

REVIEW ARTICLE

Combined PET-CT and PET-MR: technical innovations

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Abstract

The multimodality molecular imaging has brought a new perspective into diagnostic imaging and advanced medical diagnosis considerably. Positron emission tomography (PET) is a powerful molecular imaging technique but, its inability in providing anatomical details is a major limitation for PET only systems. Combining functional imaging with anatomical imaging like computed tomography (CT) and magnetic resonance imaging (MRI) has tremendously helped in disease detection at the cellular and sub-cellular levels. The wide clinical adaptation of PET-CT technology shows the positive influence of multimodality imaging in clinical practice by providing complementary information in function and morphology. The PET technology has advanced significantly over the years alongside multidetector CT technology and now supports whole-body PET-CT imaging in less than 10 min. concurrently, the MRI modality has evolved in providing soft-tissue contrast, tumor detection, tissue characterization and some functional imaging capabilities. The idea of combining PET and MRI has been around for about two decades in harnessing the rich complementary functionality and sensitivity; combined PET-MR provides both functional and anatomical information simultaneously while retaining quantitative ability of PET. Recently, simultaneous acquisition of PET-MR in clinical environment has been realized and is a major breakthrough. Simultaneous PET-MR will open-up new possibilities in preclinical and clinical arena in disease diagnosis, therapy and also in the research and development of new drugs. Though the combined PET-MR has been available only to selected research and academic institutions at present, it is expected that the wide availability and adoption of PET-MR in clinical practice will be a paradigm shift in healthcare industry. In this review we summarize the technical innovations that have been taken place in PET-CT and PET-MR technology and their potential implications.

Key words: *PET, MRI, PET-CT, PET-MR, molecular imaging*

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Introduction

In the early 1970s, Ter-Pogossian and his research group developed the first generation positron emission tomography (PET) scanner [1]. Since then continuous research and

developments in various specialties over the period of four decades resulted in the modern PET scanners. In the late 1990s PET has transformed into a clinical tool, due mainly to the approval of ^{18}F-fludeoxyglucose (^{18}F-FDG) PET as a reimbursable imaging modality for lung cancer evaluation by the USA Food and Drug Administration (FDA). Diagnostic utility of PET in oncology has paved the way for research and development in clinical settings for various disease entities. In 1998, a prototype of combined PET and CT scanner in a practical and effective manner for acquiring co-registered anatomical and functional images in a single scanning session was introduced [2]. In 2001, PET-CT scanner was commercially introduced, since then adoption of the PET-CT technology has been rapid. Availability of 'form' and 'function' in a single scanner and imaging session resulted in the wide-spread acceptance of PET-CT in medical diagnosis, particularly in oncology. Even though PET-CT has virtually replaced the stand-alone PET through proven benefits for patients and clinical workflow, skepticism regarding the use of combined multimodality imaging still persists [3]. However, molecular imaging techniques have progressed from stand-alone modalities to multimodality methods over the last two decades, driven mainly due to the need for sophisticated *in vivo* detection techniques to better characterize the cellular and sub-cellular processes in preclinical and clinical settings.

The combination of PET and CT is a successful imaging platform and has become an important tool in clinical practice. Clinical cases have shown that the combination of anatomical structures revealed from CT, and the functional information from PET into one image with high fusion accuracy provides advanced diagnostic information. The full exploitation of PET-CT hybrid system is far from being complete both in the animals and humans and further advances in the use of PET-CT are expected in the near future. Meanwhile other hybrid systems such as combined PET and magnetic resonance imaging (MRI) have recently become a reality. It is envisioned that PET in combination with CT and/or MRI might pave the way for better understanding of physiological and morphological information of disease mechanisms in preclinical and clinical settings. However, the additional value provided by the hybrid technology usually resides in the improvement realized in sensitivity, specificity and accuracy over PET alone since, the correlation of PET tracer accumulation with structural abnormalities or normal anatomic sites may reduce false negative and false positive findings, respectively.

Clinical evidence for the diagnostic superiority of PET-CT over stand-alone PET and CT has been growing [4, 5]. This pertains to a number of indications, primarily in oncology, albeit increased interest has been shown in cardiology and neurology of late. It is envisage that similar advantages over stand-alone imaging could be expected from combining PET with high resolution MR images [6]. The key challenge for PET-MR is the acquisition of whole-body images with adequate anatomical resolution and within a reasonable total examination time, matching that of a whole-body PET-CT study. In this report we review major technical innovations and advances in hybrid PET-CT and PET-MR systems.

PET Imaging basics

PET is a molecular imaging modality that utilizes the annihilation coincidence detection of positron emitting radionuclides. Following positron decay, two 511 keV photons are emitted at an angle approximately 180° apart and simultaneously detected by scintillation crystals. The light of the scintillation crystals is further converted into electrical signals, which are subsequently processed to deliver images. PET has significant role in detection and quantification of metabolic abnormalities of disease processes. PET uses biologically significant elements like ^{13}N, ^{11}C, ^{15}O and ^{18}F, which provide visualization and quantitative assessment of physiologic, and biochemical processes within the human body. The molecular nature of PET technology resides essentially in the use of specific tracers that enter metabolic and biochemical pathways or bind to molecular targets. The intensity of PET

signals emanating from organs, tissues and tumors after the biodistribution of the tracer in the body is proportional to the amount of tracer in the anatomic region at the time of imaging and can be analyzed using quantitative methods. An important aspect of the tracer validation process is to demonstrate that the degree of tracer accumulation at target sites reflects the status of the target process or target density.

PET-CT: technical basis

PET-CT is a hybrid imaging device that combines PET technology with CT imaging modality. A prototype of combining PET and CT in a single gantry was designed in 1998 [2]; clinical evaluation of the prototype for over three years [7-9] resulted in the first commercial PET-CT system in the clinic in 2001. In PET-CT scanner, the CT and PET gantries are coupled coaxially such that CT and PET images can be sequentially acquired in the same session, thus allowing an intrinsic co-registration of the two sets of images. PET images will capture the three-dimensional biodistribution of a positron-emitting radiotracer whereas CT images will outline the anatomic location of sites that accumulate the radiolabeled compound within the body. Therefore functional images obtained by PET will be combined with and superimposed to anatomic images and fusion images can be obtained in the coronal, sagittal and transaxial planes. In a combined PET-CT scanner, the CT portion can be used for attenuation correction, although these data are acquired at a lower energy, typically at 80-120 kVp, and need to be up-scaled to the tissue absorption factors for 511 keV. The CT scan can be performed much faster than the conventional transmission scans, resulting in a drastic reduction of the overall examination time. This, combined with the additional anatomical information provided from the CT, is a major advantage of combined PET-CT over stand-alone PET.

There were initial concerns regarding manufacturing cost of PET-CT and excess radiation dose from CT portion of PET-CT, but these were far outweighed by the diagnostic information derived from whole-body dual-modality imaging [10]. The clinical impact of PET-CT was such that by year 2006, major manufactures no longer offered stand-alone PET systems and PET-CT became the standard and accepted technology [11]. In a comprehensive review of PET-CT literature in cancer imaging, Czernin *et al* [4] concluded that PET-CT offers diagnostic advantages over its individual components for the major cancers and also suggested that PET-CT has lead to a 10-15 % increase in diagnostic accuracy compared to PET or CT alone imaging. Over the period of ten years since its inception PET-CT have shown its direct impact on patient management; it has also changed the outlook of radiology and nuclear medicine in particular.

Modern PET-CT scanners

The PET technology available in combined PET-CT scanners has advanced significantly over the years [12] with the introduction of faster scintillators such as gadolinium oxyorthosilicate (GSO), lutetium oxyorthosilicate (LSO) and lutetium yttrium orthosilicate (LYSO), higher resolution detectors and improved electronics [13-15]. Advances in CT technology have been equally progressive with increased slice numbers and faster CT rotation times [16, 17]. Currently, it is not uncommon to see a PET-CT scanner with a 64-slice CT and PET component with fast scintillators having smaller detector elements. Modern PET-CT systems can acquire emission imaging of the torso from head to mid-thigh in less than 10 min. PET-CT scanners having high-end multidetector CT also allows contrast-enhanced diagnostic CT studies, which has progressively increased the clinical relevance of integrated PET-CT imaging protocols [18].

Five major vendors (GE Healthcare, Philips Healthcare, Siemens Medical Solutions, Hitachi Medical and Toshiba Medical Corporation) offer PET-CT scanners at present. Except for GE Healthcare which offers retractable septa for 2D and 3D mode data acquisition, all other vendors offer 3D only scanners. There have been a lot of emphasis in PET instrumentation improvements in PET-CT system design in regard to sensitivity, resolution and

reconstruction methods and the following sections will focus on the recent innovations in PET components.

Time-of-flight (TOF) PET

With major advances in PET detectors, positron flight time can now be measured, which has greatly reduced PET scan time [19]. Measuring positron time of flight is as good as having a new coordinate that doubles the data input from a single positron emission. In conventional PET, a valid event is formed when the two coincident 511 keV annihilation photons are detected within some pre-defined timing window, typically on the order of 4.5-10 ns. The two detectors in which interactions are measured determine a line (line of response or LOR) along which the original annihilation takes place. The location of the annihilation site is unknown and can be recovered only by image reconstruction. The image reconstruction algorithm, with no other information at its disposal, assumes that all possible locations of the annihilation site on the LOR have equal probability. In TOF PET, the actual time difference in the arrival of the two annihilation photons at the respective detectors is recorded. The time difference increases the farther the annihilation site is from the point midway between the two detectors. The utilization of TOF is known to improve the signal-to-noise ratio in PET images, by reducing the noise propagation along the LOR during the forward and back-projection steps in image reconstruction [19].

A commercial PET-CT scanner with TOF capability (Gemini TrueFlight) was first announced by Philips Healthcare [19]. Now this technology is marketed by many names: Discovery (GE Healthcare), Biograph TruePoint (Siemens Healthcare), Ingenuity TF and Gemini TF (Philips Healthcare). Each of these models essentially does the same thing: increase image resolution and reduce scan time. The clinical impact of TOF PET technology is yet to be established and more details in regard to TOF development is reviewed by Muehllehner and Karp [20].

Extended axial field of view (FOV) PET scanners

The axial FOV of most PET-CT scanners is about 16 cm; it is envisioned that increasing axial field of view (AFOV) with more detectors may considerably increase the sensitivity and reduce the scan time. PET-CT design having AFOV about 22 cm has been reported recently for improved sensitivity [21]. Increasing the axial extent of a PET scanner by 30 % reported to have been resulted in about 80 % increase in volume sensitivity in 3 D mode acquisition [11].

Improved PET reconstruction methods

PET image reconstruction algorithms have made a significant progress from the days of 2 D filtered back projection algorithms [22]. Fourier rebinning (FORE) with statistically-based expectation-maximization (EM) algorithm [23] was a major breakthrough in PET image reconstruction and was further improved by ordered-subset EM (OSEM) algorithm [24]. Modeling corrections for randoms, scatter and attenuation and implementing with OSEM further reduced the image reconstruction time [25]. Recently, the PET detector spatial response function has been included in the reconstruction model and was termed as high-definition (HD) PET [26]. The ability to measure the spatially varying point spread function and modeling them in the reconstruction algorithm has greatly enhanced the PET resolution and image quality.

Limitations of combined PET-CT

Wide clinical acceptance of PET-CT imaging is largely due to diagnostic information derived from this modality for patient management. However, there are several limitations associated with CT technology while combining for PET quantification such as metal and breathing artifacts [27, 28]. PET-CT offers significant shorter scan times compared with stand-alone PET scanners, where the attenuation correction is not based on an ultrafast CT scan. However, in regions with high density materials, such as metal implants, CT causes beam-hardening artifacts

by selectively attenuating the lower x-ray energy more than the high energies, resulting in a shift of the polychromatic x-ray spectra to higher energies [27]. This effect can cause significant artifacts in the CT images and lead to false attenuation values for the PET images. Object motion during PET data acquisition is another source of misaligned PET and CT data in PET-CT imaging [29]. CT scans are like snap shots and often acquired in inspiration phase according to standard diagnostic CT scan protocols, whereas PET scan is acquired over several minutes while the patient breathes normally. This most often results in mismatched PET and CT images, especially in areas of the thorax, and abdomen [30, 31]. Often, contrast enhanced diagnostic quality CTs are acquired with PET-CT scanners, in such cases false PET attenuation correction might occur if correction for high atomic number contrast agents were not implemented in the PET image reconstruction algorithm.

Why PET-MR?

PET has very high sensitivity for tracking biomarkers *in vivo* but has poor resolving power for morphology, whereas MRI has lower sensitivity, but produces high soft-tissue contrast. Combining PET and MRI in a single system to harness the synergy of these two modalities is not only sounds logical but also intuitive. The synergy of PET-MR has been proven as powerful tool for studying biology and pathology in preclinical settings and has great potential for clinical applications [32]. PET-MR overcomes many limitations of PET-CT, such as limited tissue contrast and high radiation doses delivered to the patient or the animal being studied [33]. In addition, recent PET-MR designs allow for simultaneous rather than sequential acquisition of PET and MRI data, which could not have been achieved through a combination of PET and CT scanners [34].

A number of recent publications indicating the potential value of PET-MR images in clinical practice, including studies in the detection of liver metastases [35, 36], head and neck [37], intracranial masses [38] and in evaluating intensity-modulated radiotherapy (IMRT) treatment planning of meningioma [39]. PET-MR imaging is likely to make a potential impact in prostate [40] and head/neck cancer imaging [37]. Though PET-MR shows early promising results, it may never replace PET-CT since both MRI and CT have their own individual strength, but the combination of PET and MRI would certainly be a valuable complementary imaging modality for PET-CT.

PET-MR design

The concept of PET-MR was conceived as early as in 1997, by Simon Cherry and Paul Marsden in a pre-clinical setting, even before the prototype PET-CT system was developed [41]. Combining PET and MRI in a single system requires three major changes in PET and MRI technology. First, the photomultiplier tube (PMT) technology in PET system has to be replaced with magnetic field insensitive PET detector; secondly, the PET detectors should be small and invisible to the magnetic field gradient and should not interfere with MR radiofrequency; finally the MRI and PET systems should be housed in a way that simultaneous acquisition is possible without mutual interference [42]. To minimize mutual interference between these two devices, different solutions have been proposed [6]. The use of optical fibers coupled to the scintillator crystals brings light to the PMTs so that only crystals are within the magnetic field of MR. Another alternative approach is to replace the PMT scintillators for solid-state scintillation detectors, such that the avalanche photodiodes (APD). Compared with PMT, APD have unfortunately a lower gain and are more sensitive to temperature variations. However, the major advantage of APD is that they are insensitive to magnetic fields. The best solution is a combination of the two, using a short optical fiber to place APD outside the MR field of view.

Attenuation correction of PET images using MR pose a challenge in PET-MR scanner design. PET imaging provides accurate attenuation correction which is less direct with MR than CT, since MR provides proton density map, while tissue attenuation is

proportional to electron density. The main drawback in MR-based PET attenuation correction is that attenuation is not directly correlated to MR signal measurement. Recently, several methods have been proposed for PET attenuation correction based on MR images to overcome this problem [43-45]. Furthermore, because of the strong magnetic fields of MRI systems, patients with pacemakers, defibrillators or other implanted electronic devices could not be scanned with the PET-MR system unless those devices are specifically indicated for use in the MRI environment. The progress in PET-MR scanner design while overcoming above said challenges has been slow but steady and now we have a clinical PET-MR scanner capable of performing simultaneous PET and MRI acquisitions [34].

Current status of whole-body PET-MR scanners

The development of PET-MR was confined entirely in the preclinical area for nearly two decades until, in 2006, when the first PET-MR brain scanner capable of obtaining simultaneous MR and PET images was developed [46]. As discussed earlier the major challenge for bringing PET and MR technologies physically together is to avoid degradation of the performance of either modality.

Currently, three types of combined PET-MR scanners are available for clinical use. The first and simplest method is to use a tandem configuration, where PET, or PET-CT and MR are acquired sequentially one after another in two separate rooms. Essential feature of this design is that a common patient transfer table is used for both PET and MR imaging sessions and the patient can be transferred from one scanner to another without having to move; such a scanner was installed by General Electric Healthcare at the Zurich University Hospital in late 2010 as a prototype for testing. The second PET-MR design using the same tandem configuration with the exception that both PET and MR scanners are housed in the same room was developed and marketed by Philips Healthcare, first in 2010, using a whole-body TOF PET system and a 3-T MR system with a common patient transit table. Mount Sinai Hospital in New York and Geneva University Hospital in Geneva have got these scanners installed for clinical use [6]. These two PET-MR designs are cost effective, since PET or MR only scans can also be performed besides having the combined imaging feature. The drawback of tandem configuration is that increased scan time and possible motion artifacts.

The third and most challenging design is integrated PET-MR based on a PET detector ring designed as an insert that can be placed inside a MR scanner so that both PET and MR can be acquired simultaneously. Two prototype PET-MR scanners developed by Siemens Medical Solutions (Biograph mMR) capable of acquiring simultaneous PET and MR images have been installed in clinical settings at the Technical University of Munich and the University of Tübingen [18]. The Biograph mMR PET-MR scanner has APD-LSO PET detectors integrated in between MR body coil and the gradient coils. The MR system uses the TrueForm magnet design for improved MR image quality. The transaxial FOV of the MR is 50 cm, and the PET axial FOV of 25.8 cm. This scanner design fully utilizes the simultaneous PET and MR acquisition and results in reduced scan time and better image quality while reducing motion artifacts and the performance measurements show promising results [34].

Future of PET-CT and PET-MR

The diagnostic value of PET-CT is often proven far superior to PET or CT alone particularly in oncology applications [4]. Similar advantages of PET-MR over stand-alone PET or MRI is envisioned and the early clinical results are promising [35, 36, 40]. The greatest advantage of CT is that high resolution whole-body images can be obtained within seconds, whereas whole-body MRI takes about the same time as of a whole-body PET or even more. MRI offers excellent soft-tissue contrast, might be also useful in studying tissue perfusion, diffusion and metabolism [42].

The initial enthusiasm in embracing any new technology is common and PET-MR is not an exception, but careful balancing of capabilities and limitations of PET-MR must be analyzed and more importantly it must be determined in which unfulfilled clinical needs that PET-MR can fill-in. In clinical settings there are certain merits for replacing CT with MR in neuroscience and brain imaging. Whole-body PET-MR can be useful and more sensitive than PET-CT in detecting brain, bone and liver metastasis, while PET-CT is more accurate in the detection of lymph nodes metastasis and therapy monitoring [18, 35, 37, 40]. Combined PET-MR has the potential to be the gold standard for non-invasive assessment of myocardial viability, evaluation of ventricular structure and function together with detection of myocardial infarction [47]. PET-MR also has the potential for reducing radiation exposure, since MR uses non-ionizing radiofrequency waves; this would be particularly useful while performing repeated whole-body imaging for therapy monitoring, and in imaging younger patients.

Though there were widespread debate on whether PET-MR would replace PET-CT [18, 48], it is still early to predict the future of PET-MR simply because, the very existence of much established PET-CT itself is a biggest challenge to the concept of PET-MR. Finally, the cost-benefit analysis is also plays an important role in deciding between PET-CT and PET-MR besides, scientific and medical aspects. The cost of a PET-CT scanner ranges anywhere between $1.9 million and $2.4 million, depending on the system configuration; this is much larger than the cost of a stand-alone PET or CT scanner. The cost of PET-MR scanner is expected to be anywhere between $2.5 million and $3 million. So, careful evaluation cost-benefit is warranted before investing in PET-MR over PET-CT. As said earlier the complete potential of PET-CT is yet to be utilized and there have been ongoing efforts in improving the technology meanwhile, it is encouraging to see the promising results out of early combined PET-MR clinical studies. All these augur well for the co-existence of PET-CT and PET-MR as complementary modality for the betterment of human healthcare.

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