Editorial

Clinical Birth of PET/MR and Future Expectations

Khairy, AT

Professor of Radiology and Nuclear Medicine, Ain Shams University, Cairo, Egypt.
Senior Consultant Radiologist (Nucl. Med.), Hamad MedicalCorporation, Doha, Qatar.

The idea of combining functional and anatomical images for better localization and characterization of the lesion started long time ago, using **side-by-side comparison** of hard copy films. To overcome the limitation of such comparison, induced by variation in geometric factors governing a functional study, like a nuclear medicine PET scan, and an anatomical one, such as a CT scan, the idea of image fusion emerged. This employed computer software programs that allow electronic fusion of images produced by two different machines, for example a radionuclide scan and a CT scan. Obviously the aim was to improve superimposition of images towards better localization, characterization and assessing the metabolic status of lesions.

SPECT and PET are nuclear medicine techniques that provide molecular functional images, while CT scan or MRI produces the cross sectional anatomical images. Image overlay and **software fusion programs** included any combination of SPECT or PET on one hand and CT or MRI on the other hand, representing the overlay of functional and structural (anatomical) images respectively.

Several problems emerged and hampered the precision and practicality of such electronic image fusion technology. One important difficulty was the need for repositioning the patient in a more or less the same exact way for the two studies, the gamma camera (SPECT) and the CT scanning, for example. This was more of a problem for body imaging, of the thorax, abdomen and pelvis, than it is for the brain[(1)]. The other major problem encountered was the signal attenuation for nuclear medicine emissions, which was not corrected. Such problems degraded prompt localization and characterization of lesions and resulted in unavoidable misleading or imprecise fused images.

Medical imaging has entered a revolutionized era since the introduction of **hybrid imaging**, utilizing a single “two in one” machine, like SPECT/CT or PET/CT, where functional data and structural information are acquired in a fast sequential mode, at the same clinical imaging setting, without having to change the position of the patient, thus alleviating the need for accurate repositioning of the patient, as was the case prior to integrating the two machines into one.

The introduction of SPECT/CT in 1998 was the first clinical expression of hybrid imaging. PET/CT then creeped into clinical practice in the year 2000 with increasing spread since then. This means that PET/CT has been clinical lyon board since more than a decade[(1)].

Corresponding author: Dr.Khairy, AT **Email:**atalaat51@hotmail.com

Initial Obstacles for PET/MRI Integration:

Thoughts about PET/MR integration existed at the same time as for SPECT/CT and PET/CT. However, the idea could not be realized at the same time, mainly because of the fact that the magnetic field of MRI distorts the function of photomultiplier tubes (PMTs), which constitute a fundamental component of the nuclear medicine detector systems. The PMT sensitivity to electromagnetic fields on one hand and the conducting and radiofrequency radiating components of PET scanners that interfere with the MRI system on the other hand, were the main initial obstacles towards successful integration of PET and MRI technologies[3].

Many attempts were made to overcome the above problems of PET and MRI interference. **Fiber-optic cables** were tried to transfer scintillation light from PET detector crystals inside the magnet to PMTs that reside outside the bore of the MRI scanner. This PET/MR system is known as “Light Fiber-Based PET/MR”. However, this method degraded the performance of PET scanners that was poor compared with that of stand-alone PET scanners, simply because signal transfer via the long fiber-optic cables is accompanied by some loss of light. Besides, the length of optical fibers made the system cumbersome [3].

Evolution of Magnet Insensitive PET Detectors:

Another design configuration, to make the coupling of PET and MRI successful and practical, was based on the use of detector technologies insensitive to magnetic fields. These included **avalanche photodiodes (APDs)**, which are semi-conductor based detectors, insensitive to magnetic field, that convert the light into electrons, but the output gain of these APDs-based PET/MR is less than that of the conventional photomultiplier tubes (PMTs)[4,5].

The evolution of magnetic field insensitive detectors then has lead to the replacement of APDs detectors by the **Silicon photomultipliers (Si PMs)**, which are fine 50 x 50 μ cells[4]. Such Si PMs have then been further advanced into Digital Si PMs. The Si PMs technology has prevailed and has been employed to push the PET/MRI technology into the domain of human research and thereafter into clinical settings, where whole body PET/MR machines have already stepped on the ground of clinical practice.

In 2011, the European Union and the U.S. Food and Drug administration (FDA) granted approval to the first two commercially available PET/MR systems: the Siemens Biograph mMR and the Philips Ingenuity TF[5].

PET/MRI Machines:

In contrast to PET/CT, data acquisition with the new hybrid PET/MR scanners provides the option of real “simultaneous” acquisition, rather than “sequential” data acquisition as for PET/CT scanners. The scan duration of concurrent PET/MR data acquisition is anticipated to be similar to, or slightly longer than, that of PET/CT sequential data acquisition, depending on the MRI pulse sequence used[6].

The PET/MR machines have been produced in two forms, the one designed by Philips, is in the form of “Side-by-Side PET/MR” with smart patient bed. This is alsotermed **“Field-Cycled PET/MR”** system[7], which includes two separate machines, the PET and the MRI, placed aside facing each other in a spacious room, obviously with Si PMs utilized within the PET detector system. The smart patient's bed transfers the patient from one machine to the other in a clever way, which is safe and fast enough to maintain patient's position unchanged. In effect this PET/MR design, like the PET/CT, results in sequential rather than simultaneous imaging [7].

The other form of PET/MR machines, introduced by Siemens, is a **"Two in One"**PET/MRsystem, where the PET detectors, including Si PMs, are inserted within the radio-frequencycoils (RF coils) of the MRI. This device looks like an MRI machine, but having within it PET inserts. This design allows for "simultaneous" data acquisition, which is a physical advantage.

Attenuation Correction:

The CT component of the PET/CT is well utilized for attenuation correction. Using MRI for the same purpose was not as simple or as effective. Researches were directed towards better utilization of MRI for correcting the attenuation effects of the PET emissions. One method is known as **Segmentation–based** attenuation correction, which uses different MRI slices for pattern recognition[8,9]. Another method is the **Atlas-based**method that requires database and the third, more preferable, method is the **Atlas/Pattern Recognition** method of attenuation correction, which combines both technologies, the atlas-based data and the estimate-based patient's data of pattern recognition, i.e. the segmentation method[7,9].

Clinical Impact:

PET/MR shall not replace PET/CT, just as MRI has not replaced CT. Similarly, PET/MR will not replace stand-alone MRI. The value of utilizing the new hybrid imaging modality, PET/MR, would actually be derived from highlighting the clinical areas where it should stand as the imaging tool of first choice.

The MRI has its known useful applications in assessing brain lesions and whenever detailed soft tissue resolution is needed, as in various musculoskeletal disorders. The PET component of PET/MR shall add metabolic information to the fine and detailed structural resolution provided by MRI in such cases[6]. This addition shall be positively counted if the management strategy would be affected.

In fact the indications of PET/MR and those of PET/CT are generally governed by the prime indications of the stand-alone CT and the stand-alone MRI, with the added gain of the metabolic information provided by the PET component. However, there are some gray clinical zones, particularly in oncology, where still there is a debate about whether CT or MRI, and hence PET/CT or PET/MR, should take the lead in imaging[8]. These areas would definitely attract the attention of many researchers.

After the introduction of PET/CT in 2000, most of research work focused on discovering its useful clinical applications on one hand, and comparing the PET/CT with the stand-alone PET and with the stand–alone CT scanner on the other hand. The upcoming research expectation for PET/MR however, is also expected to include PET/MR versus MRI comparisons, but would also be directed to explore and highlight the useful clinical indications of

PET/MR, and certainlyalso to compare PET/CT and PET/MR in some specific clinical problems. Like PET/CT the PET/MR shall be assessed in oncology, but is expected to expand more than PET/CT in non-oncologic applications.

The primary data and the future expectation of research directions predict that PET/MRshall be mainly assessed in oncology, particularly brain tumors, followed by neurology, psychiatry and cardiology.

Oncologic Applications:

PET/CT shall maintain superiority over PET/MR in lung tumors and solitary pulmonary nodules, simply because of the far more superior resolution of the lungs by advanced CT scanners than by MRI. Also, CT is superior to MRI in malignant lymph nodes' involvement, such as in lymphoma. Hence, PET/CT is expected to remain the leading imaging modality in these conditions[7].

On the other hand, PET/MR will most likely take the upper hand in neuroimaging in general, not only in **brain tumors** but also in other non-oncologic applications in neurology and psychiatry.

PET/MR is highly expected to be more preferable than PET/CT in some other tumors, such as those of the **breast**, **liver**, **prostate** and other solid **tumors of the pelvis**, such as gynecological malignancy [3,5].

Tumors where MRI is preferredmore than CT, and hence PET/MR than PET/CT, include **soft tissue sarcoma** and tumors of the **head and neck**.

There is a high expectation that PET/MR, when available, will become the hybrid imaging modality of choice in **pediatric oncology**, simply because PET/MR employs much less ionizing radiations than PET/CT [3,5].

The above expectations shall definitely be backed up by researches, and the PET/MR versus PET/CT comparison would not only be governed by clinical impact but certainly also by availability and cost-effectiveness.

The complementary rather than competitive attitude of CT and MRI should be utilized to its best contribution in certain tumors. For example the borders of a newly diagnosed soft tissue sarcoma might be difficult to perceive on CT. In such cases, a high quality MRI scan should be more useful to study the tumor itself and a PET/CT could be done to search for possible pulmonary, bone or other remote sites metastases[5]. This example throws a light on an important fact in medical imaging, which conveys that all three modalities, namely PET, CT and MRI, are much needed in practice as they do complement each other.

Non-oncologic applications:

PET/MR is expected to take the lead in **neuroimaging**, particularly in areas where the PET-derived metabolic information is a useful addition to the results of MRI alone, with useful contribution to the diagnosis and management of patients.

In **cardiology**, the future researches shall reveal whether or not PET/MRI will provide a useful addition in patients with coronary artery disease and other cardiac diseases, and how this compares to other imaging modalities, including SPECT, SPECT/CT, CT alone, PET/CT and MRI alone.

It is also possible that PET/MR may prove a useful contribution to other benign disorders, such as assessing the metabolic activity and the response to treatment of some **musculoskeletal** disorders [3].

SUMMARY:

The clinical birth of PET/MR occurred a decade later than that of PET/CT due to physical problems that hampered the integration of PET and MRI, but such problems have passed through different solutions until they were overcome and a useful PET/MR machine has been born in 2011.

Different designs were implemented for the PET/MR machines, but the MRI with PET inserts that allows for simultaneous data acquisition is expected to prevail.

In terms of attenuation correction, the combined utilization of patient's pattern recognition data and an atlas-based data seem to work well towards utilizing MRI to correct for the attenuation effects of PET emissions.

Regarding the clinical indications of PET/MR compared to PET/CT, it will begenerally governed by the prime CT and MRI indications. The PET is the common addition of metabolic information to either of them.

The clinical utility of PET/MR is expected to be mainly in oncology. The PET/MR applications in non-oncologic disorders may exceed those of PET/CT, and may involve new clinical zones as well. The near future may explore "unexpected" clinical areas with a useful potential for PET/MR. The future research shall likely also compare PET/MR with MRI on one hand and with PET/CT on the other hand.

On another note, there is no doubt that the clinical expansion of PET/CT and PET/MR shall stimulate the introduction of new PET tracers that would be more specific in particular clinical problems.

The PET/MR is still in its clinical infancy and is wide open for research in order to assign its place amongst other imaging modalities, particularly in relation to PET/CT hybrid imaging.

On the other hand, the ultra-high cost of PET/MR may slow down its expected rate of growth, and would likely expand slower than was the case for PET/CT. Therefore the availability and cost effectiveness shall influence, but definitely will not prevent, the future growth of this newborn baby of hybrid imaging.

The added functional information provided by PET on one hand and the complementary advantages of CT and MRI on the other hand, impose the utilization of the three devices in practice. For instance, PET/CT is used to stage soft tissue sarcoma, but loco-regional MRI is often needed for assessing the primary tumor, because MRI provides better border definitions and resolution than CT, which is needed prior to planning for local resection and/or radiotherapy. Therefore, I might not be dreaming when I expect a future merge of the three modalities into one machine, something like PET/CT/MR. This is, in a way, like putting all eggs in one basket, but no worry as similar individual eggs are always around.

Although this three-in-one dream sounds unrealistic at present, yet the world of science and medicine hastaught us that the dreams of today become the reality of tomorrow, as long as scientific manpowerdo not give up, and the rule of thumb tells us they will never do. One example of the obstinacy of scientists is the struggle met over the past decade that ended up bytheclinical birth of PET/MR, the beautiful baby of hybrid imaging.

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