L'imaging nel follow up : Il ruolo della medicina nucleare

Dott.ssa Donatella Riolo
Specializzanda Medicina Nucleare

SAPIENZA
UNIVERSITÀ DI ROMA

FACOLTÀ DI MEDICINA
E PSICOLOGIA

Approccio multidisciplinare alle neoplasie maligne del SNC

Roma 31 Gennaio 2020

Indications for amino acid PET

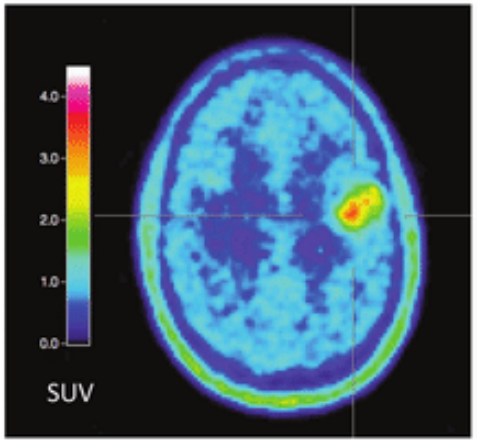
Suspected primary glioma on MRI → Resection or biopsy → Radiotherapy or chemotherapy or both → Maintenance therapy → Follow-up

Rationale for initial AA PET:
- Differentiation neoplastic vs. non-neoplastic tissue
- Delineation of tumor extent for resection planning
- „Hot-Spot" localization for biopsy planning
- Prognostication

Rationale for AA PET after surgery:
- Assessment of resection extent
- Planning of radiotherapy
- Baseline AA PET for monitoring of radio(chemo)therapy
- Prognostication

Rationale for AA PET within first 12 weeks after radio(chemo)therapy:
- Diagnosis of treatment-induced changes (e.g., pseudoprogression) versus treatment relapse
- Follow-up AA PET for monitoring of radio(chemo)therapy
- Baseline AA PET for adjuvant therapy monitoring

Rationale for AA PET during follow-up:
- Diagnosis of treatment-induced changes (e.g., radionecrosis) versus treatment relapse
- Follow-up AA PET for adjuvant therapy monitoring
- Delineation of tumor extent for resection planning



Pseudo-progressione

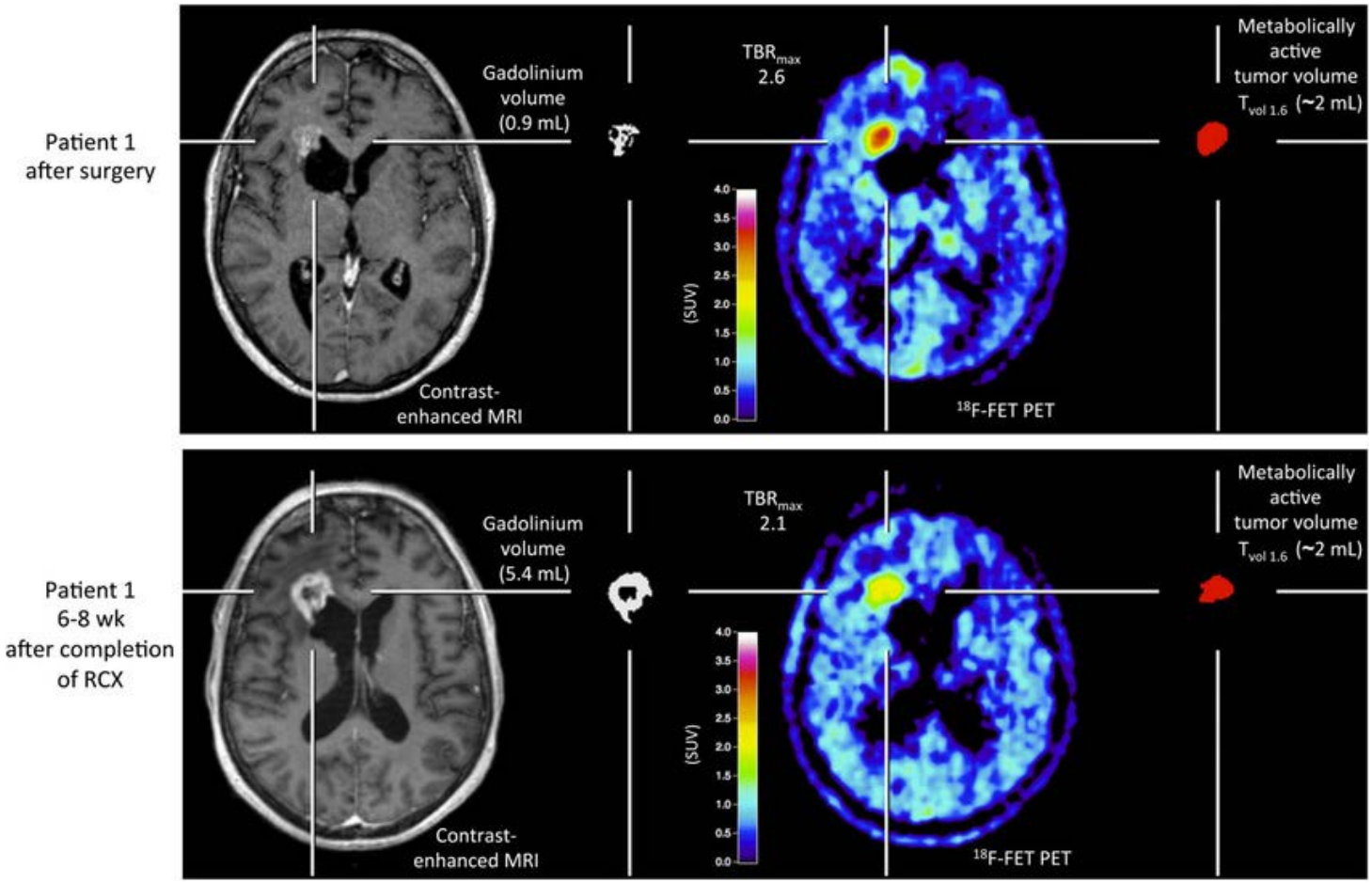
Represents instead mainly a subacute post-treatment reaction, which usually happens within 12 weeks post-RT.

In this scenario, MRI could give misleading information as pseudo-progression is characterized by increased lesion enhancement and/or edema, thus reproducing radiological findings of tumor progression and recurrence.

Typically, in case of glioblastomas, it occurs after combined chemo-irradiation treatment with temozolomide, which represents the current standard protocol.

However, pseudo-progression can be unmasked during further follow-up because of a stabilization or decrease in size of the lesion without any new treatment.

Pseudo-progressione



Patient example of pseudoprogression (patient 1). Brain imaging after surgery (upper; MRI-/FET-1) and 6–8 wk after completion of radiochemotherapy (lower; MRI-/FET-3). Contrast-enhanced MRI with corresponding Gd-volume is shown on left and 18F-FET PET with corresponding Tvol 1.6 on right. Enlargement of Gd-volume on MRI after 6- to 8-wk completion of RCX (lower) is suggesting tumor progression, whereas 18F-FET PET indicates responder with decreasing amino acid uptake (reduction of TBRmax) and unchanged Tvol 1.6. Patient had favorable outcome, with PFS of 14.1 and OS of 16.1 mo.

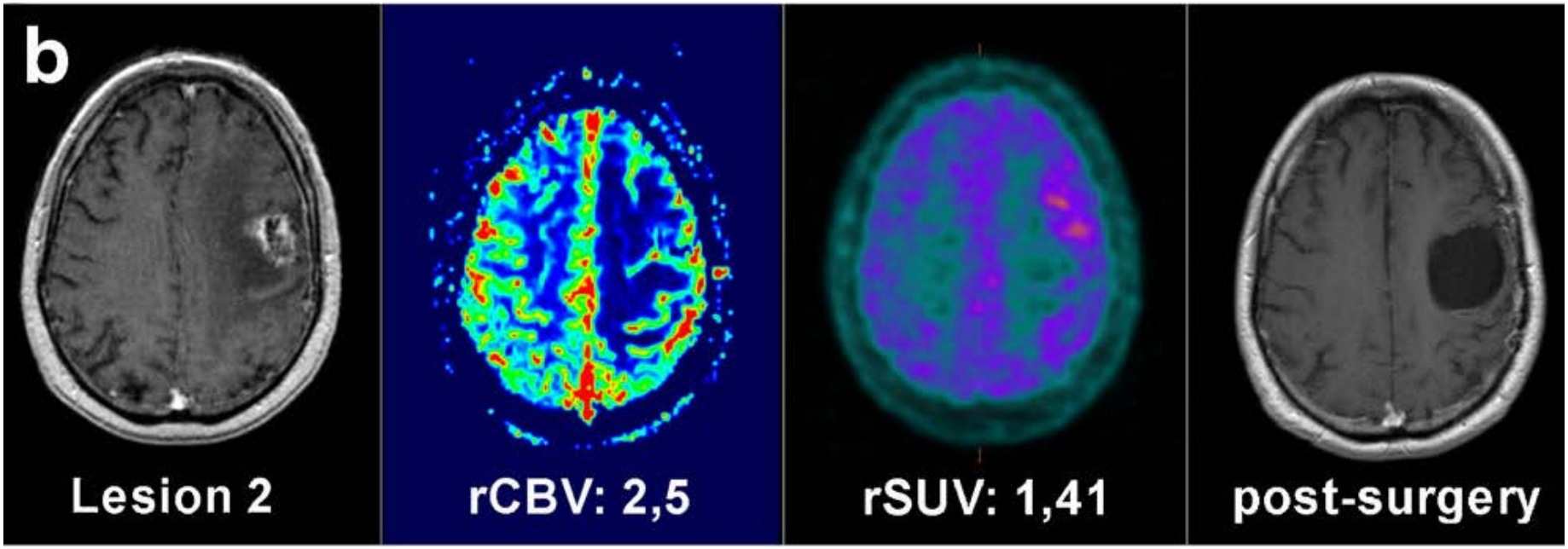
Radionecrosi

Usually represents a later complication that manifests within six months but it can also happen within years after standard RT.

From a radiological point of view, on MRI, radiation necrosis is associated with edema, it shows contrast enhancement and presents mass effect, next to original lesion.

More in particular, both CT and MRI rely on BBB damage, which is usually present in higher grades (III and IV) and absent in lower grades (I and II), and morphological characteristics such as presence of necrosis and vascularity.

Radionecrosi



Left frontal lesion showing increased rCBV and low rSUV values. The lesion was surgically excised, confirming a diagnosis of RN (viable neoplastic cells <20% in the surgical specimen). The postsurgical follow-up image shows successful removal of the lesion. The patient was still free of progression 25 months after surgery.

Pseudo-risposta

Recently, anti-VEGF agents have been utilized for high-grade glioma treatment in several trials.

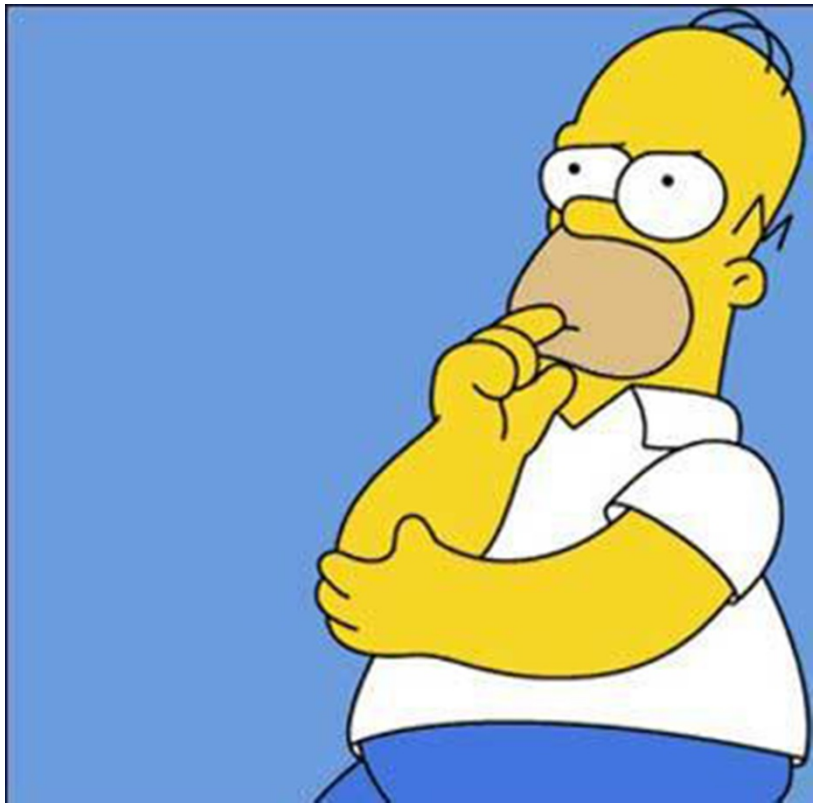
Anti-VEGF agents produce "normalization" of the blood-brain barrier, sometimes within hours.

On imaging, there is a reduction in the degree of enhancement by the tumor and a decrease in the surrounding edema on fluid-attenuated inversion recovery (FLAIR).

Such an imaging appearance, which imitates a favorable treatment response, is termed "pseudoresponse" because this is due to alterations in vascular permeability instead of tumor response to treatment.

So, this radiologic response should be interpreted with caution.

Quale radiofarmaco utilizzare?



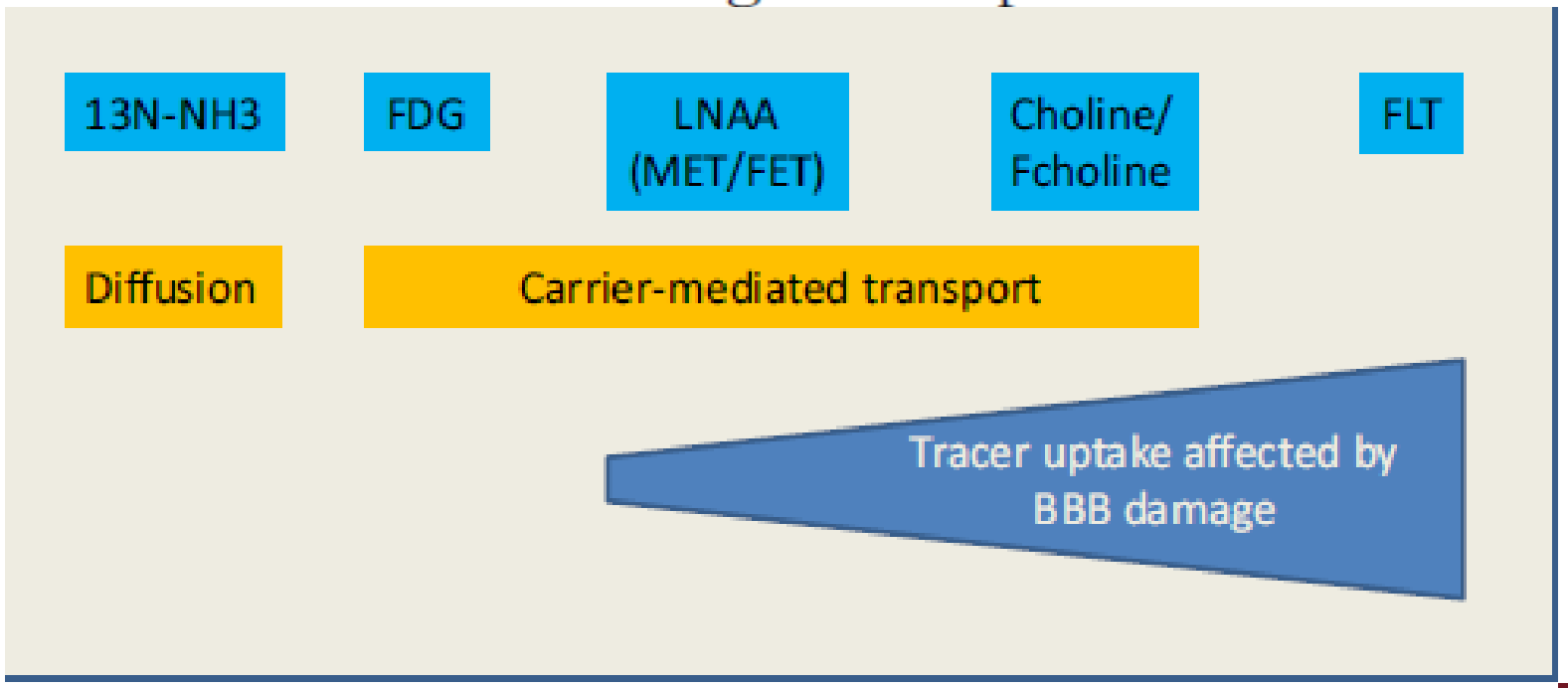
Quale radiofarmaco utilizzare?

- **Metabolismo glucidico**: **2-deoxy-2[^{18}F]fluoro-D-glucosio (FDG)**
- **Metabolismo lipidico di membrana:^{18}F-Colina**;
- **Sintesi DNA**: **^{18}FLT** (**Fluorotimidina**);
- **Analoghi degli aminoacidi**: **^{18}F-fluoro-L-dihydroxy-phenylalanina (F-DOPA); ^{18}F-fluoroethyl-tyrosina (FET), ^{18}F-EM (Fluorometiltirosina)**, **^{11}C-methionina.**

Semin Nucl Med. 2017 Jan;47(1):5-17.

Brain Tumors: An Update on Clinical PET Research in Gliomas.

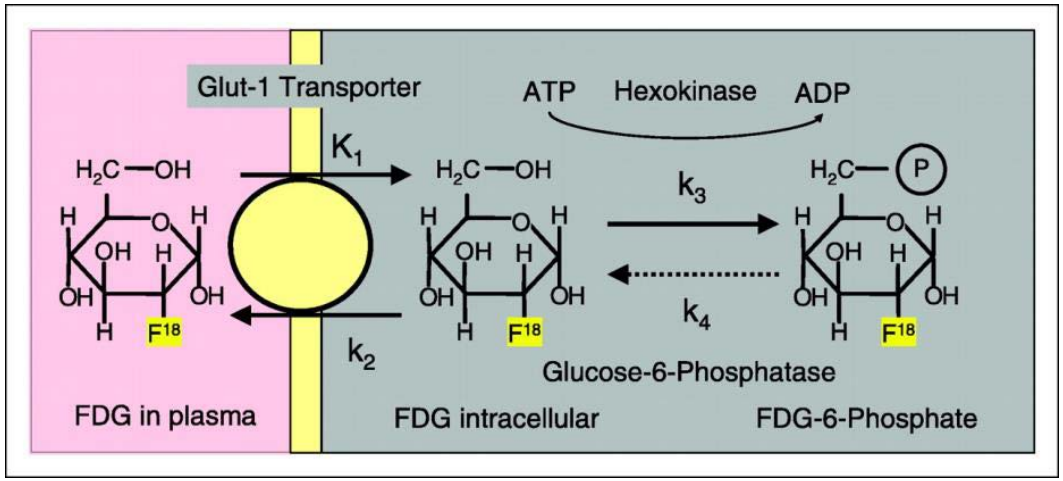
There are two main mechanisms that characterize the essential features of brain tumor tracers and they are as follows: transport across the blood-brain barrier and metabolism in tumor cells. Typically, the latter is supposed to provide differentiation and specificity, but for most tracers the former is the main factor determining tracer uptake into the tumor



J Neurosci Res. 2011 Dec; 89(12): 10.1002/jnr.22738.

GLUT-1 GLUCOSE TRANSPORTERS IN THE BLOOD-BRAIN BARRIER: DIFFERENTIAL PHOSPHORYLATION

Glut1 principale trasportatore FDG alla BEE

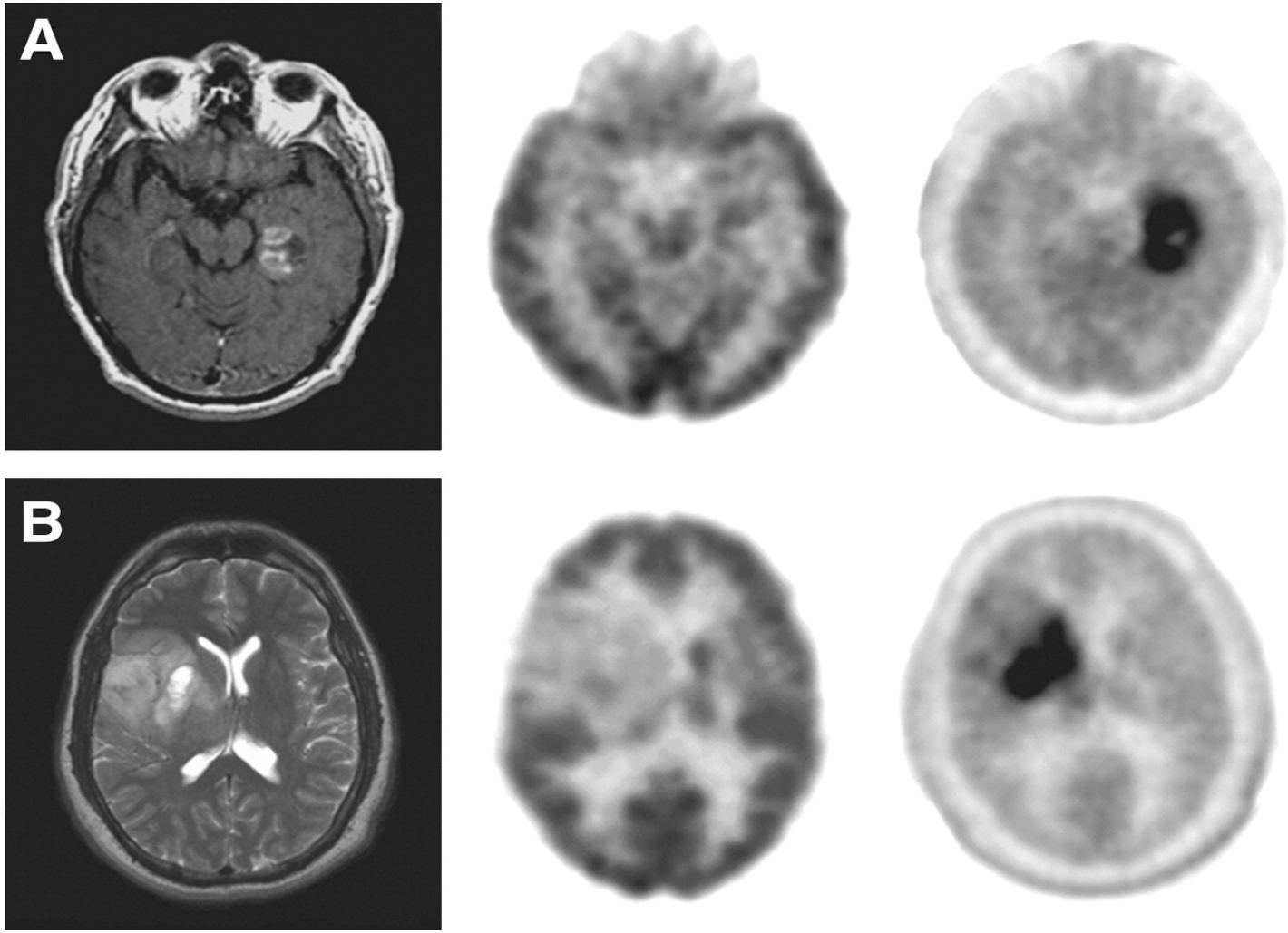


Aumento attività esochinasica anche nei gliomi

J Nucl Med **June 2006** vol. 47 no. 6 **904-911**

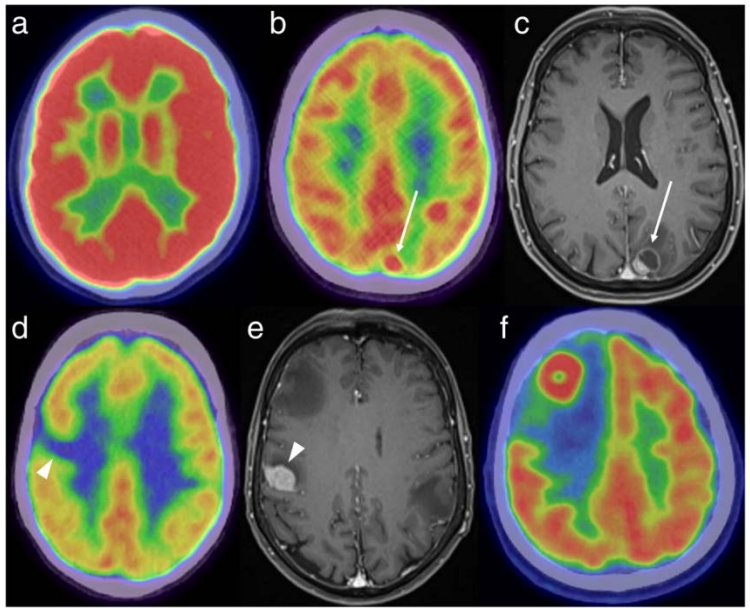
^{18}F-FDOPA PET Imaging of Brain Tumors: Comparison Study with ^{18}F-FDG PET and Evaluation of Diagnostic Accuracy

F-FDG was the first oncologic application of PET. However, recent studies demonstrated its diagnostic limitations. Because of the high physiologic rate of metabolism of glucose by normal brain tissue, the detectability of tumors with only modest increases in glucose metabolism, such as low-grade tumors and, in some cases, recurrent tumors, is difficult.



MRI (left), ^{18}F-FDG PET (middle), and ^{18}F-FDOPA PET (right) of newly diagnosed tumors. (A) Glioblastoma. (B) Grade II oligodendroglioma

How we read: the combined use of MRI and novel PET tracers for the characterisation and treatment planning of masses in neuro-oncology



FDG-PET demonstrating normal high background uptake (a) - uptake is higher in the grey matter than in the white matter. A focus of high FDG uptake in the left parietal lobe (b, white arrow) corresponds to a mixed solid/cystic metastasis on the post-contrast MRI (c). An area of low uptake (d, white arrowhead) can also be due to a metastasis, as demonstrated on the corresponding MRI (e). FDG-PET in another patient (f) shows an FDG-avid mass in the right frontal lobe with surrounding photopaenia, consistent with oedema. Histology confirmed a solitary metastasis from a lung primary

Clin Transl Imaging (2017) 5:209–223

Amino acid PET and MR perfusion imaging in brain tumours

These radiolabelled amino acids are not incorporated into proteins; nevertheless, their uptake mechanisms are highly efficient, leading to very favourable tumor-to-background ratios.

The uptake of radiolabelled amino acids is based on the expression of the Na-independent large neutral amino acid transporters on the cell surface of tumor cells, namely, LAT1 and LAT2.

This mechanism is independent from blood–brain barrier permeability; therefore, amino acid probes are able to depict non contrast-enhancing brain tumor regions, which are a clear advantage over other PET tracers, such as 30-deoxy-30- [^{18}F]fluorothymidine (FLT) and ^{18}F-Fluorocholine (FCH). MET and FDOPA uptakes are thought to be largely due to LAT1, while FET is transported by both LAT1 and LAT2.

Clin Transl Imaging (2017) 5:209–223

Amino acid PET and MR perfusion imaging in brain tumours

System L amino acid transporters (such as LAT1, LAT2, LAT3, and LAT4) transport a variety of neutral amino acids:

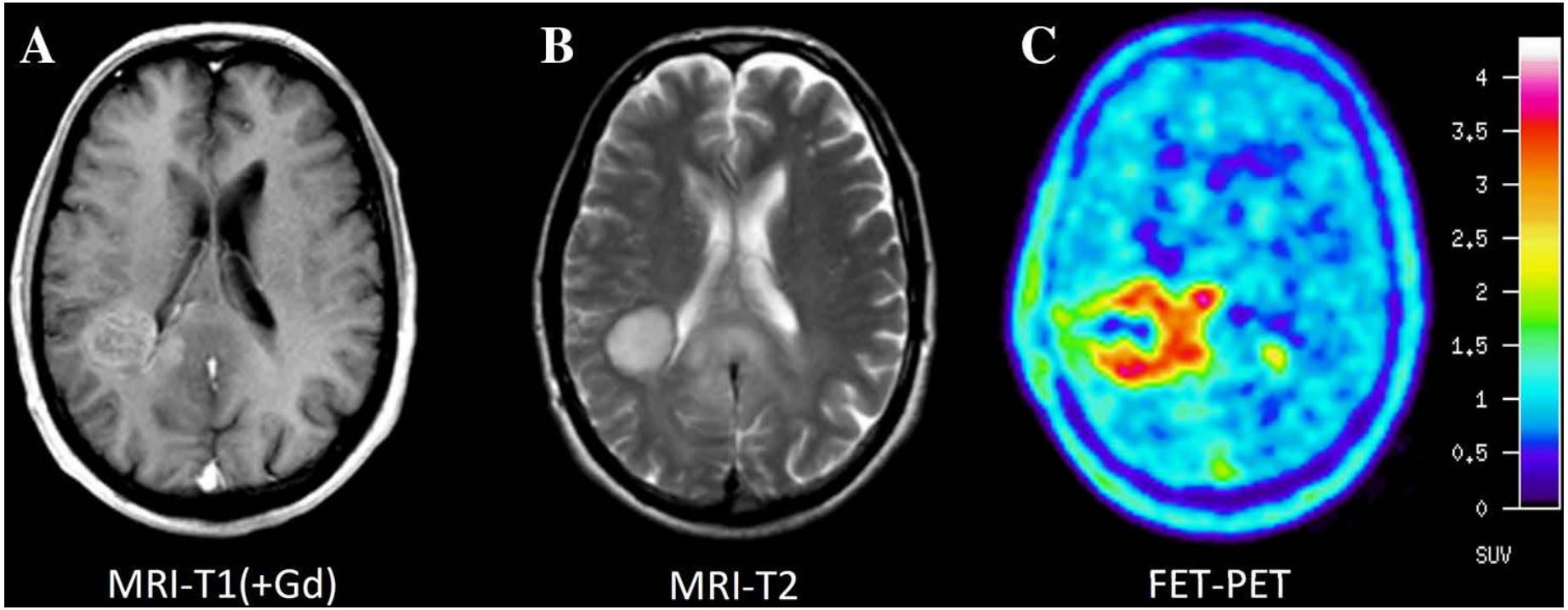
LAT1 is widely expressed in primary human cancers and cancer cell lines and plays an essential role in the survival and growth of tumors

LAT2 is predominantly expressed in other cell types and carries small neutral amino acids

LAT3 and LAT4 have a narrower substrate selectivity (preferring phenylalanine)

Clin Transl Imaging (2017) 5:209–223

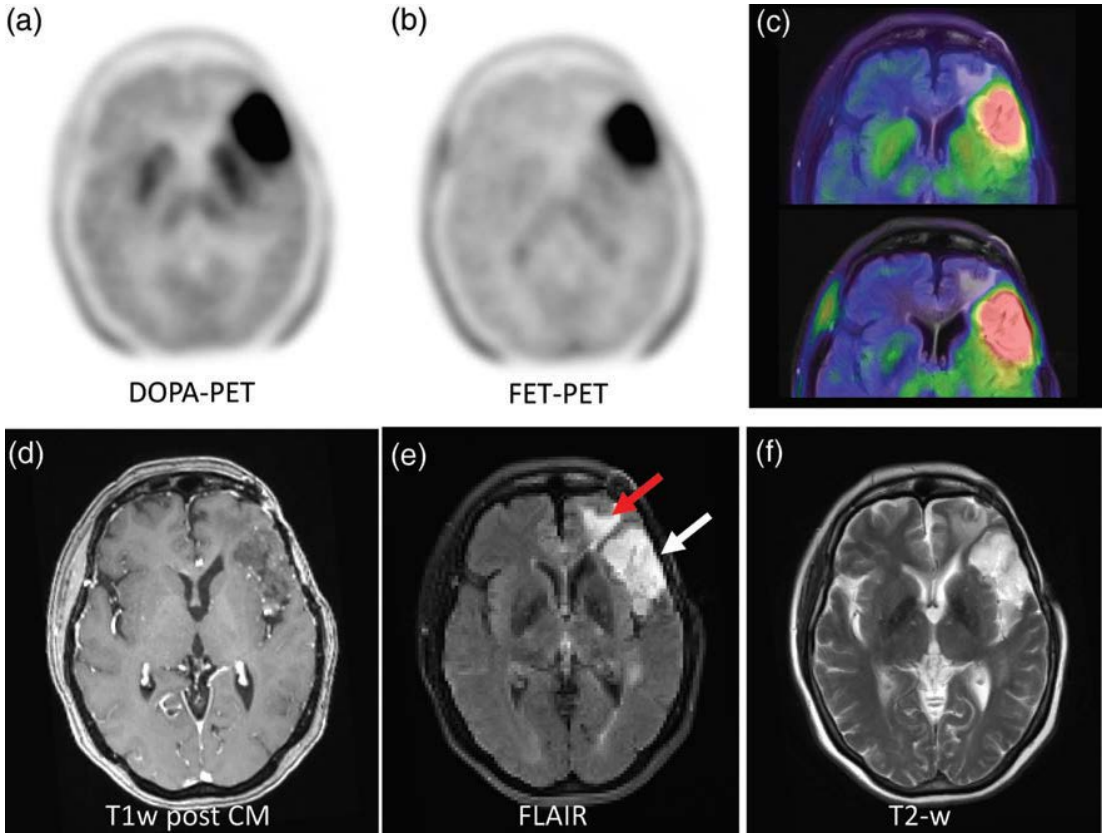
Amino acid PET and MR perfusion imaging in brain tumours



Comparison of MRI and FET-PET of patient with an anaplastic astrocytoma WHO grade III.
(A-B) Contrast-enhanced T1-weighted MRI shows pathological contrast enhancement in the vicinity of the posterior horn of the right ventricle and corresponding signal abnormalities in the T2-weighted image
(C) FET PET detects metabolically active tumor tissue extending beyond the abnormalities in MRI

Neuro-Oncology 16(3), 434–440, 2014

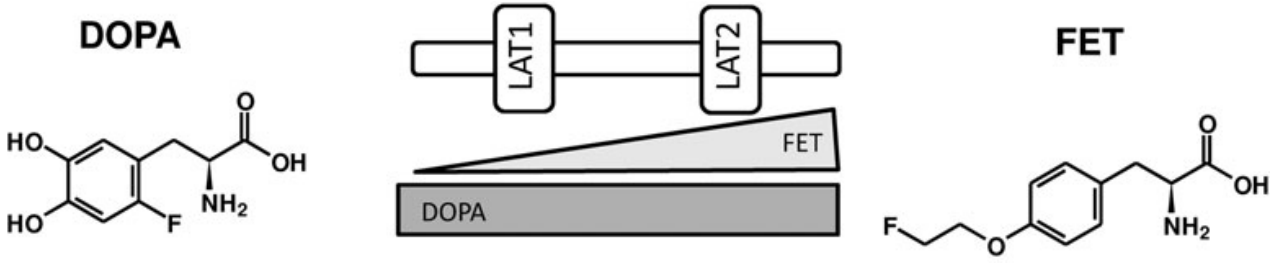
Intra-individual comparison of 18F-FETand 18F-DOPA in PET imaging of recurrent brain tumors



A participant with low-grade glioma, which is rarely delineable in contrast-enhanced T1w (d). The FLAIR (e) and T2 (f) weighted sequences demonstrate elevated signal intensity in the anterior temporal (e, white arrow) and the lateral frontal lobe (e, red arrow) but cannot differentiate between tumor and edema. With both, DOPA (a) and FET (b) PET, the malignant tissue was equally demarcated as presented in the fusion images (c).

Neuro-Oncology 16(3), 434–440, 2014

Intra-individual comparison of 18F-FETand 18F-DOPA in PET imaging of recurrent brain tumors



L-3,4-Dihydroxy-6-18F-fluoro-phenyl-alanine

- Superior contrast tumor-to-blood
- Peaks 8 min p.i. for Glioma and 10 min p.i. for Astrocytoma (imaging 10-20 min p.i. independent of tumor grading)
- Multi-targeted molecule, also suitable for movement disorders, carcinoids, pheochromocytoma/paraganglioma.
- Not suitable for grading of recurrent tumors
- Premedication with Carbidopa is recommended to inhibit tracer metabolism

O-(2-18F-fluoroethyl)-L-tyrosine

- Superior contrast tumor-to-striatum
- Peaks 8-10 min. p.i for Glioma and 40 min. p.i. for Astrocytoma (time-point of imaging depends on tumor grading)
- Production efficancy
- Imaging based grading of recurrent tumors
- High in-vivo stability even without additional co-medication

Br J Radiol. 2018 Apr;
91(1084): 20170847

^{18}F-DOPA uptake parameters in glioma: effects of patients' characteristics and prior treatment history

- Age and gender have an impact on ^{18}F-DOPA physiological uptake. In particular, age showed a significant positive correlation with SUVbg, consistently with previous observations, and with the hypothesis of age-related differences in dopamine turnover.
- Overall, female showed higher background and basal ganglia uptake.
- Increased striatal and cortical dopaminergic activity had already been observed in female patients with Parkinson's disease, suggesting an implication of oestrogens in the regulation of dopamine metabolism.

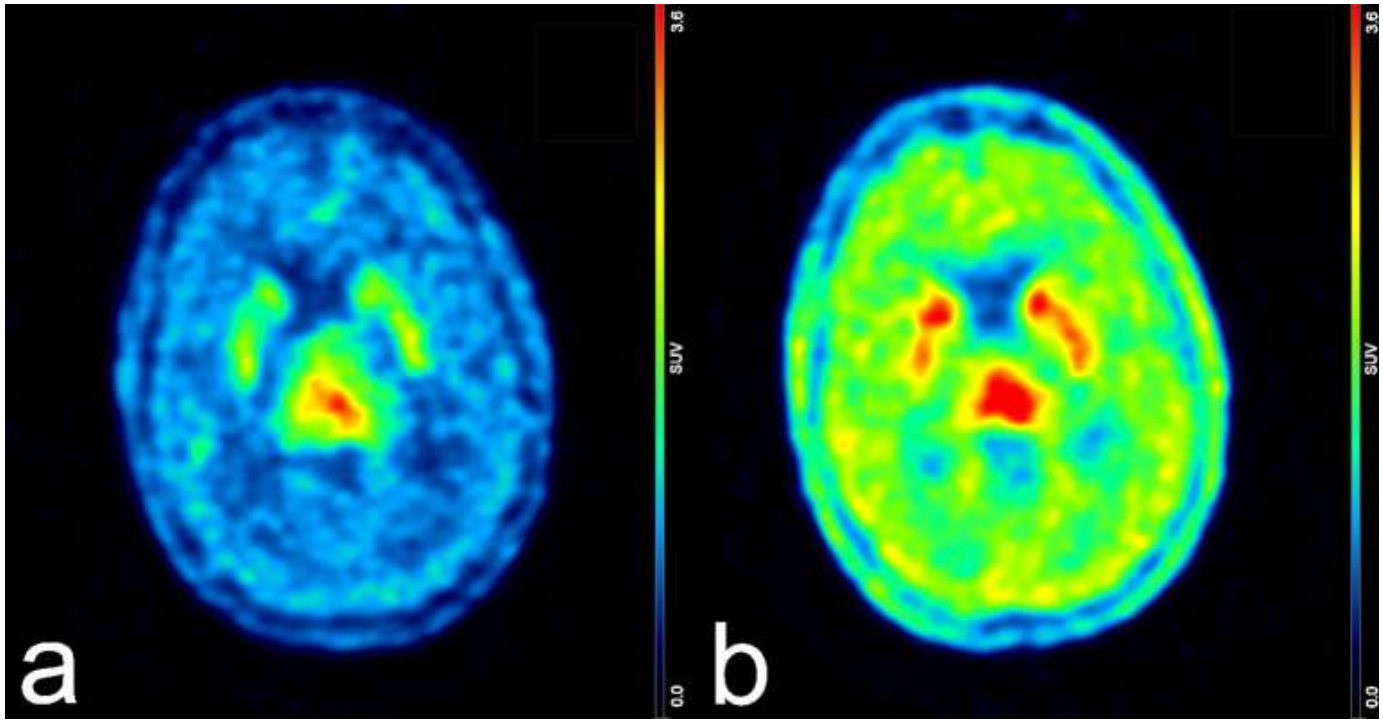
Br J Radiol. 2018 Apr;
91(1084): 20170847

^{18}F-DOPA uptake parameters in glioma: effects of patients' characteristics and prior treatment history

- TMZ chemotherapy induces prominent changes in physiological ^{18}F-DOPA uptake.
- In particular, the uptake of cortical structures, including both grey and white matter, is significantly reduced in patients under TMZ treatment compared to patients who discontinued TMZ more than 1 month before the PET/CT examination.
- These effects of TMZ treatment on physiological uptake were significant in female subjects only

Br J Radiol. 2018 Apr;
91(1084): 20170847

^{18}F-DOPA uptake parameters in glioma: effects of patients' characteristics and prior treatment history



Example of variations of ^{18}F-DOPA uptake induced by TMZ chemotherapy. The left panel (a) represents the brain PET scan of a female patient with a high-grade astrocytoma acquired during the course of TMZ treatment. SUVbckgr, SUVbg and TBR were 0.87, 1.86 and 2.91, respectively. The right panel (b) shows the same patient imaged 3 years later, after conclusion of chemotherapy. Notably, a "rebound effect" can be seen at sites of physiological uptake, whilst the opposite effect is observed for TBR. In fact, SUVbckgr and SUVbg increased to 1.78 and 3.42, respectively, whereas TBR dropped to 2.19 despite an increase of SUV max from 3.62 to 5.47. Both images were scaled to the same maximum signal intensity. ^{18}F-DOPA, ^{18}F–fluoro-l–phenylalanine; PET, positron emission tomography; SUV, standardized uptake value; TBR, tumour-to-brain ratio; TMZ, temozolomide.

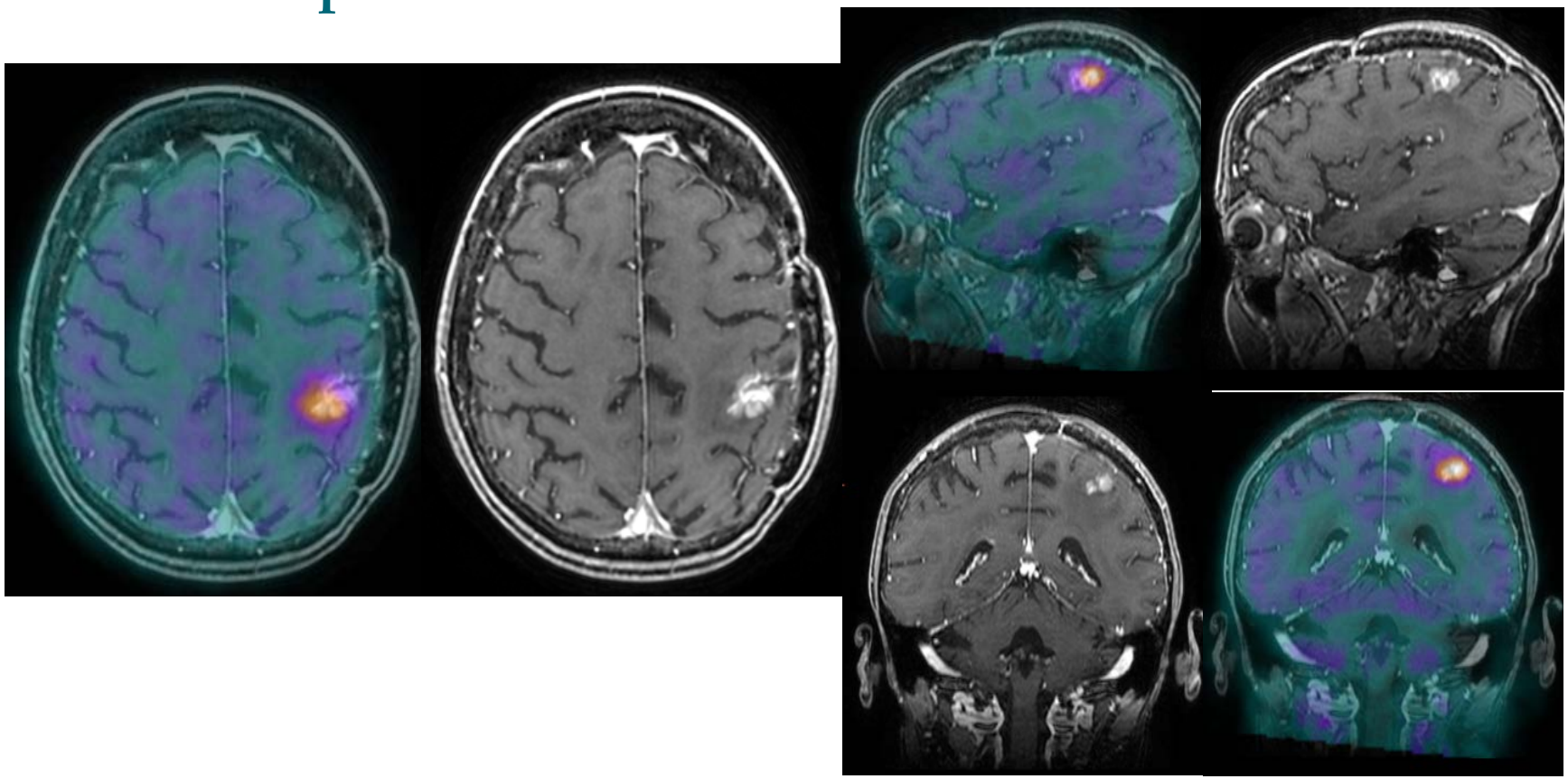
Eur J Nucl Med Mol Imaging (2015) 42:103–111

Accuracy of F-DOPA PET and perfusion-MRI for differentiating radionecrotic from progressive brain metastases after radiosurgery

- **The best diagnostic performance was obtained using the semiquantitative PET parameter maximum lesion to maximum background uptake ratio (SUVLmax/Bkgrmax).**

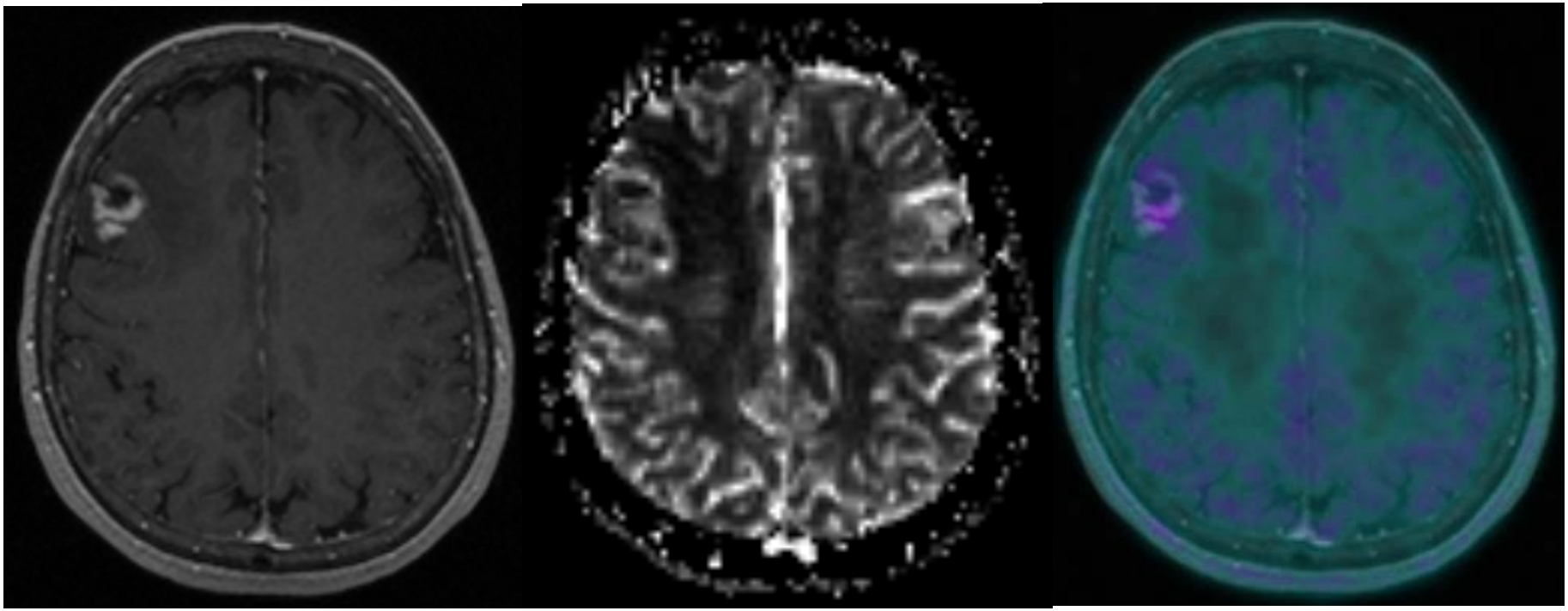
- **With a cut-off value of 1.59, a sensitivity of 90 % and a specificity of 92.3 % were achieved in differentiating RN from PD lesions (accuracy 91.3 %).**

Fusione ^{18}F-DOPA-PET e RM post-processing: la nostra esperienza



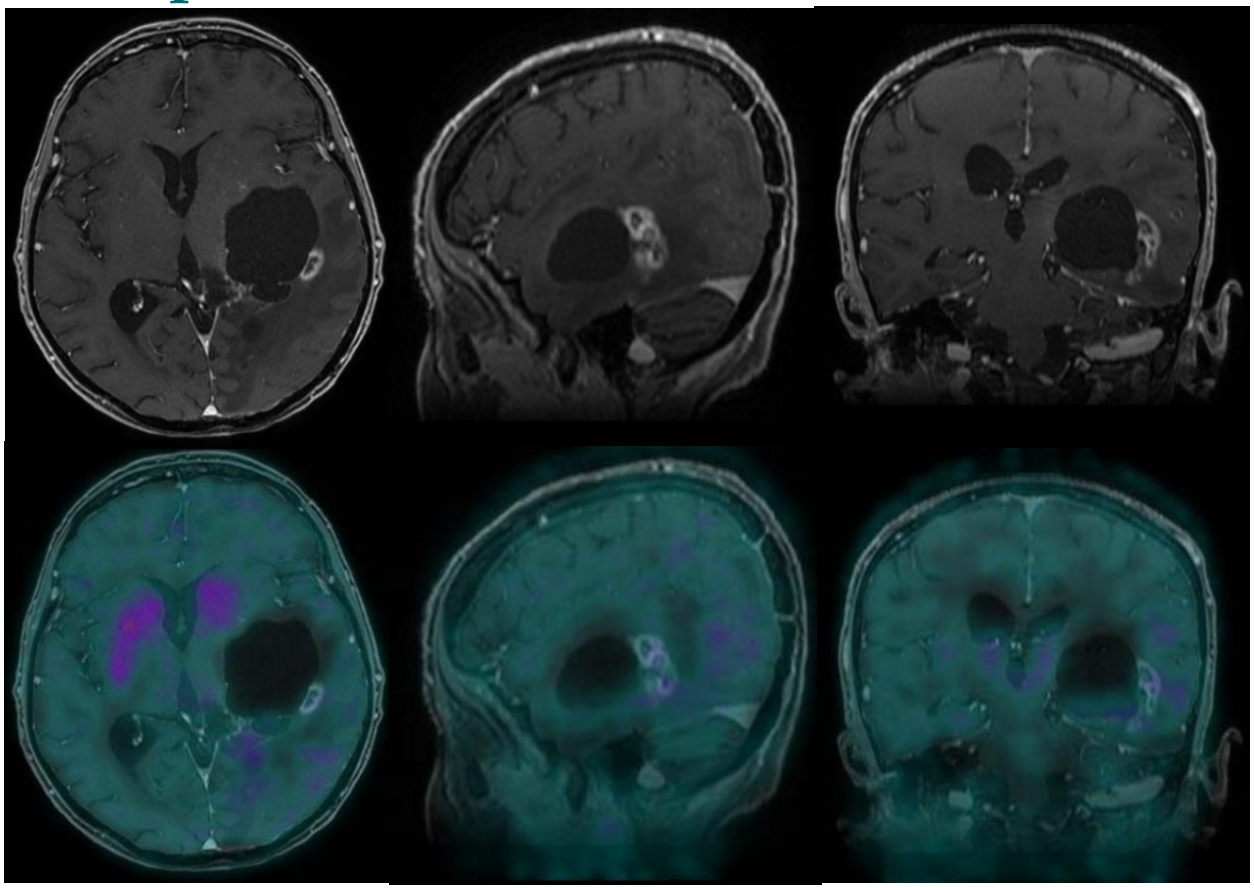
Pz con metastasi cerebrali da carcinoma mammario, sottoposta nel Dicembre 2012 a WBRT; nel 2016 comparsa di lesione parietale sinistra sottoposta a SRS in data 31/05/16; a Maggio 2017 intervento sulla lesione parietale sinistra, risultata radionecrosi. Ultima RM del 8/2/18 mostrava presenza di tessuto solido caratterizzato da discreto potenziamento post-contrastografico riferibile a residuo/recidiva di malattia. PET del 5/4/18.

Fusione ^{18}F-DOPA-PET e RM post-processing: la nostra esperienza



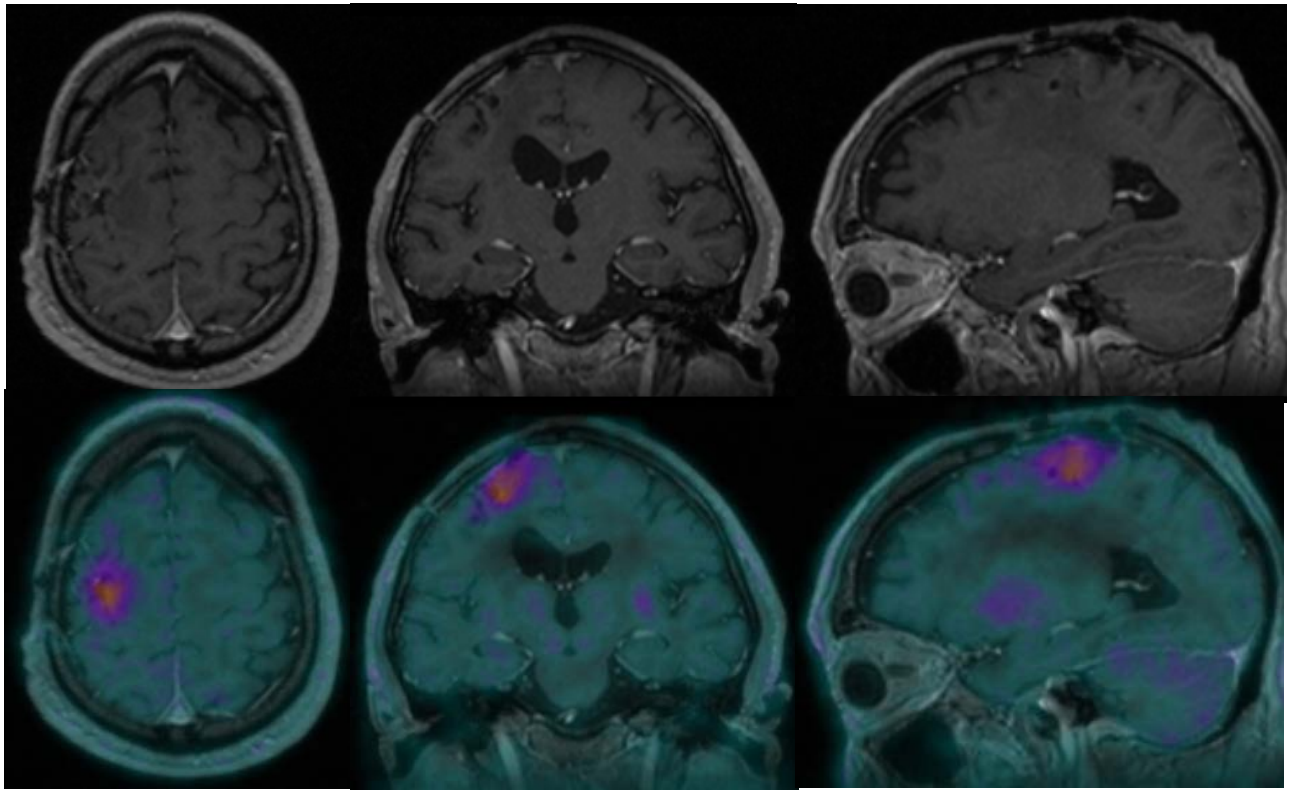
Paziente con metastasi cerebrale da NSCLC, trattata mediante SRS nel 2008. L'ultima RM del 12/09/2014: mostrava "modesto aumento del potenziamento della lesione cortico-sottocorticale frontale media dx con evidente incremento del CBV con aspetto compatibile con progressione di malattia". PET del 25/09/14. Ripete PET in data 11/05/17.

Fusione ^{18}F-DOPA-PET e RM post-processing: la nostra esperienza



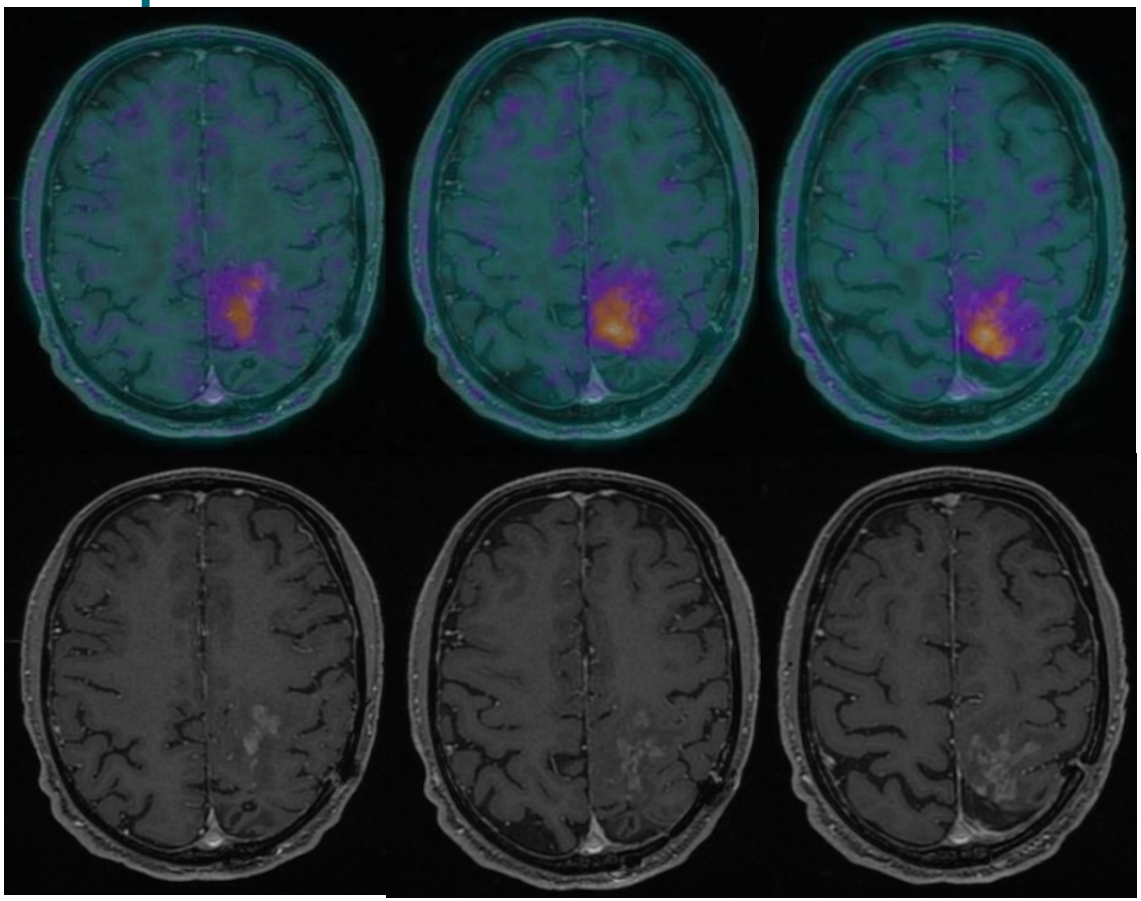
Paziente sottoposta a Dicembre 2013 ad asportazione di GBM in sede temporo-mesiale posteriore, cui segue radio-chemio concomitante + CHT per 2 anni. L'ultima RM del 19/01/17 mostrava «aumento delle dimensioni dell'area focale periferica e posteriore al cavo, a margini sfrangiati ed irregolari, con evidenza di presa di contrasto disomogenea e più netto nucleo di potenziamento contrastografico", nonché "aumento della perfusione di alcune aree periferiche al cavo". PET del 18/02/17.

Fusione ^{18}F-DOPA-PET e RM post-processing: la nostra esperienza



Paziente sottoposto in data 11/7/2014 ad intervento di asportazione di GBM in sede fronto-parietale destra, seguito da radio-chemio concomitante e successiva CHT fino a Settembre 2015. All'ultima RM encefalo del 9/1/17 appariva "invariata l'estensione dell'area di ipersegnale in T2 localizzata in sede cortico-sottocorticale frontale destra. Immodificato anche il lineare potenziamento post-contrastografico perifericamente al cavo chirurgico. Lo studio di perfusione non ha documentato incrementi del parametro rCBV." PET del 18/2/17.

Fusione ^{18}F-DOPA-PET e RM post-processing: la nostra esperienza



Paziente sottoposto ad Agosto 2014 ad intervento chirurgico di asportazione di neoformazione in sede parietale sinistra (e.i.: GBM, non metilato). Successivo trattamento radioterapico sul cavo chirurgico con Temozolomide concomitante, seguito da CHT con Temozolomide per un anno. PET del 12/10/17.

Grazie per l'attenzione