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Clinical Applications of Positron Emission Tomography (PET) Imaging in Medicine: Oncology, Brain Diseases and Cardiology

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Abstract: Positron Emission Tomography (PET) is a diagnostic imaging procedure used regularly to acquire essential clinical information. The PET–CT hybrid, which consists of two scanning machines: PET scanner and an x-ray Computed Tomography (CT). At present these represent the technological hierarchy of Nuclear Medicine, occupying an important position in diagnostics. In fact, PET–CT has the capability to evaluate diseases through a simultaneous functional and morphostructural analysis. This allows for an earlier diagnosis of the disease state which is crucial for obtaining the required information to provide a more reliable prognosis and therapy. Presently, the most frequently used PET radiotracer [^{18}F]fluorodeoxyglucose (FDG) has a major role in oncology. Useful information is being regularly obtained by using both FDG and a selection of radiotracer compounds to evaluate some of the most important biological processes. Thus, creating an opening for 'Molecular Imaging' and providing a platform for a potential revolution in the clinical diagnostic field. In this review, we hope to present the most interesting technicalogical and methodological advances in clinical diagnostics for oncology, neurology, and cardiology. A particular attention is dedicated to the applications of PET in neuropsychiatric diseases and its connections with receptor imaging.

Keywords: PET, PET–CT, Positron emitters, [^{18}F]Fluorodeoxyglucose, FDG, Nuclear Medicine, Oncology, Neuropsychiatry, Cardiology.

Dedicated to the neurologist Dr Johann te Water Naude.

1. INTRODUCTION

The imaging of the human body can be traced back to 1895 with the discovery of x-rays by the 1901 Nobel Laureate Wilhelm Conrad Röntgen [1]. Today, a variety of imaging techniques have been added to traditional Radiology (Rx) to assist with the diagnosis of various disease states in humans. Although the planar image continues to have the capacity to reliably answer a variety of clinical questions as demonstrated by Mammography (Mx) or Chest x-rays. The 'new' diagnostic imaging tools which include Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Ultrasound (US) and Nuclear Medicine (NM), are mainly based on 3-*D* anatomical and functional images of the human body [2]. During the past several decades, some new imaging tools for Nuclear Medicine have emerged. These include the usage of gamma emitters for Single Photon Emission Computed Tomography (SPECT) and positron emitters for Positron Emission Tomography (PET). The PET capabilities in Nuclear Medicine technology have evolved from several key discoveries (Fig. **1**) [3].

The PET approach provides a clear and effective expression of radionuclide imaging and in contrast with other imaging techniques based on a (morphostructural change in structural images) premise that is standard Rx, CT, US and MRI, thus providing an insight into the biochemical and physiological processes of the human body [4]. Also, the techniques defined above as 'morphostructural' can give functional information, for example, after administering the contrast medium. Radionuclide techniques are unique because none of the other procedures use radiotracers to provide functional imaging. For instance, a whole body 'scan' evaluation more thoroughly provides the quantitative analysis which is the gold standard of Nuclear Medicine.

The biochemistry and physiology of the body is altered when it is in a disease state. Since, altered function precedes structural changes, PET has the capability to permit an earlier diagnosis, giving also information better related to prognosis and therapy. Therefore, it is acquiring a primary role in diagnosing and evaluating many disease states, with main reference to cancer. PET utilizes 'positron' emitting radiotracers to deliver images of the human body. These radiotracers must be synthesized very quickly due to the short half-life ($t_{1/2}$) of the most used nuclides such as carbon-11 ($t_{1/2}$ = 20.4 minutes), nitrogen-13 ($t_{1/2}$ = 9.98 minutes), oxygen-15 ($t_{1/2}$ = 2.03 minutes) and fluorine-18 ($t_{1/2}$ = 109.8 minutes). A range of automated synthesis modules have been developed to address these short half-life problems, for example in the following radiotracers: 2-deoxy-2-[^{18}F]fluoro-*D*-glucose (FDG), the most used today, [^{13}N]ammonia, [^{11}C]methyliodide, sodium[^{11}C]cyanide and sodium[^{11}C]-acetate. The creation of these automated synthesis modules have been made possible by the use of microwaves, micro-

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arrays, micro-centrifuges, application of solid support reagents and high performance liquid chromatography (HPLC) [5].

- Identification of positrons.
- Development of coincidence detection for annihilation radiation.
- Invention of cyclotrons.
- Production of positron cameras and more recently of hybrid PET-CT systems.
- Development of a radiochemistry producing radiotracers labelled with short half-life positron emitters.
- Advancement of computer technology.
- Development of mathematical algorithms for image reconstruction.

Fig. (1). The several key discoveries of PET.

Non-invasive PET imaging has been used as a research tool in humans since the 1970s. The advance in technology and a wider application allowed a clinical role for diagnosis, staging and monitoring of disease in patients by the mid 1990s [6]. In 1953, the pioneering work of Brownell and Sweet (Fig. **2**) at Massachusetts General Hospital allowed the completion of the first positron detector to study brain function [7, 8].

Many of the key discoveries in the clinical use of PET have been pioneered by a number of scientists including D. Kuhl, M. Ter Pogossian, A. Wolf, L. Sokoloff, M. Phelps, G. Di Chiro, A. Alavi, and H.N. Wagner Jr [9]. In the nineties Wagner showed the application of the glucose analogue, FDG could be used in PET studies to contribute to clinical evaluation of the patient. The earliest applications of clinical interest were carried out in the study of brain diseases, with main references to cancer and dementia [10-21].

In the late eighties, since technological advances permitted a faster and more accurate whole body examination (Fig. **3**); PET with FDG started to become a primary clinical tool in oncology, finding its main role in diagnosing, staging and re-staging of different types of cancer in patients on a daily basis. However, it was not until 1997, when approval was granted by the US Food & Drugs Administration (FDA), that PET could be considered seriously as a major imaging instrument in the diagnostic field [22]. Subsequently, PET-FDG became an established imaging tool in the clinical assessment of many neoplasms, finding a role also in non-malignant diseases such as dementia, myocardial ischaemia, inflammation and infection [23,24].

The diagnostic accuracy of PET-FDG in certain clinical oncological examinations including lung, colorectal, oesophagus cancers, melanoma, lymphomas, breast, head-and-neck cancers, sarcoma [25] is higher than other diagnostic imaging techniques. The clinical results are shown in Table **1**. and give a comparison between a standard approach, mainly based on CT and PET imaging. These results demonstrate the early utilization of PET imaging in the detection of cancers [26].

At this stage in the review it is important to stress that the clinical utilization of PET with FDG in differential diagnosis of solitary pulmonary nodules is not used alone in the routine diagnosis of primary tumours. Due to the higher accuracy of CT the best approach is to use the hybrid PET-CT scanner to diagnose primary tumours to avoid the possibility of obtaining false negative and false positive results. At present, the most relevant clinical application is in re-staging (and staging) of cancer, where PET is acquiring a pivotal position in the diagnosis of the majority of neoplasm (Fig. **4**).

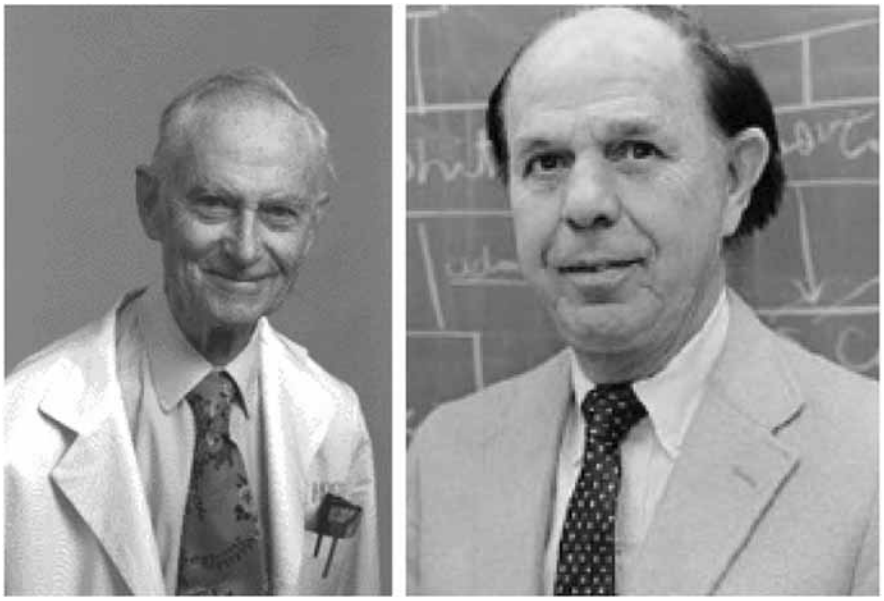

Fig. (2). H H Sweet & G Brownell 'PET Pioneers' who built the first positron detector to detect annihilation photons by the means of coincidence counting.

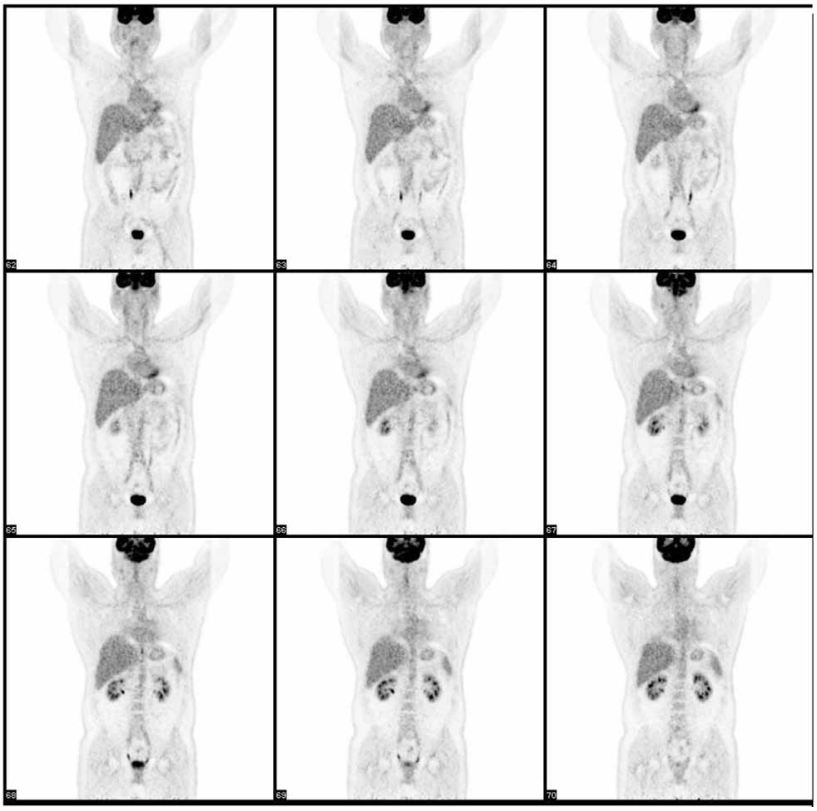

Fig. (3). Whole body PET-FDG scans showing normal FDG distribution.

Table 1. Shows Information on PET-FDG Diagnostic Accuracy for Specific Cancers [12**] (refer to: The Journal of Nuclear Medicine Supplement, Volume 42, Number 5, May 2001)**

Type of Cancer	Conventional Imaging (%)	PET (%)
Breast	67	89
Colorectal	80	94
Gastro-Oesophageal	68	83
Head-and-Neck	65	87
Liver	81	93
Lung	68	82
Lymphoma	64	88
Melanoma	80	91
Pancreatic	65	81
Testicular	68	92
Uterine/Cervical	43	87

More recently, many studies have demonstrated that FDG can be used as an early marker for tumour response with respect to CT therefore, increasing its application in the follow up of patients affected by numerous cancers (Fig. **5**).

In the evaluation of tumour response, the role of PET-FDG in patient follow-up is already clinically relevant, because of advantages in respect to CT and MRI in diagnosis of 'tumour' recurrence. In fact, no FDG uptake can be pre-

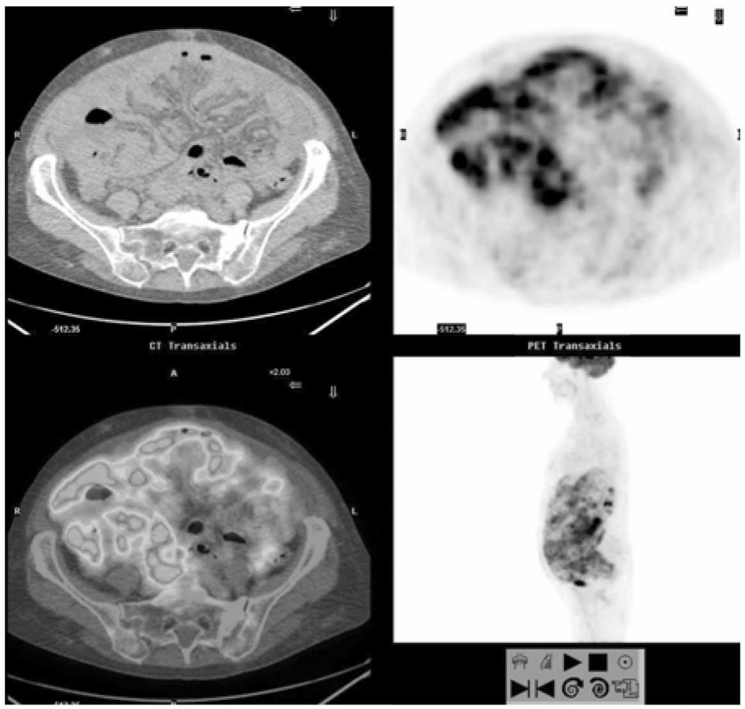

Fig. (4). PET-FDG scan of ovarian cancer with metastatic spread.

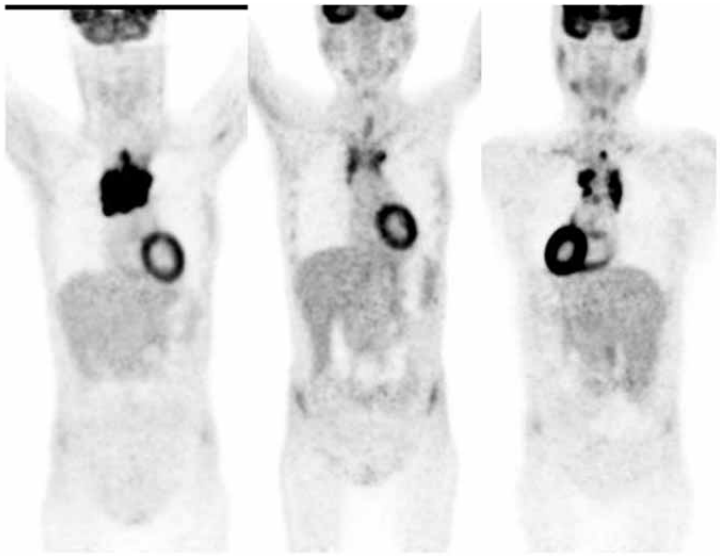

Fig. (5). A series of PET-FDG scans showing Hodgkin Lymphoma – Therapy monitoring from left to right: 1) Baseline: Intense mediastinal uptake; 2) After 2 cycles of chemotherapy: Partial response; 3) End of chemotherapy: Persistent disease.

sent in the absence of cells. Therefore, it is important to differentiate recurrence by either necrosis and/or fibrosis, which is remedied by a morphostructural approach. It has to be highlighted that, together with a very high negative predictive value of finding the tumour, few false positive results can be observed when using PET, because of the interfering uptake of the radiotracer at the level of an inflammatory reaction. The hybrid PET-CT scanner has the capability to add morphostructural data to the functional part of the scan to significantly improve the accuracy due to the generation of complementary information achieved by the combined techniques. With respect to the evaluation of tumour response, changes in FDG uptake observed by PET is an early indication on how accurate the therapeutic efficacy responds to changes in size and structure as assessed by CT.

Together with the increasing clinical role in humans, the introduction of the PET micro-scanners has allowed researchers to develop a link with molecular imaging assays. This is a field where Nuclear Medicine is occupying a leading position. In fact, because of the capability of obtaining images of the detecting substances (radiotracers) which are

of the order of nano/pico mole dosages in PET. These dosages are many times lower than used in CT and MRI scanners where the detection levels are in micro/millimoles. The imaging techniques of PET and SPECT share a common platform with Optical Imaging (OI) by providing the highest sensitivity and capability to study physiological biochemical processes without affecting them.

Unfortunately, Optical Imaging (OI) can only study superficial structures and therefore Nuclear Medicine is unique in permitting the best molecular imaging in humans to date. In addition, PET micro-scanners enable the evaluation of novel and existing PET radiotracers on small animals before their usage on humans. The PET micro-scanner contributes to the elucidation of specific *in vivo* metabolic pathways and toxicology of the radiotracers [27]. For example, the development of PET reporter gene assays from mice studies to humans have been used to trace and locate the level of expression of genes by using various radiotracers [28].

Today the majority of clinical PET imaging is based on the utilization of FDG, a glucose analogue permitting a high diagnostic accuracy in the evaluation of patients with cancer leading to more reliable prognosis information. FDG is also the most diffuse radiotracer in neuropsychiatry, having a pivotal role in differentiating between diagnosing opposing conditions for example dementia, cardiology and in the latter due to the high sensitivity in detecting viable myocardium [29].

The aim of this review is not to discuss every clinical aspect of PET-FDG or its hybrids but only to give an insight into a select number of applications. The authors wish to clarify that FDG uptake for inflammatory disease processes, presents a problem in differential diagnosis of cancer. This anomaly resulting from inflammatory diseases finds a new clinical role in patients with fever-of-unknown-origin (FUO). Hence, in defining the presence of radiotracer (activity) as premise for the best definition of therapeutic strategies in patients with inflammatory diseases such as tuberculosis and sarcoidosis (Figs. **6, 7**). Therefore, it is warranted in patients with inflammation and infection. This clinical area requires further development in PET-FDG studies [30].

After a brief report about the basic knowledge of PET and on some key examples regarding the clinical role of FDG in oncology, this review will describe some of the most intriguing perspectives achievable by using a range of radiotracers. Unfortunately, having a full insight into the applications of PET would require books and not a review [31, 32].

The relevance of this review would contribute to the reduced number of publications in the field of neuropsychiatry, where the most intriguing clinical perspectives are linked with PET radiotracers. Since, various PET studies have been carried out to elucidate the role of dopamine and serotonin neurotransmission processes in the brain [33]. These neuroradiotracers have probed deep into the areas of the brain and central nervous system (CNS) to help and understand storage, re-uptake, post-synaptic binding and signalling mechanisms. Research continues to develop diagnostic imaging in the area of PET-immunology to target monoclonal antibodies against tumour associated antigens. The design of flourine-18 PET reporter probes such as [^{18}F]fluoropenciclovir (FPCV) has been developed to image herpes simplex virus type-1 and thymidine kinase (HSV1-tk) for reporter

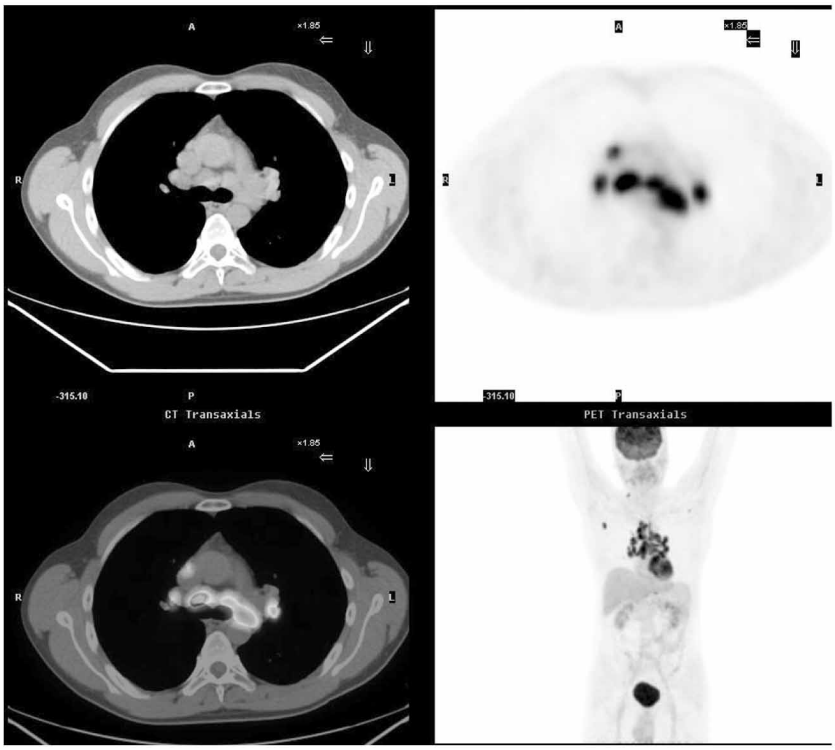

Fig. (6). A PET-FDG scan of a patient with sarcoidosis.

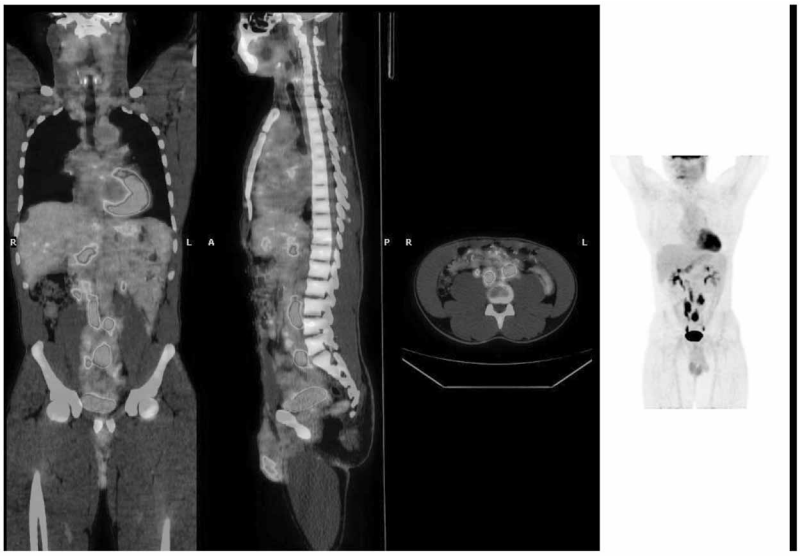

Fig. (7). A PET-FDG scan of a patient with tuberculosis.

expression [34]. Other research areas include the use of PET imaging to track the transplantation of stem cells into disease areas of myocardial infarction and Parkinson's disease [35].

The major interest in the development of clinical PET radiotracers is mostly devoted to the use of fluorinated radiopharmaceuticals. This is due to practical and technical achievements in the corporation of the positron emitter flourine-18 into the chemical structure. Other clinical radionuclide tracers labelled with carbon-11 ($t_{1/2}$ = 20.4 minutes) and nitrogen-13 ($t_{1/2}$ = 9.98 minutes) are at a disadvantage due to having a fast half-life. The radionuclides copper-64 ($t_{1/2}$ = 3.3 days) and iodine-124 ($t_{1/2}$ = 4.2 days) suffer from having a longer half-life and are more difficult to produce. A major research interest is based on radiochemistry using radionuclide generators such germanium-68/gallium-68 [36]. Using gallium-68 ($t_{1/2}$ = 68 minutes), many molecules of biological interest such as peptides can be chelated to create further openings in the PET clinical field.

New PET technologies have brought about commercial multi-ring scanners which have enhanced spatial resolution to less than 5 mm coupled with a greater sensitivity, axial coverage and increased image volume. The spatial resolution of PET is going to be comparable with that of Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) [37]. This resolution will allow for whole-body PET studies to be carried out rapidly [38].

A major improvement has been permitted by the production of the so called 'hybrid machines', allowing the possibility to image on the same cross-sectional slice and simultaneously obtain both functional information acquired by PET (or SPECT) and morphostructural data achieved by CT.

Research is ongoing into PET–MRI prototypes which is hoped will produce a dual image at the cerebral level. At present this is as yet unavailable due to the technologies required to fuse the two image components together not developed at an appropriate clinical level. Other relevant technological improvements such as respiratory gating which is based on 4-*D* Tomography will permit a significant improvement not only in diagnosis, but also in a more reliable target definition in Radiotherapy (Figs. **8, 9**) [39-41]. Hence, this gating is a system that tracks a patient's normal respiratory cycle with an infrared camera and chest/abdomen marker. The system is co-ordinated to only deliver radiation when the tumour is in the treatment field.

The future of PET imaging will play a pivotal role in 'personalized medicine' by routine screening and monitoring of malignant disease states, enabling to reach the capability of a tailored therapy. According to Ronald L. van Heer tum MD [42] of the University of Columbia, '*PET is revolu tionizing the fields of oncology, cardiology, neurology, and psychiatry, with a major impact on patient management.*'

Fig. (8). A PET scan showing respiratory motion artefacts seen as cold areas parallel to the diaphragm.

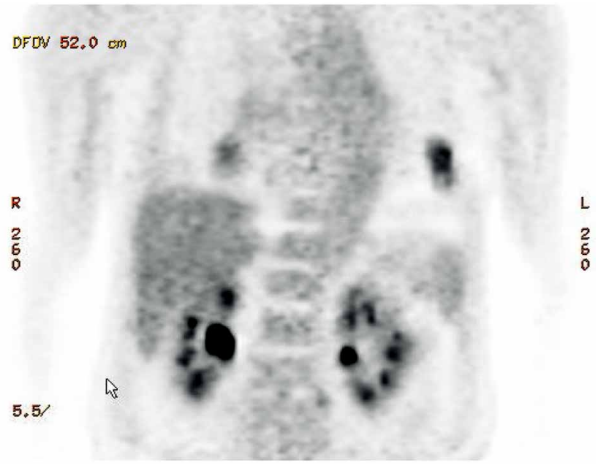

Fig. (9). A` PET scan showing an over estimation of lesion volume in a patient with a lung cancer.

2. BASIC PRINCIPLES OF PET IMAGING

PET imaging of the human body works by detecting *in vivo* radiation. The radiation is generated from the decay of radiotracers containing an unstable radionuclide. In the decay process a positron (β^+) particle together with a neutrino are emitted [43]. Essentially, the positron is an anti-matter electron (β^-) with identical mass to an electron but possessing a positive charge. During the decay process the ejected positron loses kinetic energy by colliding with the surrounding atoms. Hence, this event results in the positron coming to an abrupt rest within nanoseconds. These positrons have typical energies peaking at 0.63MeV and have a very short range within the tissue.

The positron then combines with an electron (β^-) resulting in an annihilation reaction and the mass of the positron and electron are converted into energy. This energy produces two 'annihilation' photons (511keV), from the point of (β^+ - β^-) interaction in opposite directions (approximately 180 degrees apart). The 'annihilated' photons are measured using the principles of PET coincidence detection (Fig. **10**).

For example, the radioactive fluorine-18 [^{18}F], produced from the cyclotron, is a positron emitter. The positron from the unstable [^{18}F] nucleus collides with an electron and both are annihilated. This results in two gamma rays of equal energy but going in opposite directions. The gamma rays leave the patient's body and interact with the scintillation crystals such as BGO (bismuth germinate), LSO (lutetium oxyorthosilicate), GSO (cerium-doped gadolinium silicate), LYSO (Cerium-doped Lutetium Yttrium Orthosilicate) and the photomultiplier tubes in the detectors. These crystals act like transducers by converting the gamma rays into 'light' photons. The photons are then converted into electrical signals that are registered by the tomography electronics. The information is then processed by a computer to form a complex 3-*D* real time image of a particular part of the body such as the brain or a whole body scan [44].

Using BGO system the acquisition times are between 4 to 6 minutes per 'table' position. The newer crystal detectors reduce the scanning time intervals to 2-3 minutes per 'table' position. PET and CT scanner technology is allowing for

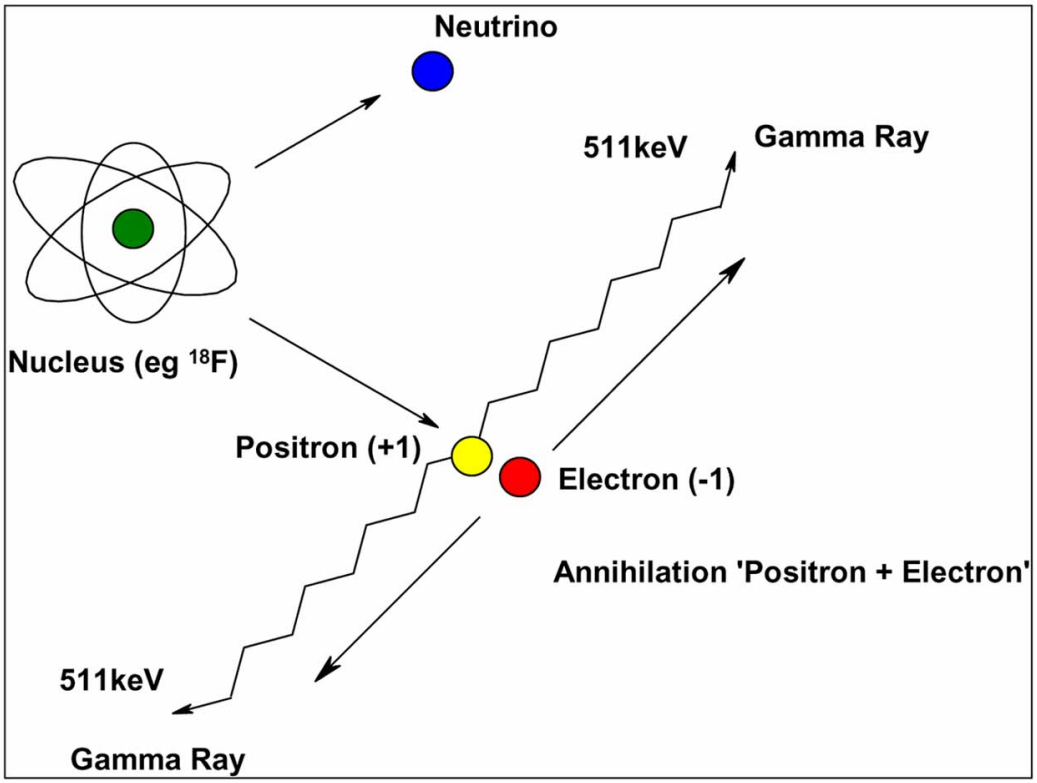

Fig. (10). A schematic diagram showing positron emission during the decay process of a radionuclide.

higher throughput of patients and these are most noticeably in using LSO detectors. The advantage of LSO is that it provides a higher photon output than compared to conventional BGO detectors. Hence, giving shorter scintillation decay times resulting in the improvement of the count rate. For example high FDG doses can be injected and images can be acquired in the 3-*D* mode giving better spatial resolution. This allows for the completion of whole-body PET-CT scan in less than 15 minutes (Figs. **10a, 10b**).

The rapid technological advances especially in the area of solid state chemistry are giving way to novel scintillation crystal forms which will help to deliver much improved detector electronics for the next generation of PET scanners. Major contributions in this area have already developed a micro-PET/CT scanner prototypes used for animal imaging [45].

New capabilities are emerging in the clinical practice in humans which are connected to the so called Time-of-Flight (TOF) systems that are being utilized in commercial PET scanners. These new scanners are creating a better signal-to-noise ratio and therefore, producing more accurate quantitative information for image reconstruction. Consequently, being one of the main goals in Nuclear Medicine is to produce 'real-time' superior images of the human body [46]. At present, almost all the systems acquired by hospitals and research institutions working in the clinical field are hybrid machines that are comprehensive in obtaining a CT scan simultaneously with a PET scan. Unfortunately, the axial CT scanner is no longer commercially available and only used for attenuation correction or to locate a radiotracer's uptake.

At present the output from hybrid CT scanners give spiral 'diagnostic' information involving a number of slices up to 64 or more. The minimal number of 16-32 slices is only needed when angiographic information is required from cardiovascular CT scan. When PET-CT is used in oncology and other pathological conditions not requiring a fine vascular evaluation the number of slices can be less than 16 to give the required clinical information. It must be noted that the acquisition protocol for CT, when used for this purpose, is not the best for a CT analysis, being optimized for the lowest achievable radiation dose. Similarly, in acquiring simultaneously CT and PET scans some artefacts can be produced. To circumvent these problems a technological solution uses a gating respiratory system to permit a more reliable analysis

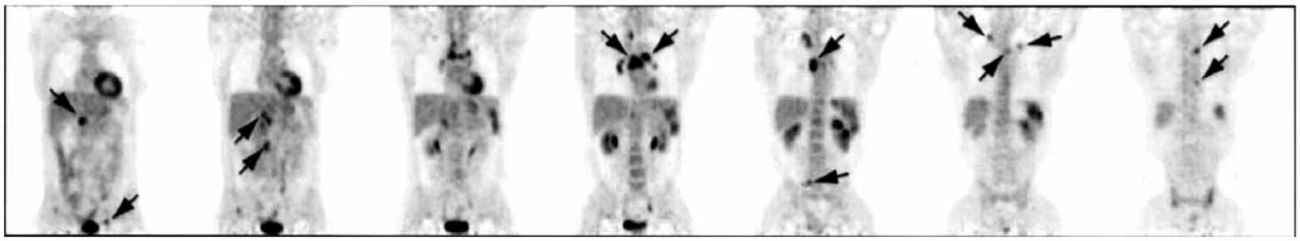

Fig. (10a). A series of PET/CT-FDG scans of a patient with testicular cancer. These scans were taken using LSO detectors and the 'photon' data was collected over a 2 minutes interval. The total imaging duration was less than 12 minutes. The arrows on the scans indicate areas of abnormal uptake of FDG being consistent with a metastatic disease profile.

Fig. (10b). The Coronal CT scan on the left was acquired using the hybrid PET-CT scanner in the same patient as in Fig. (**10a**). The whole body PET scan (shown on the right) was acquired using the hybrid PET-CT scanner in the same patient. The five arrows indicate metastatic lesions. The arrows to the right indicate spleen lesions not seen by CT.

of organs in movement. This allows for a better definition of a 'tumour' target to be treated with radiotherapy by obtaining improved image quality and quantitative data.

Today, patients have to travel to hospitals and institutions to have a PET or PET-CT scan. To enable a wider distribution of these imaging techniques to the general population in poor and developed countries the use of mobile PET or hybrid scanners would be beneficial to the detection of early disease states. Also, a deeper analysis of technical information, including possible artefacts determined by contrast medium used for CT, is out of the scope of this review [47].

3. PET RADIOTRACERS

PET imaging has proved to be an excellent tool in the area of drug discovery by providing crucial *in vivo* information about the understanding of pharmacokinetics of potential 'early' drug candidates [48]. For example, valuable information can be extracted from the studies of drug-receptor occupancy in determining drug efficacy and most importantly mechanism of action. PET is also used in the biological characterization of disease states by probing active sites with PET radiotracers. The most important positron emitting radionuclides used for PET studies are carbon-11, nitrogen-13, oxygen-15 and fluorine-18. All of these radiotracers are cyclotron products with a short half-life. However, differences in decay between these radionuclides create different necessities for their clinical application. In this sense oxygen-15 and derived radiotracers can only be used when the cyclotron is adjacent to the PET scanner's room. Carbon-11 and nitrogen-13 radiotracers can be utilized only when the cyclotron is close to the institution where the PET scanner is installed. A completely different situation is operative for radio-fluorinated compounds. The advantage of tracers labelled with fluorine-18 produced by the cyclotron is due to the longer half-life of 109.8 minutes. Therefore, these tracers can be produced at PET facilities, which may be hours away from their utilization.

This advantage has been a major value in the expansion of PET in the clinical field with the use of fluorinated radiotracers, especially FDG, generated from the vast number of commercial cyclotrons. This means that there is a wide distribution of PET in the most advanced industrial nations, able to address the everyday increasing clinical needs of patients. More recently, the easier availability of radionuclide generator systems for example germanium-68/gallium-68 can help further develop the necessary radiochemistry through better labelling techniques including the chelation of a diverse range of molecules such as 'biological' peptides.

In Table **3** some of the first radiotracers proposed for a clinical use with PET are presented. Noticeably, the major diffusion is certainly related to FDG and today these radiotracers have primary relevance in oncology. Also, they have a role in the diagnosis of dementia and in the detection of viable myocardium. Hence, they can be used to decide cardiovascular interventions or to evaluate the efficacy of certain revascularization processes.

PET radiotracers used in the human body are generally analogues of biological molecules. Therefore, in most cases a true representation of biological and physiological processes can be obtained after *in vivo* administration, generating a molecular image. Hence, the majority of radiotracers are labelled with one of the four common positron emitters carbon-11, oxygen-15, nitrogen-13 and fluorine-18 by replacing the atoms of oxygen, carbon, nitrogen or hydrogen in the compound [49].

Oxygen-15 ($t_{1/2}$ = 2.03 minutes) is produced by deuteron bombardment of natural nitrogen *via* a nuclear reaction [$^{14}N(d, n)^{15}O$]. The oxygen-15 can produce molecular oxygen [$^{15}O_2$], carbon dioxide [$C^{15}O_2$] by mixing the tracer gas with 5% of natural carbon dioxide. Carbon monoxide [$C^{15}O$] can be produced by the reduction of $C^{15}O_2$. Carbon-11 ($t_{1/2}$ = 20.4 minutes) is produced by proton bombardment of natural nitrogen *via* a nuclear reaction. A target gas mixture of 2% oxygen in nitrogen will produce radioactive [$^{11}CO_2$] and 5% hydrogen in nitrogen will afford methane [$^{11}CH_4$]. Nitrogen-13 ($t_{1/2}$ = 9.98 minutes) is produced by proton bombardment of distilled water *via* a nuclear reaction [50]. Other less commonly used positron emitters include oxygen-14 ($t_{1/2}$ =

Table 3. PET Radiotracers and their Associated Applications

PET Radiotracer	Physical Half-Life ($t_{1/2}$)/Minutes	Physiological Process or Function	Clinical Application	Production Method
[^{13}N]Ammonia	9.8	Blood perfusion	Myocardial perfusion	Cyclotron
[^{15}O]Water	2.1	Blood perfusion	Brain activation studies	Cyclotron
2-Deoxy-2-[^{18}F]fluoro-*D*-glucose (FDG)	109.8	Glucose metabolism	Oncology, Cardiology, Neuropsychiatry	Cyclotron
[^{11}C]Raclopride	20.3	D_2 receptor agonist	Movement disorders	Cyclotron
[^{11}C]Methionine	20.3	Protein synthesis	Oncology	Cyclotron
[^{11}C]Flumazenil	20.3	Benzodiazepine receptor antagonist	Epilepsy	Cyclotron
[^{15}O]Carbon dioxide	2.1	Blood perfusion	Brain activation studies	Cyclotron
[^{18}F]Fluoromizonidazole	109.8	Hypoxia	Oncology-response to radiotherapy	Cyclotron

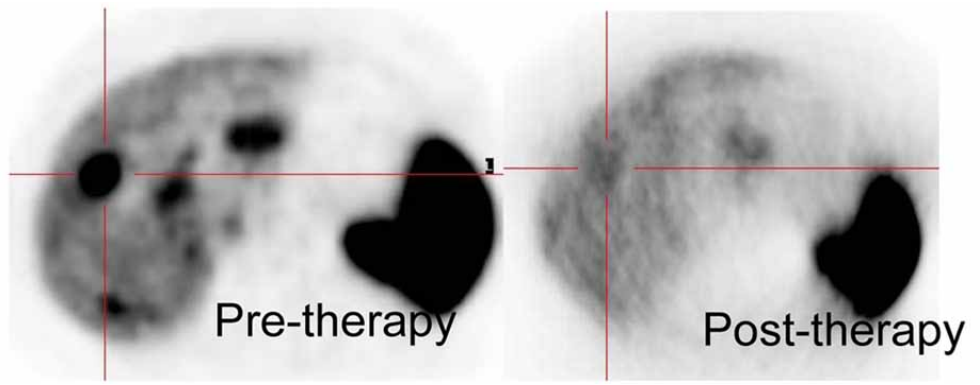

Fig. (11). The left image (at the intersection) shows a ^{68}Ga-DOTATOC-PET scan of liver metastases from pancreatic neuroendocrine tumours (NETs). The right image (at the intersection) shows a tumour response after ^{90}Y-DOTATOC therapy.

70.6 seconds), copper-64 ($t_{1/2}$ = 12.7 hours), copper-62 ($t_{1/2}$ = 9.7 minutes), iodine-124 ($t_{1/2}$ = 4.2 days), bromine-76 ($t_{1/2}$ = 16.2 hours) and rubidium-82 ($t_{1/2}$ = 76 seconds) [51]. PET radionuclides can also be produced by radionuclide generators. In particular, the possibility to produce gallium-68 ($t_{1/2}$ = 68 minutes) through a generator and the development of radiochemistry 'chelation' methods to label many molecules such as somatostatin analogues (Figs. **11, 12**). The gallium-68 radionuclide is creating a significant interest in labelling and is a possible substitute for technician-99m labelling kits used in SPECT imaging.

In recent years there have been significant advances in the development of small accelerators such as tandem cascade accelerators (TAC). Of course the availability of generator systems is a further possibility to produce and utilize positron emitters also having a short half-life, without the need of an expensive cyclotron.

The most widely used 'whole body' PET imaging ligand is 2-deoxy-2-[^{18}F]fluoro-*D*-glucose (FDG) and was first synthesized in 1978 [52]. Also, 6-[^{18}F]fluoro-*L*-DOPA ([^{18}F]-DOPA) is used in PET brain imaging in humans [53], finding more recently new indications in oncology, mainly in detection of neuroendocrine tumours (NETs) [54]. PET is the only 'real time' imaging technique that can be used to study important processes such as glucose metabolism and amino acid transport in tumours [55]. FDG is a glucose analogue capable of penetrating cellular membranes by taking advantage of the sodium and glucose transport systems. Inside the cell, FDG undergoes phosphorylation by the action of the enzyme hexokinase to produce FDG-6-phosphate

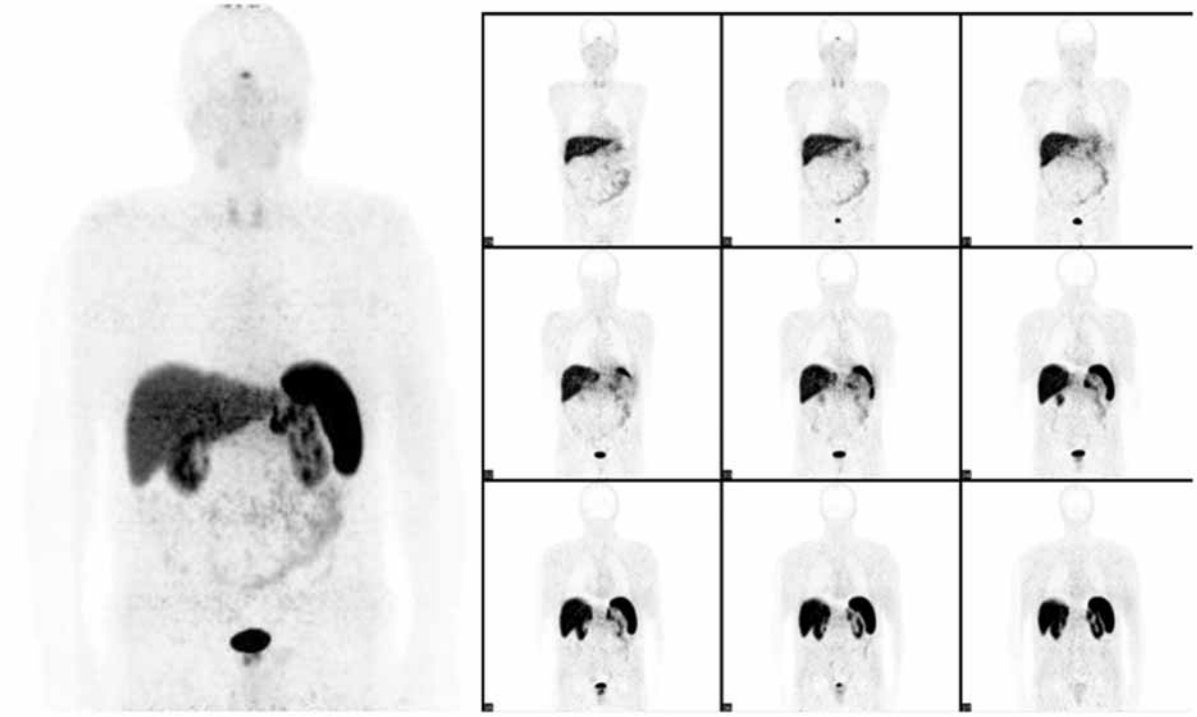

Fig. (12). ^{68}Ga-DOTATOC-PET scan showing normal distribution.

(FDG-6-P). The FDG-6-P remains trapped in the tissue and glucose is diffused out [56]. Typical doses of FDG used in PET oncological scans are in the range of 200-400 MBq for an adult human [57]. Various PET radiotracers are given in Appendix **1** and this is not a complete list due to the numerous new proposals.

The replacement of the ring hydroxyl group in glucose by fluorine-18 generates FDG. This chemical modification prevents the next step in glucose metabolism in all cells and therefore no further reactions occur in FDG. Furthermore, most tissues except the liver and kidneys cannot remove the phosphate added by hexokinase to the FDG.

Therefore, FDG-6-P is trapped in the cell until it decays. The resulting ionic charge on the phosphorylated FDG is not able to exit from the cell. This results in radiolabelling of tissues with high glucose uptake, such as the brain, the only organ only utilizing glucose as metabolic carburant, the liver, and most cancers. As a result, PET imaging with FDG can also be used at different stages of many cancers. At the present the main role is in re-staging and staging of many tumours such as lymphomas, lung, melanoma, head-and-neck, and breast. A further role is also in the prognostic evaluation of differentiated tumours such as thyroid cancer, where it is normally negative but becoming positive only when undifferentiated lesions appear [58]. More recently an interest is the possibility to use FDG as an 'early' marker for a therapeutic response with respect to standard strategies which utilize CT.

Another growing clinical indication is to use PET-CT for a more precise definition of the tumour target in radiotherapy due to its capacity to single out the viable part of the malignant neoplasm (cancer). In this field a further technological improvement has been added by the respiratory-gated acquisition, mainly useful in radiotherapy of lung cancers.

4. CLINICAL APPLICATIONS OF PET IMAGING

PET imaging is a Nuclear Medicine technique which generates 3-*D* images of functional processes in the human body. One of its major usages is the detection of a wide variety of malignant cancers. In particular, the staging of cancer (the quantity of cancer in the human body and position) and the re-staging of cancer (the extent to which the cancer reappears).

The role in differential diagnosis is partially affected by the presence of false negative results, mainly connected with differentiated neoplasm, and false positives, more frequently due to inflammation and infection. Conversely, the increased uptake in active inflammatory diseases is not only a problem for the differential diagnosis of malignancy becoming also an opportunity. For example, clinical indications that is present in patients with fever-of-unknown-origin (FUO), where PET-FDG is the most sensitive procedure. *Note* FUO refers to a condition in which the patient has an elevated temperature which is of unknown origin. In some cases those with suspicious inflamed and infected prosthesis produce results mimicking FDG uptake indicating a marker of active disease.

There is clinical perspective to be achieved in using PET-FDG to evaluate in diseases of the heart by detecting viable myocardium, in conjunction with the usage of flow radiotracers such as [^{13}N]ammonia, or more recently catecholamine analogues. A clinical interest is also present in a variety of neurological disorders and the evaluation of some psychiatric disorders [60]. In particular, FDG is proving to be useful tool in diagnosis of dementia, with a possible role also in patients with mild cognitive impairment (MCI).

It is an interesting perspective to combine the application of amyloid radiotracers in the diagnosis of Alzheimer's disease (AD) with the application of the same radiotracer neurotransmitters to evaluate the dopamine centres of the brain in Parkinson's disease. Therefore, at present PET imaging is proving mainly useful in three broad categories of disease states (Table **4**).

The PET procedure simply involves a patient lying on a horizontal moving bed and injected with a harmless radiotracer, which acts as an imaging agent. The body is easily able to absorb and eliminate the radiotracer without any significant toxicity. The patient then moves through the 'hole' of the PET scanner. Then the scanner interacts with the radiation emitted by the radiotracer injected in the patient to

Table 4. Shows Three Main Clinical Areas of PET Imaging

Oncology [57]	• is a useful technique in staging and re-staging malignant tumours • can be helpful to increase accuracy in differentiating malignant from benign tumours, as in solitary pulmonary nodules • is helping to locate the best site for biopsy of a suspected tumour • is helping to define the tumour target in radiotherapy • is useful in monitoring the effects of therapy (either radiation or chemotherapy or both) • is able to detect the sites of recurrent disease and differentiate it from radiation tissue necrosis • today, the most important applications of PET (FDG) are its ability to detect malignant lesions in restaging and staging of patients with lymphoma, cancers of breast, lung etc at a stage when the conventional imaging tools fail to do so
Cardiology [59]	• PET can be used to assess the extent of cardiovascular disease, especially coronary artery disease (CAD), and is particularly centred on the detection of viable myocardium • PET helps in identifying patients who are likely to benefit from heart bypass surgery
Neurology [60]	• PET is useful in diagnosis, planning treatment and predicting outcomes in various neurological disease states

1 Doctor sends the patient for a PET scan	2 The radiopharmacist prepares the radiotracer to be injected into the patients body	3 Once injected into the patient the radiotracer will accumulate in regions of high activity such as a brain tumour
4 The patient lies down on a moveable bed which enters into the PET scanner *via* the gantry	5 The patient slowly moves through the gantry and cross sectional slices of the body are scanned	6 The positrons emitted from the radiotracer collide with the surrounding electrons and generate gamma photons which are recorded by the outer detector ring
7 Over a million events are recorded in minutes to generate a slice of information to show biological activity	8 Computer software combines the slices into a complete image	9 Finally, a radiologist examines the images to formulate an opinion for the doctor

Fig. (13). A matrix showing the steps involved in a typical 'hospital' PET imaging procedure.

create a colour (or a black and white) coded matrix image of the patient's biochemical and physiological functions. Today, the most diffuse tool is the hybrid machine PET–CT scanner capable of producing a simultaneous image. The image is generated from the functional data obtained by the PET component and the morphostructural information by the CT scanner. It is not the objective of this review to discuss the technological advances of PET because these can be better understood by other publications.

Today, a typical PET scan procedure, previously taking up to one hour, is now feasible within 25 minutes. The radiation dose received by the patient is generally lower compared to CT and conventional x-ray techniques (Fig. **13**).

5. PET & NEUROLOGY

The standard basic principle of PET neuro-imaging, using FDG glucose or flow radiotracers, is based on an assumption that the radiotracer uptake is related to brain activity [60]. This activity can be evaluated by measuring the blood flow to various regions of the brain by administering the radiotracer oxygen-15. The disadvantage of using this radiotracer is its very short half-life of 2.03 minutes. Therefore, on its output from the cyclotron it must be immediately transported and administered to the patient. The most consolidated approach is based on the principle that the brain utilizes glucose in its metabolism [61] as is demonstrated in the series of PET scans shown in Fig. (**14**).

It is evident from the series of brain images that the highest physiological activity is observed at the level of grey matter, where FDG's uptake is around 4 times higher with respect to white matter. No activity is observed at the level of the liquor. A disease state determining a pathological distribution can be detected both as reduced uptake as in Alzheimer's disease and in benign tumours. Also, in areas of increased concentration which are observed in malignant tumours and in ictal (seizures) epilepsy.

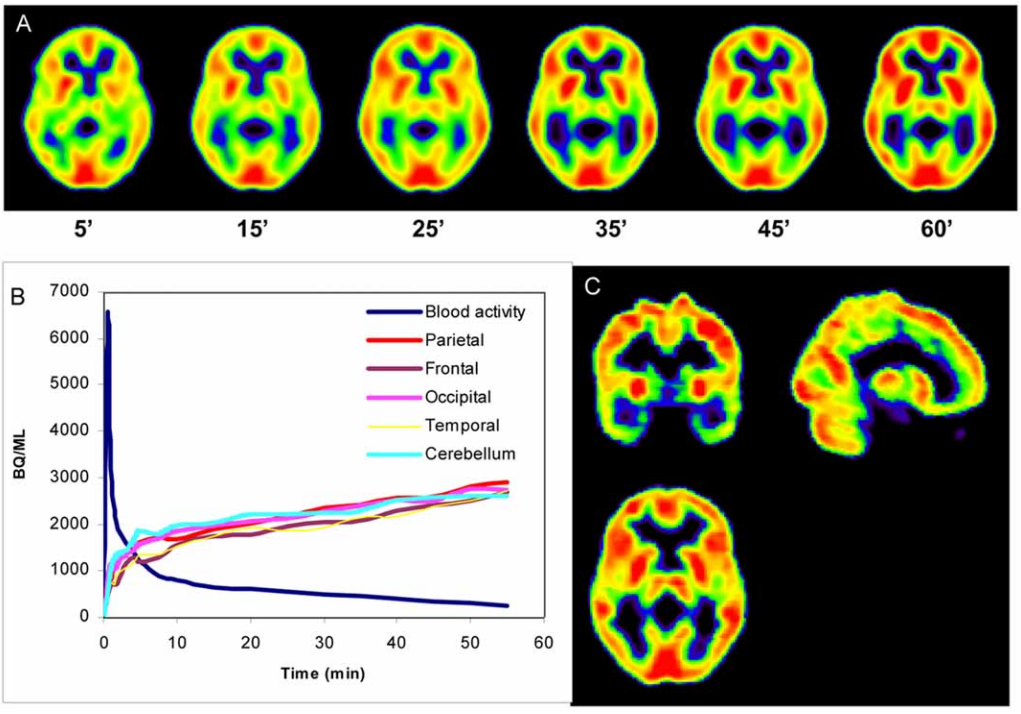

Fig. (14). Shows a series of PET-FDG scans of a healthy brain (**Panel A**). The images were taken at 5, 15, 25, 35, 45, 60 minutes from a healthy 52 year old control patient. The PET-FDG scan looks typical for that age with a good cortical signal in the outer rim of this transverse section through the brain. **Panel B** shows FDG counts at each time point in blood (blue line) and several cortical areas. **Panel C** shows Ki images (coronal, sagittal and axial view) estimated using patlak approach.

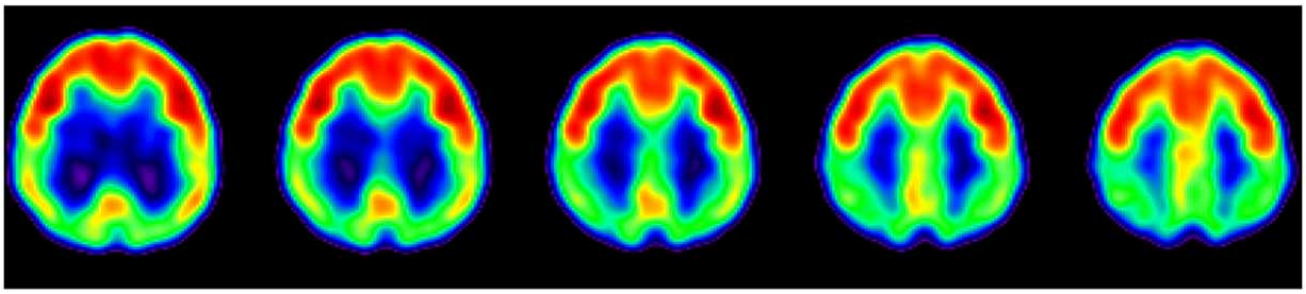

Fig. (15). Shows a series of PET-FDG scans of a patient with Alzheimer's disease.

Alzheimer's Disease

In patients with Alzheimer's disease (AD) the PET-FDG scans show gradual deterioration of the brain. Alzheimer's disease leads gradually to loss of memory and breakdown of cognitive thinking patterns [62,63]. The diagnosis of Alzheimer's disease in patients can sometimes be made by carrying out a number of psychometric tests to evaluate the level of cognitive ability. PET-FDG imaging can confirm a conclusive diagnosis of AD, finding a clinical role in patients with suspected dementia. The series of PET brain scans given in Fig. (**15**) show a reduction in glucose metabolism in the cerebral cortex which is a thin outer layer of the brain at the level of the parietotemporal cortex, responsible for memory, language and alertness. The next generation of PET scanners will have the capability to detect early signs of altered distribution at the level of the posterior cingulated cortex and of hippocampus in AD patients.

PET-FDG imaging of the brain may also be used to differentiate Alzheimer's disease from other dementia conditions (Fig. **16**). The most important consideration for any patient is an early diagnosis of the onset of Alzheimer's disease so treatment can be started as soon as possible [64a].

Huntington's Disease

Huntington's disease is a degenerative neurological disorder manifesting in abnormal involuntary movement, psychiatric disorder and dementia. PET-FDG imaging shows a brain dysfunction beginning many years before clinical presentation with evidence of decreased striatal FDG-uptake [64b] (Fig. **16a**). Dynamic FDG-PET studies have shown an alteration in the kinetics of striatal glucose in patients with Huntington's disease (Fig. **16b**).

A wide range of carbon-11 radiotracers have been developed for PET imaging that are specific neuro-receptor subtypes are outlined in Table **5**. These radiotracers are used mainly for research purposes in PET centres which have a cyclotron and a qualified radiochemistry, act as either agonists or antagonists to allow the visualization of neuro-receptor sites in particular neurological disease states. For example the radiotracer *N*-methyl-[^{11}C]-2-(4'-methylaminophenyl)-6-hydroxybenzothiazole known as [^{11}C]PIB or Pittsburgh Compound-B is a novel PET probe which helps in the visualization of beta-amyloid (Aβ) plaques in the brains of Alzheimer's patients (Fig. **17**). *Note* beta-amyloid (Aβ) is a peptide of 39–43 amino acid units that appear to be the main

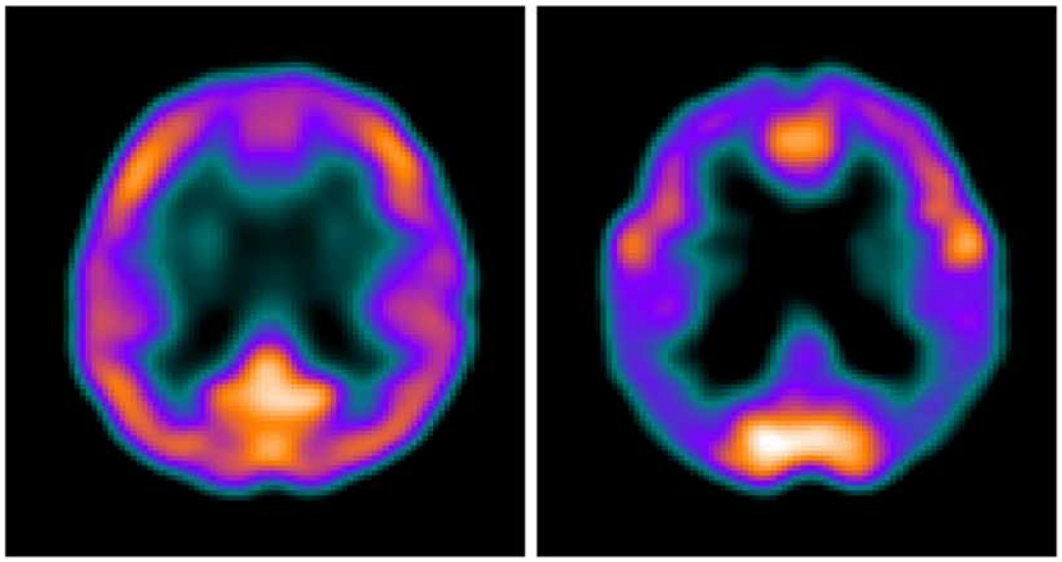

Fig. (16). These PET images show normal brain activity (left scan) and reduced brain activity as a result of Alzheimer's disease (right scan). The diminishing of the intense red and yellow areas in the right scan indicates mild Alzheimer's disease (AD), with the increase of blue colours showing decreased brain activity.

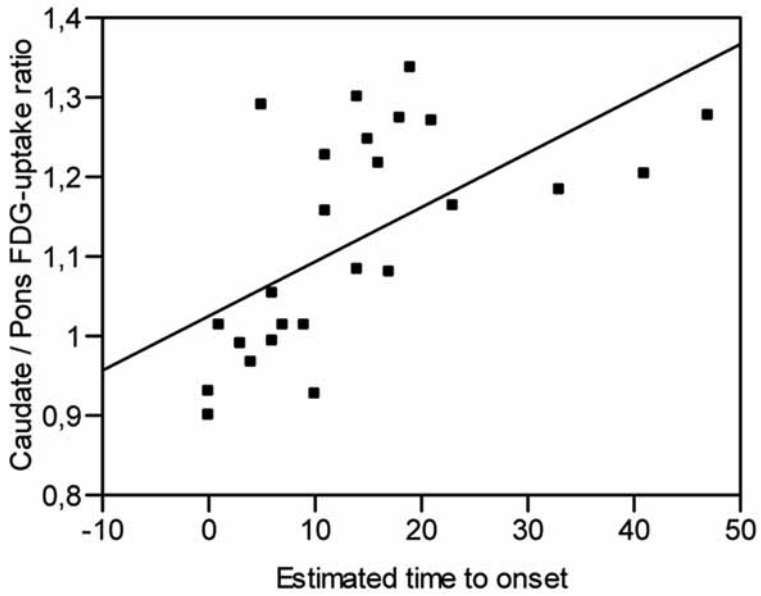

Fig. (16a). This plot shows a linear correlation of caudate FDG-uptake verses the estimated time to clinical presentation of Huntington's disease (R2=0.36; p=0.0004).

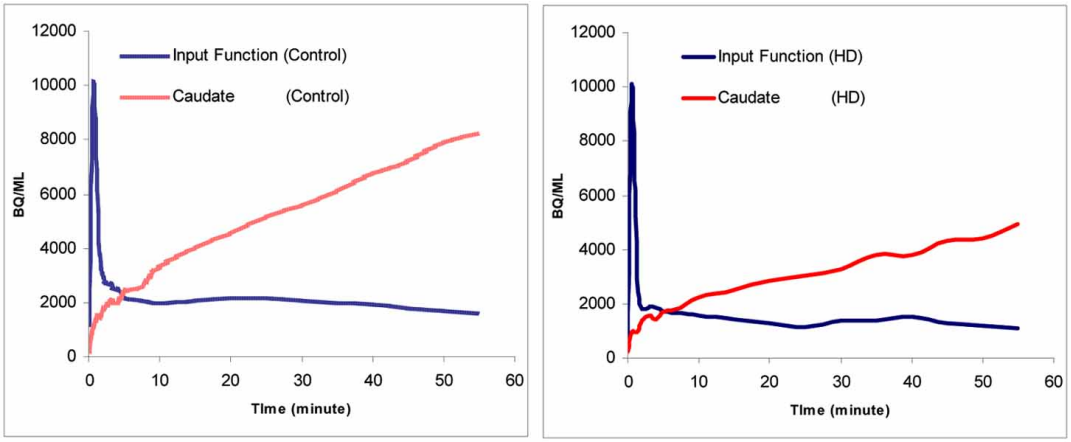

Fig. (16b). The left control plot shows whole blood and caudate activity in healthy and HD subjects. The right plot shows a different slope and amount of FDG-uptake in a patient having Huntington's disease compared to a control.

constituent of amyloid plaques in the brains of Alzheimer's disease.

PET amyloid plaque imaging with [^{11}C]PIB is shown to have a higher accumulation in patients diagnosed with AD and also in its early stages in comparison to patients with no dementia. Most importantly, [^{11}C]PIB confirms the existence of Aβ plaques prior to the onset of dementia. Hence, PET [^{11}C]PIB imaging can now detect preclinical AD pathology with the same accuracy as seen in post-mortem examinations [65]. It has however to be pointed out that the clinical role of PIB both in patients with AD and in those affected with its first clinical step, the Mild Cognitive Impairment (MCI), has not been yet generally accepted, requiring a wider clinical experience. In particular, the possible role of PIB not only in early diagnosing MCI, but also in individually defining the evolution from MCI to AD could be a pivotal acquisition, if connected with the availability of new drugs or strategies avoiding this clinical path. A major advantage for a wider distribution of neuroreceptor imaging, needed to create a clinical role, is connected with flourine-18 radiotracers for the imaging of the same receptor subtypes presented in Table **5**. In fact, it has to be noted that fluorinated agents can be used also in PET centres without a cyclotron or qualified radiochemistry, therefore creating a major opening to the clinical diffusion of these procedures.

Parkinson's Disease

In movement disorders and in other diseases of the motor system, the contribution of PET–FDG is useful, but doesn't have the capability to answer some relevant clinical questions [66]. A major interest is therefore connected to other radiotracers. Dopamine [67] is a 'phenethylamine' neurotransmitter and is produced in several areas of the brain including the substantia nigra. There are five types of dopamine receptors called D_1, D_2, D_3, D_4 and D_5. The PET radiotracer 4,5-dihydroxy-2-[^{18}F]fluoro-*L*-phenylalanine ([^{18}F-

Table 5. PET Imaging Using Carbon-11 Radiotracers Subtypes Used in Neurology [47]

Neurotransmitter Group	PET Radiotracer
Dopamine D_1	[^{11}C]SCH 23390 [^{11}C]NNC 112
Dopamine D_2	[^{11}C]Raclopride [^{11}C]NMSP [^{11}C]FLB 457
Dopamine transporters	[^{11}C]Methylphenidate [^{11}C]PE2I
Serotonin 5-HT_{1A}	[^{11}C]WAY-100635
Serotonin 5-HT_{2A}	[^{11}C]NMSP [^{11}C]MDL-100907
Serotonin (5-HT) transporters	[^{11}C]McN [^{11}C]DASB [^{11}C]MADAM
Opiate	[^{11}C]Diprenorphine [^{11}C]Carfentanil
Neurokinin-1	[^{11}C]SPA-RQ
GABA-Benzodiazepine	[^{11}C]Flumazenil
Peripheral Benzodiazepine	[^{11}C]PK11195

DOPA]) is widely used in the study of the dopaminergic system in movement disorders. [^{18}F]DOPA is taken up by the terminals of dopaminergic neurons and converted to [^{18}F]dopamine by the enzyme dopa decarboxylase and other dopamine metabolites. [^{18}F]DOPA-PET can provide *in vivo* diagnostic information about the function of the pre-synaptic dopaminergic terminals (Fig. **18**). Other PET tracers that bind to pre-synaptic dopamine transporters include [^{11}C]methylphenidate and [^{11}C]dihydrotetrabenazine.

Parkinson's disease (PD) [68] is the result of loss of dopaminergic neurons in the substantia nigra. The greatest loss of neurons is seen in the ventrolateral tier of the pars compacta, with lesser involvement in the dorsomedial tier. These areas can be detected by PET-[^{18}F]DOPA and show a decline in [^{18}F]DOPA levels in the putamen contralateral area of the brain.

The presence of PET radio-compounds tracing all the steps of dopamine neurotransmission could open up a future clinical role not only for an early diagnosis and a prognostic evaluation, but also for a better definition of therapeutic strategies. At present, the most important clinical information allowed by dopamine receptor imaging is the differential diagnosis between Parkinsonism and essential tremor. This is also achievable by SPECT using [^{123}I]-ioflupane, presenting a high binding affinity for dopamine transporters in the brains of mammals, in particular the striatum region [69].

Epilepsy

Epilepsy is a disorder of the central nervous system (CNS) resulting from electrical activity in the brain, and characterized by seizures. This chronic neurological disorder occurs in about 20-50 cases in a 100,000 population sample. The seizures are the result of abnormal firing of the neurons in a cluster of brain cells (Fig. **19**). These cells become highly metabolic during the seizure period and show decease in activity between seizures than normal functioning brain cells [70].

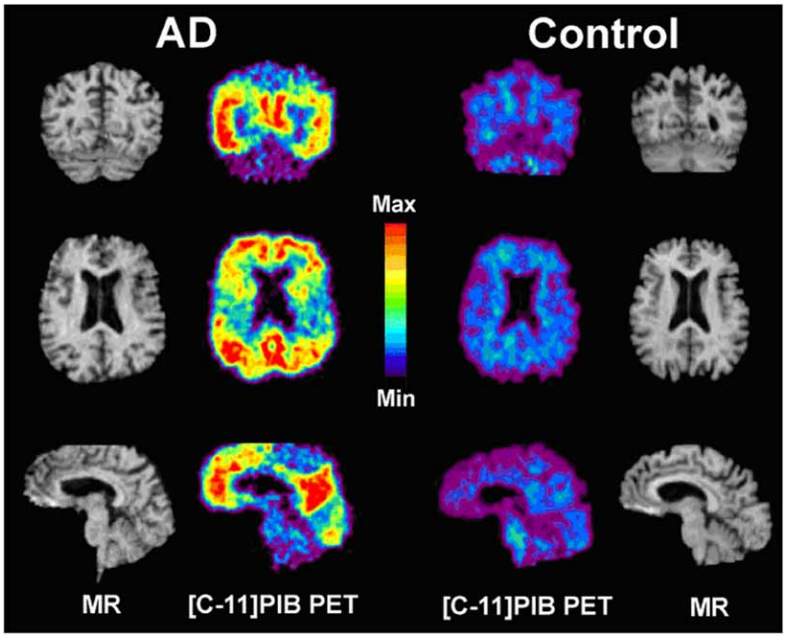

Fig. (17). These PET images are the result of using the radiotracer Pittsburgh [^{11}C]PIB. This radiotracer causes the cortical areas in an Alzheimer brain to 'light' up to indicate amyloid plaques.

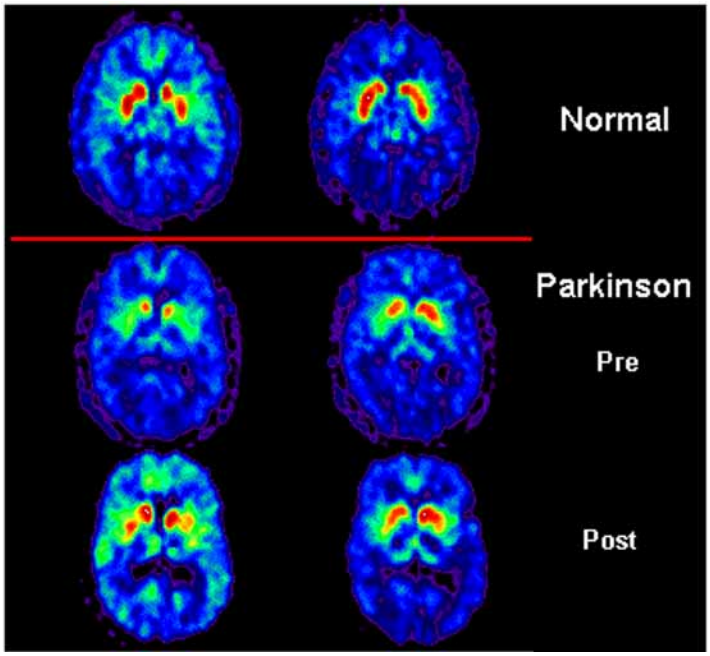

Fig. (18). These PET images of the brain show if the patient has Parkinson's disease. The labelled amino acid [^{18}F]DOPA is used with PET to see if your brain has a deficiency in the neurotransmitter dopamine. If no deficiency is shown then the patient does not have Parkinson's disease and therefore the tremors can be treated differently.

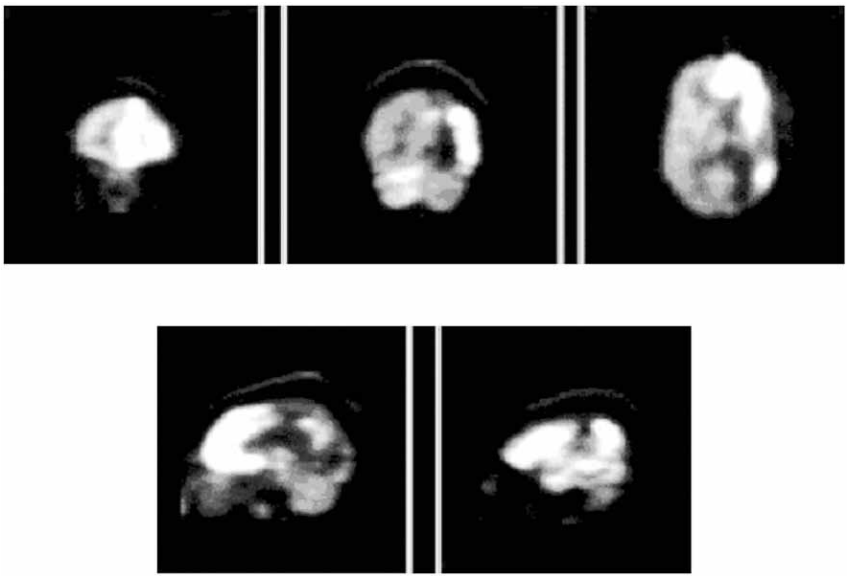

Fig. (19). Shows a series of PET-FDG scans resulting from epileptic seizures.

The application of PET-FDG imaging in epileptic patients is to determine the regions in the brain which show epileptogenic foci. PET imaging was first introduced in the 1980s to study epilepsy following the observation of regional glucose hypo-metabolism in patients with partial seizures using the radiotracer FDG (Fig. **20**). Hence, PET can provide information on cerebral blood flow, oxygen consumption and cerebral glucose metabolism. In partial seizures, there is an increase in glucose metabolism and cerebral blood flow in the region of the epileptogenic foci during the ictal (seizure) period. A scan performed during the ictal period creates more favourable conditions to detect the focus, acquiring a further clinical relevance when a fusion imaging with MRI (or CT) permits a precise anatomical localization.

PET-FDG imaging shows how the tissues in the brain are functioning. The regions of lower function will use less energy in comparison with high metabolic regions, which consume lots of energy. The PET scan will show the difference in functional activity. Diagnosis is facilitated during a seizure, because pathological regions will be detected (light up) as areas of increased glucose metabolism. Following the

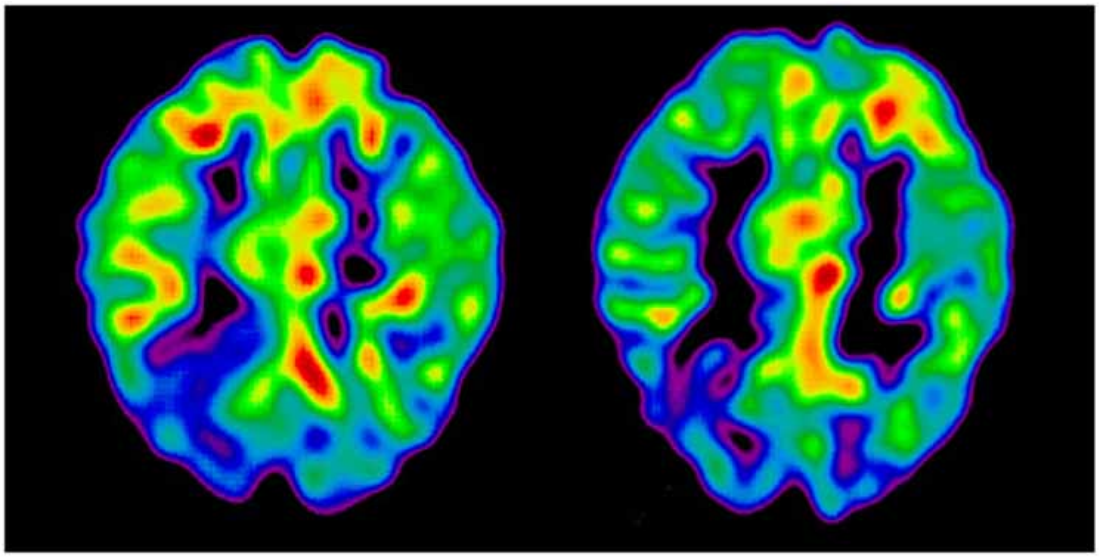

Fig. (20). Both PET-FDG scans show epileptic hypo-metabolism in the right posterior parietal region. Using the technique Ictal EEG demonstrated seizure onset from the right parietal lobe.

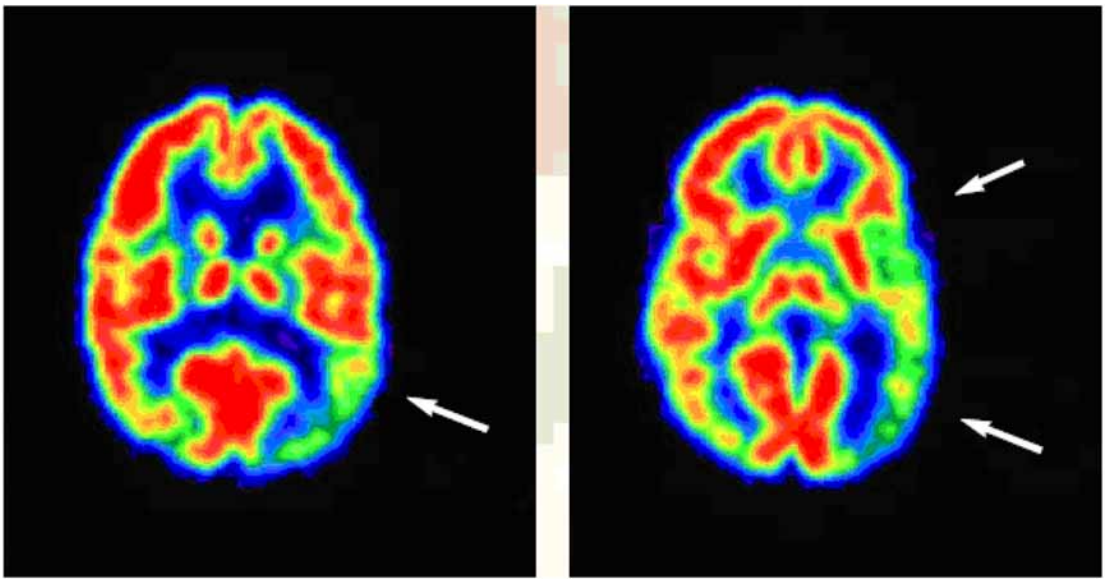

Fig. (21). Both PET-FDG scans indicate abnormal high glucose metabolism levels in the brain.

seizure, the brain glucose level can decrease or remain elevated for couple of days (Fig. **21**).

In between seizures, PET-FDG will show a pattern of slightly reduced need for glucose and therefore, because of the uptake at the level of the normal brain, the epileptic focus is in many cases not easily detectable.

The advantage of using PET-FDG imaging is in its ability to provide an insight as to the degree of severity of the epilepsy thus preventing invasive surgery or conversely providing information regarding a surgical strategy. In some cases, surgery requires electrodes being placed directly on the surface of the brain to monitor electrical activity. The majority of epileptic patients can control their condition with powerful drugs and therefore do not require surgical intervention. If neurosurgery is required a PET scan helps to decide the best option for brain surgery to remove defective tissue and reduce the frequency of seizures.

At present, the most important clinical indication of PET-FDG is in detection of the epileptogenic regions in patients with temporal lobe epilepsy (TLE) reducing the need for invasive electro-encephalogram (EEC) studies. Temporal lobe epilepsy (TLE) is a form of focal epilepsy, a chronic neurological condition characterized by recurrent seizures. PET can also measure the binding of specific radiotracers to 'brain' receptors, which contribute to the formation of seizures. For example serotonin 5-HT_{1A} receptor binding is shown to decrease in TLE [71]. To date, PET-FDG performed during a seizure remains the most sensitive, non-invasive imaging tool for temporal lobe seizures compared to MRI [72], which is however mandatory both for a better

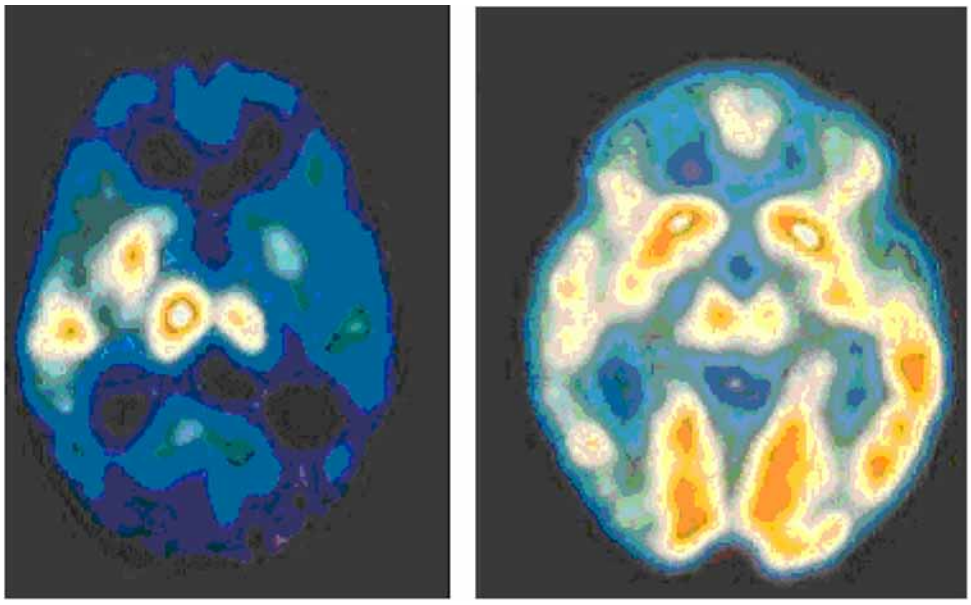

Fig. (22). PET-FDG scans comparing brain activity during periods of depression (left) with normal brain activity (right). An increase of blue and green colours, along with decreased white and yellow areas, show decreased brain activity due to depression.

anatomical location and for the detection in between seizures.

The PET radiotracer [^{11}C]flumazenil has been used to study the BZD receptors in the role of epilepsy [73]. These BZD receptors are situated in the same region as the γ-aminobutyric acid (GABA) receptors. The latter being the most important inhibitory neurotransmitters in the CNS. A reduction in [^{11}C]flumazenil binding has been observed at the mesial temporal lobe in TLE patients from the amygdale (an 'almond-sized' shaped brain structure linked to the person's mental and emotional state) and hippocampus region of the brain which is located in the medial temporal lobe.

6. PET & PSYCHIATRY

A large number of compounds (drugs) have been synthesized with carbon-11 or fluorine-18 radiolabels and tested for selectively binding at specific neuro-receptors, which are of interest in psychiatric disorders. PET radiotracers that bind to dopamine, serotonin, opioid receptors and other sites have been used in human studies. Research has evaluated the changes in the neuro-receptors of psychiatric patients com-

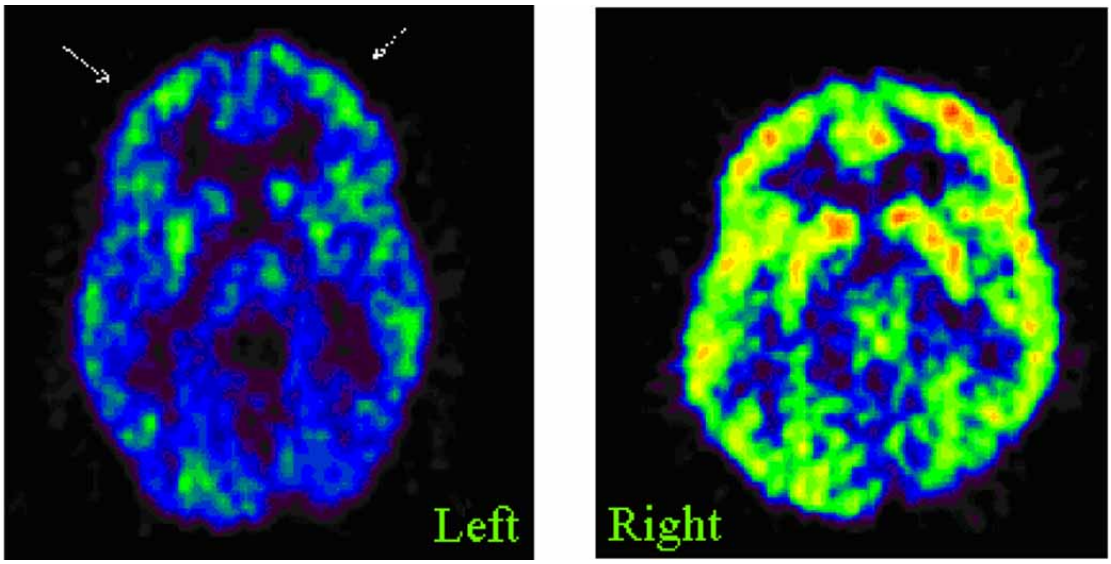

Fig. (23). PET-FDG scans demonstrating a comparison between a clinically depressed patient (right scan) and a control patient with no depression (left scan). The blue colour represents less activity (glucose metabolism) while the red represents more activity (glucose metabolism). *Note* the relative hyperactivity of the cortex on the right scan with marked hyperactivity of the prefrontal, frontal and deeper basal ganglia.

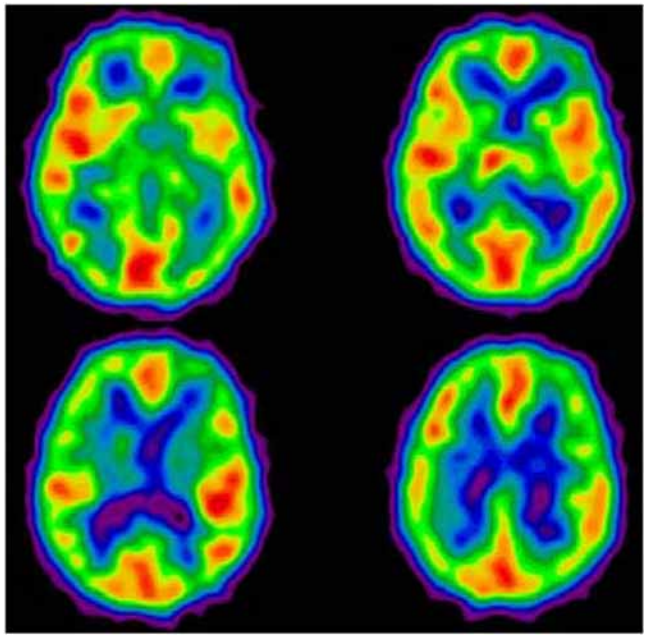

Fig. (24). This perfusion PET image of the brain was carried out with the radiotracer [^{15}O]H_2O and completed in one minute. The radiotracer diffuses freely from the capillaries into the brain tissue after the intravenous injection.

pared to healthy controls for schizophrenia, substance abuse, mood disorders and other psychiatric conditions [71,74]. Although this indication is not in the clinical field, for the first time the PET images in Fig. (**22**) and Fig. (**23**) are able to be used as a diagnostic tool to detect depression in an individual.

7. PET & ONCOLOGY

Clinical applications of PET imaging in oncology have been developed since the 1980s at first in brain tumours [14,16,20,21] and subsequently for whole body evaluation. In the last decade this imaging technique has become an essential tool in the assessment of cancer [75]. The Centers for Medicine and Medicaid Services (CMS) in the USA first approved PET for use in oncology in 1998 [75] and today PET with FDG has a major role in oncology. Essentially, this review is not able to report on the pathophysiological premise of all clinical information regarding a deeper analysis of normal distribution, physiological and pathological distributions of PET radiotracers, and its associated pitfalls. For this purpose many publications and books can address these issues more thoroughly [31].

Presently, research into cancer focuses on prevention by avoiding associated predisposing risk factors, diagnosis and effective and subsequent treatments. The challenge for cancer research is to develop *in vivo* and *vitro* models in order to understand complex biological processes and subsequently to transfer these 'cancer' models into the clinical field. Consequently, some of the most promising applications of PET include: tumour imaging and diagnosis with molecular markers, including apoptosis markers and analysis of the tumour environment (hypoxia, neo-angiogenesis) prior to therapy [76].

One of the advantages of Nuclear Medicine over conventional Radiology is its ability to provide physiological rather than anatomical information. PET imaging techniques map out the bio-distribution of an administered radiotracer (Fig. **24**) [50]. It is accepted that the rate of glucose metabolism is much higher in cancer than in normal tissues. This behaviour is dependent on faster cell division with respect to normal cells and to an increased anaerobic metabolism determining a higher FDG uptake which is related to malignancy/disease.

The accelerated rate of glycolysis results from increased levels of hexokinase activity. This hexokinase activity also results in an increased concentration of glucose transport proteins in the tumour cells. This property can be exploited to confirm a diagnosis of a brain tumour/cancer by using PET-FDG (Fig. **25**).

It has to be pointed out that the brain normally consumes glucose and therefore this can represent some difficultly in analysis for FDG, because of the relatively low tumour and background ratio achievable. Therefore, although PET-FDG represents a useful tool, mainly for diagnosis of tumour recurrence or for a prognostic evaluation of malignancy, it is not too accurate in detecting brain metastases, where a diagnosis with CT or MRI is preferable. Conversely, an easier analysis is possible for a whole body evaluation.

A further limitation of using the PET radiotracer FDG in oncology is that glucose metabolism is not significantly increased in every tumour. For example, it can be low in prostate carcinoma or in well differentiated tumours, like thyroid carcinomas and neuroendocrine tumours (NETs). Other false negative results can be obtained for tumour lesions smaller than 0.5-1.0 cm, with low accuracy in the presence of a higher background uptake. Another significant disadvantage for the diagnostic role of FDG in oncology is that it is not specific entirely to the tumour. Some disease states, with the presence inflammation and/or infection can lead to elevated levels of FDG uptake [77].

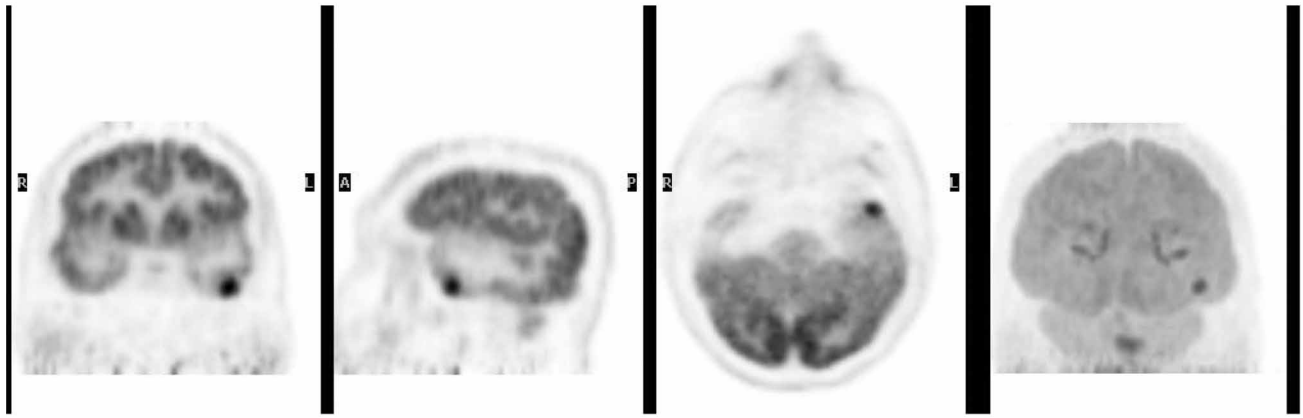

Fig. (25). Shows a series of PET-FDG scans indicating an intense uptake at level of a brain tumour in the temporal lobe.

Therefore FDG is to be used only where it can significantly determine diagnostic accuracy as opposed to using a standard approach – otherwise, it must be used with caution – for example differential diagnosis of solitary pulmonary nodules. Conversely the FDG role is ever more important in restaging (and staging) of patients with tumours showing high uptake at their presentation, because of a higher sensitivity in detecting metastases, with main reference to lymph nodes as opposed to a standard approach. In patient follow-up, a high clinical value is also obtained from information relating to diagnosis of disease recurrence. More recently, the capability of FDG to represent an earlier marker of tumour response with respect to CT is creating a new and very important field of application in oncology.

Difficulties in the assessment of brain tumours, because of the high uptake of FDG in normal tissue, allowed for the introduction of alternative radiotracers to provide a deeper pathophysiological evaluation. For example, brain tumours can often be associated with oedema and unfortunately, imaging techniques such as MRI are unable to distinguish between extra- and intracellular environments. The radionuclide [^{76}Br]bromide has been used to measure the regional extracellular space in a variety of brain tumours due to the fact that bromide ions can distribute exclusively in the extracellular space (Fig. **26**). The knowledge gained from extracellular brain oedema imaging is essential since it can be used to define the diffusion properties of drugs used in tumour treatment [78].

A quantitative measurement of the blood brain barrier (BBB) permeability can be obtained by using the radiotracer [Ga-68]EDTA complex [79]. The quantitative analysis significantly increases achievable information, as demonstrated both in neoplasm and in multiple sclerosis (MS) [80,81]. As previously said, PET-FDG doesn't have a clinical role in diagnosis (and staging) of well differentiated tumours, such as thyroid carcinomas, where the examination is less sensitive because of the absence of FDG uptake at the level of slow growing malignancies.

Since there is an increased glucose metabolism in tumour cells the PET-FDG radiotracer can target the thyroid metastases as the tumour cells become undifferentiated, losing their capability to concentrate iodine.

In the follow-up of patients with thyroid cancer, presenting high serum thyroglobulin (Tg) levels, FDG's uptake can therefore define a difficult prognosis indicating that certain patients cannot be cured with radionuclide therapy using iodine-131 [82] (Figs. **27, 28**).

[^{18}F]Fluoromisonidazole

PET-FDG is an established imaging technique for targeting volume delineation (tumour shrinkage) following radiotherapy treatment for example in head-and-neck cancers [83]. In addition, the radiotracer [^{18}F]fluoromisonidazole has been used to assess the hypoxic level in a variety of tumours (Fig. **29**). Tumour hypoxia has been shown to be one of the

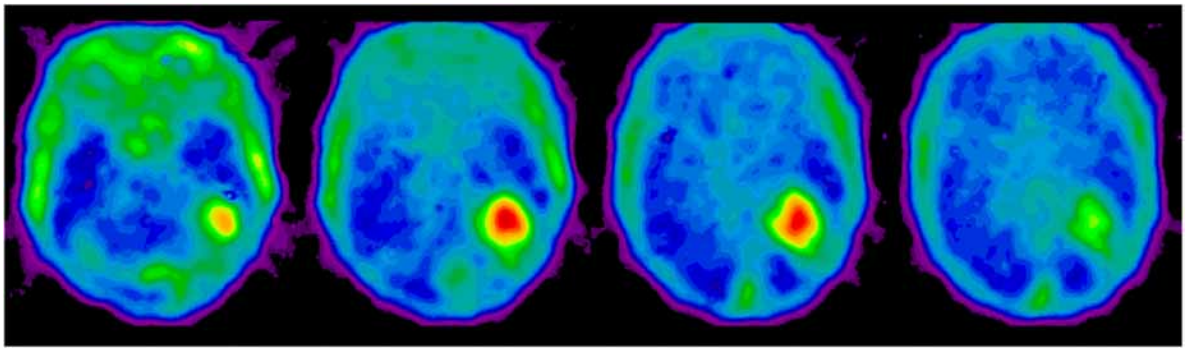

Fig. (26). A series of PET-[^{76}Br]bromide scans revealing circumscribed extracellular oedema in the tumour are shown by the red region.

Fig. (27). Shows a typical PET-FDG scan indicating (*via* arrows) undifferentiated thyroid cancer metastases.

major contributory factors affecting the ability to treat tumours. The hypoxia is a consequence of an irregular vascular structure of a tumour in which excessive proliferation plays a role. Tumour tissues that show high metabolic activity often have enhanced proliferation rates, which may lead to tumour hypoxia. Glucose metabolism may also be activated under hypoxic conditions [84].

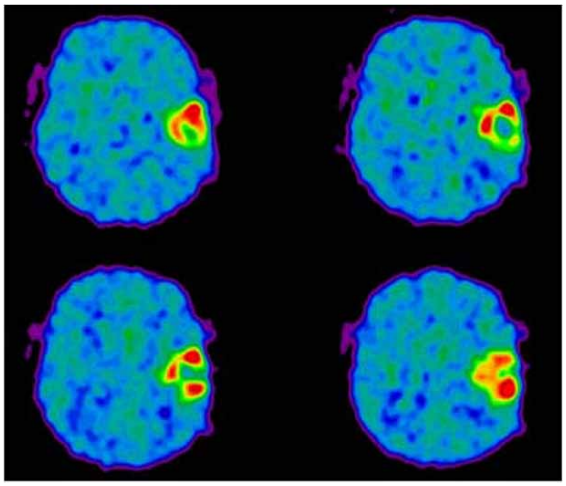

Fig. (29). Shows four PET scans from the injection of [^{18}F]fluoromisonidazole acquired after 150-180 minutes to locate a glioblastoma multiforme tumour in the left temporal lobe. Hence, there is high uptake in the tumour rim and not in its centre.

Lung cancer, FDG and [^{18}F]Fluorothymidine

PET is one of the most important tools in lung cancer imaging since the introduction of Computed Tomography (CT) [85]. Lung cancer cells have shown to have a high affinity for FDG and therefore PET can help in the diagnosis, prognosis, staging and re-staging of lung cancer. The major-

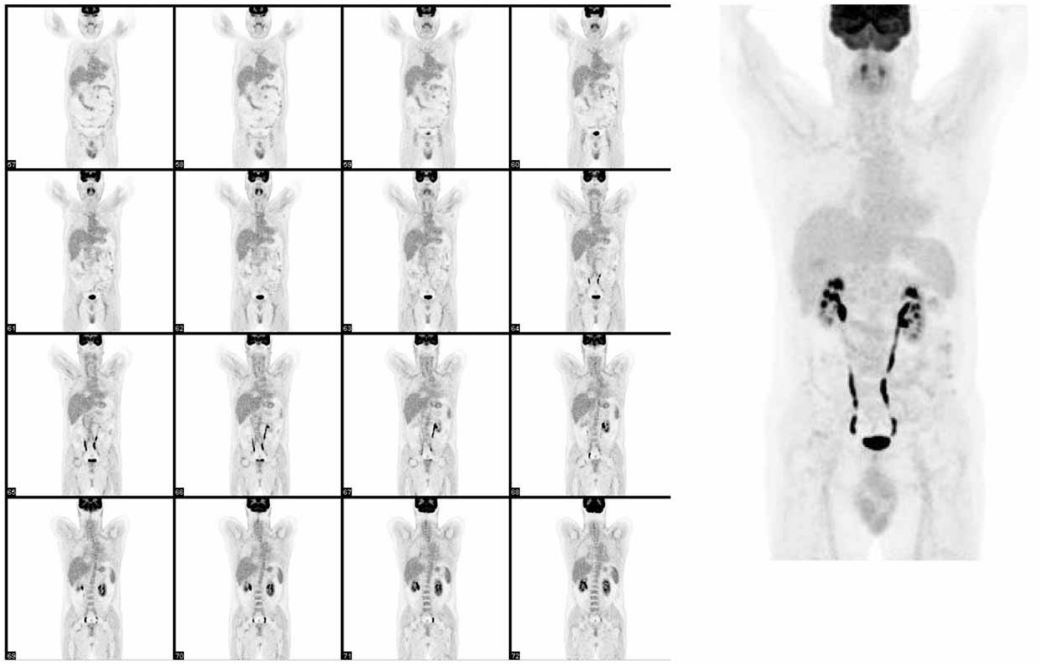

Fig. (28). Thyroid cancer follow-up after surgery and radionuclide therapy with iodine-131 indicating a false-positive increase of Tg serum levels providing a true-negative PET result.

ity of published work in lung cancer relates to non-small-cell-lung-cancer (NSCLC), but evidence suggests that PET is also an excellent method for imaging small-cell-lung-cancer, presenting an important clinical role, mainly in re-staging [86]. The thymidine radiotracer analogue [^{18}F]fluorothymidine [87] has a greater uptake in lung cancers with high proliferating cell activity. [^{18}F]Fluorothymidine is not usually expected to be concentrated in inflammatory lesions. This observation can lead to a wider clinical experience creating an important premise both in increasing diagnostic accuracy at the first diagnosis and defining '*in vivo*' prognosis on the basis of the analysis of the DNA doubling rate.

Lymphoma

Malignant lymphomas are the fifth most frequency occurring type of cancer in the USA [88]. In 2005 there were 7,350 new cases of Hodgkin's disease (HD) and 56,390 new cases of non-Hodgkin's lymphoma (NHL) diagnosed [89]. NHL's are a heterogeneous group of diseases that vary in prognosis according to histological and clinical features.

PET-FDG imaging has gained a role in the staging and assessment of Hodgkin's disease and non-Hodgkin's lymphomas completely replacing gallium-67 ($t_{1/2}$ = 78 hours) as a radiotracer (Fig. **30**) [90]. Today there are many protocols for considering the possible role of PET-CT as an alternative to CT alone for better staging and re-staging of lymphomas.

Breast Cancer

Breast cancer accounts for 33% of all cancers in women with 44,000 new cases reported each year in the UK. The male population is also susceptible to breast cancer but this is rarer with approximately 250 new cases diagnosed each year. Breast cancer develops in the milk-producing glands and in the passages or ducts that deliver milk to the nipples. A major problem is that some breast cancers may spread to other parts of the body for example, the lymph nodes. The UK breast cancer death rate has fallen by 20%, due to advances in treatment and medical imaging techniques [91].

Breast cancer can be accurately detected, staged and re-staged by using PET-FDG imaging (Fig. **31**). The PET-FDG images are classified into unlikely malignant, probably malignant and definitely malignant cancers. Thus breast cancer exhibits increased FDG uptake that is more prominent in infiltrating ductal than in lobular carcinomas. Therefore, FDG uptake in breast cancer can be increased and the degree of uptake is correlated to histological characteristics of breast tumours. It has to be clarified that, because of the presence of false negative and false positive results, PET-FDG cannot be considered an alternative to Mammography (Mx) for screening of breast cancer. Similarly, a higher sensitivity in detecting millimetric lesions is present in MRI which has to be selected as a back-up choice for improving Mx sensitivity. Another important diagnostic tool is ultrasound which can be used instead of/or with Mx prior to any surgical pro-

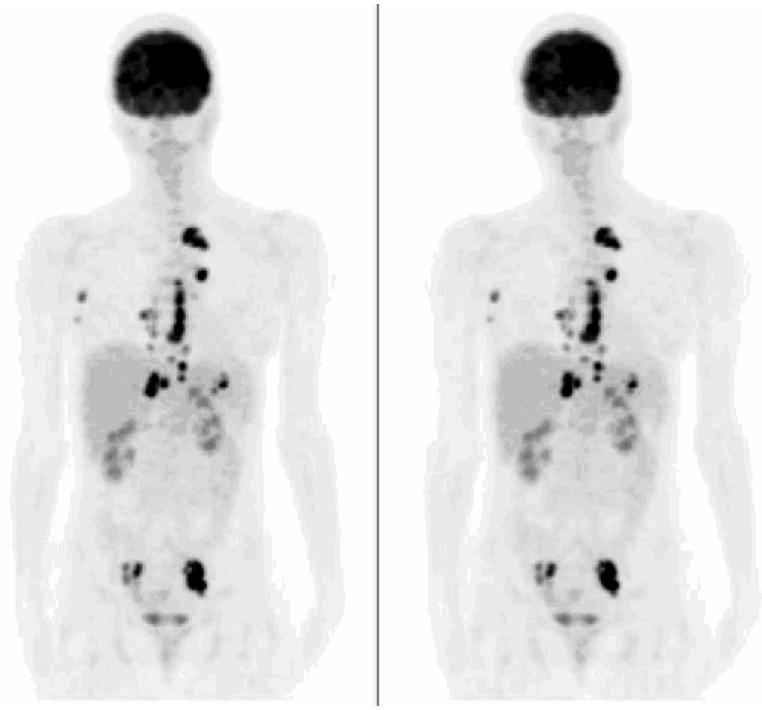

Fig. (30). Shows two PET scans of a patient with *infra* and *supra*-diaphragmatic lymph nodes. These PET images allow complete staging with just one test and serves as the basis to check treatment efficacy.

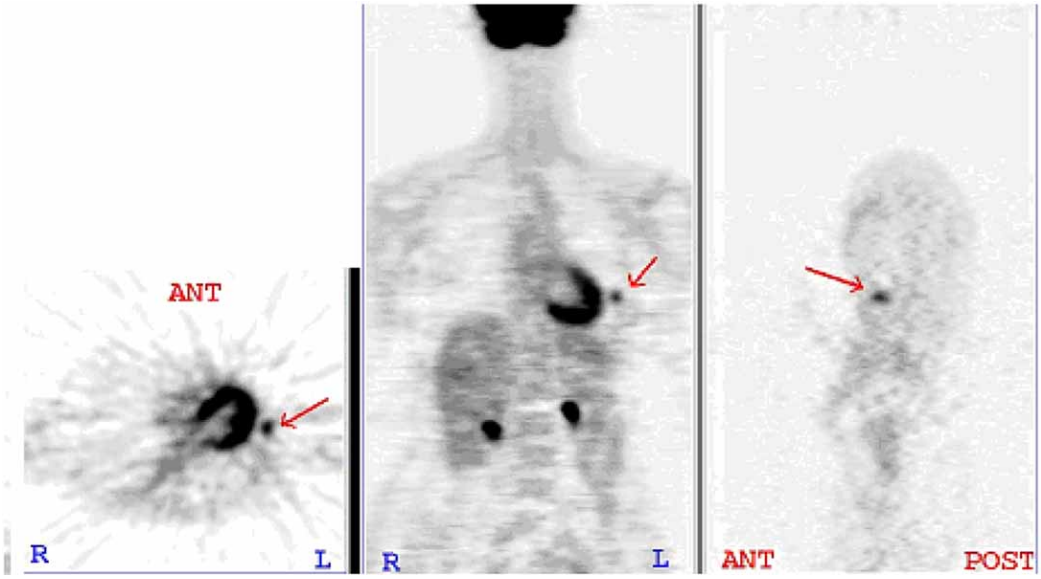

Fig. (31). Shows a PET-FDG whole body scan of a patient with breast cancer and metastatic lymph node cancer. From left to right: Transverse, Coronals and Sagittal scans.

cedure and also to guide cytological analysis. However, in patients of low probability of cancer, with a T1 (small, minimally invasive within primary organ site), N0 (no lymph node involvement), M0 (no distant metastases) stage, the best analysis of lymph node involvement today is connected with radio-guided surgery, using the 'sentinel node' technique. Although due to accuracy, PET–FDG alone should not be used as a technique for breast cancer screening and diagnosis. A possible role for PET–FDG imaging could be found for diagnosis and staging in women with dense or scarred breasts. Other applications include recurrent cancer, in staging of patients with advanced cancer; in restaging of patients with high probability of future metastases can also be considered [92a].

There is an interesting emerging perspective with the studies demonstrating the possible role of PET–FDG as an early marker of a therapeutic response. Clinical trials are in progress using PET Imaging with copper-64 labelled trastuzumab in HER2+ in metastatic breast cancer. The PET scan shown (Fig. **32**) is typical of the radiotracer copper-64 [92b].

[^{11}C]Choline and [^{18}F]Choline

Choline is a natural blood constituent and is capable of penetrating cell membranes. Therefore, [^{11}C]choline was introduced as an alternative radiotracer to address the limitations of using PET-FDG **[**93**]**. In tumours the only metabolic pathway of [^{11}C]choline is its integration into phospholipids. After several metabolic processes it is integrated into the lecithin cell membrane of the tumour. The tumour cells have the ability to undergo rapid duplication and subsequently produce cell membranes at a similar rate. Therefore, the rate of uptake of [^{11}C]choline in tumours is proportional to the rate of tumour duplication. PET-[^{11}C]choline enables the visualization of malignant tumours through the increased demand for cell membrane building blocks during duplication [94]. The [^{11}C]choline tracer has been detected in the liver, renal cortex, salivary glands and kidneys.

Less consistent results were obtained in the lungs, spleen, skeletal muscles and the bone marrow. Variable uptake of the radiotracer was observed in the pancreatic region and a linear uptake in the abdomen. [^{11}C]Choline uptake in the brain was negligible and no uptake was observed in the mediastinum and myocardium. [^{11}C]Choline was shown to accumulate in prostate and bladder carcinomas [95]. Interesting results have also been published in liver cancer, where FDG is affected by a low sensitivity. More recently, the availability of the fluorine-18 substituted choline analogue, [^{18}F]fluoroethylcholine (FECH), as a radiotracer of cancer detection strongly stimulated the diffusion of this procedure for a clinical role in tumours where FDG is not indicated (Figs. **33-35**).

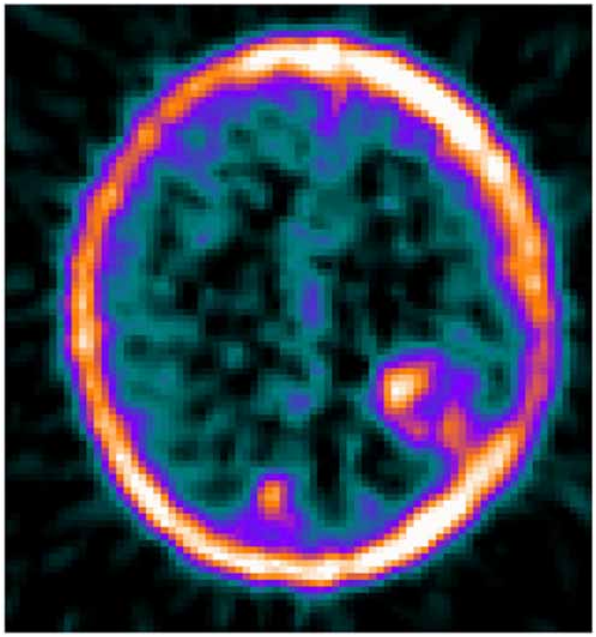

Fig. (32). Show a typical PET scan of breast cancer using the 'positron' radiotracer copper-64.

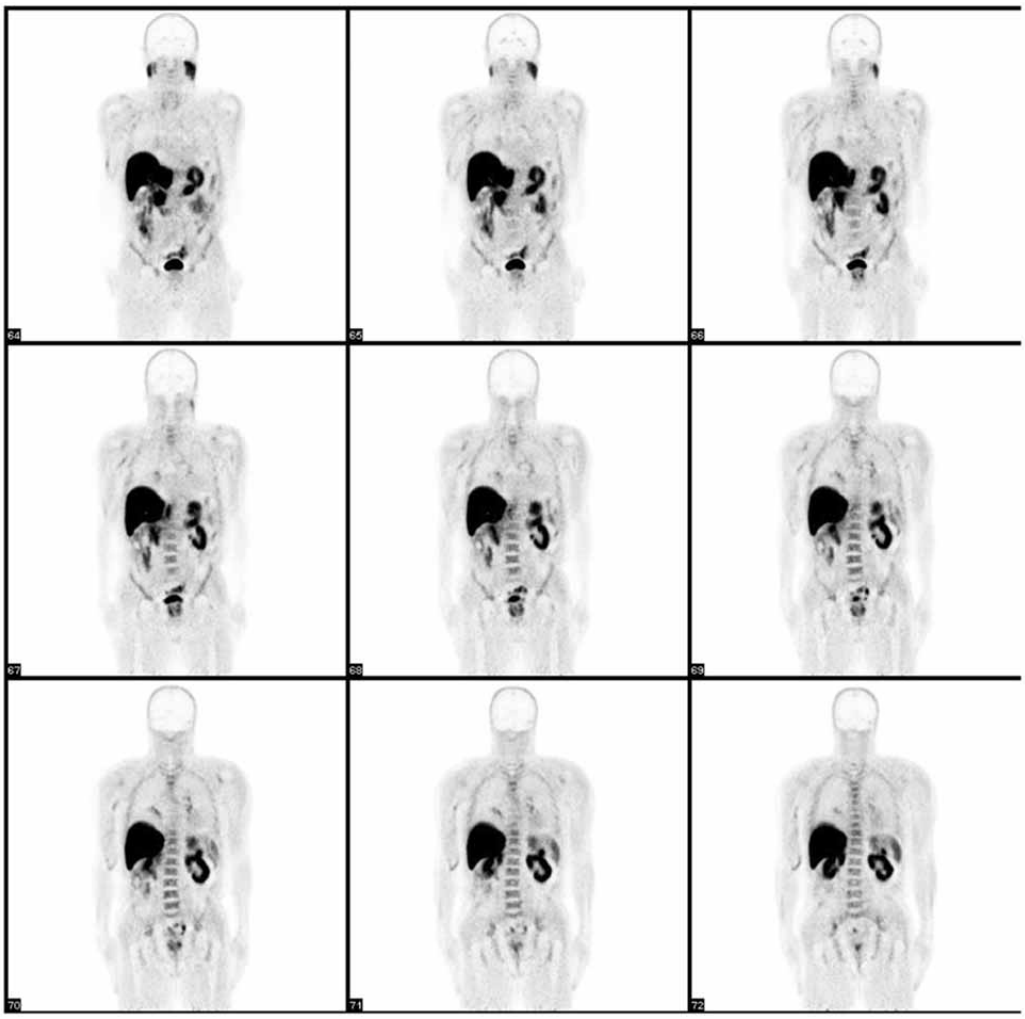

Fig. (33). Shows a PET-FECH scan indicating normal FECH uptake.

[^{11}C]Methionine and [^{18}F]Fluoroethyltyrosine

The PET radiotracer amino acids such as [^{11}C]methionine (C-MET) and [^{18}F]fluoroethyltyrosine (FET) are capable of visualizing tumours by their ability to accumulate in surrounding tissues [96,97]. [^{18}F]Fluoroethyltyrosine was first synthesized in 1988 and studies have shown it usefulness in the evaluation of protein synthesis in brain tumours. This radiotracer has also found application in whole body PET tumour imaging with some degree of success.

The *in vivo* metabolic pathway of [^{11}C]methionine mimics unlabelled methionine unlike other radiotracers. [^{11}C]Methionine is taken up by tumour cells resulting in an increase of intracellular amino acid activity. Conversely, [^{18}F]fluoroethyltyrosine is taken up by tumour cells in a stereospecific manner, which is mediated by the leucine amino acid transport system. [^{18}F]Fluoroethyltyrosine is not incorporated into proteins and is inert to intracellular metabolism unlike [^{11}C]methionine. Tumour uptake of [^{18}F]fluoroethyltyrosine is enhanced due to unexplained cellular mechanisms. In some research studies [^{11}C]methionine and [^{18}F]fluoroethyltyrosine complement PET-FDG for tumour targeting in areas of high glucose metabolism such as the brain [96]. It permits more specific information and accuracy in diagnosis of tumour recurrence and better defines the viable part of the tumour for a more precise biopsy.

Nevertheless, since C-MET and FET uptake is also present in low grade tumours there is a lower prognostic value at the first diagnosis. Therefore it must be done with PET-FDG.

8. PET & CARDIOLOGY

The current applications of PET imaging in cardiology [59] include the measurement of regional myocardial blood flow and the investigation of the patients susceptibility to ischaemic myocardium. The main clinical application is in the definition of the viable myocardium [98]. During the last decade, cardiac PET imaging has become an useful diagnostic tool to determine the vascular condition of the heart. PET imaging provides – in the best way - accurate qualitative and quantitative assessment of the physiological processes in the heart. Therefore, the clinical applications of PET imaging in cardiology are the assessment of the myocardial blood flow understanding of myocardial metabolism and the individual

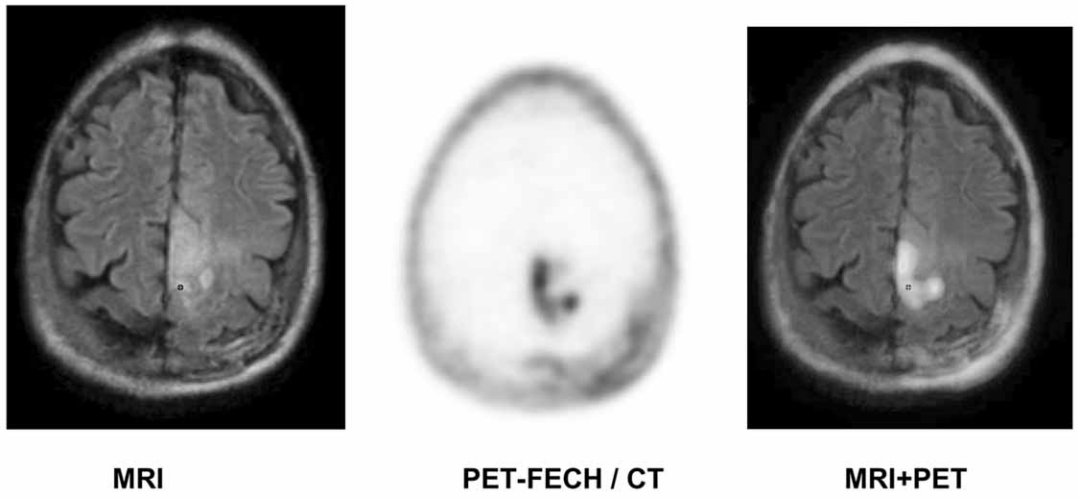

Fig. (34). Shows a PET-FECH scan indicating uptake at the level of a brain tumour; no uptake was shown by the normal brain.

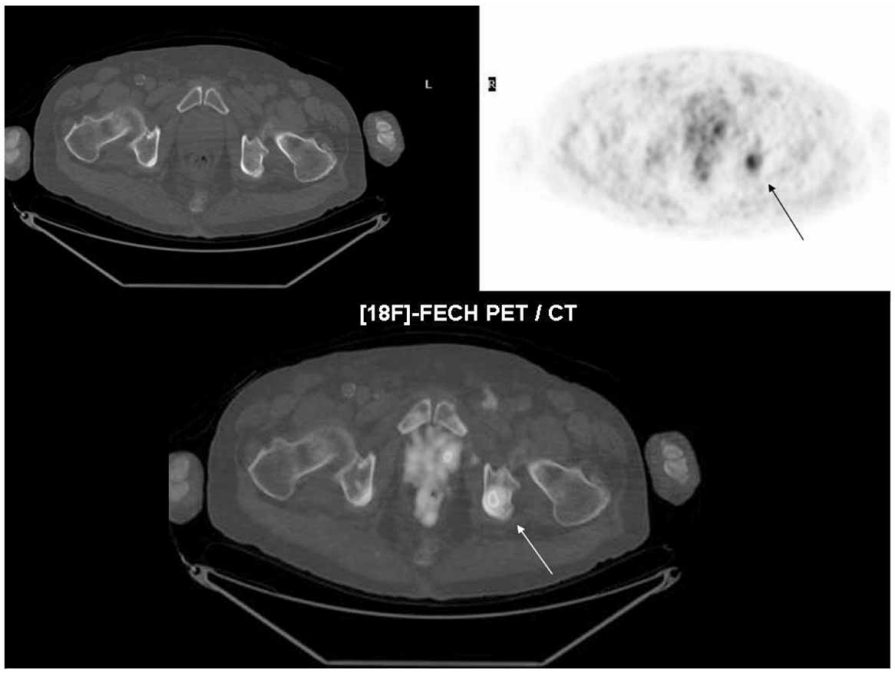

Fig. (35). Shows a PET-FECH scan indicating prostate cancer metastases.

patient risk of developing coronary heart disease (CAD) [99].

There are only three cardiac PET radiotracers, which have been given FDA approval in America. These include rubidium-82 and [^{13}N]ammonia for myocardial perfusion imaging (MPI) studies. The remaining radiotracer is FDG and is used to assess the degree of ischaemic heart disease in the myocardium (Fig. **36**). Cardiac PET-FDG is a well-established imaging technique and has now become the gold standard [100].

Another application of myocardial perfusion imaging (MPI) includes the evaluation of beta receptors or sympathetic receptors in the heart. The distribution of radiotracers in the myocardium is determined by the amount of radiotracer that crosses the capillary membranes in a single injection [59].

The radiotracer [^{13}N]ammonia has a short half-life of 9.8 minutes. At cardiac rest 95-100% it will cross the capillary membranes. The increased blood flow will cause [^{13}N]ammonia to diffuse back into the vascular space. The [^{13}N]ammonia crosses the myocardial cell membrane by the process of passive diffusion. It then becomes trapped in the myocardium *via* the glutamate-glutamine reaction [101].

Rubidium-82 has a very short half-life of 1.3 minutes and behaves like a potassium cation analogue. This radiotracer is absorbed and retained in the myocardium *via* the Na-K activated ATPase system. The rubidium-82 PET tracer in the form of ^{82}Rb-RbCl is easily produced on site of use at the

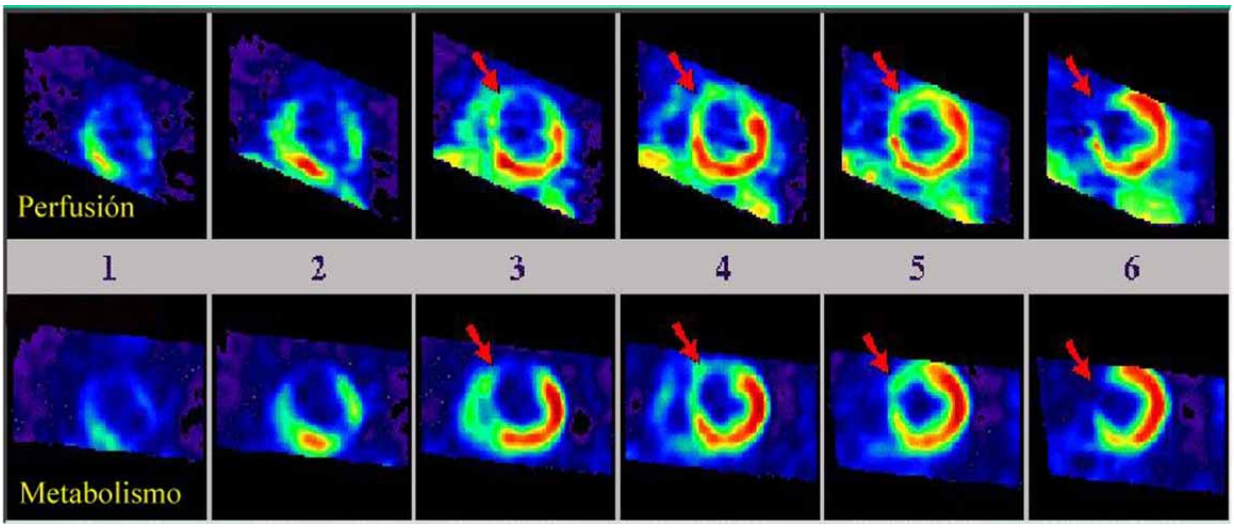

Fig. (36). These series of myocardium perfusion and metabolism PET images of the anteroseptal region of the heart were done using the radiotracers [^{13}N]ammonia and FDG respectively. These scans indicate a weakness in the myocardium and make the patient a suitable candidate for heart bypass surgery.

hospital by a strontium-82/rubidium-82 [^{82}Sr-^{82}Rb] generator system. The imaging properties of rubidium-82 are very similar to thallium-201 with high extraction and high flow thus allowing a series of myocardial perfusion images to be taken at short time intervals [101]. Rubidium-82 causes less toxic side effects to the liver or bowel regions in the body compared to other imaging radiotracers such as thallium-201 and technetium-99m sestamibi [102].

The advantage of using [^{15}O]water is that it is freely diffused with an extraction fraction approaching 100%. Its myocardial uptake is largely independent of blood flow or radiotracer metabolism. The problem with this tracer is that it is concentrated not only in the myocardium but is also distributed into the blood pool and adjacent tissue of the lungs. The accurate assessment of [^{15}O]water uptake into the myocardium therefore requires correction for blood pool activity, which can be carried out using carbon [^{15}O]dioxide or carbon [^{15}O]monoxide [103]. Therefore, as new PET radiotracers for cardiac metabolism are developed, the diagnostic usefulness of PET imaging will improve.

Interesting perspectives, not yet in clinical practice, are also connected with many other research proposals. These include permitting the evaluation of staminal cells and gene therapies [104-107], that are clinically useful such as radio compounds tracing free fatty acids, apoptosis/necrosis, and finally the active plaque [108-112].

9. CONCLUSION

In the areas of oncology, neurology, and cardiology clinical PET imaging is playing an important role in the understanding of biochemical and physiological disease mechanisms. This safe, non-invasive imaging technique uses low 'radiotracer' doses. These radiotracer doses have a very short half-life and in the large majority of cases, are quickly metabolized in the human body. Therefore, they must be administered with minimum toxicity to the patient. PET imaging is able to provide relevant information such as those on tissue perfusion, drug target binding and *in vivo* distribution of 'radiotracer' drugs in cells. The future direction of PET imaging will address and detect a variety of changes in

Table 6. A Summary of the Clinical Benefits of PET Imaging

Disease Category	PET Imaging Diagnosis
Oncology	• Distinguish benign from malignant tumours • Stage cancer by showing metastases anywhere in the body • Prove whether or not treatment therapies are working
Cardiology	• Quantify the extent of heart disease • Decide, after a heart attack if the heart muscle would benefit from surgery
Neurology	• Positively diagnose Alzheimer's disease for early intervention • Locate tumours in the brain and distinguish tumours from scar tissue • Location of seizures for epilepsy patients • More accurately assess the type and size of tumour and other defective sites in the brain for neurosurgery

the human body such as: patterns in oxygen flow including the heart and lungs, cellular transport systems, cell proliferation, gene expression, protein production, receptor systems, cellular enzyme and metabolism systems (Table **6**).

Following, the importance of PET in oncology, it will evolve into a routine diagnostic tool for many underlying neurological diseases such as dementia and Parkinson's disease (PD). Recently PET imaging has played a key role in the fight against Alzheimer's disease (AD) with the development of the radiotracer Pittsburgh Compound B ([^{11}C]PIB) used to detect amyloid plaques in the brain. Hence, PET provides an early warning system and therefore the opportunity to be given appropriate drug therapy.

The field of oncology is also reaping the rewards of PET imaging from the use of FDG as a tracer of glucose metabolism. FDG is an established radiotracer, readily available and reimbursed by US medical insurance schemes for the diagnosis, initial staging and follow up of various cancers. Recently, it has become a useful monitoring tool in cancer treatment and in radiation therapy planning. PET imaging is also essential for assessing the size and volume of a variety of 'brain' tumours following chemotherapy treatment.

PET Cardiology has been used on patients who are at a high risk of coronary heart disease (CAD) and heart failure. The cardiac PET imaging procedures examine the density and activity of adrenergic receptors and provide a technique for the detection of early heart disease. Continued research and development in PET imaging will contribute to even earlier diagnosis of more disease states and could potentially lead to a 'personalized medicine' culture which would be governed by our own genetic signature.

ACKNOWLEDGEMENTS

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APPENDIX 1

A selection of PET radiotracers used in the clinical field for the measurement of transport, cerebral blood flow, and metabolism in the human body.

PET Radiotracer	'Clinical' Application
[^{15}O]CO	Blood volume
[^{15}O]H_2O	Blood flow
[^{15}O]O_2	Oxygen consumption
[^{11}C]Acetate	Oxidative metabolism in the heart
[^{11}C]Carfentanil	μ-Opiate receptors in the brain
[^{11}C]CFT	Dopamine re-uptake sites in the brain
[^{11}C]Choline	Choline metabolism, tumours
[^{11}C]CIT	Dopamine re-uptake sites in the brain

Appendix 1. Contd….

PET Radiotracer	'Clinical' Application
[^{11}C]Deprenyl	Monoamine oxidase B in the brain
[^{11}C]DOPA	Pre-synaptic dopaminergic function in the brain
[^{11}C]FLB 457	Dopamine D_2 receptors in the brain
[^{11}C]Flumazenil	Benzodiazepine receptors in the brain
[^{11}C]6-OH-BTA-1 ([^{11}C]-PIB)	Amyloid plaques in the brain
[^{11}C]MADAM	Serotonin re-uptake sites in the brain
[^{11}C]MeAIB	System A amino acid transporters
[^{11}C]Methionine	Amino acid transport, tumours
[^{11}C]Metomidate	11β-hydroxylase activity in adrenal cortical tissue
[^{11}C]MHED	Adrenergic receptors in the heart
[^{11}C]MP4A	Acetylcholine esterase activity in the brain
[^{11}C]MP4B	Butyrylcholine esterase activity in the brain
[^{11}C]NMSP	Dopamine D_2 and serotonin 5-HT_2 receptors in the brain
[^{11}C]NNC 756	Dopamine D_1 receptors in the brain
[^{11}C]Palmitate	Fatty acid metabolism in the heart
[^{11}C]PE2I	Dopamine re-uptake sites in the brain
[^{11}C]PK 11195	Peripheral benzodiazepine receptors
[^{11}C]Raclopride	Dopamine D_2 receptors in the brain
[^{11}C]SCH 23390	Dopamine D_1 receptors in the brain
[^{11}C]SCH 39166	Dopamine D_1 receptors in the brain
[^{11}C]WAY 100635	Serotonin 5-HT_{1A} receptors in the brain
[^{18}F]CFT	Dopamine re-uptake sites in the brain
[^{18}F]EF5	Tissue hypoxia
[^{18}F]FBPA	Amino acid transport, boron carrier for BNCT
[^{18}F]FDG	Glucose metabolism
[^{18}F]FDOPA	Pre-synaptic dopaminergic function in the brain
[^{18}F]FETNIM	Tissue hypoxia
[^{18}F]Fluoride	Bone scintigraphy
[^{18}F]Fluorodopamine	Adrenergic receptors and tone in the heart
[^{18}F]Fluorometaraminol	Adrenergic receptors in the heart
[^{18}F]FTHA	Fatty acid metabolism
[^{18}F]SPARQ	NK1 receptors in the brain

Appendix 1. Contd….

PET Radiotracer	'Clinical' Application
^{68}Ga-EDTA	Blood-brain barrier
^{82}Rb(ion)	Blood-brain barrier
[^{11}C]-O-Methyl-glucose	Glucose transport
[^{15}O]-Butanol	Cerebral blood flow
[^{11}C]-Butanol	Cerebral blood flow
[^{18}F]-Fluromethane	Cerebral blood flow
[^{11}C]-Albumin	Plasma volume
[^{11}C]-Carbon monoxide	Erythrocyte volume
[^{15}O]-Carbon dioxide	Cerebral blood flow
[^{11}C]-2-Deoxy-D-glucose	Cerebral metabolic rate of glucose
[^{11}C]-D-Glucose	Cerebral metabolic rate of glucose
[^{11}C]-Carbon dioxide	pH
[^{11}C]-5,5-Dimethyl-2,4-oxazolidinedione	pH
O-(2-[^{18}F]-Fluoroethyl)-L-tyrosine	Amino acid uptake
[^{11}C]-Aminocyclohexane carboxylate	Amino acid uptake
[^{11}C]-Leucine	Protein synthesis
L-2-[^{18}F]-Fluorotyrosine	Amino acid uptake, protein synthesis
2-[^{11}C]-Thymidine	DNA synthesis
3-'Deoxy-3'-[^{18}F]-fluorothymidine	DNA synthesis
[^{124}I]-Iododeoxyuridine	DNA synthesis
[^{124}I]-2'-Fluoro-2'-deoxy-5-iodo-1-β-D-arabinofuranosyluracil	HSV-tk expression
$H_2{}^{15}O$	Cerebral blood flow
[^{11}C]-Diprenorphine	Opiate receptor binding
[^{18}F]-Cyclofoxy	Opiate receptor binding

REFERENCES

[1] Mould, R.F. Invited review: Rontgen and the discovery of x-rays. *Br. J. Radiol.*, **1995**, *68*, 1145-1176.

[2] Dawson, L.A.; Sharpe, M.B. Image-guided radiotheraphy: rationale, benefits, and limitations. *Lancet Oncol*., **2006**, *7*, 848-858.

[3] Raichle, M.E. Positron emission tomography. *Ann. Rev. Neurosci.*, **1983**, *6*, 249-267.

[4] Cherry, S.R. The 2006 Henry N. Wagner Lecture: of mice and men (and positrons) – advances in PET imaging technology. *J. Nucl. Med*., **2006**, *47*, 1735-1745.

[5] Nishimura, S.; Yajima, K.; Harada, N.; Ogawa, Y.; Hayashi, N. Automated synthesis of radiopharmaceuticals for PET: an apparatus for [1-^{11}C]labeled aldoses. *J. Autom. Chem.*, **1994**, *16*, 195-204.

[6] Cherry, S.R. Fundamentals of positron emission tomography and applications in preclinical drug development. *J. Clin. Pharmacol*., **2001**, *41*, 482-491.

[7] Nutt, R. The history of positron emission tomography. *Mol. Imaging Biol*., **2002**, *4*, 11-26.

[8] Brownell, G.L. A history of positron imaging. Available at http://www.mit.edu/~glb/pethis.pdf print [Accessed Monday, 21 December 2009].

[9] Wagner, H.N. *A Personal History of Nuclear Medicine*, Springer Ed; London, **2006**.

[10] Chase, T.N.; Foster, N.L.; Mansi, L. Alzheimer's disease and the arietal lobe. *Lancet*, **1983**, *7*, 225-227.

[11] Di Chiro, G.; Oldfield, E.; Bairamian, D.; Patronas, N.J.; Brooks, R.A.; Mansi, L.; Smith, B.H.; Kornblith, P.L.; Margolin, R. Metabolic imaging of the brain stem and spinal cord: studies with PET using [F-18]-2-deoxyglucose in normal and pathological cases. *J. Comput. Assist. Tomogr.*, **1983**, *7*, 937-945.

[12] Chase, T.N.; Foster, N.L.; Fedio, P.; Brooks, R.A.; Mansi, L.; Di Chiro, G. Regional cortical disfunction in Alzheimer's disease as determined by positron emission tomography. *Ann. Neurol.*, **1984**, *15* (suppl), S170-S174.

[13] Chase, T.N.; Foster, N.L.; Fedio, P.; Brooks, R.A.; Mansi, L.; Kessler, R.; Di Chiro, G.T. Gilles de La Tourette syndrome: studies with the fluorine-18 labelled fluorodeoxyglucose positron emission tomography method. *Ann. Neurol.*, **1984**, *15*(suppl), S175.

[14] Patronas, N.; Di Chiro, G.; Smith, B. H.; De La Paz, R.; Brooks, R.A.; Milam, H.L.; Kornblith, P.L.; Bairamian, D.; Mansi, L. Depressed cerebellar glucose metabolism in supratentorial tumors. *Brain Res*., **1984**, *291*, 93-101.

[15] Foster, N.L.; Chase, T.N.; Mansi, L.; Brooks, R.A.; Fedio, P.; Patronas, N.; Di Chiro, G. Cortical abnormalities in Alzheimer's disease. *Ann. Neurol.*,**1984**, *16*, 649-654.

[16] Di Chiro, G.; Brooks, R.A.; Patronas, N.; Bairamian, D.; Kornblith, P.L.; Smith, B.; Mansi, L.; Barker, J. Issues in the *in vivo* measurement of glucose metabolism of human central nervous system tumors. *Ann. Neurol.*, **1984**, *15* (suppl), S138-S146.

[17] Chase, T.N.; Fedio, P.; Foster, N.L.; Brooks, R.A.; Di Chiro, G.; Mansi, L. Wechsler adult intelligence scale performance: cortical localization by fluorodeoxyglucose F18-positron emission tomography. *Arch. Neurol.*, **1984**, *41*, 1244-1247.

[18] Ito, M.; Patronas, N.; Di Chiro, G.; Mansi, L.; Kennedy, C. Effect of moderate level x-radiation to brain cerebral glucose utilization. *J. Comput. Assist. Tomogr.*, **1984**, *10*, 584-588.

[19] Di Chiro, G.; Brooks, R.; Bairamian, D.; Patronas, N.; Kornblith, P.L.; Smith, B.H.; Mansi, L. Diagnostic and prognostic value of positron emission tomography using F-18 in brain tumors. In: *Positron Emission Tomography*; Reivich, M.; Alavi, A.; Eds.; Alan R. Liss: New York, **1985**, pp. 291-309.

[20] Di Chiro, G.; Oldfield, E.; Bairamian, D.; Brooks, R.; Patronas, N.; Mansi, L.; Kornblith, P.L.; Smith, B.H.; Sank, V.; Margolin, R.A. *In vivo* glucose utilization of tumors of brain stem and spinal cord in the metabolism of the human brain studied with positron emission tomography. Greitz, T.; Ed. Raven Press: New York, **1985**, pp. 351-361.

[21] Chase, T.N.; Brooks, R.; Di Chiro, G.; Fedio, P.; Foster, N.L.; Kessler, R.A.; Mansi, L.; Manning, R.G.; Patronas, N. Focal cortical abnormalities in Alzheimer's disease. *The Metabolism of the Human Brain Studied with Positron Emission Tomography*. Greitz, T.; Ed. T. Raven Press: New York, **1985**, pp. 433-440.

[22] Hung, J.C. USP and PET radiopharmaceuticals: 1997 FDAMA puts standard-setting body at center of regulatory process. *J. Nucl. Med.*, **2004**, *45*, 13-16.

[23] Klabbers, B.M.; Lammertsma, A.A.; Slotman, B.J. The value of positron emission tomography for monitoring response to radiotherapy in head-and-neck cancer. *Mol. Imag. Biol.*, **2003**, *4*, 257-270.

[24] Coleman, R.E.; Hoffman, J.M.; Hanson, M.W.; Sostman, H.D.; Schold, S.C. Clinical application of PET for the evaluation of brain tumors. *J. Nucl. Med.*, **1991**, *32*, 616-622.

[25] Czernin, J. Clinical applications of FDG-PET in oncology. *Acta Med. Austriaca*, **2002**, *29*, 162-170.

[26] Jaffer, F.A.; Weissleder, R. Molecular imaging in the clinical arena. *JAMA.*, **2005**, *293*, 855-862.

[27] Meyers, R. The biological applications of small animal PET imaging. *Nucl. Med. Biol.*, **2001**, *28*, 585-593.

[28] Eckelman, W.C. The use of gene-manipulated mice in the validation of receptor binding radiotracers. *Nucl. Med. Biol.*, **2003**, *30*, 851-860.

[29] Venuta, S.; Ferraiuolo, R.; Ambesi-Impiombato, F.S.; Morrone, G.; Mansi, L.; Salvatore, M. The uptake of Tl-201 in normal and transformed cell lines. *J. Nucl. Med. Allied. Sci.*, **1979**, *4*, 163-166.

[30] Salvatore, M.; Mansi, L.; Morrone, G.; Ferraiuolo, R.; Venuta, S. *In Vitro* Techniques to Study the Transport of Radiotracers. In: *Biological Transport of Radiotracers*; Colombetti, L.; Ed.; CRC Press: Boca Raton, **1982**, pp. 290-309.

[31] Fanti, S.; Farsad, M.; Mansi, L. Atlas of PET-CT. A quick guide to image interpretation, Springer Ed; Berlin, **2009**.

[32] Fanti, S.; Farsad, M.; Mansi, L. (In Press) *Non-FDG PET-CT Atlas*, Springer Ed. Berlin, **2009**.

[33] Lee, C-M.; Farde, L. Using positron emission tomography to facilitate CNS drug development. *TRENDS Pharmacol. Sci.*, **2006**, *27*, 310-316.

[34] Jain, M.; Batra, S.K. Genetically engineered antibody fragments and PET imaging: A new era of radioimmunodiagnosis. *J. Nucl. Med.*, **2003**, *44*, 1970-1972.

[35] Beeres, S.L.M.A.; Bengel, F.M.; Bartunek, J.; Atsma, D.E.; Hill, J.M.; Vanderheyden, M.; Penicka, M.; Schalij, M.J.; Wijns, W.; Bax, J.J. Role of imaging in cardiac stem cell therapy. *J. Am. Coll. Cardiol.*, **2007**, *49*, 1137-1148.

[36] Cicoria, G.; Marengo, M.; Pancaldi, D.; Di Pierro, D.; Rizzello, A.; Lodi, F.; Fanti, S.; Boschi, S. Acceptance tests and quality control of 68Ge/68Ga generators. *Curr. Radiopharm.*, **2009**, *2*, 165-168.

[37] Schulthess von, G.K. Positron emission tomography versus positron emission tomography/computed tomography: from 'unclear' to 'nuclear' medicine. *Mol. Imaging Biol.*, **2004**, *6*, 183-187.

[38] Surti, S.; Karp, J.S. Imaging characteristics of a 3-dimensional GSO whole-body PET camera. *J. Nucl. Med.*, **2004**, *45*, 1040-1049.

[39] Fioroni, F.; Grassi, E.; Sghedoni, R.; Sarti, M.A.; Versari, A.; Salvo, D.; Borasi, G. Use of positron emission tomography for target volume definition generators. *Curr. Radiopharm.*, **2009**, *2*, 144-148.

[40] Iori, M.; Paiusco, M.; Cagni, E.; Riccardi, S.; Lambertini, D.; Bizzocchi, N.; Borasi, G.; Iotti, C.; D'Abbiero, N.; Nahum, A.E. The intensity modulated multiple arc (IMMA) technique: forward & inverse planned procedures to deliver hypo-fractionated IMAT treatments. *Curr. Radiopharm.*, **2009**, *2*, 149-159.

[41] Versari, A.; Iotti, C.; Merli, F. Impact of PET on the radiation treatment of Hodgkin's lymphoma. *Curr. Radiopharm.*, **2009**, *2*, 169-174.

[42] Positron Emission Tomography (PET): A revolutionary diagnostic and imaging tool, Available at www.columbiapet.org print [Accessed Monday, 21 December 2009].

[43] Kumar, U.; Shukla, A.K. Positron emission tomography: an overview. *J. Med. Phys.*, **2006**, *31*, 13-21.

[44] Tai, Y.F.; Piccini, P. Application of positron emission tomography (PET) in neurology. *J. Neurol. Neurosurg. Psychiatry*, **2004**, *75*, 669-676.

[45] Pichler, B.J.; Wehrl, H.F.; Judenhofer, M.S. Latest advances in molecular imaging instrumentation. *J. Nucl. Med.*, **2008**, *49*, **(**Suppl 2), 5S-23S.

[46] Mansi, L. The absolute (quantitative): dialogue between St. Thomas and Lord Kelvin: interview with Stephen L. Bacharach, as recorded by Luigi Mansi. *Eur. J. Nucl. Med. Mol. Imaging*, **2008**, *35*, 1725-1728.

[47] Kitajima, K.; Murakami, K.; Yamasaki, E.; Domeki, Y.; Tsubaki, M.; Sunagawa, M.; Kaji, Y.; Suganuma, N.; Sugimura, K. Performance of integrated FDG PET/contrast-enhanced CT in the diagnosis of recurrent colorectal cancer: comparison with integrated FDG PET/non-contrast-enhanced CT and enhanced CT. *Eur. J. Nucl. Med. Mol. Imaging*, **2009**, *36*, 1388-1396.

[48] Klimas, M.T. Positron emission tomography and drug discovery: contributions to the understanding of pharmacokinetics, mechanism of action and disease state characterization. *Mol. Imag. Biol.*, **2002**, *4*, 311-337.

[49] Lomena, F.; Soler, M. Clinical application of PET. *Braz. Arch. Biol. Technol.*, **2005**, *48*, 179-183.

[50] Production of PET radionuclides, Available at, http://www.petnm.unimelb.edu.au/pet/detail/radionuc.html print [Accessed Monday 21, December 2009].

[51] Qaim, S.M. Use of cyclotrons in medicine. *Radiat. Phys. Chem.*, **2004**, *71*, 917-926.

[52] Ido, T. Labeled 2-deoxy-D-glucose analogs: ^{18}F labeled 2-deoxy-2-fluoro-D-glucose, 2-deoxy-2-fluoro-D-mannose and ^{14}C-2-deoxy-2-fluoro-D-glucose. *J. Label. Compd. Radiopharm.*, **1978**, *14*, 175-183.

[53] Chen, W.; Silverman, D.H.S.; Delaloye, S.; Czernin, J.; Kamdar, N.; Pope, W.; Satyamurthy, N.; Schiepers, C.; Cloughesy, T. ^{18}F-FDOPA PET imaging of brain tumors: comparison study with ^{18}F-FDG PET and evaluation of diagnostic accuracy. *J. Nucl. Med.*, **2006**, *47*, 904-911.

[54] Al-Nahhas, A.; Win, Z., Szyszko, T.; Singh, A.; Nanni, C.; Fanti, S.; Rubello, D. Gallium-68 PET: a new frontier in receptor cancer imaging. *Anticancer Res.*, **2007**, *27*, 4087-4094.

[55] Barros, L.F.; Porras, O.H.; Bittner, C.X. Why glucose transport in the brain matters for PET. *TRENDS Neurosci.*, **2005**, *28*, 117-119.

[56] Smith, T.A. Mammalian hexokinases and their abnormal expression in cancer. *Br. J. Biomed. Sci.*, **2000**, *57*, 170-178.

[57] Rohren, E.M.; Turkington, T.G.; Coleman, R.E. Clinical applications of PET in oncology. *Radiology*, **2004**, *231*, 305-332.

[58] Khan, N.; Oriuchi, N.; Higuchi, T.; Endo, K. Review of fluorine-18-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) in the follow-up of medullary and anaplastic thyroid carcinomas. *Cancer Control*, **2005**, *12*, 254-260.

[59] Plein, S.; Sivananthan, M. The role of positron emission tomography in cardiology. *Radiography*, **2001**, *7*, 11-20.

[60] Herholz, K.; Heiss, W-D. Positron emission tomography in clinical neurology. *Mol. Imag. Biol.*, **2004**, *6*, 239-269.

[61] Kumar, S.; Rajsshekher, G.; Prabhakar, S. Positron emission tomography in neurological diseases. *Neurol. India*, **2005**, *53*, 149-154.

[62] Venneri, A. Imaging treatment effects in Alzheimer's disease. *Magn. Reson. Imaging*, **2007**, *25*, 953-968.

[63] Silverman, D.H.S.; Cummings, J.L.; Small, G.W.; Gambhir, S.S.; Chen, W.; Czernin, J.; Phelps, M.E. Added clinical benefit of incorporating 2-deoxy-2-[^{18}F]fluoro-D-glucose with positron emission tomography into the clinical evaluation of patients with cognitive impairment. *Mol. Imag. Biol.*, **2002**, *4*, 283-293.

[64a] Nordberg, A. PET imaging of amyloid in Alzheimer's disease. *Lancet Neurol.*, **2004**, *3*, 519-527.

[64b] Ciarmiello, A.; Cannella, M.; Lastoria, S.; Simonelli, M.; Frati, L.; Rubinsztein, D.C.; Squitieri, F. Brain white-matter volume loss and glucose hypometabolism precede the clinical symptoms of Huntington's disease. *J. Nucl. Med.*, **2006**, *47*, 215-222.

[65] Klunk, W.E.; Engler, H.; Nordberg, A.; Wang, Y.; Blomqvist, G.; Holt, D.P.; Bergstrom, K.; Savitcheva, I.; Huang, G.F.; Estrada, S.; Ausen, B.; Debnath, M.L.; Barletta, J.; Price, J.C.; Sandell, J.; Lopresti, B.J.; Wall, A.; Koivisto, P.; Antoni, G.; Mathis, C.A.; Langstrom, B. Imaging brain amyloid in Alzheimer's disease with pittsburgh compound-B. *Ann. Neurol.*, **2004**, *55*, 306-319.

[66] Hatazawa, J.; Brooks, R.A.; Dalakas, M.C.; Mansi, L.; Di Chiro, G. Cortical motor-sensory hypometabolism in amyotrophic lateral sclerosis: a PET study. *J. Comput. Assist. Tomogr.*, **1988**, *12*, 630-636.

[67] Volkow, N.D.; Fowler, J.S.; Gatley, S.J.; Logan, J.; Wang, G-J.; Ding, Y-S.; Dewey, S. PET Evaluation of the dopamine system of the human brain. *J. Nucl. Med.*, **1996**, *37*, 1242-1256.

[68] Piccini, P.; Whone, A. Functional brain imaging in the differential diagnosis of Parkinson's disease. *Lancet Neurol.*, **2004**, *3*, 284-290.

[69] Catafau, A.M.; Tolosa, E. Impact of dopamine transporter SPECT using 123I-ioflupane on diagnosis and management of patients with clinically uncertain Parkinsonian syndromes – DaTSCAN clinically uncertain Parkinsonian syndromes study group. *Mov. Disord.*, **2004**, *19*, 1175-1182.

[70] Casse, R.; Rowe, C.C.; Newton, M.; Berlangieri, S.U.; Scott, A.M. Positron emission tomography and epilepsy. *Mol. Imag. Biol.*, **2002**, *4*, 338-351.

[71] Kitson, S.L. 5-Hydroxytyptamine (5-HT) receptor ligands. *Curr. Pharm. Des.*, **2007**, *13*, 2621-2637.

[72] Cliffe, I.A. A retrospect on the discovery of WAY-1000635 and the prospect for improved 5-HT1A receptor PET radioligands. *Nucl. Med. Biol.*, **2000**, *27*, 441-447.

[73] Bouvard, S.; Costes, F.; Bonnefoi, F.; Lavenne, F.; Mauguiere, F.; Delforge, J.; Ryvlin, P. Seizure-related short-term plasticity of benzodiazepine receptors in parial epilepsy: a [^{11}C]flumazenil – PET study. *Brain*, **2005**, *128*, 1330-1343.

[74] Parsey, R.V.; Mann, J.J. Applications of positron emission tomography in psychiatry. *Semin. Nucl. Med.*, **2003**, *33*, 129-135.
[75] Keppler, J.S. Federal regulations and reimbursement for PET. *J. Nucl. Med. Technol.*, **2001**, *29*, 173-179.
[76] Price, P. PET as a potential tool for imaging molecular mechanisms of oncology in man. *TRENDS Mol. Med.*, **2001**, *7*, 442-446.
[77] Sarji, S.A. Physiological uptake in FDG PET simulating disease. *Biomed. Imaging. Interv. J.*, **2006**, *2*, 1-6.
[78] Bruehlmeier, M.; Roelcke, U.; Blauenstein, P.; Missimer, J.; Schubiger, P.A.; Locher, J.T.; Pellikka, R.; Ametamey, S.M. Measurement of the extracellular space in brain tumors using ^{76}Br-bromide and PET. *J. Nucl. Med.*, **2003**, *44*, 1210-1218.
[79] Iannotti, F.; Fieschi, C.; Alfano, B.; Picozzi, P.; Mansi, L.; Pozzilli, C.; Punzo, A.; Del Vecchio, G.; Salvatore, M.; Conforti, P. Simplified non invasive PET measurement of blood-brain barrier permeability. *J. Comput. Assist. Tomogr.*,**1987**, *11*, 390-397.
[80] Pozzilli, C.; Bernardi, S.; Mansi, L.; Picozzi, P.; Iannotti, F.; Alfano, B.; Bozzao, L.; Lenzi, G.L.; Salvatore, M.; Conforti. P.; Fieschi, C. Quantitative assessment of BBB permeability in multiple sclerosis using Ga-68 EDTA and PET. *J. Neurol. Neurosurg. Psych.*, **1988**, *51*, 1058-1062.
[81] Fieschi, C.; Pozzilli, C.; Bernardi, S.; Mansi, L.; Picozzi, P.; Alfano, B.; Iannotti, F.; Bozzao, L.; Lenzi, G.L.; Salvatore, M.; Conforti, P. Measurement of BBB permeability with PET in patients with multiple slerosis. *Trends in European Multiple Sclerosis Research*. Confavreux, C.; Ed.; Elsevier Science Publishers: Lyon, France, 1**988**, pp. 273-278.
[82] Barrington, S.F. Whole body applications of positron emission tomography in oncology. *Imaging*, **2001**, *13*, 185-196.
[83] Thorwarth, D.; Eschmann, S-M.; Holzner, F.; Paulsen, F.; Alber, M. Combined uptake of [^{18}F]FDG and [^{18}F]FMISO correlates with radiation therapy outcome in head-and-neck cancer patients. *Radiother. Oncol.*, **2006**, *80*, 151-156.
[84] Eschmann, S-M.; Paulsen, F.; Bedeshem, C.; Machulla, H-J.; Hehr, T.; Bamberg, M.; Bares, R. Hypoxia-imaging with ^{18}F-misonidazole and PET: changes of kinetics during radiotherapy of head-and-neck cancer. *Radiother. Oncol.*, **2007**, *83*, 406-410.
[85] McLoud, T.C. A system for the clinical staging of lung cancer-A commentary. *Am. J. Roentgenol.*, **2006**, *187*, 269-270.
[86] Baardwijk, van A.; Bosmans, G.; Dekker, A.; Kroonenburgh, van M.; Boersma, L.; Wanders, S.; Ollers, M.; Houben, R.; Minken, A.; Lambin, P.; Ruysscher, de D. Time trends in the maximal uptake of FDG on PET scan during thoracic radiotheraphy. A prospective study in locally advanced non-small cell lung cancer (NSCLC) patients. *Radiother. Oncol.*, **2007**, *82*, 145-152.
[87] Cobben, D.C.P.; Elsinga, P.H.; Hoekstra, H.J.; Suurmeijer, A.J.H.; Vaalburg, W.; Maas, B.; Jager, P.L.; Groen, H.M.J. Is ^{18}F-3'-fluoro-3'-deoxy-L-thymidine useful for the staging and restaging of non-small cell lung cancer? *J. Nucl. Med.*, **2004**, *45*, 1677-1682.
[88] Sutinen, E.; Jyrkkio, S.; Varpula, M.; Lindholm, P.; Gronroos, T.; Lehikoinen, P.; Teras, M.; Minn, H. Nodal staging of lymphoma with whole-body PET: comparison of [^{11}C]methionine and FDG. *J. Nucl. Med*., **2000**, *41*, 1980-1988.
[89] Jemal, A.; Murrey, T.; Ward, E.; Samuels, A.; Tiwari, R.C.; Ghafoor, A.; Feuer, E.J.; Thun, M.J. Cancer statistics 2005. *CA Cancer J. Clin*., **2005**, *55*, 10-30.
[90] Okada, J.; Yoshikawa, K.; Imazeki, K.; Minoshima, S.; Uno, K.; Itami, J.; Kuyama, J.; Maruno, H.; Arimiza, N. The use of FDG-PET in the detection and management of malignant lymphoma: correlation of uptake with prognosis. *J. Nucl. Med*., **1991**, *32*, 686-691.
[91] Breast cancer at a glance, Available at http://info.cancerresearchuk.org/cancerandresearch/cancers/breast/?a=5441 print [Accessed Monday, 21 December 2009].
[92a] Czernin, J. FDG-PET in breast cancer: a different view of its clinical usefulness. *Mol. Imaging Biol.*, **2002**, *4*, 35-45.
[92b] van Dongen, G.A.M.S.; Visser, G.W.M.; Lub-de Hooge, M.N.; de Vries, E.G.; Perk, L.R. Immuno-PET: a navigator in monoclonal antibody development and applications. *Oncologist*, **2007**, *12*, 1379-1389.
[93] Tian, M.; Zhang, H.; Higuchi, T.; Oriuchi, N.; Endo, K. Oncological diagnosis using ^{11}C-choline-positron emission tomography in comparison with 2-deoxy-2-[^{18}F]fluoro-D-glucose-positron emission tomography. *Mol. Imag. Biol.*, **2004**, *6*, 172-179.
[94] Shinoura, N.; Nishijima, M.; Hara, T.; Haisa, T.; Yamamoto, H.; Fujii, K.; Mitsui, I.; Kosaka, N.; Kondo, T.; Hara, T. Brain tumors: detection with C-11 choline PET. *Radiology*, **1997**, *202*, 497-503.
[95] Hara, T. ^{11}C-Choline and 2-deoxy-2-[^{18}F]fluoro-D-glucose in tumor imaging with positron emission tomography. *Mol. Imag. Biol.*, **2002**, *4*, 267-273.
[96] Jager, P.L.; Vaalburg, W.; Pruim, J.; de Vries, E.G.E.; Langen, K-J.; Piers, D.A. Radiolabeled amino acids: basic aspects and clinical applications in oncology. *J. Nucl. Med.*, **2001**, *42*, 432-445.
[97] Maffione, A.M.; Nanni, C.; Ambrosini, V.; Trespidi, S.; Lopci, E.; Allegri, V.; Castellucci, P.; Montini, G.; Boschi, S.; Fanti, S. ^{11}C-Methionine PET/CT in central nervous system tumours: a review. *Curr. Radiopharm.*, **2009**, *2*, 160-164.
[98] Keng, F.Y.J. Clinical applications of positron emission tomography in cardiology: a review. *Ann. Acad. Med. Singapore*, **2004**, *33*, 175-182.
[99] Schindler, T.H.; Zhang, X-Li.; Vincenti, G.; Mhiri, L.; Lerch, R.; Schelbert, H.R. Role of PET in the evaluation and understanding of coronary physiology. *J. Nucl. Cardiol.*, **2007**, *14*, 589-603.
[100] Jeremy, R.W. Positron emission tomography in cardiology. *Aust. Prescr*., **1995**, *18*, 13-15.
[101] Noto, R.B. Cardiac applications of positron emission tomography (PET). *Med. Health. R I*, **2003**, *86*, 139-142.
[102] Schwaiger, M.; Bengel, F.M. From thallium scan to molecular imaging. *Mol. Imag. Biol.*, **2003**, *4*, 387-398.
[103] Watabe, H.; Jino, H.; Kawachi, N.; Teramoto, N.; Hayashi, T.; Ohta, Y.; Iida, H. Parametric imaging of myocardial blood flow with ^{15}O-water and PET using the basis function method. *J. Nucl. Med*., **2005**, *46*, 1219-1224.
[104] Macías, M.T. Use of radionuclides in cancer research and treatment. *Clin. Transl. Oncol*., **2009**, *11*, 143-153.
[105] Yamagami, T.; Kanda, K.; Okuyama, C.; Nishimura, T. Tc-99m-MIBI scintigraphy in evaluating the effect of hepatocyte growth factor gene therapy for peripheral arteriosclerosis obliterans. *Ann. Nucl. Med*., **2009**, *23*, 205-208.
[106] Leriche, L.; Björklund, T.; Breysse, N.; Besret, L.; Grégoire, M.C.; Carlsson, T.; Dollé, F.; Mandel, R.J.; Déglon, N.; Hantraye, P.; Kirik, D. Positron emission tomography imaging demonstrates correlation between behavioral recovery and correction of dopamine neurotransmission after gene therapy. *J. Neurosci*., **2009**, *29*, 1544-1553.
[107] Finnberg, N.; Wambi, C.; Ware, J.H.; Kennedy, A.R.; El-Deiry, W.S. Gamma-radiation (GR) triggers a unique gene expression profile associated with cell death compared to proton radiation (PR) in mice *in vivo*. *Cancer Biol. Ther*., **2008**, *7*, 2023-2033.
[108] Jain, D.; He, Z-X. Direct imaging of myocardial ischemia: a potential new paradigm in nuclear cardiovascular imaging. *J. Nucl. Cardiol*., **2008**, *15*, 617-630.
[109] De Saint-Hubert, M.; Prinsen, K.; Mortelmans, L.; Verbruggen, A.; Mottaghy, F.M. Molecular imaging of cell death. *Methods*, **2009**, *48*, 178-187.
[110] Mishani, E.; Abourbeh, G.; Eiblmaier, M.; Anderson, C.J. Imaging of EGFR and EGFR tyrosine kinase over expression in tumors by nuclear medicine modalities. *Curr. Pharm. Des.*, **2008**, *14*, 2983-2998.
[111] Blankenberg, F.G. Monitoring of treatment-induced apoptosis in oncology with PET and SPECT. *Curr. Pharm. Des.*, **2008**, *14*, 2974-2982.
[112] Bural, G.G.; Torigian, D.A.; Chamroonrat, W.; Houseni, M.; Chen, W.; Basu, S.; Kumar, R.; Alavi, A. FDG-PET is an effective imaging modality to detect and quantify age-related atherosclerosis in large arteries. *Eur. J. Nucl. Med. Mol. Imaging*, **2008**, *35*, 562-569.

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