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Published in:

The Quarterly Journal of Nuclear Medicine and Molecular Imaging

DOI:

[10.23736/S1824-4785.20.03293-8](https://doi.org/10.23736/S1824-4785.20.03293-8)

Publication date:

2021

Document Version

Peer reviewed version

[Link to publication in Discovery Research Portal](#)

Citation for published version (APA):

Reich, C. M., Sattler, B., Jochimen, T. H., Unger, M., Melzer, L., Landgraf, L., Barthel, H., Sabri, O., & Melzer, A. (2021). Practical setting and potential applications of interventions guided by PET/MRI. *The Quarterly Journal of Nuclear Medicine and Molecular Imaging*, 65(1), 43-50. <https://doi.org/10.23736/S1824-4785.20.03293-8>

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QJNMMI 2021

TITLE: Practical Setting and Potential Applications of Interventions Guided by PET/MRI

RUNNING TITLE: Intervention Guiding with PET/MRI

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KEY WORDS: Intervention, Molecular Imaging, PET/MRI, FUS

ABSTRACT

INTRODUCTION: Multimodality imaging has emerged from a vision thirty years ago to routine clinical use today. Positron Emission Tomography (PET)/Magnetic Resonance Imaging (MRI) is still relatively new in this arena and particularly suitable for clinical research and technical development. PET/MRI guidance for interventions opens up opportunities for novel treatments but at the same time demands certain technical and organizational requirements to be fulfilled.

Materials and Methods: The combination of PET with its superior quantitative physiologic information and the various unique imaging characteristics of MRI on one hand and the reduced radiation exposure, on the other hand, are the most relevant advantages of this technique. As a non-invasive interventional tool, Focused Ultrasound (FUS) ablation of tumor cells would benefit from PET/MRI imaging for diagnostics, treatment planning and intervention. Yet, technical limitations might impede preclinical research, given that PET/MRI sites are per se not designed as interventional suites. Nonetheless, several approaches have been offered in the past years to upgrade MRI suites for interventional purposes.

Results: Taking advantage of state of the art and easy to use technology it is possible to create a supporting infrastructure that is suitable for broad preclinical adaption. Several aspects are to be addressed, including remote control of the imaging system, display of the imaging results, communication technology, and implementation of additional devices such as a FUS platform and an MR-compatible robotic system for positioning of the FUS equipment.

CONCLUSIONS: Most PET/MRI sites could allow for interventions with just a few additions and modifications, such as communication, in room image display and systems control. By

unlocking this feature, and drive preclinical research in interventional PET/MRI translation of the protocol and methodology into clinical settings seems feasible.

INTRODUCTION

The combination of PET/MRI opens the field of cross-modality imaging to the marriage of the sensitive functional PET imaging with the spatially defined soft-tissue contrast at variable weightings that MRI provides. PET and MRI have been well established as clinical molecular tomographic imaging modalities for more than three decades. While MRI originally aimed at imaging soft tissue structures and vascular functions, PET primarily aimed at imaging physiologic and pathophysiologic processes to image oncologic, neurologic, cardiologic, infection and inflammation diseases. For the past ten years, it has been the aim to investigate the combination of PET and MRI. Integrated PET/MR imaging provides a promising variety of clinical applications with a clear focus on hybrid molecular neurologic (brain-) imaging but also some oncologic and cardiac diseases [1-6]. In contrast to PET/CT, the main advantages are superior and variable soft-tissue contrast, improved motion correction, and reduced radiation exposure which is especially relevant in high-risk patients [7]. Meanwhile, the advantages of interventional MRI [8] in comparison of traditional x-ray based techniques have been laid out by many research groups in recent years and became to some extent clinical routine in i.e. MRI-guided breast biopsy.

MRI also became a tool for monitoring tumor tissue ablation e.g. with radiofrequency (RF), LASER or focused ultrasound (FUS). This paper describes our project to set up a PET/MRI-guided Intervention for diagnostic biopsy and focused ultrasound therapy.

Focused Ultrasound Therapy

FUS or high intensity focused ultrasound (HIFU) represents the use of bundled ultrasonic waves to increase the temperature within biological tissue [9]. By contrast to diagnostic imaging transducers working with frequencies of 2-20 MHz, therapeutic ultrasound

operates at frequencies of 250 kHz up to 3 MHz whereby ultrasound waves can be precisely targeted at a point e.g. by a curved shape of the transducer, by reflections or by modulating phased array transducers. Only in the focal point with the highest energy, the temperature in tissue increases and surrounding tissue can be spared. Temperatures of up to 70°C are feasible in clinical settings for tissue ablation leading to coagulation and subsequent necrosis. Due to the use of MR imaging techniques for therapy planning and guidance as well as thermal effects limited to the target volume deep in the tissue (without any injury of the surrounding tissue), the procedure is considered non-invasive and is currently clinically approved for the treatment of uterine myomas, essential tremor and prostate cancer [10-12]. In addition to tissue ablation at high temperatures and high energies, FUS is intensively investigated in other areas. In this context, FUS can also be used for moderate heating to temperatures in the range of 41-47°C, which could potentially be used to sensitize tumor cells for chemo- and radiotherapy [13]. Furthermore, FUS can open specific transport systems such as liposomes or microbubbles to release antibodies, vectors or drugs only at the intended site of action. In connection with neurodegenerative diseases, the safe opening of the blood-brain barrier using FUS has already been demonstrated in Alzheimer's patients [14]. Especially FUS at low energies is very attractive for neurostimulative approaches. Moreover, FUS shows an effect of immune modulation by increasing antigen expression and due to the fact that low-temperature ablation leaves significant tumor cell proteins intact.

MRI (magnetic resonance imaging) allows for therapy planning and, at the same time, MRI Proton Resonance Frequency Shift (PRF) thermometry enables among other MR sequences quantification of the heat generated in the depth of the treated tissue during FUS intervention [15-18]. MRI, however, provides only the temperature mapping and imaging of oedema caused by the ablation. PET imaging provides visualization of metabolically active tumor

areas. Thus, FUS treatment would benefit from hybrid imaging consisting of PET and MRI, because the metabolic activity of the tumor can be analyzed after the intervention and a second FUS treatment could be applied if necessary if there was tumor metabolism still present. Until now, PET imaging subsequent to FUS/HIFU in humans has only been used in prostate cancer patients to detect local recurrences after HIFU therapy. For this purpose, ^{68}Ga -PSMA-11 and ^{18}F -choline were used as radioligands [19, 20]. It has to be considered that within hours after a thermal ablation PET the signal can raise due to the healing effect and hypoxia of the lesion. Therefore it seems obvious to apply PET during and immediately after the FUS therapy [21].

Additionally, FUS has potential to support radiation therapy and drug delivery which can be monitored by PET. Special PET tracers allow the detection of hypoxic tumor areas [22]. The selective therapy of these regions with FUS could lead to better blood circulation, the reduction of hypoxia and the associated radiosensitization of exactly these areas were the effect of the radiotherapy shall be maximized. In only one preclinical study known so far, hypoxic areas were ablated in vivo in mice using ^{18}F -fluoromisonidazole (^{18}F -MISO) in murine SCK and 4T1 breast cancer [23]. The study showed the feasibility of PET/MRI-assisted FUS and a reduction in tumor volume after ablation and irradiation (see Fig.1).

Concerning neurodegenerative diseases such as dementia and Alzheimer's disease, the use of PET/MRI has improved diagnosis [24-27]. Simultaneous imaging of e.g. phosphorylated tau protein using PET and planning and execution of FUS with MRI would represent a milestone in the therapy of Alzheimer's disease. Recently, the reduction of phosphorylated tau after opening of the blood-brain barrier by FUS was shown in an Alzheimer mouse model [28].

Furthermore, preclinical in vivo results demonstrated safety, feasibility and advantages of PET/MRI-guided FUS with a novel MR-compatible preclinical FUS phased-array

transducer (11 x 11 elements, copper shielding, aperture size of 10x10 mm, and frequency of 960 kHz from Fraunhofer IBMT, St. Ingbert, Germany), installed in rat bed of 7 T MRI with a PET insert for simultaneous in vivo imaging (MR solutions Ltd, UK) (Figure 2). Further in-vivo tests e.g. with tumor bearing mice are needed to evaluate tumor ablation via FUS using simultaneous MRI and PET guidance.

Figure 1: *PET/MRI-guided ablation of hypoxic tumor regions in vivo in murine mammary carcinoma model. a) Schematic representation of the steps including injection of the tracer, detection of hypoxic tissue and ablation with FUS. b) Co-registration of T2-weighted MR-images and the ^{18}F -MISO PET signal. c) Delay of tumor growth after combined tumor ablation and radiotherapy (20 Gy). Image adapted according to Koonce et al. [23]*

Figure 2: Exemplary tests of a preclinical FUS transducer in a small animal PET/MRI 7T system. a): Set up of the experiment with a mouse in rat bed and fixed transducer on top. b): MR-compatible US research platform DiPhAS (Fraunhofer IBMT) outside the 5 Gauss line c): Data acquisition of the PET signal (^{18}F -Fludeoxyglucose ($\text{C}_6\text{H}_{11}\text{FO}_5$), mass: 181.1495 g/mol, biological half-life: 110 min (70%), $\lambda = 3.24 \times 10^{-3}$, activity: 7.29 MBq injected, PET scan time: 10 min). d): Data analysis.

Additional in-vivo tests e.g. with tumor bearing mice are needed to evaluate tumor ablation via FUS using simultaneous MRI and PET guidance.

Technical Prerequisites for PET/MRI-guided Interventions

Computer-assisted feedback loops ensure easy handling for the interventionalist, safety, and control of the procedure for the patient. For system integration, several interfaces have to be provided. Common MRI and PET/MRI sites are not equipped with a preinstalled technical setup to support clinicians during MRI-guided interventions. Therefore, the PET/MRI system console and control unit, the patient monitoring hardware, the system user interface, a video display and communication system need to be accessible and operational from within the imaging room. Additionally, the FUS system needs to be integrated into the technical setup. Radiofrequency (RF) induced heating and inadvertent movements due to magnetic field forces pose threats when using electronic devices in the MR environment. Rather than expensive MR Safe labelled technology like RF-shielded monitors (Cambridge Research Systems Ltd. Rochester, UK) or infrared communication system (Optoacoustics LTD. Or Yehuda, Israel), we decided to use off-the-shelf technology and equipment with no need for specially trained experts to implement and use it, and we have enabled an exemplary setup of an interventional PET/MRI suite environment. In an iterative process, it has been possible to individually combine locally available devices and upgrade the present infrastructure in order to customize it for the support of interventional procedures.

Experimental setup

To start, the PET/MRI system's input devices can be routed into the magnet room via optical USB extension cable (OPTICIS CO., LTD, Korea) to pass the faraday cage's wall via a waveguide. Several off-the-shelf human interface devices (HID), e.g. a wireless mouse (Targus, Anaheim, US) and to some extent a wired pedal (dr. dresing & pehl GmbH, Marburg, Germany), can be installed at a safe distance to the bore to manipulate the user settings and parameters of the PET/MRI system. Built-in ferromagnetic components should be removed if necessary, batteries (AAA- or AA-type) can be replaced by rechargeable

lithium polymer batteries that are non-ferromagnetic. The video signal of the PET/MRI console can be fed into a DVI-splitter and routed via optical fibre cables and adapters (LINDY-Elektronik GmbH, Mannheim, Germany) to a monitor or projector (NEC Corporation, Minato, Japan) located in the imaging system room and firmly attached to the walls or furniture.

For each component installed it is advisable to run MR imaging using the standards calibration phantoms provided by the MR vendor to check for noise, spikes and other image disturbances. For the permanent installation of the components we had professional support and where it was needed protection for the magnet bore i.e. with a plywood plate. During routine diagnostic imaging, all components are physically disconnected or removed from the MRI room as not to compromise imaging quality.

To facilitate the realisation of communication in- and outside the imaging room state-of-the-art VoIP (Voice over Internet Protocol) technology with a locally hosted network consisting of a router (AVM Computersysteme Vertriebs GmbH, Berlin, Germany), mobile devices [29] and in-ear (noise-cancelling) Bluetooth headphones (Bose Corporation, Framingham, US) underneath the noise-protectors are a simple solution. Ethernet network connections can be established by using media converters (Allied Telesis International GmbH, Aschheim-Dornach, Germany) in order to pass the waveguide via fibre optic duplex patch cables (Telegärtner Karl Gärtner GmbH, Steinenbronn, Germany). In Table I the devices we used successfully for setups are listed with the approximate price at the time of purchase. No functional impairment was observed when using them outside the 5 Gauss line, some even closer to the bore (esp. handhelds). When using portable devices inside the 5 Gauss line securing is mandatory, e.g. hand straps, MRcompatible (3D-printed) mounting racks or anything applicable for fixation of the specific hardware.

Virtual Network Computing (VNC) (VNC) server-client software (TighVNC, GlavSoft LLC, Tomsk, Russia) extends the applicability of proprietary soft- and hardware, by enabling remote control of computers reachable via the network. Administrative or service access to the PET/MRI console workstation opens up even more opportunities for in-room imaging system control [30] but may require vendor approval and ethical approval for human use. This VNC connection could be used to control the FUS unit from the control room also, to access patient databases via tablet devices, or display imaging data or clinical reports from inside the imaging system room. Figure 3 represents a fully equipped interventional PET/MRI suite that was demonstrated in the Department of Nuclear Medicine of the University Hospital Leipzig. Although there are several additional devices, most of them are barely visible or out of the usual moving range of the technicians. Therefore, the interventionalist experiences no additional constraints of his movements, which allows him to concentrate on the patient and the procedure itself.

Robotic systems offer the possibility to position equipment (e.g. interventional needle, transducer with high precision based on image data. Figure 4 shows an extended setup,

Table I: *List of exemplary equipment used to set up the technical infrastructure for interventional PET/MRI. No claim is made that this is complete nor that other manufacturers may have adequate devices as well. In comparison cost for MR approved equipment are about 21,500€ for an RF-shielded monitors (Cambridge Research Systems Ltd. Rochester, UK) or 60-100.000 € for infrared communication system (Optoacoustics LTD. Or Yehuda, Israel) our approach cost less than 6.000 € including installation.*

	<i>Product</i>	<i>Approx. price (€)*</i>

**Table note: The prices are approximate and can deviate regionally*

*** IBSmm is a specialized OR monitor with touch screen functions and high end video recording.*

Figure 3: *Schematic view of an interventional PET/MRI setup: multiple input and output devices, in-room network for VoIP and VNC connection, and a FUS system.*

allowing for in-room-control of a robotic arm (Innomotion, IBSmm Engineering, CZ) holding the transducer [31, 32]. To mount the robotic arm onto the patient table a custom-modelled 3D-printed PLA-rack (MakerBot Industries, LLC, New York, USA) was attached

to the rails that are used for fastening straps of the receiving coils. A dedicated interventional 8 channel receiving coil the DuoFlex Suite was developed together with MR Instruments (Minneapolis, MN, US) which fits to the robotic arm front end. Both this coil and the robotic arm were tested for its attenuation of 511keV gamma radiation as measured for PET imaging (see Figure 5)

Figure 4: *Experimental setup of INNOMTION robot in PET/MRI (Siemens Biograph mMR 3T). a): Pneumatic robotic arm with ultrasound transducer attached over an abdominal phantom (CIRS Inc., Norfolk, USA). The control ultrasound control unit and GUI (graphical user interface) is positioned nearby the gantry. b): A mouse and the mounted tablet that displays the robots control software are located at the foot end of the patient table. In the background the PET/MRI console GUI is projected on the roll screen (s).*

Figure 5: *a): The DuoFlex Suite (MR Instruments, Minneapolis, US) dedicated interventional 8 channel receiving coil. Its Attenuation map is visualized by superimposition of a maximum-intensity projections of the linear attenuation coefficient of 511-keV PET annihilation photons (in 1/cm) obtained by a stand-alone PET system (ECAT EXACT, HR+, SIEMENS Healthineers, Knoxville, US) equipped with $^{68}\text{Ge}/^{68}\text{Ga}$ -rod sources for 511keV gamma ray transmission measurements. b): Attenuation map of the robotic arm visualized by two perpendicular maximum-intensity projections of the linear attenuation coefficient for 511-keV PET annihilation photons. The color scale represents the linear attenuation coefficient (in 1/cm).*

To integrate the system into the existing clinical infrastructure, the hardware, which contains the planning software of the robotic arm, was virtualized using Oracle VirtualBox (Oracle Corporation, Redwood Shores, CA, USA). This virtual machine was placed on the Linux server, which is attached to the PET/MRI system for post-processing, storage and distribution of data. In this way, image data can be transferred easily and efficiently to the planning software that acts as a DICOM receiver (Figure. 6).

Figure 6: *Clinical integration: The robotic arm system is placed in the magnet room. A DICOM service provider handles the imaging. The procedure is planned via remote desktop on the virtualized PC.*

Preliminary “phantom” experiment

To validate and test the concept and set up of PET/MRI-guided interventions a simplified Phantom experiment was conducted following basic standards of MRI guidance by interventional MRI [33] and a good technical practice to conduct phantom measurements with PET. Approximately 5 MBq of ^{18}F -FDG were injected into the pomelo at a single location using a syringe. PET data were acquired for 5 min. The following settings were used for the PET reconstruction: OSEM (8 iterations, 21 subsets), the, Dixon-based attenuation correction, a relative scatter correction, a 256x256 image matrix, 2.8 zoom and a Gauss-Filter with 3 mm FWHM. For localization, an anatomical T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) sequence with TE=2.5ms and TR=1900ms was also acquired. Further, the interventional needle was placed following the image guidance using the fused PET and MRI information (see Figure 7). The correct position of the needle was verified cutting the pomelo and comparing it to the imaged location of the activity spot.

Figure 7: *“Phantom” experiment (a) with a pomelo, injected with about 5MBq ^{18}F -FDG, (b) image-guided positioning, and verification of an interventional needle in the spot of activity.*

Discussion

Technical developments of the past years enabled implantation of Augmented Reality to guide needle-based interventions in a closed-bore system [34] showing promising results in comparison to already well-elaborated techniques [35, 36]. By combining such strategies with the improved imaging data information from PET/MR, new possible clinical applications open up. The notorious cross-modality image co-registration from diagnostic data (ultrasound or MRI) to the interventional CT data would be obsolete to perform accurate interventions [37]. Most research setups address needle-guided biopsy or ablation as a use-case, due to its relatively high clinical incidence. PET/MRI combines the ability to detect and characterize lesions due to their metabolic activity or behaviour with superior soft-tissue contrast while reducing radiation exposure (by sparing out CT).

PET/MRI procedures, although relatively expensive, carry the potential of a “one-stop-shop” technology for integrated diagnosis and therapy.

Prior to any clinical use, both the technical setup as well as the clinical workflow of the procedure need to be developed [38]. The current work was dedicated to the technical setup, the workflow will be developed as the next step.

In our technical development of the appropriate setup of PET/MRI-guided interventions, we have analysed the commercially available systems with MR approval. MR-safe labelled technology like RF-shielded monitors or infrared communication system, are expensive and the latter is difficult to use. Therefore we selected off-the-shelf technology and equipment with intuitive well-known usability to avoid the need for in-depth special training. Handheld devices such as tablets, smartphones, BT headsets and other HID, however, are not approved for use in an MR environment and, therefore, need to be tested individually for each installation and the safe use is at the responsibility of the site personal. [30, 33].

Radiofrequency (RF) induced noise and attraction due to magnetic field forces pose threats when using electronic devices in the MR environment. Commercial TV/monitors or projectors can be placed in the MR room but need to be firmly attached to the walls, ceiling or to furniture which is firmly attached to the same. Smaller devices might also be secured by a hand strap if applicable. To check for noise, spikes and other image disturbances, it is advisable to run MR imaging using the standard calibration phantoms provided by the vendor and to do this for each component with and without being installed.

Installation of the permanently used components requires professional support and protection for the bore i.e. with a plywood plate in front of the bore. The RF shielding vendor should be contacted for advice. The MRI supplier should be consulted for any of the used solutions. During routine diagnostic imaging, all wired components should either be physically disconnected or completely removed from the imaging room.

CONCLUSION

By taking advantage of the sustaining attention of the research community to develop interventional techniques for MRI-guided therapies the development of PET/MRI-guided interventions is the next logical step. Combining several technical systems and devices to integrate imaging information and enable presentation and manipulation from inside the imaging systems room will be one of the future tasks to enable novel treatments with PET/MR imaging. Interventional equipment to perform interventions in the MR environment are rare on the market and topic of R&D projects. Thus, this rather early stage of development allows researchers and clinicians to work together with manufacturers. While technical solutions in the form of an interventional setup exist already, usability and clinical validation need to be thoroughly investigated and performed, respectively.

Although commercial equipment for communication, visualization and in-room control require individual testing of MR safety and professional support for each installation its use seems cost-effective, intuitive, reliable and safe provided safety rules are in place and staff training of MR safety are in place. First phantom investigations including the use of an MR-compatible robotic arm as well as a specially developed interventional coil in a hybrid imaging setting have proven the principle and shown the overall feasibility of guiding interventional procedures with cross-modality hybrid PET/MRI.

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Conflicts of interest: The authors declare to have no conflict of interest with respect to the review presented here.

Funding:

The PET/MRI System at the Department of Nuclear Medicine of the University Hospital Leipzig was funded within a Major Devices Initiative of the German research council (Grant code SA 669/9-1). Parts of the project on which this report is based on was sponsored by the Federal Ministry for Education and Research under the funding code 13GW0365C. The responsibility for the content of this publication lies with the authors.

Author contributions:

CMR, THJ, MU, LM contributed to the concept of this manuscript, designed and facilitated the practical work in at the PET/MRI site; LL, OS, BS, AM acquired the funding, defined the project and the design of the experiments, have drafted and internally reviewed the manuscript and conducted hands on experiments

Acknowledgements:

The authors wish to express their gratitude to Cornelia Pötzsch, Torsten Böhm and Christian Lorz, the Technologists at the Department of Nuclear Medicine at the University Hospital Leipzig for assisting with the hands on experiments. Special thanks to Steffen Tretbar and Marc Fournelle from Fraunhofer Institute for Biomedical Engineering and Angela Mega-Camacho from MR Solutions in Dijon.