Integrated Imaging of Brain Tumours

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Introduction

The incidence rate of all primary malignant and non-malignant brain and CNS tumours is 21 cases per 100,000. Gliomas are a broad term, which includes all tumours arising from glia and represents 30 % of all brain tumours and 80 % of all malignant brain tumours. Gliomas are the second leading cause of cancer mortality in people under the age of 35.

Pathoanatomically gliomas are graded from grade I to grade IV using the World Health Organisation (WHO) criteria. Grades I and II are considered low-grade glioma (LGG) and grades III and IV are classified as high-grade glioma (HGG). LGG have a malignant potential and usually all will transform before or later to HGG. The risk of transformation is in the order of 10–25 %/year, but there are patients with LGG that have lived for 20 years before transformation. Thus, a low-grade glioma that gives significant clinical symptoms or appears to have a malignant potential will usually be operated on, while "wait and scan" will be the strategic choice for the more indolently appearing tumours.

Glioblastomas (GBM), the most aggressive variant, represent 15–20 % of all primary brain tumours and 50 % of all gliomas. The standard GBM treatment today consists of maximal surgical resection, but the tumour's ability to infiltrate into the ambient tissue makes it challenging. Postoperatively patients are offered radiotherapy in combination of concomitant and adjuvant chemotherapy with temozolomide yielding a median overall survival of 14–16 months in clinical trial populations [1].

Magnetic resonance imaging (MRI) is the primary imaging modality in the management of primary brain tumours including initial diagnosis, tumour grading, treatment planning prior to surgery and radiotherapy planning, postoperative evaluation, monitoring treatment response and progression. The most important clinical sequences are T1-weighted imaging without and with contrast medium and T2-weighted as well as fluid-attenuated inversion recovery (FLAIR) sequences.

Although MRI is a very useful and powerful technique, it has its shortcomings. These are the whole raison d'être for performing positron emission tomography (PET) scanning in brain tumours. PET scanning is a molecular imaging method, which uses various tracers to visualise biological processes. In clinical PET of brain tumours, the most established and available radiotracers deal with glucose metabolism (^{18}F-2-fluoro-2-deoxy-D-glucose (FDG)), amino acid transport ([^{11}C-methyl]-methionine (MET), O-(2-[^{18}F]-fluoroethyl)-L-tyrosine (FET) and 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine (FDOPA)) and somatostatin receptor II binding ligands such as ^{68}Ga-DOTA(0)-Phe(1)-Tyr(3)octreotide (DOTATOC).

FDG

Mechanism Many tumours overexpress the glucose transporters (GLUT) and hexokinase enzymes leading to an increased accumulation and metabolic fixation of FDG in the tissue.

The advantages:

1. *Availability*. Ease of use and a widely distributed availability as a result of the acceptance of whole-body FDG PET scanning within oncology in general.
2. *Short scan duration*. A 10 min static PET scan about 40 min postinjection makes FDG PET brain scanning a cost-effective technique.
3. *Delayed or dual-time-point imaging*. Potential improvement in diagnostic quality by supplementing with late FDG scans 3–6 h postinjection. The metabolically active tumour area is enhanced because of a differential clearance of FDG in healthy and malignant tissue [2].

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The disadvantages:

1. *High physiological uptake in healthy brain tissue*. Thus, it may be very difficult to differentiate active tumour tissue from physiological uptake with the present limitations in scanner resolution. Some of these limitations can be overcome by fusing the FDG PET image to recent MRI scans of the patient – particularly T1-weighted MRI scans with contrast – and the FLAIR sequences are mandatory in this context (Figs. 1 and 4).
2. *No uptake in LGG*. This makes PET FDG tumour delineation impossible (Fig. 1a).
3. *Tumour-associated epileptiform activity*. Almost all patients with brain tumours are in antiepileptic treatment. Epileptic seizure activity that is present during the uptake phase of FDG will give rise to a two- to tenfold increase in FDG uptake. Epileptic seizures need not be clinically manifest. This depends on the localisation and the extent of the seizure. Particularly seizures in the frontal lobes may be clinically silent. Thus, a regional signal change in FDG may be the only sign of the event and may be confused with active tumour tissue. This condition can be identified as hypermetabolic areas of varying extend in normally appearing cortex particularly on the T2-weighted MRI sequences.

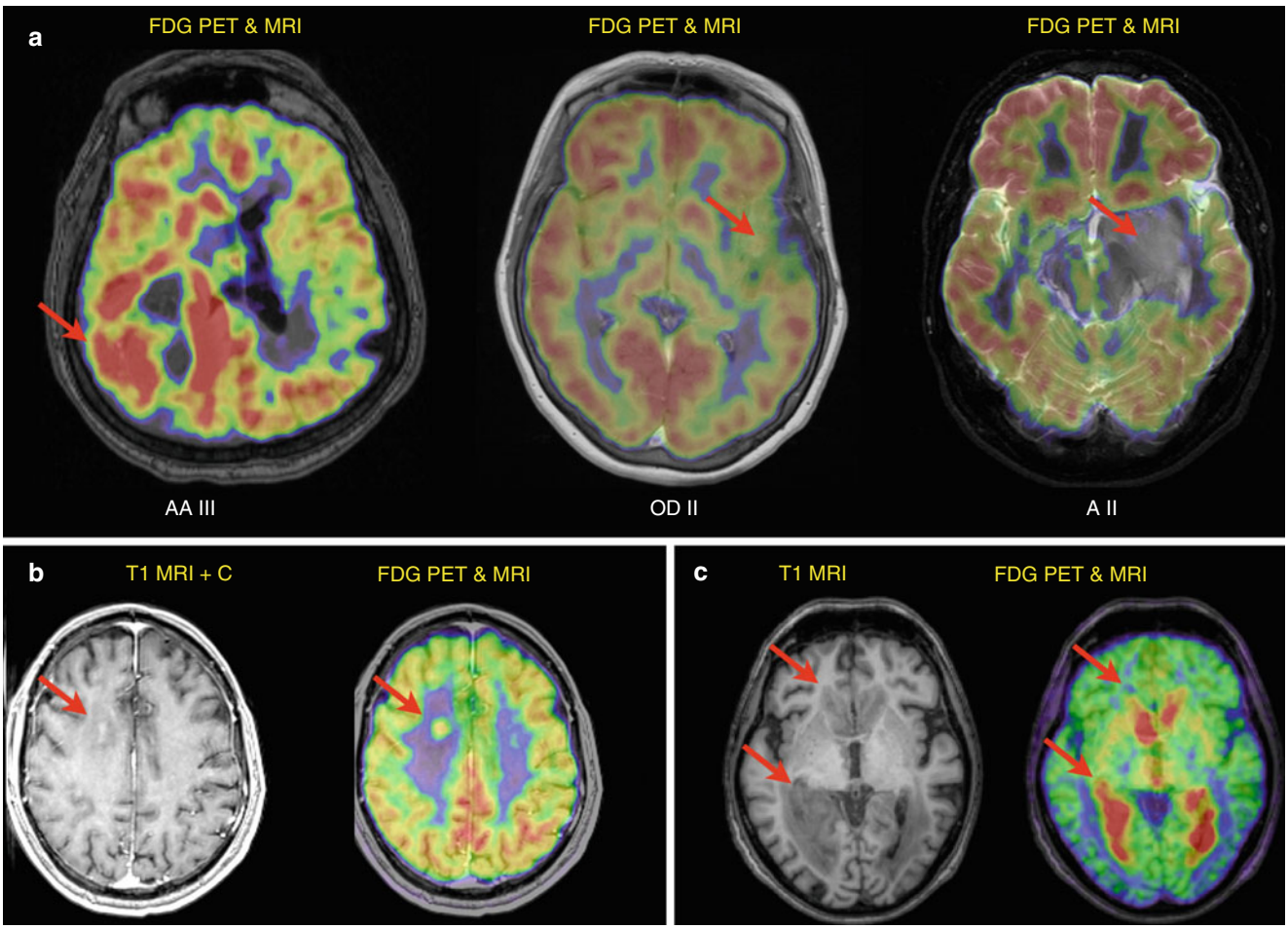

Fig. 1 Co-registered FDG PET to MRI images showing typical examples of uptake in brain tumours. (**a**) *FDG uptake in high- and low-grade glioma*. From *right to left*: Anaplastic glioma (*AA III*) in the right parieto-occipito-temporal region with invasion of the central area and a cystic/necrotic area, oligodendroglioma (*OD II*) in the left insula and anterior temporal region and astrocytoma (*A II*) in the left insula and inferior temporal region. High-grade gliomas (III, IV) typically have uptake above healthy white matter, and low-grade gliomas (II) have uptake below healthy white matter. Oligodendroglioma II (*centre*) may deviate from this pattern with uptake larger than white matter. Note the relatively difficult tumour delineation in areas bordering to the high physiological uptake in healthy grey matter. (**b**) *Recurrence of glioblastoma multiforme or treatment damage*? Focal FDG uptake in slightly contrast-enhancing area in right mesial centrum semiovale indicating recurrent tumour. (**c**) *FDG uptake in primary CNS lymphoma* (*PCNSL*). Immunocompetent patient showing FDG PET fused with axial non-contrast T1 MRI prior to treatment showing highly avid FDG uptake extending along the ependymal surfaces of the lateral ventricles indicative of liquoral spread. This is a common feature of PCNSL. In the differential diagnosis between PCNSL and high-grade glioma, a very high FDG uptake supports PCNSL. PCNSL should be biopsied and not resected. *Red arrows* point to tumours. Left is to the right of the image

4. *FDG uptake modification of other causes*:
   (a) *Inflammation/infection* (abscesses, parasitoses, sarcoidosis, TB, hematoma, histiocytosis, recent stereotactic radiation).
   (b) *Drug effects*: High doses of cortisol are administered to patients with clinically significant tumour oedema. Cortisol decreases the uptake of FDG across the blood-brain barrier (BBB) and increases noise. However, the uptake is reduced more in healthy tissue than in tumour tissue, thus, somewhat counteracting the deteriorating noise effects. There is a marked cytolytic and FDG-reducing effect on primary CNS lymphoma, so preferably patients should be scanned before treatment initiation. It is not indicated to pause with cortisol prior to scanning.
   (c) *Effects of blood glucose*: As in other tissue, a high blood glucose concentration will compete with and reduce the uptake of FDG. In glioma the reduction in uptake is more pronounced in healthy tissue than in glioma, thus increasing the ability to identify malignant tissue.

Amino Acid/Amino Acid Analogue PET Tracers (MET, FET, DOPA)

To overcome some of the FDG disadvantages, there is a growing interest in the use of more specific tracers, particularly amino acid or amino acid analogue PET tracers (MET, FET, FDOPA). The best known is MET with a 30-year history of use. However, in larger-scale routine clinical use, FET (Figs. 1, 2, 3 and 4) or FDOPA [3] predominates.

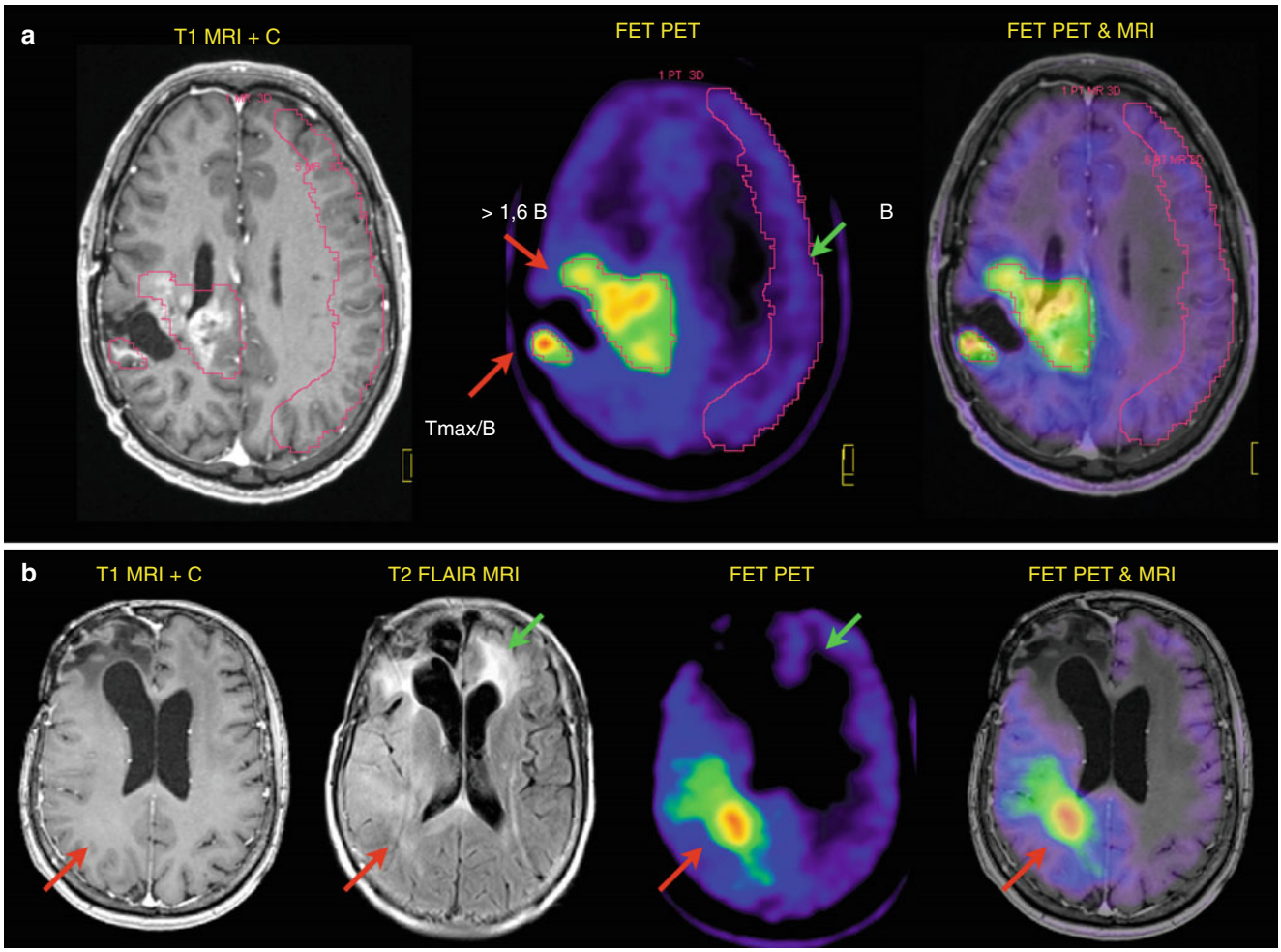

Fig. 2 (**a**) *Data analysis using FET PET*. The biological tumour volume (BTV) is defined as FET uptake in a scan 20–40 min after injection with values above 1.6 times the activity in a region (*B*) of healthy-appearing cortical grey and white matter in the contralateral hemisphere [9]. The maximal uptake (Tmax/B) is calculated and defined as the biopsy target. (**b**) *Recurrence of glioblastoma*: After antiangiogenic treatment a glioblastoma may transform into a diffusely infiltrating gliomatose phenotype predominantly coopting existing vasculature instead of stimulating new vascular growth. The metabolically active tumour in the right subcortical parieto-occipito-temporal region (*red arrows*) is not visualised on post-contrast MRI, but can be seen as a diffuse signal change and architectural disruption on T2 FLAIR. This sequence, however, also shows unspecific signal changes in the frontal lobes without increased activity (*green arrows*) possibly ischemia, demyelination, oedema or gliosis

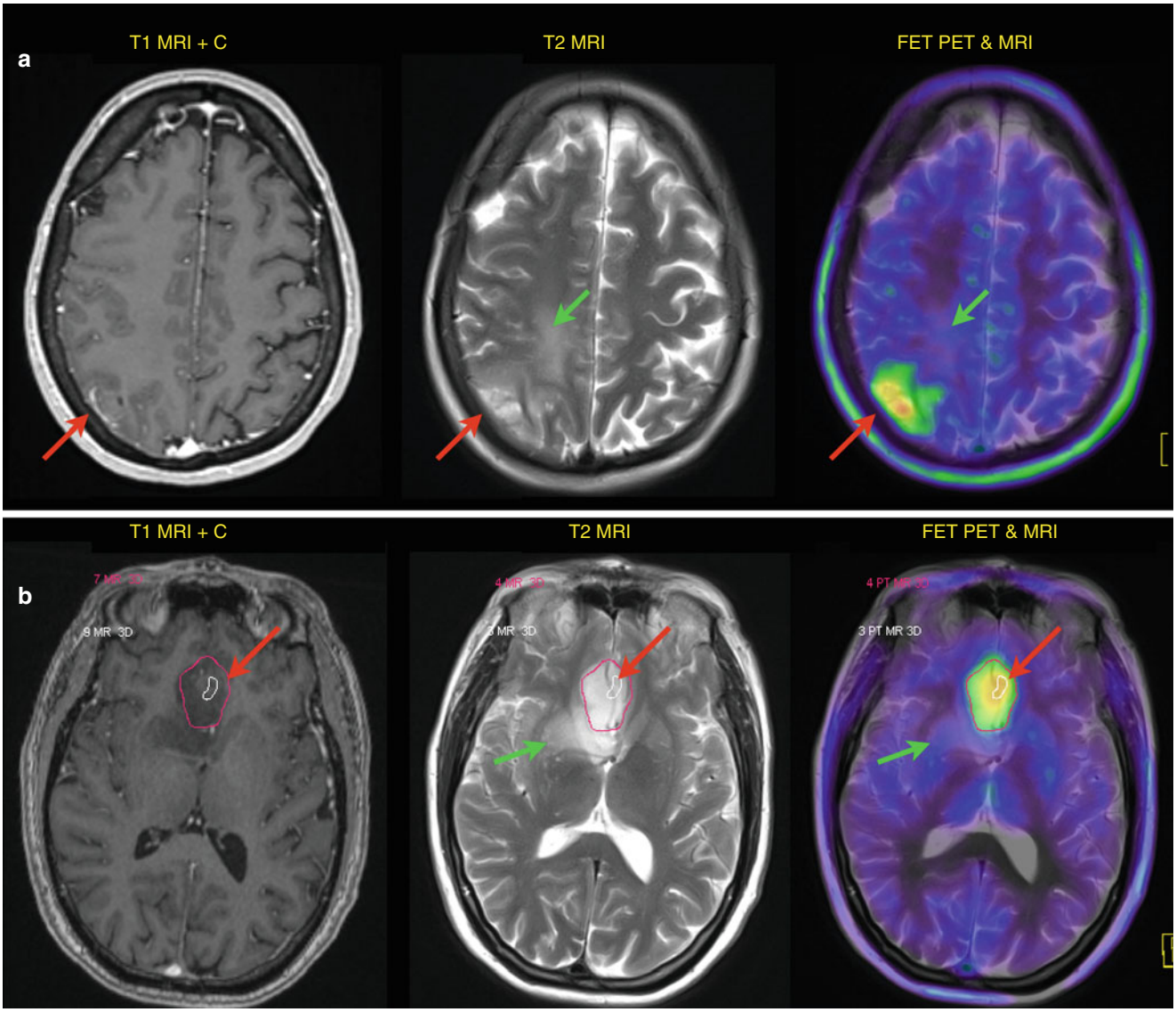

Fig. 3 Biopsy guidance. (**a**) Diffusely infiltrating tumour on T2 MRI with uncertain contrast enhancement. Focally increased FET uptake in right parietal cortex (*red arrow*). No uptake in subcortical T2 signal changes (*green arrow*). Histology showed oligodendroglioma II. (**b**) Diffusely infiltrating tumour (red arrow) on T2 MRI in mesial frontal lobe and right anterior striatum without contrast enhancement on T1 MRI. The borders of the metabolically active tumour (*magenta*) and peak area (*white*) suggested for biopsy trajectory are indicated. No uptake in subcortical T2 signal changes in right anterior striatum (*green arrow*). Histology showed glioblastoma multiforme

MET, FET and FDOPA

Mechanism Gliomas overexpress the L-amino transporters (LAT). MET and FDOPA are transported via LAT1 and LAT2, and FET predominantly via LAT2. LAT1 is overexpressed in inflammation, while LAT2 is more tumour selective [3]. These tracers are not fixed and will be cleared from the brain and tumour.

The advantages:

1. *Image contrast*: There is very little uptake in healthy tissue. There is, thus, a high target to background ratio (Fig. 4).
2. *Uptake in LGG*: LGG can be delineated (Fig. 3a).
3. *Tumour grading*: Glioma can be graded (only FET) based on the shape of the time activity curve [3, 4].
4. *Better specificity than FDG* (Fig. 4). However, there may still be an uptake in astrogliosis (FET) or microglia (MET) caused by inflammatory lesions, such as multiple sclerosis and treatment damage [5–7].
5. *F18-labelled radio synthesis* (FET, FDOPA): The F18 half-life is 2 h. This is essential for the broad clinical acceptance of the technique for routine clinical use. One production can supply 20 patients or more depending on the number of scanners used. The shelf life is up to 8 h, so they can be transported to neighbouring PET centres.

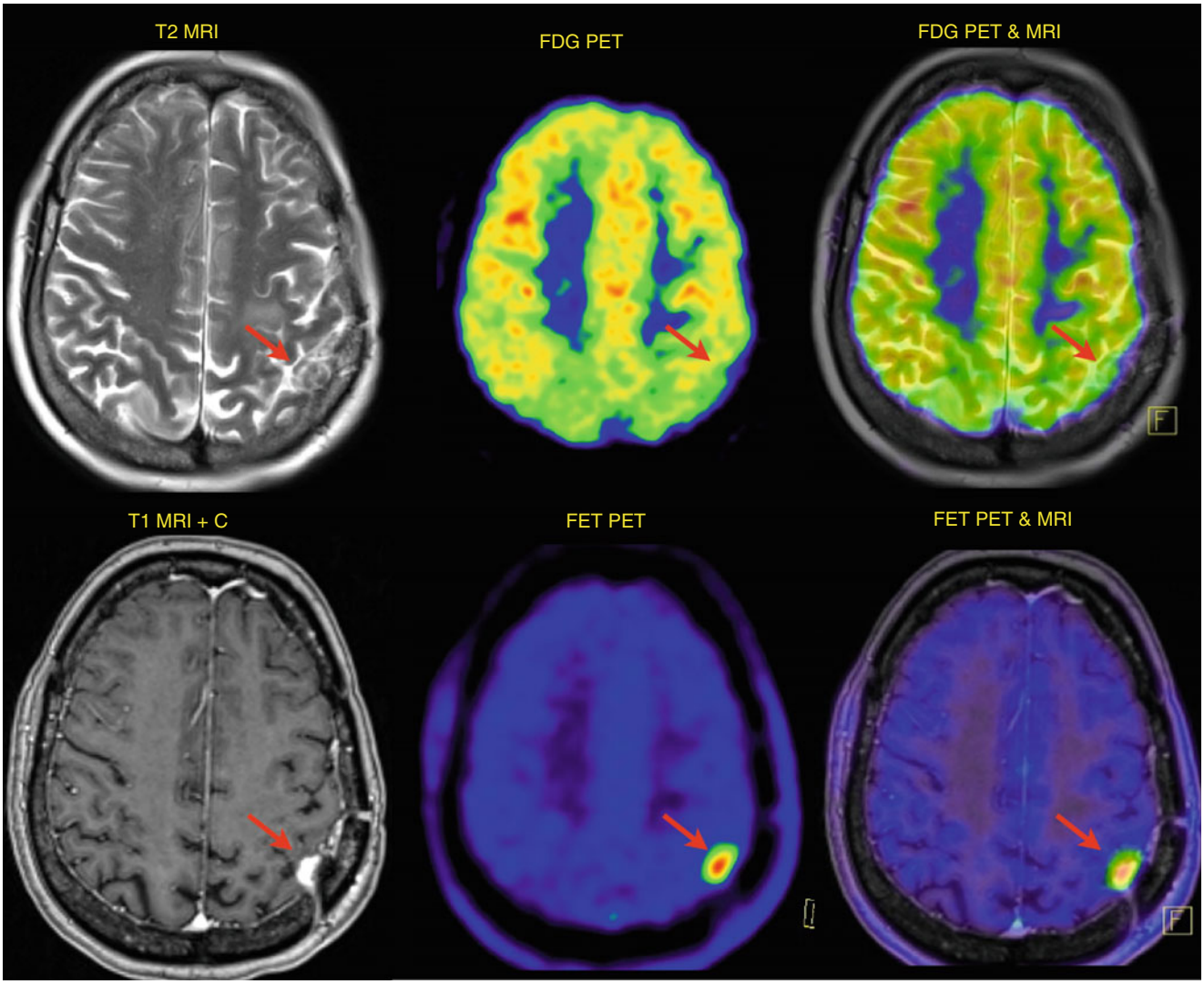

Fig. 4 Recurrence of glioblastoma multiforme or treatment damage? Comparison of tumour uptake using FDG (*top*) or FET (*bottom*) in the same patient with glioblastoma multiforme in postoperative follow-up. The metabolic activity in contrast-enhancing area (*red arrows*) is difficult to evaluate using FDG because of the high physiological uptake in adjacent healthy cortex. FET shows focal increase. Recurrence confirmed on re-resection

6. *Can identify both solid and infiltrative tumour components*. Thus, the tumour margins defined by T1 contrast enhancement will often exceed these tracers [8] (Figs. 2 and 3).

The disadvantages:

1. *C11-labelled radio synthesis* (only MET): C11 half-life is only 20 min. Capacity limitation to 1–2 patients per production.
2. *Blood volume background* (*only FET*): FET is only slowly excreted in the kidneys, so there is moderate activity in the blood vessels that in selected case can confuse the image reading.
3. *Longer scan duration* (only FET): Glioma grading requires a 40 min dynamic scan, reducing cost-effectiveness [4].
4. *High striatal uptake* (*only FDOPA*): Difficult delineation of tumours infiltrating into central areas [3].
5. *Lack of biopsy proven threshold for tumour tissue* (*only FDOPA*): For MET and FET, the threshold of uptake is 1.3 [8] and 1.6 times (Fig. 2) [9] relative to healthy cortex, respectively.
6. *Pretreatment with carbidopa to inhibit metabolism* (*only FDOPA*) [3].

PET Brain Tumour Indications

Glioma Grading and Malignant Transformation

There are clinically important implications associated with the ability to differentiate between LGG and HGG. This distinction can be difficult with MRI. Usually contrast

enhancement would be a characteristic that would be emphasised. However, about 40–50 % of non-enhancing lesions with an MR presentation that would be identified as LGG are found subsequently to be HGG [10] (Fig. 3) and LGG can be contrast enhancing. Usually, it is the distinction between grade II and grade III that proves to be most difficult.

PET scanning can be used in support of either a "wait and scan" strategy in the metabolically inactive tumours or an aggressive surgical strategy in the active tumours. None of the tracers, however, can obviate the need for tissue verification, but it can change the time point for sampling.

FDG

The regional FDG uptake correlates to cellular density and regional anaplasia. FDG is trapped metabolically and is only removed slowly. As a rule LGG has low uptake and HGG has increase uptake. In a retrospective study of 333 patients, tumour grading could be done using the metabolic activity in white matter as a visual threshold. Of all HGG 84 % had uptake above this level and only 7 % of the LGG (Fig. 1). It should be noted that a number of LGG, such as grade I glioma (pilocytic astrocytoma), and hamartomas (dysplastic gangliocytoma) are characterised with a very large FDG uptake. However, these have a characteristic appearance on MRI, so usually clinical PET scanning is not required. The FDG uptake is prognostic for overall survival and a better prognosticator of WHO grade. If an LGG increases its metabolism during the cause of observation, this can be indicative of malignant transformation and should be followed by histological verification.

FET

About 60–70 % of the LGG show uptake [11, 12] and close to 100 % for HGG [13]. Hence, no grading information can be derived from the uptake itself. Nevertheless, the FET uptake can possibly prognosticate progression in LGG. A lack of FET uptake in a circumscribed tumour predicts slow progression, while increased uptake in a diffuse tumour predicts faster progression [11]. This has, however, recently been disputed [12].

Several studies have shown that the 40 min dynamic uptake curve in the most active regions can be used to grade glioma [4]. Thus, LGG has typically a steadily increasing curve, while HGG have a typically fast uptake and washout or a plateau. The mechanism behind has not been clarified, but it does not seem to be related to the presence or absence of a BBB defects. This allows for a sensitivity and a specificity of 80–90 % [4, 14]. Both tumour-to-brain uptake and kinetic parameters of FET PET uptake can provide valuable diagnostic information for the noninvasive detection of malignant progression of LGG [15].

Primary Intracerebral Lymphoma (PCNSL)

Primary CNS lymphoma (PSNSL) is a rare form of extranodal non-Hodgkin's lymphoma (NHL) confined to the brain and account for 1–6 % of all intracranial tumours. PCNSLs are highly proliferative tumours and usually show high FDG uptake (Fig. 1c). FDG PET is useful for the differentiation between lymphomas and infectious lesions in AIDS patients [16]. However, with improved HIV treatments, these are rarely seen. The major MRI differential diagnosis of PCNSL is GBM. This is clinically important for correct preoperative planning. PCNSL should be biopsied and treated with chemotherapy, while GBM should be resected. PCNSL has significantly larger FDG uptake than GBM and is useful for this indication [17, 18].

Optimising Tumour Biopsy

FDG, MET and FET can be used to optimise the diagnostic quality of a tumour biopsy (Fig. 3) by directing sampling at the most metabolically active areas [19]. This may be used both in grading and in confirmation of tumour recurrence. In a prospective study, MRI yielded a sensitivity of 96 % for the detection of tumour tissue but a specificity of only 53 %, and combined use of MRI and FET PET yielded a sensitivity of 93 % and a specificity of 94 % [9]. Simulations indicate that FET PET may be cost-effective if used in biopsy planning [20].

Postoperative Monitoring

After surgical intervention and concomitant radiochemotherapy, the patients are monitored for recurrent tumour, which can lead to additional surgical intervention, second- and third-line chemotherapy and re-irradiation. Using MRI to distinguish recurrent tumour from treatment damage is difficult. As a rule PET HGG are metabolically very active while treatment damage is inactive or less active (Figs. 1, 2 and 4). However, tumour tissue and treatment damage can coexist, and reactive tissue changes will increase activity. The best diagnostic accuracy with reference to histology has been found with MET/FET. For FET the ratio of maximal tumour uptake to average background in normally appearing cortical tissue (Tmax/B) is calculated (Fig. 2a). A Tmax/B threshold above 2.4 will have a specificity of 90–100 %, while the sensitivity would be approximately 75 % [4]. A Tmax/B of 2.0–2.4 with a focal uptake would be interpreted

as recurrence, while crescent-shaped diffuse uptake around the resection cavity is more likely reactive changes. Sensitivity and specificity at this cut-off are 100 % and 78–100 %, respectively. It should be noted that the patients in some of these studies receive unusual and experimental treatment, such as radioimmunotherapy (RIT). This may lead to a high level of local tissue damage and reaction and, thus, influence the specificities calculated. Furthermore, the thresholds are dependent on a close duplication of the scan set-up used in these studies. If the pattern is equivocal, a fast rescan <6 weeks can be recommended.

The diagnostic accuracy of FDG (Fig. 1) is worse than MET/FET with an overall sensitivity of 80–90 % and a specificity of 50–90 % [21]. One caveat of these studies, however, is that the studies are performed on older generations of PET scanners with lower resolution, not all studies have used MRI co-registration and they are often subject to sampling bias.

Meningiomas and Somatostatin Receptor-Based Tracers

Meningiomas represent 34 % of all primary brain tumours, making them the most common primary brain tumour. Almost all meningiomas show high expression of somatostatin receptors subtype 2 (SSTRII) that may be efficiently visualised with PET using DOTATOC. This is particularly useful in meningiomas at the skull base, because of postoperative changes and tumour infiltration into cavities, sinuses (Fig. 5a) and bone. DOTATOC PET/CT for target volume delineation for intensity modulated RT, fractionated stereotactic RT or proton therapy has been shown to change the planning target volume significantly in several publications [22]. On average the target volume was modified in 80 % and reduced in 54 % of patients, but the clinical impact remains to be documented in long-term follow-up. DOTATOC PET is likely to be useful

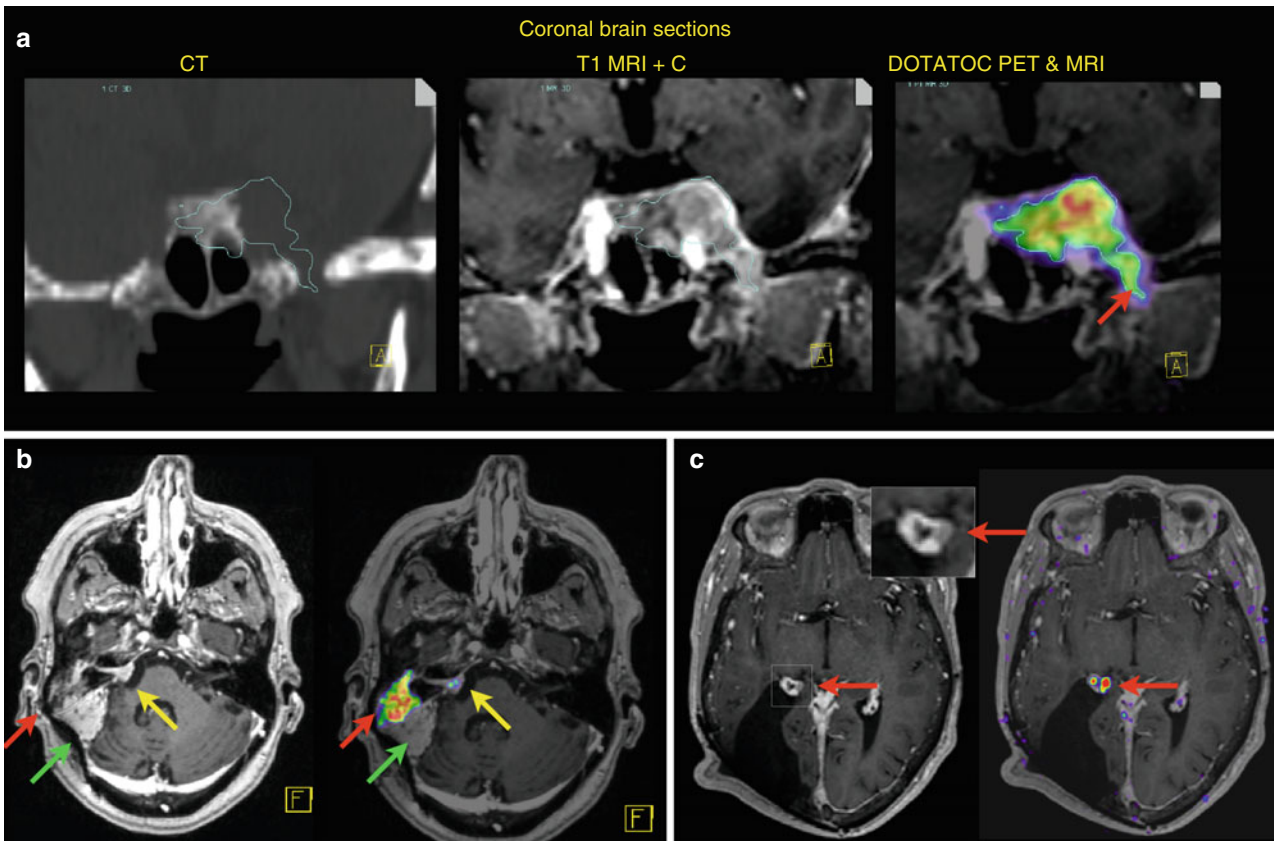

Fig. 5 Examples of DOTATOC PET use in meningioma management. (**a**) *Recurrent meningioma* (*WHO I*) *referred for radiotherapy planning*. The patient suffered from trigeminus neuralgia and was treated without effect with dilation of the foramen ovale unaware that the tumour is infiltrating into the same opening (*red arrow*). Coronal CT shows an increased foramen ovale and tumour contours in *blue*. The tumour invading the ethmoidal sinuses is hard to delineate on post-contrast T1 MRI, but can easier be detected on DOTATOC PET scanning. (**b**) *Recurrent meningioma* (*WHO I*) *referred for radiotherapy planning*. Previous resection for a meningioma in the anterior right cerebellar hemisphere with fat tissue inserted to support the organ (*green arrow*). The patient was referred for radiotherapy planning of small relatively inactive tumour lateral to the right pons (*yellow arrow*). The MR signal changes in the right pars petrosa (*red arrow*) were originally interpreted as reactive changes, but DOTATOC PET scanning indicated bone invasion, and the planning field was subsequently modified. (**c**) *Staging DOTATOC PET scan prior to surgery of recurrent malignant meningioma* (*WHO III*). The finding of an additional 3 mm in diameter recurrence (*red arrow*) not identified initially on MRI and hidden in the right choroid plexus (*insert*) changed the treatment from surgery to radiation therapy [23]

in biopsy planning, in differentiating active tumour tissue from posttreatment damage (Fig. 5b) and in selection of treatment strategies, e.g. operative vs. radiation therapy (Fig. 5c) [23]. Furthermore, DOTATOC might be used in dosimetry planning of peptide receptor radionuclide therapy (PRRT) using ^{90}Y-DOTATOC, ^{177}Lu- DOTATATE or ^{177}Lu-DOTATOC in non-resectable locally recurring, progressive or symptomatic meningiomas, but the clinical effects need to be documented in randomised clinical trials [24].

Simultaneous PET/MRI Imaging

At our institution, we have implemented our hybrid PET/MR system for routine clinical MRI and FET PET imaging of patients with gliomas. This provides simultaneous structural and metabolic evaluation under identical physiological condition with the addition of various advanced MRI techniques in a single examination of 20–40 min [25], e.g. combined FET and tumour blood volume (BV) imaging using T2* dynamic susceptibility contrast (DSC) (Fig. 6). DSC has been suggested as a cost-effective substitute for PET scanning. However, in postoperative glioma patients, we found that the spatial congruence of BV and FET was remarkably poor. MRI susceptibility artefacts affected the ability to evaluate BV DSC in FET-avid tumour areas in 56 % of patients [25]. T1 dynamic contrast enhanced (DCE) has a higher resolution, is not subject to susceptibility artefacts and may be a more attractive alternative to explore [26, 27].

As PET scanning is a quantitative technique, good attenuation correction is essential. This has been the primary technical limitation of the present PET/MRI systems [28]. Thus, at our unit patients presently receive a low-dose CT scanning of the head for this purpose, while other strategies are being considered [29].

PET/MR may increase the overall diagnostic quality, decrease clinical decision time and increase acceptance of PET imaging with patients and treating clinicians in clinical

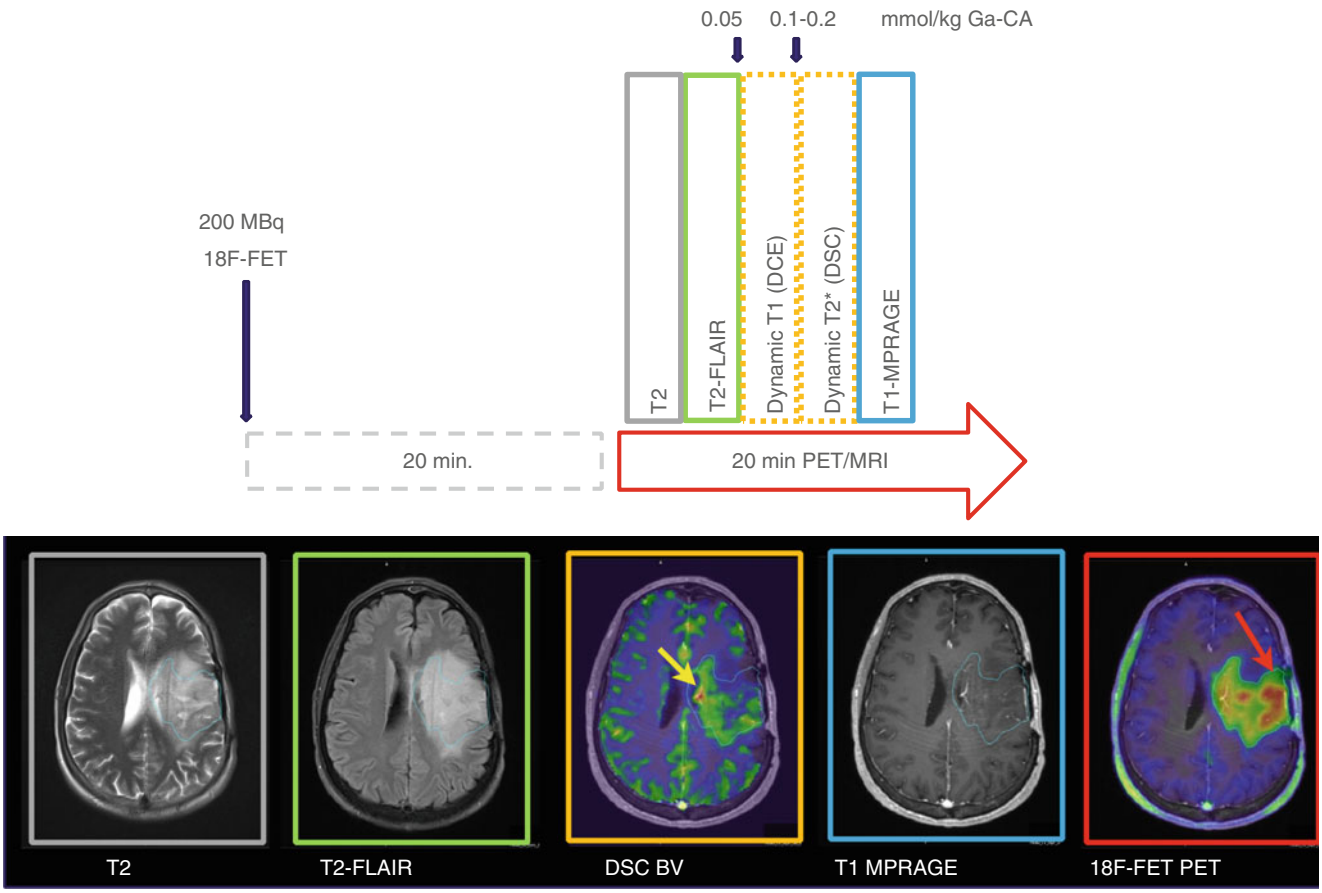

Fig. 6 Integrated multiparametric brain tumour imaging using PET/MRI and FET. Workflow illustrating a combined 20 min FET PET/MRI and tumour blood volume (*DSC BV*) scanning session of a patient with non-contrast-enhancing oligodendroglioma III. Intravenous injection of 200 MBq FET is performed 20 min prior to simultaneous FET PET and standard MRI scanning. T2* dynamic susceptibility contrast (*DSC*) or T1 dynamic contrast-enhanced (DCE) MRI imaging after contrast injection will supply measurements of tumour blood volume. Notice the areas of increased blood volume (*yellow arrow*) and metabolic activity (*red arrow*) are not congruent [25]

management and in trials. This might be particularly important in paediatric neurooncology requiring the use of anaesthesia only once. CNS tumours are the leading cause of cancer-related deaths from solid tumours in children under age 20, and the clinical use of PET scanning in this patient group is not fully developed [6, 30].

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