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REVIEW ARTICLE

PET/MRI and brain tumors: focus on radiation oncology treatment planning

Oliver Oehlke[1] · **Anca-Ligia Grosu**[1,2,3]

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Abstract In brain tumors, imaging by magnetic resonance imaging (MRI) can very accurately visualize anatomy and morphology of healthy and malignant tissue, but neither contrast-enhancing areas in T1-weighted sequences, nor hyperintensities in T2/FLAIR sequences are specific for tumor tissue, especially when considering the manifold alterations resulting from previous treatment. Imaging the biology of tumor tissue by positron emission tomography (PET), therefore, is a highly interesting approach to improve the detection of macroscopic tumor which is the prerequisite for high-precision radiotherapy treatment planning. This review will focus on the benefits of amino acid tracers (L-[methyl-^{11}C]methionine (MET) and *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine (FET)) in neurooncology and their implementation in radiation oncology. Furthermore, a brief overview of the current impact of 2-deoxy-2-(18F)fluoro-D-glucose (FDG), nucleic acid analogs, hypoxia tracers, and Somatostatin receptor (SSTR) analogs on radiotherapy planning in brain tumors is provided. Among advances in multiparametric MRI, Diffusion-weighted imaging (DWI) has attracted particular attention since it can predict prognosis, as well as indicate response to treatment and has already been introduced into target volume definition for radiotherapy of various cancers (e.g., prostate and rectal cancer). Additionally, advances in MR spectroscopy (MRS) are mentioned. Finally, these findings will be discussed concerning their influence on current aspects of integrated PET/MR hybrid imaging.

Keywords *O*-(2-[^{18}F]Fluoroethyl)-L-tyrosine · *L*-[Methyl-^{11}C]methionine · 30-Deoxy-30-[^{18}F]-fluorothymidine · 1*H*-1-(3-[^{18}F]Fluoro-2-hydroxypropyl)-2-nitroimidazole · Radiotherapy · Target volume definition

Introduction

In brain tumors, imaging by magnetic resonance imaging (MRI) can very accurately visualize anatomy and morphology of healthy and malignant tissue, is widely available and, therefore, the standard imaging modality after onset of symptoms or in follow up after multimodal (surgery, chemotherapy, radiotherapy) treatment. Nevertheless, neither contrast-enhancing areas in T1-weighted sequences, nor hyperintensities in T2/FLAIR sequences are specific for tumor tissue, especially when considering the manifold alterations resulting from previous treatment [1]. New concepts such as pseudoprogression and pseudoresponse [2] add another level of complexity and underline the limits of conventional MRI in the care of patients with brain tumors [3].

In the brain, it is now possible to irradiate irregularly shaped and complex target volumes with a precision of less than 1 mm without the need of invasive fixation, while in parallel vastly sparing normal tissue. This setting is the prerequisite for a significant escalation of the radiation dose for the tumor tissue and by that increasing local

✉ Anca-Ligia Grosu
anca.grosu@uniklinik-freiburg.de

Oliver Oehlke
oliver.oehlke@uniklinik-freiburg.de

[1] Department of Radiation Oncology, Medical Center-University of Freiburg, Robert-Koch-Str. 3, 79106 Freiburg, Germany

[2] German Cancer Research Center (DKFZ), Heidelberg, Germany

[3] German Cancer Consortium (DKTK), Partner Site Freiburg, Germany

control rates. The advantages of high precision radiotherapy can only be achieved, however, when the tumor extent can be accurately determined [4]. Along this line, imaging the biology of tumor tissue by positron emission tomography (PET) is a highly interesting approach to improve the detection of macroscopic tumor (gross tumor volume, GTV) for radiotherapy treatment planning [5, 6].

This review will focus on amino acid (AA) tracers and their implementation in radiation oncology treatment planning, and give a brief overview of recent reports on 2-deoxy-2-(^{18}F)fluoro-D-glucose (FDG), proliferation and hypoxia tracers in this context, as well as the impact of somatostatin receptor (SSTR) analogs for target volume delineation of meningeoma. Among advances in multiparametric MRI, Diffusion-weighted imaging (DWI) has attracted particular attention since it can predict prognosis, as well as indication response to treatment and has already been introduced into target volume definition for radiotherapy of various cancers (e.g., prostate and rectal cancer). Additionally, advances in MR spectroscopy (MRS) are mentioned. Finally, these findings will be discussed against the background of current aspects of PET/MR hybrid imaging.

PET for radiation oncology treatment planning

2-Deoxy-2-(^{18}F)fluoro-D-glucose (FDG)

PET imaging using 2-deoxy-2-(^{18}F)fluoro-D-glucose (FDG) nowadays is of limited use either in the primary diagnostic setting, or in the differentiation between tumor recurrence and post-treatment changes due to its high physiological glucose uptake in normal brain tissue [8] and its accumulation in macrophages and granulation tissue [8].

A potentially interesting method to improve the distinction between tumour and normal gray matter is delayed scanning [9]. Results on a voxel-based level indeed demonstrated a significant improvement in sensitivity for brain tumor diagnosis using dual-time-point imaging, compared with standard 18F-FDG, but the methodology was of limited value for tumor volume delineation [10].

Amino acid tracers

The most commonly used amino acid (AA) tracers in brain tumor diagnostic, radiation oncology treatment planning, and response assessment in Europe are L-[methyl-^{11}C]methionine (MET) and *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine (FET) [11]. Shortly after the introduction of brain imaging with radiolabeled AA [12], the first reports already indicated its potential benefit in diagnostic accuracy, as well as tumor extent of glioma compared to CT [13] or MRI [14]. In contrast to FDG, especially FET shows significantly lower uptake in non-neoplastic inflammatory cells [15]. In the following decades, the higher sensitivity and specificity of AA-PET in the diagnosis of gliomas in comparison to CT and standard MRI was demonstrated in many clinical trials involving over 2000 patients in general and nearly 700 investigated by PET/MRI/CT and verification by stereotactical biopsies [6]. Taken together, these studies have shown that the specificity of MET- and FET-PET for malignant gliomas is significantly higher (85–95 %) in comparison to standard MRI, which also has a high sensitivity but a lower specificity [6, 16]. Furthermore, AA-PET may have the potential to predict treatment response and survival time at an early stage of disease [17], as well as differentiating pseudoprogression from early progression [18].

Whereas the use of MET is limited to centers with an on-site cyclotron due to the short half-life (20 min) of carbon-11 [12], the possibility to radiolabel FET with fluorine-18 (physical half-life 110 min) [19, 20] helped to distribute metabolic brain tumor imaging to smaller centers without on-site cyclotron. Despite the development of amino acid tracers with longer half-lives, molecular imaging in neurooncology is still far more limited than oncologic PET scans using ^{18}F-FDG for non-CNS malignancies [21].

In an experimental setting, FET accumulated to a significantly greater extent in tumour cells than in inflammatory cells, compared to MET. These marked differences suggest that FET and MET are substrates of different subtypes of the L system of amino acid transport [22]. Clinically, both tracers have a comparable uptake and image contrast [23], and are, therefore, considered equivalent concerning their application in radiation oncology treatment planning [24].

Along the line of improved detection of glioma tissue, amino acid PET imaging found its way into adjuvant radiotherapy treatment planning [25] of high-grade glioma (HGG). In 39 patients with high grade gliomas imaged postoperatively, tumor contrast enhancement in MRI and AA uptake significantly corresponded in only 13 % of the patients. On average, only 32 % of the tumor volume defined on AA-PET also showed contrast enhancement on MRI. For radiotherapy treatment planning, these significant non-overlap volumes would result in critically different target volumes. In a small single-center prospective nonrandomized cohort of 44 patients, the implementation of biological imaging into radiation oncology treatment planning of recurrent HGG resulted in a significant increase in overall survival, compared to patients treated based on CT and/or MRI only [26].

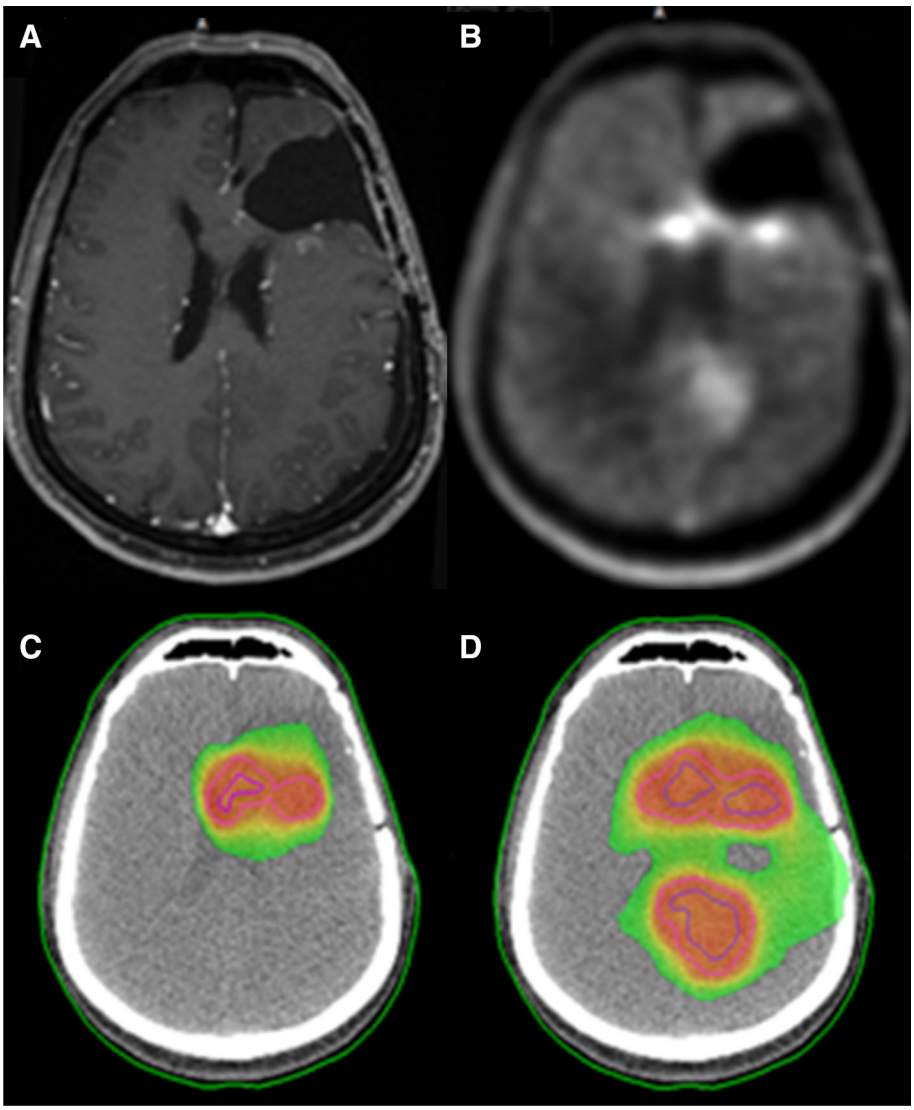

Fig. 1 Impact of AA-PET in target volume delineation of recurrent HGG. **a** Contrast-enhanced T1-weighted MRI of a 47 year old male patient with a multifocal recurrence of a glioblastoma surrounding the resection cavity. **b** The corresponding FET-PET acquired at the same day shows an additional lesion dorso-cranial to the left lateral ventricle that does not take up contrast in MRI. The images in the lower row depict the resulting radiotherapy treatment plans, either according to MRI (**c**) or FET-PET (**d**). The gross tumor (*violet*), planning target volumes (*pink*), and isodose distribution (*yellow* 95 % isodose, *green* 50 % isodose) differ significantly (Courtesy of: Dept. of Radiation Oncology, Medical Center—University of Freiburg)

However, up to date there are no data from randomized trials demonstrating the impact of AA-PET based irradiation treatment on the clinical follow-up in comparison to a traditional MRI based treatment. This lack of data is sought to be filled by the results of the GLIAA trial (Amino-acid PET versus MRI guided re-irradiation in patients with recurrent glioblastoma multiforme, NCT01252459, clinicaltrials.gov), a randomized prospective multicenter phase II trial, which is actively recruiting in 15 centers throughout Germany (Principal Investigator: Dept. of Radiation Oncology, Medical Center—University of Freiburg). All patients in this trial will receive pretreatment FET-PET and MRI and will then be randomized either into reirradiation (39 Gy in 13 fractions of 3 Gy, 5× per week) planned according to a target volume derived from AA-PET GTV, or according to contrast-enhancement on T1-weighted MRI (standard arm, see Fig. 1). This is, to our knowledge, the first phase II randomized study evaluating the impact of molecular imaging on patient outcome (primary endpoint: progression-free survival 6 months after randomization) after radiotherapy for brain tumor patients.

Early-phase nonrandomized clinical trials have been undertaken to further investigate the possible impact of implementing AA-PET in dose-intensified radiotherapy treatment planning for HGG at initial diagnosis [27, 28], but failed to show a clear clinical benefit in terms of progression-free or overall survival. This could potentially be explained by the fact that for over 90 % of the patients [29], the FET-PET-positive volume can be found inside the clinical target volume (CTV) based on contrast-enhancement in T1-weighted MRI with 20 mm margin [30].

Nucleic acid analogs

As for all malignant tumors, proliferation of cells is the basic mechanism for progressive disease. The thymidine

analog 30-deoxy-30-[^{18}F]-fluorothymidine (FLT) is retained in the cell after phosphorylation by thymidine kinase 1, whose levels correlate with cell proliferation [31]. The kinetics of FLT uptake in malignant gliomas correlates with cell proliferation measured by Ki-67 [32, 33]. Since ^{18}F-FLT does not cross intact brain-blood-barrier (BBB) it does not show increased uptake in low-grade tumors but visualize high-grade lesions with a disruption of the BBB [34]. Due to this limitation, FLT in radiotherapy treatment planning of glioma has not been clinically validated, as it has been shown for head and neck squamous cell carcinoma (HNSCC) for example [35].

Hypoxia tracers

1*H*-1-(3-[^{18}F]fluoro-2-hydroxypropyl)-2-nitroimidazole ([^{18}F]-Fluoromisonidazole, FMISO) is a nitroimidazole derivative used to image the hypoxic cell fraction of tissue [36], a marker for radioresistance [37]. Although initial data demonstrating a subpopulation of hypoxic cells in malignant glioma were published more than 20 years ago [38], still today FMISO is not yet well established as a potential tracer to guide adaption of established radiotherapy treatment planning and dose prescription concepts [39, 40], whereas data again in HNSCC suggest a strong correlation of degree of hypoxia with outcome after radiochemotherapy [41, 42].

Somatostatin receptor (SSTR) analogs

Analogs of the somatostatin receptor subtype 2 (SSTR2), ^{68}Ga-DOTA-D-Tyr3-octreotate (^{68}Ga-DOTATATE) or ^{68}Ga-DOTA-D-Phe1-Tyr3-octreotide (^{68}Ga-DOTATOC), are used for improved target volume delineation for meningiomas [43] and glomus tumours [44]. In both entities, PET indispensably improves target volume delineation (especially following surgery), helps to reduce interobserver variability, and significantly alters the assessment of tumor extent compared to MRI alone.

Advances in MR imaging for radiation oncology treatment planning

Among the advances in multiparametric MR imaging, Diffusion-weighted imaging (DWI) has attracted particular attention (for a concise review see [45]). DWI measures the mobility of water within a tissue and is independent on the application of a contrast agent [46]. Impaired diffusion correlates with high cellularity due to the impaired movement of water through the densely packed cluster of cells [47]. The apparent diffusion coefficient (ADC) inversely correlates with cellularity, meaning that low ADC values are observed in proliferative areas of a tumor. An increase in ADC values reflects decrease in cellularity [48], which is a surrogate for therapy response in glioma [49]. Low ADC values are associated with a poor prognosis [50]. The potential of DWI for integration in target volume definition is furthermore reflected by the fact that it is already in clinical use in radiotherapy of prostate [51, 52] or rectal cancer [53], among others [45]. Although a biopsy controlled study in glioma showed that ADC mapping may insufficiently distinguish tumour from peritumoral tissue [54], a recent report introduced the low ADC subvolume, that is not fully covered by the 95 % isodose of prescribed radiation dose, as a significant negative predictor for PFS [55].

Along this line, a surgical series of 15 patients with proton MR spectroscopy (^{1}H-MRS) integrated with neuronavigation for metabolic glioma resection indicated that it contributes to a better prognosis [56]. Outcome evaluation of integration of MRS data into radiotherapy treatment planning is currently under investigation in a French prospective phase III trial [57].

Integration of Perfusion-weighted imaging (PWI) into radiotherapy treatment planning of glioma has not been reported so far, but PWI can be a very useful modality in the question of tumor recurrence vs. radiation necrosis [58, 59].

PET/MRI for target volume definition in radiation oncology

Integration of imaging modalities into 3D conformal radiotherapy always required image fusion with the underlying planning CT depicting the patient in treatment position. In the brain, this task can be accomplished in an automated fashion with great accuracy due to the possibility to easily immobilize the head of the patient and due to the lack of intrinsic intracranial motion of organs [60], raising the question of the clinical need for integrated PET/MRI [61]. This review will in general not cover the physical and technical disadvantages of missing attenuation correction in PET/MR hybrid imaging (for review see [62]), but it should be mentioned that omission of bone and its replacement by soft tissues in attenuation maps may in the brain lead to SUVs that differ by as much as 25 % from the correct values [63, 64].

In initial studies comparing MET or ^{68}Ga-DOTA-*D*-Phe1-Tyr-octreotide (^{68}Ga-DOTATOC) PET/CT and PET/MRI performed on the same day, no significant artifacts and very good accordance of tumor-to-reference tissue ratios have been observed, indicating that anatomical and molecular imaging in patients with brain tumors is feasible with diagnostic imaging quality using simultaneous hybrid PET/MR image acquisition [65]. With

advancing scanner technology, ^{68}Ga-DOTATOC-PET/MRI now provides flawless image quality and presents an ideal combination of high sensitivity/specificity of tumor detection (PET) with the best possible morphological visualization of meningiomas (MRI) [66]. Indeed, clinical superiority of simultaneous PET/MR compared to separate MR and PET/CT has been prominently demonstrated in a case report describing target volume delineation for radiotherapy treatment planning in a patient with meningioma [67]. However, it has to be noted that the brain PET insert used in this study outperforms the spatial resolution in commercially available whole-body PET/MR scanners.

The only study describing the use of integrated PET/MR imaging for the definition of radiotherapy target volumes in high grade glioma describes a certain amount of MET uptake even in patients who received a gross total resection on MRI. When defining hyperintensities in FLAIR MRI sequences plus a 10 mm margin as the clinical target volume, areas of MET uptake where in all cases included in this volume without any requirement to increase the target volume [68]. These findings, however, could have also been made by separate MET-PET/CT and MRI with subsequent image fusion.

A potential application, where integrated PET/MR imaging in neurooncology is superior to separate PET and MRI, may emerge elsewhere. Treatment options in recurrent high-grade glioma are limited so that many patients will ultimately receive antiangiogenic therapy, despite the fact that two large phase III trials failed to show a survival benefit for glioma patients treated by antiangiogenic therapy with bevacizumab, an antibody against vascular endothelial growth factor (VEGF), in addition to standard radiochemotherapy [69] in the first line [70, 71]. The increasing use of bevacizumab in glioma patients introduces new challenges in response assessment and follow-up, because bevacizumab, by restoring the BBB, reduces contrast enhancement in T1-MRI and also hyperintensities in T2 and FLAIR sequences, and may hence mask detection of progression (Fig. 2) [72]. Patients under antiangiogenic therapy may profit from integrated PET/MR imaging during follow-up, because AA-PET imaging is promising in detecting response to bevacizumab [73] or, vice versa, treatment failure before morphological changes become evident [74]. However, the advantage of integrated PET/MR imaging in this context is mainly achieved due to logistic advantages (one scan instead of two), all diagnostic questions are possible to answer by separate AA-PET/CT and MRI.

Summary and conclusion

Integration of functional imaging (multiparametric MRI and PET) has already critically influenced modern target volume concepts in radiation oncology, as well as contributed to a more and more individualized cancer treatment in general [75, 76]. To date, at least for its application in radiotherapy treatment planning in neurooncology, there is no distinct indication where PET/MRI clearly outperforms separate PET/CT and MRI with subsequent image fusion. Nevertheless, with emerging therapeutic strategies influencing conventional and advanced imaging, such as antiangiogenic therapy [74, 77] or immunotherapy [78], simultaneous non-invasive assessment of anatomic, physiological and molecular information will become more and

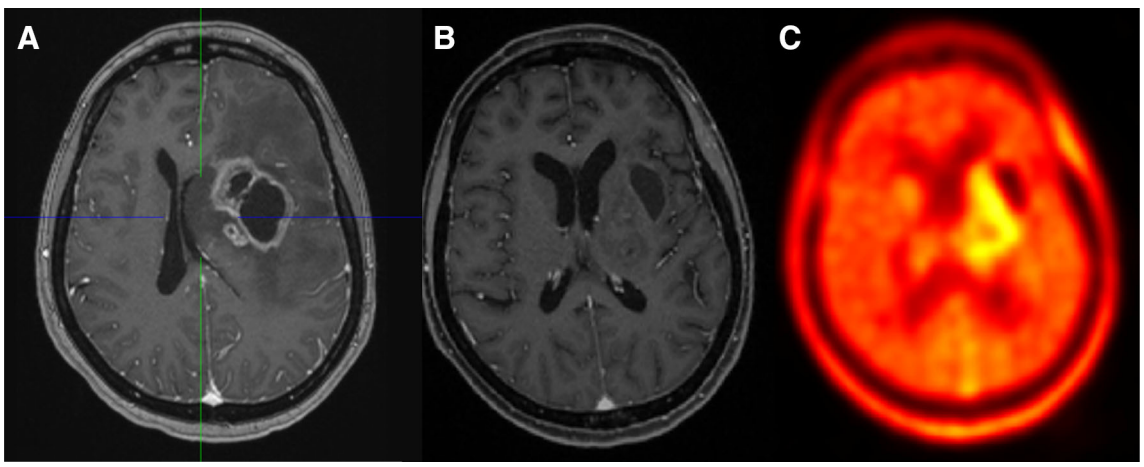

Fig. 2 Pseudoresponse after antiangiogenic therapy with bevacizumab. **a** Contrast-enhanced T1-weighted MRI of a patient with recurrent glioblastoma. **b** After antiangiogenic therapy with bevacizumab, contrast enhancement, as well as peritumoral edema, shows a complete remission. **c** In contrast to the morphological response to bevacizumab in T1-MRI, FET-PET shows a significant amount of biologically active tumor in the area of former contrast enhancement (Courtesy of: Dept. of Radiological Diagnostics and Therapy, Medical Center—University of Freiburg)

more important, and may account for an increased demand of integrated PET/MR imaging [79], but it should be pointed out that at the moment there is no distinct physiological aspect in brain tumor diagnosis, radiotherapy treatment planning, or response assessment that inevitably requires hybrid imaging with PET and (functional) MRI.

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Compliance with ethical standards

Authors' contribution O. Oehlke: Content planning, Literature Search and Review, Manuscript Writing. A.-L. Grosu: Content planning, Literature Search and Review, Manuscript Writing.

Conflict of interest Oliver Oehlke and Anca-Ligia Grosu declare that they have no conflict of interest.

Ethical approval For this type of study formal consent is not required. This article does not contain any studies with human or animal subjects performed by any of the authors.

References

1. Weber WA, Grosu AL, Czernin J (2008) Technology Insight: advances in molecular imaging and an appraisal of PET/CT scanning. Nat Clin Pract Oncol 5(3):160–170. doi:10.1038/ncponc1041
2. Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorensen AG, Galanis E, Degroot J, Wick W, Gilbert MR, Lassman AB, Tsien C, Mikkelsen T, Wong ET, Chamberlain MC, Stupp R, Lamborn KR, Vogelbaum MA, van den Bent MJ (2010) Chang SM (2010) Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. J Clin Oncol 28(11):1963–1972. doi:10.1200/JCO.2009.26.3541
3. Brandsma D, Stalpers L, Taal W, Aminia P, van den Bent MJ (2008) Clinical features, mechanisms, and management of pseudoprogression in malignant gliomas. Lancet Oncol 9:453–461. doi:10.1016/S1470-2045(08)70125-6
4. Grosu AL, Molls M, Zimmermann FB, Geinitz H, Nüsslin F, Schwaiger M, Nieder C (2006) High-precision radiation therapy with integrated biological imaging and tumor monitoring: evolution of the Munich concept and future research options. Strahlenther Onkol 182:361–368
5. Grosu AL, Piert M, Weber WA, Jeremic B, Picchio M, Schratzenstaller U, Zimmermann FB, Schwaiger M, Molls M (2005) Positron emission tomography for radiation treatment planning. Strahlenther Onkol 181:483–499
6. Grosu AL, Weber WA (2010) PET for radiation treatment planning of brain tumours. Radiother Oncol 96:325–327. doi:10.1016/j.radonc.2010.08.001
7. Di Chiro G, DeLaPaz RL, Brooks RA, Sokoloff L, Kornblith PL, Smith BH, Patronas NJ, Kufta CV, Kessler RM, Johnston GS, Manning RG, Wolf AP (1982) Glucose utilization of cerebral gliomas measured by [^{18}F] fluorodeoxyglucose and positron emission tomography. Neurology 32:1323–1329
8. Kubota R, Yamada S, Kubota K, Ishiwata K, Tamahashi N, Ido T (1992) Intratumoral distribution of fluorine-18-fluorodeoxyglucose in vivo: high accumulation in macrophages and granulation tissues studied by microautoradiography. J Nucl Med 33:1972–1980
9. Spence AM, Muzi M, Mankoff DA, O'Sullivan SF, Link JM, Lewellen TK, Lewellen B, Pham P, Minoshima S, Swanson K, Krohn KA (2004) ^{18}F-FDG PET of gliomas at delayed intervals: improved distinction between tumor and normal gray matter. J Nucl Med 45:1653–1659
10. Prieto E, Martí-Climent JM, Domínguez-Prado I, Garrastachu P, Díez-Valle R, Tejada S, Aristu JJ, Peñuelas I, Arbizu J (2011) Voxel-based analysis of dual-time-point 18F-FDG PET images for brain tumor identification and delineation. J Nucl Med 52:865–872. doi:10.2967/jnumed.110.085324
11. la Fougère C, Suchorska B, Bartenstein P, Kreth FW, Tonn JC (2011) Molecular imaging of gliomas with PET: opportunities and limitations. Neuro Oncol 13:806–819. doi:10.1093/neuonc/nor054
12. Hübner KF, Purvis JT, Mahaley SM Jr, Robertson JT, Rogers S, Gibbs WD, King P, Partain CL (1982) Brain tumor imaging by positron emission computed tomography using 11C-labeled amino acids. J Comput Assist Tomogr 6:544–550
13. Bergström M, Collins VP, Ehrin E, Ericson K, Eriksson L, Greitz T, Halldin C, von Holst H, Långström B, Lilja A, Lundqvist H, Nagren K (1983) Discrepancies in brain tumor extent as shown by computed tomography and positron emission tomography using [^{68}Ga]EDTA, [^{11}C]glucose, and [^{11}C]methionine. J Comput Assist Tomogr 7:1062–1066
14. Mosskin M, Ericson K, Hindmarsh T, von Holst H, Collins VP, Bergström M, Eriksson L, Johnström P (1989) Positron emission tomography compared with magnetic resonance imaging and computed tomography in supratentorial gliomas using multiple stereotactic biopsies as reference. Acta Radiol 30:225–232
15. Kaim AH, Weber B, Kurrer MO, Westera G, Schweitzer A, Gottschalk J, von Schulthess GK, Buck A (2002) ^{18}F-FDG and ^{18}F-FET uptake in experimental soft tissue infection. Eur J Nucl Med 29:648–654. doi:10.1007/s00259-002-0780-y
16. Dunet V, Rossier C, Buck A, Stupp R, Prior JO (2012) Performance of ^{18}F-fluoro-ethyL-tyrosine (^{18}F-FET) PET for the differential diagnosis of primary brain tumor: a systematic review and metaanalysis. J Nucl Med 53(2):207–214. doi:10.2967/jnumed.111.096859
17. Galldiks N, Langen KJ, Holy R, Pinkawa M, Stoffels G, Nolte KW, Kaiser HJ, Filss CP, Fink GR, Coenen HH, Eble MJ, Piroth MD (2012) Assessment of treatment response in patients with glioblastoma using *O*-(2-^{18}F-fluoroethyl)-L-tyrosine PET in comparison to MRI. J Nucl Med 53:1048–1057. doi:10.2967/jnumed.111.098590
18. Galldiks N, Dunkl V, Stoffels G, Hutterer M, Rapp M, Sabel M, Reifenberger G, Kebir S, Dorn F, Blau T, Herrlinger U, Hau P, Ruge MI, Kocher M, Goldbrunner R, Fink GR, Drzezga A, Schmidt M, Langen KJ (2015) Diagnosis of pseudoprogression in patients with glioblastoma using O-(2-[18F]fluoroethyl)-L-tyrosine PET. Eur J Nucl Med Mol Imaging 42:685–695. doi:10.1007/s00259-014-2959-4
19. Wester HJ, Herz M, Weber W, Heiss P, Senekowitsch-Schmidtke R, Schwaiger M, Stöcklin G (1999) Synthesis and radiopharmacology of *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine for tumor imaging. J Nucl Med 40:205–212
20. Heiss P, Mayer S, Herz M, Wester HJ, Schwaiger M, Senekowitsch-Schmidtke R (1999) Investigation of transport mechanism and uptake kinetics of *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine in vitro and *in vivo*. J Nucl Med 40:1367–1373
21. Heiss WD (2014) Clinical Impact of Amino Acid PET in Gliomas. J Nucl Med 55:1219–1220. doi:10.2967/jnumed.114.142661
22. Stöber B, Tanase U, Herz M, Seidl C, Schwaiger M, Senekowitsch-Schmidtke R (2006) Differentiation of tumour and inflammation: characterization of [methyl-^{3}H]methionine (MET) and *O*-(2-[^{18}F] fluoroethyl)-L-tyrosine (FET) uptake in human tumour

and inflammatory cells. Eur J Nucl Med Mol Imaging 33:932–939. doi:10.1007/s00259-005-0047-5
23. Weber WA, Wester HJ, Grosu AL, Herz M, Dzewas B, Feldmann HJ, Molls M, Stöcklin G, Schwaiger M (2000) *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine and *L*-[methyl-^{11}C]methionine uptake in brain tumours: initial results of a comparative study. Eur J Nucl Med 27:542–549
24. Grosu AL, Astner ST, Riedel E, Nieder C, Wiedenmann N, Heinemann F, Schwaiger M, Molls M, Wester HJ, Weber WA (2011) An interindividual comparison of *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine (FET)- and *L*-[methyl-^{11}C]methionine (MET)-PET in patients with brain gliomas and metastases. Int J Radiat Oncol Biol Phys 81:1049–1058. doi:10.1016/j.ijrobp.2010.07.002
25. Grosu AL, Weber WA, Riedel E, Jeremic B, Nieder C, Franz M, Gumprecht H, Jaeger R, Schwaiger M, Molls M (2005) *L*-(methyl-^{11}C) methionine positron emission tomography for target delineation in resected high-grade gliomas before radiotherapy. Int J Radiat Oncol Biol Phys 63:64–74
26. Grosu AL, Weber WA, Franz M, Stärk S, Piert M, Thamm R, Gumprecht H, Schwaiger M, Molls M, Nieder C (2005) Reirradiation of recurrent high-grade gliomas using amino acid PET (SPECT)/CT/MRI image fusion to determine gross tumor volume for stereotactic fractionated radiotherapy. Int J Radiat Oncol Biol Phys 63:511–519
27. Piroth MD, Pinkawa M, Holy R et al (2012) Integrated boost IMRT with FET-PET-adapted local dose escalation in glioblastomas. Results of a prospective phase II study. Strahlenther Onkol 188:334–339. doi:10.1007/s00066-011-0060-5
28. Miwa K, Matsuo M, Ogawa S, Shinoda J, Yokoyama K, Yamada J, Yano H, Iwama T (2014) Re-irradiation of recurrent glioblastoma multiforme using ^{11}Cmethionine PET/CT/MRI image fusion for hypofractionated stereotactic radiotherapy by intensity modulated radiation therapy. Radiat Oncol 9:181. doi:10.1186/1748-717X-9-181
29. Munck af Rosenschold P, Costa J, Engelholm SA, Lundemann MJ, Law I, Ohlhues L, Engelholm S (2015) Impact of [^{18}F]-fluoro-ethyL-tyrosine PET imaging on target definition for radiation therapy of high-grade glioma. Neuro-Oncology 17:757–763. doi:10.1093/neuonc/nou316
30. Niyazi M, Brada M, Chalmers AJ, Combs SE, Erridge SC, Fiorentino A, Grosu AL, Lagerwaard FJ, Minniti G, Mirimanoff RO, Ricardi U, Short SC, Weber DC, Belka C (2016) ESTRO-ACROP guideline "target delineation of glioblastomas". Radiother Oncol 118:35–42. doi:10.1016/j.radonc.2015.12.003
31. Shields AF, Grierson JR, Dohmen BM et al (1998) Imaging proliferation in vivo with [F-18]FLT and positron emission tomography. Nat Med 4:1334–1336
32. Ullrich R, Backes H, Li H, Kracht L, Miletic H, Kesper K, Neumaier B, Heiss WD, Wienhard K, Jacobs AH (2008) Glioma proliferation as assessed by 3′-fluoro-3′-deoxy-L-thymidine positron emission tomography in patients with newly diagnosed high-grade glioma. Clin Cancer Res 14:2049–2055. doi:10.1158/1078-0432.CCR-07-1553
33. Ferdová E, Ferda J, Baxa J, Tupý R, Mraček J, Topolčan O, Hes O (2015) Assessment of grading in newly-diagnosed glioma using ^{18}F-fluorothymidine PET/CT. Anticancer Res 35:955–959
34. Chen W, Cloughesy T, Kamdar N, Satyamurthy N, Bergsneider M, Liau L, Mischel P, Czernin J, Phelps ME, Silverman DH (2005) Imaging proliferation in brain tumors with ^{18}F-FLT PET: comparison with ^{18}F-FDG. J Nucl Med 46:945–952
35. Hoeben BA, Bussink J, Troost EG, Oyen WJ, Kaanders JH (2013) Molecular PET imaging for biology-guided adaptive radiotherapy of head and neck cancer. Acta Oncol 52:1257–1271. doi:10.3109/0284186X.2013.812799
36. Cher LM, Murone C, Lawrentschuk N, Cher LM, Murone C, Lawrentschuk N, Ramdave S, Papenfuss A, Hannah A, O'Keefe GJ, Sachinidis JI, Berlangieri SU, Fabinyi G, Scott AM et al (2006) Correlation of hypoxic cell fraction and angiogenesis with glucose metabolic rate in gliomas using ^{18}F-fluoromisonidazole, ^{18}F-FDG PET, and immunohistochemical studies. J Nucl Med 47:410–418
37. Brown JM (2001) Therapeutic targets in radiotherapy. Int J Radiat Oncol Biol Phys 49:319–326
38. Valk PE, Mathis CA, Prados MD, Gilbert JC, Budinger TF (1992) Hypoxia in human gliomas: demonstration by PET with fluorine-18-fluoromisonidazole. J Nucl Med 33:2133–2137
39. Götz I, Grosu AL (2013) [^{18}F]FET-PET imaging for treatment and response monitoring of radiation therapy in malignant glioma patients—a review. Frontiers Oncol 3:104. doi:10.3389/fonc.2013.00104
40. Ahmed R, Oborski MJ, Hwang M, Lieberman FS, Mountz JM (2015) Malignant gliomas: current perspectives in diagnosis, treatment, and early response assessment using advanced quantitative imaging methods. Cancer Manag Res 6:149–170. doi:10.2147/CMAR.S54726
41. Zschaeck S, Haase R, Abolmaali N, Perrin R, Stützer K, Appold S, Steinbach J, Kotzerke J, Zips D, Richter C, Gudziol V, Krause M, Zöphel K, Baumann M (2015) Spatial distribution of FMISO in head and neck squamous cell carcinomas during radiochemotherapy and its correlation to pattern of failure. Acta Oncol 54:1355–1363. doi:10.3109/0284186X.2015.1074720
42. Wiedenmann NE, Bucher S, Hentschel M, Mix M, Vach W, Bittner MI, Nestle U, Pfeiffer J, Weber WA, Grosu AL (2015) Serial [^{18}F]-fluoromisonidazole PET during radiochemotherapy for locally advanced head and neck cancer and its correlation with outcome. Radiother Oncol 117:113–117. doi:10.1016/j.radonc.2015.09.015
43. Milker-Zabel S, Zabel-du Bois A, Henze M, Huber P, Schulz-Ertner D, Hoess A, Haberkorn U, Debus J (2006) Improved target volume definition for fractionated stereotactic radiotherapy in patients with intracranial meningiomas by correlation of CT, MRI, and [^{68}Ga]-DOTATOC-PET. Int J Radiat Oncol Biol Phys 65:222–227
44. Astner ST, Bundschuh RA, Beer AJ, Ziegler SI, Krause BJ, Schwaiger M, Molls M, Grosu AL, Essler M (2009) Assessment of tumor volumes in skull base glomus tumors using Gluc-Lys[(18)F]-TOCA positron emission tomography. Int J Radiat Oncol Biol Phys 73(4):1135–1140. doi:10.1016/j.ijrobp.2008.05.037
45. Tsien C, Cao Y, Chenevert T (2014) Clinical applications for diffusion magnetic resonance imaging in radiotherapy. Semin Radiat Oncol 24:218–226. doi:10.1016/j.semradonc.2014.02.004
46. Le Bihan D, Breton E, Lallemand D, Grenier P, Cabanis E, Laval Jeantet M (1986) MR imaging of intravoxel incoherent motions: application to diffusion and perfusion in neurologic disorders. Radiology 161:401–407
47. Szafer A, Zhong J, Gore JC (1995) Theoretical model for water diffusion in tissues. Magn Reson Med 33:697–712
48. Chenevert TL, Stegman LD, Taylor JM, Robertson PL, Greenberg HS, Rehemtulla A, Ross BD (2000) Diffusion magnetic resonance imaging: an early surrogate marker of therapeutic efficacy in brain tumors. J Natl Cancer Inst 92:2029–2036
49. Moffat BA, Chenevert TL, Lawrence TS, Meyer CR, Johnson TD, Dong Q, Tsien C, Mukherji S, Quint DJ, Gebarski SS, Robertson PL, Junck LR, Rehemtulla A, Ross BD (2005) Functional diffusion map: a noninvasive MRI biomarker for early stratification of clinical brain tumor response. Proc Natl Acad Sci U S A 102:5524–5529
50. Zulfiqar M, Yousem DM, Lai H (2013) ADC values and prognosis of malignant astrocytomas: does lower ADC predict a worse prognosis independent of grade of tumor? a meta-analysis. AJR Am J Roentgenol 200:624–629. doi:10.2214/AJR.12.8679

51. Liney GP, Holloway L, Al Harthi TM, Sidhom M, Moses D, Juresic E, Rai R, Manton DJ (2015) Quantitative evaluation of diffusion-weighted imaging techniques for the purposes of radiotherapy planning in the prostate. Br J Radiol 88:20150034. doi:10.1259/bjr.20150034
52. Iannelli G, Caivano R, Rago L, Simeon V, Lotumolo A, Rabasco P, Villonio A, Gioioso M, Mastrangelo P, Barchetti F, Panebianco V, Macarini L, Guglielmi G, Cammarota A (2016) Diffusion-weighted magnetic resonance imaging in patients with prostate cancer treated with radiotherapy. Tumori 102:71–76. doi:10.5301/tj.5000415
53. Burbach JP, Kleijnen JJ, Reerink O, Seravalli E, Philippens ME, Schakel T, van Asselen B, Raaymakers BW, van Vulpen M, Intven M (2015) Inter-observer agreement of MRI-based tumor delineation for preoperative radiotherapy boost in locally advanced rectal cancer. Radiother Oncol pii S0167–8140(15):00614–30000. doi:10.1016/j.radonc.2015.10.030
54. Pauleit D, Langen KJ, Floeth F, Hautzel H, Riemenschneider MJ, Reifenberger G, Shah NJ, Müller HW (2004) Can the apparent diffusion coefficient be used as a noninvasive parameter to distinguish tumor tissue from peritumoral tissue in cerebral gliomas? J Magn Reson Imaging 20:758–764
55. Pramanik PP, Parmar HA, Mammoser AG, Junck LR, Kim MM, Tsien CI, Lawrence TS, Cao Y (2015) Hypercellularity Components of Glioblastoma Identified by High b-Value Diffusion Weighted Imaging. Int J Radiat Oncol Biol Phys 92:811–819. doi:10.1016/j.ijrobp.2015.02.058
56. Zhang J, Zhuang DX, Yao CJ, Lin CP, Wang TL, Qin ZY, Wu JS (2016) Metabolic approach for tumor delineation in glioma surgery: 3D MR spectroscopy image-guided resection. J Neurosurg 124:1585–1593. doi:10.3171/2015.6.JNS142651
57. Ken S, Vieillevigne L, Franceries X, Simon L, Supper C, Lotterie JA, Filleron T, Lubrano V, Berry I, Cassol E, Delannes M, Celsis P, Cohen-Jonathan EM, Laprie A (2013) Integration method of 3D MR spectroscopy into treatment planning system for glioblastoma IMRT dose painting with integrated simultaneous boost. Radiat Oncol 8:1. doi:10.1186/1748-717X-8-1
58. Di Costanzo A, Scarabino T, Trojsi F, Popolizio T, Bonavita S, de Cristofaro M, Conforti R, Cristofano A, Colonnese C, Salvolini U, Tedeschi G (2014) Recurrent glioblastoma multiforme versus radiation injury: a multiparametric 3-T MR approach. Radiol Med 119:616–624. doi:10.1007/s11547-013-0371-y
59. Sacconi B, Raad RA, Lee J, Fine H, Kondziolka D, Golfinos JG, Babb JS, Jain R (2016) Concurrent functional and metabolic assessment of brain tumors using hybrid PET/MR imaging. J Neurooncol 127:287–293. doi:10.1007/s11060-015-2032-6
60. Grosu AL, Lachner R, Wiedenmann N, Stärk S, Thamm R, Kneschaurek P, Schwaiger M, Molls M, Weber WA (2003) Validation of a method for automatic image fusion (BrainLAB System) of CT data and ^{11}C-methionine-PET data for stereotactic radiotherapy using a LINAC: first clinical experience. Int J Radiat Oncol Biol Phys 56:1450–1463
61. Herzog H (2012) PET/MRI: challenges, solutions and perspectives. Z Med Phys 22:281–298. doi:10.1016/j.zemedi.2012.07.003
62. von Schulthess GK, Kuhn FP, Kaufmann P, Veit-Haibach P (2013) Clinical Positron Emission Tomography/Magnetic Resonance Imaging Applications. Semin Nucl Med 43:3–10
63. Martinez-Möller A, Souvatzoglou M, Delso G, Bundschuh RA, Chefd'hotel C, Ziegler SI, Navab N, Schwaiger M, Nekolla SG (2009) Tissue classification as a potential approach for attenuation correction in whole-body PET/MRI: evaluation with PET/CT data. J Nucl Med 50:520–526. doi:10.2967/jnumed.108.054726
64. Hofmann M, Bezrukov I, Mantlik F, Aschoff P, Steinke F, Beyer T, Pichler BJ, Schölkopf B (2011) MRI-based attenuation correction for whole-body PET/MRI: quantitative evaluation of segmentation- and atlas-based methods. J Nucl Med 52:1392–1399. doi:10.2967/jnumed.110.078949
65. Boss A, Bisdas S, Kolb A, Hofmann M, Ernemann U, Claussen CD, Pfannenberg C, Pichler BJ, Reimold M, Stegger L (2010) Hybrid PET/MRI of intracranial masses: initial experiences and comparison to PET/CT. J Nucl Med 51:1198–1205. doi:10.2967/jnumed.110.074773
66. Afshar-Oromieh A, Wolf MB, Kratochwil C, Giesel FL, Combs SE, Dimitrakopoulou-Strauss A, Gnirs R, Roethke MC, Schlemmer HP, Haberkorn U (2015) Comparison of ^{68}Ga-DOTA-TOC-PET/CT and PET/MRI hybrid systems in patients with cranial meningioma: initial results. Neuro Oncol 17:312–319. doi:10.1093/neuonc/nou131
67. Thorwarth D, Henke G, Müller AC, Reimold M, Beyer T, Boss A, Kolb A, Pichler B, Pfannenberg C (2011) Simultaneous ^{68}Ga-DOTATOC-PET/MRI for IMRT treatment planning for meningioma: first experience. Int J Radiat Oncol Biol Phys 81:277–283. doi:10.1016/j.ijrobp.2010.10.078
68. Navarria P, Reggiori G, Pessina F, Ascolese AM, Tomatis S, Mancosu P, Lobefalo F, Clerici E, Lopci E, Bizzi A, Grimaldi M, Chiti A, Simonelli M, Santoro A, Bello L, Scorsetti M (2014) Investigation on the role of integrated PET/MRI for target volume definition and radiotherapy planning in patients with high grade glioma. Radiother Oncol 112:425–429. doi:10.1016/j.radonc.2014.09.004
69. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U, Curschmann J, Janzer RC, Ludwin SK, Gorlia T, Allgeier A, Lacombe D, Cairncross JG, Eisenhauer E, Mirimanoff RO; European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups; National Cancer Institute of Canada Clinical Trials Group. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 352:987–996
70. Chinot OL, Wick W, Mason W, Henriksson R, Saran F, Nishikawa R, Carpentier AF, Hoang-Xuan K, Kavan P, Cernea D, Brandes AA, Hilton M, Abrey L (2014) Cloughesy T (2014) Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. N Engl J Med 370(8):709–722. doi:10.1056/NEJMoa1308345
71. Gilbert MR, Dignam JJ, Armstrong TS, Wefel JS, Blumenthal DT, Vogelbaum MA, Colman H, Chakravarti A, Pugh S, Won M, Jeraj R, Brown PD, Jaeckle KA, Schiff D, Stieber VW, Brachman DG, Werner-Wasik M, Tremont-Lukats IW, Sulman EP, Aldape KD, Curran WJ Jr, Mehta MP (2014) A randomized trial of bevacizumab for newly diagnosed glioblastoma. N Engl J Med 370(8):699–708. doi:10.1056/NEJMoa1308573
72. Hutterer M, Hattingen E, Palm C, Proescholdt MA, Hau P (2015) Current standards and new concepts in MRI and PET response assessment of antiangiogenic therapies in high-grade glioma patients. Neuro Oncol 17:784–800. doi:10.1093/neuonc/nou322
73. Galldiks N, Rapp M, Stoffels G, Fink GR, Shah NJ, Coenen HH, Sabel M, Langen KJ (2013) Response assessment of bevacizumab in patients with recurrent malignant glioma using [^{18}F]fluoroethyl-L-tyrosine PET in comparison to MRI. Eur J Nucl Med Mol Imaging 40:22–33. doi:10.1007/s00259-012-2251-4
74. Hutterer M, Nowosielski M, Putzer D, Waitz D, Tinkhauser G, Kostron H, Muigg A, Virgolini IJ, Staffen W, Trinka E, Gotwald T, Jacobs AH, Stockhammer G (2011) *O*-(2-^{18}F-fluoroethyl)-L-tyrosine PET predicts failure of antiangiogenic treatment in patients with recurrent high-grade glioma. J Nucl Med 52(6):856–864. doi:10.2967/jnumed.110.086645
75. Nestle U, Weber W, Hentschel M, Grosu AL (2009) Biological imaging in radiation therapy: role of positron emission tomography. Phys Med Biol 54:R1–R25. doi:10.1088/0031-9155/54/1/R01

76. Thorwarth D (2015) Functional imaging for radiotherapy treatment planning: current status and future directions-a review. Br J Radiol 88:20150056. doi:10.1259/bjr.20150056
77. Huang RY, Rahman R, Ballman KV, Felten SJ, Anderson SK, Ellingson BM, Nayak L, Lee EQ, Abrey LE, Galanis E, Reardon DA, Pope WB, Cloughesy TF (2016) Wen PY (2016) The Impact of T2/FLAIR Evaluation per RANO Criteria on Response Assessment of Recurrent Glioblastoma Patients Treated with Bevacizumab. Clin Cancer Res 22(3):575–581. doi:10.1158/1078-0432.CCR-14-3040
78. Okada H, Weller M, Huang R, Finocchiaro G, Gilbert MR, Wick W, Ellingson BM, Hashimoto N, Pollack IF, Brandes AA, Franceschi E, Herold-Mende C, Nayak L, Panigrahy A, Pope WB, Prins R, Sampson JH, Wen PY, Reardon DA (2015) Immunotherapy response assessment in neuro-oncology: a report of the RANO working group. Lancet Oncol 16:e534–e542. doi:10.1016/S1470-2045(15)00088-1
79. Jadvar H, Colletti PM (2014) Competitive advantage of PET/MRI. Eur J Radiol 83:84–94. doi:10.1016/j.ejrad.2013.05.028