Is there a role for PET imaging in CNS metastases?

Norbert Galldiks

Dept. of Neurology, University of Cologne, Germany
Research Center Juelich, Germany
Center of Integrated Oncology (CIO), University of Cologne, Germany

8th Annual Brain Mets congress / 21. September 2018 / Marseille

2016; 12:375-76

nature REVIEWS NEUROLOGY

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

Karl-Josef Langen and Colin Watts

2017; 19:279-89

nature REVIEWS NEUROLOGY

Advances in neuro-oncology imaging

Karl-Josef Langen[1,2], Norbert Galldiks[1,3,4], Elke Hattingen[5] and Nadim Jon Shah[1,2,6]

Neuro-Oncology 2016; 18:1199-208

Response Assessment in Neuro-Oncology working group and European Association for Neuro-Oncology recommendations for the clinical use of PET imaging in gliomas

Nathalie L. Albert, Michael Weller, Bogdana Suchorska, Norbert Galldiks, Riccardo Soffietti, Michelle M. Kim, Christian la Fougère, Whitney Pope, Ian Law, Javier Arbizu, Marc C. Chamberlain, Michael Vogelbaum, Ben M. Ellingson, and Joerg C. Tonn

- It has been emphasized that for gliomas the additional clinical value of amino acid PET compared to standard MRI is outstanding and allows the widespread clinical use

- the uptake of radiolabeled amino acids in gliomas is independent from a disruption of the BBB and is determined by the expression of amino acid transporters (LAT)

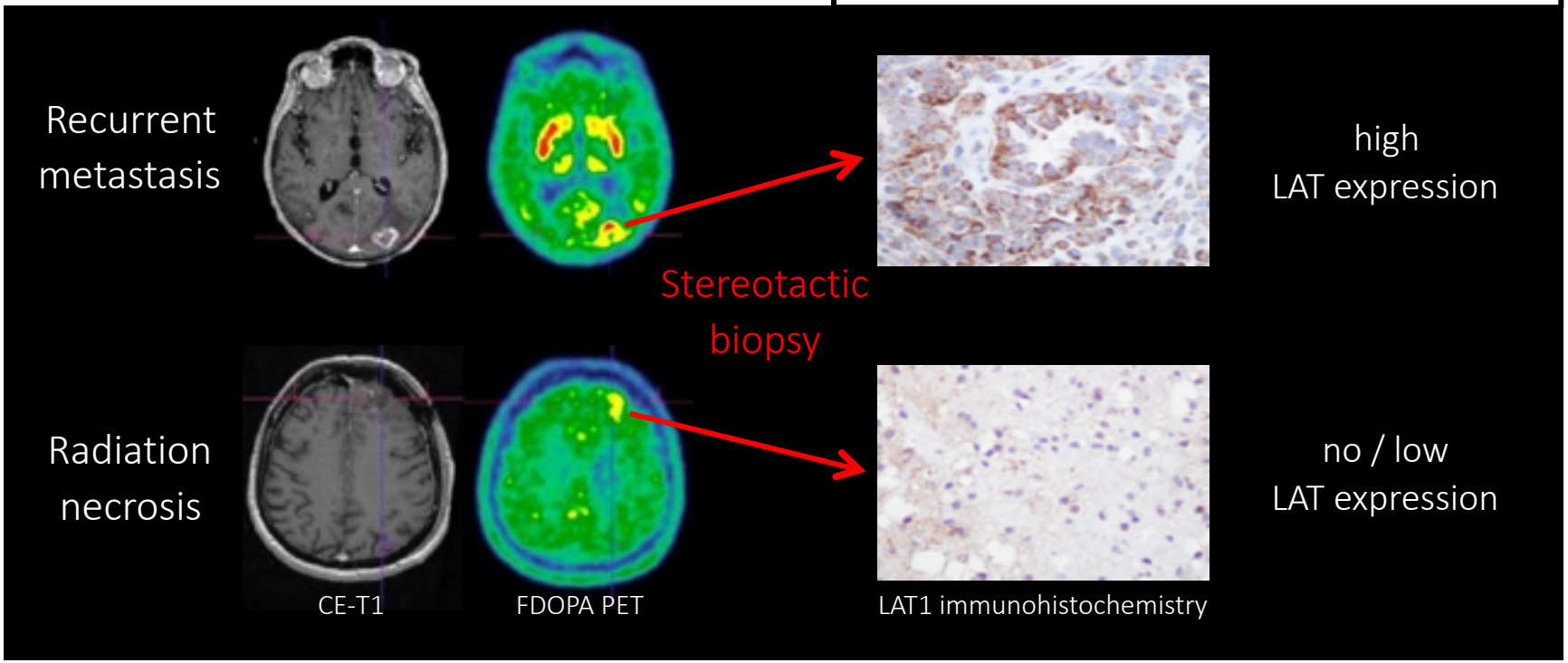
PLOS ONE | 2016; 11:e0157139

RESEARCH ARTICLE

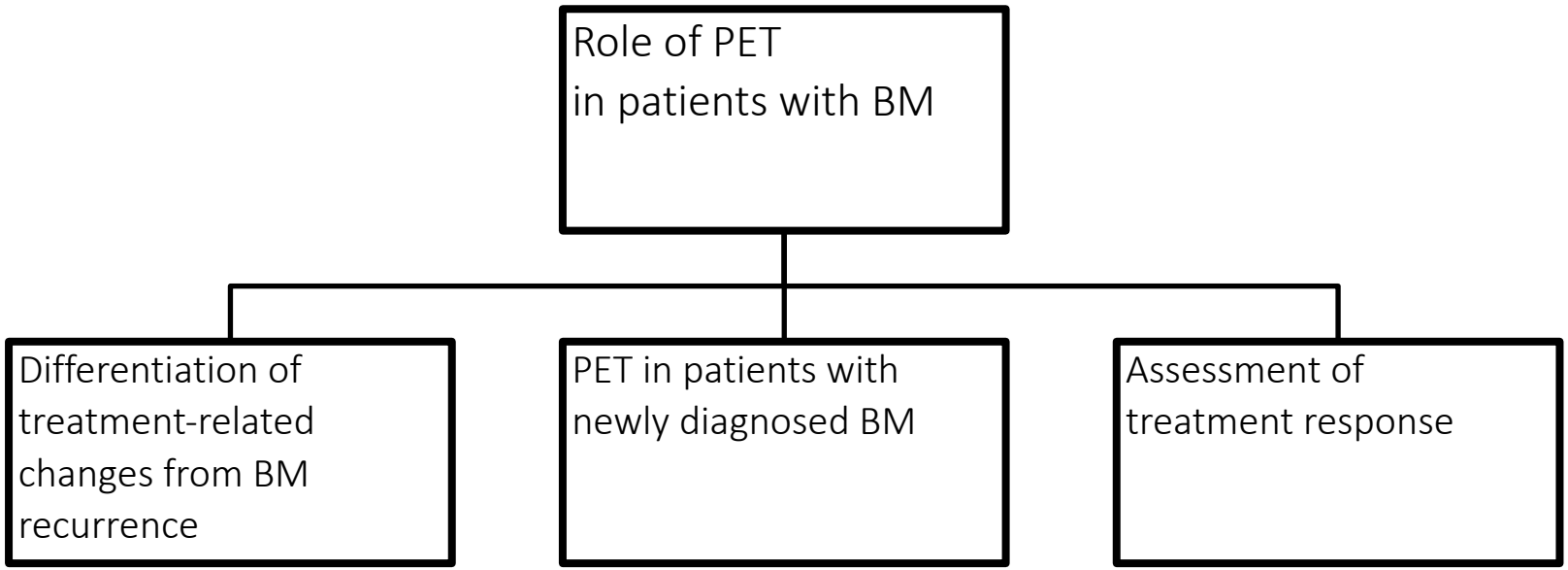
Study of LAT1 Expression in Brain Metastases: Towards a Better Understanding of the Results of Positron Emission Tomography Using Amino Acid Tracers

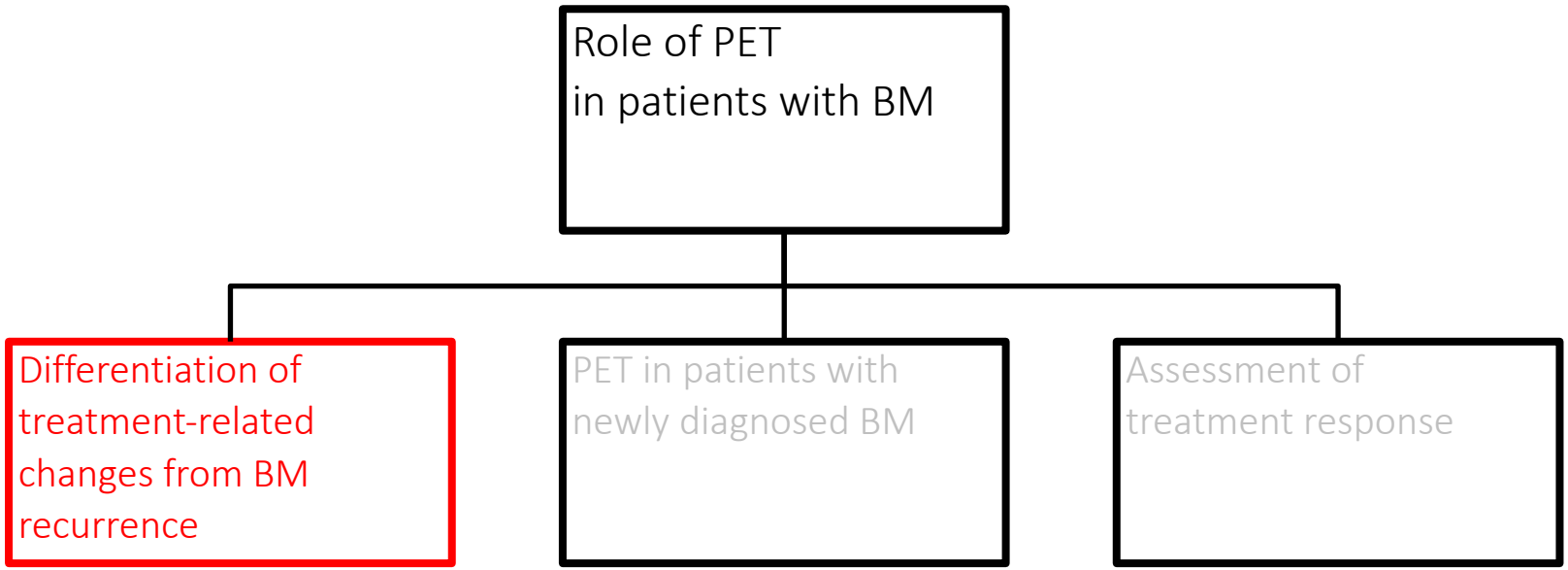
Caroline Papin-Michault[1], Christelle Bonnetaud[2], Maxime Dufour[3,4], Fabien Almairac[5], Mickael Coutts[1], Stéphanie Patouraux[1], Thierry Virolle[6], Jacques Darcourt[3,4], Fanny Burel-Vandenbos[1,6]*

- BM also express LAT-amino acid transporters and are therefore an interesting target for amino acid PET
- LAT expression was significantly increased in BM
- Amino acid PET uptake was strongly correlated with LAT expression



Outline


Role of PET
in patients with BM
Differentiation of treatment-related changes from BM recurrence
PET in patients with newly diagnosed BM
Assessment of treatment response


Role of PET
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Assessment of treatment response

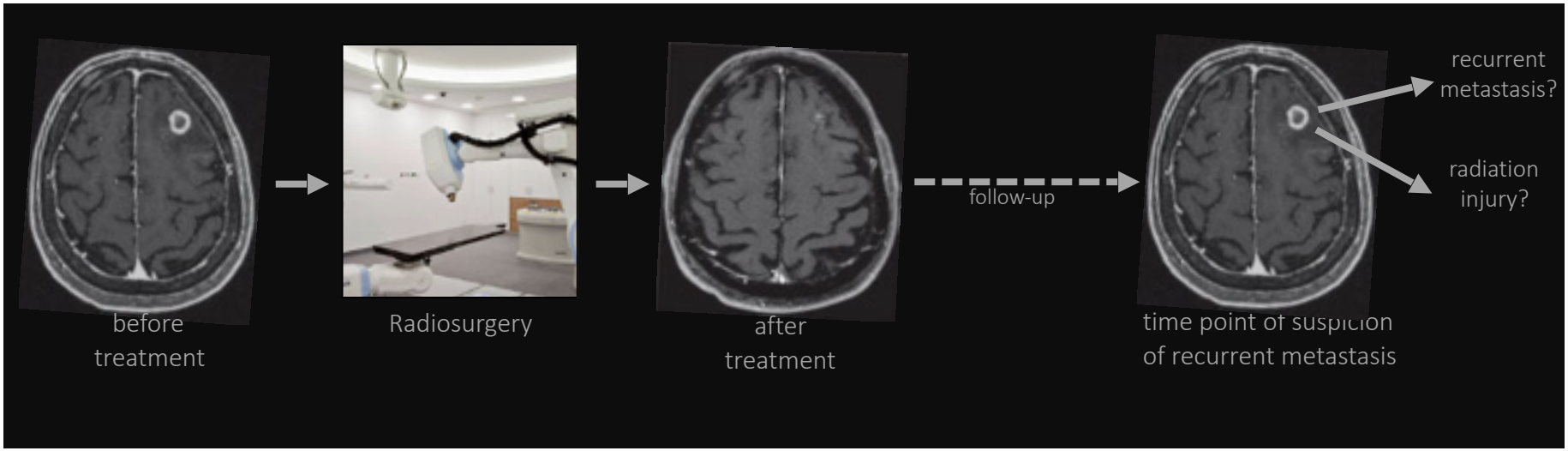
Treatment-related changes

- are of high clinical relevance because a premature discontinuation of an effective therapy may have a negative impact on survival
- the efficacy of the subsequent therapy can be overestimated
- may occur after standard therapy (e.g. radiotherapy) and newer therapy options (e.g., immunotherapy)

Treatment-related changes after radiotherapy

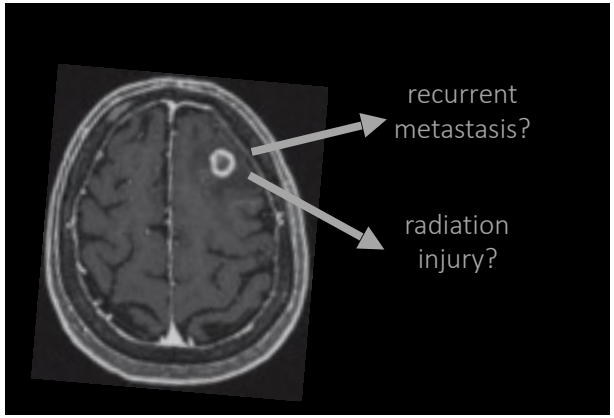
- Patients with BM are increasingly treated with radiosurgery

- PROBLEM: Following radiosurgery, standard MRI cannot reliably differentiate between radiation injury and recurrent metastasis



Vallow, 2009 Nat Rev Clin Oncol

Is amino acid PET able to solve this problem?



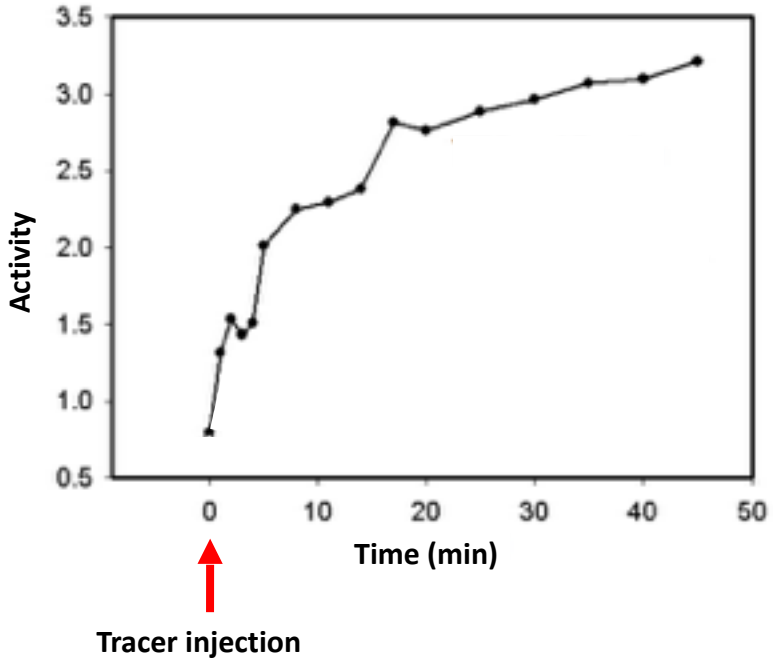
The differentiation of radiation injury from BM recurrence using amino acid PET is currently evaluated best

	Tsuyuguchi et al., 2003 J Neurosurg	Terakawa et al., 2008 J Nucl Med	Galldiks et al., 2012 J Nucl Med	Lizarraga et al., 2014 J Nucl Med	Cicone et al., 2015 EJNMMI	Minamimoto et al., 2015 PLoS One	Romagna et al., 2016 Radiat Oncol	Ceccon et al., 2017 Neuro Oncol	Tomura et al., 2017 AJNR	Yomo et al., 2017 BMC Cancer
n Patients	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
Sensitivity	78%	79%	74%	81%	90%	82%	86%	86%	90%	82%
Specificity	100%	75%	90%	73%	92%	86%	79%	88%	75%	75%
Accuracy	89%	77%	82%	77%	90%	83%	83%	87%	84%	79%
Threshold (TBR)	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

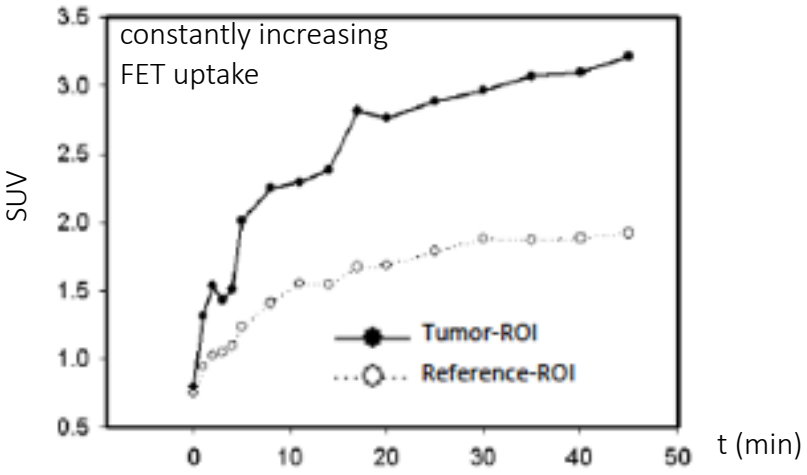
The kinetic analysis of the amino acid PET tracer FET was able to provide additional diagnostic information

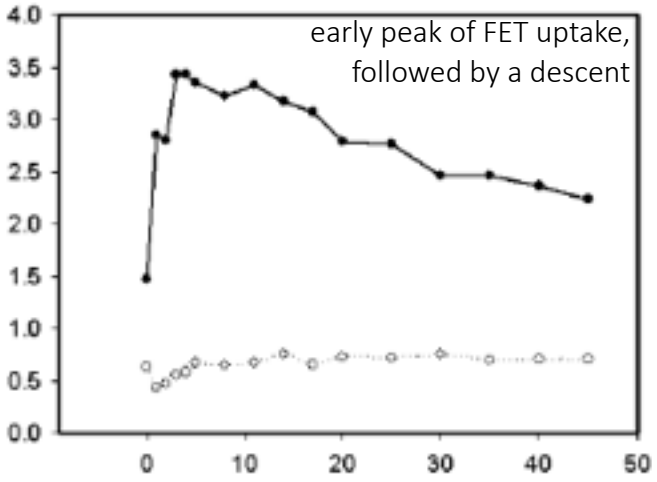
- the kinetic analysis allows the characterization of the temporal pattern of FET uptake by deriving a time-activity curve (TAC)
  - seems to be a special property of FET PET, not observed with other amino acid PET tracers

- the configuration of TAC may contain additional diagnostic information
  - *e.g., for prognostication, diagnosis of treatment-related changes



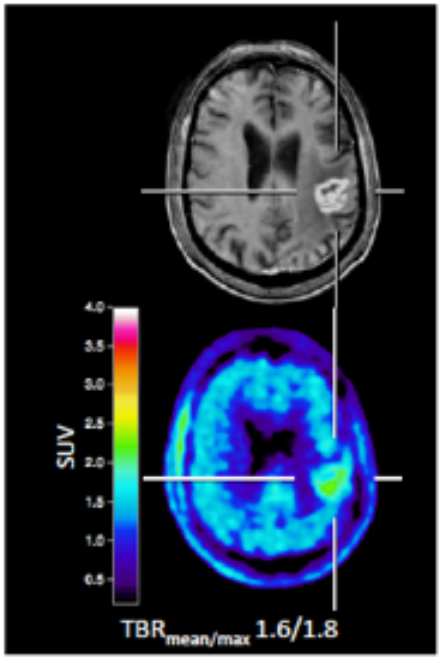
*e.g., Albert et al., 2016 Eur J Nucl Med Mol Imaging
Galldiks et al., 2013 J Nucl Med
Calcagni et al., 2011 Clin Nucl Med
Pöpperl et al., 2006 J Nucl Med
Galldiks et al., 2015 Neuro Oncol
Ceccon et al., 2017 Neuro Oncol





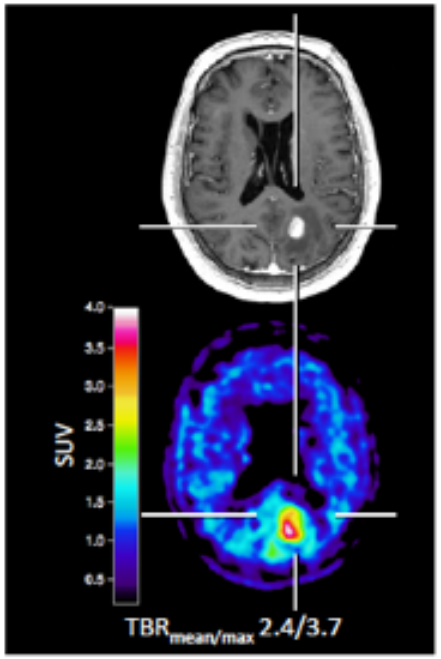
Radiation necrosis
(after SRS of a breast cancer BM)

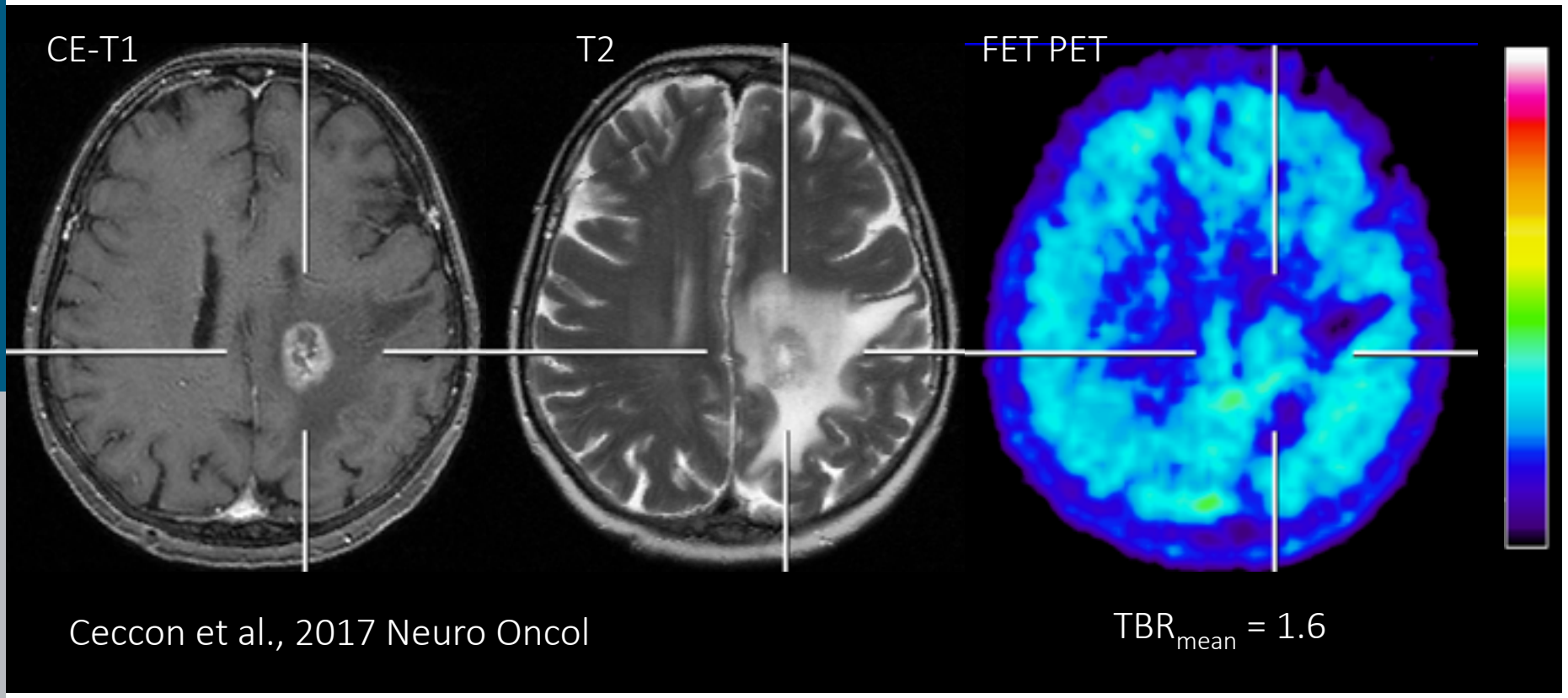
Recurrent metastasis
(after SRS of a malignant melanoma BM)

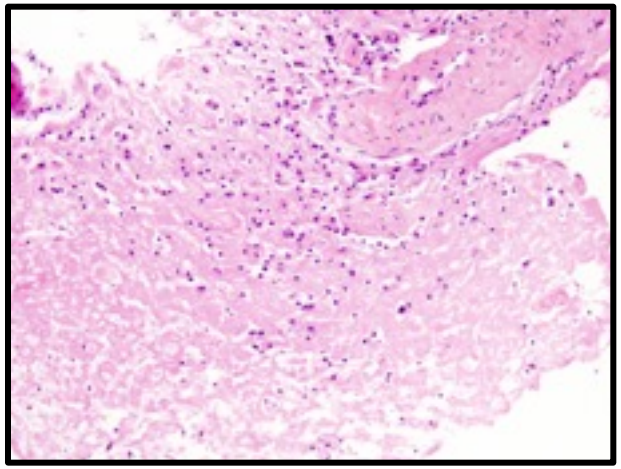


Different kinetic pattern in recurrent metastasis than in radiation injury

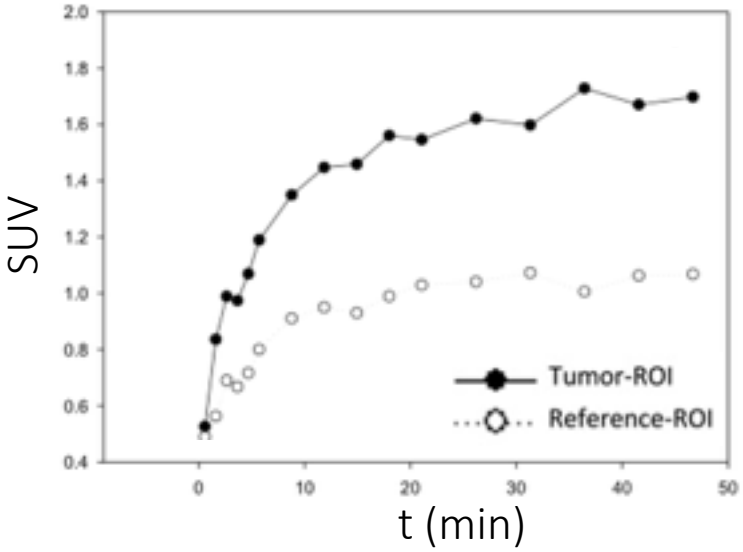
Galldiks et al., 2012 J Nucl Med
Romagna et al., 2016 Radiat Oncol
Ceccon et al., 2017 Neuro Oncol



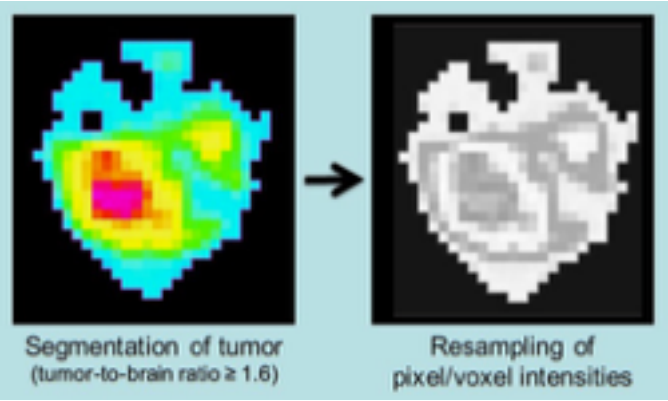




Radiation necrosis, occured 9 months after radiosurgery (BM of a NSCLC)



Radiomics



Lohmann et al., 2018 Sci Rep

- it allows the high-throughput extraction of a large amount of quantitative imaging data, usually from MRI or PET
- Assumption: The microstructure of a lesion depends on the underlying pathology and is reflected in subtle imaging differences
  - in many cases, these differences cannot be detected by means of human perception
- one Radiomics method is the extraction of so-called textural features which quantitatively describe heterogeneity of a lesion
  - e.g., grey levels (contrast), uniformity (entropy), and spatial organization of voxels can be analyzed

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

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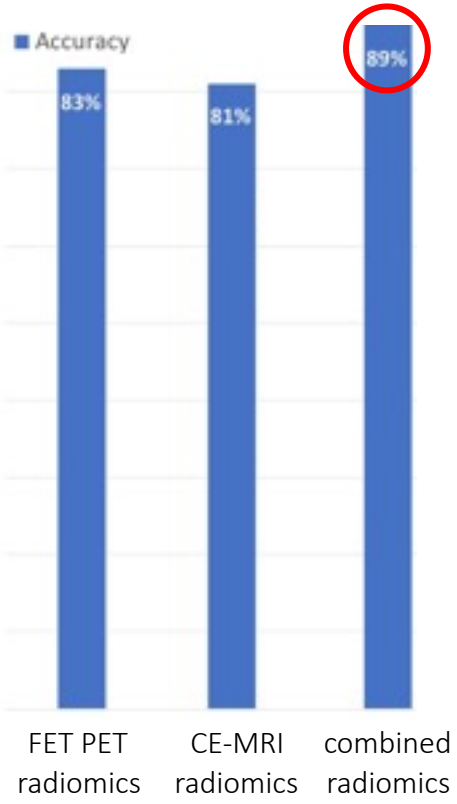
Epub ahead of print

Combined FET PET/MRI radiomics differentiates radiation injury from recurrent brain metastasis

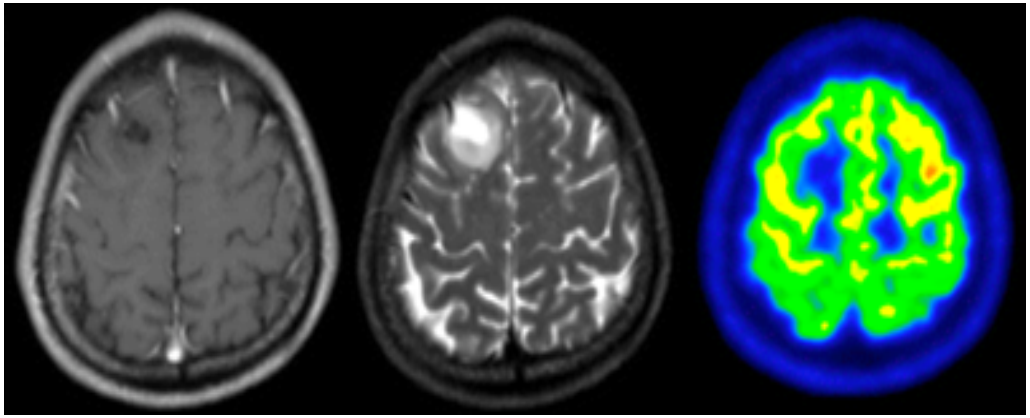
Philipp Lohmann [a, b], Martin Kocher [a, b, 1], Garry Ceccon [c], Elena K. Bauer [c], Gabriele Stoffels [a], Shivakumar Viswanathan [a], Maximilian I. Ruge [b], Bernd Neumaier [a], Nadim J. Shah [a, d], Gereon R. Fink [a, c], Karl-Josef Langen [a, e], Norbert Galldiks [a, c, f]

- PET and MRI textural feature analysis was performed in 52 previously irradiated patients with BM
- all patients had newly diagnosed contrast-enhancing lesions suspicious for local BM recurrence
- combined radiomics encodes more diagnostic information than either modality alone



How about FDG PET for the differentiation of radiation injury from BM recurrence ?

- Among PET tracers, FDG is the most widely studied and validated tracer to date
- Disadvantage: Tumor delineation in the brain is difficult due to physiological high glucose uptake of the cortex



CE-T1 T2 FDG

Diffuse Astrocytoma (WHO grade II)

FDG PET is unable
to delineate the tumor extension

Value of FDG PET for the differentiation of radiation injury from BM recurrence

	Chao et al., 2001 Int J Cancer	Belohlavek et al., 2003 EJNMMI	Chernov et al., 2005 Minim Invasive Neurosurg	Lai et al., 2015 AJNR	Hatzoglou et al., 2016 Neuro Oncol	Tomura et al. 2017 AJNR
n Patients	32	25	9	14	24	15
n Lesions	36	57	9	14	26	18
Tracer	FDG	FDG	FDG	FDG	FDG	FDG
Sensitivity	65%	75%	50%	83%	82%	40%
Specificity	80%	94%	80%	75%	80%	50%
Accuracy	73%	84%	67%	79%	81%	45%
Threshold	visually	visually	visually	3.0 (SUV)	1.4 (TBR_{mean})	0.97 (TBR_{max})

FDG might be helpful, but there is a large variety of diagnostic accuracy and thresholds are not well defined

How about treatment-related changes derived from systemic therapy?

THE LANCET Oncology

Long et al., 2018

Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study

Tawbi et al., 2018

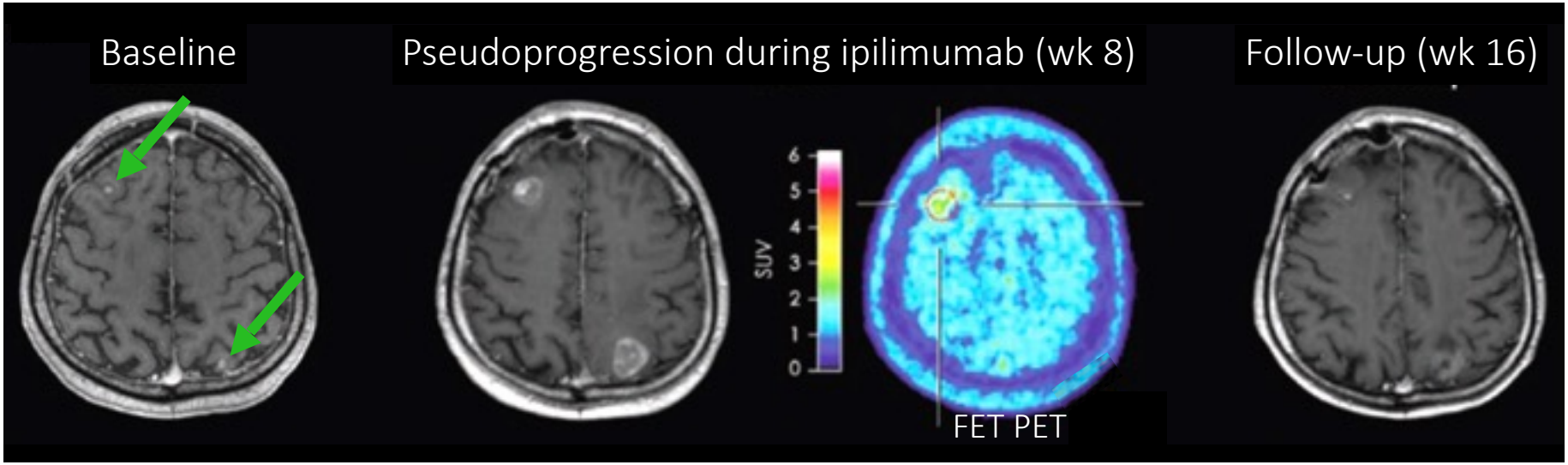
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Combined Nivolumab and Ipilimumab in Melanoma Metastatic to the Brain

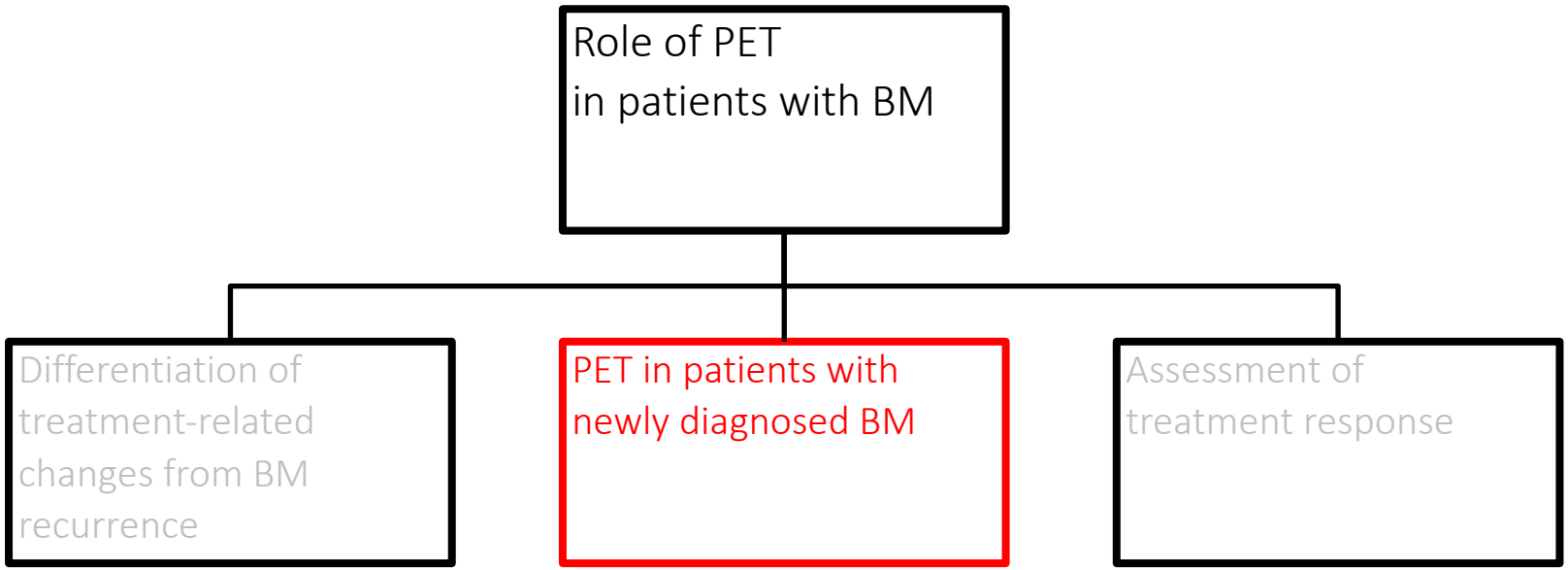
- Immunotherapy using checkpoint inhibitors is effective for melanoma brain metastasis treatment

- CLINICAL PROBLEM: Checkpoint inhibitor-related pseudoprogression
  - Okada et al., 2015 Lancet Oncol (iRANO)
  - Wolchok et al., 2009 Clin Cancer Res



- FET PET may detect pseudoprogression under checkpoint inhibitor blockade, indicating its potential for treatment monitoring
- in contrast to the progressive MRI, FET PET shows only minimal / no FET uptake
- In addition to MRI improvement at follow-up, the patient was clinically stable for more than 6 months

Kebir, Rauschenbach, Galldiks, et al., 2016 Neuro Oncol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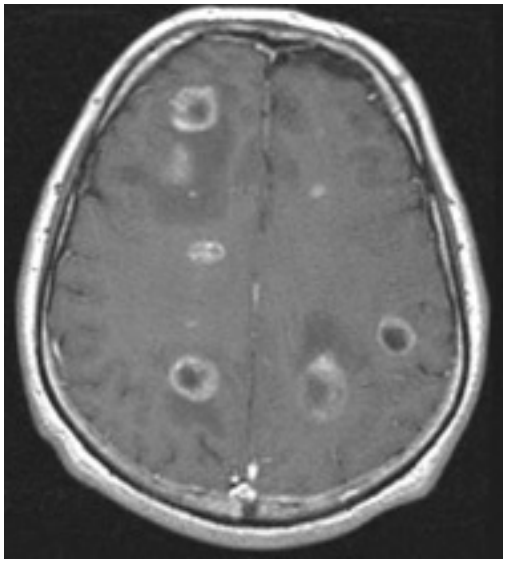
Contrast-enhanced MRI

- CE-MRI is the method of choice for BM detection
- MRI slice thickness should be 1 mm to avoid overlooking very small BM
- MRI sensitivity for BM detection is high, various efforts aimed to further improve sensitivity
  - injection of double-dose contrast medium*
  - use of ultra high field MRI (≥ 7 T)**



thin-slice CE-T1

*Ochi et al., 2014 Mag Reson Med Sci; **Noebauer-Huhmann et al., 2015 Eur Radiol

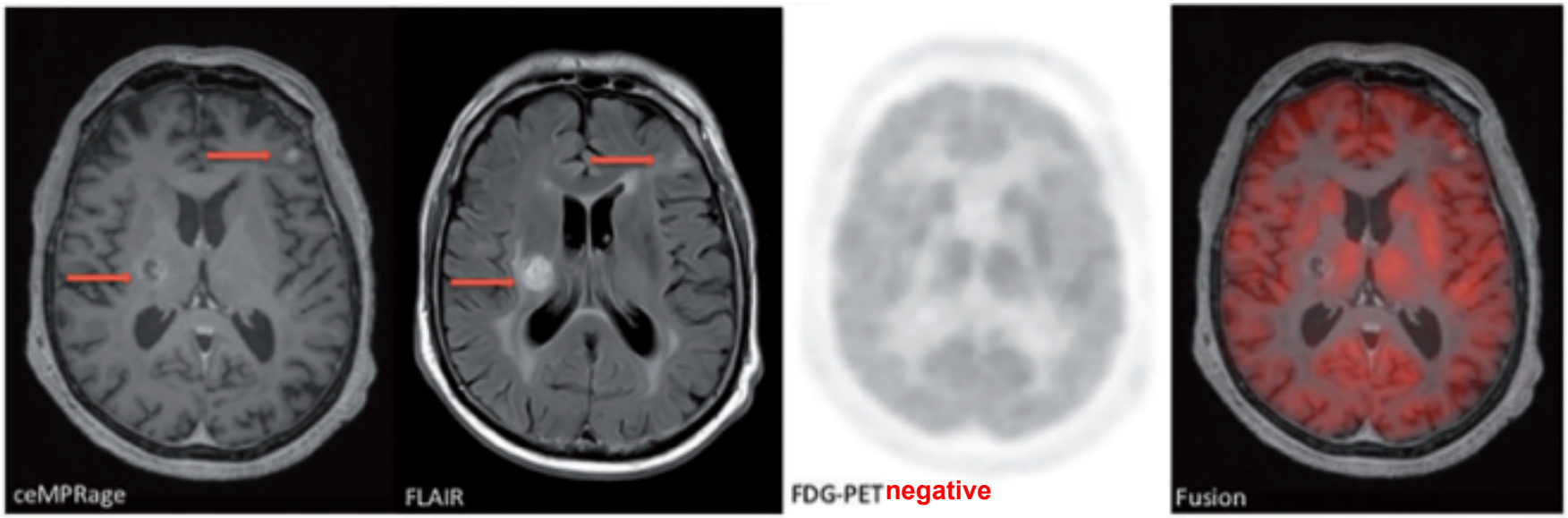
How about the value of

FDG PET

for the detection of BM?

FDG PET has a low sensitivity for the detection of BM

Deuschl et al., 2017 *Acta Radiol*



- A recent meta-analysis revealed that the sensitivity of FDG PET for BM detection is only 21%
  - n=941 patients; Li et al., 2017 Oncotarget

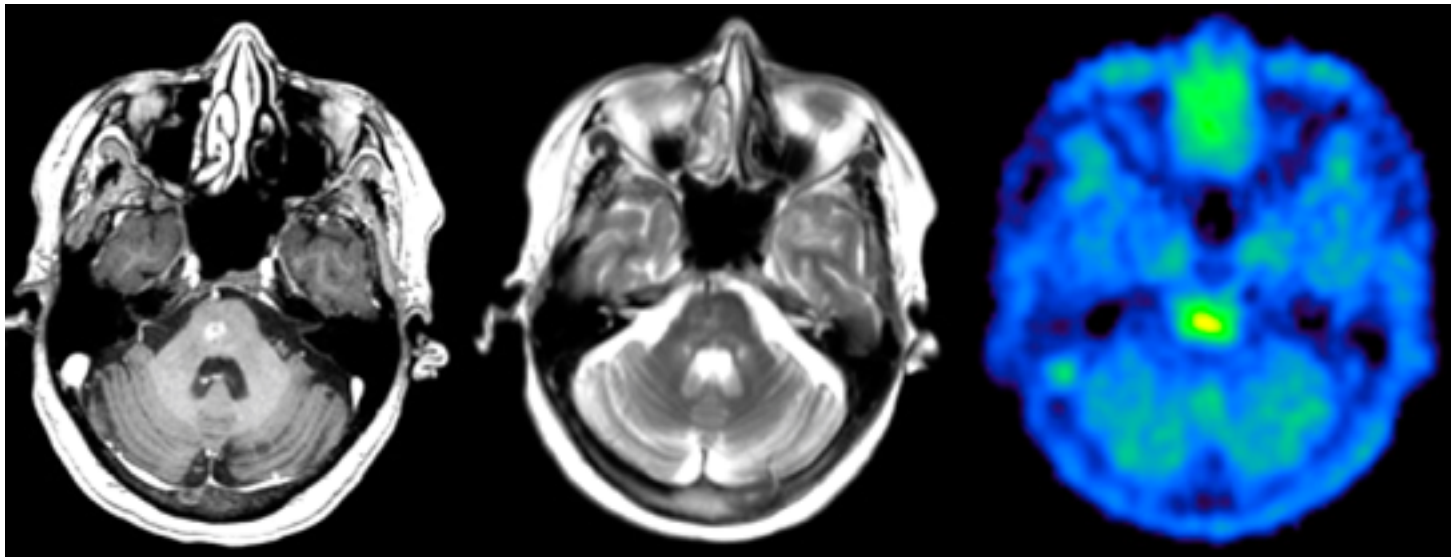
^{18}F-FET PET Uptake Characteristics in Patients with Newly Diagnosed and Untreated Brain Metastasis

Marcus Unterrainer[1], Norbert Galldiks[2,3], Bogdana Suchorska[4], Lara-Caroline Kowalew[1], Vera Wenter[1], Christine Schmid-Tannwald[5], Maximilian Niyazi[6,7], Peter Bartenstein[1], Karl-Josef Langen[2,8,9], and Nathalie L. Albert[1]

2017; 58: 584-89

JNM
The Journal of Nuclear Medicine

- Pilot study in patients with newly diagnosed BM (n=45)
- the sensitivity of FET PET for BM detection was 90% and clearly higher than that of FDG PET
  - in cases with negative FET PET (n=5), BM were smaller than 1 cm



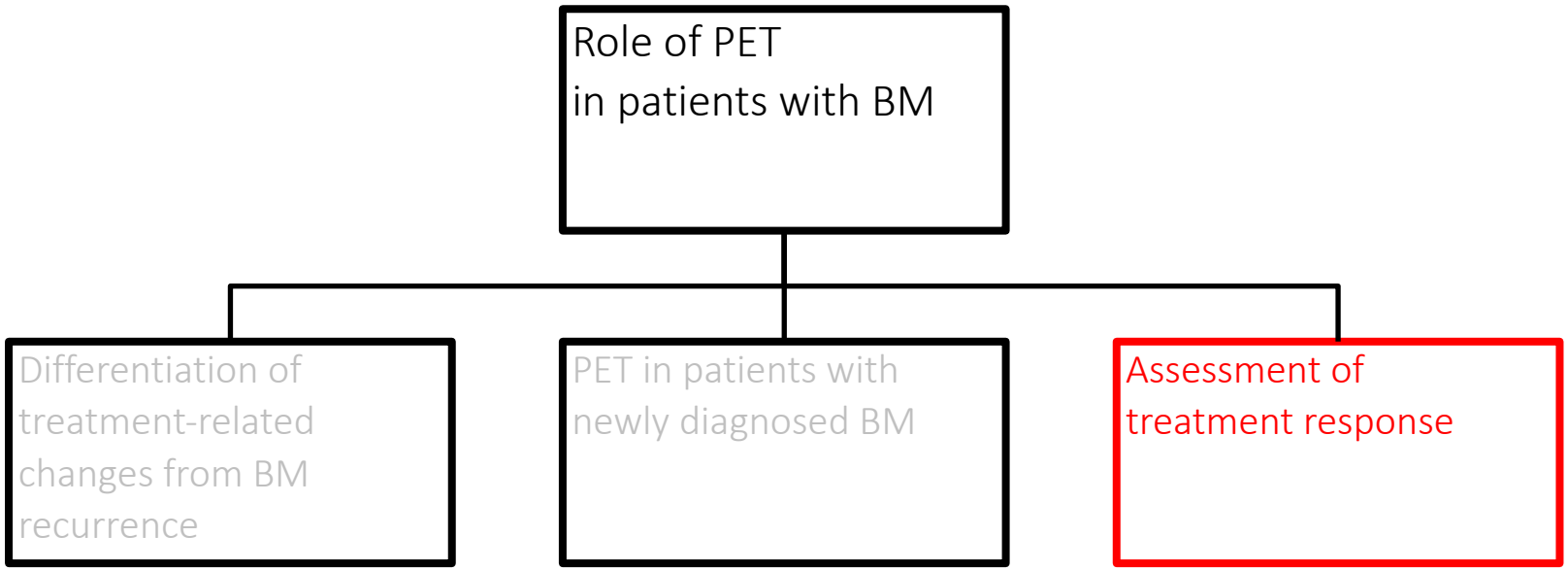
NSCLC-BM

Which other PET indications in patients with newly diagnosed BM have been evaluated?

- Prediction of BM origin
  - is of clinical relevance, particularly in CUP
  - depending on the originating primary tumor, FET uptake characteristics seem to be different (Unterrainer, Galldiks et al., 2017 J Nucl Med)

- Differentiation between BM and gliomas
  - glioblastomas seem to have higher metabolic activity (Kamson et al., 2013 Mol Imaging)

PET might be helpful, but the number of studies is very low and data are still premature


Role of PET
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Assessment of treatment response

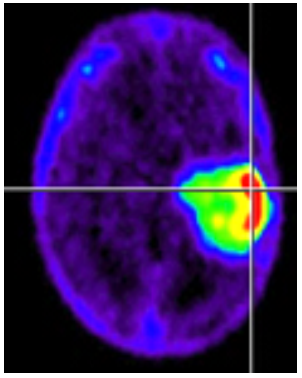
- CE-MRI is the method of choice
  - evaluation may be hampered by treatment-related changes
- Newer systemic treatment options such as targeted therapy and immunotherapy have other requirements on neuroimaging
- Imaging tools which provide additional information on tumor metabolism (e.g., amino acid transport) and tumor proliferation become increasingly important

frontiers in Oncology
2018; 8:18

Targeted Therapy and Immunotherapy Response Assessment with F-18 Fluorothymidine Positron-Emission Tomography/Magnetic Resonance Imaging in Melanoma Brain Metastasis: A Pilot Study

Nghi C. Nguyen[1], Melissa K. Yee[2], Abuzar M. Tuchayi[1], John M. Kirkwood[2], Hussein Tawbi[2,3] and James M. Mountz[1]**

FLT

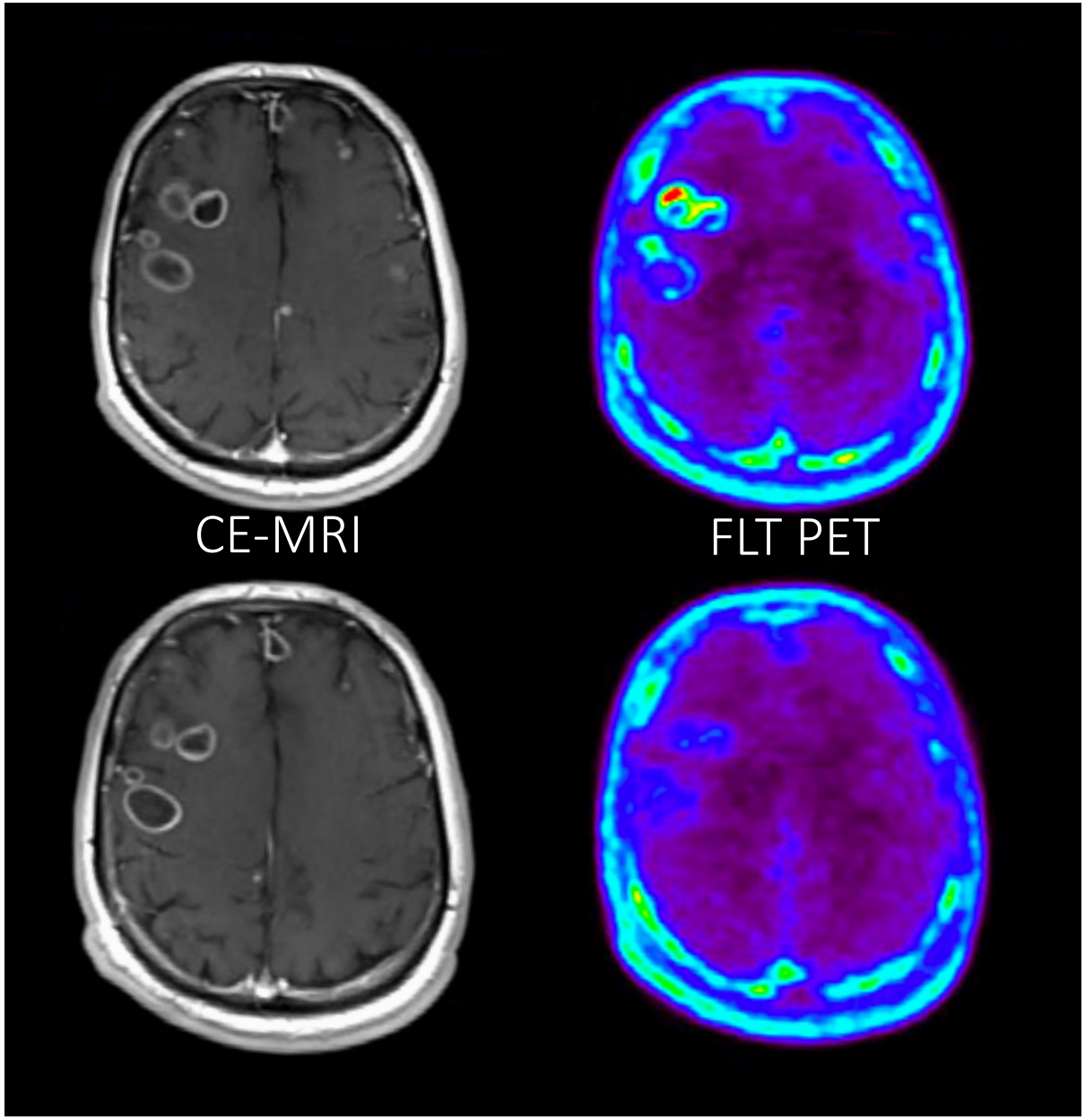


3´-deoxy-3´-^{18}F-fluorothymidine

- Pilot study, n=5 patients with 22 BM secondary to malignant melanoma were treated with BRAF/MEK inhibitors or checkpoint inhibitors
- Standard MRI and FLT PET was performed at baseline and after 3-4 treatment weeks
- Responding patients showed a clear decrease of proliferative activity, whereas MRI findings were almost unchanged
  - PET responders were clinically stable for > 12 months

- PET tracer designed to assess cellular proliferation
- Principle: the radiolabelled DNA component thymidine is integrated into DNA
- excellent tumor/background contrast

Patient with multiple melanoma brain metastases (BRAF-mutated)



Baseline

Dabrafenib + Trametinib over 3 weeks

Follow-up

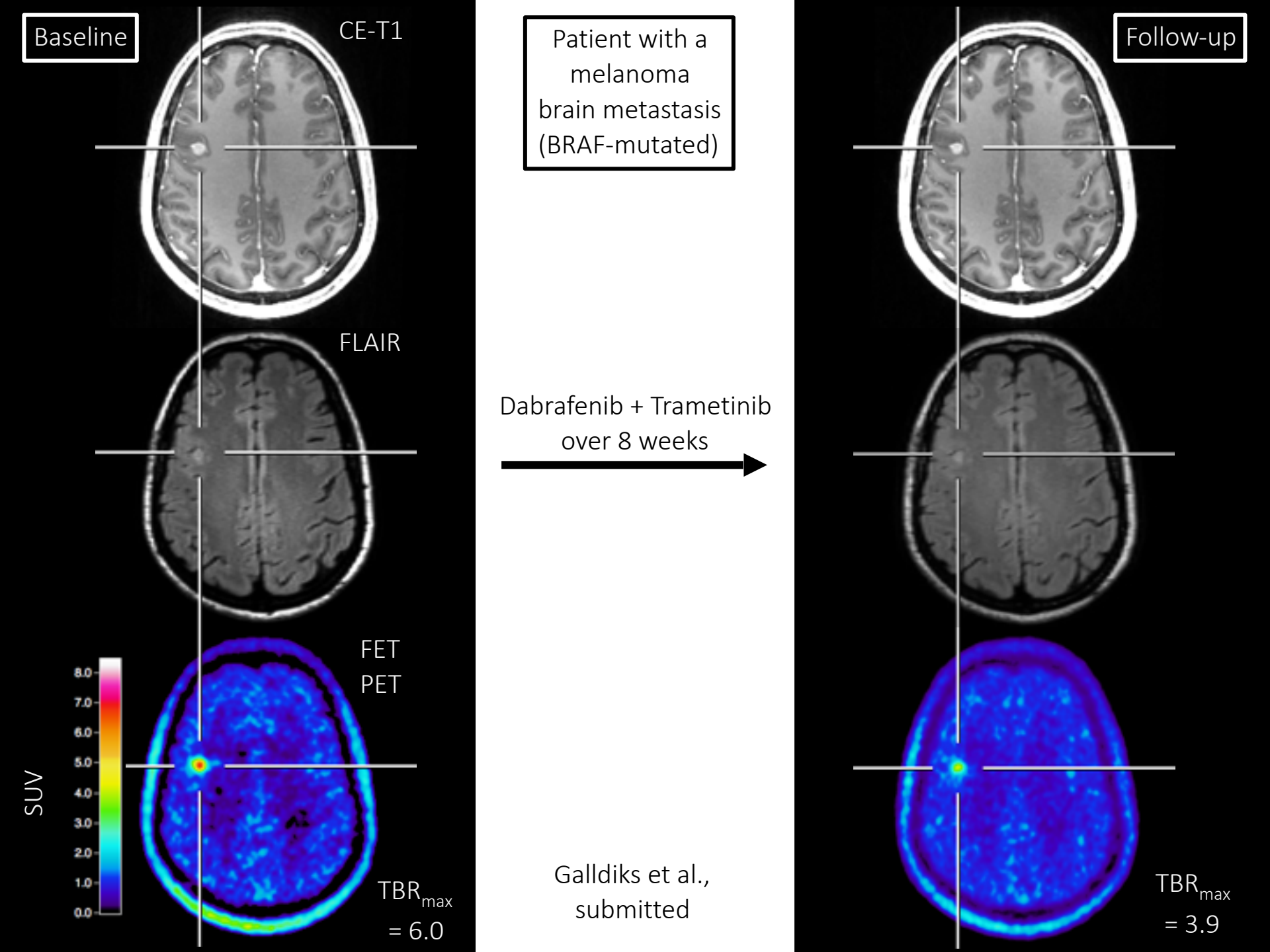
Significant reduction of proliferation, anatomical MRI almost unchanged

Nguyen et al., 2018 Front Oncol

Amino acid PET for the assessment of treatment response?

- for gliomas, the additional value of this technique has been demonstrated in several studies*
- in patients with BM there are currently no studies available
- Single reports suggest that amino acid PET is valuable for this indication

*e.g., Galldiks et al., 2012 J Nucl Med; Roelcke et al., 2016 Neuro Oncol; Suchorska et al., 2018 J Neurooncol; Galldiks et al., 2018 Eur J Nucl Med Mol Imaging


Baseline
CE-T1
FLAIR
FET
PET
SUV
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
TBR$_{max}$
= 6.0
Patient with a melanoma brain metastasis (BRAF-mutated)
Dabrafenib + Trametinib over 8 weeks
Galldiks et al., submitted
Follow-up
TBR$_{max}$
= 3.9

Summary

- the differentiation of radiation injury from BM recurrence using amino acid PET is currently evaluated best
  - in contrast to FDG PET, amino acid PET shows consistently a high diagnostic accuracy
  - data were derived mainly from retrospective studies performed in single centers, in approx. only 1/3 of patients diagnoses could be confirmed histologically
- various PET agents show promising results in terms of treatment response assessment
  - up to now, a relatively low number of patients was evaluated
- At present, PET in newly diagnosed BM plays only a minor role

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Dept. of Neurology
- V. Dunkl, G. Ceccon, C. Tscherpel, E.K. Bauer, J. Steger, J.-M. Werner, J. Kraus, J. Rosen, M. Wollring

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