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Multimodality imaging techniques

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In multimodality imaging, the need to combine morphofunctional information can be approached by either acquiring images at different times (asynchronous), and fused them through digital image manipulation techniques or simultaneously acquiring images (synchronous) and merging them automatically. The asynchronous post-processing solution presents various constraints, mainly conditioned by the different positioning of the patient in the two scans acquired at different times in separated machines. The best solution to achieve consistency in time and space is obtained by the synchronous image acquisition. There are many multimodal technologies in molecular imaging. In this review we will focus on those multimodality image techniques more commonly used in the field of diagnostic imaging (SPECT-CT, PET-CT) and new developments (as PET-MR). The technological innovations and development of new tracers and smart probes are the main key points that will condition multimodality image and diagnostic imaging professionals' future. Although SPECT-CT and PET-CT are standard in most clinical scenarios, MR imaging has some advantages, providing excellent soft-tissue contrast and multidimensional functional, structural and morphological information. The next frontier is to develop efficient detectors and electronics systems capable of detecting two modality signals at the same time. Not only PET-MR but also MR-US or optic-PET will be introduced in clinical scenarios. Even more, MR diffusion-weighted, pharmacokinetic imaging, spectroscopy or functional BOLD imaging will merge with PET tracers to further increase molecular imaging as a relevant medical discipline. Multimodality imaging techniques will play a leading role in relevant clinical applications. The development of new diagnostic imaging research areas, mainly in the field of oncology, cardiology and neuropsychiatry, will impact the way medicine is performed today. Both clinical and experimental multimodality studies, in humans and animals, will have to demonstrate an efficient use of the imaging information provided by the modalities to affect the future of medical imaging.

Keywords: PET-CT; PET-MR; multimodality imaging; molecular imaging

1. INTRODUCTION

Physicist Allan Cormack (1) developed the concept that scanning an object from many angles allows extraction of the information contained in it, although studies were not carried into practice owing to the limitations of computers of that era. The origins of multimodality tomography in the field of diagnostic imaging date back to 1966 with the first prototype of CT-SPECT that obtained thoracic images of a patient (2). Despite its closely related origin, the development of both functional (SPECT and PET) and morphological tomographic images (CT and MRI) was carried out independently. Godfrey Hounsfield is undoubtedly the central figure in the development of the CT as he developed a prototype and built the first CT for clinical use (3). Few medical discoveries have received such an immediate and enthusiastic acceptance. Hounsfield and Cormack shared the Nobel Prize in Medicine in 1979.

In the 1990s, the need to combine morphologic and functional information began to be seriously considered. To address this problem, two approaches were taken (4): either images acquired at different times were fused through digital image manipulation techniques or the simultaneously acquired images merged automatically.

The asynchronous post-processing solution presents various constraints, mainly conditioned by the different positioning of the patient in the two scans acquired at different times in separated machines. The problem of positioning concordance was addressed either by placing external markers on the patient or by identifying the same internal structures in both examinations. Merging images using software was largely accepted in neurological studies because of the rigidity of the intracranial structures. Unfortunately, coregistration is less accurate in body examinations because of movement (5).

The best solution to achieve consistency in time and space was carried out by synchronous acquisition of images (6). The pioneering work of Hasegawa *et al*. in 1990 (7), building a device that simultaneously detected photons (SPECT) and X-rays (CT), paved the way for hybridization.

Since the commercial introduction of SPECT-CT and PET-CT (1998), the use of this equipment has grown exponentially. The simultaneous acquisition of images obviates the need for complex post-processing transformations to ensure proper

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alignment. In these multimodal systems, the main limitation is still related to the movement of internal organs that sometimes originates misregistration errors in the fused images. The problem of breathing related positional misregistration can be solved using synchronized acquisition systems.

These devices are usually called hybrid techniques, but the term multimodal exploration seems to be more appropriate (8). The most efficient use of information provided by multimodality image will certainly affect the future of the two medical imaging specialties (nuclear medicine and radiology). Although there are many multimodal technologies in the era of molecular imaging (9–11), in this review we will focus on those multimodality image techniques more commonly used in the field of diagnostic imaging.

2. SPECT-CT

The first SPECT-CT commercial prototype was developed by Hasegawa and colleagues at the University of San Francisco (California) (7) and sponsored by General Electric (GE Healthcare, 'Infinia Hawkeye'). It consisted of a conventional dual-head and variable geometry gamma camera coupled in a single case (gantry) to an X-ray source of 140 kV and 2.5 mA with a sliding ring detector (12). This prototype has evolved over time to the current GE Infinia Hawkeye-4 using a CT which operates at 120–140 kV and consists of a low-output X-ray tube (2.5 mA). Typical radiation doses are $<$5 mGy (500 mrad) (13). Also Siemens (Symbia) and Philips (Precedence) have made available to the market SPECT-CT scanners with CT components that in addition to performing attenuation correction and lesion location, have diagnostic quality (14,15). The Symbia is available in 1, 2, 6 and 16 slice CT options with variable tube currents (20–345 mA). The Precedence, with a dual-head Skylight manufactured by Philips Medical Systems, is available in 16 and 40 slice CT options with variable tube currents (20–500 mA). Radiation doses from these systems are in the order of 20 mGy (2 rad) when the techniques are used for diagnostic quality image production (13). The implementation of 64-slice CT allowed, as discussed below, to carry out cardiac SPECT-CT studies with an excellent morphofunctional quality.

On the other hand, current scintillation detector gamma cameras will surely experience an improvement with the use of new semiconductor detector materials that will overcome the spatial and energetic resolution while simultaneously detecting the radiopharmaceutical photons and X-rays (14,15).

In 2009, Philips Healthcare and GE Healthcare introduced two new SPECT/CT. GE Healthcare announced the European launch of Discovery NM/CT 670, a hybrid imaging platform designed to improve workflow, dose management and overall image quality, during the EANM'09 Annual Congress of the European Association of Nuclear Medicine, held in Barcelona, Spain. The system combines GE Healthcare's BrightSpeed Elite 16-slice CT, a newly designed SPECT gantry for greater positional flexibility, and the latest advancements in Nuclear Medicine detectors. Keeping the patient in mind, the system is said to be able to shorten scan time dramatically. This reduction in time reduces patient movement due to pain or uncomfortable positioning, minimizing artifacts in the scan. The Discovery NM/CT 670 is 510(k) pending at FDA.

At the RSNA 2009 annual meeting in Chicago, Philips Healthcare featured the new BrightView XCT. Joining SPECT and CT in innovative ways, the new BrightView XCT uniquely integrates Philips BrightView SPECT in a co-planar design with advanced Philips flat detector X-ray CT technology to take full advantage of both SPECT and CT without compromising either. Flat panel X-ray detector is used for the purpose of anatomic localization and attenuation correction. The high resolution of the flat panel allows for true isotropic voxels and provides high-quality images when viewed at any angle. Co-planar SPECT and CT capabilities eliminate the need to index the bed between the two acquisitions for many studies, providing greater confidence in image registration. BrightView XCT uses Astonish image reconstruction technology. This provides 50% better spatial resolution in bone and cardiac SPECT studies compared to SPECT studies using filtered back projection.

The current clinical applications of SPECT-CT are multiple, and some of them will be commented on here.

2.1. Endocrinology

The main indications are the detection, typification and staging of neuroendocrine tumors and differentiated thyroid carcinoma and the evaluation of primary hyperparathyroidism (Fig. 1).

Scintigraphic examination of neural crest tumors (pheochromocytoma, neuroblastoma) is performed with metaiodobenzylguanidine (MIBG) labeled with ^{123}I or ^{131}I, a molecule similar to catecholamines focusing on storage granules in adrenergic nerves (16). Although initial diagnostic techniques for detection of these tumors are CT and/or MRI (17), indications of MIBG are misleading mass characterization, detection of extraadrenal involvement and objectification of relapses (18,19).

In gastroenteropancreatic tumors, scintigraphic examination uses ^{123}I-pentreteotide as radiopharmaceutical in tumor cells that express the highest density of somatostatin receptors (SSR). Its main indications are preoperative staging, recurrence detection and, when medical treatment is chosen, qualitative determination of the number of receptors as a prognostic therapeutic response factor (20). Carcinoid metastases may be heterogeneous for SSR, some being positive and some negative even in the same patient. When these tumors become more undifferentiated, they may lose their SSR expression and become ^{18}F-FDG positive. PET-CT should be reserved for patients who have negative SSR scintigraphy or additional lesions on CT or MRI that are not SSR avid (21). In the study of neuroendocrine tumors, SPECT-CT scanners contribute to eliminate the uncertainty of physiological accumulation of the radiopharmaceutical (source of false positive) and facilitate correct anatomical location of the findings (22,23).

In differentiated thyroid cancer, ^{131}I plays a dual diagnosis-treatment key role. After surgery, the administration of a therapeutic dose of ^{131}I removes residual thyroid, whereas in patient monitoring, scan with ^{131}I, US and thyroglobulin determination are used to evaluate recurrence. The use of SPECT-CT scans allows an accurate location of ^{131}I deposits, increasing the specificity of the technique by correcting errors resulting from the physiological elimination of the radiopharmaceutical (24).

In suspected parathyroid adenomas, the combination of ^{99}mTc-MIBI scintigraphy and US give the best results. SPECT-CT will be useful in locating ectopic parathyroid adenomas and in patients with distorted post-surgical neck anatomy (25).

2.2. Infection

CT and MR allow the location and define the extension of most infectious processes. In discordant cases, ^{67}Ga Citrate and labeled-white blood cell (WBC) SPECT-CT can be used for disease localization (26).

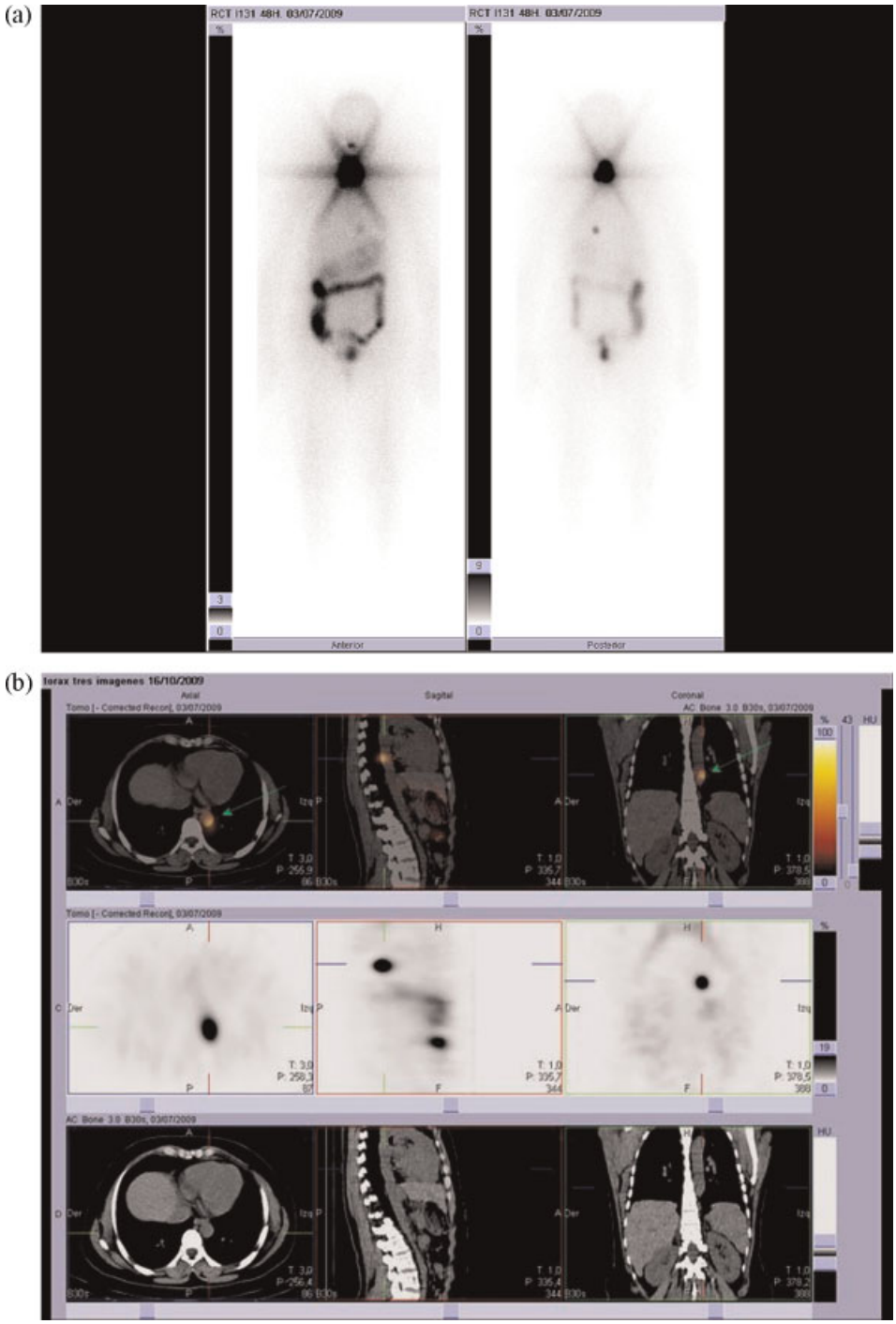

Figure 1. SPECT-CT in a patient with total thyroidectomy for differentiated thyroid carcinoma after ^{131}I ablative treatment. (A) The post-treatment SPECT scan shows a chest focus uptake. (B) The focus is localized by SPECT-CT in the left hemithorax, near the thoracic aorta (pulmonary nodule with a positive uptake of radioiodine). Courtesy of Virgen de las Nieves Hospital, Granada.

SPECT-CT with ^{111}In- or ^{99}Tc-HMPAO-WBC in patients with inflammatory bowel disease has been also employed to confirm the diagnosis in patients with high clinical suspicion but incongruent imaging results and to evaluate the extent of the disease (27).

2.3. Musculoskeletal imaging

Bone scintigraphy is one of the most common investigations performed in nuclear medicine. Bone scan has high sensitivity, but specificity is frequently limited. SPECT/CT provides accurate localization and characterization of equivocal lesions seen on the bone scan, improving therefore the specificity over the planar imaging and the SPECT alone (28,29).

In patients with known or suspected cancer, fused images allows the precise localization of abnormal radiotracer uptake and facilitates the differentiation of benign degenerative process from metastatic foci. Spinal abnormalities involving the vertebral body or the pedicle alone are more likely to represent malignant

disease compared with abnormalities confined to the periphery of the body or facet joint (30–32). Although the majority of bone metastases appear as hot spots, some appear as cold lesions. Photon-deficient areas are due to metallic objects, such as jewellery, pacemakers, coins, belts, breast prosthesis and benign bone lesions, such as haemangioma. On the other hand, aggressive or purely lytic metastases may not generate a visible osteoblastic response and appear as a purely cold lesion difficult to identify on a routine whole-body bone scan. The differentiation between benign and malignant lesions can usually be achieved by SPECT/CT (33).

Even-Sapir *et al.* (34) reported that SPECT/CT allows a definite diagnosis for the majority of indeterminate scintigraphic findings in nononcologic situations. Scintigraphic activity correlates with the symptoms of degenerative joint disease (35) and serves as a strong negative predictive value for the progression of joint degeneration (36). SPECT-CT is useful in localizing active arthritis, especially in areas where the number and configuration of joints are complex (37). In patients with back pain the SPECT/CT allows differentiation of costovertebral joint osteoarthritis from facet joint involvement and guides therapeutic intervention (38). Moreover, fused images can allow the diagnosis of unexplained hip pain, such as femoral acetabular impingement syndrome (39). In patients with a painful knee, SPECT/CT is useful in localizing and characterizing lesions, such as osteoid osteoma, loosening of a total knee replacement, bone remodeling at the site of an anterior cruciate ligament repair, patella maltracking/subluxation and osteochondral defects (40). Scintigraphic tracer uptake occurs early in response to injury, which often allows fracture identification in situations in which radiography has known limitations (stress fractures, ribs, sacrum, scaphoid, femoral neck and ankle) (41). In patients with bone injuries, SPECT/CT is also an ideal method for detecting complications, such as the chronic regional pain syndrome (reflex sympathetic dystrophy) and nonunion with more convincing accuracy (42). SPECT/CT using ^{111}In-WBC combined with ^{99}mTc-MDP or ^{99}mTc-sulfur colloid appears to be one of the best imaging techniques for diagnosis of bone and joint infections (43).

2.4. Oncology

SPECT-CT is used in radioimmuno-scintigraphy. As an example, ^{111}In-antibody against prostate specific membrane antigen (PSA) can be used to identify the tumor and its metastases, evaluate recurrence and guide the placement of radioactive seeds in brachytherapy (44).

In those centers without access to PET-CT technology, ^{67}Ga can still be used in the evaluation of patients with lymphoma. SPECT-CT improves the sensitivity of planar studies, decreases the number of false positives due to physiologic radiopharmaceutical excretion and facilitates the precise anatomical location of lesions (45,46).

SPECT-CT is increasingly used for sentinel node evaluation. The sentinel lymph node is the hypothetical first group of lymph nodes reached by metastasizing cancer cells from a primary tumor. Its detection and biopsy after peritumoral injection of colloid labeled with ^{99}mTc are fundamental to performing minimally invasive surgery avoiding extensive ganglionar dissection and postoperative morbidity. Both in breast cancer and melanoma, sentinel node identification has become an essential technique, its use being increasingly extended to other types of tumors. Although planar scintigraphy combined with intraoperative probe is usually employed, SPECT-CT allows a more accurate sentinel node anatomical location. This aspect is particularly important in the evaluation of internal mammary chain, interpectoral and intramammary nodes in breast cancer (47,48), in the study of head and neck tumors (49) and in those tumors draining to pelvic lymph nodes (50). SPECT-CT is also accurate in identifying nodes close to the injection site, deeply located and in-transit (51). In melanoma, SPECT/CT is useful in anatomically complex regions and in those where lymphatic drainage can be variable, such as the head and neck or the trunk, or draining to multiple sites, including cervical, supraclavicular and inguinal lymph nodes (21).

2.5. Cardiology

Myocardial perfusion scans (^{201}Tl, ^{99}mTc-Sestamibi, ^{99}mTc-tetrofosmin) are widely used in diagnostic and prognostic evaluation of patients with coronary disease to define the functional severity of an angiographically significant stenosis. The vast majority of these studies are performed using physical or pharmacological stimuli tests. The SPECT sensitivity for detecting $>$50% angiographic stenosis is 87% (range, 71–97%), whereas specificity is 73% (range, 36–100%). Attenuation correction methods improve specificity, especially among patients undergoing exercise stress testing (52). SPECT-CT attenuation correction further improves the diagnostic accuracy by a proper assessment of the diaphragmatic surface (53). However, the existence of respiratory and cardiac motion may cause false-positive spurious perfusion defects in apex and left ventricle anterior wall (54).

The incorporation of 64-slice and flat detectors CT to SPECT imaging has allowed, owing to its high temporal and spatial resolution, to 'freeze' cardiac motion and even simultaneously obtain a coronary angiogram. Furthermore, it can also detect and quantify the extent of coronary artery calcification. The multimodal SPECT-CT information provides a diagnostic and prognosis value of first magnitude (55,56).

An alternative to NaI (Tl) crystal scintillators normally used in SPECT systems is the use of semiconductor detectors such as cadmium zinc telluride (CZT) with better spatial and energy resolution (Tl) (57). This technology, already used for scintimammography (58), has been taken up recently by GE Healthcare (Alcyone detector) for cardiology equipment (59). This device shows a great improvement in resolution and sensitivity over conventional SPECT equipment. Therefore, spatial resolutions of 5 mm are obtainable with acquisition times of 3–5 min in typical clinical imaging situations. This technology is designed to be compatible with current GE CT systems in an integrated configuration to acquire transmission maps for attenuation correction, calcium scoring, and coronary CT angiography (13).

3. PET-CT

The first PET-CT prototype dates from 1998, was introduced by Siemens and was clinically evaluated at the University of Pittsburgh (60). The following year, GE Healthcare introduced the first commercial equipment (Discovery LS). Several months later Biograph (Siemens Medical Systems) appeared and subsequently Gemini (Philips Medical Systems) (61). Recent developments in CT technology (such as increased number of detector rows, shorter turnaround times and radiation dose modulation) and PET technology (new and more efficient scintillation crystals, 3D and 4D detection technology, time of

flight technology and iterative reconstruction algorithms) have been spectacular, being a source of healthy competition among the leading companies in electromedicine.

Positron-emitting radionuclides for PET images are created in a cyclotron (^{18}F, ^{11}C, ^{15}O, ^{64}Cu, ^{124}I, ^{13}N) or in a generator (^{68}Ga). For logistical reasons, the most commonly used is ^{18}F because of its long half-life (110 min), allowing transportation to distant places from it production origin.

Although the effective doses from a whole body PET/CT study were about 25 mSv (62), recent technological developments have significantly lowered these values. The main indications for PET-CT are in the field of oncology, neurology and cardiology.

3.1. Oncology

^{18}F-FDG glucose analog is the most commonly used radiopharmaceutical due to the faster glucidyc metabolism observed in cancerous tissues. Other radiopharmaceuticals labeled with ^{18}F can also be used to assess other relevant aspects. In this way, ^{18}F-fluoride is used for bone metabolism, ^{18}F-fluorothymidine for the synthesis of DNA, ^{18}F-choline and ^{18}F-acetate for the synthesis of membrane lipids, ^{18}F-FDOPA for protein transport and synthesis, ^{18}F -fluoromisonidazole for tumor hypoxia, ^{18}F-annexin for apoptosis, ^{18}F-RGD for angiogenesis and ^{18}F-fluoroestradiol for estrogen receptors. Many chemotherapeutic agents have also been labeled with ^{18}F to precisely depict its pharmacokinetics and pharmacodynamics (11,63). In neuroendocrine tumors, somatostatin analogs are radiolabeled with ^{68}Ga to stage tumors and define treatment options and follow-up in nonresectable tumor (64).

There is wide evidence that PET-CT provides greater diagnostic accuracy than PET and CT examinations alone (65). The main indications for PET-CT in oncology are the positive diagnosis of malignancy (differentiating malignant from benign disease) (Fig. 2), identifying sites of disease, detecting the primary tumor when unknown, staging the disease (Figs 3 and 4), estimating

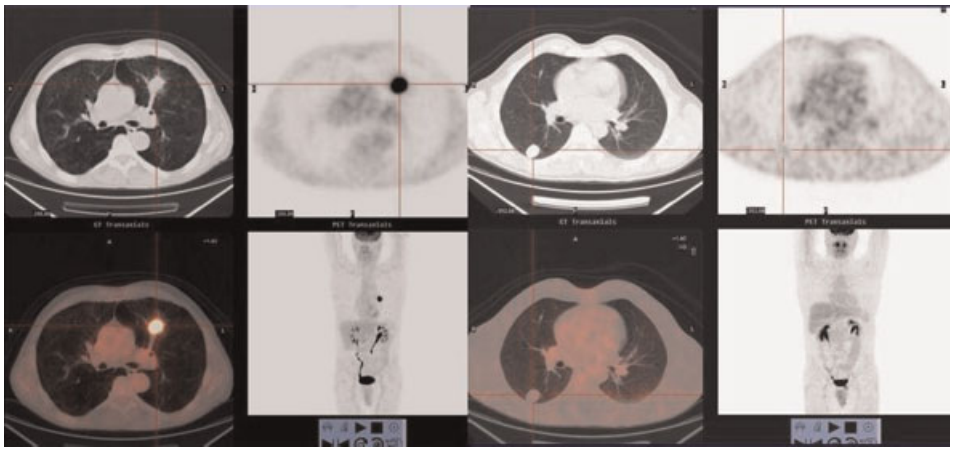

Figure 2. PET-CT. Hypermetabolic pulmonary nodule (malignant) (left). Ametabolic pulmonary nodule (benign) (right).

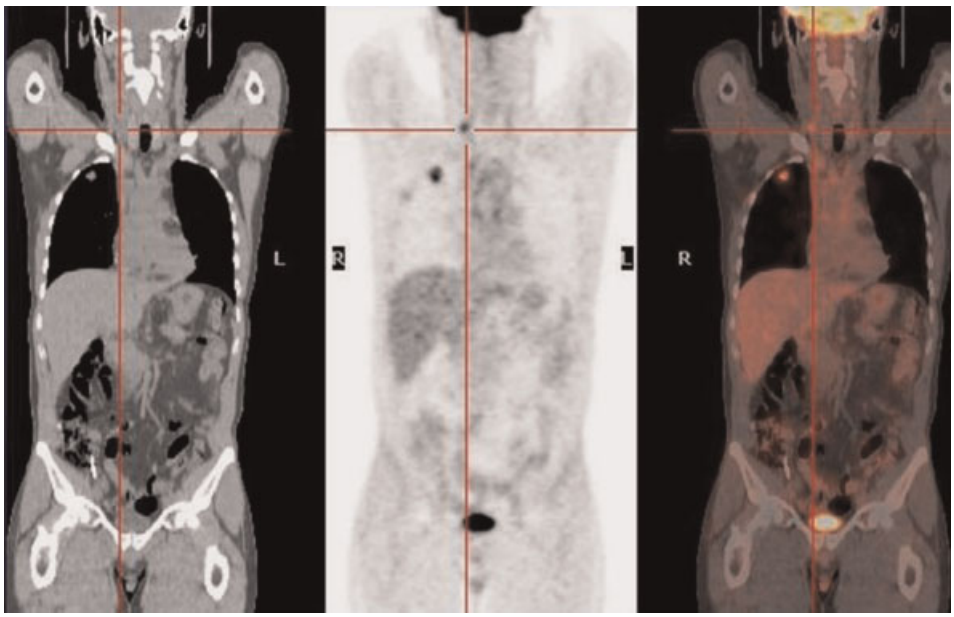

Figure 3. PET-CT. Patient with nonsmall cell lung carcinoma referred for staging with a right supraclavicular adenopathy that modifies the therapeutic management.

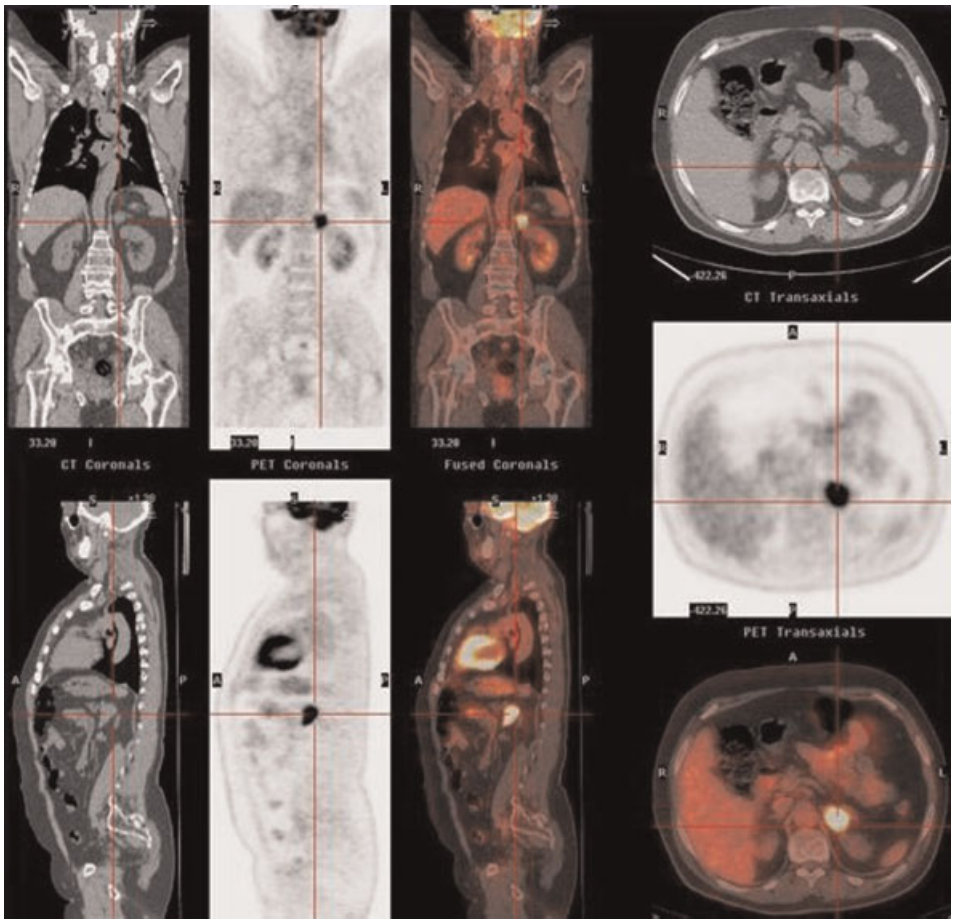

Figure 4. PET-CT. Patient with nonsmall cell lung carcinoma remitted for re-staging: a hypermetabolic nodule corresponding to an adrenal metastasis is demonstrated.

prognosis (Fig. 5), identifying residual disease (Fig. 6) and confirming the sites of recurrence, radiotherapy planning [with the novel concepts of 'dose painting' for scaling the dose and 'theragnostic' to prescribe the distribution of the radiotracer dose in four dimensions (66,67)], predicting the early response after treatment initiation, and objectifying the efficacy of treatment (63).

3.2. Neurology

In the clinical context of dementia, ^{18}F-FDG exploration in suspected Alzheimer's disease provides objective information on brain metabolism, being particularly useful for the differential diagnosis with frontotemporal dementia. CT images allow exclusion of the metabolic disorder being caused by structural changes (68). Also, quantitative studies allow monitoring of the therapeutic response. The ability to label amyloid compounds with ^{11}C or ^{18}F, facilitating their *in vivo* objectification, opens a new field of diagnostic and monitoring possibilities (69) in Alzheimer's disease.

In drug-resistant epilepsy, ^{18}F-FDG studies in the ictal and interictal phases provide the location of seizure focus (70). ^{18}F-FDG can also show the diaschisis phenomena. In the study of movement disorders, PET-CT imaging enables assessment of the

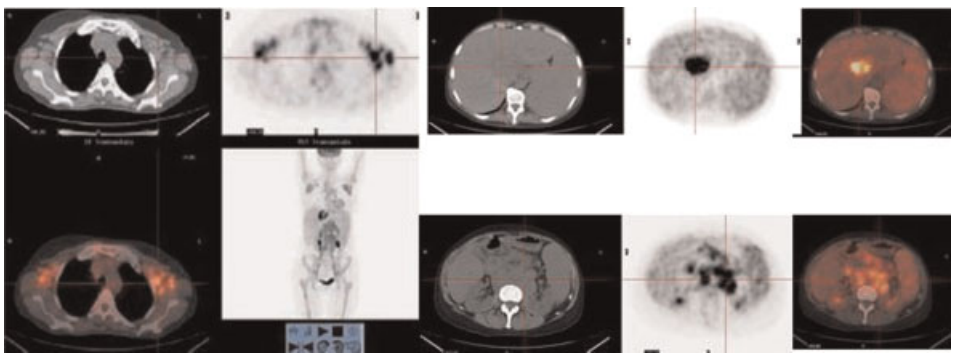

Figure 5. PET-CT. Patient with non-Hodgkin lymphoma referred for staging. Supra and infradiaphragmatic disseminated involvement was identified.

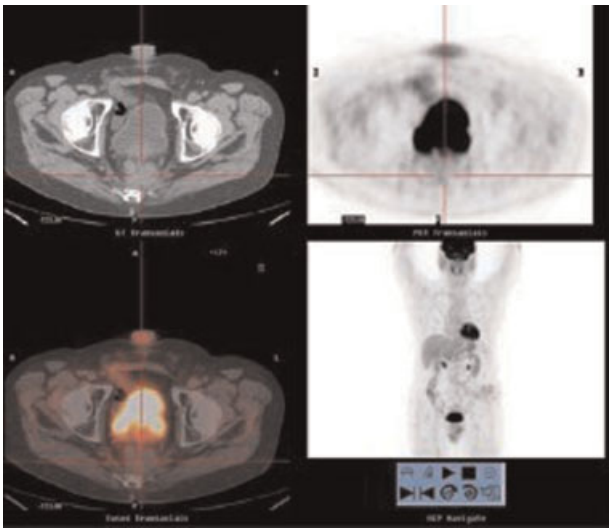

Figure 6. PET-CT. Patient with suspected presacral recurrence. PET-CT shows an ametabolic lesion that corresponds to fibrosis.

dopaminergic pre- (^{18}F-FDOPA) and postsynaptic (^{11}C-raclopride) systems and, therefore, the differential diagnosis between Parkinson's disease and progressive supranuclear palsy or multiple system atrophy (71). In addition to motor disorders, dopaminergic imaging may be also used in the assessment of some psychiatric disorders (schizophrenia, depression, attention disorders, phobias, compulsive behaviors). Further, it has also been proven the relationship between the effectiveness of antipsychotic medication and D2 dopamine receptors (72).

In the evaluation of vascular pathology, PET-CT technique may be used to quantify carbohydrate metabolism (^{18}F-FDG) and to study cerebral blood flow ((^{15}O -water), blood volume (^{15}O-carbon monoxide or carbon dioxide) and oxygen extraction fraction (inhaled ^{15}O) in order to obtain hemodynamic information (73).

Finally, opiate receptors image can be used in the evaluation of pain, epilepsy syndromes and movement disorders and in the field of addiction psychiatry (74).

3.3. Cardiology

In comparison to SPECT-CT, PET-CT advantages lie in the quantification of myocardial blood flow and coronary reserve using ^{15}O -labeled water, providing data of important prognostic value, and its greater sensitivity in detecting regional perfusion defects of the left ventricle.

Multimodality PET-CT allows to perform CT-angiography (coronary, aorta and pulmonary arteries) while obtaining functional information of the hemodynamic significance of the stenosis by the PET component, increasing the overall accuracy (75).

In myocardial viability studies, ^{18}F-FDG has been considered the gold standard. Currently, the European Society of Cardiology (76) recommends this technique in cases of discrepancy between clinical suspicion and other imaging tests like SPECT-CT and MR.

The study of sympathetic and parasympathetic receptors allows imaging of cardiac neuronal functionality, which has been very useful in the study of cardiomyopathy, arrhythmias and heart failure (77). The development of new tracers that allow identification of vulnerable atheromatous plaques or monitoring of gene therapy is opening a huge range of new possibilities (75).

4. PET-MR

In relation to CT, MR imaging has some advantages, providing excellent tissue contrast and multidimensional functional, structural and morphological information (e.g. spectroscopy and MR-BOLD). The combination of multidimensional and molecular information provided by PET-MR will undoubtedly be an essential value of this multimodality technique. Further, the ability to simultaneously acquire different functional imaging will help to more precisely understand the complex pathophysiological processes involved in diseases. Furthermore, the radiation dose for PET-MR will be lower than that for PET-CT, being of particular importance for repeated studies aimed to evaluate disease progression and therapy response.

First approaches to this technology presented many technical challenges arising from the mutual interference between the subsystem components (PET and MR). Electronic PET devices cause artifacts in MR scanners, leading to a degradation of the image quality. The magnetic fields of MR interfere with scintillation detectors and multiplier tubes that amplify the PET signal. The use of new solid-state light detectors in PET equipments that can operate at high magnetic fields strengths will probably change the panorama (78).

The first prototypes designed for pilot studies with small animals have opened the way for PET-MR equipment in clinical applications, mainly in the fields of cardiology, neurology and monitoring different cellular processes. Neuroreceptors and neurotransmitters kinetic studies, together with activation studies, will play a key role in preclinical research and clinical neuropsychiatry (79). Currently, major limitations of PET-MR are the restricted disponibility and high costs of the equipments.

The use of MRI equipment produces images with excellent tissue contrast, dynamic and functional information. The simultaneous acquisition of PET and MR images allows temporary correction of dynamic PET studies (79–81). However, the use of this method also poses some disadvantages resulting from mutual interference and proper correction of photon attenuation in PET imaging (80,81).

PET may interfere with magnetic field and radiofrequency from MR imaging while MR can affect PET since both magnetic field and radiofrequency can interfere with the electronics of the PET. To minimize mutual interference between these two devices, different solutions have been proposed. The use of optical fibers coupled to the scintillator crystals brings light to the photomultiplier tubes so that only crystals are within the magnetic field of MR. Another alternative approach is to replace the photomultiplier tubes scintillators (PMT) for solid-state scintillation detectors, such as thre 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 (80,81).

Furthermore, PET imaging provides accurate attenuation correction which is less direct with MR than CT, as MR provides information on proton density while the attenuation is proportional to electron density. The main problem in MR-based PET attenuation correction is that attenuation is not directly

correlated to the signal measured by MR. The most obvious examples are compact bone and air: in MR imaging, both show the same (essentially zero) signal with standard MR sequences, whereas 511 keV-ray attenuation values of bone and air, respectively, are widely divergent. Currently, there are two major approaches to solving this problem. The first approach is based on a two- or three-component segmentation of the MR images, using atlas information to correlate known attenuation values to segmented anatomical structures. The disadvantage of this procedure is that atlases do not reflect inter-subject anatomic variability, which might make correlation between anatomic structures and MR segmentations problematic. Distortion artifacts or truncation of organs outside the MR field of view, like arms, cannot be accounted for by this method. Another approach for MRI-based attenuation correction is a combination of atlas registration and local pattern recognition to capture global variations and predict attenuation maps purely based on the MR information (80,81).

5. THE FUTURE

It is safe to predict the explosive implementation of medical multimodality imaging in the near future. As mentioned, the next frontier is to develop efficient detector systems and electronics capable of detecting two modality signals at once. Science progress is not only made by successive accumulation of quantitative knowledge, but also and mainly by new discoveries that produce barely predictable qualitative leaps (82).

Multimodality imaging techniques will play a leading role in clinical applications and development of diagnostic imaging research, primarily in oncology, cardiology, neuropsychiatry and experimental studies in small animals. Not only PET-MR but also MR-US or optic-PET will be introduced in clinical scenarios. Even more, MR diffusion-weighted, pharmacokinetic imaging or spectroscopy imaging will merge with PET tracers to further increase molecular imaging as a highly relevant medical discipline.

Future progress may be also hampered by tracer disponibility. Currently, the supply of Tc ^{99}Mo/^{99}m is suffering a serious global problem. There are three reactors available in Europe. The High Flux Reactor in Petten (The Netherlands), which provides approximately 60% of supply, had to stop production from September 2008 to mid-February 2009 due to a breakdown. The scheduled stop of the other two reactors in Europe caused a significant reduction in the availability of ^{99}Mo/^{99}m Tc. As PET-CT with ^{18}F-fluoride can evaluate bone pathology much better, it could replace ^{99}m Tc-MDP bone scintigraphy if the shortage continues. ^{18}F-fluoride is a positron-emitting bone-seeking agent that reflects blood flow and remodeling of bone. Although the ^{18}F-fluoride uptake mechanism corresponds to osteoblastic activity, it is also sensitive for detection of lytic and early marrow-based metastases, by identifying their accompanying reactive osteoblastic changes, even when minimal. The instant fusion of increased ^{18}F-fluoride uptake with morphological data of CT improves the specificity in cancer patients by accurately differentiating between benign and malignant uptake sites (83). The development and implementation of smaller and cheaper cyclotrons will surely increase the use of PET-CT.

The development of new tracers and smart probes as technological innovations are the two main key points that will condition multimodality image and certainly diagnostic imaging professionals' future.

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