Clin Transl Imaging (2017) 5:151–158
DOI 10.1007/s40336-017-0222-2

EXPERT REVIEW

Positron emission tomography and magnetic resonance spectroscopy in cerebral gliomas

Thomas Pyka[3] · Jens Gempt[1] · Stefanie Bette[2] · Florian Ringel[1] · Stefan Förster[3,4]

Received: 31 August 2016 / Accepted: 9 January 2017 / Published online: 28 January 2017

Abstract
Purpose Conventional MRI, the gold standard in structural brain imaging, alone has its limitations in pre-operative tumour grading, biopsy targeting, determination of accurate tumour margins prior to surgical resection/radiation therapy, detection of tumour recurrence and determination of early therapeutic response. The aim was to introduce and review two of the recently most discussed adjunct modalities for molecular imaging in glioma: PET and MRS, and the combination of both.
Methods A PubMed search with a combination of the terms "MRS", "glioma" and "glioblastoma", "brain tumour", "positron emission" and "PET" was carried out. These results were complemented with a search of the authors' own files. Preclinical in vitro studies as well as animal studies were excluded.
Results Published single modality data show that ^{1}H-MRS and PET perform similarly in answering clinical questions, which cannot be adequately answered by conventional MR imaging alone. Original articles including patients with gliomas and combining the PET and MRS modalities within the same study were scarce and resulted in 17 research papers. These articles especially point to a spatial correlation between ^{1}H-MRS metabolic ratios and amino acid uptake and a positive relationship with histologically proven cell proliferation markers, indicating diagnostic improvement in the differentiation between glioma and benign lesions, in the delineation of brain tumours and in the differentiation between treatment-related changes and tumour progression.
Conclusion PET and ^{1}H-MRS have shown their value in the non-invasive diagnosis of gliomas delivering metabolic tumour information in addition to pure structural information from conventional MRI or CT alone. The very few studies, which were conducted evaluating ^{1}H-MRS and PET in combination, indicate a diagnostic benefit from a combined imaging approach in glioma and encourage more systematic investigation—ideally carried out in multicentric settings, in experienced neuroimaging centres (with access to integrated PET/MRI scanners), using standardized imaging- and analysis protocols.

Keywords PET · MRI · MRS · glioma

✉ Stefan Förster
stefan.foerster@klinikum-bayreuth.de

[1] Neurochirurgische Klinik und Poliklinik, Klinikum Rechts Der Isar, Technische Universität München, Ismaninger Str. 22, 81675 Munich, Germany

[2] Abteilung für Neuroradiologie, Klinikum Rechts Der Isar, Technische Universität München, Ismaninger Str. 22, 81675 Munich, Germany

[3] Nuklearmedizinische Klinik und Poliklinik, Klinikum Rechts Der Isar, Technische Universität München, Ismaninger Str. 22, 81675 Munich, Germany

[4] Klinik und Institut für Nuklearmedizin, Klinikum Bayreuth, Preuschwitzer Str. 101, 95445 Bayreuth, Germany

Purpose

Conventional magnetic resonance imaging (MRI) has been established as the gold standard for structural imaging of primary brain tumours. However, not all common clinical questions occurring in the management of gliomas are adequately answered by conventional MRI alone, including pre-operative tumour grading, optimization of biopsy targeting and determination of accurate tumour margins for resection and radiation therapy planning. During follow-up,

difficulties may arise regarding the detection of tumour recurrence and its differentiation from post-therapeutic changes as well as regarding the determination of early response to radiochemotherapy or antiangiogenic therapy. Recently introduced, sophisticated imaging methods aiming to provide biochemical and molecular information of glioma, which we summarized under the headword of 'molecular imaging', seek to complement the conventional MRI technique. In this article, we review two of the recently most discussed modalities for molecular imaging in glioma: positron emission tomography (PET) and magnetic resonance spectroscopy (MRS), as well as their combination. Both modalities have been used for several years now, but in many aspects they are still limited to highly specialized imaging centres and not established for broader clinical use.

Methods

Positron emission tomography

Positron emission tomography (PET) is a nuclear medicine imaging technique that produces three-dimensional images of functional processes in the body. The PET scanner detects pairs of anti-parallel gamma rays emitted after the annihilation of positrons which are in turn generated during the decay of certain radioisotopes. Agents studied for imaging of brain tumours include radionuclide-labelled glucose, amino acids and nucleosides. A favourable trait of PET is the possibility to accurately quantify radiotracer concentrations which are known to be increased in cancer tissue compared with normal cells.

While the technique of PET imaging in principle reveals excellent molecular sensitivity down to nanomolar concentrations, resolution is limited physically to a few millimetres, and its diagnostic value is greatly influenced by the biodistribution of the radiopharmaceutical used, as well as its specificity for the process to be imaged. The elegance and effectiveness of PET imaging are furthermore accompanied by several drawbacks related to the production of radiopharmaceuticals: the most commonly used radioisotopes 18-fluoride (18F) and 11-carbon (11C) are cyclotron-produced and short-lived. Consequently, on-site cyclotrons have to be available for 11C-labelled compounds (20 min. half-life). 18F features a little more convenient 110 min, which allows for the delivery of the radiotracer within a radius of about 200 km around the site of production. Radiation has to be taken into account (2–4 mSv using current scanners, equalling 1–2 diagnostic cranial CT scans), but is acceptable, considering the still relatively limited prognosis of brain tumour patients.

18F-fluorodeoxyglucose (FDG)

FDG has long been used to measure metabolic brain activity, as glucose is the main substrate for cerebral energy supply. FDG is transported into the cell and subsequently phosphorylated to FDG phosphate, but does not enter the Krebs cycle or non-oxidative glycolysis, and therefore accumulates in proportion to glucose transporter and hexokinase activity. This property is taken advantage of in neuro-oncologic imaging, as tumours are supposed to exhibit increased glucose uptake and/or metabolism. However, several limitations exist: the marked background brain uptake especially in grey matter hampers identification and quantification particularly in smaller lesions; low-grade gliomas often do not exhibit increased FDG uptake due to moderate metabolic activity; and unspecific tracer uptake, e.g. in case of inflammation, occurs and reduces specificity. Nevertheless, FDG has been used to distinguish low-grade (grade I/II) from high-grade (grade III/IV) gliomas [1, 2], and has shown a certain ability to differentiate between tumour recurrence and therapy-related changes during follow-up [3], while intensity of FDG uptake has been linked to prognosis and survival [4].

18-F-fluoroethyltyrosine (FET) and 11-C-methionine (Met)

Amino acid radiotracers are another class of long-established oncologic PET agents. While FDG is nowadays preferred for tumour imaging at most sites in the body, FET and Met are particularly attractive for imaging of brain tumours: normal brain tissue shows only low background activity, and increased amino acid uptake can be demonstrated in most high-grade gliomas and in a fair proportion of low-grade gliomas even in the absence of a disturbed blood–brain barrier [5]. The uptake mechanism in brain tumours is still under investigation, but over-expression of amino acid transporters such as LAT1 [6] appears to play a crucial role. Met was introduced earlier and has been shown to provide good imaging characteristics; however, the short half-life of its 11C-labelling limits the use to centres with an on-site cyclotron. 18F-FET-PET has demonstrated similar imaging properties to 11C-Met-PET, and is therefore often preferred due to its more convenient use. Sensitivity and specificity for the detection of glioma tissue have been shown to be satisfying for the amino acid tracers [7], and the area of increased uptake in PET is often larger than that of MRI or CT contrast enhancement, improving identification of tumour margins

and infiltration zones [8]. Biopsy targeting may be improved by FET and Met imaging as well, due to their correlation with cell density and metabolism [9]. Finally, amino acid PET is a valuable tool to differentiate treatment effects from tumour progression [10]. The added value of dynamic FET imaging, usually covering 40 min of continuous PET acquisition, is discussed somewhat controversially [11], but may provide useful information with respect to pre-operative grading and follow-up imaging [12–14]. In addition, metabolic volume and uptake heterogeneity in FET-PET imaging might give clues to the prognosis of glioma patients [15–17], and there have been studies pointing out a potential role of pre-operative FET-PET imaging for the recognition of histopathological characteristics of gliomas [18, 19]. Current recommendations by the Response Assessment in Neuro-Oncology (RANO) working group propose amino acid PET to complement MRI in a number of clinical questions, and point out the superiority over FDG imaging in brain tumours [20, 21].

Dihydroxy-18F-fluoro-L-phenylalanine (F-DOPA)

The main application of PET with F-DOPA, another amino acid tracer, is the assessment of presynaptic dopamine synthesis capacity in the brain, e.g. in the evaluation of movement disorders such as Parkinson's disease. That said, its kinetics are relatively similar to FET and methionine, and an elevated PET signal in brain tumours has been reported several years ago [22]. Akin to the amino acid tracers discussed above, the uptake of F-DOPA appears to depend on amino acid transporters such as LAT1 and 2 [23]. While one study suggested superior imaging properties compared to the more established amino acid tracers [24], this has been contradicted by newer results [25]. The current consensus is that F-DOPA has no major advantages or disadvantages over FET and methionine, but this topic is subject to further research. Due to the high physiological F-DOPA uptake in the striatum F-DOPA, PET might be inferior to FET- or Met-PET in the accurate delineation of brain tumours located in the deep white matter in close vicinity to the striatum. The decision which agent to use might in some cases also depend on the local situation regarding tracer approval by regulatory authorities and the more complex synthesis of F-DOPA compared to FET.

18F-fluorothymidine (FLT)

Radio-labelled nucleosides have been proposed as an alternative to the above-mentioned tracers as indicators of cellular proliferation, DNA and RNA synthesis. FLT is supposed to be metabolized by thymidine-1-kinase [26] and correlates well with histologic markers of mitosis [27]. However, penetration of the blood–brain barrier is very limited, and low-grade gliomas normally do not show significantly elevated tracer uptake [28]. While FLT is relatively seldom used compared to the above-mentioned tracers, its link to proliferative activity may make it a favourable agent for therapy monitoring of gliomas in the future.

Proton magnetic resonance spectroscopy

Magnetic resonance spectroscopy (MRS) non-invasively delineates brain tumours by their biochemical profiles. In brain tumour imaging, proton MRS (^{1}H-MRS) is commonly used while other MRS-types like ^{31}P-MRS and ^{13}C-MRS are of minor importance up to now [29]. ^{1}H-MRS exhibits information on metabolite levels in brain tissue, depicting this information in spectra (see Fig. 1). Important metabolites that can be shown in ^{1}H-MRS are as follows:

- Lactate (Lac): Lactate is produced via aerobic glycolysis by tumour cells and normally not found in healthy brain tissue [29–32].
- N-Acetyl aspartate (NAA): NAA is a known neuronal marker and shown to be decreased in glioma tissue [29, 33–35].
- Creatine (Cr): Creatine is involved in cellular energy metabolism [29, 36].
- Choline (Cho): Choline metabolism is known to be important for oncogenesis; elevated choline levels are typical in proliferative diseases [29, 37].
- Lipids (Lip): lipids correlate with necrosis in brain tumours and are usually not found in healthy brain tissue [29, 38, 39].
- Glutamate (Glu): glutamate is an important neurotransmitter and shown to be important for gliomagenesis [40–42].

MRS can be performed as single-voxel (SV) which might be more suitable for focal lesions and as multi-voxel (MV) or chemical shift imaging (CSI) which shows spectra of multiple regions [43]. Besides the metabolites, also the ratios of metabolites play an important role in the diagnosis of intracranial neoplasms. Intracranial tumours display the following typical spectra:

- Reduction of NAA as well as the NAA/Cr ratio due to the reduced number of viable neurons.
- Decrease of Cr.
- Increase of Cho as well as the ratios Cho/NAA and Cho/Cr due to the high proliferation of tumours.
- Lactate peak [29, 43–47].

The Cho/NAA ratio was shown to be a robust parameter for the diagnosis of tumours in ^{1}H-MRS [46]; this was also confirmed by histopathological analysis [48, 49]. The Cho/

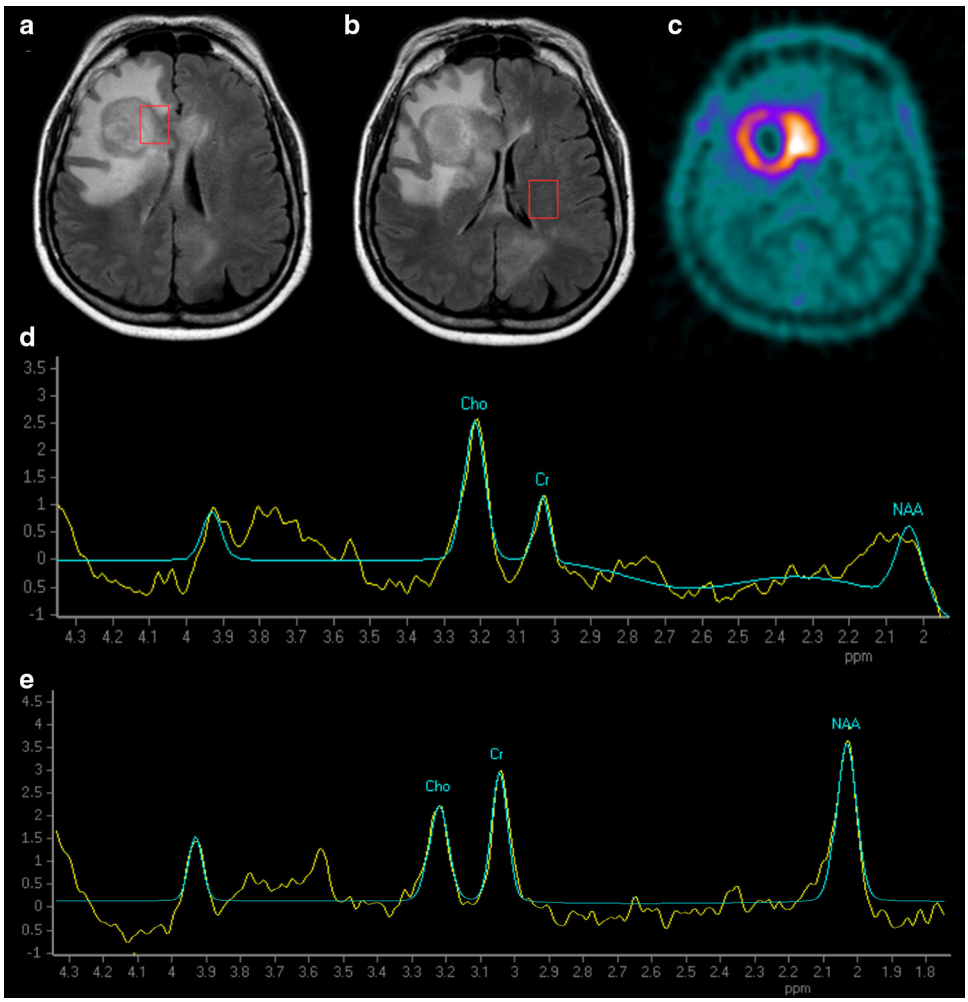

Fig. 1 Example MR spectroscopy and FET-PET in a patient with glioblastoma. A 58-year-old patient with untreated right frontal glioblastoma. **a**, **d** 1H-MRS in the tumour shows elevated choline and decreased creatine and NAA levels, **b**, **e** 1H-MRS in normal brain tissue for comparison, **c** FET-PET scan 30 min after tracer injection

NAA ratio showed higher sensitivity and specificity in the delineation of low-grade and high-grade gliomas than the NAA/Cr and Cho/Cr ratios [50]. The Cho/Cr ratio correlates with cell density in histopathological analysis [49]. Discrimination between radionecrosis and viable tumour via the Cho/Cr ratio as well as the Cho/NAA ratio was reported with only moderate accuracy [51].

In the beginning of ^{1}H-MRS, studies have shown differences in metabolite levels between healthy brain tissue and brain neoplasms [52]. Thus, spectroscopic parameters are considered as prognostic biomarkers in the initial evaluation of glioma patients. There have been several studies illustrating the value of ^{1}H-MRS in the diagnosis of brain tumours regarding the prediction of tumour grade [53, 54] and patient's prognosis [55, 56]. A previous study suggested ^{1}H-MRS in combination with diffusion-weighted imaging as a promising tool for differentiation between tumour progression and pseudoprogression [57].

Another interesting approach is the 2-hydroxyglutarate MRS [58]. Mutation of isocitrate dehydrogenase (IDH) is common in WHO grade 2 and 3 tumours, and plays an important role for patients' outcome which has also been addressed in the new classification of CNS tumours of 2016 [59]. Patients with mutation of IDH show an accumulation of 2-hydroxyglutarate (2-HG) [60]. Choi et al. described that 2-HG MRS is able to detect IDH mutations non-invasively in vivo [58, 61] in gliomas. This might not only be important for initial diagnosis and differentiation from other diseases such as inflammation but also for diagnosis of recurrent disease of IDH-mutated gliomas [61].

Drawbacks of MRS include a relatively high sensitivity to susceptibility artefacts, a property that precludes the use of the method especially in patients with tumours close to the air-filled spaces of the sinuses in frontobasal or temporal locations. Higher magnetic field strengths improve the resolution of MRS, but also increase the tendency of producing artefacts.

Multi-parametric imaging combining MRS and PET

Multi-parametric imaging using both ^{1}H-MRS and PET, combining and analysing the modalities in an appropriate

Table 1 Studies comparing ^{1}H-MRS and PET

Study	Purpose	MRS parameters	PET tracers	Pat.#	Added value	Results/comments
Alger et al. [33]	Initial evaluation	Lac, NAA, Cho, Cr	FDG	28	n/a	Correlative study
Floeth et al. [70]	Diff T/NN	Cho/NAA	FET	50	yes	Combination superior
Stadlbauer et al. [79]	Correlation, grading	Cho/NAA	FET	15	n/a	Good correlation
Nakajima et al. [72]	Diff P/RN	Cho/Cr, Lac/Cho	MET	18	n/a	MRS similar to MET
Prat et al. [62]	Diff P/RN	Cho/NAA	FDG	26	n/a	MRS superior to FDG
Weber et al. [66]	Biopsy targeting	Cho/Cr, Cho/NAA	FLT, FDG	61	n/a	Similar target areas
Hipp et al. [64]	Spatial correlation	Cho/NAA	FDG	37	n/a	Moderate spatial correlation
Goda et al. [69]	Grading prognostication	Cho/Cr, Cho/NAA	FDG	20	n/a	MRS superior to FDG
Bisdas et al. [74]	Grading	Cho/Cr, Cr/NAA, Cho/NAA	MET	28	n/a	MRS superior to MET
Yoon et al. [68]	Grading	Cho/Cr, Lip/Cr, Lac/Cr	FDG	60	n/a	FDG similar to MRS
Gempt et al. [49]	Biopsy targeting	Cho/Cr, Cr/NAA	FET	38	yes	Combination superior
Imani et al. [67]	Diff P/RN	Cho/Cr, Cho/NAA	FDG	12	yes	Combination superior
Dunet et al. [73]	Grading	Cho/Cr	FET	38	yes	ADC superior to MRS
D'Souza et al. [71]	Diff P/RN	Cho/Cr	MET	29	n/a	MET similar to MRS
Mauler et al. [75]	Spatial correlation	Cho/NAA	FET	14	n/a	Poor spatial correlation
Morana et al. [76]	Diff T/NN prognostication	Lip, Lac	F-DOPA	27	n/a	F-DOPA similar to MRS
Collet et al. [65]	Grading	Cho/Cr, Cr/NAA, Cho/NAA	FLT	39	n/a	FLT superior to MRS

Diff T/NN differentiation tumour/non-neoplastic, *Diff P/RN* differentiation progression/radionecrosis, *Cho* choline, *Cr* creatine, *NAA* N-acetylaspartate, *Lip* lipids, *Lac* lactate, *ADC* apparent diffusion coefficient

manner, promises to enhance sensitivities and specificities, and consequently increase the value for the clinician. However, relatively few studies have been conducted to directly compare and correlate 1H-MRS and PET in brain tumours. We performed a PubMed search with a combination of the terms "MRS", "glioma" and "glioblastoma", "brain tumour", "positron emission" and "PET"; the results were complemented with a search of the authors' own files. Original articles including human patients with gliomas and actually combining the modalities within the same study were extracted, resulting in 17 research papers. Table 1 provides an overview of the articles.

Results

Pioneering work, with regard to FDG and ^{1}H-MRS, was carried out by Alger et al. comparing FDG uptake and spectroscopy in intracranial gliomas, showing moderate correlations [33]. Prat et al. found in a series of 26 patients that ^{1}H-MRS using the Cho/NAA ratio was superior to FDG in detecting progression in glioma after therapy, but suggested that a multi-modal approach would be preferable, although this claim was not backed up by a dedicated analysis [62]. To the contrary, Imani et al. [63] reported a slightly higher accuracy for FDG PET than for Cho/Cr spectroscopy in a cohort of grade 2 and grade 3 gliomas, and a congruency of diagnoses in 75% of cases. In a study on paediatric brain tumours, moderate spatial agreement of hot spots in Cho/NAA ^{1}H-MRS and FDG PET could be shown [64]. For a combination of FLT PET and ^{1}H-MRS, Colet et al. could demonstrate accurate pre-therapeutic grading of gliomas [65], and Weber et al. showed that similar targets for biopsies are identified by FLT PET, FDG PET and ^{1}H-MRS [66]. In more recent publications, it has been shown that FDG PET and MRS can be combined favourably in order to detect progression in gliomas [67], while grading information was congruent [68]. In paediatric patients, ^{1}H-MRS was able to detect diffuse brainstem glioma, and was superior to FDG PET for this purpose when combined with diffusion- and perfusion-weighted MR imaging [69].

The growing interest in amino acid PET tracers fosters their use in multi-modal imaging studies. Floeth et al. compared ^{1}H-MRS Cho/NAA ratios and FET uptake for differentiation between glioma and benign lesions [70] and showed that, while performing quite similar in this setting, a combination of the two modalities results in further diagnostic improvement. In an investigation on high-grade gliomas after

radiochemotherapy, D'Souza et al. demonstrated the improved diagnostic performance for detection of recurrence of both methionine PET and ^{1}H-MRS using Cho/Cr ratios compared to conventional MRI, but did not execute analyses on agreement and added value of the two modalities [71]. Nakijima et al. published congruent results, emphasizing the importance of the high specificity of amino acid PET which can be of use for multi-modal analyses [72]. In another study by Dunet et al., dynamic FET-PET was compared with diffusion-weighted imaging and Cho/Cr spectroscopy for pre-operative grading of gliomas, showing that the first two modalities exhibited good accuracy which increased further when combined, while ^{1}H-MRS was not comparatively useful in this cohort [73]. Furthermore, methionine PET uptake and Cr/NAA ratio were correlated in a study by Bisdas et al. [74], while Gempt et al. verified this relation for FET and additionally showed that biopsies taken from glioma metabolic hot spots determined by FET-PET and ^{1}H-MRS had higher Mib1 values, corresponding to increased mitotic activity [49]. Mauler et al., to the contrary, demonstrated only poor spatial congruence of FET uptake and Cho/NAA spectroscopy [75]. In a recent work by Morana et al., the performance for the detection of vital tumour and prognostication in paediatric supratentorial gliomas was assessed, and F-DOPA and ^{1}H-MRS performed similarly in this setting [76].

To sum up, published data suggest that ^{1}H-MRS and PET perform similarly in answering critical clinical questions which cannot be adequately answered by conventional MR imaging, including pre-operative detection, staging and delineation of brain tumours, and differentiation between treatment-related changes and tumour progression during follow-up. However, only a handful of studies commented on the added value provided by the combination of both modalities, a topic which is becoming of particular interest with the advent of simultaneous PET/MRI, offering increased patient convenience in the sense of a 'one-stop-shop' and improving spatial and temporal coregistration. Imaging protocols are currently being established for integrated PET/MRI scanners [77], and new applications for the combination of PET and ^{1}H-MRS, such as PET-guided spectroscopy, are thought up and are waiting to be evaluated systematically [78]. The published results regarding multi-modal analysis of combined ^{1}H-MRS and especially amino acid PET are promising, constantly showing a significant benefit through the combination of both modalities. Nevertheless, data on the topic are still scarce, and further studies with larger patient numbers are needed to establish the usefulness of a combined multi-modal approach.

Conclusion

Since several years now, PET and ^{1}H-MRS have shown their value in the non-invasive diagnosis of gliomas delivering metabolic tumour information in addition to pure structural information from conventional MRI or CT alone. To date, only few studies were conducted evaluating ^{1}H-MRS and PET in combination, indicating a benefit from a combined imaging approach, and encouraging further studies on the topic—ideally carried out in experienced neuroimaging centres with access to integrated PET/MRI scanners.

Compliance with ethical standards

Conflict of interest None.

References

1. Di Chiro G et al (1982) Glucose utilization of cerebral gliomas measured by [18F] fluorodeoxyglucose and positron emission tomography. Neurology 32(12):1323–1329
2. Delbeke D et al (1995) Optimal cutoff levels of F-18 fluorodeoxyglucose uptake in the differentiation of low-grade from high-grade brain tumors with PET. Radiology 195(1):47–52
3. Glantz MJ et al (1991) Identification of early recurrence of primary central nervous system tumors by [18F] fluorodeoxyglucose positron emission tomography. Ann Neurol 29(4):347–355
4. Holzer T et al (1993) FDG-PET as a prognostic indicator in radiochemotherapy of glioblastoma. J Comput Assist Tomogr 17(5):681–687
5. Herholz K et al (1998) 11C-methionine PET for differential diagnosis of low-grade gliomas. Neurology 50(5):1316–1322
6. Habermeier A et al (2015) System L amino acid transporter LAT1 accumulates O-(2-fluosroethyl)-L-tyrosine (FET). Amino Acids 47(2):335–344
7. Pauleit D et al (2005) O-(2-[18F]fluoroethyl)-L-tyrosine PET combined with MRI improves the diagnostic assessment of cerebral gliomas. Brain 128(Pt 3):678–687
8. Arbizu J et al (2012) Quantitative volumetric analysis of gliomas with sequential MRI and (1)(1)C-methionine PET assessment: patterns of integration in therapy planning. Eur J Nucl Med Mol Imaging 39(5):771–781
9. Pirotte B et al (2004) Comparison of 18F-FDG and 11C-methionine for PET-guided stereotactic brain biopsy of gliomas. J Nucl Med 45(8):1293–1298
10. Galldiks N et al (2015) The use of dynamic O-(2-18F-fluoroethyl)-L-tyrosine PET in the diagnosis of patients with progressive and recurrent glioma. Neuro Oncol 17(9):1293–1300
11. Piroth MD et al (2013) Monitoring of radiochemotherapy in patients with glioblastoma using O-(2-(1)(8)Fluoroethyl)-L-tyrosine positron emission tomography: is dynamic imaging helpful? Mol Imaging 12(6):388–395
12. Galldiks N et al (2015) The use of dynamic O-(2-18F-fluoroethyl)-L-tyrosine PET in the diagnosis of patients with progressive and recurrent glioma. Neuro Oncol 17(9):1293-1300
13. Gempt J et al (2015) 18F-fluoro-ethyl-tyrosine positron emission tomography for grading and estimation of prognosis in patients with intracranial gliomas. Eur J Radiol 84(5):955–962

14. Popperl G et al (2007) FET PET for the evaluation of untreated gliomas: correlation of FET uptake and uptake kinetics with tumour grading. Eur J Nucl Med Mol Imaging 34(12):1933–1942
15. Bette S et al (2016) Static FET–PET and MR imaging in anaplastic gliomas (WHO III). World Neurosurg 91:524–531
16. Suchorska B et al (2015) Biological tumor volume in 18FET-PET before radiochemotherapy correlates with survival in GBM. Neurology 84(7):710–719
17. Pyka T et al (2016) Textural analysis of pre-therapeutic [18F]-FET-PET and its correlation with tumor grade and patient survival in high-grade gliomas. Eur J Nucl Med Mol Imaging 43(1):133–141
18. Bette S et al (2016) Prognostic value of O-(2-[18F]-fluoroethyl)-L-tyrosine-positron emission tomography imaging for histopathologic characteristics and progression-free survival in patients with low-grade glioma. World Neurosurg 89:230–239
19. Jansen NL et al (2012) Prediction of oligodendroglial histology and LOH 1p/19q using dynamic [(18)F]FET-PET imaging in intracranial WHO grade II and III gliomas. Neuro Oncol 14(12):1473–1480
20. Albert NL et al (2016) Response Assessment in Neuro-Oncology working group and European Association for Neuro-Oncology recommendations for the clinical use of PET imaging in gliomas. Neuro Oncol 18(9):1199–1208
21. Langen KJ, Watts C (2016) Neuro-oncology: amino acid PET for brain tumours—ready for the clinic? Nat Rev Neurol 12(7):375–376
22. Heiss WD et al (1996) F-Dopa as an amino acid tracer to detect brain tumors. J Nucl Med 37(7):1180–1182
23. Youland RS et al (2013) The role of LAT1 in (18)F-DOPA uptake in malignant gliomas. J Neuro oncol 111(1):11–18
24. Kratochwil C et al (2014) Intra-individual comparison of (1)(8)F-FET and (1)(8)F-DOPA in PET imaging of recurrent brain tumors. Neuro Oncol 16(3):434–440
25. Lapa C et al (2014) Comparison of the amino acid tracers 18F-FET and 18F-DOPA in high-grade glioma patients. J Nucl Med 55(10):1611–1616
26. Rasey JS et al (2002) Validation of FLT uptake as a measure of thymidine kinase-1 activity in A549 carcinoma cells. J Nucl Med 43(9):1210–1217
27. Chen W et al (2005) Imaging proliferation in brain tumors with 18F-FLT PET: comparison with 18F-FDG. J Nucl Med 46(6):945–952
28. Jacobs AH et al (2005) 18F-fluoro-L-thymidine and 11C-methylmethionine as markers of increased transport and proliferation in brain tumors. J Nucl Med 46(12):1948–1958
29. Chaumeil MM, Lupo JM, Ronen SM (2015) Magnetic resonance (MR) metabolic imaging in glioma. Brain Pathol 25(6):769–780
30. Poteet E et al (2013) Reversing the Warburg effect as a treatment for glioblastoma. J Biol Chem 288(13):9153–9164
31. Vander Heiden MG, Cantley LC, Thompson CB (2009) Understanding the Warburg effect: the metabolic requirements of cell proliferation. Science 324(5930):1029–1033
32. Warburg O (1956) On the origin of cancer cells. Science 123(3191):309–314
33. Alger JR et al (1990) Metabolism of human gliomas: assessment with H-1 MR spectroscopy and F-18 fluorodeoxyglucose PET. Radiology 177(3):633–641
34. Law M et al (2003) Glioma grading: sensitivity, specificity, and predictive values of perfusion MR imaging and proton MR spectroscopic imaging compared with conventional MR imaging. AJNR Am J Neuro radiol 24(10):1989–1998
35. Miller BL (1991) A review of chemical issues in ^{1}H NMR spectroscopy: *N*-acetyl-L-aspartate, creatine and choline. NMR Biomed 4(2):47–52
36. Patra S et al (2012) A short review on creatine–creatine kinase system in relation to cancer and some experimental results on creatine as adjuvant in cancer therapy. Amino Acids 42(6):2319–2330
37. Glunde K, Bhujwalla ZM, Ronen SM (2011) Choline metabolism in malignant transformation. Nat Rev Cancer 11(12):835–848
38. Negendank W, Sauter R (1996) Intratumoral lipids in ^{1}H MRS in vivo in brain tumors: experience of the Siemens cooperative clinical trial. Anticancer Res 16(3B):1533–1538
39. Zoula S et al (2003) Correlation between the occurrence of ^{1}H-MRS lipid signal, necrosis and lipid droplets during C6 rat glioma development. NMR Biomed 16(4):199–212
40. Campbell SL, Buckingham SC, Sontheimer H (2012) Human glioma cells induce hyperexcitability in cortical networks. Epilepsia 53(8):1360–1370
41. Robert SM, Sontheimer H (2014) Glutamate transporters in the biology of malignant gliomas. Cell Mol Life Sci 71(10):1839–1854
42. Takano T et al (2001) Glutamate release promotes growth of malignant gliomas. Nat Med 7(9):1010–1015
43. Brandao LA, Domingues RC (2004) MR Spectroscopy of the Brain. Lippincott Williams & Wilkins, Philadelphia, Pennsylvania
44. Gyngell ML et al (1992) Localized proton NMR spectroscopy of experimental gliomas in rat brain in vivo. NMR Biomed 5(6):335–340
45. Luo Y et al (1999) In vivo observation of lactate methyl proton magnetization transfer in rat C6 glioma. Magn Reson Med 41(4):676–685
46. McKnight TR et al (2001) An automated technique for the quantitative assessment of 3D-MRSI data from patients with glioma. J Magn Reson Imaging 13(2):167–177
47. Remy C et al (1994) In vivo, ex vivo, and in vitro one- and two-dimensional nuclear magnetic resonance spectroscopy of an intracerebral glioma in rat brain: assignment of resonances. J Neurochem 62(1):166–179
48. Chang SM et al (2009) Integration of preoperative anatomic and metabolic physiologic imaging of newly diagnosed glioma. J Neurooncol 92(3):401–415
49. Gempt J et al (2014) Multimodal imaging in cerebral gliomas and its neuropathological correlation. Eur J Radiol 83(5):829–834
50. Wang Q et al (2016) The diagnostic performance of magnetic resonance spectroscopy in differentiating high-from low-grade gliomas: a systematic review and meta-analysis. Eur Radiol 26(8):2670–2684
51. Zhang H et al (2014) Role of magnetic resonance spectroscopy for the differentiation of recurrent glioma from radiation necrosis: a systematic review and meta-analysis. Eur J Radiol 83(12):2181–2189
52. Bruhn H et al (1989) Noninvasive differentiation of tumors with use of localized H-1 MR spectroscopy in vivo: initial experience in patients with cerebral tumors. Radiology 172(2):541–548
53. Sahin N et al (2013) Advanced MR imaging techniques in the evaluation of nonenhancing gliomas: perfusion-weighted imaging compared with proton magnetic resonance spectroscopy and tumor grade. Neuroradiol J 26(5):531–541
54. Liu ZL et al (2012) Noninvasive evaluation of cerebral glioma grade by using diffusion-weighted imaging-guided single-voxel proton magnetic resonance spectroscopy. J Int Med Res 40(1):76–84
55. Yamasaki F et al (2011) Magnetic resonance spectroscopic detection of lactate is predictive of a poor prognosis in patients with diffuse intrinsic pontine glioma. Neuro Oncol 13(7):791–801
56. Hattingen E et al (2008) Prognostic value of choline and creatine in WHO grade II gliomas. Neuroradiology 50(9):759–767

57. Kazda T et al (2016) Advanced MRI increases the diagnostic accuracy of recurrent glioblastoma: single institution thresholds and validation of MR spectroscopy and diffusion weighted MR imaging. Neuroimage Clin 11:316–321
58. Choi C et al (2012) 2-Hydroxyglutarate detection by magnetic resonance spectroscopy in IDH-mutated patients with gliomas. Nat Med 18(4):624–629
59. Louis DN et al (2016) The 2016 World Health Organization classification of tumors of the central nervous system: a summary. Acta Neuropathol 131(6):803–820
60. Lu C et al (2012) IDH mutation impairs histone demethylation and results in a block to cell differentiation. Nature 483(7390):474–478
61. de la Fuente MI et al (2016) Integration of 2-hydroxyglutarate-proton magnetic resonance spectroscopy into clinical practice for disease monitoring in isocitrate dehydrogenase-mutant glioma. Neuro Oncol 18(2):283–290
62. Prat R et al (2010) Relative value of magnetic resonance spectroscopy, magnetic resonance perfusion, and 2-(18F) fluoro-2-deoxy-D-glucose positron emission tomography for detection of recurrence or grade increase in gliomas. J Clin Neurosci 17(1):50–53
63. Imani F et al (2012) Comparison of proton magnetic resonance spectroscopy with fluorine-18 2-fluoro-deoxyglucose positron emission tomography for assessment of brain tumor progression. J Neuroimaging 22(2):184–190
64. Hipp SJ et al (2012) Molecular imaging of pediatric brain tumors: comparison of tumor metabolism using (1)(8)F-FDG-PET and MRSI. J Neurooncol 109(3):521–527
65. Collet S et al (2015) [(18)F]-fluoro-L-thymidine PET and advanced MRI for preoperative grading of gliomas. Neuroimage Clin 8:448–454
66. Weber MA et al (2010) Biopsy targeting gliomas: do functional imaging techniques identify similar target areas? Invest Radiol 45(12):755–768
67. Imani F et al (2014) Molecular and metabolic pattern classification for detection of brain glioma progression. Eur J Radiol 83(2):e100–e105
68. Yoon JH et al (2014) Grading of cerebral glioma with multiparametric MR imaging and 18F-FDG-PET: concordance and accuracy. Eur Radiol 24(2):380–389
69. Goda JS et al (2013) Can multiparametric MRI and FDG-PET predict outcome in diffuse brainstem glioma? A report from a prospective phase-II study. Pediatr Neurosurg 49(5):274–281
70. Floeth FW et al (2005) Multimodal metabolic imaging of cerebral gliomas: positron emission tomography with [18F]fluoroethyl-L-tyrosine and magnetic resonance spectroscopy. J Neurosurg 102(2):318–327
71. D'Souza MM et al (2014) 11C-MET PET/CT and advanced MRI in the evaluation of tumor recurrence in high-grade gliomas. Clin Nucl Med 39(9):791–798
72. Nakajima T et al (2009) Differential diagnosis between radiation necrosis and glioma progression using sequential proton magnetic resonance spectroscopy and methionine positron emission tomography. Neurol Med Chir (Tokyo) 49(9):394–401
73. Dunet V et al (2014) Combination of MRI and dynamic FET PET for initial glioma grading. Nuklearmedizin 53(4):155–161
74. Bisdas S et al (2013) Metabolic mapping of gliomas using hybrid MR-PET imaging: feasibility of the method and spatial distribution of metabolic changes. Invest Radiol 48(5):295–301
75. Mauler J et al (2015) Congruency of tumour volume delineated by FET PET and MRSI. EJNMMI Phys 2(Suppl 1):A61
76. Morana G et al (2015) Diagnostic and prognostic value of 18F-DOPA PET and 1H-MR spectroscopy in pediatric supratentorial infiltrative gliomas: a comparative study. Neuro Oncol 17(12):1637–1647
77. Bailey DL et al (2015) Combined PET/MR: the real work has just started. Summary report of the third international workshop on PET/MR imaging; February 17–21, 2014, Tubingen, Germany. Mol Imaging Biol 17(3):297–312
78. Kim ES et al (2016) A novel, integrated PET-guided MRS technique resulting in more accurate initial diagnosis of high-grade glioma. Neuroradiol J 29(3):193–197
79. Stadlbauer A et al (2008) Metabolic imaging of cerebral gliomas: spatial correlation of changes in O-(2-18F-fluoroethyl)-L-tyrosine PET and proton magnetic resonance spectroscopic imaging. J Nucl Med 49(5):721–729