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REVIEW

PET/MR — a rapidly growing technique of imaging in oncology and neurology

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Abstract

INTRODUCTION: The combination of positron emission tomography (PET) and magnetic resonance (MR) has become a subject of interest for researchers in the recent several years. Positron emission tomography in combination with magnetic resonance (PET/MR) is the most recent imaging technique classified in the so called hybrid systems category.
AIM: This review briefly discusses the development history of PET/MR scanners, the principle of their operation, of tandem systems, as well as fully integrated devices. Further, it summarizes recent reports on the application of PET/MR scans and their possible future role in oncological and non-oncological diagnostics.
CONCLUSIONS: Recent reports regarding the application of PET/MR scanners show huge potential of simultaneously received images, which exceed the advantages of either of those scans used separately. However, the results so far remain uncertain and require further investigations, especially in terms of clinical studies, not only for scientific purposes.

KEY words: PET/MR, imaging, oncology, neurology

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Background

Morphological and molecular imaging using magnetic resonance (MR) or computer tomography (CT) with positron emission tomography (PET) plays a key role in oncological diagnostics (staging before treatment, evaluation of treatment response, detection of recurrence etc.), as well as other areas, e.g. cardiology, neurology, psychiatry and others. Despite the large role these scans fulfil in imaging diagnostics of various conditions, each of them has certain well known limitations.

The combination of anatomical and functional images in order to improve the quality of the acquired images has already been used for a significant time. The end of the 1980s saw the first hybrid devices being applied, which are used up to this day and combine single photon emission computer tomography (SPECT) with CT [1, 2]. Another hybrid device which completely revolutionized imaging diagnostics, especially in the area of oncology, was the 1998 introduction of PET/CT scanners [3]. In both cases of hybrid systems, the more functional imaging methods, i.e. SPECT and PET, have been merged with more anatomical images received in CT, thereby creating a single image. With the commencement of PET/CT scanner use in clinical diagnostics in 2001, it soon turned out, that the combination of both scan types into one system is beneficial, as it ensures simultaneous anatomic and functional imaging [4, 5]. Ever since PET/CT scans have started being used routinely, it became obvious, that those scans have a significant influence on the therapeutic process in oncology, even in up to 50% of cases [6].

The creation of hybrid PET/MR devices utilizes the advantages of MR scans over CT which has been currently applied in PET/CT scans. The primary advantages of MR include:

— possibility of reducing the patient's exposure to radiation, as during the MR scan ionizing radiation is not used, which is especially important in case of children, as well as in situations which require repeated PET scans;
— MR ensures high resolution of anatomical and functional images, offering better resolution of soft tissue contrast and high diversity of tissue contrast compared with CT;
— MR, using functional MR imaging (fMRI) and MR spectroscopy (MRS), provides additional information which may increase the diagnostic efficiency and possibility of quantitative assessment of PET scans and may be helpful in handling the patient and understanding the tumor biology.

On the other hand, MR has several disadvantages:

— significantly longer scan time compared with CT;
— contraindications in patients with various metal implants, pacemakers and foreign bodies;
— significantly higher cost compared with CT [7].

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History of PET/MR scanner development

The promising results of pre-clinical PET/MR imaging have encouraged one of the primary companies dealing in production of diagnostic equipment (Siemens) to create the first clinical PET/MRI

prototype (BrainPET), created for the purpose of simultaneous PET and MR imaging of the brain, which was installed at the University of Tübingen in Germany [8, 9]. The system was evaluated in clinical conditions for 3 years (2008–2011). The anatomical potential of MR was investigated in relation to the high contrast of soft tissues, utilizing various possibilities of MR scan imaging, i.e. BOLD — a system of blood oxygen level dependent MR signal intensity, functional MR (fMRI), diffusion-weighted imaging (DWI), perfusion-weighted imaging (PWI) and diffusion tensor imaging (DTI) [10, 11]. In this system, the sequential connection of PET and MR was intended for molecular and genetic imaging of the brain by docking separate PET and MR systems connected by a joint bed which moved through the field of view of both imaging devices [12]. This was achieved by combining two high class devices, namely high resolution research tomography (HRRT) and 7 Tesla powered MR (7T MRI).

Until concurrently, operating PET/MR whole body imaging technologies have become more available and economically viable, other approaches, namely sequential PET/MR scans were researched [13]. One of such systems is the Philips Ingenuity TF PET/MR, which is a hybrid imaging system with a GEMINI TF PET component and an Achieva 3.0T X-series MR component [14]. Although such a device structure does not allow simultaneous PET and MR imaging, it does allow for automatic superimposition of sequentially recorded PET and MR images. Such systems have been installed in New York (Mount Sinai Medical Center), at the University Hospital in Geneva and in Dresden (Forschungszentrum Dresden-Rossendorf). Adhering to the structural rules applied when building PET/MR scanners for brain imaging, Siemens developed a system for simultaneous PET and MR imaging of the whole body in the form of the Biograph mMR scanner. The first such device was installed in November 2010 at the University in Munich. Subsequent Siemens PET/MR scanners were installed at the Tübingen and Erlangen Universities in Germany and in Boston at the Massachusetts General Hospital.

In Poland there are currently (2016) two PET/MR scanners installed, namely at the Center of Oncology in Bydgoszcz and the Laboratory of Medical Imaging at the Białystok Science and Technology Park. In both instances these are Biograph mMR scanners manufactured by Siemens.

Technological achievements of PET/MR systems

There are currently two types of commercially available devices which combine PET and MR, namely the tandem system, in which the PET and MR devices are in one or two rooms, and a fully integrated system, in which the PET and MR devices are built into one gantry [15–17]. Tandem PET/MR device systems allow for minimal interference between those systems and for that reason require only small changes in composition of PET and MR devices. On the other hand, fully integrated PET/MR systems require completely new structural design and technological solutions. These systems, however, make it possible to achieve truly simultaneous acquisition, which significantly reduces the total acquisition time and the spatial requirements [18].

The primary technological challenge is posed by the fact that photomultipliers used in traditional PET scanners which register the light signal from scintillation crystals are unable to operate within a strong magnetic field. Tandem systems circumvent this problem by physically separating the devices and appropriately screening the individual components. Integrated PET/MR devices manufactured so far use light signal reading semi-conductor technology, so called avalanche photodiodes instead of photomultipliers which are unaffected by magnetic fields [17].

Another important technological challenge of tandem and fully integrated PET/MR systems is photon attenuation correction, which is necessary to maintain the correct image of radionuclide distribution independent of the tissue density. MR does not provide information regarding the radiological density of tissues. That is why development of new attenuation correction methods in PET/MR systems is required. The method currently used in PET/MR devices is to receive the sequences devoted to MR in order to classify voxels in the body into different tissue types, with the omission of the cortical layer of bones [19, 20]. This method works reliably at the cost of slight underestimation of tracer uptake value in foci of increased uptake located inside or in close proximity to the bones, in comparison to PET/CT scans. An alternative approach proposed for PET data attenuation correction in PET/MR is the one based on an atlas (map) [21]. It should be noted that the proposed correction techniques apply only to attenuation generated by the patient, and not to that caused by scanner equipment components, such as the bed on which the patient lies and the massive MR coils [22, 23]. For that reason equipment attenuation maps are generated, which are stored in the system and included with human attenuation maps. Another method of attenuation correction are the so called templates. An attenuation map template is created as the mean of images from several available transmission scans [24]. Another PET data attenuation correction method is a direct approach based on segmentation. This approach works directly in standard T1-dependent MR images routinely for every patient. The most difficult task in using these images is the differentiation between bone tissue and air-filled spaces, as the same intensity range appears in both those tissue types [25].

Application of PET/MR scans in oncology

In oncology, imaging scans play a significant role in staging, evaluation of treatment response and early detection of recurrence. In PET/CT scans involving ^{18}F-FDG a possibility of accurate assessment of the T stage was documented in many diagnoses, e.g. in head and neck tumors, non-small-cell carcinoma of the lungs and large intestine cancer [26–29]. The evaluation of local tumor invasion is based primarily on morphological data, that is why the MR component in PET/MR scans may turn out to be better than CT in PET/CT scans, especially in those tumors, in which high soft tissue contrast in MR images would enable higher image accuracy, as for example, in breast, prostate, head and neck, liver cancer, muscle and bone system or brain tumors. In the case of head and neck tumors, studies so far have shown superior results in assessment of local staging achieved by PET/MR scans as compared to PET/CT [30]. In case of breast cancer, MR mammography shows high sensitivity and relatively low specificity; however, FDG PET/CT scans are more specific and less sensitive [31, 32]. An increase in specificity from 53% to 97% was observed by adding up data from the PET and MR image [33]. In case of colorectal cancer, reports regarding fusion of PET and MR images have not

shown superiority compared with PET/CT [34]. When it comes to hepatocellular carcinoma (HCC), so far there has been no data published regarding PET/MR imaging in the assessment of tumor size; however, it seems that the combination of PET and MR images, especially fMR — functional MR — will make it possible to achieve images better than with PET/CT scans [7]. In primary bone tumors and soft tissue sarcomas the MR scan is the method of choice for staging. Because studies so far have shown high accuracy in the staging assessment of these tumors in PET/CT scans [35], the addition of PET images to MR images would make it possible to gain additional information (^{18}F-FDG distribution), which may be useful in accurate specification of the biopsy location in tumors and planning of surgical procedures and radiotherapy [36]. Similar reports indicating superior accuracy of PET/MR images compared to PET/CT were shown in the case of prostate cancer. This is especially significant in relation to patients with chronically increased PSA values and negative biopsy results, for whom a PET/MR scan allows for more accurate specification of the biopsy location [37]. There is a large amount of reports regarding ^{18}F-FDG PET/CT in the assessment of Hodgkin and non-Hodgkin lymphoma staging, indicating high accuracy, which has led to the widespread application of this method [38–40]. PET/MR scans may be an alternative to PET/CT scans for young patients, especially children, in order to reduce exposure to ionizing radiation; however, at the moment there is only little data on the subject [41].

The FDG PET/CT is more accurate than just a CT in the assessment of N stage of various types of cancer [42]. The advantage of the FDG PET/CT scan over a CT scan is the acquisition of additional information on lymph node metabolism. It should be noted that the size of lymph nodes alone does not enable determination of their malignancy, small nodes (< 1 cm) are not always benign, and enlarged ones are not always malignant. For that reason, it is expected that PET/MR scans, especially fMR will enable detection of malignant lesions in lymph nodes similarly to, or even with higher accuracy than PET/CT.

Certain studies have compared full-body PET/CT and MR scans in the assessment of distant metastases [43–47]. Results are varied for anatomically different regions; the PET/CT scan is more appropriate for evaluating metastases to the lungs, while MR for lesions in the liver, bones, bone marrow and brain. The combination of PET and MR imaging may prove significant in the assessment of metastasized lesions in those organs, especially in the case of bone marrow invasion.

In various malignancies, the assessment of response to treatment is based on a systematic evaluation of tumor size using corresponding criteria, e.g. RECIST; it has been show, however, that such evaluation has certain limitations. The application of a PET/CT exam has facilitated the assessment of treatment response in case of solid tumors, as well as lymphomas, based not only on the size of lesions, but also on the assessment of the metabolism [48, 49]. In recent years, clinical studies have shown that diffusion-weighted MR imaging (DWI) may be useful in the assessment of treatment response as well [50–53]. In this context, PET/MR scans, especially involving functional MR, can improve treatment result evaluation, as well as detection of early relapse [7]. The first prospective research examining the value of PET/MR in evaluating the response to treatment in head and neck tumors has shown excellent results combining a high negative prediction value of PET scans with the high sensitivity of MR scans [54]. In other types of malignant disease, the potential of PET/MR scans in the evaluation of treatment response or recurrence requires further study.

Application of PET/MR scans in neurology

PET/MR brain imaging, contrary to whole-body imaging, is significantly easier, because the examined organ (the brain) may be completely scanned within just one bed movement during the scan. This decreases the scan duration, which results in a decreased amount of data. PET/MR brain scanning is usually comprised of various MR sequences T1 and T2 dependent images with or without contrast, MR angiography, diffusion-weighted imaging (DWI), perfusion-weighted imaging (DPI), MR spectroscopy (MRS) and diffusion tensor imaging (DTI).

The MR scan is essential in the assessment of most neurological conditions, while the PET scan provides supplementary information in many clinical situations. Due to the high value of molecular imaging in dementia diagnostics, the PET tracers have been included in guidelines for the assessment of neurodegenerative disorders. PET scans also provide supplementary information in patients with brain tumors, epilepsy and stroke. The combination of the two imaging techniques into one system has become a logical solution providing additional information in pathology of the central nervous system.

The imaging of β-amyloid deposits in the brain using PET/MR scans of adult patients with cognitive disorders may allow differentiating between such conditions as Alzheimer's disease (AD), Lewy body dementia, dementia in the course of Parkinson's disease. A negative result indicates the presence of a small number of amyloid plaques and reduces the probability of the occurrence of AD as a cause of a cognitive disorder [55, 56].

In brain tumor imaging, due to the high amino-acid metabolism in astrocytes two specific radiopharmaceuticals, namely ^{18}F-FET (fluoro-ethyl-tyrosine), ^{11}C-MET (methionine) are useful in the differentiation of malignant and benign disease [57]. Boss et.al. have used spectroscopic MR and PET using ^{11}C-MET to classify ambiguous images in MR in low or high grade gliomas and to detect the most suitable areas for surgical biopsy [58]. Preuss et.al. have used the MR scan and ^{11}C-MET for biopsy planning and for neuronavigation in children with brain tumors [59].

MR allows for evaluation of the cause of acute brain strokes, i.e. ruptured blood vessels or vascular obstruction, as well as the size, localization and even reversibility of ischemic lesions. Additionally, MR scans are used to select patients with ischemic strokes, who will benefit from thrombolytic treatment within 4.5 h from the ischemic event [60]. The term of critical, but reversible decrease of cerebral blood flow (CBF) has been transferred from H_2O PET imaging [^{15}O], where it was originally developed for MR imaging [61]. Another technique used to evaluate brain perfusion using MR is the method of arterial spin labeling (ASL). Zhang et.al. have evaluated brain perfusion of ten healthy subjects simultaneously using the ASL technique and H_2O PET [^{15}O]. They have shown moderate overestimation of CBF in the arterial spin labeling (ASL method) compared to PET, but have also noted a good correlation between the measurements [62]. Despite the fact, that there are currently no studies on the subject of PET/MR devices in brain stroke diagnostics, it seems that a PET/MR hybrid would be an ideal

tool for examining stroke patients, combining, for example, two important stroke assessment parameters: diffusion-weighted MR imaging (DWI) and quantitative CBF assessment in a PET scan.

In order to identify the focal point of epilepsy prior to surgical treatment, MR imaging is the first choice. However, in approximately 20% of patients with temporal lobe epilepsy (TLE), MR is non-diagnostic or MR and EEG scans are incompatible. In such cases, the incorrect brain function should be evaluated using another, non-invasive examination, for example magnetoencephalography (MEG), as well as SPECT and PET. PET scans using ^{18}FDG, which during the interictal period show hypometabolism in the epileptic focal point, was the first imaging technique used prior to planned treatment with temporal lobe epilepsy [63]. Scans combining MR and ^{18}FDG PET in pre-operative evaluation of an epileptic focus have been verified by Lee and Salamon [64]. They documented that a combination of MR and PET images improves identification of the focal point and results of surgical epilepsy treatment.

Simultaneous PET and MR imaging is also very beneficial in the case of complex brain activity scans, in which quick brain signal fluctuations should be monitored on many levels. Additionally, hybrid PET/MR will enable simultaneous evaluation of various neurochemical and functional parameters which are involved in cognitive processes, e.g. observation of the nicotine receptor use and parallel BOLD fMRI — assessment of the blood oxygen level dependent MRI signal intensity.

Conclusions

The quantitative approach to hybrid PET/MR imaging has become the area of extensive research. The physical and technical aspects which could potentially influence the quantitative approach to the PET portion of PET/MR imaging, especially attenuation correction, are still being studied and developed. At the current stage of technological development, PET/MR systems are based on two methods of imaging, namely tandem devices, equipped with elements combining both devices and software used to integrate images, and fully integrated systems.

Data gathered so far regarding the application of PET/MR devices in clinical setting, especially in oncology and neurology, is promising and it significantly exceed the potential of using those imaging methods separately. Additionally, the integrated PET/MR system is an alternative to PET/CT if a low dose of radiation is required, namely when examining children and when multiple images are required. However, further research is warranted in order to test the diagnostic accuracy of PET/MR. It seems that the predominant opinion of the involved researchers is that PET/MR and PET/CT will play a complementary role in different clinical situations.

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