

REVIEW ARTICLE

Paving the way for modality choice of the future: challenges and expectations of the first simultaneous whole-body PET-MRI molecular imaging in the UK

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Abstract Following the success of PET-CT in the last decade, there have been high expectations regarding the development of new hybrid imaging modalities such as PET-MRI. After years of development, the first simultaneous, fully integrated, whole-body PET-MRI scanner has been released and first clinical results have been published.

PET-MRI offers numerous advantages such as excellent soft-tissue contrast, significantly lower radiation dose than PET-CT and a wide variety of functional MR imaging combined with PET. However, there are some technical and operational challenges to be addressed. The main objectives of this study were to review the challenges and expectations in the installation, siting, and patient service provision of the Biograph mMR, the first simultaneous whole-body PET-MRI system installed in the UK and to underline the various feasible solutions.

The paper incorporates an extensive literature review, several visits to the installation site and productive discussions with associated scientists and Siemens Healthcare (Biograph mMR manufacturer). With regards to room shielding and siting requirements, several unique characteristics were observed as they had to meet the local regulations for both the PET and the MRI components. Local patient service provision requirements were addressed through developing new clinical examination protocols and through additional safety considerations. Further research will be necessary for optimising these procedures and to ensure widespread clinical adoption of the PET-MRI imaging system.

Key words: *Simultaneous PET-MRI, Biograph mMR, integrated PET-MRI system*

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Introduction

The last decade has seen remarkable developments in hybrid medical imaging technology. The scientific community and the healthcare industry have both shown an increasing interest in research in the field and serious investments have been made in order to produce cutting-edge multimodality imaging systems.

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Imaging modalities such as computed tomography (CT), single-photon emission computed tomography (SPECT), positron emission tomography (PET), and magnetic resonance imaging (MRI) are well known for their unique role in current diagnostic medicine. Integration of these imaging modalities in hybrid imaging systems can significantly improve the diagnostic yield. The overwhelming success of PET-CT is evidenced by the fact that the hybrid PET-CT has now displaced the stand-alone PET systems [1]. Although PET-CT provides extremely useful clinical data, it has some limitations and drawbacks such as a high radiation dose and poor soft-tissue contrast. Consequently, the idea of combining PET with MRI, for the latter's null ionising radiation dose and excellent soft-tissue contrast was conceived so as to overcome these limitations. It was first proposed at approximately the same time as PET-CT, i.e. early 1990s [2].

The combination of PET with MRI has a number of advantages over other hybrid imaging modalities. The superior diagnostic information regarding soft-tissue analysis, tissue characterisation, tumour staging and some functional imaging that MRI provides, combined with the high sensitivity of functional imaging of PET, offers an excellent diagnostic tool. However, its technical development and clinical application is still very challenging. Various aspects such as attenuation correction, body-motion, MR-compatible detection systems and installation and workflow challenges need further research and innovative solutions before PET-MRI will be fully introduced for widespread clinical practice.

This study initially provides a general theoretical background regarding hybrid imaging and in particular, PET-MRI technology, and identifies and presents the advantages and the challenges of this advanced technology in the delivery of clinical services of the first fully-integrated and simultaneous PET-MRI system in the UK.

Hybrid imaging

In diagnostic imaging, there is a strong reliance on anatomically based techniques such as X-rays, MRI, ultrasound and CT, whereas this is not always the case for molecular or functional imaging techniques. Clinicians often tend to describe nuclear medicine techniques using the popular epithet of 'unclear medicine' [3] which is due in part to the poor spatial resolution of functional imaging, giving the impression that it is somehow less valid than radiological techniques. Additionally, the complexity of the principles behind functional imaging such as compartmental models, time-activity curves and deconvolutional analysis might be beyond common understanding. However, molecular and functional imaging provides significant diagnostic information regarding radioisotope uptake, actual tumour volume, etc., which is crucial for accurate diagnosis and treatment planning. Hybrid imaging is an integration of both functional and anatomical imaging techniques in the same modality and it represents the various advantages of both modalities. The combined devices in an integrated system complement each other technically and clinically. The acquired images match significantly better than software fusion of images acquired on separate devices, the clinical workflow is improved and most of the integrated systems have long-term financial advantages over separate systems [4].

Recent developments in hybrid imaging

The main and most recent developments in hybrid imaging technology are SPECT-CT PET-CT, and PET-MR. Other imaging systems are also under design or in the exploratory phase. Developments such as small animal SPECT-MR and less obvious combinations including CT-MR and PET-optical are also being studied [5].

The success of PET-CT in replacing the stand-alone PET, demonstrates the potential of integrated technology in replacing the conventional systems. Significant investments have been made in instrumentation and R&D, which has facilitated manufacturing of the new hybrid systems.

PET-CT has revolutionized the way that clinicians perceive molecular imaging. Fused images are becoming the preferred diagnostic tool as they increase the accuracy in localising the abnormalities and thus the clinicians' confidence in treatment planning. PET-CT has rapidly improved PET acquisition times from more than one hour to less than 20 minutes. As a consequence, patient tolerance has improved, a larger number of scans are being undertaken, and there is more efficient use of radiotracers with rapid radioactive decay, together with more productive use of medical staff, with a resultant reduction in the overall costs [3].

Using CT to obtain attenuation correction maps has been extremely beneficial and has not only improved the quality of the PET scan but has also replaced the time-consuming transmission scans using radioactive sources. Since the attenuation characteristics of x-rays are significantly different from the annihilation photons, correction factors are required to convert from a CT attenuation map to an appropriate 511 keV map, which can lead to discordances.

Although the combination of CT with SPECT and PET for hybrid imaging is currently being utilized in many studies with promising results, there are some issues remaining to be addressed. As data acquisition is not simultaneous but sequential, patient-movement or respiration may influence the images and introduce body-motion artifacts. Various solutions have been proposed to address these issues through a number of ongoing research projects. There are also some shortcomings in the use of CT as a complementary modality which include a high radiation dose (especially significant for young patients) and poor soft-tissue contrast. These two limitations however do not apply to MRI, and unlike PET-CT, simultaneous acquisition is feasible with an integrated PET-MRI system.

Positron emission tomography

In clinical PET imaging, a positron emitter radiolabelled molecule is administered to a patient via injection (Table 1). The positron after a few millimeters random walk within the tissue, annihilates with an electron and two 511 keV gamma-rays are emitted in almost opposite directions. These gamma-rays are detected as coincidence events when registered within a short-time window and assigned to a line of response (LOR). With coincident detection, the resolution along the LOR remains quite constant providing significantly greater efficiency and improved uniformity of spatial resolution about 100 times that of SPECT [3]. Furthermore, the higher sensitivity of PET enables identification delivery of pictogram quantities of radiochemical compound, i.e. toxic cocktail, to target organs for oncology purposes [7].

The detection of 511 keV photons has some minimum requirements such as good timing and energy resolutions (~3ns and ~13% FWHM respectively), high coincidence photo peak efficiency (~41%) and fast scintillation decay constant (<300 ns) [7]. The commonly used scintillation materials are bismuth germinate (BGO), cerium-activated lutetium oxyorthosilicate (LSO), cerium-activated gado linium oxyorthosilicate (GSO) and thallium-activated sodium iodide (NaI). In the design of the current PET-CT systems, scintillation blocks are attached to photo multiplier tubes (PMTs), whereas in integrated PET-MRI systems, avalanche photodiode detectors (APDs) are utilized as PMTs are not able to function in a high magnetic field.

Due to the high penetration of the 511 keV annihilation photons of the PET radiotracers, which make the patient a high source of radioactivity, it is necessary to carefully design the radiation shielding to protect both the staff and the general public. One has to consider the type and the amount of the radioisotope that will be administered, the length of time that patient will remain at the facility, the location of the facility as well as the general environment [10]. The principal aim of radiation protection is to maintain the dose to both radiation workers and the public as low as reasonably as achievable (ALARA). High-density materials such as lead, steel and concrete can be used for radiation shielding. The appropriate shielding thicknesses (x) can be calculated for transmitted radiation intensity (I) through an absorbing material [9].

Table 1 *PET radiotracers and some of their properties*

Nuclide	Half-life	Decay mode	Positron max energy (MeV)	Photon emission (keV)	Dose rate constraint (μSv/m²/MBq/h)	1 hour integrated dose (μSv/m²/MBq)
^{11}C	20.4 min	β+	0.96	511	0.148	0.063
^{13}N	10.0 min	β+	1.19	511	0.148	0.034
^{15}O	2.0 min	β+	1.72	511	0.148	0.007
^{18}F	109.8 min	β+, EC	0.63	511	0.143	0.119
^{64}Cu	12.7 h	β-, β+, EC	0.65	511, 1346	0.029	0.024
^{68}Ga	68.3 min	β+, EC	1.9	511	0.134	0.101
^{82}Rb	76 s	β+, EC	3.35	511, 776	0.159	0.006
^{124}I	4.2 d	β+, EC	1.54, 2.17	511,603,1693	0.185	0.184

The appropriate build-up function for the shield geometry should be used:

$$I=I_o b(\mu x)e^{\mu x}$$

where, I_o is incident intensity, $b(\mu x)$ is build-up function, μ is the linear attenuation coefficient and x is the thickness of the shielding material.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) does not rely on ionizing radiation (as CT and conventional radiography do), nor does it depend on the transmission of energy through tissue (unlike ultrasound imaging), rather it takes advantage of an entirely different physical principle, i.e. the interaction of atomic nuclei with imposed magnetic fields, which causes radiofrequency NMR signals. These signals provide unique information about tissue chemistry, and MRI images reflect this information that is altered depending on the tissue type and its characteristics. Figure 1, shows a schema of a complete MRI system consisting of a large bore magnet, stable power supplies, RF transmitter-receiver electronics, small field-of-view receiving coils for specific anatomy, moving patient table with embedded the associated computer and array processor with fast Fourier transform [7].

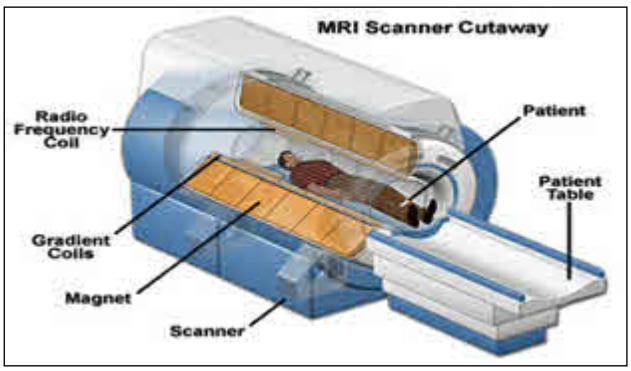

Figure 1 *A complete MRI system (courtesy Siemens Healthcare)*

The various MRI techniques provide the clinicians with very high diagnostic quality images and excellent soft-tissue contrast with no exposure to ionizing radiation. MRI can successfully display chemical differences of various tissue types (on a grayscale) and blood flow (as a high-intensity image). The functional MRI (fMRI) technique enables studying of the transit through the brain in real time (using echo planar imaging) and maps blood volume during brain activity [5].

Diffusion-weighted MR (DW-MR), where the magnetic field with different gradients is used to map phase differences in the MRI signal caused by diffusing molecules, can be used to study functional processes in living subjects. DW-MR has clinical applications including fiber

tracking, diagnosing Alzheimer's disease, charac terization of tissue structure, cancer detection, and evaluation of ischaemia and multiple sclerosis. Magnetic resonance spectroscopy (MRS), which applies selective radiofrequency excitation pulses, is used to analyze molecular composition of tissues and to define biopsy targets by separating areas of active tumour from inflammation, necrosis or fibrosis [12].

PET-MRI: potential advantages

The idea of combined PET and MRI was expressed in the 1990s (earlier than proposal for the combined PET-CT). Simon Cherry and Paul Marsden [11] observed the potential of such modality, but there were many techno logical challenges to overcome before the first clinical PET-MRI could be launched. The advantages of this hybrid imaging are numerous with high commercial interests. PET-MRI is a combination of excellent soft-tissue contrast, high spatial resolution, functional imaging and high sensitivity, which enables assessment of metabolic abnormalities and changes in mass lesions, well before tumour size changes can be measured.

Another essential advantage of PET-MRI is the lower radiation exposure with significantly lower overall examination doses in comparison to PET-CT. A whole-body ^{18}F-PET-CT dose-estimation study of a male patient, demonstrated that the effective total doses (for three different CT scanning protocols) were 13.65, 24.80 and 32.18 mSv, whereas the PET component dose contribution was only 6.23 mSv. It is quite clear that CT is responsible for the greatest amount of radiation dose. Replacing the CT with MRI considerably lowers radiation doses from 54% up to 83% [13]. This advantage is of great importance in imaging children and young adults with potentially curable oncological diseases, patients with non-oncological indications, in repeated examinations, and dynamic contrast-enhanced studies, though this may be of less importance in patients with limited life expectancy.

The high sensitivity of PET is complementing the poor signal strength inherent in current functional MRI imaging, whereas the MRI strong magnetic field is improving PET resolution as it limits the positron range prior to annihilation [15]. For simultaneous data acquisition, PET-MRI not only allows high spatial overlay accuracy, but also allows exceptional temporal co-registration, which enables MR-based PET image motion-correction for precise cardiac and abdominal imaging [12].

In theory, MRI appears to be a perfect anatomical complement to PET preferred for abdominal and pelvic imaging whereas PET-CT is still the preferred choice for thoracic tumours [12]. Co-registered anatomy and metabolic images can enable better lesion identification and staging in a variety of malignancies such as liver, bone metastases, brain tumours, rectal, prostate, breast, gynaecological and head and neck oncological studies.

In the detection of bone metastases, FDG PET-CT has been shown to provide false-negative results, especially in early metastases, as FDG metabolism might not be visualized due to the normal bone marrow uptake. On the contrary, MRI has proven to image bone marrow itself, and therefore PET-MRI holds the potential to demonstrate these secondary manifestations [12]. Nonetheless, the diagnostic and clinical value of the PET-MRI is yet to be proven unequivocally despite its uniqueness and superiority over other hybrid modalities in several aspects. The clinical results should justify the longer examination times and the high capital maintenance and the workflow costs. It also needs to be proven that an integration of the both modalities is economically superior to two individual systems. The main argument for the integration of PET and MRI examinations, in addition to the earlier stated benefits, is to reduce the duration of the subsequent imaging which is extremely unpleasant for patients.

PET-MRI: clinical expectations

The clinical success of PET-CT has paved the way for the development of integrated PET-MR multimodality imaging system with high clinical

expectations. However, it is anticipated that fully comprehensive clinical applications of the integrated PET-MR imaging system, will require some time as it has been mostly utilized in research environment. Given the fact that research has been undertaken sequentially in various modalities and with simultaneous Brain-PET-MRI prototype in the recent years, there are strong indications that hardware-fusion PET-MRI has the potential to provide clinicians with various applications mainly in the following subspecialties

Neurology

The human brain is the most investigated clinical area with PET-MRI so far. Various studies [5, 16, 17] have shown that brain imaging could greatly benefit from the additional morphological and functional information that is provided by PET-MRI. It enhances the diagnostic sensitivity for gliomas and can thus improve the 'wait-and-see' approach for low-grade gliomas with regards to extent and timing of surgery. Furthermore, simultaneous Brain-PET-MRI (^{11}C-methionine or ^{68}Ga-DOTATOC) demonstrates its use-fulness for intracranial tumour assessment and image quality similar to that using PET-CT [18]. Simultaneous PET-MRI also appears to have a great potential in neuroscience research, predominantly for the imaging of molecular processes such as cell trans plantation, gene transfer and for multi-parametric analysis of functions in neutral networks [5].

Head and neck

Many tumours in the head and neck area are very sensitive to radiotherapy and the higher soft-tissue contrast of MRI can be especially useful and crucial in the accurate localization of tumours and follow-up radiotherapy treatment planning. Recent studies have shown that simultaneous PET-MRI is feasible and that there is no notable degradation in MRI or PET image quality seen [19]. Better assessment of skull base infiltration, improved detection of lymph node metastases and more exact delineation of metabolically active tumours results from the excellent soft-tissue contrast of MRI, the improved spatial resolution of the PET component of the Brain-PET and its smaller diameter compared to a conventional PET-CT [19]. Although, small streak artifacts were observed, it did not significantly influence tumours evaluation. Further studies and developments aim to prove the superiority of PET-MRI in head and neck examinations.

Cardiology

PET-MRI cardiac imaging may introduce a new level of diagnosis. The variety of possible combinations for molecular imaging is incredibly wide and of great clinical interest. Cardiac MRI or whole-body MRI angiography combined with PET could provide improved differentiation and detection of vulnerable plaques. PET-MRI cardiac stress examinations or late-enhancement MRI with FDG-PET may expand the clinical view of current cardiac imaging as well. Dual functional studies such as perfusion in PET with radioactive water or ammonia and perfusion in MRI using arterial spin labelling or MRI contrast agents can be carried out to correlate and compare the same parameters. PET perfusion can be also correlated with the MRI BOLD (Blood Oxygen Level Dependent) effect [5]. Simultaneously acquired cardiac PET-MRI will allow accurate body motion correction and thus very precise imaging. Figure 2 shows a cardiac image from the first integrated PET-MRI system (Biograph mMR).

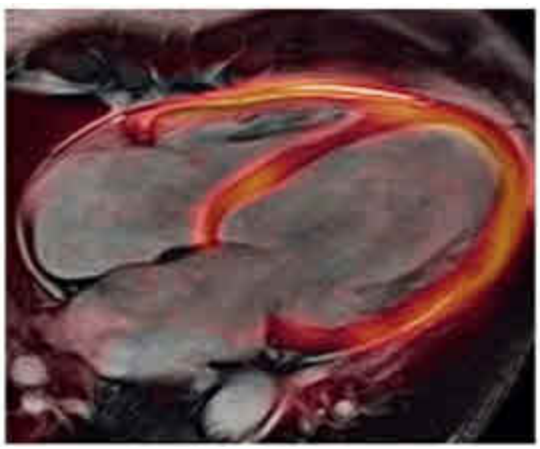

Figure 2 *Cardiac imaging, mMR technology eliminates motion effects and PET image degradation, whilst gating and triggering tools deliver excellent MRI images (courtesy Siemens Healthcare)*

Oncology

PET-MRI may be useful in extracerebral oncology applications. A recent summarized review by Antoch and Bockisch [21] claims that PET-MRI could be more accurate and perform better than PET-CT for T-staging for oncological examinations. Both systems show similar accuracies for N-staging, whereas PET-MRI may provide better accuracy for M-staging than PET-CT depending on the area of metastases. PET-MRI may also provide a better diagnosis in patients with osteomyelitis including those with diabetic foot disease, since MRI detects abnormalities within bony structure (e.g. marrow). FDG-PET is useful for the diagnosis of acute infections and can also exclude the diagnosis of osteomyelitis. In addition, PET-MRI holds a great potential for replacing PET-CT in evaluating treatment response for chronic diseases that require repeated examinations.

PET-MR system designs

Sequential configuration

Sequential design, where both systems were placed in tandem and physically separated was one of the first approaches in configuration of a clinical whole-body PET-MR system. The advantage of this configuration is that it can be constructed with a minimum adjustment of the already existing individual systems and software packages, which could lead to a quick product development. Furthermore, the separation between the two modalities demands a less complicated electromagnetic shielding for the PET component and intrinsic problems can be avoided. Moreover, it is a way to improve physical access to the patient and reduce patient claustrophobia. The disadvantages of this design concept include accommodating long examination times and an inability to acquire simultaneous imaging, and therefore co-registration errors could occur leading to image quality degradation. The space availability and associated cost can also be a limiting factor [22].

Insert architecture

The recent approach of building a removable MR-compatible PET insert and placing it within a conventional MRI system was the first attempt at simultaneous PET-MRI data acquisition known as Brain-PET-MRI prototype system (Figure 3). The development was carried out by a collaborative team of the German and US researchers from the Universities of Tubingen and Tennessee, as well as the Siemens Healthcare [23]. The simultaneous acquisition, not only offers a reduction in the overall acquisition time and excellent geometrical co-registration, but also opens the way to a wide variety of innovative applications such as kinetic studies, functional MRI, etc. Furthermore, medical centers with access to the in-house MRI can easily acquire a flexible and non-dedicated PET-MR system with a relatively cost-effective approach. However, due to the small bore diameter, this architecture is limited to brain studies [22].

Figure 3 *Brain-PET-MRI prototype with a MR-compatible PET insert is placed within a Siemens MAGNETOM Trio MR scanner (courtesy Siemens Healthcare)*

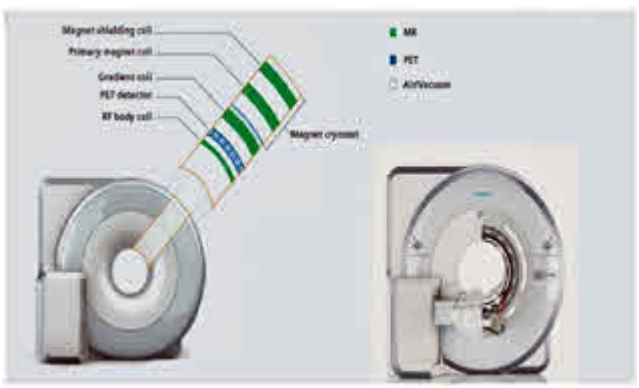

Figure 4 *Biograph mMR, a fully integrated, simultaneous whole-body PET-MRI system (courtesy Siemens Healthcare)*

Integrated Architecture
The approach describes a complete integration of a PET detector and electronics within a MRI scanner, which is the most challenging and sophisticated solution (Figure 4).

PET-MR: technological challenges and drawbacks

As with any new and innovative technology, various problems and challenges also materialized in the construction, installation and operation of the combined PET-MRI. In the late 1990s, when the idea was firstly conceived, the construction of a simultaneous whole-body PET-MRI appeared to be unlikely, whereas the fully integrated PET-MR system is now not only a reality but the initial clinical results are being published [25].

MR-compatible PET detectors
The main detection technology that is embedded in clinical PET and PET-CT scanners is based on the light sharing and mapping many small scintillation crystals to the light detectors (PMTs). The intense MR magnetic field severely affects the function of PMTs and image quality (Figure 5). To tackle this limitation, a sequential PET and MRI acquisition has been proposed, although this technique does not allow simultaneous acquisition and is associated with the body-motion risks and the long examination times.

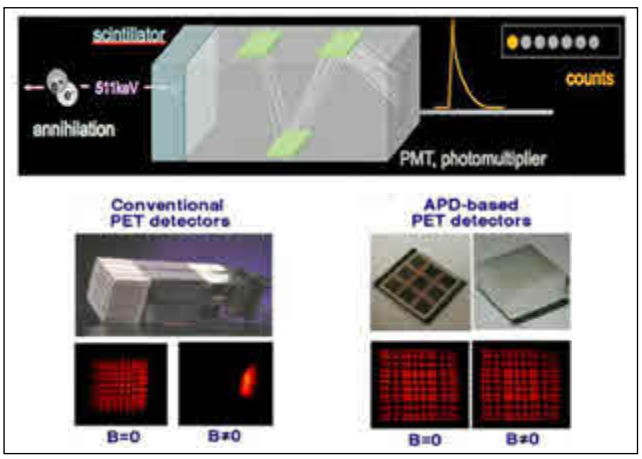

Figure 5 *Schematic diagrams of the detection process (top); conventional PET (bottom left) and APD-based (bottom right) detectors response to magnetic field*

Another solution proposed the use of optical fibers to lead the light signal from the scintillation crystals outside the magnetic field in order to minimize the interference. Split magnets, with a PET detector positioned between the two magnet halves, and connected with the optical fibers, have also been proposed [1]. However, the long optic fibers cause signal degradation and inferior PET performance. A recent study by Mackewn et al. [26] has also shown that the proposed systems suffers from a reduced PET-SNR as a result of the light attenuation in the optical fibers (3.5 meters long), which can in part be overcome by the MR-compatible gamma shields. The gamma shields significantly reduces the scatter ratio and improves the quality of the image. However, the limited axial coverage coupled with practical disadvantages such as space requirements and higher cost has hampered this solution.
The most realistic and accepted solution is to replace the PMTs with avalanche photodiode detectors (APDs), which are the semiconductor equivalent of PMTs and can function in strong magnetic fields (Figure 5).

Unlike PMTs, APD-PET systems can be easily switched on and off without requiring long warming-up times and unlike PMTs does not require a large space. This principle was successfully demonstrated in the prototype Brain-PET-MR system in 2006 and various studies have proved the feasibility of the concept [16, 27]. The proposed PET assembly comprised of 192 LSO detector blocks arranged in six rings. Each block has a 12 x 12 matrix of 2.5 x 2.5 x 20 mm3 crystals with an axial field of view (FOV) of 19.25 cm, which is coupled to a compact 3 x 3 APD array. The PET system has a 5.6% point source sensitivity and 2.1 mm spatial resolution in the center of the FOV [5].

Based on the success of the APD detection technology, a dedicated whole-body PET-MRI system, the Biograph mMR, has been developed (Figure 6). The mMR hybrid system has 64-LSO-APD detector blocks, each with a block area of 32 x 32 mm^2 which form one PET detector ring. The PET detector unit has 8 rings in total, with an axial FOV of 25.8 cm.

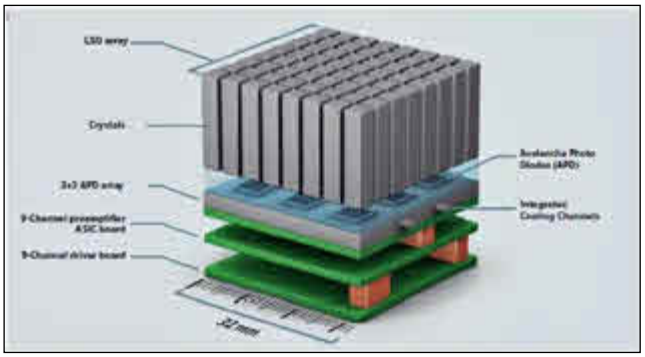

Figure 6 *APD-based PET detector used in mMR (courtesy Siemens Healthcare)*

The size of the each LSO crystal is 4 x 4 x 20 mm^3, which is the finest crystal dimension in the current market [28]. However, the APD-PET systems are still slower than the conventional PMTs-PET modalities. Research on the development of dedicated silicon photomultipliers (SiPM) is currently undertaken, which can increase the PET effective sensitivity up to 10 times, when it is supported with the Time-of-Flight PET and the short coincidence time resolution (<200ns) [29]. The proposed time resolution can only be measured by having a scintillation detector with appropriated characteristics and adequate electronics. The scintillation materials such as LaBr3 and LuI2 are promising.

MR-based attenuation correction

Another critical question in the development of an integrated and simultaneous PET-MR imaging system is the provision of the MRI attenuation map for the correction of the PET reconstructed images, due to the attenuation and scattering of 511 keV in the body and the hardware (e.g. RF coils and moving tables). Traditionally, for the stand-alone PET systems, topography of attenuation values (μ-map) could be reconstructed by rotation of a radioactive ^{68}Ge 511 keV source around the patient. This technique is time-consuming as the source has to rotate slowly in order to achieve a higher count rate. For the current PET-CT systems, the CT scans are used to estimate the expected attenuation, by converting the attenuation values from the 70-120 keV to 511 keV, which provides a reliable and quick attenuation correction μ-map of the patient and the hardware in the PET-FOV.

MR imaging is based on photon densities and T1 and T2 relaxation times which provides tissue type-class information rather than the photon absorption information and therefore, unlike CT, it is not able to measure physical quantities that would allow a direct derivation of μ-maps [30]. Various MRI-based attenuation correction methods such as atlas-based methods or image-segmentation-based efforts, have been proposed to overcome the problem [30-32]. A recent study by Moller *et al.* [31] has shown that segmentation of the attenuation map in 4 classes (background, lungs, fat and soft-tissue) appears to be valid and practical for MRI-based attenuation correction. A CT attenuation correction method was used as a *gold standard* in order to quantify the effects of segmentation on the standardized uptake values (SUV). The segmentation effects showed a slight decrease in the SUV value, particularly in bone lesions (13.1%), whereas the decrease for the neck and the lung lesions was minor (≤8%). In comparison to the CT- based attenuation map, the variations observed in the segmented method, were not adequate to deter the use of the technique in a PET-MRI scan. Although the impact of the attenuation on the pelvic lesions is higher, due to the fact that bones cannot be segmented in whole-body MR imaging, it does not lead to clinical misinterpretations. The impact however is more noticeable and introduces bias in neurology and more specifically in brain studies and therefore the segmented attenuation map is not suitable for neurologic PET and consequently different methods need to be applied [31].

An alternative approach for MRI-based attenuation correction which takes bone into account is the atlas based registration [33]. This technique captures global variation of anatomy to predict pseudo-CT image from a given MR image, and then use the images to create attenuation maps as it would be performed in a PET-CT examination. A study

of human brain by Hofmann *et al.* [33] which combines local pattern recognition with the atlas-based registration, has demonstrated that an estimation of pseudo-CT images can be performed successfully. It has also enabled PET quantification, with a mean error of 3.2% in comparison to the CT-based correction utilizing the predefined ROI. The results demonstrate that atlas MRI-based attenuation correction is a feasible method, with high accuracy for brain imaging, but further research is needed to validate the method for whole-body imaging.

A novel dual-echo ultra-short echo time (DUTE) MRI sequence proposed by Catana *et al.* [27] suggested that the method could potentially be useful for neurologic PET-MRI studies and it even appeared to be superior to the atlas-based methods, for patients with modified bone anatomy [27]. An alternative reliable MR-based method, which targets patient-specific quantitative analysis in time-of-flight PET-MRI, was proposed by Salomon *et al.* [34]. The possibility of introducing a transmission scanner to the PET-MRI system was also considered but various issues such as interference, additional radiation dose, considerable development effort, and additional cost have to be considered [35]. The lack of MRI attenuation information in patient imaging appears to be a drawback in combined PET-MR imaging although various MR-based AC methods have been proposed and are appearing to be robust enough to be used in clinical applications.

MR-based motion correction

PET provides an estimation of radiotracer concentration, but its degradation in quan titative accuracy and spatial resolution is inevitable due to subject motion. The motion-correction technique can be developed in simultaneously PET-MR imagining, by taking advantage of the MRI as it has been shown in the recent studies [36-37].

Motion-correction is more crucial in whole-body imaging than in brain studies, as the subject motion in brain can be estimated well by using external motion tracking devices and the image processing techniques. However, in whole-body imaging, the complex deformations and the image degradation may occur due to the respiration, peristalsis, cardiac contraction and the arbitrary patient movement [38]. Tsoumpas *et al.* [37] compared PET and MR based motion correction techniques and concluded that the performance of the latter is superior to the PET-based motion correction as PET systems have limited FOV and therefore cannot measure motion at the edges. Moreover, the PET images are too noisy to employ non-rigid registration, and due to the rapid tracer kinetics, the activity varies significantly with time and with the patient's physiological response. On the contrary, MRI provides the excellent soft-tissue contrast and thus it is an extremely useful tool for the estimation of motion in human anatomy.

The use of novel MRI techniques may provide continuous and synchronous motion monitoring during the PET acquisition which could be proven to be the ideal solution to back the arguments for an integrated and simultaneous PET-MRI system. However, fast MR sequences and an image processing tool to characterize the motion is required. Moreover, there are many other issues such as eddy current artifacts, degradation of gradient coil performance, RF noise or signal loss and uniformity of magnetic fields, which could degrade the overall performance of the system. In addition, although minimizing the current lengthy PET-MRI examination times is challenging but is necessary to avoid image degradation as a result of body motion.

Fully integrated PET-MR system: installation challenges

Technical Specifications

The Biograph mMR (Figure 4) is the first fully integrated PET-MRI system. It is an integration of a 3-Tesla (3T) whole-body MRI system with an incorporated isocenter PET detector. Diameter of the patient bore is 60 cm, the magnet length is 163 cm, and the system covers 199 cm length which enables whole-body imaging.

The magnet type is Niobium-Titanium and its weight including cryogens is 6300 kg. The magnetic field shimming, i.e. the process of improving field homogeneity by compensating for imbalances in the main magnetic field of an MRI system, is approximately 20 sec. The Biograph mMR incorporates *zero-helium-boil-off* technology and the helium capacity is approximately 1500 litres. The maximum acoustic noise level is 115 dB and the MRI resolution in the FOV varies from 5 mm to 500 mm [40]. The PET detector assembly is a combination of LSO crystals (4x4x20 mm^3 per crystal) and APD which can detect gamma rays in strong magnetic fields. Each PET detector ring consists of 64 detector blocks with 32x32 mm^2 area per block. The full PET detector unit consists of 8 rings which form an axial FOV of 25.8 cm. It is larger than the conventional current PET/CT systems which usually have a 20-22 cm axial FOV.

Siting

Various unique parameters have to be considered in relation to siting a PET-MRI hybrid imaging modality. Since the combination of MR with PET in the same room is a technology at early stage, routine installation protocols and thorough design for facilities and workplace requires to be developed. This review underlines the proposed solutions.

Table 2 *Guidelines for a minimum distances between the magnet isocenter and different objects including maximum weights for metallic materials*

	Minimum distances magnet - magnet (SIEMENSE)				
	0.2T	**0.35T**	**1.0T**	**1.5T**	**3.0T**
0.2T	10	10	5	6	10
0.35T	10	10	5	6	10
1.0T	5	5	4.5	5	6
1.5T	6	6	5	5	6
3.0T	10	10	6	6	6

	Object	Minimum clearance		Max. weight
		radial (X/Y)	axial (Z)	
Guidelines for	Water cooling system	4.0 m	4.0 m	
minimum	Wheelchairs up to approx. 50 kg	5.5m	0.5 m	
clearances	Calls up to approx. 200 kg	6.0 m	7.0 m	
and	Transformers < 10D0 kVA	14.3 m	15.0 m	
maximum	High voltage cables < 1000 A	12.0 m	5.0 m	
weights	Cars up to approx. 900 kg	0.5 m	B.0 m	
	Trucks up to approx. 4500 kg, Lifts	7.0 m	9.5 m	
	Street cars, trams	40.0 m	40.0 m	
	Angiography systems with magnetic navigation	30.0 m	30.D m	
	Reinforcement steer in the floor	> 1.25 m below	magnet centre	≤ 100 kg /m2
	Iron beam mass in the floor	> 1.25 m below	magnet centre	≤ 100 kg / m

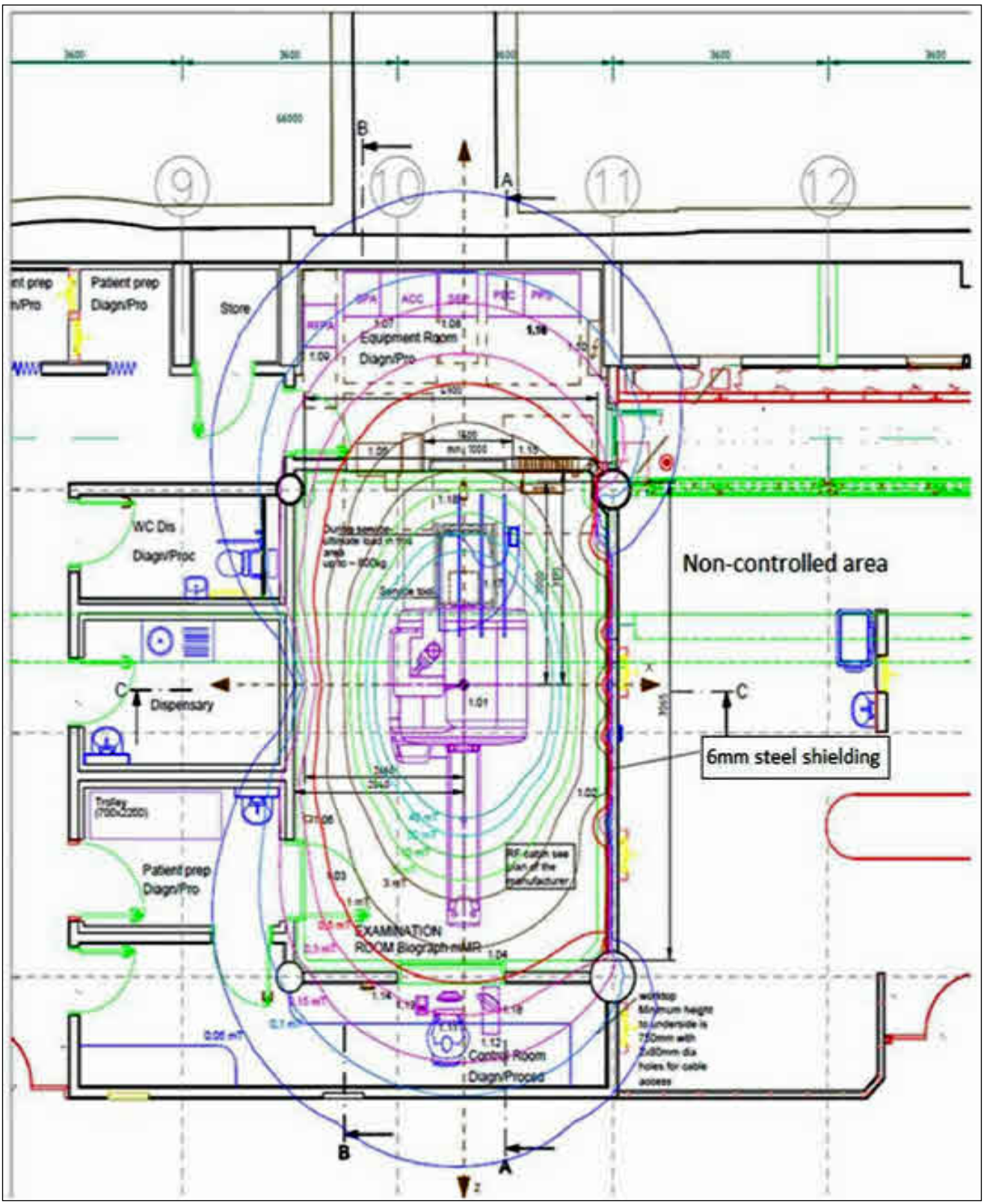

Figure 7 *The detailed floor plan of the PET-MRI facilities and magnetic field extend. Patients preparation rooms, toilet, dispensary, storing space, equipment and control rooms and adjacent non-controlled area are shown above (couretsy Siemens Healthcare)*

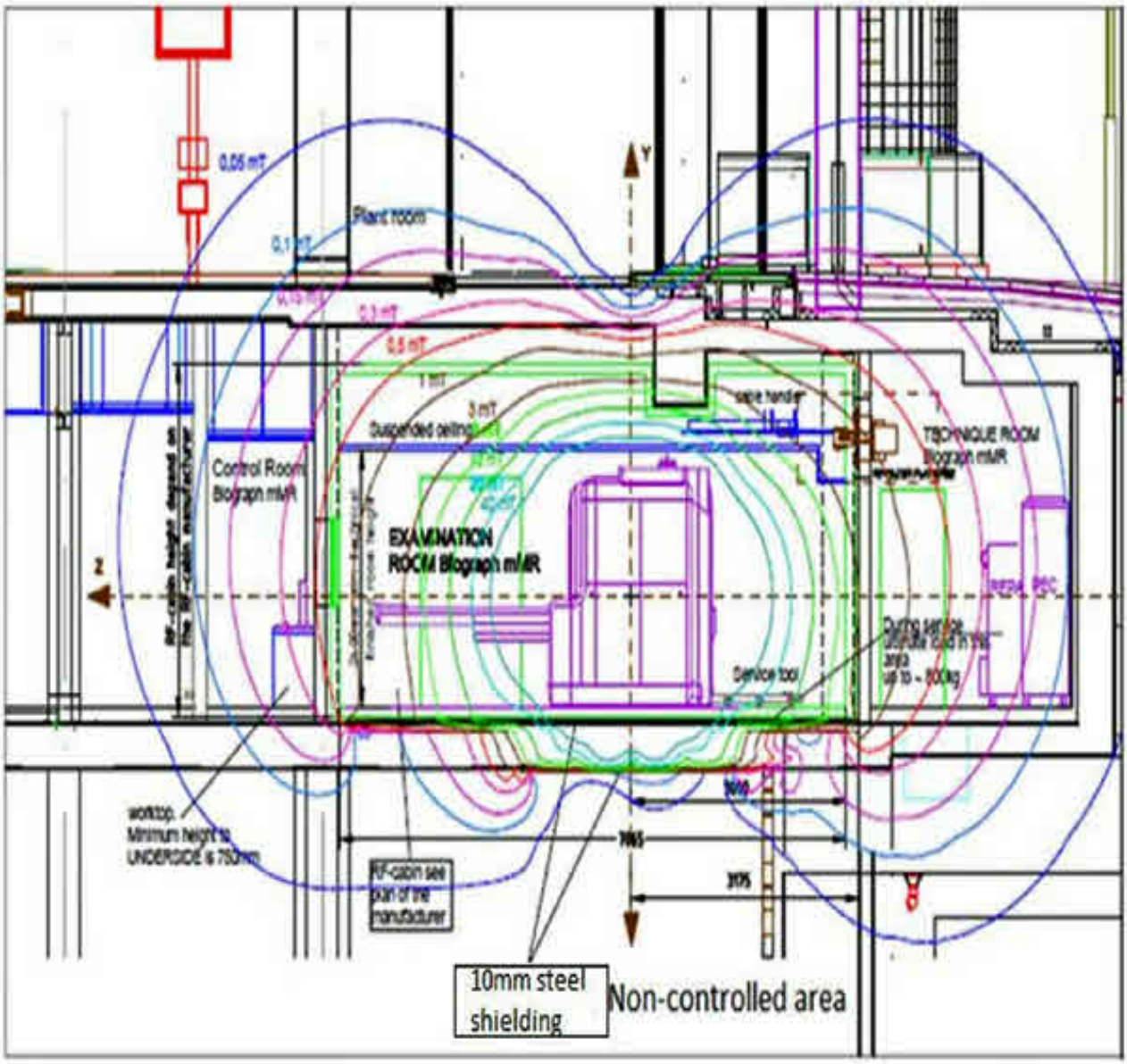

Figure 8 *The cross-section of the PET-MRI facilities showing the extent of the magnetic field above and underneath the mMR floor (courtesy Siemens Healthcare)*

Magnetic field shielding

MRI uses high magnetic field (3T for the mMR) and therefore, magnetic shielding is crucial for both safety and field homogeneity.

Protecting the immediate environment from the effect of the magnetic field is significant for the various follow-up reasons: a) it can disrupt pacemakers or insulin pumps function; b) a great potential health hazard is associated with ferromagnetic objects such as scissors, knifes or oxygen cylinders that are accelerated in the field and can become dangerous projectiles; c) has serious impact on function of computers, other medical devices, cameras and a wide variety of other electronic devices [42]. Moreover, the homogeneity of the magnetic field itself can also be affected by the ferromagnetic objects which can lead to the image degradation and artifacts, and therefore, guidelines for a minimum distances between the magnet isocenter and other devices or ferromagnetic objects should be followed (Table 2).

The official regulations require magnetic fields up to 0.5mT to be restricted in a controlled area, posing any threat. Figures 7 & 8 describe the floor plan and cross-section of the whole mMR facility, showing the strength of the magnetic fields in various distances from the magnet isocenter and how the 0.5mT field is restricted almost completely within the examination room. The non-controlled area on the right side of the mMR examination room had to be protected from the 0.5mT magnetic field as the patient rooms were located here and therefore, 6 mm thick carbon steel plates had to be placed on the wall between the mMR examination room and the non-controlled area (Figure 7). In addition, for the protection of the non-controlled area underneath, a carbon steel plate of 7x4 m^2 in surface area and 10 mm in thickness was placed on the either side of the floor slab of the mMR examination room. The minimum distance that ferrous components can be placed below the magnet field strength is 300-400 mm, and since the thickness of the floor slab below the magnet is 400 mm, no interactions between the magnet and the steel plate are expected [43].

Radiofrequency shielding

The examination area should be shielded to provide a reduction of radiofrequency waves originating from external transmitters, and to protect the environment from the internal RF waves originating from the MRI. A copper RF cabin (Faraday cage) was installed in the examination room in order to provide the required attenuation (90 db) of the radio-frequency in the range of 15-128 MHz [43].

The PET electronics and cables are vulnerable to radiofrequencies, causing downgrading of performance and therefore, an extra RF filter panel is required for the PET-MRI installation. Moreover, the MRI cable trays must be separated from the PET cable trays with a minimum distance of 800 to 1000 mm, and the cables which connect the PET electronic equipment to the PET detector should be also routed via a cable handler and should be mounted above the ceiling of the RF cabin with a minimum clearance of 255 mm [43]. In order to avoid electromagnetic interactions, optical glass fibers could be a feasible alternative to the conventional coaxial cables that are currently used for the MRI and PET interconnections. Optical glass fibers only transmit optical signals and they are totally immune to the electromagnetic interferences. In addition they are able to carry huge amounts of data and have exceptionally stable signal intensity and flexible small cross sections. The recent study by Yuan et al. [44] demonstrated that the optical glass fibers are a feasible solution for MRI and PET-MRI systems. Future research and development of less expensive optical fiber materials, may further support the use of this technology in medical imaging systems.

Ionizing radiation shielding

In addition to the magnetic and RF shielding for PET-MRI facilities, radiation shielding due to the ionizing radiation of 511 keV gamma rays is also required. For the Biograph mMR facilities lead chevrons were placed as the main radiation shielding in addition to the building concrete walls and the steel plates of the magnetic shielding. Figure 9 illustrates the lead shielding for sections of the room, where 21 mm lead chevrons were installed on the wall between the examination room and the adjacent non-controlled area and 11 mm lead were placed between the control room and the examination area. The control room window was shielded with RF and a radiation absorbing lead glass. Since, the thickness of the concrete (400mm) was adequate to attenuate all the emitted radiation, lead was not placed on the floor and on the ceiling. The rest of the walls were not shielded with lead as the adjacent areas (toilets and preparation rooms) had their own lead shielding [43].

Additional considerations

The loading capacity of the floor must be designed in order to support the weight of: PET-MR system (up to 10,500 kg); the RF cabin, the iron and the radiation shielding; the load of the electronic equipment of both modalities (approximately 4000 kg) and the additional load for service purposes (up to 1000 kg). In addition, the mass of the floor should be adequate enough to isolate sound and vibrations in order to prevent

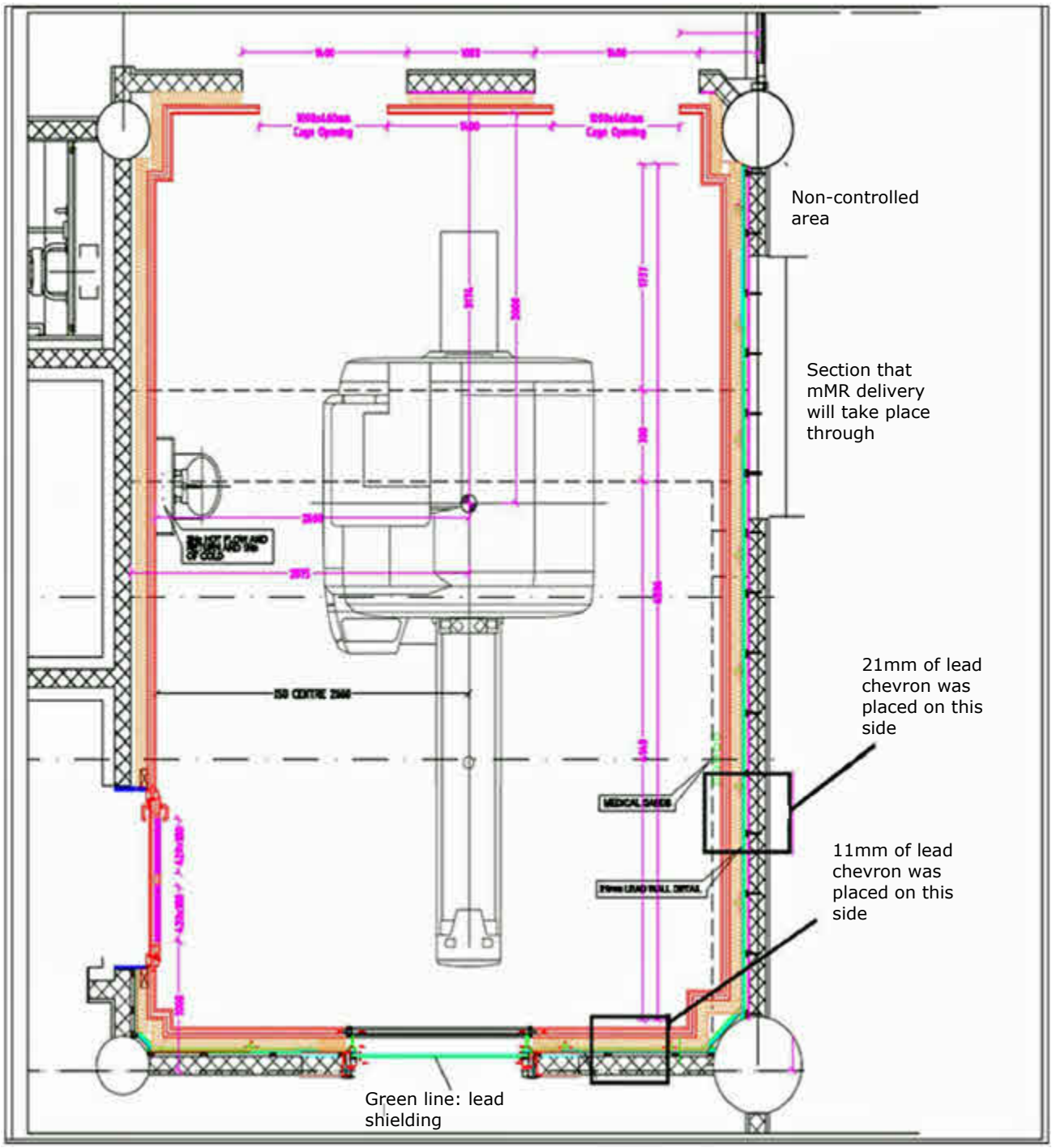

Figure 9 *Biograph mMR floor plan (courtesy Siemens Healthcare)*

prevent inhomogeneity in the magnetic field and in the image quality [43].

For conventional MRI, a chilled water system is required at all times to cool the head and the gradient systems. For the PET-MRI, the cooling system can be also used to cool down the additional PET equipment. The recommended piping materials should be stainless steel, non-ferrous metal (copper or brass) and synthetic materials such as plastic. Materials, such as aluminum, iron, carbon

steel, zinc and standard steel pipes may cause damage to the cooling system and should be avoided.

Rust and flakes may be produced within the pipes as a result of oxidation processes, which can destroy the electronic equipment. For the current PET-MRI facilities, piping materials of carbon steel has been used and therefore a barrier filter has to be placed to filter out all the rust and the flakes. Cautious monitoring of the filter is required as it can get clogged with debris resulting in slowing down of the cold water supply and can eventually cause the cryogens to boil off (quench). The power supply, the heat dissipation and the water supply requirements of the mMR are 30% higher than those of a conventional 3T-MR system [43].

PET-MR service delivery challenges

Potential risk and safety aspects

The ionizing and non-ionizing radiation safety aspects of PET and MRI are well known and the established safety protocols have been followed in medical imaging departments. However, for PET-MRI examinations, there are additional safety considerations that should be evaluated.

During PET examinations, various equipment such as injection systems, syringes, radioactive source containers and other routinely used equipment, may pose a hazard to patients due to the high magnetic field of MRI. PET-MRI examinations should be avoided for patients with passive implants such as catheters, heart valve prostheses, orthopaedic prostheses, vascular clips, sheets and screws or for patients with active implants such as heart pacemakers and defibrillators, electronic drug infusion pumps, cochlear implants and other objects made of ferromagnetic materials such as bullets or pellets [42]. In order to eliminate or to minimize the impact of the hazardous situations, careful interview of the patients and the provision of metal detectors in the entrance of the PET-MRI facilities are necessary.

Some studies have demonstrated that mild hyperthermia caused by the RF fields has a radiosensitizing effect in tumours and low frequency or static magnetic fields may enhance the genotoxic potential of ionizing radiation. Although, pregnant women are allowed to undertake MRI examinations in the first trimester for special medical conditions, PET-MRI examinations should be avoided due to the effect of additional ionizing radiation of PET imaging which could seriously damage the foetus [42].

Examination times

The PET and MRI imaging techniques both require relatively long examination times, although the simultaneous acquisition of the Biograph mMR dramatically reduces the overall imaging time, however further reduction in the simultaneous image acquisition period remains a clinical challenge. Lengthy examination times (20-50 min) cause various problems such as patient discomfort, claustrophobia and image artifacts as a result of volunteer or non-volunteer body motion. In particular, reducing the imaging time in pediatric oncology is crucial. The examination times are driven mainly by the MRI and therefore there is a need for development of a faster MRI sequences.

New clinical protocols

The objectives of clinical protocols are to standardize and to raise quality of medical care for reducing patients' health risk and to ensure the cost effective medical procedures. As such, either a new optimized imaging protocol should be developed for the PET-MRI studies or the already existing PET and MRI protocols modifed by taking into the considerations all the specificities of the new modality. The need for modifying or developing a protocol for ^{82}Rb-PET-MR myocardial perfusion imaging is a clear example that appears to be difficult and challenging. ^{82}Rb is a generator product with a physical half-life of 75 seconds, which has a significant advantage of having no need for on-site cyclotron [46]. The ^{82}Rb generator-injection system is placed beside the conventional PET or the PET-CT systems for injecting the ^{82}Rb radiopharmaceutical directly

into the patients. This approach is not feasible in MRI environment, due to the ferrous materials of the ^{82}Rb generator. A proposed solution is to place the ^{82}Rb generator outside the examination room and to inject the radiopharmaceutical remotely, using a longer injection system supported by a pump. However, the proposal might face some drawbacks and consistent radiotracer delivery may not be guaranteed. Provision of a MRI-compatible generator can be a potential solution, although as with any other MRI-compatible medical equipment, the cost could be up to three times higher. Moreover, during the rest-stress ^{82}Rb-PET-MR myocardial perfusion studies, unlike the ^{82}Rb-PET-CT, a clinician cannot be in the examination room, especially during the online injection, and the possibility of immediate intervention in health risk situations needs to be addressed by developing remote and automated monitoring systems.

Scientific teams "fusion"
Another practical but major challenge is to put together two scientific teams with a very different background knowledge. PET scientists need to deeply understand the complex MRI physical principles, working procedures and safety aspects and vice versa. Hence, new training programs should be developed in order to prepare a new generation of PET-MRI specialists.

New tracers
Additional field of research with a potentially high interest is the development and production of tracers, which can simultaneously generate signals for the both PET and MRI imaging. The study by the Lee *et al.* demonstrated the production of polyaspartic acid particles, which were coated with the cyclic RGD peptide via a polyethylene glycol spacer and DOTA. It not only has excellent magnetic properties for MRI but at the same time it could be efficiently labelled with ^{64}Cu for the PET imaging [48].

Discussion

The current development of the new hybrid PET-MRI imaging technology may open a new horizon in diagnostic imaging and establishes a modality of choice for a variety of studies.

The potential advantages and clinical applications of PET-MRI are numerous. The excellent soft-tissue contrast, high spatial resolution and functional imaging (fMRI, DW-MRI, MRS) of MR, in combination with the high sensitivity functional imaging of PET, enables the assessment of metabolic abnormalities and changes in mass lesions before the tumour size changes can be measured and therefore, facilitates and enhances cancer diagnosis to reach new levels.

The lower radiation dose of PET-MRI in comparison to the PET-CT dose (54% to 83% lower dose) is another considerable crucial advantage, especially while imaging children and patients with potentially curable oncological diseases [13]. Moreover, the strong magnetic field of the MRI may improve the PET resolution, as it limits the positron range prior to the annihilation [15]. For simultaneous data acquisition, PET-MRI not only allow for high spatial overlay accuracy, but the exceptional temporal co-registration also enables the MR-based PET image motion-correction for precise cardiac and abdominal imaging [12]. In addition the simultaneous acquisition significantly reduces the overall examination time of the individually acquired PET and MRI.

Considering the above factors, MRI appears to be a perfect anatomical complement to PET although, there are remaining disadvantages and drawbacks in PET-MRI technology that needs to be overcome.

One of the main identified challenges and the follow-up solutions was to develop a MR-compatible PET detector and to replace the associated PMTs with APDs capable of functioning within strong magnetic fields. Various studies [5, 16, 25, 27] and Siemens' choice of APDs, for the construction of the Biograph mMR, demonstrated the superiority of this solution.

Development of a MRI-based attenuation correction map for combined PET-MRI is

another challenge especially for the whole-body imaging. Various studies [30-33] have indicated the atlas MRI-based attenuation correction as the preferred method for head and neck imaging, whereas the segmentation based methods perform better for the rest of the body. The results show that the MRI-based attenuation correction is feasible with no significant effects on the clinical analysis, though further research is needed to validate these methods and to achieve a superior quality of the CT-based attenuation correction maps. The various drawbacks such as motion-correction and electromagnetic interactions between the PET and MRI systems (eddy currents artifacts, RF noise, signal loss and degradation of gradient coil performance) need to be addressed although, it appears that the issues can be successfully overcome with no significant effect on the overall performance of an integrated PET-MRI system [28, 37].

The use of iron shielding to restrict the 0.5mT magnetic field within the mMR room, is shown in Figures (7-8). A copper RF cabin was installed to provide attenuation of 90 db in the frequency range of 15-128 MHz. As the PET electronics and cables are vulnerable to radiofrequencies, an extra RF filter panel was placed to shield the PET electronics in the equipment room. The PET and the MRI cable trays should be separated by a minimum of 800 to 1000 mm in order to avoid any cross interferences. The connection between PET detectors and their electronic equipment should be routed via a cable handler and should be mounted above the ceiling of the RF cabin with a minimum clearance of 255 mm. The cooling system should be able to cool down the PET and the MRI equipment. The power supply, the heat dissipation and the water supply requirements are 30% higher than for a conventional 3T-MR system.

The prospective hazards of PET examination equipment made from ferrous materials (e.g. injection systems, syringes, radioactive source containers, etc.) have to be addressed and therefore, nonferrous materials should be used in order to avoid potential health risks. PET-MRI examination times have been estimated to be 20-50 minutes, which are relatively long, in particular for paediatric studies. However, the ability to simultaneously acquire PET and MRI data is extremely valuable and its potential clinical benefits appear to justify the prolonged examination times.

Future considerations

MR-based attenuation correction: More research in MR-based attenuation correction, especially for the whole-body scans is needed. Although, some alternative methods such as novel eual-echo ultrashort time echo MRI sequences or time-of-flight PET-MRI have been proposed by Catana *et al.* and Salomon *et al.* [27, 34].

APDs: Further development in APDs although, Silicon Photomultipliers (SiPMs) might be a feasible alternative solution in the near future to achieve a better time resolution [29].

Bore and FOV: A larger bore and FOV which reduce artifacts and improve patients comfort (the current system has a bore diameter of 60 cm). The need for imaging large patients is growing.

New dual-function agents: Agents which can be used simultaneously as contrast agents for MRI and specific tracers for PET.

Protocol optimization: An optimized and faster protocols for MR imaging (e.g. fast-spin echoes) to reduce the overall examination times.

Monitoring Systems: The production of automated monitoring systems or MR-compatible medical equipment. The Lack of specific equipment such as ^{82}Rb generators, could pose a drawback for future studies.

Conclusions

The long-awaited simultaneous whole-body PET-MR imaging modality has finally entered the realms of practical nuclear medicine. As is the case with the early years of every cutting-edge technology, it must prove its worth and translate its technologic advances into the clinical benefits. Various challenges have been identified whilst some are still pending

solution. The Biograph mMR (and every other integrated PET-MRI system) still needs to address the question, as to whether this clinical tool can offer something unique and expand the boundaries of medical imaging. The first clinical results are extremely promising and it is very likely that PET-MRI will be the imaging modality of choice for the next decade.

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