MINI-REVIEW

Hybrid Imaging in Oncology

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Abstract

In oncology various imaging modalities play a crucial role in diagnosis, staging, restaging, treatment monitoring and follow up of various cancers. Stand-alone morphological imaging like computerized tomography (CT) and magnetic resonance imaging (MRI) provide a high magnitude of anatomical details about the tumor but are relatively dumb about tumor physiology. Stand-alone functional imaging like positron emission tomography (PET) and single photon emission tomography (SPECT) are rich in functional information but provide little insight into tumor morphology. Introduction of first hybrid modality PET/CT is the one of the most successful stories of current century which has revolutionized patient care in oncology due to its high diagnostic accuracy. Spurred on by this success, more hybrid imaging modalities like SPECT/CT and PET/MR were introduced. It is the time to explore the potential applications of the existing hybrid modalities, developing and implementing standardized imaging protocols and train users in nuclear medicine and radiology. In this review we discuss three existing hybrid modalities with emphasis on their technical aspects and clinical applications in oncology.

Keywords: Hybrid imaging - PET/CT - PET/MR - PET/SPECT - anatomometabolic aspects

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Introduction

Over the last 100 years myriads of imaging methods have been introduced which have made diagnosis and follow up possible in a non-invasive way. We are cognizant of the fact that disease originates from physical distress as well as from alterations at molecular and functional levels. Anatomical imaging methods often needs gross structural changes caused by the disease to be apparent before the diagnosis is definitive. The reliance on anatomical information for diagnosis also makes it difficult to monitor the response of diseased and normal tissues in the critical post-therapy period (Castellino et al., 1996). While nuclear medicine imaging methods do provide invaluable information about the functional, metabolic, and molecular status of tissues but with well-known recognized limitations in spatial resolution and statistical quality of images (Jaszczak et al., 1980). Importance of combined structural and functional imaging has been well recognized by medical community and best illustrated by the term "anatometabolic imaging" introduced about two decades back (Wahl et al., 1993). As a matter of fact physicians were aware of usefulness of combining morphological and functional imaging as early as 1960 (Wagner 2005). Earlier, side-by-side comparison or software co-registration methodologies were used but suffered from various technical limitations related to the non-identical geometries of the imaging devices, variability in the positioning of patients and different placement of mobile structures between studies (Hutton et al., 2002; Papathanassiou and Liehn 2008). The development of the first hybrid positron emission tomography (PET) and computed tomography (CT) device struck a chord with the medical imaging community that is still ringing loudly throughout the world. This was followed by unveiling of hybrid single photon emission computed tomography and computed tomogram (SPECT/CT) and recent arrival of positron emission tomography and magnetic resonance imaging (PET/MRI). The primary reasons for warm acceptability of dual modality hybrid imaging are the provision of high magnitude of information from single examination, high diagnostic accuracy and better liaison between diagnosticians (Townsend 2008). Oncology is the major arena of the dual modality hybrid imaging where it is being extensively and effectively used for staging, restaging, response evaluation and follow up of various cancers.

In this review we would discuss three existing hybrid modalities with emphasis on their technical aspects and clinical applications in oncology.

SPECT/CT

In 1996, Blankespoor and co-workers unveiled a

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combined SPECT/CT having a clinical SPECT camera and clinical single slice CT arranged in a tandem (Blankespoor et al., 1996). They acquired CT images first followed by SPECT images and then resultant anatomical and functional images were co-registered. They also used CT data to generate attenuation correction map for SPECT images. In SPECT imaging attenuation correction is more advantageous than PET because the SPECT attenuation correction factors primarily depend on (unknown) depths in tissue of the detected photons (Beyer et al., 2011). The first generation commercially available SPECT/CT system (with low power CT) was introduced in 1999 but CT was of suboptimal diagnostic quality and added significantly to the total acquisition time of a routine SPECT study. However, various studies with these early systems did show utility of co-registration of low resolution anatomical images with SPECT with better interpretation (Buck et al., 2008). In 2004 and onward various vendors have introduced combined SPECT with high powered clinical CT (2 to 16 or even 64 slices) able to acquire high resolution CT images in short time but with higher radiation exposure. SPECT/CT has shown significant expansion over the last few years and as of June 2007 there were approximately 600 SPECT/CT installations worldwide (over 200 in USA only) [www-pub.iaea.org/MTCD/publications/PDF/te_1597_web.pdf).

Clinical Applications of SPECT/CT

Since its commercial introduction in 2004, SPECT/CT has been rapidly adopted for oncology and cardiology as 21 million SPECT studies were done as compared with 1.5 million PET and PET/CT in USA in 2006 (Beyer et al., 2011). In oncology SPECT imaging is equipped with a much wider range of clinically useful labeled biomarkers than clinical PET, which, today, is limited mainly to 18Fluorodeoxyglucose (^{18}FDG) for glucose utilization.

Skeletal scintigraphy is the most commonly used modality for skeletal survey for staging and restaging of various cancers. However, its limited specificity poses problem in case of solitary enhanced uptake as it could be secondary to trauma or infection rather than neoplastic process. Although SPECT-only does help in this respect but combined SPECT/CT significantly improves diagnostic accuracy by differentiating among trauma, infection and tumor at expense of additional acquisition time and radiation exposure (Figure 1) (Bockisch et al., 2008).

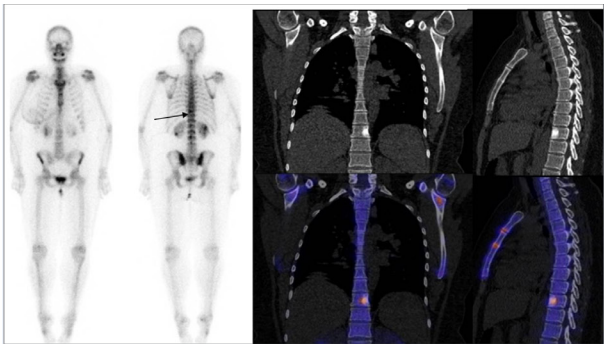

Figure 1. 38 Year Old Woman with Right Breast Cancer with Recent Onset of Back Pain. (A) 99mTc-MDP Bone scan shows a focal area of increased uptake at T10 vertebra on the left side (arrow) which is equivocal for bone metastasis. **(B)** CT scan shows a sclerotic lesion at T10 vertebra. **(C)** On the fused SPECT/CT the increased tracer uptake corresponds to the sclerotic lesion metastasis. SPECT/CT was helpful in confirming the equivocal/indeterminate tracer uptake as definitive bone metastasis

Radioiodine scintigraphy when combined with SPECT/CT has become a powerful diagnostic tool for identification of regional and distant metastases in patients with well differentiated thyroid cancers. The synergistic combination of functional and anatomic information provided by SPECT/CT has substantially improved the interpretation of classic radioiodine scintigraphy. Radioiodine SPECT/CT contributes to completion of staging for patients with well differentiated thyroid cancer by better characterization of nodal and distant metastases (Thamnirat et al., 2015). However, SPECT/CT has limitation of spatial resolution for smaller lesions due to partial volume effect (PVE), insensitivity for detection of locally aggressive residual disease (Avram, 2012) and false negative results in iodine non-avid disease which is seen in about 30% (Mian et al., 2008). SPECT/CT has changed the field and demands revisit of current management guidelines in thyroid cancers.

In neural crest tumors like pheochromocytoma, paraganglioma, neuroblastoma and ganglioblastoma, 123I/131I MetaIodo Benzyl Guanithidine (MIBG) scintigraphy is useful for localizing the primary tumors and to monitor the pattern of metastatic spread (with an overall 92% sensitivity and 96% specificity) and response to treatment (Rufini et al., 2006). However, combined SPECT/CT images have further improved the diagnostic accuracy, especially in patients with inconclusive planar or SPECT-only imaging with respect to the precise anatomic localization of the lesions. Furthermore, hybrid imaging also helps to characterize tumor recurrence in close vicinity of organs with high physiological MIBG uptake like heart and liver. Similarly in pediatric patients SPECT/CT may help to elucidate the physiologic tracer uptake in the right ventricle sometimes misinterpreted as malignant mediastinal or bony (sternal or vertebral) involvement by tumor (Keidar et al., 2003).

Sentinel node biopsy in breast cancer with clinically negative axilla is considered as a standard of care. Various studies have shown superiority of SPECT/CT over planar imaging by improving false negative rate, minimizing the false positive rate and precise localization of hot nodes per-operatively (Even-Sapir et al., 2003; Lerman et al., 2006; Amoui et al., 2012). SPECT/CT is particularly of high importance in obese and overweight patients who are prone to have higher false negative rate and increased odds of lymphedema after an unjustified axillary nodal dissection (Lerman et al., 2007).

In carcinoma of prostate, 111Indium-Capromab (ProstaScint®) is considered as a reliable tool for detection of local or nodal recurrence but suboptimal quality of planar and SPECT only images has considerably limited its widespread use (Petronis et al., 1998). However, use of SPECT/CT in ProstaScint® imaging has shown remarkable

advancement with clinical implications for diagnosis, treatment planning, and prognosis (Sodee et al., 2007). In addition, ^{18}FDG PET/CT has significantly diagnostic accuracy for detecting primary tumor in cases with metastatic cancer of unknown origin (Kaya et al., 2008).

PET/CT

Currently PET/CT is considered as the standard of care in oncology due to provision of high magnitude of anatomical and metabolic information about tumor which increases the diagnostic accuracy and helps the oncologists to tailor the chemotherapy and planning the radiation treatment. The concept of PET/CT was produced in 1990 by Townsend and co-workers and first prototype was operational in 1998. Although this concept was first proposed by researchers at Gunma University Japan in 1984 but was not publicized (Beyer et al., 2011). The first commercial PET/CT was unveiled in 2001 followed by presentation from major vendors and currently about six vendors offer more than 20 different designs of PET/CT (sequential but integrated system with CT in front of PET scanner on the same gantry) (Sodee et al., 2007).

PET is an in-vivo three-dimensional (3D) imaging technique, swapping physical collimation required for SPECT imaging with the electronic collimation of coincidence detection of PET isotopes. The diagnostic accuracy of PET depends upon sensitivity and spatial resolution. Sensitivity has been improved by using fast scintillators with high stopping power like LSO ((lutetium oxyorthosilicate), LYSO (Cerium-doped Lutetium Yttrium Orthosilicate) and GSO (gadolinium silicate) with short coincidence time window (4.5-6 nanosecond) compared with traditional BGO (Bismuth germinate) with longer time window (Watson et al., 2005). Sensitivity has also been improved by increasing the axial length of the tomograph from 16 cm to 22 cm. Similarly spatial resolution has also been improved by using smaller detectors (≈4 x 4 mm) although it has resulted in increased cost of the system. Time of flight (TOF) mode has also improved signal to noise ratio with significantly improved image quality especially in obese patients with lower injected radiotracer dose and better dosimetry. Iterative reconstruction technique (OSEM= Ordered Subset Expectation Maximization) for PET and CT images has essentially replaced analytical filtered back projection (FBP) with improved image quality and lower radiation exposure as well (Flohr et al., 2010).

Recently a vendor has introduced the first digital PET/CT system using silicon digital photomultiplier detectors instead of traditional analog detectors which has doubled the sensitivity gain, volumetric resolution and quantitative accuracy compared to analog systems (http://www.healthcare.philips.com/us_en/clinicalspecialities/Radiology/Solutions/vereos.htm).

Clinical Applications of PET/CT

Robust development in PET/CT technology and introduction of various PET tracers over the last few years has established its accuracy in diagnosis, staging and restaging of various cancers. PET/CT has ability to precisely identify the tumor, thus helping the surgeons to perform a targeted surgery with minimal morbidity. Studies have shown that accuracy of PET/CT has changed staging and restaging in 10-15% of various cancers compared with PET or CT alone (Czernin et al., 2007) and treatment plans are obviously changed in such scenarios. The list includes cancer of head and neck, thyroid, lung, breast, oesophageal, colorectal, lymphoma, sarcoma, gastrointestinal stroma tumour (GIST), carcinoma of unknown primary (CUP), and melanoma (Figure 2). Alteration in management of cancer driven by PET/CT has a positive impact by avoiding unjustified surgeries, associated morbidities and cost savings too.

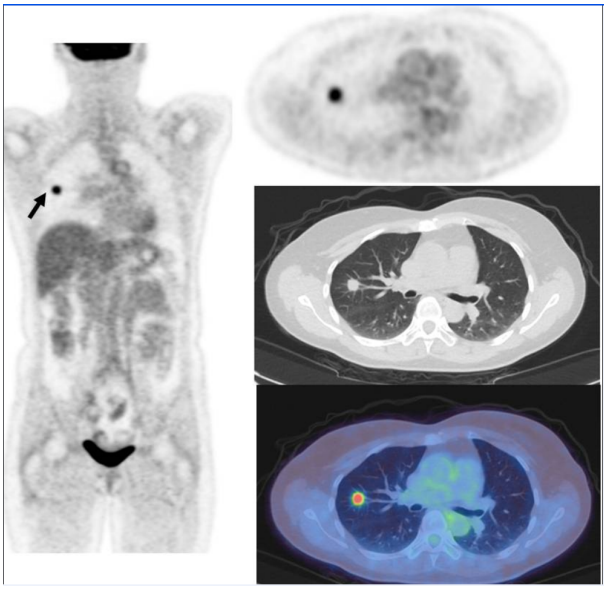

Figure 2. Solitary Pulmonary Nodule: 55 Year Old Woman with a Right Upper Lobe Nodule on CT. PET scan for further assessment. 18F-FDG PET-CT scan: There is increased FDG uptake in the right upper lobe nodule (maximum SUV 7.6) [arrow]. The scan appearances are suggestive of a malignant lesion in the right lung

In current era, role PET/CT from staging and restaging has been shifted to early assessment of treatment response. Studies have proven that most of the drugs used in modern cancer treatment are effective in less than 60% of patients (Aspinall and Hamermesh 2007). Furthermore, the behavior of tumor deposits can be different from primary tumor or response of same cancer may be different among different patients (Ben-Haim and Ell 2009). PET/CT (using ^{18}FDG primarily and few newer radio-probes as well) has ability to identify a responder from non-responder early in the treatment path. PET/CT has introduced disease-modifying approaches which stop the use of ineffective drugs, thereby achieving relevant cost savings, and to select alternative therapies.

Albeit standalone PET has been confirmed as a good and effective modality for the early diagnosis of cancer recurrence, hybrid PET/CT appears to be the better tool for the estimation of tumor extent. Better detection rate of recurrent tumor has potential to demonstrate presence and extent of disease which guides to minimize further morbidity and expenses associated with superfluous

radical treatment (Strauss and Conti 1991). Reports have also shown superiority of ^{18}FDG PET/CT for detecting bone metastases than conventional bone scan or standalone CT or PET (Liu et al., 2013).

PET/MRI

The idea of PET/MRI was conceptualized by Simon Cherry and Paul Marsden in mid-1990s even before PET/CT was introduced. While performing preclinical hybrid imaging they felt to combine high soft tissue contrast MRI images with molecular information derived by PET (Shao et al., 1997). Currently three PET/MRI systems have been launched by 3 major vendors, 2 with sequential and 1 with simultaneous acquisition of PET and MRI images. According to placement of PET and MRI scanners, these can be broadly classified as tandem and integrated configuration. In tandem configuration PET and MRI data are acquired sequentially one after other by two separate scanners mounted in a same or two separate rooms. Philips Healthcare's commercially available PET/MRI (IngenuityTF PET/MRI) consists of two scanners placed in the same room about 2.5 meters apart with imaging turntable in between to allow the patient to be moved from one scanner to other without getting off the table (Pichler et al., 2010) (Figure 3a). GE Healthcare has chosen the "trimodality solution", comprising a top PET/CT scanner, allowing measured attenuation correction, and MRI systems in two adjacent imaging rooms with the patient transported from one scanner to the other using a dockable table operating as a shuttle (Mansi et al., 2012) (Figure 3b). The advantages of the tandem configuration are cost effectiveness as only additional magnetic shielding is required for MR without major modification in PET electronics and use of a sharing bed. Other advantages include lack of claustrophobia due to space between two system and simplicity of image co-registration. The major drawbacks of the tandem configuration with sequential acquisition are organ motion effects which reduces the precision of quantification, lack of correlation between functional PET and fMRI (particularly in brain studies) and requirement of larger room space (Zaman et al., 2014).

In integrated configuration two modalities are deployed in a single instrument and hence sequential imaging can be acquired. However, this configuration has many technical challenges as high magnetic field prevents the normal functioning of photomultiplier tubes (PMTs), interfering front-end electronics of PET and also presence of PET detectors may cause inhomogeneity in magnetic fields (Figure 3c). After preclinical prototypes and clinical PET/MR for brain only, recently a whole body PET/MRI has been introduced by a vendor (Biograph mMR, Siemens) which can acquire PET and MRI (3 Tesla) simultaneously as PET detector is placed between body and gradients coils of MRI. As a major modification step, PMTs have been replaced with Avalanche Photodiodes (APDs) coupled with lutetium oxyorthosilicate (LSO). These PET blocks are well shielded to virtually eliminate magnetic field interference in the PET data processing chain and also has integrated cooling feature (water-cooled) (Delso et al., 2011). The major advantages of this whole body PET/MRI configuration are simultaneous acquisition of PET and MRI which ensures precise alignment, minimal motion artifacts, precise spatial registration and shorter acquisition time. Furthermore, it is cost effective as one room is required for two systems, one cooling system, one operator and increase patients' throughput. However, limited temporal resolution of APD based system makes it incompatible with time of flight (TOF) technique which

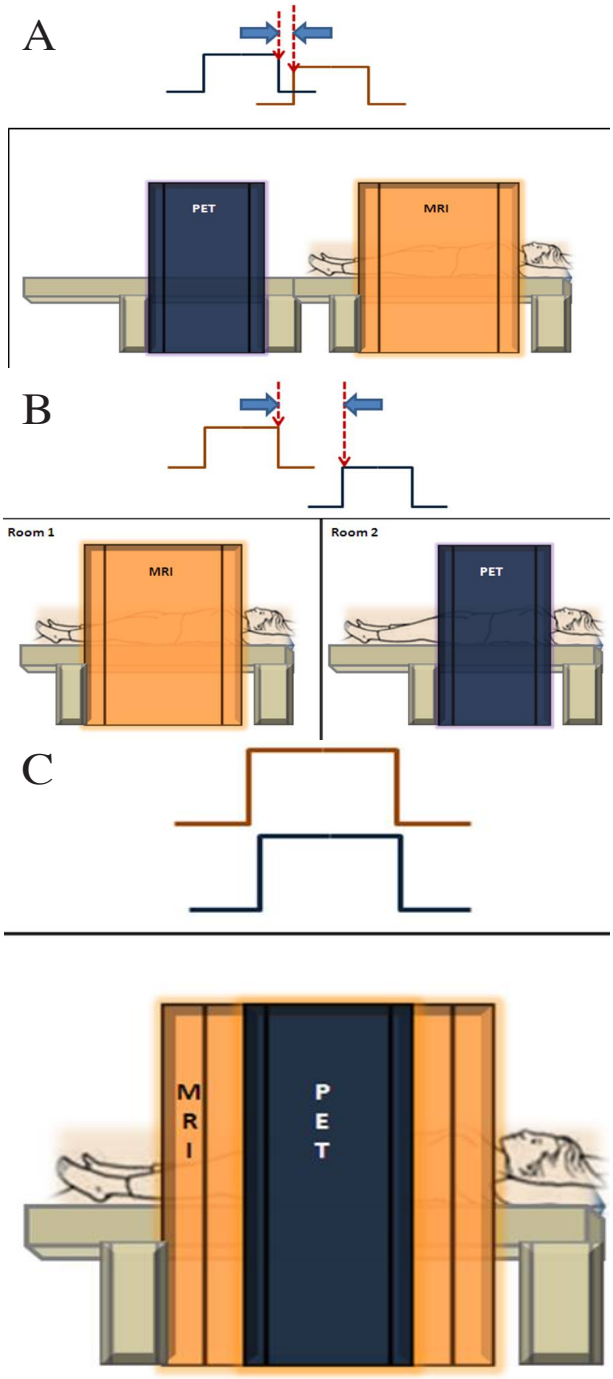

Figure 3. A) Tandem Configuration with Sequential PET and MRI Imaging with Scanners Placed in Same Room with a Common Imaging Bed. B) Tandem Configuration with Sequential PET and MRI Imaging with Scanners Placed in Different Rooms with a Dockable Common Bed. C) Integrated Configuration with Simultaneous PET/MRI Imaging with PET Fitted within MRI (One Room, One Scanner, One Imaging)

ensures better signal to noise ratio in PET/CT (Fontaine et al., 2009). A study performed on whole body Biograph mMR (Siemens) has shown negligible interference of PET on MRI (Buck et al., 2008). The Biograph mMR has received approval from US Food and Drug Administration (FDA) and European Union too in 2011 (Mansi et al., 2012). Only the simultaneous acquisition may allow the so-called 3rd eye vision, in which the fusion of functional PET data with either morphostructural or functional MR data can mirror the real-time correspondence of MR and PET signals (Pichler et al., 2010) and has made it commercially viable in the existing PET/CT dominated diagnostic arena. However, important limitations of PET/MRI are cost, longer acquisition time, loss of MRI signal by metallic implants or pacemaker resulting in underestimation of tracer uptake and reduced sensitivity for lung lesions (Pace et al., 2013).

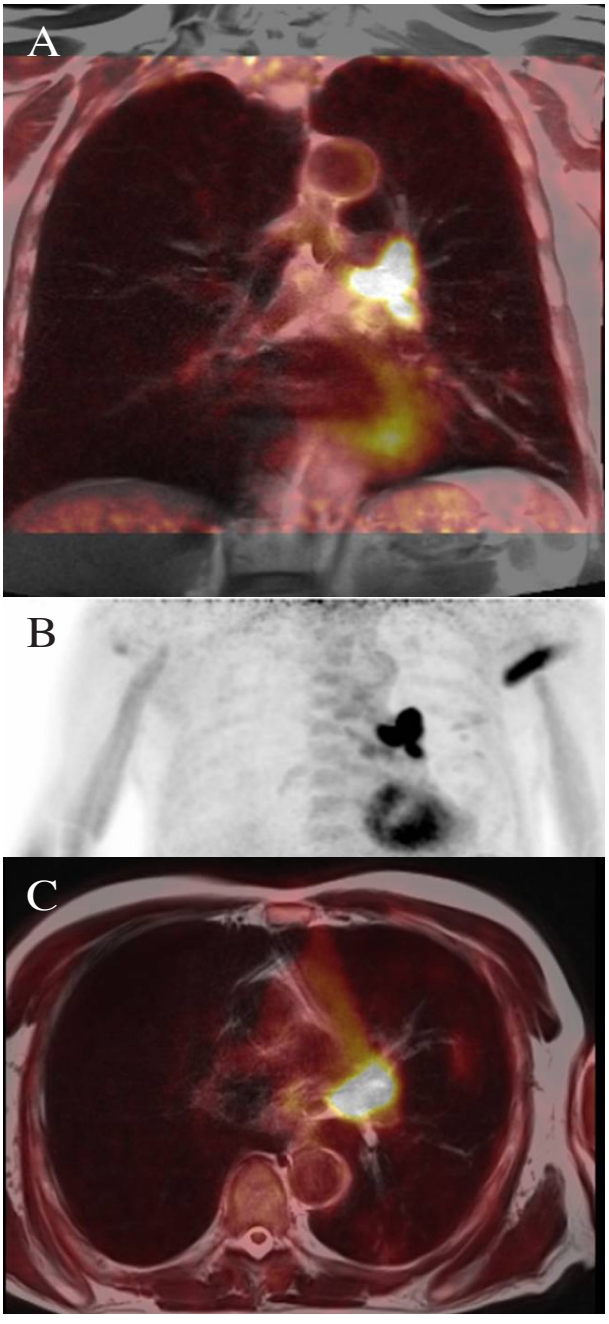

Figure 4. A) Coronal Image with Fusion between T2-Weighted MRI and PET Showing Central Bronchial Carcinoma Infiltrating the Left Hilum; B) PET Image Showing a Maximal Intensity Projection (MIP) of an Entire Bed Position with a 18F-FDG Uptake by Left Central Bronchial Carcinoma; (C) Axial Image with a Fusion between T2-weighted BLADE Image and 18F-FDG PET Showing the Same Tumor *(Images Provided by Dr Felix Nensa, University Hospital Essen, Germany)*

Clinical Applications of PET/MRI

Currently PET/CT using ^{18}FDG (and other probes as well) has been considered as standard of care in staging various cancers. However, due to superior soft tissue contrast of MRI, whole body PET/MRI can be anticipated a better alternative in breast, brain, head and neck, liver and musculoskeletal cancers. In addition, MR spectroscopy and fMRI (perfusion, BOLD effect, diffusion imaging) provide humongous information which further enhances the diagnostic and quantitative strength and precision of PET (Fontaine et al., 2009). Therefore this new hybrid imaging has potential to improve patient management and understanding of tumor biology as compared to PET/CT with significantly lower radiation exposure (Figure 4). Various comparative studies have shown better sensitivity and specificity of PET/MRI than PET/CT in breast cancer, hepatoma, colorectal cancers and soft tissue sarcomas (Tateishi et al., 2009; Moy et al., 2010; Park et al., 2010; Mainenti et al., 2011). So far low sensitivity of PET/MRI for lung lesions is considered a limitation but certain sequences (single-shot, turbo spin echo) and diffusion weighted imaging has shown to improve detection of pulmonary metastases (Liu et al., 2011). Similarly using fMRI (diffusion weighted imaging), detection rate of metastases in normal-sized lymph nodes increased from 7% to76% (Vandecaveye et al., 200). In lymphomas (Hodgkin and non-Hodgkin types) ^{18}FDG PET/CT shows a high diagnostic accuracy in staging and response evaluation. However, in younger and pediatric population, ^{18}FDG PET/MRI could be an alternative option by avoiding radiation exposure although no published data are available so far (Fontaine et al., 2009). PET/CT has limited sensitivity for detection of diffuse infiltration of bone marrow and PET/MRI is considered as procedure of choice (Schmidt et al., 2007).

Morphological criteria have usually been used for assessment of therapy response and tumor recurrence by different criteria with its limited accuracy. Therefore, PET/CT has become the major tool in this arena for various solid tumors including lymphomas. With the advent of PET/MRI (with fMRI and spectroscopy) various clinical studies have been published showing that mid-treatment diffusion weighted imaging could be used as a biomarker for response. Various recently published trials with head to head comparison of PET/CT and PET/MRI (with fMRI) have shown promising results in cancers of head and neck, breast, liver, colorectal and lymphomas (Fontaine et al., 2009). Interestingly in younger patients with lymphoma, PET/MRI has good accuracy in differentiating recurrence from thymic rebound using chemical shift (fMRI) and

markedly low radiation exposure in pediatric and younger population (Inaoka et al., 2007).

Since the introduction of PET/MRI there has been a debate whether it would replace PET/CT as later has replaced standalone PET. PET/MRI has potential to repeat the success of PET/CT due to better soft tissue contrast (in soft tissue tumors), fMRI and significantly low radiation exposure. However, PET/MRI has limitations of humongous cost, longer acquisition time affecting patients' throughput, underestimation due to metallic implants and lower sensitivity in certain anatomical districts like lungs. These limitations need to be addressed before considering it a replacement of PET/CT. Hence on the basis of existing evidence we can anticipate that PET/MRI will probably not replace PET/CT in all cases but rather be used as complimentary imaging option in some clinical conditions but preferred hybrid modality in other indications, especially in pediatric and younger population.

PET/CT is one of the most successful stories in imaging world which has paved the path for SPECT/CT and PET/MR and potentially more in future. The hybrid imaging has revolutionized patients' care in oncology due to its proven diagnostic accuracy. It is the time to explore the potential applications of the existing hybrid modalities, developing and implementing standardized imaging protocols and train users in nuclear medicine and radiology.

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