At **least 6 months** between pre-irradiation and randomization
- Recurrence can be defined on CE-T1MRI and FET-PET with the **maximum diameter** (or the sum of the maximum diameters) between **1 and 6 cm**
- Target volume definition and planning possible using CE-T1MRI and FET-PET
- **Start SFRT within max. 2 weeks of FET-PET and MRI**

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Inclusion and exclusion criteria

- **Exclusion criteria:**

- Therapy with **bevacizumab/other targeted therapies** < 6 months before MRI/FET-PET
- **Surgery < 3 weeks** before SFRT
- SFRT based on MRI or FET-PET not possible
- etc.

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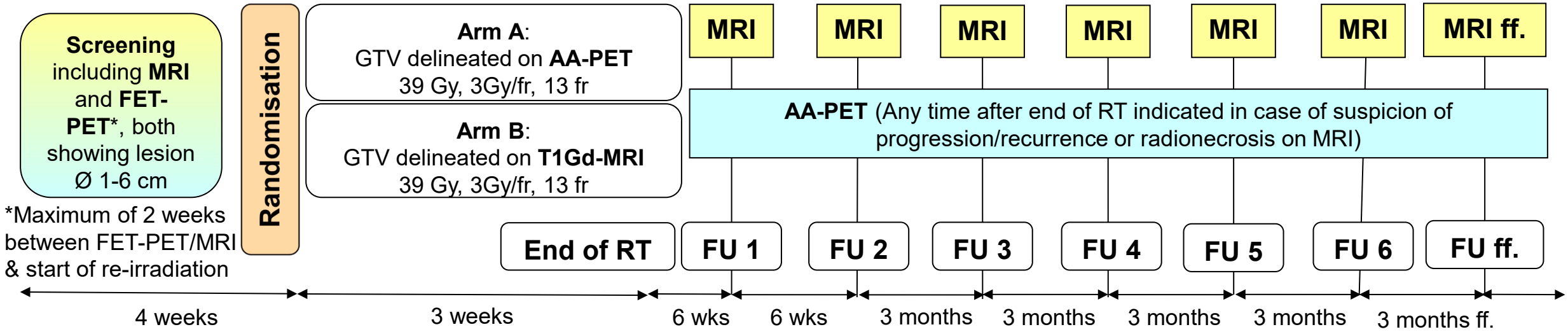
Flowchart



Pharmacovigilance:
Assessment until 7d after application of FET

Radiotherapy:
Assessment once a week during radiotherapy and at end of radiotherapy:
1) Radiotherapy toxicity
2) Serious Adverse Events (irrespective of relationship to Radiotherapy)

Follow up (FU):
Assessment at each FU-visit:
1) Radiotherapy toxicity
2) Serious Adverse Events (SAEs) irrespective of relationship to radiotherapy until 30 days after end of radiotherapy
3) Serious Adverse Events (SAEs) related to radiotherapy until end of follow up

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Primary endpoint: PFS

- defined from the day of randomisation to the day of tumor progression, based on **MRI (RANO) confirmed by AA-PET** and/ or **positive biopsy/ surgery**, or **the day of death of any cause, whichever occurs first**
- negative PET-scan excludes progression while a positive PET scan, if unclear was followed by biopsy
-
- patients receiving any **new systemic tumor treatment other than preplanned chemotherapy** (TMZ, CCNU) for their reGBM, in the absence of diagnosed tumor progression were considered as having had an event for the endpoint PFS, at the date that treatment was initiated
- patients receiving **surgery for distant progression** were considered as having had an event for the endpoint PFS
- patients receiving **Avastin** were considered as having an event for the endpoint PFS
- **tumor progression was divided as <u>local</u> or <u>distant</u> progression**

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Secondary endpoints

- **Overall survival (OS**)
- **Local control (LC)**
- **Volumetric analysis of GTVs (MRI and PET)**
- Progression pattern (topography of recurrences after re-irradiation)
- Evaluation of patients with long-term survival
- **Toxocity** and role of FET-PET in the diagnosis of radiation necrosis
- **Pharmacovigilance 18-FET**
- Quality of life (QoL)
- Role of diffusion/perfusion-weighted MRI in comparison to FET-PET

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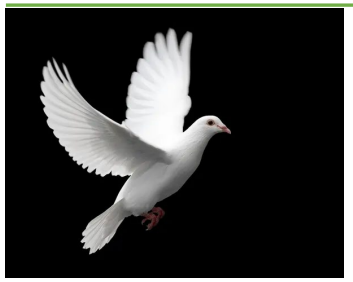
Participating centers: 14 centers



- The study was registered at the Federal Institute for Drugs and Medical Devices (BfArM - Germany).
- The **18F-FET** tracer was manufactured at the University Medical Center Freiburg in accordance with the German Medicines Act (AMG) and distributed to the other centers.
- The evaluation of pharmacovigilance was an important endpoint of the study.

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18F-FET-PET - Protocol

FET-PET injected activity [MBq]

Randomized radiation	*Total*	*Missing*	*Total valid*	*Mean*	*Std*	*Minimum*	*1. Quartile*	*Median*	*3. Quartile*	*Maximum*
AA-PET (intervention)	100	0	100	221.8	29.3	167.0	204.5	213.0	225.5	308.0
MRI (control)	100	0	100	220.1	23.6	177.0	206.0	214.0	222.0	302.0
Total	200	0	200	221.0	26.5	167.0	205.5	213.5	224.0	308.0

FET-PET scan start post injection [min]

Randomized radiation	*Total*	*Missing*	*Total valid*	*Mean*	*Std*	*Minimum*	*1. Quartile*	*Median*	*3. Quartile*	*Maximum*
AA-PET (intervention)	100	0	100	19.2	3.6	0.0	20.0	20.0	20.0	30.0
MRI (control)	100	0	100	18.6	4.7	0.0	20.0	20.0	20.0	27.0
Total	200	0	200	18.9	4.2	0.0	20.0	20.0	20.0	30.0

FET-PET duration of scan (acquisition time) [min]

Randomized radiation	*Total*	*Missing*	*Total valid*	*Mean*	*Std*	*Minimum*	*1. Quartile*	*Median*	*3. Quartile*	*Maximum*
AA-PET (intervention)	100	0	100	20.4	4.8	15.0	20.0	20.0	20.0	40.0
MRI (control)	100	0	100	21.2	6.2	8.0	20.0	20.0	20.0	45.0
Total	200	0	200	20.8	5.6	8.0	20.0	20.0	20.0	45.0

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Demographic data

	FET-PET-Arm (n=100)	MRI-Arm (n=100)
Age, years	59.3 ± 11.0 (median 59.5; 27-82)	60.6 ± 9.9 (median 60.5; 30-83)
Gender, n (%)		
female	45 (45.0)	40 (40.0)
masculine	55 (55.0)	60 (60.0)
Karnofsky Index, n (%)		
90%-100% = ECOG 0	52 (52.0)	49 (49.0)
70%-80% = ECOG 1	48 (48.0)	51 (51.0)
Time after first RT	11,6 (5.8-80.6)	12,0 (5.6-106.2)
≤ 14 months (n, %)	58 (58.0)	61 (61.0)
>14 months (n, %)	42 (42.0)	31 (31.0)
MGMT-Status, n (%)		
methylated	41 (41.0)	41 (41.0)
not methylated	31 (31.0)	31 (31.0)
at randomisation unknown	28 (28.0)	28 (28.0)
Chemotherapy – TMZ and/or CCNU parallel and/or sequentiell to reRT		
no	23 (46.0)	25 (50.0)
yes	27 (27.0)	25 (25.0)
option not allowed (before amendment)	50 (50.0)	50 (50.0)

RESULTS

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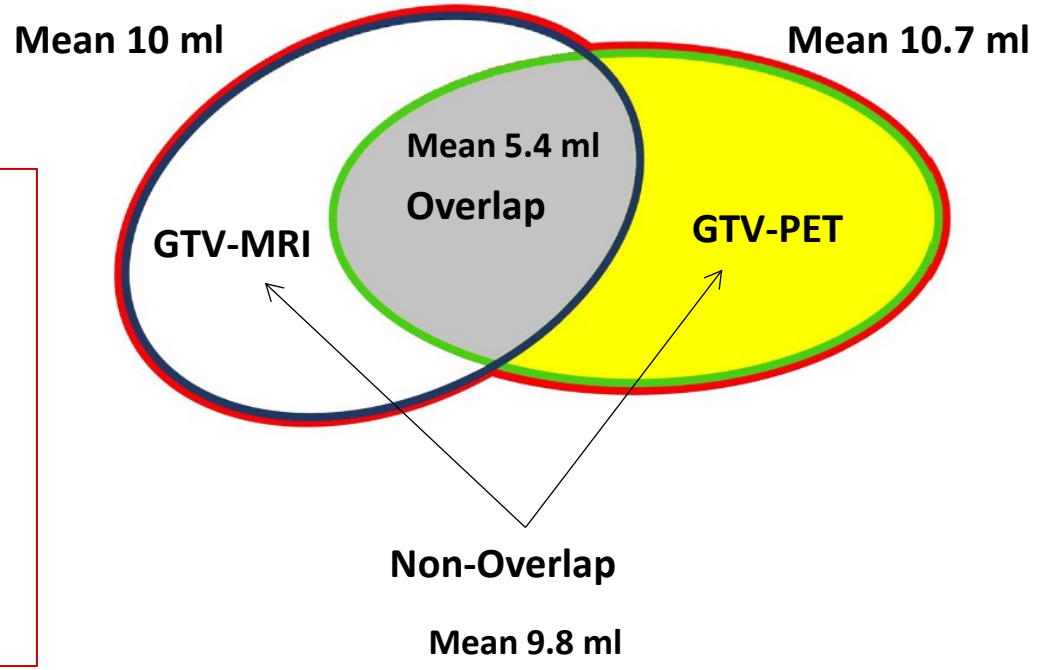
Volumetric assessment

- The non-overlapping volume was 9.6 ± 9.6 ml in arm A and 10.1 ± 8.4 ml in arm B
- The overlapping volume was 5.1 ± 5.9 ml in arm A and 5.7 ± 6.3 ml in arm B.
- **In 82% of patients in Arm A and 84% of patients in Arm B there was a relevant difference of at least 2 ml** between MRI and PET GTV.

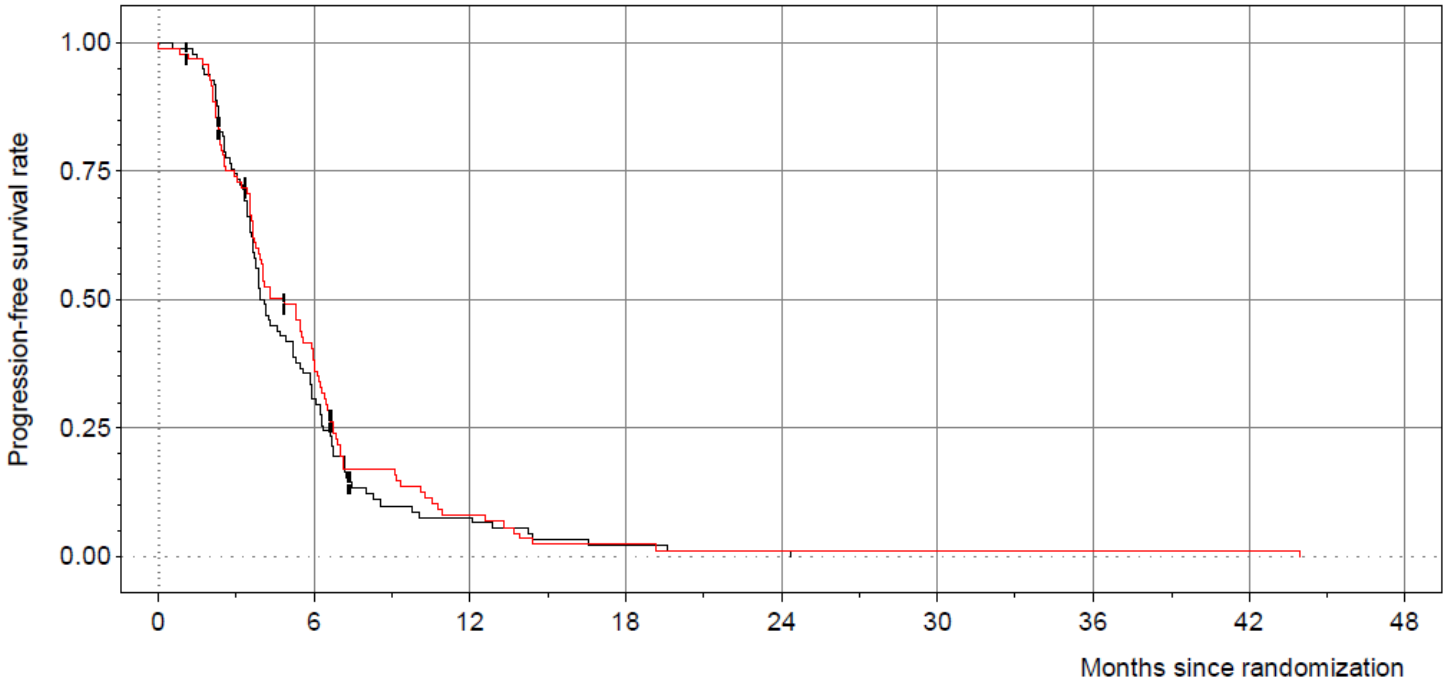
- **Arm A (PET-based reRT)**
  - 93% (± 13.6%) of GTV-MRI received at least 30 Gy
  - 88% (± 17.7%) of GTV-MRI received at least 37 Gy

- **Arm B (MRI-based reRT)**
  - 94% (± 14.5%) of GTV-PET received at least 30 Gy
  - 90% (± 15.9%) of GTV-PET received at least 37 Gy



GLIAA

Primary endpoint – progression-free survival



Number at risk

AA-PET (intervention)	98	30	7	2	1	0	0	0	0
MRI (control)	97	35	7	2	1	1	1	1	0

Randomized radiation — AA-PET (intervention) — MRI (control)

PET:
median **PFS = 4.0 months**
(95% CI 3.7-5.2 months)

MRI:
median **PFS = 4.9 months**
(95% CI 3.7-6.0 months)

HR PET vs. MRI = **1.14**
[95% CI 0.85-1.52], **p=0.39**

einseitiger Log-Rank-Test
p=0.98

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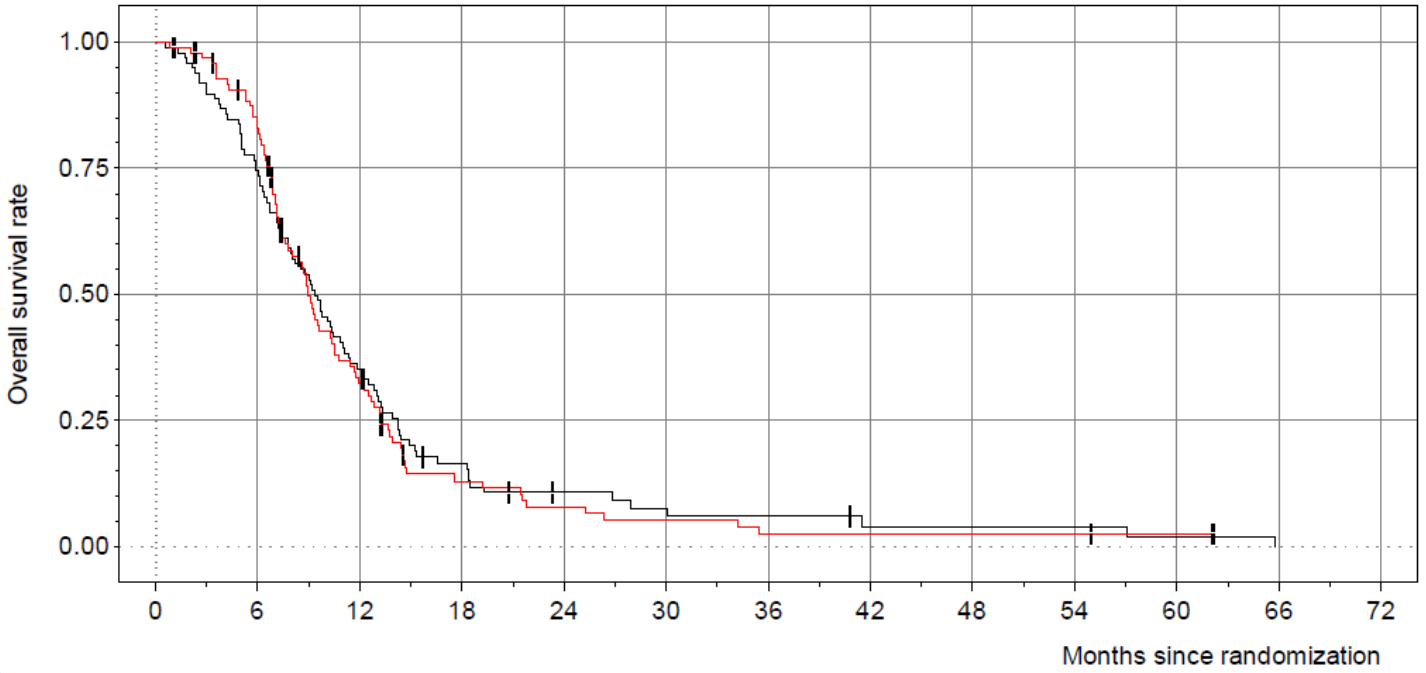
Overall survival



Number at risk

AA-PET (intervention)	98	73	34	14	7	5	4	2	2	2	1	0	0
MRI (control)	97	78	28	10	6	4	2	2	2	2	1	0	0

PET:
median OS = **9.4 months**
(95% CI 7.8-11.1 months)

MRI:
median OS = **9.0 months**
(95% CI 7.6-10.5 months)

HR PET vs. MRI = **1.01**
[95% CI 0.75-1.37], **p=0.92**

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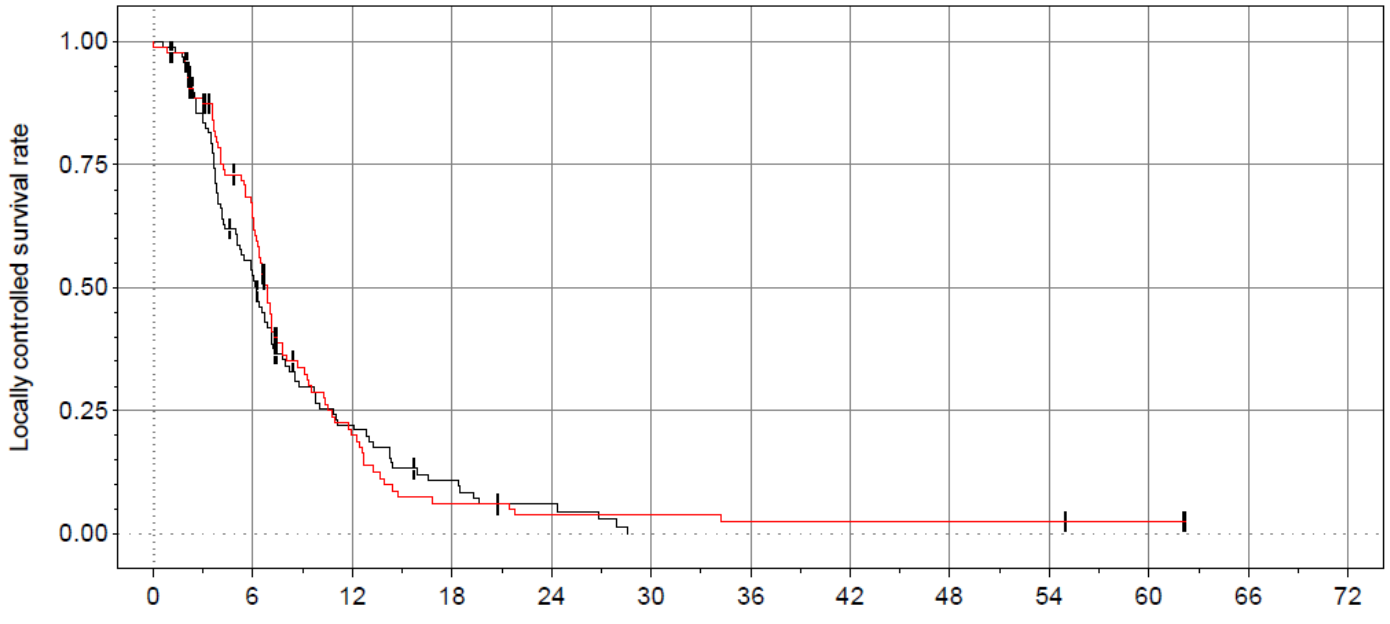
Locally controled survival



Number at risk													
AA-PET (intervention)	98	50	20	9	4	0	0	0	0	0	0	0	0
MRI (control)	97	59	16	5	3	3	2	2	2	2	1	0	0

Randomized radiation — AA-PET (intervention) — MRI (control)

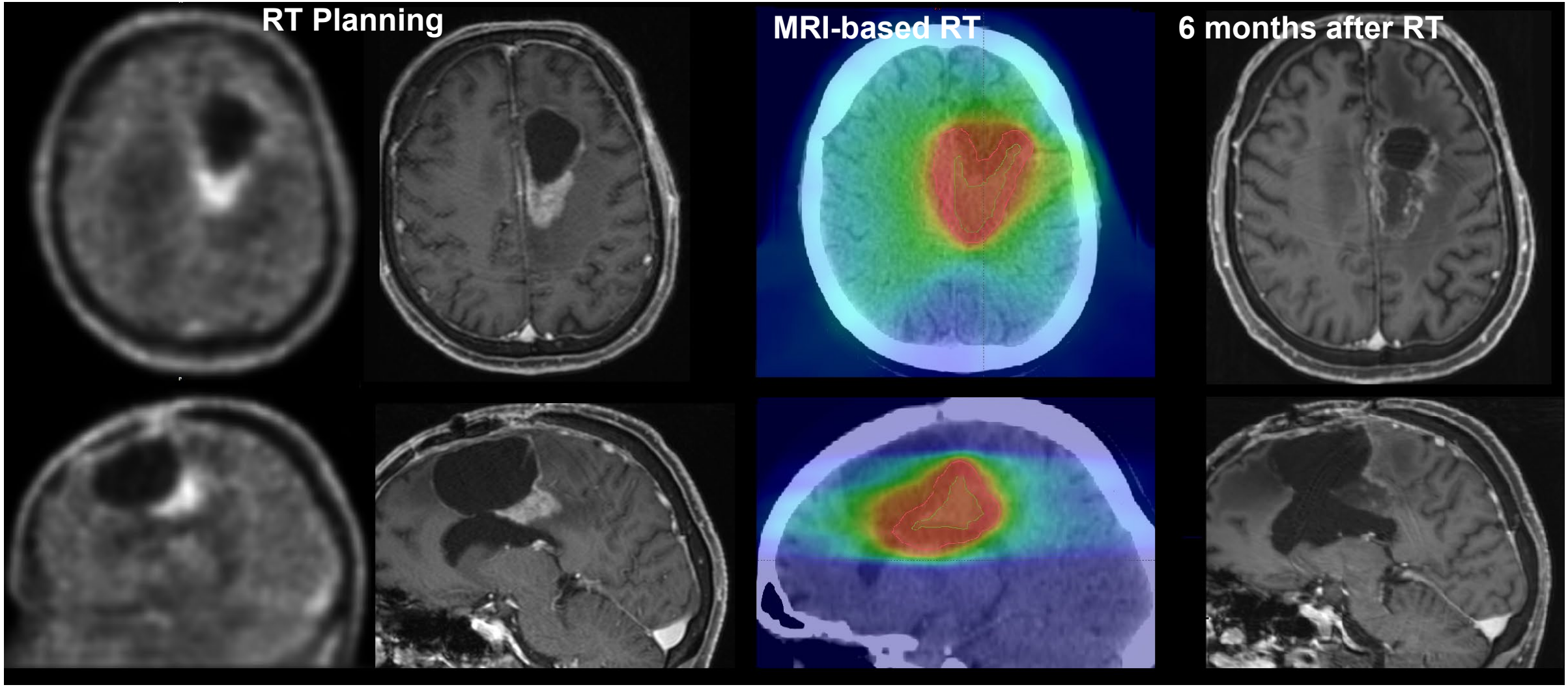
PET:
Median LCS = **6.3 months**
(95% CI 5.1-7.2 months)
12-Mo – LTC = 22%

MRI:
Median LCS **= 6.8 months**
(95% CI 6.2-7.3 months)
12-Mo – LTC = 20%

HR PET vs. MRI = **1.20**
[95% CI 0.88-1.62], **p=0.25**

GLIAA

Locally controled survival



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Toxicity

- **Acute toxicity** grade 3-4: 7 patients in PET arm vs. 4 patients in MRI arm

< 90 days after re-irradiation	FET-PET-Arm	MRI-Arm
Focal seizures	1	0
Generalized tonic–clonic seizure	0	1
Hemiparesis	3	0
Difficulties in concentration	1	0
Cognitive impairment	1	0
Leukoencephalopathy	0	1
Headache	0	1
Fatigue	1	1

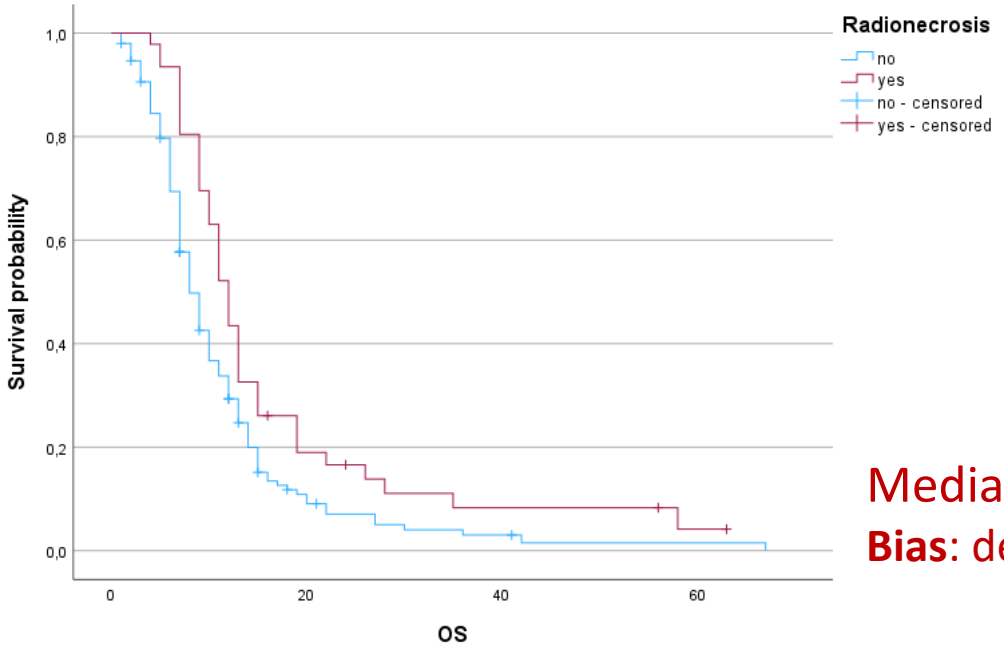
- **Late toxicity** grade 3-4: 8 patients in PET arm vs. 2 patients in MRI arm

≥ 90 days after re-irradiation	FET-PET-Arm	MRT-Arm
Focal seizures	1	0
Hemiparesis	2	1
Aphasia	1	0
Hearing loss	1	0
Personality disorder	1	0
Cognitive impairment	2	0
Fatigue	0	1

- **Radiation necrosis (after PET and/or histology): 25.5% in PET arm vs. 21.6% in MRI arm**

Toxicity – impact of radiation necrosis

			Hazard ratio 95%-CI		
Factor	Value	Hazard ratio	CI Lower limit	CI Upper limit	p-value
Randomized radiation	AA-PET (intervention) vs. MRI (control)	1.00	0.74	1.35	0.9928
Radionecrosis during follow-up	Yes vs. no	0.75	0.52	1.08	0.1222
Tumor progression during follow-up	Yes vs. no	1.22	0.84	1.78	0.3025



HR: positive effect of radiation necrosis on OS is higher than the negative effect of tumor progression on OS and persists independently of tumor progression

Median **OS 12 Mo** vs**. 8 Mo** in pts. with vs. w/o radionecrosis, p=0.006

Bias: death as competing risk not taken into consideration **for Kaplan Meier**

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CONCLUSION

- This is the first randomized study to compare two imaging modalities: FET-PET and CE-MRI to delineate the target volume for radiation treatment planning in GBM. The study shows in 200 evaluated patients, that both imaging modalities are equivalent for the re-irradiation of reGBM. Therefore, in this case, one of the two modalities could be chosen to determine the target volume.
- Stereotactic re-irradiation with 39 Gy in 3 Gy fractions was shown to be a safe and effective treatment option for reGBM.
- Patients who have developed radiation necrosis have a significantly better outcome.
- The patient cohort who had received the FET tracer was defined as the pharmacovigilance population. The evaluation was carried out in the entire cohort. The FET-PET examination and in particular the FET application have proven to be safe.

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