Advantages and limitations of amino acid PET for tracking therapy response in glioma patients

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ABSTRACT

Introduction: Today, magnetic resonance imaging (MRI) is the standard method for monitoring patients with brain tumours. The ability of conventional MRI in differentiating neoplastic tissue from non-specific, treatment-related changes after surgery, radio-, chemo- or immunotherapy, however, remains limited. Therefore, advanced MRI sequences and positron emission tomography (PET) are increasingly being considered to improve decision making.

Areas covered: PET using radiolabeled amino acids has evolved into an important diagnostic tool to overcome some of the shortcomings of conventional MRI. In view of the rapidly developing novel treatment strategies, a reliable statement on the response to therapy is becoming increasingly important. This article gives an overview of the current results of PET with radiolabelled amino acids in therapy monitoring of standard therapy as well as various innovative approaches in the treatment of patients with cerebral gliomas.

Expert commentary: Amino acid PET has proven to be helpful in therapy monitoring of gliomas, the costs are low in relation to the costs of therapy and the clinical benefit, and a widespread clinical use is highly desirable.

Key Words: cerebral glioma; PET; radiolabeled amino acids; treatment monitoring

1. Introduction

Glial neoplasms of the central nervous system are the most common type of primary brain tumours and arise with an incidence of 5 to 6 new cases per 100.000 persons per year [1]. The treatment of patients with cerebral glioma consists of surgical resection and depending on the molecular profile local radiotherapy followed by concomitant and adjuvant chemotherapy with alkylating agents. Despite all efforts, the results of treatment, measured in terms of survival time, remain unsatisfactory over the decades to this day, especially in malignant gliomas. Magnetic resonance imaging (MRI) with its excellent soft tissue contrast and a high spatial resolution of 1 millimeter is currently the method of first choice for the diagnosis of brain tumours. Nevertheless, it remains difficult to differentiate brain tumours from signal abnormalities caused by non-neoplastic alterations in the tissue especially after surgery, radio- and chemotherapy [2]. These shortcomings of MRI represent a major challenge in neurooncology, as therapy response assessment in gliomas is of paramount importance for an optimal treatment strategy. In particular, the timely identification of therapy failure allows the early termination of an ineffective therapy and the avoidance of side effects such as bone marrow depression, fatigue, nausea and vomiting. The change to a more efficient chemotherapy can be done with sufficient bone marrow reserve. This helps to improve patients' survival and quality of life, but also to reduce costs, as new systemic treatments are very expensive.

Therefore, a number of diagnostic approaches with a focus on metabolic and functional imaging methods are under investigation [3]. Positron emission tomography (PET) is a well-established method in nuclear medicine that is able to detect the distribution of radiolabelled molecules in the human body with high sensitivity and a spatial resolution of 3 - 5 mm. Since numerous metabolic substrates, receptor ligands or pharmaceuticals can be labelled with positron-emitting isotopes such as carbon-11, nitrogen-13 or fluorine-18, PET offers great

potential for the assessment of metabolic and physiological processes. However, radiolabelling of the molecules with short-lived positron emitters is a rather sophisticated procedure. In addition, the tracers must meet a number of conditions such as high in vivo stability, high specificity and a sufficient residence time in the target tissue in order to be clinically useful.

The most widely used PET tracer for tumour imaging is 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG) which accumulates in almost all tumours due to high glucose metabolism. In the case of gliomas, however, it is difficult to delineate the tumour tissue owing to the high rate of glucose metabolism in normal brain tissue. Although FDG has been applied in numerous brain tumour studies and provides relevant information for certain clinical questions such as grading of gliomas and prognostics, the procedure has only achieved a low priority in the clinical setting.

In the last decades, radiolabelled amino acids have emerged as the PET tracers of choice for the diagnosis of gliomas [4]. This is mainly due to the fact that the uptake of radiolabelled amino acids by normal brain tissue is relatively low and brain tumours can be distinguished from the surrounding normal tissue with high contrast. Equally important is the ability of these tracers to pass the intact blood-brain barrier (BBB) and to depict the tumour mass beyond contrast enhancement in MRI [3] and to differentiate tumour progression from non-specific, treatment-related changes [5]. The Response Assessment in Neuro-Oncology (RANO) working group has recently recommended the use of amino acid PET imaging for brain tumour management in addition to conventional MRI at every stage of disease[4, 6].

This article gives an overview of the current results of PET with radiolabelled amino acids in therapy monitoring of standard therapy as well as various innovative approaches in the treatment of patients with cerebral gliomas. References for this Review were identified through searches of PubMed with the search terms “glioma”, “PET”, “radiolabeled amino acid”, “treatment monitoring”, “pseudoprogression”, “pseudoresponse”,

"radiochemotherapy", "check-point inhibitors", "antiangiogenic", "radiosurgery", "from Jan 1, 1979 to Oct 30, 2019. Articles were also identified through searches of the authors' own files. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this Review.

2. Limitation of conventional MRI for tracking therapy response in glioma patients

Changes of contrast enhancement on MRI after injection of paramagnetic contrast agents are considered as an indicator of therapy response or tumour relapse [7, 8]. Contrast enhancement , however, reflects an increased permeability of the BBB and is not specific for neoplastic tissue and its changes do not necessarily reflect response to therapy or tumour relapse [9, 10]. Following first-line chemoradiation of glioblastoma with temozolomide, progressive contrast enhancing lesions are frequently observed on MRI, which are not related to tumour progression, but are due to treatment-related effects. These lesions may remain stable or regress during further follow-up MRI without further treatment or any change of treatment [11]. This phenomenon of progressive, radiation- or chemoradiation-induced, enhancing MRI lesions in patients with malignant gliomas, with spontaneous improvement is called pseudoprogression [12, 13]. If no biopsy is taken, pseudoprogression is usually diagnosed retrospectively based on clinical findings and follow-up MRI. Pseudoprogression occurs typically within the first 12 weeks after radiotherapy with concomitant and adjuvant temozolomide for glioblastomas in 20 – 30 % of the patients [13, 14] and has been incorporated into the criteria defined by the RANO working group [8]. Pseudoprogression has also been described during immunotherapy of brain metastasis or glioblastoma by blocking immune checkpoints such as cytotoxic T lymphocyte-associated antigene 4 (CTLA-4) using ipilimumab and programmed cell death 1 receptor (PD-1) using pembrolizumab or nivolumab [15-17].

Since the introduction of antiangiogenic agents such as bevacizumab the problem of pseudoresponse complicates the assessment of treatment response using Macdonald criteria alone [7]. Bevacizumab can rapidly decrease contrast enhancement after initiation of treatment [18], producing an apparently high response rate. Some of the improvement observed on contrast-enhanced MRI results from a rapid normalization of abnormally permeable blood vessels that restores, at least in part, the integrity of the BBB. Hence, the extent of reduction of contrast enhancement may not always reflect the true anti-tumour activity of the antiangiogenic agent [19]. Thus, the use of antiangiogenic drugs likely alters the image characteristics of enhancing tumours more effectively than that of non-enhancing ones [19]. The RANO group suggested in 2010 new recommendations for evaluating response considering FLAIR or T2 signal hyperintensity as a surrogate marker for non-enhancing tumour to help determine tumour progression [8] but these criteria do not provide quantitative values to estimate response to therapy. Furthermore, tissue alterations such as tumour-related edema, radiation injury, demyelination, ischemia, and infection can result in hyperintense FLAIR or T2 signal, which is difficult to distinguish from non-enhancing tumour [9].

3. Radiolabeled amino acid for PET imaging of gliomas

The longest-established amino acid tracer for PET is [^{11}C-methyl] -L-methionine (MET) , which shows uptake via the System L amino acid transporter as well as an incorporation into protein and participation in other metabolic pathways [20]. Alpha-[^{11}C]-methyl-L-tryptophan (AMT) has been proposed as an alternative to MET because of its involvement in the kynurenic pathway, which may play a role in immune response regulation in gliomas [20, 21]. These tracers, however, are restricted to a few neurooncological centres since the short half-life of carbon-11 (20 min) requires an onsite cyclotron [22] . Therefore, amino acids labelled with fluorine-18 (half -life of 109.8 min) such as O-(2- [^{18}F]-fluoroethyl) -L-tyrosine

(FET) [23, 24], 3,4-dihydroxy- 6- [^{18}F]-fluoro -L-phenylalanine (FDOPA) [25], L-[3-^{18}F]-α-methyl tyrosine (FMT) [26], and anti-1-amino-3-^{18}F-fluorocyclobutane-1-carboxylic acid (FACBC, fluciclovine) [27] are increasingly gaining acceptance owing to logistical advantages compared with C-11-labelled amino acids. FDOPA is approved in some European Countries for clinical use, fluciclovine has orphan drug status for brain tumours in the USA [28] and FET is approved for clinical use in brain tumour imaging in France and Switzerland [29]. In Europe, the high clinical interest in this method has led to >10,000 FET PET scans being performed in some centres [30]. Uptake of these amino acids occurs predominantly via the transport system L for large neutral amino acids namely the subtypes LAT1 and LAT2 although other transport systems may also play a role [31-33]. Imaging of brain tumours with MET, FET and FDOPA is very similar [34-36]. Static scans made between 20 and 60 min after tracer injection are normally used for the interpretation of PET images [6]. For FET and FDOPA, the additional analysis of the time-activity curves of tracer uptake in the tumour can be helpful in differential diagnosis [37-40]. When using FDOPA, an increased uptake in the striatum has to be considered, as the molecule is a precursor of dopamine, which may cause problems in the delineation of gliomas affecting the striatum [41]. Since MRI is indespensible, amino acid PET represents an additional investigation and there is limited availability but it appears to be attractive to clinicians because the method is robust, image interpretation is simple and the metabolically active brain tumour tissue is visualized with a high tumour-to-background contrast.

4. Amino acid PET in assessment of tumour resection

Assessment of residual tumour following surgery is usually done by contrast-enhanced MRI which should be performed within 72 h after surgery since it becomes challenging to differentiate contrast-enhancing tumour tissue from treatment-related changes at later time points [42]. Contrast enhancement in early postoperative MRI, however, may not detect the full extent

of the residual tumour since glioma tissue may extend beyond the area of contrast enhancement [43, 44].

Several studies have investigated the role of the amino acid PET in determining the extent of tumour resection in patients with cerebral gliomas. In a PET study using MET, residual tumour was successfully detected in 13 out of 19 pediatric brain tumours which was confirmed by repeated surgery or tumour progression in all cases [45]. The same authors reported on the prognostic role of total resection of MET-positive tissue in a group of 43 adult patients with high-grade glioma while a total removal of contrast enhancement in MRI did not correlate with survival [46]. For PET using FET the most extensive study to date in a group of 62 reported that FET PET detected residual tumour tissue more frequently than MRI [47]. In another study, the authors demonstrated a high correlation between elevated tracer uptake on the postoperative FET PET scans and the sites of subsequent tumour recurrence [48]. A recent study compared residual FET uptake after surgery in 31 patients with glioblastomas with intraoperative fluorescence after the application of 5-aminolevulinic acid (5-ALA)[49]. In that study, 13 patients showed residual FET accumulation beyond contrast enhancement in MRI and 5-ALA fluorescence. Moreover, residual tumour tissue in FET PET with a volume greater than 4.3 ml was associated with a significant shorter overall survival time.

In an experimental study with rat gliomas, we observed increased FET uptake at the rim of the resection cavity within the first two weeks following glioma resection, especially in the first few days after surgery [50]. Since this uptake decreased in the second week after surgery, it was recommended that FET PET should be performed later than two weeks after resection. In summary, amino acid PET provides valuable information for assessing the success of glioma resection but the intervention can also lead to an increased tracer uptake that warrants further investigation.

5. Tracking radio- and chemotherapy in malignant glioma

Maximum complete resection followed by radiotherapy with concomitant and adjuvant temozolomide is currently the standard of care for patients with glioblastoma [51]. The prognostic value of early changes of FET uptake after postoperative chemoradiation has been evaluated in a prospective study with glioblastoma [52]. In that study 25 patients with glioblastoma were investigated by MRI and FET PET after surgery, one week after completion of chemoradiation with temozolomide, and 6-8 weeks later. Early after completion of chemoradiation, a decrease of both the maximum and mean tumour-to-brain ratios were highly significant and independent statistical predictors for progression-free survival and overall survival. A decrease of the maximum tumour-to-brain ratios of more than 20% predicted favourable survival with a sensitivity of 83% and a specificity of 67%. Oppositely, changes of the volume of contrast enhancement in MRI had no significant predictive value for survival. Examples of response assessment with FET PET in chemoradiation with temozolomide in a patient with glioblastoma is shown in Figure 1 and in a patient treated with lomustine in Figure 2. An overview on the cut-off values of amino acid PET to assess response to treatment in gliomas is shown in Table 1. Reliable monitoring of temozolomide and nitrosourea-based chemotherapy (combined procarbazine, lomustine and vincristine, or combined lomustine and vincristine or lomustine monotherapy) has also been demonstrated in patients with recurrent malignant glioma [53-56]. In another study, the value of FET PET for monitoring stereotactic brachytherapy using iodine-125 seeds was investigated in patients with recurrent malignant glioma [57]. In that study, FET PET differentiated late posttherapeutic effects after 6 months from local tumour progression with a high diagnostic accuracy but an early increase of FET uptake 3 months after seed implantation was not necessarily associated with tumour progression. The authors speculated that this observation might be caused by changes in blood-brain barrier permeability or reactive processes and recommended that changes of amino acid uptake in the early phase

after brachytherapy of recurrent high-grade gliomas should be considered with caution. Further studies of treatment monitoring with radiolabeled amino acids during experimental treatment options for malignant gliomas such as convection-enhanced delivery of paclitaxel, intracavitary radioimmunotherapy, stereotaxy-guided laser-induced interstitial thermotherapy, immunotherapy with dendritic cell vaccination as well as adjuvant maintenance therapy with imatinib in combination with hydroxyurea reported that decreasing tracer uptake was associated with better outcome [58-62]. Furthermore, a recent study investigated the changes of FET uptake in patients with glioblastoma during therapy with tumour-treating fields (TTF) which deliver low-intensity, alternating electric fields as a locoregional intervention that inhibits cell division and causes neoplastic cell death. In two patients treated solely with TTF without any other concurrent neurooncological therapy, serial PET revealed a decrease of FET uptake over a follow-up of 6 months in accordance with stable disease [63]. Similar results have also been reported with AMT [64].

In summary, the vast majority of studies show that a response of malignant gliomas to different forms of therapy is associated with a decrease in amino acid accumulation, predicting a response to therapy earlier than MRI.

6. Assessment of response to antiangiogenic therapy in malignant gliomas

As outlined above, the assessment of treatment response of recurrent glioblastoma to antiangiogenic agents such as bevacizumab is complicated by the problem of pseudoresponse. Bevacizumab can rapidly decrease contrast enhancement after initiation of treatment [18], producing an apparently high response rate. The persistence of non-enhancing tumour tissue, however, is crucial for the further course of the disease and is difficult to identify by MRI. A number of studies have investigated whether amino acid PET is more reliable than MRI to assess treatment response to antiangiogenic therapy. Using FET PET, two studies with

smaller groups of patients (10 and 11) investigated therapy monitoring of glioblastomas during anti-angiogenic therapy [65, 66]. In both studies, changes of the metabolic tumour volume in FET PET proved to be more accurate than MRI in assessing response and predicting survival time, with the latter study also taking into account kinetic parameters of FET PET. Another study investigated therapy monitoring during combined therapy with bevacizumab and the nitrosourea lomustine in 21 patients with recurrent glioblastoma [67]. While early treatment response as assessed by RANO criteria was not predictive for overall survival, reductions of all FET PET parameters significantly predicted an overall survival of more than 9 months. The role of FDOPA PET to monitor anti-angiogenic therapy with Bevacizumab was investigated in a larger series of 30 patients with recurrent high-grade gliomas [68]. Similar to FET PET, the decrease in metabolic tumour volume predicted response to therapy more reliably than changes in MRI. In contrast to these results, a study with MET PET in 20 patients with recurrent glioblastomas showed that a decrease in tracer uptake 4 weeks after the start of anti-angiogenic therapy did not allow a prediction of therapy response [69]. A more recent study using MET and Hybrid PET/MRI in 11 patients, however, reported that both a decrease in tumor-to-brain ratio and metabolic tumor volume predicted response to anti-angiogenic therapy [70].

The prospective REGOMA phase 2 trial [71] showed an encouraging and significant survival benefit for glioblastoma patients at first progression treated with the oral multikinase inhibitor regorafenib, which has antiangiogenic properties. A recent pilot study of 5 patients revealed that FET PET allows an early diagnosis of both pseudoresponse and pseudoprogression already 8 weeks after initiation of regorafenib treatment [72].

In summary, amino acid PET has been shown to be helpful in assessing the success of antiangiogenic therapy of glioblastomas. However, further investigations assessing the value of amino acid PET in a larger number of patients undergoing antiangiogenic treatment are warranted.

7. Assessment of therapy response in non-enhancing low-grade glioma

While treatment monitoring in patients with malignant glioma with MRI is usually based on volumetric changes of contrast enhancement, it is more difficult to assess therapy response in non-enhancing lower-grade gliomas (i.e. gliomas of the WHO grade II and III). Abnormalities in T2-weighted/ FLAIR MRI may represent a combination of infiltrating tumour cells, necrotic areas, tumour edema, and treatment-related leukoencephalopathy. FET PET has been used to assess effects of temozolomide chemotherapy according to the European Organisation for Research and Treatment (EORTC) protocol 22033-26033 (application of 75 mg/m^2 temozolomide per day over 21 days in a 28-day cycle) in patients with progressive non-enhancing WHO grade II glioma [73]. In responding patients, a reduction of the FET-positive tumour volume could be observed substantially earlier than volume reductions on FLAIR sequences. Similar findings were reported by a subsequent multicenter PET study in a larger number of patients [74]. In two other studies, MET PET was applied to assess response or failure of iodine-125 seed brachytherapy in patients with WHO grade II glioma. Twelve months after brachytherapy, MET uptake was significantly reduced in the tumours, whereas glucose metabolism as assessed by FDG PET remained unchanged [75, 76]. The largest study to date included 61 patients with non-enhancing WHO grade II or III glioma who received chemotherapy with temozolomide or CCNU/procarbazine [77]. The patients were studied by FET PET before and 6 months after initiation of chemotherapy. Patients with a decrease in either metabolic tumour volume ≥ 25% and/or maximum tumour-to-brain ratios ≥ 10% exhibited a significantly longer progression-free survival than patients with stable or increasing FET uptake.

Another important aspect in the monitoring of WHO grade II gliomas is the detection of malignant transformation. In patients with low-grade gliomas following a watch-and-wait strategy, malignant progression has been reported in more than 50 % within a median follow-up time of 7 years [78]. A study using FET PET in 27 patients with histologically proven low-

grade glioma demonstrated that changes of tumour-to-brain ratios and kinetic parameters of FET uptake identified malignant progression with a significantly higher diagnostic accuracy than changes of contrast enhancement in MRI [79].

Summarizing, similar to the results in malignant gliomas, amino acid PET proved to be a reliable tool for tracking therapy response non-enhancing low-grade gliomas.

8. Differentiation of tumour recurrence and treatment-related changes

The differentiation between tumour relapse and therapy-induced changes represents one of the most frequent indications for the use of the amino acid PET in clinical practice. Although it cannot be regarded directly as part of therapy monitoring, it plays an important role in this context and should be considered in this review. As outlined above, pseudoprogression in MRI is a frequent problem following first-line chemoradiation of glioblastoma with temozolomide. FET PET has been shown to differentiate progressive gliomas from pseudoprogression with high accuracy [80, 81]. Concerning the differentiation of recurrent tumour versus radionecrosis or other treatment-related changes, several studies have reported an accuracy ranging from 80 to 90 % for FET or FDOPA PET [5, 82-86]. For MET PET, a recent meta-analysis including 891 patients reported on a pooled sensitivity and specificity of 88 % and 85 % in the differential diagnosis of glioma recurrence [87]. For AMT, a first study in a series of 22 patients reported on a 100 % accuracy to differentiate between recurrent glioma and radiation injury [88]. Thus, amino acid PET has developed as a reliable method to distinguish the frequent therapy-induced structural changes in MRI from tumour progression, which is of crucial importance in therapy monitoring.

9. Cost-effectiveness of treatment monitoring using amino acid PET

The scientifically documented utility of amino acid PET for tracking therapy response in glioma patients emphasizes its use in clinical practice in order to avoid overtreatment and

unnecessary side effects. However, since additional PET examinations are costly, it is important to consider cost efficiency of PET. Some studies addressed the cost-effectiveness using a model-based approach relying on the best available evidence. One study estimated the effectiveness and cost-effectiveness of the addition of FET PET to structural MR imaging for the management of antiangiogenic treatment in patients with recurrent high-grade glioma compared with MR imaging alone [89]. The use of FET PET resulted in a number needed to diagnose of 2.4, indicating that 3 additional patients have to be diagnosed to avoid one wrong diagnosis. From the perspective of the Statutory Health Insurance in Germany the incremental cost-effectiveness ratio of FET PET/MR imaging compared with MR imaging alone was at least 5,725 € per life-year. Thus, costs of FET PET appear to be well justified by their clinical utility. A recent study analyzed cost-effectiveness of follow-up FET PET performed on patients with glioblastoma after surgery and before initiation of temozolomide maintenance treatment [90]. Based on cost calculations from the perspective of the National Institute for Health and Disability Insurance (NIHDI) in Belgium two cost-effectiveness ratios were determined for overall survival and progression-free survival rates. Both of these calculations yielded very similar results: incremental cost-effectiveness ratios of 1,365.86 and 1,357.38 €, respectively, for each identified non-responder. The authors concluded that FET PET is a valuable tool for predicting the treatment responses of patients with glioblastomas to follow-up temozolomide maintenance treatment under consideration of cost-effectiveness.

10. Conclusions

Treatment monitoring of gliomas is still associated with significant shortcomings in the age of high-resolution structural imaging with MRI, which can be solved in many cases by the use of amino acid PET. This method is helpful to assess the extent of tumour resection, to assess therapy response to chemoradiation and other treatment options in patients with malignant gliomas as well as in non-enhancing lower-grade gliomas. The method helps to overcome

pseudoprogression and pseudoresponse, two frequent diagnostic problems of conventional MRI that respectively occur at an early stage after chemoradiation and antiaangiogenic treatment. The costs of amino acid PET appear to be well justified in relation to the clinical benefit. A further establishment of the method in clinical practice is desirable, in order to avoid overtreatment and unnecessary side effects.

11. Expert opinion

Molecular imaging of cerebral gliomas with amino acid PET is becoming more and more available for clinical use. The more widespread use of amino acid PET for the management of patients with brain tumours has been strongly recommended by the RANO group [4, 6].

In view of the rapidly developing novel treatment strategies, a reliable statement on the response to therapy is becoming increasingly important. The available literature convincingly demonstrates the potential of amino acid PET to track therapy response in cerebral gliomas but the number of studies is still too small to draw final conclusions.

Concerning the evaluation of tumour resection some studies observed advantages of amino acid PET over early postoperative MRI.

Tracking therapy response with amino acid PET is best established in malignant gliomas, especially in chemoradiation with temozolomide as well as anti-angiogenic therapy with bevacizumab. Here, the improved identification of pseudoprogression and pseudoresponse plays an important role.

Experience with experimental forms of therapy suggest that molecular imaging with amino acid PET will be helpful to track novel therapeutic approaches in neurooncology.

Furthermore, in non-enhancing lower-grade gliomas, amino acid PET proved to be a reliable tool for tracking therapy response, which is of particular importance as the efficiency of monitoring with conventional MRI is limited in these tumours.

Overall, the data situation has to be improved and an intensification of research is necessary. Unfortunately, amino acid PET is not yet available at every oncologic center treating brain tumours. A limitation for the widespread clinical use of amino acid PET in treatment monitoring of gliomas remains the lack of approval and reimbursement by national insurances. State authorities usually require a proven patient-relevant benefit and/or demonstration of cost-efficiency. This is usually established by randomized, blinded, two-arm multicentre studies, in which patients with brain tumours are diagnosed and monitored with MRI only or amino acid PET and MRI. Such studies take many years but there is little interest for commercial support, because the synthesis of most amino acid tracers has been published and no patent is pending. Furthermore, such studies rise ethical questions since 50 % of the patients would not be given access to a diagnostic method that provides valuable additional information according to current literature. Fortunately, there are exceptions in some countries for university clinics and specialized centers to use amino acid PET in patients with cerebral gliomas for clinical purposes. Owing to the relatively low incidence of cerebral gliomas, this provides access to amino acid PET for a large part of the population in some countries in Western Europe.

Functional or molecular MRI methods, such as perfusion-weighted and diffusion-weighted imaging and proton magnetic resonance spectroscopy are currently under clinical evaluation to overcome the shortcomings of conventional MRI. The fact that amino acid PET is widely used in centres that have full access to the spectrum of functional and molecular MRI methods emphasizes the value of amino acid PET beyond these alternative MRI methods. Nevertheless, reliable treatment monitoring can probably best be achieved by a combination of different imaging techniques [91]. The advent of hybrid PET/MRI offers the opportunity to investigate several parameters in a ‘one-stop shop’. Using hybrid PET/MRI scanners, several studies have been started to investigate these aspects and should lead to meaningful results in the near future. In addition, novel radiopharmaceuticals for PET are being tested, which could

lead to further progress in these issues. Although hybrid PET/MRI has practical advantages and is more convenient for patients, the higher cost of these systems must be weighed against the additional effort of sequential tests.

Thus, it is to be expected that more effective treatment monitoring will become available in the next years leading to a considerable benefit for brain tumour patients.

Article Highlights

- Amino acid PET provides significant additional information for tracking therapy response in glioma patients
- Amino acid PET requires additional scanning but is robust and attractive for clinicians in neurooncology because of easy scan reading
- Amino acid PET in therapy monitoring of gliomas is cost efficient and well justified to avoid overtreatment and unnecessary side effects.
- Improvement of therapy monitoring in gliomas is necessary because therapy is extremely expensive and efficient use of these therapies is mandatory

FIGURES

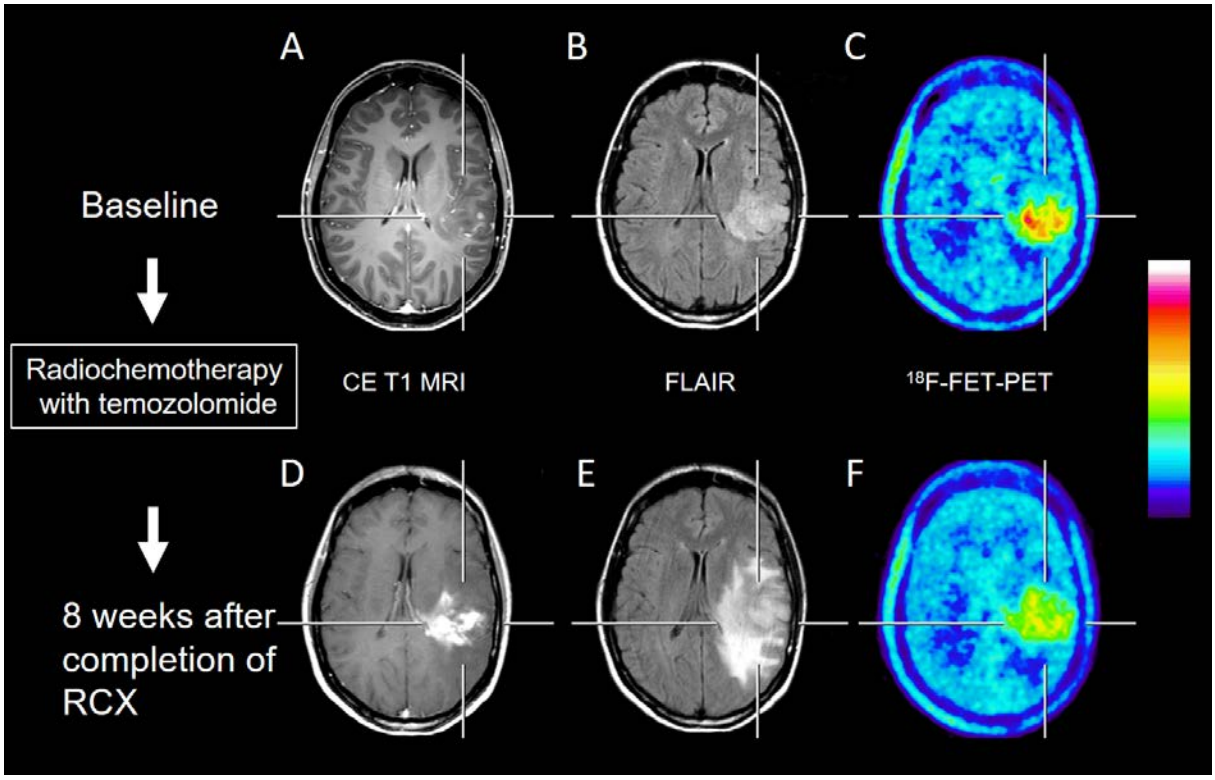

Figure 1: Therapy monitoring in a 47-year-old patient with glioblastoma. Contrast-enhanced MRI (CE T1 MRI), fluid-attenuated inversion recovery (FLAIR) MRI and FET PET (A-C) at baseline and 8 weeks after completion of chemoradiation with concomitant and adjuvant temozolomide (RCX)(D-F). Enlargement of contrast enhancement and FLAIR abnormalities suggest tumour progression whereas FET PET shows decreased metabolic activity compared to initial FET PET demonstrating pseudoprogression which was confirmed by follow-up MRI at 3 months after RCX.

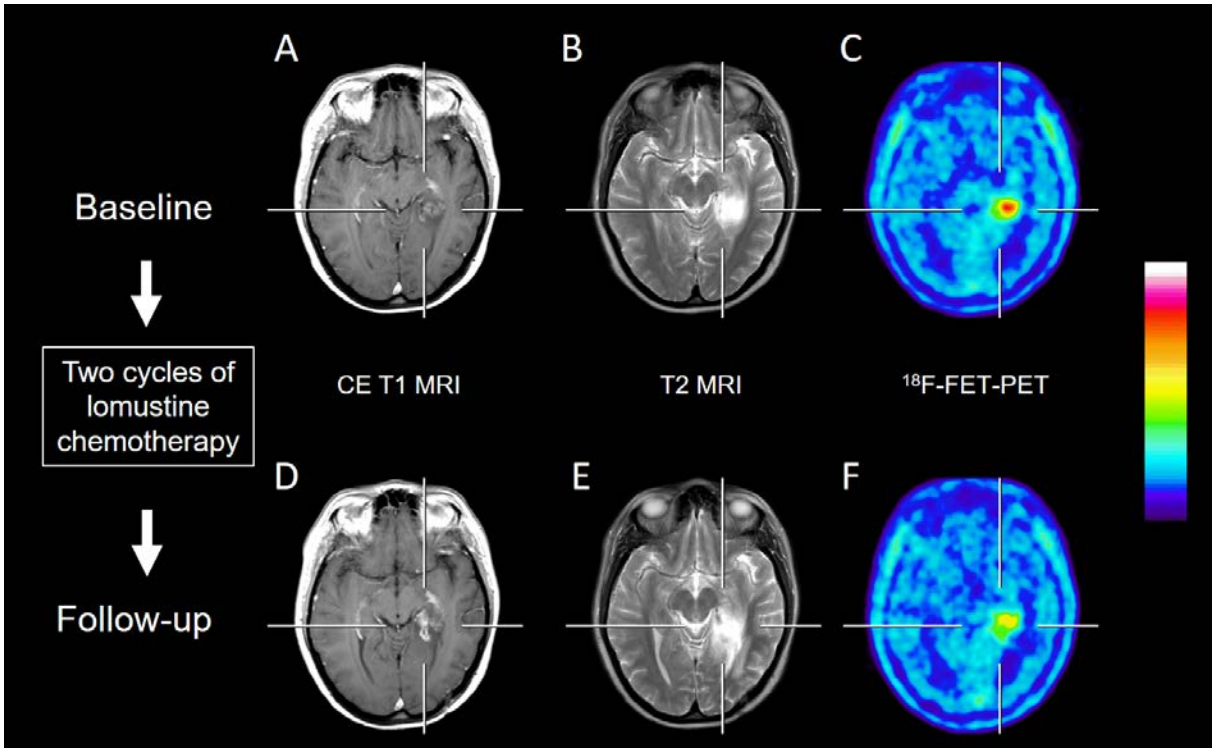

Figure 2: Therapy monitoring in a 31-year-old patient with a recurrent anaplastic astrocytoma in the left parahippocampal region after brachytherapy and radiotherapy with concomitant and adjuvant temozolomide. Contrast-enhanced MRI (CE T1 MRI), T2-weighted MRI and FET PET (A-C) at baseline and 4 months later after 2 cycles of lomustine chemotherapy (D-F). Enlargement of contrast enhancement and the T2 signal suggest tumour progression whereas FET PET indicates a reduction of metabolic activity and response to therapy.

Table 1: *Overview of cut-off values of amino acid PET to assess response to treatment*

Therapy /diagnostic problem	Tracer	Parameter	Cut off	Reference
Differentiation of tumour recurrence/progress versus treatment-related changes	FET	TBR_{max} (ROI Ø 1.6 cm); TTP	>1.9-2.3; TTP < 45 min	[5, 80, 81]
	MET	TBR_{max}	>1.9	[92, 93]
	FDOPA	TBR_{max}	>2.0	[86]
Malignant transformation of low-grade gliomas	FET	TBR_{max}	increase > 33%	[79]
Radiochemotherapy with temozolomide in glioblastoma	FET	TBR_{max}	decrease > 20 %	[52]
Chemotherapy with temozolomide in low-grade gliomas	MET	MTV	decrease > 80 %/65 %	[74]
Antiangiogenic therapy with Bevacizumab/Irinotecan in glioblastoma	FET	BTV	decrease > 45 %	[65, 66]
Temozolomide or lomustine/procarbazine in non-enhancing gliomas	FET	$TBR_{max;}$ BTV	decrease > 10 %; >25 %	[77]
Temozolomide in malignant gliomas	MET	TBR_{max} (ROI Ø 1.2 cm	decrease > 5 %	[53]
Antiangiogenic therapy with bevacizumab in recurrent gliomas	MET	TBR_{mean}	decrease > 25%	[70]
	FDOPA	BTV	decrease > 35 %	[68]

Abbreviations: TBR_{max} /TBR_{mean}= Maximum/mean tumour to brain ratio: TTP = Time-to-peak in time activity curve; MTV/BTV = metabolic or biological tumour volume; ROI = Region-of-interest

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