METHODOLOGIC PERSPECTIVES

Switching on the Lights for Real-Time Multimodality Tumor Neuroimaging: The Integrated Positron-Emission Tomography/MR Imaging System

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SUMMARY: A recent report of the feasibility of simultaneous PET/MR imaging of the healthy human brain has sparked excitement in the field of neuroimaging because of its potential influence and utility in clinical neuroscience research. The aim of this communication is to discuss the benefits and current drawbacks of the hybrid imaging system and to highlight some perspectives of the new technique for brain neoplasms.

ABBEVIATIONS: ^{11}C = carbon 11; ^{18}F = fluorine 18; FDG = fluorodeoxyglucose; FET = fluoroethyltyrosine; FLT = fluorothymidine; FMISO = fluoromisonidazole; H_2 = hydrogen 2; ^{15}O = oxygen 15; ^{17}O = oxygen 17; PET = positron-emission tomography; PMTs = photomultiplier tubes; SUV = standardized uptake value

Neuroradiology is strongly dependent on medical imaging technology and is often the very first application field for novel technologic progress. Modern neuroimaging surpasses the need for morphologic information and sheds light on the complex brain functions by means of a comprehensive assessment of anatomic, functional, and molecular information. Different imaging modalities are now available for experimental and clinical brain surveys, but MR imaging and PET remain the cutting-edge methods for acquiring excellent spatial brain images combined with physiologic and functional information about brain tissue. Although MR imaging and PET have evolved remarkably since their advent, their clinical applications remain distinct and one cannot be substituted for the other. Thus, combining these 2 imaging modalities into 1 multitechnique unit is important for the following reasons: 1) The combined unit may improve diagnostic accuracy by achieving an excellent spatial correlation between PET and MR imaging acquisitions, 2) it may improve tissue characterization by enabling real-time functional and physiologic imaging and avoiding diagnostic compromises due to a 2-step data acquisition and a side-by-side reading, and 3) the combined PET/MR imaging may reduce the overall patient time and financial burden, offering a wider population penetration for the new technique.

Our aim is to discuss the benefits and current drawbacks of hybrid PET/MR imaging, highlighting some perspectives of the new technique for tumor neuroimaging.

Hybrid PET/MR Imaging Systems

When combining 2 imaging modalities into 1 multitechnique machine, one must be assured that the imaging systems can coexist without mutual interference while maintaining their full individual performances. Furthermore, the available space for accommodating the different hardware has to be accordingly modified, and the software components have to be integrated into 1 single analysis software package, enabling an advanced workflow in routine radiology. One first realization of a multitechnique unit is the combination of PET and CT.[1] For instance in PET/CT, there is a common patient bed for the 2 scanners and the data are acquired not simultaneously but sequentially. Nevertheless, the major advantage of PET/CT is the use of CT for anatomic landmarks and PET for attenuation correction.

Integration of PET and MR imaging has become a topic of increasing interest to the imaging community in the past few years and, until now, was mainly pursued by the small-animal imaging research community. After the first attempts at tackling the compatibility problems of integration between PET and MR imaging units, researchers conceived 3 strategies for the multitechnique PET/MR imaging: separate imaging, sequential imaging, and fully integrated systems.[2] In PET/CT and single-photon emission CT/CT, such fully integrated systems are also conceivable but would require development of new detectors that can simultaneously detect and discriminate gamma rays and CT x-rays. Furthermore, software fusion of PET and MR images obtained by separate or sequential imaging has certain limitations: Spatial resolutions are different and may have distortion; partial volume effects cannot be compared; and dynamic changes cannot be followed in an identified structure.

Although the fusion of brain images is relatively easy due to the firm anatomic "framing" of the intracranial structures, an exact relocation of the patient is difficult and may contribute to alignment variations, especially concerning multifunctional information from PET, diffusion tensor imaging, perfusion-weighted MR imaging, functional MR imaging, and MR spectroscopy, which may include temporal and spatial fluctuations. Obviously, fusion software presents serious pitfalls in imaging the abdomen or thorax, which necessitates time-consuming side-by-side reading; thus, these anatomic

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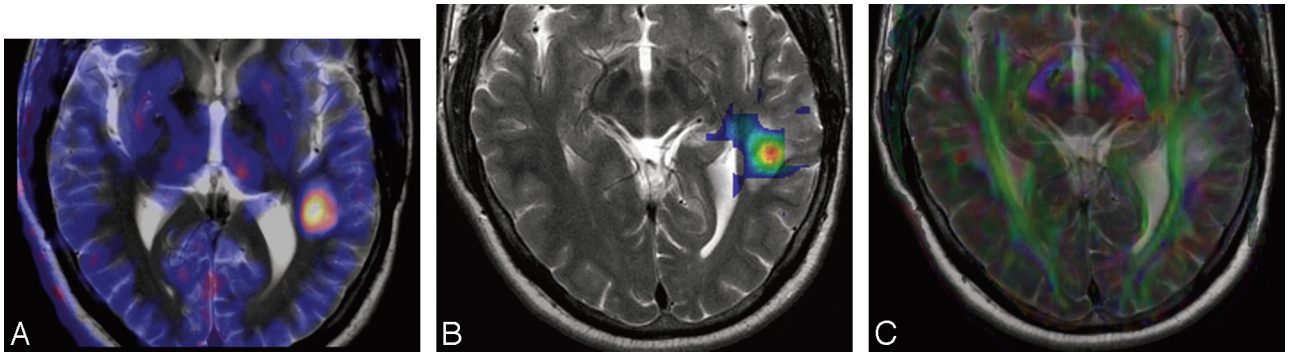

Fig 1. An example of ^{11}C-methionine simultaneously acquired and superimposed on PET/MR imaging anatomic (*A*), proton MR spectroscopy (*B*), and diffusion tensor (*C*) imaging of a 42-year-old patient with an atypical neurocytoma on the left temporo-occipital lobe. Note the superior anatomic information provided by the spatial matching between MR images and PET images, the avid tracer uptake in the tumor, the spatial correlation with the spectroscopic findings, and the clear relationship to the adjacent optic radiation.

regions may be the next application field of an integrated PET/MR imaging scanner.

Technical Considerations and Advantages of Integrated PET/MR Imaging

Conventional PET detectors are based on PMTs, which are notoriously sensitive to magnetic fields and, therefore, are not suitable for combined PET/MR imaging. The solution to this problem appeared to be new semiconductor-based light detectors, such as avalanche photodiodes.[3] The first feasibility studies with an integrated PET/MR imaging system in small animals[4,5] and very recently in humans[6] showed encouraging results. Since March 2008, the Department of Radiology of the University Hospital of Tübingen (S.B., H.-P.S., T.N., C.D.C., U.E.) and its Laboratory for Preclinical Imaging and Imaging Technology of the Werner Siemens-Foundation (B.P.) have had available 1 of the 3 worldwide MR imaging–compatible clinical PET scanners, which is mounted in a standard 3T MR imaging scanner (Trio; Siemens Medical Systems, Erlangen, Germany). Compared with state-of-the-art whole-body PET scanners, dedicated MR imaging–compatible brain PET has an increased point source sensitivity of >6% and a much better spatial resolution (approximately 3 mm).[6] Furthermore, the inherent advantages may be translated into shorter PET acquisition times for the same image quality or reduced quantity of the injected tracer for the same acquisition time, while the increased resolution may detect early tissue changes and save re-examinations.

An important issue when developing a multitechnique imaging like PET/CT or PET/MR imaging is the attenuation correction, which is the prerequisite for rendering the true tracer spatial distribution and applying any quantification (eg, in terms of SUV). The correction may be rather straightforward by using a bilinear transformation for converting CT numbers to 511 keV attenuation coefficients, though iodine-based contrast media and metals confound the process. Thus, CT is apparently advantageous for an attenuation correction due to fast acquisition and low noise. In PET/MR imaging, photon attenuation may occur due to the MR imaging gradient and radio-frequency coils with their electronic components and due to the tissue of the patient. While the latter is easily handled in PET/CT with the aforementioned transformation, MR imaging yields only tissue proton densities and magnetic relaxation times. Notably, bone and air appear with similar low-signal MR imaging intensity despite having the highest and lowest photon-attenuation coefficients, respectively. A number of different approaches are being explored and are based mainly on MR imaging segmentation[7] and registration to an atlas of MR and CT image pairs to create a "pseudoCT" scan.[8] Finally, an approach under consideration is to incorporate a pulse sequence into the PET/MR image that may generate signal intensity from bone. Further investigation will be required to identify the most accurate and reliable methodology for MR imaging–based attenuation correction.[9]

Nevertheless, a major advantage of the integrated PET/MR imaging prototype for neuroimaging lies in its simultaneous acquisition nature. Together with the aforementioned spatial and temporal fluctuations of functional data in the brain tumor microenvironment, certain tracers (like $H_2{}^{15}O$) have very short half-lives with rapid influx and efflux in the volume of interest, while other tracers (like $^{13}NH^3$ ammonia) reach a tissue equilibrium state depending on the tissue perfusion. In such cases, simultaneous PET/MR imaging is mandatory for a reliable coregistration and quantification process as well as for correlation with dynamic MR imaging. Finally, simultaneous imaging not only improves the diagnostic value of PET/MR imaging but also enables respiratory or cardiac motion correction and tracks any patient movement.

Concerning the radiologic workflow, multitechnique integration obviously outperforms any separate or sequential imaging because neither scanning unit remains idle during the acquisitions. This also has direct implications on the patient's comfort and compliance with the examination.[2]

Future Endeavors of an Integrated PET/MR Imaging System

Principally, the installation of a PET/MR imaging system in a clinical neuroscience environment unfolds a spectrum of combined assessments of biologic properties of brain tumors already used in preclinical research. Without a doubt, ^{18}F-FDG is the most widely used oncologic PET tracer; nonetheless, the generally high uptake of FDG in high-grade tumors can be less than or similar to that in normal gray matter, especially after treatment.[10] This decreased specificity of FDG in brain tumors may be overcome with amino acid PET tracers, like ^{11}C-methionine, or aromatic amino acid analog PET tracers, like ^{18}F-FET and ^{18}F-fluorophenylalanine. Amino acids are transported into the cell via carrier-mediated processes,

and the transport is up-regulated in malignant transformation even in the absence of increased vascular permeability and breakdown of the blood-brain barrier.[11] Thus, combined amino acid and MR imaging will enhance the diagnostic sensitivity for gliomas and may allow a closer correlation between the tracer uptake and the metabolic changes (eg, choline peaks in MR spectroscopy) in the neoplastic tissue (Fig 1).

Likewise, arterial spin-labeling estimations of perfusion and diffusion changes occurring in low-grade gliomas may now be studied in conjunction with each PET-tracer imaging to establish reliable disease markers. Consequently, the "wait-and-see" approach in low-grade gliomas may optimize the timing and extent of surgery.[12] Furthermore, the precise coregistration of the excellent MR imaging spatial resolution, improved by new multichannel head coils, will add substantial value to the already-established worth of somatostatin-analog imaging for meningiomas. This is clinically important in 3 respects: First, meningiomas may be considerably small-sized, and osseous structures (eg, skull base) may hamper the diagnosis; second, radiation therapy of meningiomas may experience a new era with the integrated PET/MR imaging as it is proved that the fused MR imaging and PET data may alter the radiation planning in 73% of the cases[13]; and third, recurrent meningiomas are not rare, and their localization and extent estimation may be aided by the spatial resolution of PET/MR imaging and functional MR imaging, which may give additional information about tumor spread and may be incorporated in the definition of safety margins.[14]

In modern neuroimaging, perfusion-weighted MR imaging finds an increasingly important role for other brain lesions beyond its "classic" application in patients with stroke. For the diagnosis of degenerative and neoplastic diseases, perfusion-weighted MR imaging serves as a substitute in overcoming the shortfalls of morphologic imaging. Contrast-enhanced dynamic MR imaging, which may play a more decisive role for therapy outcome in the future,[15] may now be compared with the PET-tracer kinetics, which is supposed to be the criterion standard. Although dynamic susceptibility MR imaging (or bolus tracking) and dynamic contrast-enhanced MR imaging are routinely used, the nonlinear relationship between gadolinium concentration and T1 (or 1/T1) signal intensity and T1 contamination (due to the disruption of the blood-brain barrier) is an inherent problem in the quantification of the brain perfusion parameters. The proposed models[16-18] have reasonable assumptions of deriving pharmacokinetic parameters and have already been validated with PET measurements[19]; however, methodologic flaws such as inaccuracies in the coregistration of MR imaging (especially echo-planar imaging) and PET data and differences in the inherent resolutions of PET and MR imaging may subsequently have led to poor correlation between the 2 modalities.

Hybrid PET/MR imaging now offers an opportunity for more accurate validation of the proposed pharmacokinetic models by means of simultaneously recorded ^{15}O-H_2O use in PET. Such perfusion measurements may also deliver insight into the flow-dependent kinetic constants for compartmental analysis of PET data (eg, FDG),[20] not to mention the opportunity to validate the cerebral perfusion values acquired by arterial spin-labeling and a new MR imaging tracer for oxygen use (^{17}O), whereby the inhaled ^{17}O is converted to $H_2{}^{17}O$ in proportion to the oxygen consumption, resulting in negative contrast on T2-weighted images.[21]

The integrated PET/MR imaging will allow an easier reading of complex heterogeneous glioblastoma baselines and follow-up surveys and a more reliable identification of tumor "hot spots" and correlation with the spatial distribution of perfusion, diffusion, and spectroscopic data.[22] Until now, there have been no data regarding a coupling or decoupling between the SUV of the PET tracer and the functional MR imaging data. PET/MR imaging units offer a brilliant opportunity for such studies and for a PET/MR imaging–guided biopsy in a manner similar to the double-tracer approach.[23] Thus, this technique is expected to increase the sensitivity and specificity of diagnosing a primary or recurrent brain tumor and to define the exact borders of the disease, leading to more exact surgical resection. The next step would be a multimodality-guided treatment; after one defines the baseline metabolic profile of a neoplasm, guiding treatment would be easier. Fused imaging (PET/CT) has been proved to give a significant survival advantage over treatment planning based solely on CT or MR imaging.[24] The logical hypothesis that PET/MR imaging will enhance this significant advantage has to be tested.

Currently, stereotactic radiosurgery and sophisticated radiation protocols are used more extensively; and after combining chemotherapy and radiation becomes standard practice, the incidence of radiation necrosis is likely to increase. Because the pattern of radiation injury may vary, it is difficult and challenging to differentiate it from tumor growth with PET,[25] while initial studies report an increased sensitivity when FDG-PET and MR imaging are coregistered.[26] PET/MR imaging now offers the possibility of providing this evidence and of examining the hypothesis that amino acid tracers together with MR imaging may have potentially better diagnostic performance.[27]

Without any doubt, parallel to the development of hybrid imaging, new developments in tracer diagnostics, such as ^{18}F-FLT and ^{18}F-FMISO for cell proliferation and hypoxia imaging, respectively, have to be investigated in clinical practice. Most interesting, a recent study reported that the FMISO-estimated hypoxic volume generally occupied a region straddling the outer edge of the gadolinium leaking in the T1-weighted images and the hyperintense T2-weighted zone, thus supporting the hypothesis that hypoxia may drive the growth of glioblastomas.[28] Certainly, this finding has to be validated in an integrated PET/MR imaging system and, subsequently, correlated with the perfusion metrics in the peritumoral zone.[29] Moreover, choline is also an established proliferation and membrane transport marker, which may identify potential malignancy,[30] and it would be interesting to examine the relationship between ^{11}C-choline and water proton spectroscopy–based calculated choline relationships.

PET/MR imaging is also expected to shed light on neoangiogenesis, a fundamental process in tumor physiology. The visualization, quantification, and monitoring of angiogenesis has become of major interest in oncology during the past few years. Specifically in gliomas, cerebral blood volume seems to correlate with both cell and microvessel attenuation, whereas no regional correlation has been found between the apparent diffusion coefficient and cell attenuation.[31] Concerning the

PET tracers, ^{18}F-choline and FET in rats seems to correlate better with the pattern of neoangiogenesis markers than does FDG,[32] while at the same time, FLT also shows good correlation between the uptake and proliferation index.[33,34] PET and MR imaging are probably complementary and will likely yield important information on tumor response to therapy, particularly in the setting of antiangiogenic agents, which confound the interpretation of standard contrast-enhanced MR images.[35]

Driving the new PET/MR imaging applications even further, an exploration of synergisms by combining molecular MR imaging with PET would be of great interest. Molecular MR imaging is a rapidly evolving field—that is, ultrasmall iron-oxide particles or manganese-enhanced MR imaging offers insight into vascular and tissue degradation after ischemia or depicts internucleus/transsynaptic signaling, respectively.[36] These processes are depicted in high-resolution MR images; and combining, for instance, the brain connectivity studies of manganese-enhanced MR imaging with diffusion tracking imaging and amino acid PET tracers may explain the diffuse aggressive growth of glioblastomas. On the other hand, the accumulation of paramagnetic iron in the macrophages in conjunction with PET markers of neoangiogenesis would monitor the neovasculature-diminishing agents in a more effective way.

A further extremely attractive therapy is the targeted gene transfer by viral and nonviral vectors to express foreign enzymes in cells; this strategy can be applied, for example, to make malignant cells susceptible to specific drugs that are toxic only to those cells expressing this enzyme (suicide gene therapy). In an experimental setting—model guided by PET and static MR imaging, the gene transfer therapy was effective in the treatment of rat glioma[37]; therefore, it is also an attractive therapeutic strategy for human glioblastoma, especially in conjunction with a PET/MR molecular imaging approach. Nonetheless, beyond static imaging, MR imaging has already proved capable of a range of applications to study "in vivo events at the cellular or molecular level," such as cell labeling with monitoring of cell dynamics, receptor imaging, gene expression, and enzyme activity.[36] The combination of molecular MR imaging strategies with PET imaging in an integrated system may not only expand the diagnostic possibilities but may also safely assist therapeutic applications initiated by receptor-selective contrast agent nanoparticles.[38]

Conclusions

The development of a prototype integrated PET/MR imaging scanner with no detrimental effect on the performance of PET and no degradation of MR images for a number of standard clinical MR images has put PET/MR imaging on the verge of being applied to clinical neurosciences. The combined system will certainly broaden the impact and possibilities of simultaneous imaging of morphologic, functional, and metabolic information. This discussion of perspectives of an integrated PET/MR imaging system is in part hypothetic because the presented PET/MR imaging system is in its early stages of development and several technologic and methodic issues (ie, the attenuation correction of PET data) have to be addressed before PET/MR imaging can establish itself as a routine examination. Nevertheless, the first patient data are promising and highlight the scientific and clinical potential of the integrated system. Future studies will pursue the proof of the added value of the hybrid system for the modern neuroimaging.

References

1. Beyer T, Townsend DW, Brun T, et al. **A combined PET/CT scanner for clinical oncology.** *J Nucl Med* 2000;41:1369–79
2. von Schulthess GK, Schlemmer HP. **A look ahead: PET/MR versus PET/CT.** *Eur J Nucl Med Mol Imaging* 2009;36(suppl 1):S3–9
3. Pichler BJ, Judenhofer MS, Catana C, et al. **Performance test of an LSO-APD detector in a 7-T MRI scanner for simultaneous PET/MRI.** *J Nucl Med* 2006;47:639–47
4. Judenhofer MS, Wehrl HF, Newport DF, et al. **Simultaneous PET-MRI: a new approach for functional and morphological imaging.** *Nat Med* 2008;14:459–65
5. Catana C, Procissi D, Wu Y, et al. **Simultaneous in vivo positron emission tomography and magnetic resonance imaging.** *Proc Natl Acad Sci U S A* 2008;105:3705–10
6. Schlemmer HP, Pichler BJ, Schmand M, et al. **Simultaneous MR/PET imaging of the human brain: feasibility study.** *Radiology* 2008;248:1028–35
7. Zaidi H, Montandon ML, Slosman DO. **Magnetic resonance imaging-guided attenuation and scatter corrections in three-dimensional brain positron emission tomography.** *Med Phys* 2003;30:937–48
8. Hofmann M, Steinke F, Scheel V, et al. **MRI-based attenuation correction for PET/MRI: a novel approach combining pattern recognition and atlas registration.** *J Nucl Med* 2008;49:1875–83
9. Zaidi H. **Is MR-guided attenuation correction a viable option for dual-modality PET/MR imaging?** *Radiology* 2007;244:639–42
10. Wong TZ, van der Westhuizen GJ, Coleman RE. **Positron emission tomography imaging of brain tumors.** *Neuroimaging Clin N Am* 2002;12:615–26
11. Sasajima T, Miyagawa T, Oku T, et al. **Proliferation-dependent changes in amino acid transport and glucose metabolism in glioma cell lines.** *Eur J Nucl Med Mol Imaging* 2004;31:1244–56
12. Lang FF, Gilbert MR. **Diffusely infiltrative low-grade gliomas in adults.** *J Clin Oncol* 2006;24:1236–45
13. Milker-Zabel S, Zabel-du Bois A, Henze M, et al. **Improved target volume definition for fractionated stereotactic radiotherapy in patients with intracranial meningiomas by correlation of CT, MRI, and [68Ga]-DOTATOC-PET.** *Int J Radiat Oncol Biol Phys* 2006;65:222–27. Epub 2006 Feb 20
14. Neff T, Kiessling F, Brix G, et al. **An optimized workflow for the integration of biological information into radiotherapy planning: experiences with T1w DCE-MRI.** *Phys Med Biol* 2005;50:4209–23. Epub 2005 Aug 24
15. Bisdas S, Kirkpatrick M, Giglio P, et al. **Cerebral blood volume measurements by perfusion-weighted MR imaging in gliomas: ready for prime time in predicting short-term outcome and recurrent disease?** *AJNR Am J Neuroradiol* 2009;30:681–88
16. Donahue KM, Krouwer HG, Rand SD, et al. **Utility of simultaneously acquired gradient-echo and spin-echo cerebral blood volume and morphology maps in brain tumor patients.** *Magn Reson Med* 2000;43:845–53
17. Weisskoff RM, Zuo CS, Boxerman JL, et al. **Microscopic susceptibility variation and transverse relaxation: theory and experiment.** *Magn Reson Med* 1994;31:601–10
18. Koh TS, Zeman V, Darko J, et al. **The inclusion of capillary distribution in the adiabatic tissue homogeneity model of blood flow.** *Phys Med Biol* 2001;46:1519–38
19. Ostergaard L, Smith DF, Vestergaard-Poulsen P, et al. **Absolute cerebral blood flow and blood volume measured by magnetic resonance imaging bolus tracking: comparison with positron emission tomography values.** *J Cereb Blood Flow Metab* 1998;18:425–32
20. Strauss LG, Dimitrakopoulou-Strauss A, Haberkorn U. **Shortened PET data acquisition protocol for the quantification of 18F-FDG kinetics.** *J Nucl Med* 2003;44:1933–39
21. Tailor DR, Baumgardner JE, Regatte RR, et al. **Proton MRI of metabolically produced H2 17O using an efficient 17O2 delivery system.** *Neuroimage* 2004;22:611–18
22. Floeth FW, Pauleit D, Wittsack HJ, et al. **Multimodal metabolic imaging of cerebral gliomas: positron emission tomography with [18F]fluoroethyl-L-tyrosine and magnetic resonance spectroscopy.** *J Neurosurg* 2005;102:318–27
23. Pirotte B, Goldman S, Massager N, et al. **Combined use of 18F-fluorodeoxyglucose and 11C-methionine in 45 positron emission tomography-guided stereotactic brain biopsies.** *J Neurosurg* 2004;101:476–83
24. Grosu AL, Weber WA, Franz M, et al. **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* 2005;63:511–19
25. Ricci PE, Karis JP, Heiserman JE, et al. **Differentiating recurrent tumor from radiation necrosis: time for re-evaluation of positron emission tomography?** *AJNR Am J Neuroradiol* 1998;19:407–13

26. Chao ST, Suh JH, Raja S, et al. **The sensitivity and specificity of FDG PET in distinguishing recurrent brain tumor from radionecrosis in patients treated with stereotactic radiosurgery.** *Int J Cancer* 2001;96:191–97
27. Hustinx R, Pourdehnad M, Kaschten B, et al. **PET imaging for differentiating recurrent brain tumor from radiation necrosis.** *Radiol Clin North Am* 2005;43:35–47
28. Swanson KR, Chakraborty G, Wang CH, et al. **Complementary but distinct roles for MRI and 18F-fluoromisonidazole PET in the assessment of human glioblastomas.** *J Nucl Med* 2009;50:36–44. Epub 2008 Dec 17
29. Lehmann P, Vallee JN, Saliou G, et al. **Dynamic contrast-enhanced T2*-weighted MR imaging: a peritumoral brain oedema study.** *J Neuroradiol* 2009; 36:88–92. Epub 2008 Dec 2
30. Kato T, Shinoda J, Nakayama N, et al. **Metabolic assessment of gliomas using 11C-methionine, [18F] fluorodeoxyglucose, and 11C-choline positron-emission tomography.** *AJNR Am J Neuroradiol* 2008;29:1176–82
31. Sadeghi N, D'Haene N, Decaestecker C, et al. **Apparent diffusion coefficient and cerebral blood volume in brain gliomas: relation to tumor cell density and tumor microvessel density based on stereotactic biopsies.** *AJNR Am J Neuroradiol* 2008;29:476–82
32. Wyss MT, Spaeth N, Biollaz G, et al. **Uptake of 18F-fluorocholine, 18F-FET, and 18F-FDG in C6 gliomas and correlation with 131I-SIP(L19), a marker of angiogenesis.** *J Nucl Med* 2007;48:608–14
33. Jacobs AH, Thomas A, Kracht LW, et al. **18F-fluoro-L-thymidine and 11C-methylmethionine as markers of increased transport and proliferation in brain tumors.** *J Nucl Med* 2005;46:1948–58
34. Price SJ, Fryer TD, Cleij MC, et al. **Imaging regional variation of cellular proliferation in gliomas using 3′-deoxy-3′-[18F]fluorothymidine positron-emission tomography: an image-guided biopsy study.** *Clin Radiol* 2009;64:52–63. Epub 2008 Sep 4
35. Chaskis C, Neyns B, Michotte A, et al. **Pseudoprogression after radiotherapy with concurrent temozolomide for high-grade glioma: clinical observations and working recommendations.** *Surg Neurol* 2009;72:423–28. Epub 2009 Jan 15
36. Hoehn M, Himmelreich U, Kruttwig K, et al. **Molecular and cellular MR imaging: potentials and challenges for neurological applications.** *J Magn Reson Imaging* 2008;27:941–54
37. Miletic H, Fischer YH, Giroglou T, et al. **Normal brain cells contribute to the bystander effect in suicide gene therapy of malignant glioma.** *Clin Cancer Res* 2007;13:6761–68
38. Hood JD, Bednarski M, Frausto R, et al. **Tumor regression by targeted gene delivery to the neovasculature.** *Science* 2002;296:2404–07