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Applying Amide Proton Transfer MR Imaging to Hybrid Brain PET/MR: Concordance with Gadolinium Enhancement and Added Value to [^{18}F]FDG PET

Hongzan Sun¹, Jun Xin¹, Jinyuan Zhou², Zaiming Lu¹, and Qiyong Guo¹

¹Department of Radiology, Shengjing Hospital of China Medical University, Sanhao Street No. 36, Heping District, Shenyang, Liaoning, P.R.China

²Division of MR Research, Department of Radiology, Johns Hopkins University, 600 N. Wolfe Street, Park 336, Baltimore, MD 21287, USA

Abstract

Purpose—To evaluate the diagnostic concordance and metric correlations of amide proton transfer (APT) imaging with gadolinium-enhanced magnetic resonance imaging (MRI) and 2-deoxy-2- [^{18}F]-fluoro-D-glucose ([^{18}F]FDG) positron emission tomography (PET), using hybrid brain PET/MRI.

Procedures—Twenty-one subjects underwent brain gadolinium enhanced [^{18}F]FDG PET/MRI prospectively. Imaging accuracy was compared between unenhanced MRI, MRI with enhancement, APT-weighted (APTW) images, and PET based on six diagnostic criteria. Among tumors, the McNemar test was further used for concordance assessment between gadolinium enhanced imaging, APT imaging, and [^{18}F]FDG PET. As well, the relation of metrics between APT imaging and PET was analyzed by the Pearson correlation analysis.

Results—APT imaging and gadolinium-enhanced MRI showed superior and similar diagnostic accuracy. APTW signal intensity and gadolinium enhancement were concordant in 19 tumors (100%), while high [^{18}F]FDG avidity was shown in only 12 (63.2%). For the metrics from APT imaging and PET, there was significant correlation for 13 hypermetabolic tumors ($P < 0.05$) and no correlation for the remaining six [^{18}F]FDG-avid tumors.

Conclusions—APT imaging can be used to increase diagnostic accuracy with no need to administer gadolinium chelates. APT imaging may provide an added value to [^{18}F]FDG PET in the evaluation of tumor metabolic activity during brain PET/MR studies.

Corresponding author: Jun Xin, Corresponding address: Department of Radiology, Shengjing Hospital of China Medical University, Sanhao Street No36, Heping District, Shenyang, Liaoning, P.R.China, 110004, xinj_sjcmu@126.com, Office telephone number: 86-24-96615-73258, Fax: 86-24-23929902.

Conflict of Interest Statement: The scientific guarantor of this publication is Jun Xin. The authors of this manuscript declare no relationships with any companies whose products or services might be related to the subject matter of the article. No complex statistical methods were necessary for this paper. Institutional review board approval was obtained. Written, informed consent was obtained from all subjects (patients) in this study. Methodology: retrospective, diagnostic or prognostic study, performed at one institution.

Keywords

PET/MR; APT imaging; [^{18}F]FDG; Gd contrast; brain

Introduction

An increasing number of integrated positron emission tomography (PET)/magnetic resonance imaging (MRI) systems have been introduced into clinical practice in recent years. The combination of PET metabolic and MRI structural as well as functional information provides potential advantages in oncology through whole-body or regional scanning [1]. This is also the case for suspected tumors in the brain, although conventional MRI can provide good morphological assessment, especially with gadolinium (Gd) injection. However, Gd-enhanced MRI is limited in those lesions with an intact blood-brain barrier (BBB), despite the ability to provide functional parameters from perfusion-weighted imaging about tumor angiogenesis. The glucose analog 3-deoxy-2- ^{18}F fluoro-D-glucose (^{18}F FDG) is the most popular pharmaceutical for PET in clinics, and ^{18}F FDG PET/MR and PET/x-ray computed tomograph (CT) showed equally good performance in cancer patients [2, 3]. Despite its proven utility, brain ^{18}F FDG PET/MR has obvious limitations, especially with respect to malignancy-grading in ^{18}F FDG-negative tumors, partly because of the high background ^{18}F FDG uptake in the normal brain parenchyma. There are more sensitive and non- ^{18}F FDG tracers in brain-tumor PET, such as L- ^{11}C methionine, O-(2- ^{18}F fluoro-ethyl)-L-tyrosine, ^{18}F fluoromisonidazole, etc., but these are still unavailable for routine clinical use. Moreover, ^{18}F FDG PET whole-body scanning is often necessary, since metastasis has a high onset rate among all brain tumors. Currently, for example, one standard clinical protocol for cases with suspected brain tumors obtains a brain Gd-enhanced MRI plus a whole-body ^{18}F FDG PET (often in conjunction with CT or MRI) consecutively, or a whole-body ^{18}F FDG PET/MR plus a brain Gd-enhanced PET/MR, especially in ^{18}F FDG-negative cases. However, a clinical, streamlined protocol for medical imaging should consider both economical and practical aspects. Thus, an optimal ^{18}F FDG PET/MR clinical scan protocol for brain tumor or tumor-like lesion diagnosis, grading, and staging has yet to be realized.

Regardless of Gd enhancement, another advantage for MR, with regard to brain tumor diagnosis is the use of multiple functional imaging parameters, including diffusion-weighted imaging (DWI) for cellularity, proton MR spectroscopy for cerebral metabolites, and amide proton transfer (APT) imaging for mobile cellular proteins and peptides or pH changes in tissue [4–6]. It has been shown previously that these different MR metrics are closely related to various pathological features that have been used as diagnostic clues for malignancy differentiation and tumor grading. Among all of the chemical exchange-dependent saturation transfer (CEST) MR imaging techniques, APT imaging has recently become available on clinical 3T MR scanners and has shown great potential in clinics as an important molecular imaging technique [7, 8]. However, to our knowledge, no studies have attempted CEST imaging on a clinical PET/MRI scanner or investigated its simultaneous relation to Gd enhancement and ^{18}F FDG PET.

Therefore, the purpose of this study was to evaluate the diagnostic concordance of APT imaging with Gd-enhanced MRI and [^{18}F]FDG PET, and to investigate the correlations among the imaging metrics (APT-weighted MRI signal intensities, and standardized uptake value or SUV for [^{18}F]FDG PET). If APT imaging has a value comparable to that of Gd-enhanced MRI and provides an added value to ^{18}F -FDG PET, this would be of benefit in establishing workflow and scan protocols in MRI, understanding tumor characteristics, and optimizing [^{18}F]FDG PET/MR clinical applications, such as in brain tumor diagnosis, treatment planning, and therapy response assessment [9, 10].

Materials and Methods

Subjects

From June 2014 through January 2015, subjects were enrolled in this prospective study, which was approved by the local institutional ethics committee and written, informed consent was obtained from all subjects. The inclusion criteria were: suspected brain lesions on prior CT or MRI referred for further whole-body examinations; no history of treatment, including surgery, radiotherapy, chemotherapy, or corticosteroid administration; no contraindications for Gd-enhanced MRI or PET scanning, such as metallic device implantation, pregnancy or nephropathy; normal or corrected-to-normal blood glucose level. The exclusion criteria were no final diagnosis from pathology or loss to follow-up. Subjects with inadequate or unclear images due to motion artifacts or technical problems (like image distortion caused by unknown metal implants or image misregistration caused by iatrogenic scanning errors from technicians) were also excluded. Ultimately, 21 subjects were enrolled: 12 male and nine female patients with a mean age of 54.5 (± 15.5) years, as shown in Table 1.

Imaging protocol

All examinations were performed on a clinical Ingenuity TF PET/MR scanner (Philips, Cleveland, OH), which consists of two separate scanners (the Ingenuity Time-of-Flight PET scanner and an Achieva 3T X-series MRI) linked through one rotatable patient table, thus allowing for sequential imaging. After injection with approximately 5.5 MBq/kg body-weight [^{18}F]FDG, all subjects would rest in bed for about 40 min with closed eyes and with earplugs in their ears. Then, they underwent whole-body plus Gd-enhanced brain PET/MR scans. The whole-body PET/MR scan included a dedicated T1-weighted fast-field echo sequence (termed atMR) and diagnostic T2-weighted imaging (T2WI) with the Q-Body coil, and a whole-body PET emission acquisition (10 to 12 bed positions, 2 min each). The brain PET/MR protocol consisted of an atMR, a three-dimensional PET data acquisition (12 min, one bed position), and standard diagnostic MRI sequences (acquired after additional connection with an eight-channel, sensitivity-encoding head coil), including T1-weighted imaging (T1WI), T2WI, fluid-attenuated inversion recovery (FLAIR), and DWI (TR/TE, 2144/56 ms; b values, 0 and 1000 s/mm^2), as well as Gd-enhanced, three-plane T1WI (0.2 ml/kg body weight; Magnevist; Bayer Schering, China). The APT imaging sequence was acquired before the injection of Gd contrast agent. The total duration for one case was about 37 to 40 min.

In the APT imaging part, a single-shot turbo spin-echo sequence was used: repetition time, 3,000 ms; sensitivity-encoding factor, 2; field of view, 240 mm×240 mm; matrix, 128×64 (reconstructed to be 400×400); slice thickness, 6 mm. A pseudocontinuous wave radiofrequency irradiation (saturation duration, 200 ms×4; inter-pulse delay, 10 ms; power level, 2 μ T) and a multi-offset, multi-acquisition CEST/APT imaging protocol were adopted [2]. The 31 offsets were 0 (n = 1), ± 0.25 (n = 1), ± 0.5 (n = 1), ± 0.75 (n = 1), ± 1 (n = 2), ± 1.5 (n = 2), ± 2 (n = 2), ± 2.5 (n = 2), ± 3 (n = 2), ± 3.25 (n = 2), ± 3.5 (n = 8), ± 3.75 (n = 2), ± 4 (n = 2), ± 4.5 (n = 1), ± 5 (n = 1), and ± 6 (n = 1) ppm. In order to achieve signal normalization, an unsaturated image was obtained. APT scans were located and acquired at the maximum tumor area, based on T2WI and FLAIR images, with an on-site decision from an experienced radiologist. The acquisition time was about 3 min.

Image analysis and statistics

PET and standard MR images were reviewed, fused, and analyzed using an Extended Brilliance Workspace workstation (Philips Healthcare, Cleveland, OH). APT imaging raw data were processed using the Interactive Data Language (IDL; ITT Visual Information Solutions, Boulder, CO, USA). As reported in the literature [12, 13], the APT imaging raw data were first organized into the z-spectrum. Then, the z-spectrum was fitted on a pixel-by-pixel basis, and the B0 inhomogeneity map was created. After this, the original z-spectrum was corrected for the B0 inhomogeneity effect through the interpolation and centering of the z-spectrum. Finally, the APT-weighted (APTW) image was constructed, using the magnetization transfer-ratio asymmetry at the offsets of ± 3.5 ppm. The gold standard for diagnosis reference was histopathologic results and at least one year of follow-up imaging.

Three experienced radiologists (with dual board certifications from radiology and nuclear medicine), with no knowledge of the clinical history, independently analyzed the unenhanced MRI (T1WI, T2WI, FLAIR plus DWI), enhanced MRI (T1WI), APT imaging, and [^{18}F]FDG PET at four different time points. The interval was at least two weeks to minimize recall bias. Six diagnostic criteria were used in this study: tumor detection and confirmation; lesion homogeneity or heterogeneity; presence or absence of necrosis, hemorrhage or liquefaction; good or poor delineation of tumor margins; confirmation of peritumoral edema; and final diagnosis. Table 2 illustrates these diagnostic criteria, based on morphology and final diagnosis, in detail, and a typical case is shown in Fig. 1. Accuracy for each series of images was calculated on a per-lesion basis. At each time point, a score of 1 was assigned if all three interpreters agreed with the reference, an accuracy of 2/3 or 1/3 was assigned if two or one interpreters, respectively, agreed with the reference, and 0 was assigned if none agreed with the reference. Finally, diagnostic accuracy for every metric was calculated and compared between unenhanced and enhanced MRI, APT imaging and [^{18}F]FDG PET, and enhanced MRI and APT imaging using a paired t test with bias-correction and accelerated bootstrap confidence intervals.

Among the cases diagnosed as tumors, the concordance between APTW signal intensity, Gd enhancement, and [^{18}F]FDG avidity was evaluated lesion-by-lesion, and regions of interest (ROIs) were carefully chosen after all interpreters reached consensus. According to previous studies [13, 14], ROIs were defined based on Gd enhancement, and were delineated on the

same Gd-enhanced image slice as the APTW and PET images. In each tumor, at least five ROIs were measured at the enhancing solid part, and an average of the measurements from all these ROIs was taken as the final value for the tumor. Tumor borders, large necrosis, hemorrhage, or vessels were avoided. The maximum APTW intensity (APTW_{max}), maximum SUV (SUV_{max}), mean APTW intensity (APTW_{mean}), and mean SUV (SUV_{mean}) were recorded for statistical analysis. The McNemar test was used for concordance comparison and the Pearson correlation analysis was used to evaluate the associations between these metrics. Statistical analysis was accomplished with the Statistical Package for the Social Sciences (SPSS, Version 19.0; Chicago, IL, USA). A *P* value of less than 0.05 was considered statistically significant.

Results

There was no case of image misregistration since no severe head movement occurred during scanning. Among all 21 subjects, 23 lesions were found and finally confirmed, with a diagnostic accuracy of 100% for [¹⁸F]FDG PET/MR, including 13 metastases, three gliomas (two World Health Organization [WHO] grade IV and one WHO grade II), three meningiomas (WHO grade I), and four chronic infarctions. Details are shown in Table 1. All 19 tumors were confirmed by histopathological results and all four chronic infarctions were proven by at least one year of follow-up imaging.

Comparison image series for diagnostic accuracy

The accuracies of the diagnostic criteria were calculated as the relative agreement, with the standard of reference for every series of images (unenhanced MRI, enhanced MRI, APTW image, and [¹⁸F]FDG PET). The details and comparison results are depicted in Table 3. Enhanced MRI and APT imaging showed superiority in tumor detection and final diagnosis compared to unenhanced MRI and [¹⁸F]FDG PET, respectively. There was no significant difference in accuracy between enhanced MRI and APT imaging for any diagnostic criterion, except for heterogeneity determination and component detection (such as necrosis, hemorrhage, or liquefaction).

Concordance of enhanced MRI, APT imaging, and [¹⁸F]FDG PET in tumors

All the 19 tumors showed enhancement on enhanced MRI and hyperintensity on APTW images from mild to pronounced levels, with a concordance rate of 100%. Among all these tumors, only 12 (63.2%) were hypermetabolic on [¹⁸F]FDG PET, which differed from enhanced MRI or APT imaging significantly (*P* = 0.031). As is shown in Fig. 1 and 2, the tumors (one metastasis and one meningioma) showed concordant enhancement on T1WI, high signal intensity on the APTW image, and high FDG uptake on [¹⁸F]FDG PET. Figure 3 presents a difficult case of glioblastoma (WHO Grade IV) with a cyst-like appearance and minor septum on unenhanced MRI. Mild ring enhancement indicated a possible malignancy on enhanced MRI, and obvious hyperintensity on the APTW image confirmed the diagnosis of a malignant tumor. The tumor was mildly hypointense compared to the contralateral normal-appearing white matter on [¹⁸F]FDG PET, which was mainly used to determine whether it was primary or metastatic after a whole-body examination.

Quantitative correlations between APT imaging and PET

Brain tumors show a variety of [^{18}F]FDG uptake patterns, which do not correlate with tumor grade [15]. Thus, we performed a correlation analysis in the tumor subgroups of high [^{18}F]FDG uptake (13 tumors in total with a higher [^{18}F]FDG uptake compared to gray matter and/or white matter uptake, including 11 metastases and two meningiomas) and non-avid [^{18}F]FDG uptake (six tumors including two metastases, three gliomas and one meningioma). As shown in Fig. 4, there were significant correlations between APTW_{max} and SUV_{max} ($r = 0.609$, $P = 0.027$), as well as between $\text{APTW}_{\text{mean}}$ and SUV_{mean} ($r = 0.599$, $P = 0.030$) for [^{18}F]FDG hypermetabolic brain tumors. Meanwhile, there were no significant associations between APTW_{max} and SUV_{max} ($r = -0.545$, $P = 0.263$), or $\text{APTW}_{\text{mean}}$ and SUV_{mean} ($r = -0.479$, $P = 0.337$) in any of the six [^{18}F]FDG non-avid tumors.

Discussion

As a new multiple imaging modality, hybrid PET/MR provides myriad choices in the selection of MRI sequences and contrast medium, as well as in PET radiotracers, in order to provide different aspects of pathophysiological information in lesions simultaneously. However, some procedures or information might be repetitive and unnecessary. Thus, the optimization of a PET/MR protocol and clarification of the relations between different modalities are mandatory for both routine clinical use and scientific research [16]. In this brain [^{18}F]FDG PET/MR study, we found that APT imaging and Gd-enhanced MRI were comparably superior to [^{18}F]FDG PET in diagnostic accuracy. APTW images correlated well with Gd enhancement in brain tumors, while [^{18}F]FDG avidity was not constantly hyperintense. The metrics of APT imaging and [^{18}F]FDG PET correlated well only in tumors with [^{18}F]FDG hypermetabolic activity, which represents their complementary and interactive relations during hybrid [^{18}F]FDG PET/MR imaging.

Compared to conventional unenhanced MRI and [^{18}F]FDG PET in the brain, Gd-enhanced imaging has traditionally been a superior method for lesion detection, differentiation, and final diagnosis, which was also shown in our study. The principle of contrast-enhanced imaging is based on the high concentration of contrast agent in blood vessels and in brain lesions with a BBB leak. However, functional imaging techniques, like DWI and the other novel method, APT imaging, were involved in this study to make a comparison among different techniques. DWI can reflect information about the extracellular space and cell density, which has routinely been used for the diagnosis and treatment evaluation of stroke and tumors in the clinic. APT imaging is based on the CEST signal of mobile proteins and peptides at the offset of 3.5 ppm from water, which can reflect pH information in stroke and detect endogenous mobile proteins and peptides in tumors non-invasively [3]. In contrast to a Gd chelate as an exogenous contrast medium, APT imaging, as a functional molecular imaging technique involving endogenous contrast, has become more and more useful in the evaluation and differentiation of brain lesions, including stroke, tumors, and degenerative diseases [6, 18]. Previous studies have confirmed a complementary role for APT imaging to standard MRI sequences after a direct comparison of brain tumor presentation between APTW, diffusion, and Gd-enhanced images [19, 20]. Other recent studies demonstrated an added value of APT imaging in grading glioma and differentiating tumor recurrence from

radiation necrosis, where Gd-enhanced imaging is not beneficial [21–23]. In accordance with these studies, we found that APT imaging and Gd-enhanced imaging were concordant and comparably superior to [^{18}F]FDG PET/MR in brain tumor detection and diagnosis. APT imaging showed an inferior ability to illustrate tumor heterogeneity and tumor components, compared to Gd-enhanced imaging, such as necrosis, hemorrhage, or liquefaction tissue, which might also be proteinaceous. However, standard unenhanced MRI can compensate for this shortcoming since these sequences are usually analyzed together in routine practice [24]. Thus, our study demonstrated promising results after applying APT imaging on a clinical PET/MR scanner. With the help of APT imaging, the unnecessary administration of Gd contrast will avoid the incidence of nephrogenic sclerosis and gadolinium chelate deposition in the brain [25, 26]. Meanwhile, the economic and time expenditures of Gd-enhanced imaging are eliminated and the clinical [^{18}F]FDG PET/MR protocol can be greatly streamlined.

Currently, [^{18}F]FDG PET imaging of brain tumors has shown limited value in pre-surgical diagnosis and tumor grading [27]. One reason is the heterogeneous [^{18}F]FDG uptake ability of various types of brain tumors. Some low-grade tumors, such as pilocytic astrocytomas and gangliogliomas, tend to overconsume [^{18}F]FDG. Other gliomas that are rich in hexokinase II expression ([^{18}F]FDG is phosphorylated and trapped via hexokinase) would show a falsely high uptake of [^{18}F]FDG [4]. In our study, we had two meningiomas of high [^{18}F]FDG uptake, which were ultimately confirmed as WHO grade I tumors by pathology (Fig. 2). [^{18}F]FDG uptake of brain meningiomas is related to cellular proliferative activity and recurrence rate, rather than tumor grading [29]. The other main reason is the relatively high background glucose uptake within the normal brain. In this study, in addition to the one high-grade glioma (WHO grade IV) of mild [^{18}F]FDG hypometabolism (Fig. 3), we also found a suboptimal sensitivity for [^{18}F]FDG PET in the detection of brain metastases (84.6%, 11/13). This may be attributable to the interplay of two factors: the hypometabolic nature of some tumors, and the intense physiologic background uptake. Thus, this could explain the fact that there were no correlations between the metrics from APT imaging and [^{18}F]FDG PET among an overall range of brain tumors. Brain tumors are rich in proteins and peptides, independent of their glucose metabolism. Thus, APT imaging might be complementary to PET in [^{18}F]FDG-negative tumors and provide insight into those instances where [^{18}F]FDG PET is not of benefit. However, in a tumor subgroup of [^{18}F]FDG hypermetabolism, we found a strong correlation between APTW_{max} and SUV_{max} , as well as $\text{APTW}_{\text{mean}}$ and SUV_{mean} . This indicated that the tumors characterized by glucose hypermetabolism tended to have rich amounts of proteins and peptides. This interactivity may imply a possible surrogate and confirmative value for APT imaging in [^{18}F]FDG-positive tumors, and a complementary value in differentiating [^{18}F]FDG-positive lesions.

There are still some limitations to our study. First, the sample size was not large enough. The clinical workflow and indications for PET/MR are currently under investigation, with the goal of optimization among different centers, which will result, hopefully, in large-scale prospective studies in the near future. Second, tumors without Gd enhancement, such as atypical glioblastomas and anaplastic astrocytoma, were not included in this study [5]. As reported previously [31], APT imaging has great potential in glioma grading, regardless of Gd enhancement. This might further strengthen the advantage of APTW MRI. Third, we

used single-slice APT imaging in our initial study. Thus, APT imaging in the present study did not cover the whole tumor. However, this would not affect the comparative results, such as heterogeneity assessment for APT and Gd-enhanced imaging, since the comparative assessment was performed on the same slice among different modalities. This slice was the maximum cross-sectional tumor area based on an on-site decision from an experienced radiologist. The voxel size of our two-dimensional APT imaging was $1.88 \times 3.75 \times 6$ mm, which was similar to that of Gd-enhanced imaging. This comparable spatial resolution made no difference during tumor assessment on APT or Gd-enhanced images. Notably, the clinical availability of fast three-dimensional APT imaging (< 5 min) would help to further streamline clinical PET/MR protocols by covering the whole brain, and investigate combined multiparametric analysis by improving APTW measurements [32, 33]. In addition, it is known that calculated APTW signal intensities essentially had the semi-quantification characteristic only, primarily due to the contamination of the upfield nuclear Overhauser enhancement (NOE) effect [6–8]. In addition, amine protons in glutamate (~ 3 ppm) [9] may also make contributions to APTW signals. Several alternative APTW imaging analysis or acquisition approaches have been proposed to quantify a pure APT effect [10–12]. Notably, the extrapolated semi-solid magnetization transfer reference model developed recently [13, 14] should achieve more pure APT quantification, and we will apply this promising imaging analysis method to our future research. Finally, because of the low concentration of $[^{18}\text{F}]\text{FDG}$, we neglected the effect of $[^{18}\text{F}]\text{FDG}$ on APT imaging. Inorganic fluoride ions should not contribute to the CEST effect. The hydroxyl protons of FDG can be detected by CEST at ultrahigh fields ($> 7\text{T}$) [34, 35], but their detectability would be minimal due to the fast exchange property at 3T. Thus, $[^{18}\text{F}]\text{FDG}$ may not show any effect on APT imaging, which is based on the concentration of amides.

Conclusion

The results of this hybrid brain $[^{18}\text{F}]\text{FDG}$ PET/MR study demonstrate that APT imaging not only shows good concordance with Gd-enhanced MRI, but also adds value to $[^{18}\text{F}]\text{FDG}$ PET. Thus, if further studies confirm our findings, a brain PET/MR scan protocol may be streamlined without the need to administer Gd chelates. Compared to $[^{18}\text{F}]\text{FDG}$ metabolism, the complementary information from the endogenous cellular proteins and peptides in APT imaging might strengthen and extend the clinical applications of PET/MR in tumor diagnosis, treatment planning, and therapy response assessment.

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References

1. Fraum TJ, Fowler KJ, McConathy J. PET/MRI:: Emerging clinical applications in oncology. *Acad Radiol.* 2016; 23:220–236. [PubMed: 26521689]
2. Spick C, Herrmann K, Czernin J. ^{18}F -FDG PET/CT and PET/MRI perform equally well in cancer patients: Evidence from studies on more than 2300 patients. *J Nucl Med.* 2016; 57:420–430. [PubMed: 26742709]

3. Ishii S, Shimao D, Hara T, et al. Comparison of integrated whole-body PET/MR and PET/CT: Is PET/MR alternative to PET/CT in routine clinical oncology? *Ann Nucl Med*. 2016; 30:225–233. [PubMed: 26676720]
4. Padhani AR, Liu G, Mu-Koh D, et al. Diffusion-weighted magnetic resonance imaging as a cancer biomarker: Consensus and recommendations. *Neoplasia*. 2009; 11:102–125. [PubMed: 19186405]
5. Yang D, Korogi Y, Sugahara T, et al. Cerebral gliomas: prospective comparison of multivoxel 2D chemical-shift imaging proton MR spectroscopy, echoplanar perfusion and diffusion-weighted MRI. *Neuroradiology*. 2002; 44:656–666. [PubMed: 12185543]
6. Zhou J, Payen JF, Wilson DA, Traystman RJ, van Zijl PC. Using the amide proton signals of intracellular proteins and peptides to detect pH effects in MRI. *Nat Med*. 2003; 9:1085–1090. [PubMed: 12872167]
7. Li C, Peng S, Wang R, et al. Chemical exchange saturation transfer MR imaging of Parkinson's disease at 3 Tesla. *Eur Radiol*. 2014; 24:2631–2639. [PubMed: 25038850]
8. Harston GW, Tee YK, Blockley N, et al. Identifying the ischaemic penumbra using pH-weighted magnetic resonance imaging. *Brain*. 2015; 138:36–42. [PubMed: 25564491]
9. Sun H, Xin J, Zhang S, et al. Anatomical and functional volume concordance between FDG PET, and T2 and diffusion-weighted MRI for cervical cancer: a hybrid PET/MR study. *Eur J Nucl Med Mol Imaging*. 2014; 41:898–905. [PubMed: 24463908]
10. Han M, Kim SY, Lee SJ, Choi JW. The correlations between MRI perfusion, diffusion parameters, and ¹⁸F-FDG PET metabolic parameters in primary head-and-neck cancer: A cross-sectional analysis in single institute. *Medicine (Baltimore)*. 2015; 94:e2141. [PubMed: 26632740]
11. Wen Z, Hu S, Huang F, et al. MR imaging of high-grade brain tumors using endogenous protein and peptide-based contrast. *Neuroimage*. 2010; 51:616–622. [PubMed: 20188197]
12. Zhou J, Blakeley JO, Hua J, et al. Practical data acquisition method for human brain tumor amide proton transfer (APT) imaging. *Magn Reson Med*. 2008; 60:842–849. [PubMed: 18816868]
13. Jiang S, Yu H, Wang X, et al. Molecular MRI differentiation between primary central nervous system lymphomas and high-grade gliomas using endogenous protein-based amide proton transfer MR imaging at 3 Tesla. *Eur Radiol*. 2016; 26:64–71. [PubMed: 25925361]
14. Kickingereder P, Wiestler B, Sahm F, et al. Primary central nervous system lymphoma and atypical glioblastoma: multiparametric differentiation by using diffusion-, perfusion-, and susceptibility-weighted MR imaging. *Radiology*. 2014; 272:843–850. [PubMed: 24814181]
15. Padma MV, Said S, Jacobs M, et al. Prediction of pathology and survival by FDG PET in gliomas. *J Neurooncol*. 2003; 64:227–237. [PubMed: 14558598]
16. Klenk C, Gawande R, Tran VT, et al. Progressing toward a cohesive pediatric ¹⁸F-FDG PET/MR protocol: Is administration of gadolinium chelates necessary? *J Nucl Med*. 2016; 57:70–77. [PubMed: 26471690]
17. Zhou J, Yan K, Zhu H. A simple model for understanding the origin of the amide proton transfer MRI signal in tissue. *Appl Magn Reson*. 2012; 42:393–402. [PubMed: 23243339]
18. Goerke S, Zaiss M, Kunz P, et al. Signature of protein unfolding in chemical exchange saturation transfer imaging. *NMR Biomed*. 2015; 28:906–913. [PubMed: 26010522]
19. Zhou J, Lal B, Wilson DA, Laterra J, van Zijl PC. Amide proton transfer (APT) contrast for imaging of brain tumors. *Magn Reson Med*. 2003; 50:1120–1126. [PubMed: 14648559]
20. Jones CK, Schlosser MJ, van Zijl PC, et al. Amide proton transfer imaging of human brain tumors at 3T. *Magn Reson Med*. 2006; 56:585–592. [PubMed: 16892186]
21. Zhou J, Tryggstad E, Wen Z, et al. Differentiation between glioma and radiation necrosis using molecular magnetic resonance imaging of endogenous proteins and peptides. *Nat Med*. 2011; 17:130–134. [PubMed: 21170048]
22. Togao O, Yoshiura T, Keupp J, et al. Amide proton transfer imaging of adult diffuse gliomas: correlation with histopathological grades. *Neuro Oncol*. 2014; 16:441–448. [PubMed: 24305718]
23. Park KJ, Kim HS, Park JE, et al. Added value of amide proton transfer imaging to conventional and perfusion MR imaging for evaluating the treatment response of newly diagnosed glioblastoma. *Eur Radiol*. 2016; 26:4390–4403. [PubMed: 26883333]
24. Sakata A, Okada T, Yamamoto A, et al. Grading glial tumors with amide proton transfer MR imaging: different analytical approaches. *J Neurooncol*. 2015; 122:339–348. [PubMed: 25559689]

25. Ramalho J, Semelka RC, Ramalho M, et al. Gadolinium-based contrast agent accumulation and toxicity: An update. *AJNR Am J Neuroradiol*. 2016; 37:1192–1198. [PubMed: 26659341]
26. Thomsen HS, Morcos SK, Almen T, et al. Nephrogenic systemic fibrosis and gadolinium-based contrast media: updated ESUR Contrast Medium Safety Committee guidelines. *Eur Radiol*. 2013; 23:307–318. [PubMed: 22865271]
27. Fink JR, Muzi M, Peck M, Krohn KA. Multimodality brain tumor imaging: MR imaging, PET, and PET/MR imaging. *J Nucl Med*. 2015; 56:1554–1561. [PubMed: 26294301]
28. Krohn KA, Mankoff DA, Muzi M, Link JM, Spence AM. True tracers: comparing FDG with glucose and FLT with thymidine. *Nucl Med Biol*. 2005; 32:663–671. [PubMed: 16243640]
29. Lee JW, Kang KW, Park SH, et al. 18F-FDG PET in the assessment of tumor grade and prediction of tumor recurrence in intracranial meningioma. *Eur J Nucl Med Mol Imaging*. 2009; 36:1574–1582. [PubMed: 19377904]
30. Scott JN, Brasher PM, Sevick RJ, Rewcastle NB, Forsyth PA. How often are nonenhancing supratentorial gliomas malignant? A population study. *Neurology*. 2002; 59:947–949. [PubMed: 12297589]
31. Zhou J, Zhu H, Lim M, et al. Three-dimensional amide proton transfer MR imaging of gliomas: Initial experience and comparison with gadolinium enhancement. *J Magn Reson Imaging*. 2013; 38:1119–1128. [PubMed: 23440878]
32. Zhu H, Jones CK, van Zijl PC, Barker PB, Zhou J. Fast 3D chemical exchange saturation transfer (CEST) imaging of the human brain. *Magn Reson Med*. 2010; 64:638–644. [PubMed: 20632402]
33. Zhao X, Wen Z, Zhang G, et al. Three-dimensional turbo-spin-echo amide proton transfer MR imaging at 3-Tesla and its application to high-grade human brain tumors. *Mol Imaging Biol*. 2013; 15:114–122. [PubMed: 22644987]
34. Walker-Samuel S, Ramasawmy R, Torrealdea F, et al. *In vivo* imaging of glucose uptake and metabolism in tumors. *Nature Med*. 2013; 19:1067–1072. [PubMed: 23832090]
35. Rivlin M, Horev J, Tsarfaty I, Navon G. Molecular imaging of tumors and metastases using chemical exchange saturation transfer (CEST) MRI. *Sci Rep*. 2013; 3:3045. [PubMed: 24157711]

Fig. 1.

A typical case (metastasis from lung adenocarcinoma) illustrates the six diagnostic criteria. Imaging features from unenhanced **a** T1WI, and **b** T2WI, enhanced **c** T1WI, **d** APTW image, **e** [^{18}F]FDG PET, and **f** fused PET/MRI all lead to a common diagnosis of a well-defined heterogeneous malignant tumor with necrosis and peritumoral edema. The APTW image is concordant with Gd enhancement and [^{18}F]FDG, and unenhanced MRI can compensate for its weakness in displaying the tumor components.

Fig. 2.

A low-grade meningioma (WHO grade I, meningothelial type) presents typical imaging features on unenhanced **a** T1WI, and **b** T2WI, enhanced **c** T1WI, and **d** APTW image. The tumor is moderately hypermetabolic on **e** [^{18}F]FDG PET and **f** fused PET/MRI, which is a reported indication of possible recurrence. In this case, APT imaging could replace Gd-enhanced imaging, but its metric correlation with [^{18}F]FDG PET in treatment prognosis requires further investigation.

Fig. 3.

A high-grade glioma (WHO Grade IV) presents a cyst-like lesion with minor septum, which cannot be diagnosed as benign or malignant on unenhanced **a** T1WI and **b** T2WI. Enhanced **c** T1WI shows mild ring enhancement, indicating a possible malignancy. **d** APTW image is in accordance with enhanced MRI, but the obvious hyperintensity indicates a probable malignancy. The tumor is negative on **e** [^{18}F]FDG PET and **f** fused PET/MRI; thus, this unenhanced [^{18}F]FDG PET/MR cannot differentiate, before surgery, whether the tumor is malignant or not without APT imaging.

Fig. 4. Scatterplots demonstrating the results of Pearson's correlations between APTW signal intensities and SUVs in all 13 [¹⁸F]FDG hypermetabolic tumors (**a**, **b**) and all six [¹⁸F]FDG non-avid tumors (**c**, **d**). The central solid line in each scatterplot is the best-fit line. Curves above and below the best-fit line represent the upper and lower bounds of the 95% confidence interval.

Table 1

Patient characteristics

Characteristics	Value
Age (mean±SD, years)	54.5 ± 15.5
Gender (Male/Female)	21 (12/9)
Lesion No.	23
Metastasis	13
Metastasis from lung cancer	11
Metastasis from colon cancer	1
Metastasis from esophageal cancer	1
Glioma	3
WHO Grade IV	2
WHO Grade II	1
Meningioma (WHO Grade I)	3
Chronic infarction	4
Tumor diameter (mean±SD, centimeter)	5.5 ± 3.2

Table 2

Diagnostic criteria with regard to lesion morphology and final diagnosis

Category	Unenhanced MRI	Enhanced MRI	APTW image	[¹⁸ F]FDG
Tumor (or not)	Mass effect	Mass or nodule enhancement	Hyperintense	Avidity *
Homogeneous or heterogeneous	Uniform or varying signal intensity	Uniform or varying enhancement	Uniform or varying signal intensity	Not applicable
Necrosis, hemorrhage, or liquefaction	Heterogeneity or liquid-like signal intensity	Decreased or absence of enhancement	Heterogeneity, but predominantly hyperintensity	No avidity
Tumor margins	Well- or ill-defined	Well- or ill-defined	Well- or ill-defined	Not applicable
Peritumoral edema	Differentiable or not	Differentiable or not	Differentiable or not	Differentiable or not
Final diagnosis	Diagnosis based on imaging features	Diagnosis based on imaging features	Diagnosis based on imaging features	Diagnosis based on imaging features

* Avidity was defined as visually higher [¹⁸F]FDG uptake for the lesion compared to the contralateral normal white or gray matter.

Table 3Accuracy of six diagnostic criteria in all 23 lesions between unenhanced and enhanced MRI, APT imaging, and [¹⁸F]FDG PET

Category	Unenhanced MRI	Enhanced MRI	APTW image	[¹⁸ F]FDG PET	Difference (unenhanced MRI - enhanced MRI)	Difference (APTW - PET)	Difference (enhanced MRI - APTW image)
Tumor (or not)	0.784 (0.653–0.885)	0.917 (0.833–0.984)	0.885 (0.835–0.934)	0.467 (0.283–0.651)	0.029(–0.250–0.016) *	0.001 (0.204–0.632) *	0.438 (–0.533–0.118)
Heterogeneity	0.917 (0.834–0.984)	0.884 (0.784–0.967)	0.801 (0.685–0.901)	NA	0.497 (–0.067–0.133)	NA	0.021 (0.014–0.153) *
Component detection	0.850 (0.716–0.967)	0.818 (0.718–0.901)	0.618 (0.477–0.735)	0.517 (0.333–0.710)	0.615 (–0.101–0.166)	0.309 (–0.102–0.305)	0.019 (0.036–0.363) *
Margin definition	0.884 (0.767–0.984)	0.900 (0.800–0.984)	0.850 (0.733–0.950)	NA	0.836 (–0.181–0.148)	NA	0.083 (–0.007–0.107)
Peritumoral edema	0.850 (0.732–0.967)	0.800 (0.646–0.950)	0.546 (0.392–0.721)	0.696 (0.514–0.878)	0.385 (–0.067–0.166)	0.179 (–0.383–0.082)	0.242 (–0.167–0.591)
Final diagnosis	0.800 (0.649–0.934)	0.901 (0.801–0.984)	0.885 (0.835–0.934)	0.551 (0.384–0.718)	0.030 (–0.190–0.011) *	0.003 (0.131–0.537) *	0.756 (–0.090–0.122)

Data are shown as relative agreement (1.0 = 100%) with 95% confidence intervals in brackets.

* represents significant difference since the confidence interval does not straddle zero. NA = not applicable.