Chapter 2

Molecular Imaging

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Additional information is available at the end of the chapter

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1. Introduction

Molecular imaging techniques depend upon molecular mechanisms operative in vivo. This imaging technique encompasses the visualization, characterization and measurement of biological processes at the molecular and cellular levels in humans and other living systems [1]. The techniques used include Positron Emission Tomography – Computed Tomography (PET-CT), nuclear medicine, Magnetic Resonance Imaging (MRI), Magnetic Resonance Spectroscopy (MRS), optical imaging and ultrasound.

There are escalating evidences in the published data that discussed the advantages of integrated molecular imaging technique as an accurate tool in localizing abnormal metabolic alteration and serve as a potential role as an invasive surrogate biomarker for various disease entities [2,3,4,5]. It also plays an increasingly fundamental role in drug discovery and early development in humans. The evolution of molecular imaging tool in specific PET-CT has impacted the use of molecular imaging technique in many altered cellular mechanism. In particular, PET which was introduced in the 1970 s is capable of quantifying individual changes on the different pathology that underpin the biological reprogramming in abnormal cells [6]. Intensive research activities in various PET applications gradually evolved to its clinical use first in neuropsychiatric disorders and cardiology, then in oncology.

Molecular imaging provides the key to the future of personalized medicine, which involves diagnosing, treating and monitoring patients based on their individual makeup. The amelioration in its technique has braced the one-stop-imaging strategy in various disease entities as a tool for disease localization, prediction and treatment monitoring. For the purpose of the discussion in this chapter, we highlight the integrated molecular imaging technique PET-CT employing flurodeoxyglucose (FDG) as a standard of care utility in various disease pathology.

2. Types of molecular imaging techniques

Molecular imaging, a new discipline in biomedical research has increasingly become a vital tool in disease diagnostic frontier. It offers an excellent visualization, characterization and quantification of biologic process taking place at the cellular and sub-cellular levels. As of now, there are four main categories of molecular imaging modalities; ultrasound, optical imaging, magnetic resonance imaging (MRI), and nuclear imaging techniques (Table 1). Bonekamp [7] in his paper reported that the selection of the imaging modality often is determined based on the temporal and spatial resolution, field of view, sensitivity of the imaging system, depth of the biological process, the molecular or cellular process to image, and the availability of suitable probes and labels than can be delivered to the imaging target. An overview of mechanism behind each of the modalities will be covered in the subsequent section.

Molecular Imaging Modalities	
Single modality	Multimodalities
Ultrasound	PET-CT
MRI	SPECT-CT
PET	PET-MRI
SPECT	
Optical Imaging	

Table 1. Types of Molecular Imaging Modalities

2.1. Ultrasound

Ultrasound imaging has been used for over 20 years. It uses high-frequency sound waves to view soft tissues such as muscles and internal organs inside the body. As the image of the ultrasound is captured in real-time, it enables the physician to see the movement of the body's internal organs as well as blood flowing through the vessels. In an ultrasound exam, a hand-held transducer is placed against the skin. The transducer sends out high frequency sound waves that reflect off the body structures. As sound waves directed through the body bounce back when they encounter different tissues, echoes are measured with the help of a computer and are converted into real-time images of organs and tissues. The image captured is based on the frequency and strength of the sound signal and the time it takes to return from the patient to the transducer [8].

2.2. Optical imaging

In optical imaging, light-producing proteins are designed to attach to specific molecules such as brain chemicals or molecules on the surface of cancer cells [9]. Highly sensitive detectors are employed for detection of low levels of light emitted by specific molecules from inside the body. The two major types of optical imaging are bioluminescent imaging and fluorescence

imaging. Bioluminescent imaging uses a natural light-emitting protein to trace the movement of certain cells or to identify the location of specific chemical reactions within the body. In contrast, fluorescence imaging uses proteins that produce light when activated by an external light source such as laser.

2.3. Magnetic resonance imaging

Magnetic resonance imaging or popularly known as MRI is an imaging technique used mainly in medical settings to produce high quality images of inside human body. Theoretically, the mechanism behind MRI is based on the principles of nuclear magnetic resonance (NMR), a spectroscopic technique used by scientist to obtain microscopic chemical and physical information about molecules [10]. MRI scanner has a tube surrounded by a giant circular magnet. During routine examination of MRI, patient is placed on a moveable bed that is inserted into the magnet. The presence of magnet creates a strong magnetic field that aligns the protons of hydrogen atoms, which are then exposed to a beam of radio waves [11]. This spins various protons of the body, and produces a faint signal that is detected by the receiver portion of the MRI scanner. The receiver information is processed by a computer and an image is then produced.

2.4. Nuclear Imaging

Nuclear imaging or also called as radionuclide scanning provides an effective diagnostic tools for the radiologists as it shows not only the structure of an organ but also the function of the organ. Nuclear imaging routine uses small amounts of radioactive material, or tracer for diagnostic purpose. Radioactive tracer used in nuclear imaging is normally a specifically targeted probe. It could be antibodies, ligands or substrates to specifically interact with protein targets in particular cells or sub cellular compartments. These interactions are based on either receptor-radioligand binding or enzyme mediated trapping of a radio labeled substrate [12]. Radioactive tracers used in nuclear imaging are in most cases is administered into a vein and some are given orally. After an administration of radioactive tracers, patient is required to rest for a certain period to allow distribution of radioactive tracer in the body. In the end, for imaging purpose, a specialized gamma camera is used to detect the radiation throughout the body. Most commonly used techniques in nuclear imaging are positron emission tomography (PET) and single photon emission computed tomography (SPECT).

2.4.1. Positron Emission Tomography (PET)

Positron emission tomography or known as 'PET' is a rapidly developing nuclear imaging technique, with a clinical role that now exceeds almost 15 years [13]. It is a quantitative tomographic imaging technique which produces cross-sectional images that are composites of volume elements [14]. The signal intensity for PET images in each voxel is dependent upon the activity of radionuclide tagged with radioactive tracer which intravenously administered at the earlier stage before the scanning takes place. A scanner which usually called PET scanner employs a gamma photon coincidence detection system designed for oppositely directed annihilation photons emitted indirectly by the positron decay of PET radionu-

clides. This logic allows acquisition of images that are quantitative three dimensional (3-D) maps of radiolabeled tracers in tissue. The most commonly used PET radioactive tracer is the glucose derivative, 2-[^{18}F]fluoro-2-deoxy-D-glucose or commercially known as [^{18}F]FDG, with numerous other tracers under development capable of highlighting a broad range of organ and tissue metabolic functions. In a large meta-analysis, PET was shown to change management in 30% of patients [15].

2.4.2. Single Photon Emission Computed Tomography (SPECT)

Similar to PET, single photon emission computed tomography (SPECT) also uses a radioactive tracer that is administered to the patient and a scanner to record data that a computer constructs into two or three dimensional images. However, in another note, SPECT technique employs a gamma camera that rotates around the patient to detect a radioactive tracer in the body. In contrast to PET which employs shorter half-lived tracers as opposed to the SPECT tracers [16]. If a tumor is present, the antibodies will stick to it and thus allow for detection of tumorous cells. For better understanding on strength and weakness of each imaging modalities, Table 2 below provides a summary of the imaging techniques with its respective strength and weakness.

Imaging modality	**Electro magnetic radiation spectrum**	**Advantages**	**Disadvantages**
Ultrasound	High-frequency sound	Real time and low cost	Limited spatial resolution, mostly morphologic although targeted micro bubbles under development
Optical bioluminescence imaging	Visible light	Highest sensitivity, quick, easy, low cost and relatively high throughput	Low spatial resolution, current 2-D imaging only, relatively surface weighted, limited translational research
Optical fluorescence imaging	Visible light or near-infrared	High sensitivity, detects fluorochrome in live and dead cells	Relatively low spatial resolution, relatively surface weighted
Magnetic resonance imaging (MRI)	Radio waves	Highest spatial resolution, combines morphologic and functional imaging	Relatively low sensitivity, long scan and post processing time, mass quantity of probe may be needed
Positron Emission Tomography (PET)	High energy gamma rays	High sensitivity, shorter time scan, enable quantitative analysis	PET cyclotron or generator needed, relatively low spatial resolution
Single photon emission computed tomography (SPECT)	Lower energy gamma rays	Many molecular probes available, can image multiple probes simultaneously, may be adapted to clinical imaging system	Relatively low spatial resolution, high radiation to subjects due to longer tracer half-life's, non-quantitative tool, Longer scanning time

Table 2. Key strength and weakness of the main available imaging modalities used in molecular imaging [12, 16]

3. Integrated molecular imaging techniques (FDG PET-CT)

The astonishing achievement of the molecular imaging technique rely on its ability to signal altered metabolism in a targeted pathological cells whereby two imaging modalities are integrated in a single setting (multimodality imaging technique/integrated imaging) i.e. PET-CT, SPECT-CT, PET-MRI. It includes two- or three-dimensional imaging as well as quantification over time (Figure 1). Largely independent of structural disturbances, integrated molecular imaging techniques increasingly offer high spatial resolution, but more particularly, high contrast. Minute quantities of radioactive materials, chosen because of their ability to participate in biological processes of interest, can provide highly sensitive indications of body function in health and disease. Therefore, disordered metabolism or physiology can be detected with high sensitivity and the anatomical distribution of abnormality can be determined with greater precision than the conventional technique (Table 3). The conventional imaging techniques i.e. computed tomography (CT) or standalone nuclear medicine technique – single positron emission tomography (SPECT) are relatively unpopular in a current scenario given their limitations to only evaluating the structural changes or functional changes disjointedly.

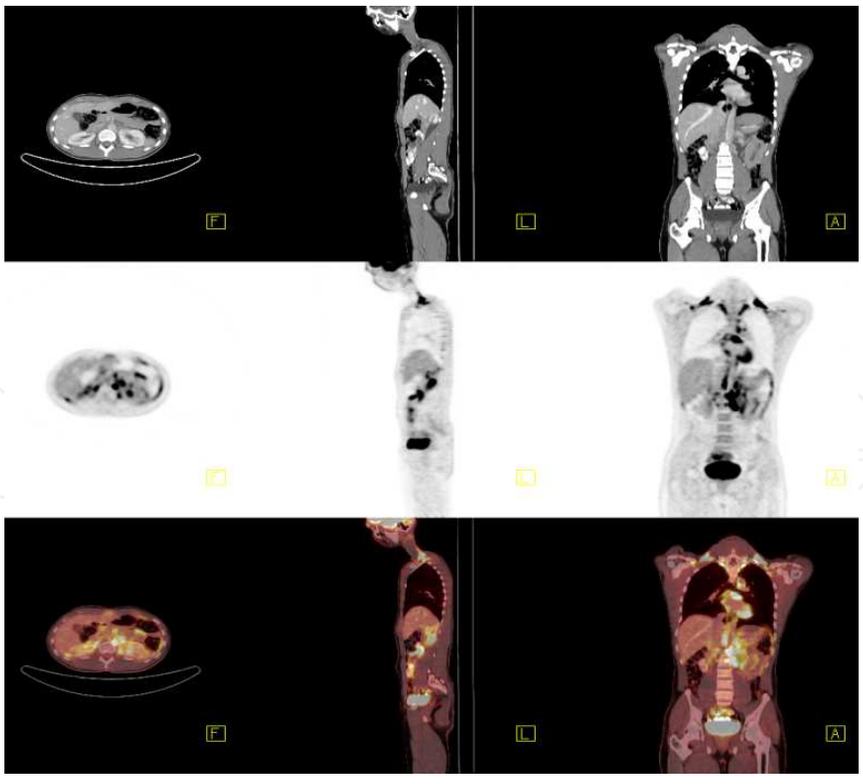

Figure 1. PET-CT image display on the Syngo console panel showing series of CT, PET and fused images.

Published data	Sensitivity versus Specificity (%)	
	PET-CT	CT
Niikura N et al Metastatic breast cancer[2]	97.4 versus 91.2	85.9 versus 67.3
Kim SK et al (solitary pulmonary lesion)[3]	97.0 versus 85	93.0 versus 31.0
Pim A. et al (malignant lymphoma)[4]	100.0versus 95.0	91.0 versus 96.0
Ozkan E et al (colorectal cancer recurrence) [5]	98.0 versus 85.0	73.0 versus 86.0

Table 3. Data shows the accuracy of the PET-Ct and the CT in the evaluation of various tumors

3.1. FDG PET-CT and Standard Uptake Value (SUV)

The imaging of the alteration of the glucose metabolism, as reflected by cellular uptake and trapping of the glucose analog 18F-FDG can suffice a response assessment that is both accurate and contemporaneously than that provided by standard morphologic imaging. Quantitative evaluation of FDG PET images provides quantitative data in the form of the standardized uptake value (SUV). This is an uptake measurement that provides a mean of comparison of FDG uptake between different lesions. Measurement of SUV requires attenuation correction to avoid the variability in FDG uptake due to the differences in tumor habitus within the body. This value normalizes the tumor FDG uptake with the FDG injected activity and the body weight [17]. The cut-off value of 2.5 in differentiating malignant to benign is at large limited due to varied tumor histological characteristic in malignant tumor [18)

3.2. FDG PET-CT and radiation issues

Being a glucose analogue, 2-[^{18}F]fluoro-2-deoxy-D-glucose or commonly known as ^{18}F-FDG, is the most commonly used positron emitting radiopharmaceutical in PET examination. The preparation of ^{18}F-FDG involves the production of radioisotope fluorine-18 to tag with glucose derivative. Fluorine-18, a positron emitters, emits gamma energy of 511 keV and due to positron annihilation, it emits total energy of 1022 keV. This is almost 10 times higher than conventional X-ray radiation. Therefore, it possesses high activity and dose exposure to radiation workers and patients.

However, the radiation exposure could be outweighed due to its benefit to the patient. This is in compliance with the International Commission on Radiological Protection (ICRP) which recommended three elements in the system of dose limitation [19]. The three elements are; justification, optimization and dose limitation. Justification means that any propose examination that may cause exposure to the patients should yield a sufficient benefit to the patients to justify the risk incurred by the radiation exposure. This element is based on the assumption that any radiation exposure, either it is in small dose, carries with it a certain level of risk that is proportional to the level of exposure. The second element is optimization, which is also

known as the practice of ALARA (as low as reasonably achievable). This by all means, the radiation exposures resulting from the examination or preparation of radiopharmaceuticals must be reduced to the lowest level possible, considering the cost of such a reduction in dose. The third element in ICRP recommendation is dose limitation. The dose limits are normally imposed by the local regulatory agencies.

To accommodate a dose exposure at minimum, certain laboratory technique can be improved when dealing with radioactive materials. The use of teleplier, long tong or robotic arms can maximize the distance between the radioactive material and personnel. This directly reduces the dose expose to the radiation worker [20]. In the administrative and procedure control aspect, the introduction of automated dose dispensing will replace the manual dose dispensing activity performs by the radiation worker to eliminate receiving of unnecessary exposure. The rotation between personnel involves in preparation of radiopharmaceutical and examination also provides an alternative way to reduce high dose expose. Nevertheless, PET utilizes ^{18}F-FDG as a radiotracer carries a low absorbed dose to patient estimated at approximately 7 mSv. The radiation (x rays) from our diagnostic CT protocol ranges from 8mSv to 16 mSv. The new technology 64 multislice CT technique is equipped with the dual focal spot that ensures more image yields without increased in the total radiation dose. The modulated tube current adaptation of higher multislice CT scanner (64 and above) technique as offered by many vendors is capable of reducing patient dose up to 20% as compared to the lower 16 multislice of the same kind. [21,22]. In a nutshell, even though the use of molecular imaging modalities possesses risk onto the patients and radiation workers, but the purpose of examination outweigh the implication of the dose receive and it offers benefit for diagnosis and treatment purpose.

4. Molecular imaging in clinical application

4.1. Utility of integrated molecular imaging (PET-CT) in oncology

Oncology is now the most important application of molecular imaging techniques i.e. PET [23]. In oncology, PET can be used for signaling biological process that underpins pathological reprogramming that promotes carcinogenesis. Among the important signaling processes involved are the altered glucose metabolism, amino acid metabolism, cell membranes metabolism and cell proliferation (Figure 2). Leveraging the rapidly increasing pace of technological and scientific innovation in molecular biology, there has been a surge in the understanding of the key drivers of malignant transformation. An important key driver in malignant transformation is the altered glucose metabolism whereby a glucose analog or Flurodeoxyglucose (FDG) has been utilized as a popular ligand used in labeling the tumor targets.

In vivo, intense FDG uptake and metabolism of glucose, a frequent characteristic of most cancer cells, is associated with an alteration in the intrinsic energy metabolism causing a shift from oxidative phosphorylation to aerobic glycolysis, a change referred to as the Warburg effect [24]. Otto Warburg, working in Germany in the 1920s, discovered that cancer cells have a characteristically increased glycolysis even under aerobic conditions. Because glycolysis is considerably less efficient than oxidative phosphorylation at producing adenosine triphosphate (ATP), the tumor cell requires acceleration in the rate of glucose uptake and use. Given the known

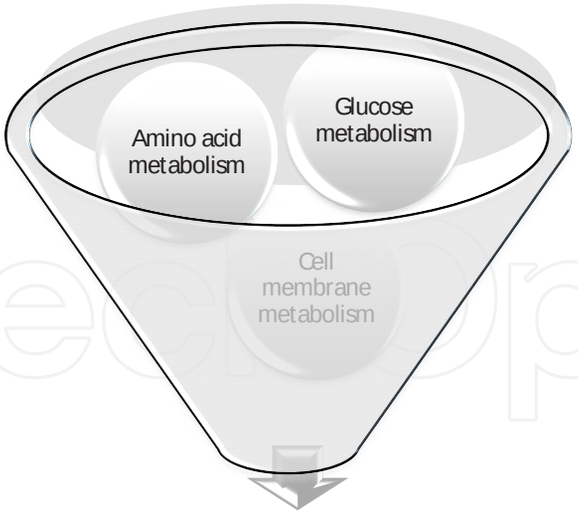

Figure 2. Biomarker signalling in a cell model 18F-FDG : Glucose metabolism, 18F-FET(fluoroethyltyrosine): amino acid metabolism, 18F-FCH(18F-fluorocholine): cell membrane metabolism

natural behaviours of tumors, [18F] FDG accumulation in tumors is used as index of increased glucose metabolism and as a marker of tumor viability for which, the degree of [18F] FDG uptake usually reflects tumor aggressiveness. The kinetics of the FDG tracers is similar to glucose. It passes through the brain-blood barrier and is phosphorylated intracellularly in a process analogous to the glucose. The phosphorylized FDG compound does not enter in the Krebs cycle, thence it is effectively trapped. FDG as a molecular marker in signifying the molecular pathways of each cancer types in different types of cancer of the study. Malignant cells have increased facilitated glucose transport and up regulation of hexokinase activity, and hence tumors can be identified by regions of increased glucose utilization [25]. The PET tracer FDG, a glucose analog, is used to image glucose metabolism in patients. Focal areas of abnormally increased FDG uptake are considered suspicious for malignant disease, particularly as metabolic changes often precede the morphological changes associated with disease. Heterogeneity of malignant cell clones in different sites within a single tumor and between different tumor sites in the body is a manifestation of the genomic instability that characterizes cancer cells [26]. Among the indication for PET-CT in oncology is shown in table 4.

Tumour localisation
Pretreatment tumour staging
Prognostic stratification
Treatment monitoring
Tumour surveillance and restaging
Radiation treatment planning
Development of new anticancer drugs

Table 4. Common indications of PET-CT study

4.2. FDG PET-CT in tumor localisation

By integrating two imaging modalities encompassing the structural and functional imaging techniques, a substantial change in the treatment planning can be achieved while reducing the cost burden and averting futile treatment to patients. Contrasted CT technique used for the evaluation of equivocal PET results promises higher achievable diagnostic results in the assessment of neuroendocrine tumor with prevalence brown fat accumulation. [27]. Furthermore, the details of the surrounding vitals structures are shown clearly on the co registered contrasted CT image for appropriate correlation with the high metabolic focus on PET [28]. The impact of PET in detecting diffuse involvement of other organ system as part of the metastatic spread or delineation of subcentimetre focus of FDG-avidity i.e. in melanoma has averted futile surgery and unnecessary treatment costs (Figure 3) [2, 29]. The combined PET-CT over scored the standalone CT and PET in the re-staging tumor after years of free-disease survival whereby the distorted anatomy may not be easily distinguished from the site of tumor recurrent [29]. 18[F] FDG PET-CT has been shown to be useful for detection of nodal and distant metastases in patients with soft-tissue sarcomas compared with that at conventional imaging [30]

4.3. FDG PET-CT in tumor staging

The evaluation of tumor prior to any treatment or surgical intervention is vital as an inappropriate staging may lead to unnecessary treatment course and cost and futile surgery. Integrated molecular imaging technique offers a high accuracy in the staging of tumor especially those which are equivocal on the structural imaging (CT, MRI) as correlated on the clinical background. Metabolic information by PET is always the essential element in the determination of an altered metabolism preceding any structural change (Figure 4). There are many published data that support this evidence in many tumor streams. A retrospective analysis included 50 patients with 55 clinical events of elevated or increasing CEA level who underwent FDG PET-CT and MDCT for suspected tumor recurrence, FDG PET-CT has higher sensitivity than MDCT in the identification of sites of recurrent and metastatic disease in patients with colorectal cancer and an elevated CEA level [31]. In a study based on 172 non small cell lung carcinoma (NSCLC) patients from a prospective clinical study who underwent diagnostic, contrast-enhanced helical CT and integrated PET-CT on the treatment costs, the diagnostic effectiveness in terms of correct TNM staging was 40% (31/77) for CT alone and 60% (46/77) for PET-CT. For the assessment of resectability (tumor stages Ia-IIIa vs. IIIb-IV), 65 of 77 patients (84%) were staged correctly by PET-CT (CT alone, 70% [54/77]). The incremental cost-effectiveness ratios per correctly staged patient were $3,508 for PET-CT versus CT alone [32]. Data on 122 patients with PET-CT scans as part of their initial staging of lymphoma, PET-CT upstages 17% of cases and detects occult splenic involvement [33]

4.4. FDG PET-CT in predicting tumor aggressiveness

In addition, the degree of metabolic defect via semi quantitative analysis, standard uptake value (SUV) could predict tumor aggressiveness and the overall patient survival as high SUV values correlates with poor disease prognosis (Figure 5). Predicting tumor aggressiveness is

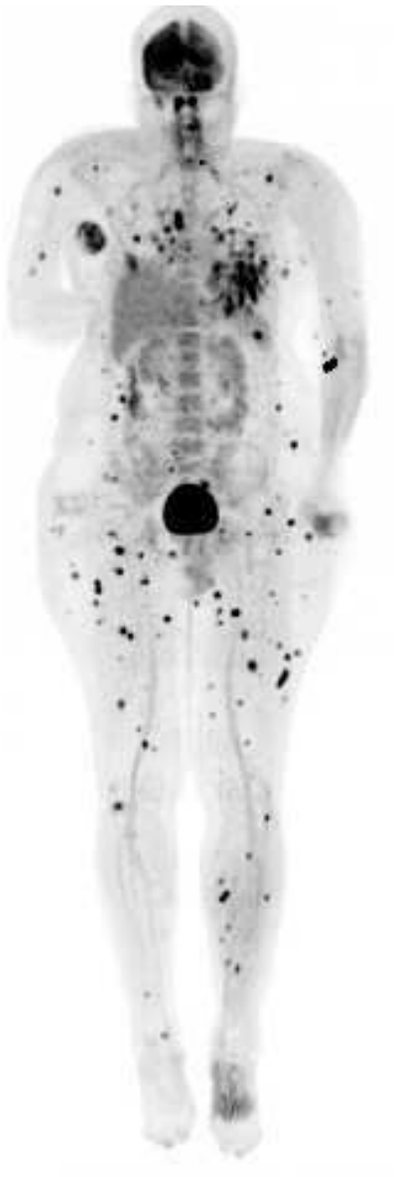

Figure 3. PET-CT restaging in 56-year-old man who had partial amputation of the right forearm for malignant melanoma. The MIP-PET image shows innumerable hypermetabolic foci of metastatic lesion throughout the body (subcentimetre lesions are imperceptible on the CT images; correlated CT image is not shown).

important as early decision on the management strategy of a patient suffering from an advance tumor could lead to an improved prognosis. A particular type of tumor i.e. thymoma which their cellular make-up does not always exhibit malignant entity when a clinical assessment is equivocally ascertained, the role of molecular imaging employing PET with glucose analog has been shown to impact the prognostic outcome in many instances [34]. In a retrospective study by Lopei et al of 91 patients with follicular lymphoma (FL), end-treatment PET-CT in FL has high accuracy and appears to be a good predictor of progression free survival (PFS) and patient outcome, irrespective of grading [35]. Due to clonal heterogeneity in some tumors, FDG-PET could potentially become a determinant factor in determining which cells types may be aggressive or have de-differentiated. In a study of 23 patients with neuroendocrine tumor

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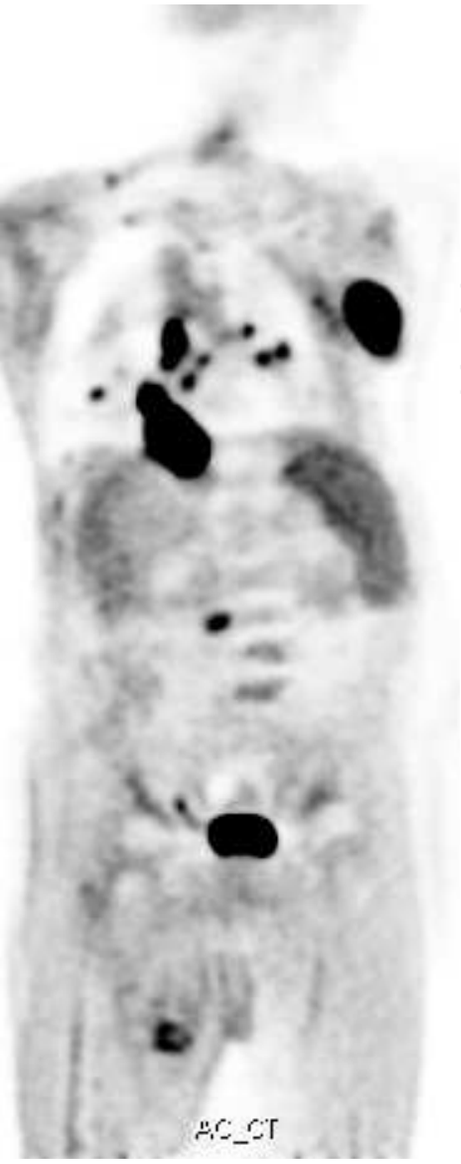

Figure 4. PET-CT Staging of recently diagnosed non-Hodgkin lymphoma by CT in 58-year-old woman. Coronal PET image shows involvement of the spleen (CT image was normal; correlated image is not shown) for which the disease was upstage to stage 3.

(NET), Fathinul et al suggested a cut-off value of 9.1 to predict tumor with an aggressive potential. This is in line with other study that suggests FDG-avid NET is usually more aggressive than FDG-negative lesions whereby the former may be benefited from systemic treatment (chemotherapy) [36]. In this regards, the role of molecular imaging is of prime important when structural changes are lacking of certain valuable information of the tumor altered cellular biology.

4.5. FDG PET-CT and the patient management

The use of PET-CT is potentially reported to change of the primary diagnosis in approximately 16% of cases, whereas PET-CT resulted in a change in staging and treatment plan in approxi-

mately 28% to 32% of the cases, respectively (Table 5) [37]. One area in which FDG PET can play a significant role is in establishing response to treatment [38]. Current procedures to monitor therapy use mainly anatomical imaging modalities, such as CT, even though metabolic changes in tumors may occur earlier than, or even instead of, anatomical size changes. A significant metabolic change can be established by comparing uptake values from pre- and post treatment scans, although such comparisons can only be made accurately on attenuation-corrected, quantitative PET images.

Patient (P)	**Histological Diagnosis**	AJCC (6th ed) Staging before PET-CT Scan	AJCC (6th ed) Staging after PET-CT Scan
P1	NPC	Stage III	Stage IVB
P2	NPC	Stage IVB	Stage IVB
P3	Ca larynx	Stage I	Stage I
P4	Sarcoma of tonsil	Stage II	
P5	Metastatic papillary carcinoma of thyroid	NA	Stage I
P6	Occult node-Metastatic carcinoma of neck	NA	FDG uptake only in Lymph nodes
P7	Primary adnexal Ca	Stage I	Stage I
P8	Ca larynx	Stage I	Stage I
P9	Thyroglossal cyst with focal papillary carcinoma	NA	Stage III
P10	NPC	Stage II	Stage IVA
P11	NPC	Stage I	Stage I
P12	NPC	Stage III	Stage IVA
P13	Ca tonsil	Stage IV	Stage IVB
P14	Lymphoma	Stage I	Stage III
P15	NPC	Stage I	Stage I
P16	Metastatic adenocarcinoma of base of skull	NA	Stage IVC
P17	Ca hard palate	Stage II	Stage IVC
P18	NPC	Stage III	Stage IVB
P19	NPC	Stage II	Stage IVC
P20	NPC	Stage II	Stage IVA
P21	NPC	Stage III	Stage IVC
P22	NPC	Stage III	Stage IVC
P23	NPC	Stage I	Stage IVC

Table 5. Data of 23 patients with head and neck tumors on the disease staging before and after the PET-CT evaluation (39)

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5. FDG PET-CT as a predictor of overall patient survival

The use of FDG as a ligand in particular for a molecular imaging technique i.e. PET-CT has been shown to provide prognostic stratification. The complete metabolic response of tumor as imaged on the FDG-PET-CT scan implies a favourable change in tumor apoptosis which is correlated with good prognosis. In a study by Fathinul et al focusing on the esophageal tumor as group-staged by I–IIA and IIB–IV had a 1-year survival of 50% and 25% respectively [40]. Patient with size of primary tumor (<4.5cm) had significantly (p< 0.036) better survival than those with large size (>4.5cm). A SUV_{max} of > 5.5 in the primary tumor [Hazard Ratio (HR) 58.65; 95% confidence interval, p=0.032] and presence of FDG-avid lymph node (HR 20.83; p = 0.010) were strongly predictive of poor overall survival on multivariate analysis Figure (5)

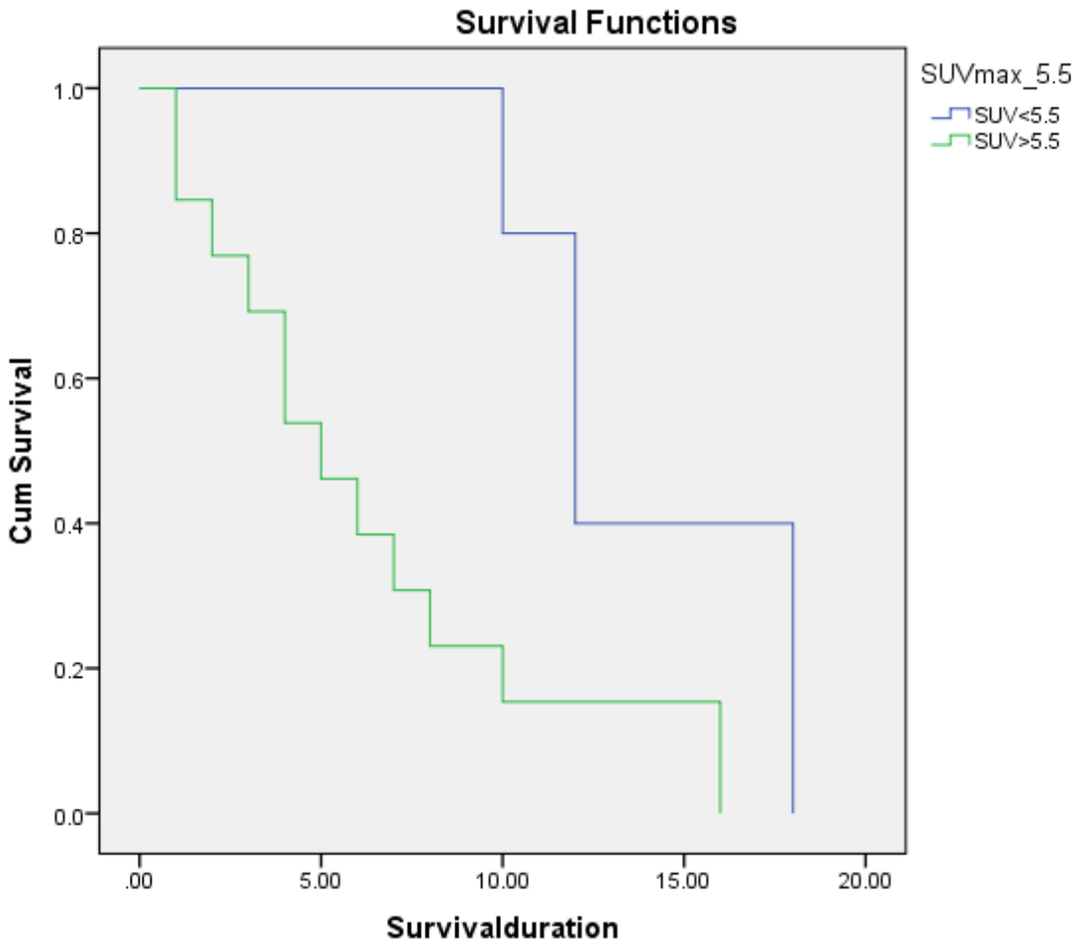

Figure 5. The survival prognostication of a cohort of 18 patients with esophageal cancers as stratified by the SUVmax cut-off of 5.5.

6. FDG-PET-CT in coronary artery disease

Cardiovascular disease is one of the leading causes of death. It carries great impact on the patients, their families as well as the country socially and financially. Cardiology is also a rapidly advancing field, with new approaches to prevention, risk stratification, diagnosis and treatment. Early detection and appropriate risk stratification will help to optimize resources and to ensure that appropriate treatment will be provided to those who would benefit from it. Diagnostic methods commonly used in the detection and risk stratification of coronary artery disease include exercise stress testing, stress echocardiography, multi-slice computed tomography, Single Photon Emission Computed Tomography (SPECT) and invasive coronary angiography. Each of these modalities has its own advantages, disadvantages and limitations.

The management of coronary artery disease includes lifestyle modifications, medications, percutaneous coronary interventions and coronary artery bypass surgery. Invasive procedures carries risks, as well as its associated costs, thus it is imperative that proper selection of patients are made based on the clinical presentation and the results of investigations. Positron Emission Tomography is a relatively new diagnostic modality with the potential to address some of the limitations of current commonly used diagnostic methods. Cardiology imaging using Integrated PET-CT equipment demonstrates an improved method in detecting abnormal coronary circulation. The resolution of PET-CT images are superior than SPECT imaging as a result of improved camera resolution and specification, high energy positron captured and CT attenuation corrected in all PET data acquisition.

In PET, 18F-FDG is the tracer most frequently used to assess myocardial viability (41-43). Since FDG is a glucose analogue, the substance is used to evaluate cardiac glucose utilization where mitochondria plays pivotal role in its utilization. The initial uptake in myocardial tissue is comparable to glucose uptake. After phosphorylation, 18F FDG-6-PO4 is trapped within cardiac tissues and the metabolism ends before the Krebs cycle enabling imaging due to the strong signal from radiation source emitted by 18-F isotope.

Evaluation of residual glucose metabolism, a hallmark of viable myocardium, by FDG –PET is considered the most sensitive non-invasive tool to assess the myocardial viability[44-45]. Viable myocardium shows preserved FDG uptake whereas, markedly reduced or absent uptake indicates scar tissue formation (Figure 6-7). Most studies relate myocardial perfusion to the FDG PET viability. FDG accumulates in the myocytes independent of the vascular enrichment. Therefore quantitative assessment of the FDG concentration in the myocardium is vital as it indicates viable tissue which is amenable to be reversed [46].

Integrated PET-CT system can be utilized in myocardial perfusion study using 82-Rubidium (Figure 8). The dynamic data acquisition during rest and stress are quantifiable using dedicated coronary flow quantification software (47-49). Abnormal readings will be obtained in coronary obstruction and endothelial dysfunction using this method. Myocardial flow reserve quantification has high sensitivity and positive predictive value in correlation with left ventricular function (Figure 9). Thus, can be recommended as a suitable non invasive tool in making clinical decision for managing patients with coronary artery disease

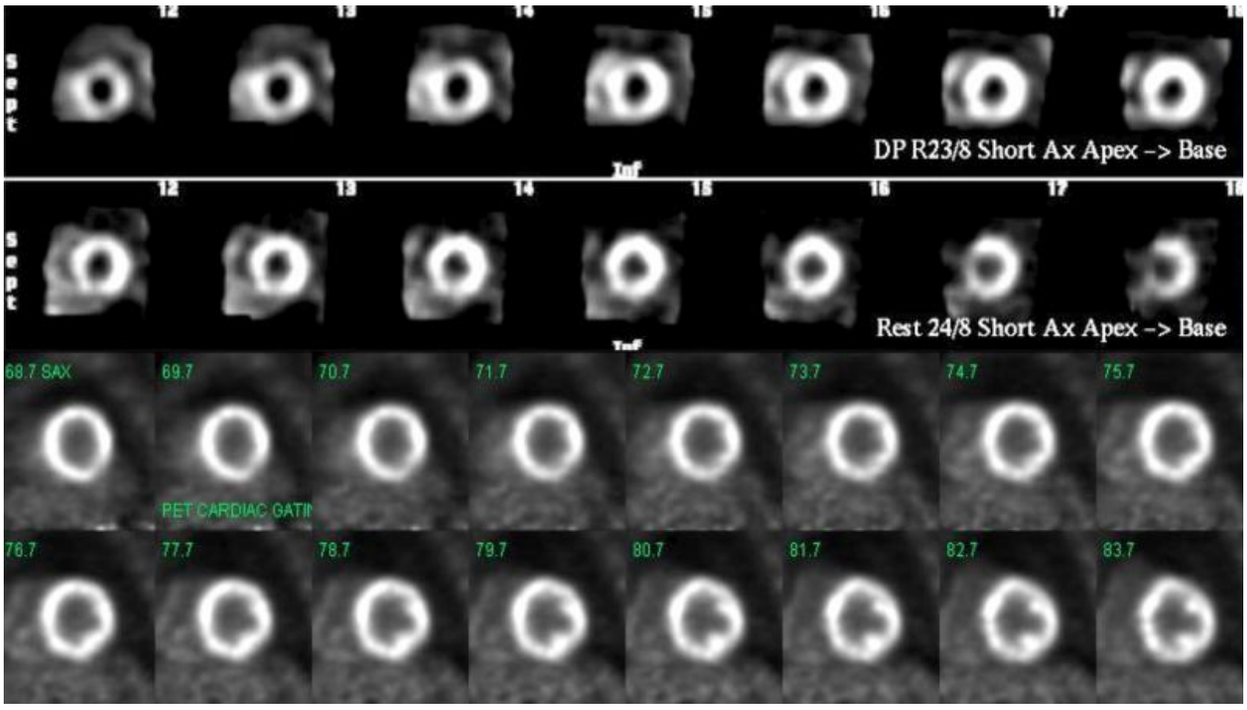

Figure 6. The transaxial non-gated static SPECT image (1st and 2nd rows from the top) and PET-CT image (3rd and 4th rows). There is a reversible defect seen affecting the posterior wall of left ventricle which filled up during FDG PET-CT study in keeping with a reversible ischaemic myocardial segment.

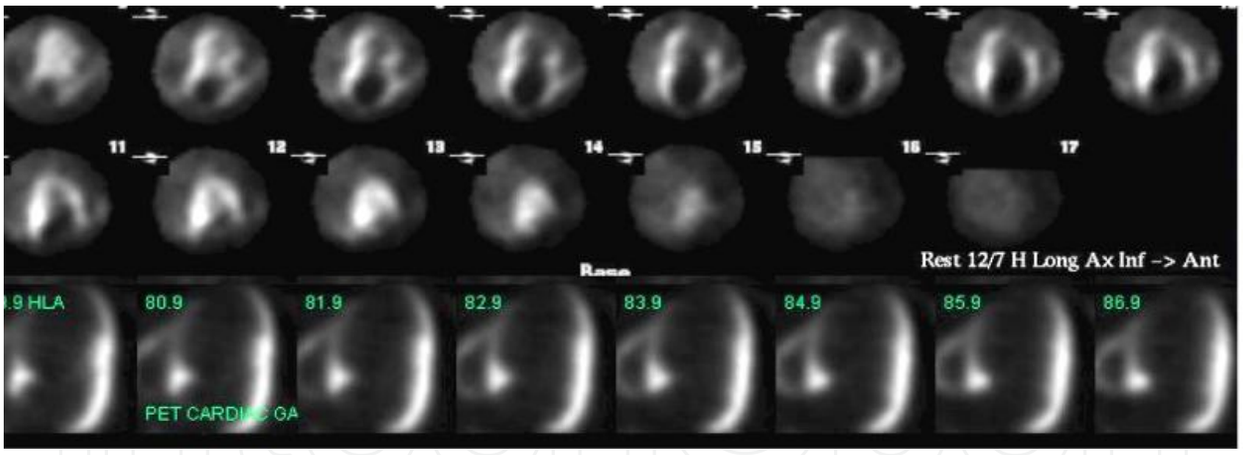

Figure 7. The horizontal long axis non-gated static SPECT image (1st and 2nd rows from the top) and PET-CT image (3rd row). There is an irreversible defect seen affecting the apex of left ventricle in keeping with an infarcted myocardial segment

7. FDG PET-CT in infection

FDG is a well known in-vivo biomarker indicating the rate of tissue metabolism. The initial course of direction for clinical utility of PET-CT in oncology is now widened into the field of infections [50-52]. Increase cancer tissue metabolism are thought to be related to raised in surrounding inflammatory reaction as demonstrated by Kubota resulting from high accumu-

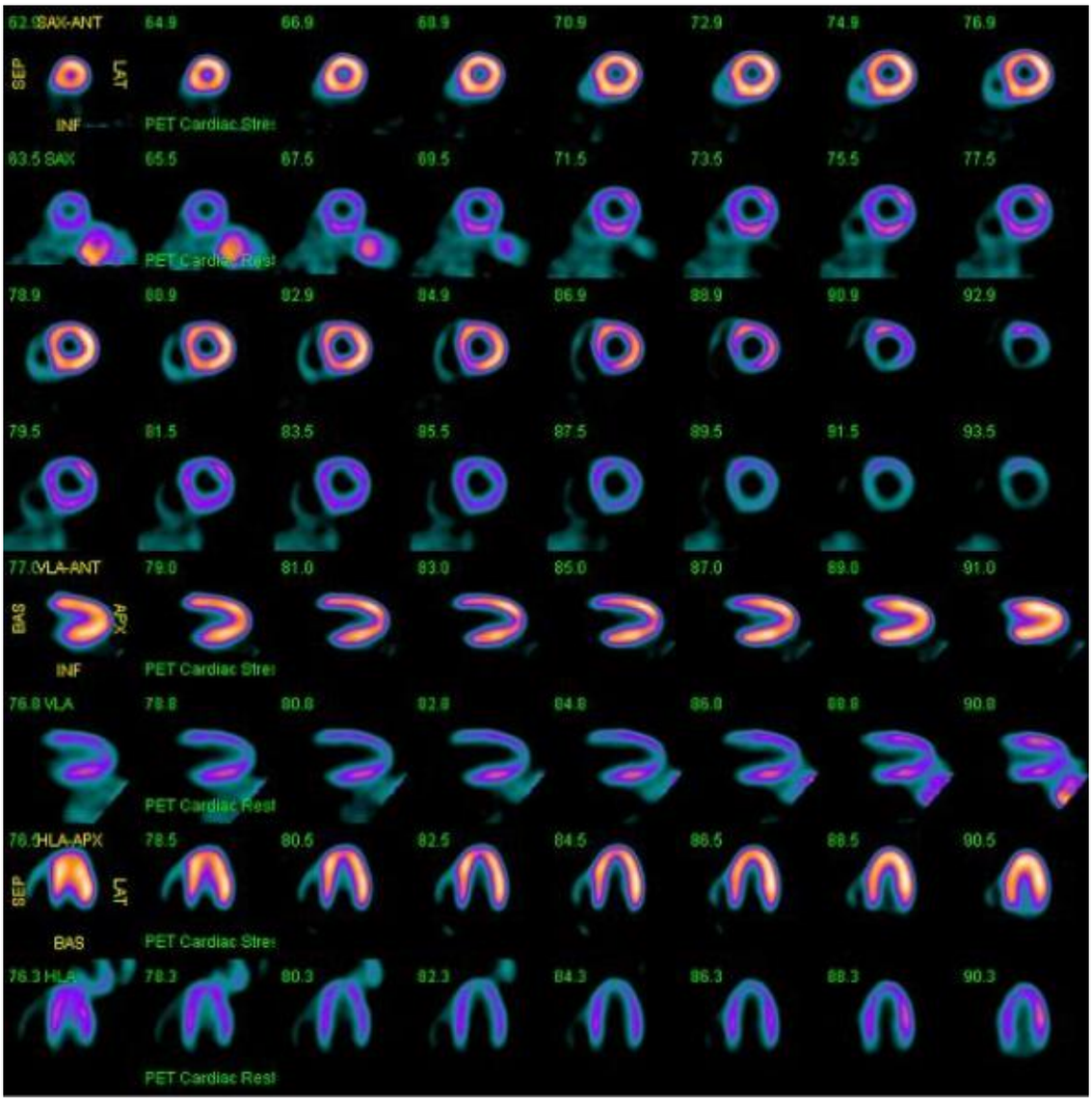

Figure 8. Myocardial perfusion 82-Rb demonstrating high quality images in a normal patient.

lation of macrophages and granulation tissues [53]. Likewise, in infection, initial increased in local hyperemia and capillary permeability will lead to aggregation of granulocytes, leucocytes and macrophage at the point of entry by pathogens. This cascade of events will lead to increased in local glucose consumption. The signals from annihilation process of positively charged beta particles emitted from radioactive fluorinated glucose molecules in-situ will be detected by PET camera during PET-CT imaging where the activity can be semi-quantified using the semi-quantitative uptake value (SUV). The SUV of infective foci are often raised above the background 18F-FDG soft tissue activity.

Despite their known clinical entity, the use of 18F-FDG PET-CT in establishing the diagnosis of infection and inflammatory condition is still controversial. A meta analysis conducted [54-62] from a series of review articles found that 18F-FDG demonstrate highest utility in cases of chronic osteomyelitis, hip prostheses, diabetic foot, fever of unknown origin, vasculitis,

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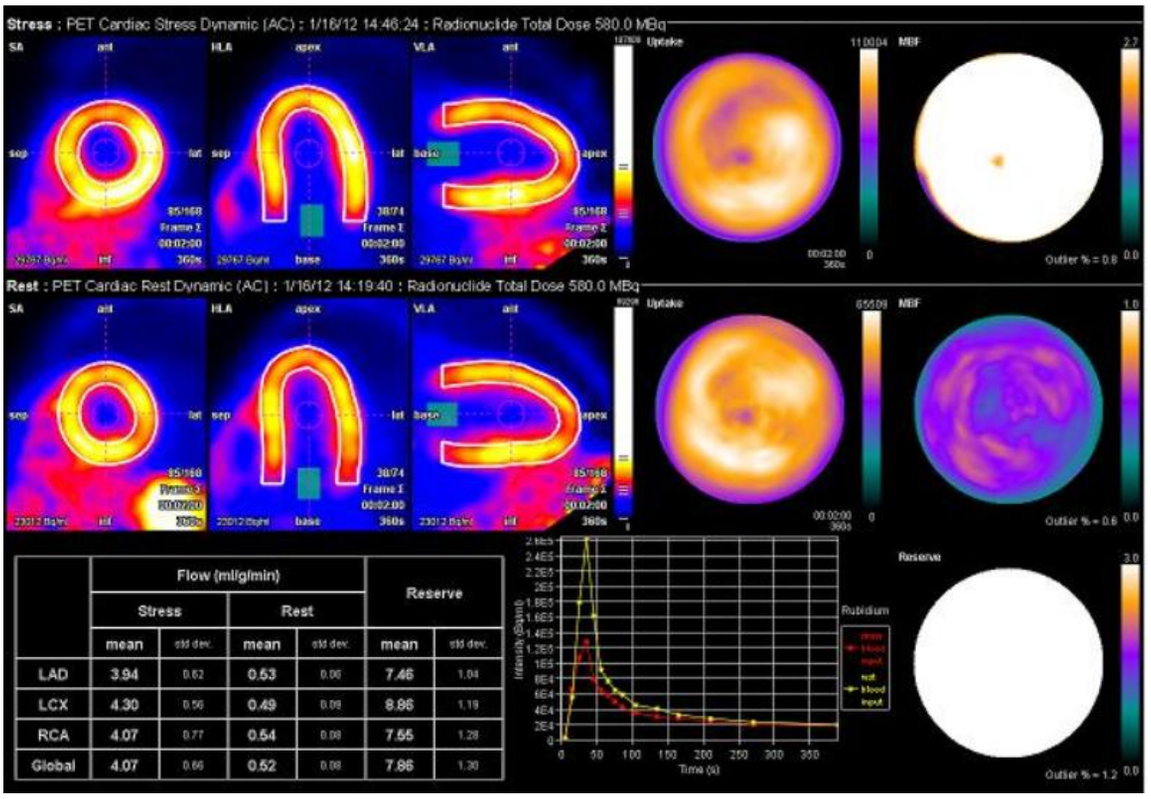

Figure 9. Quantification analysis of 82Rb Myocardial Perfusion PET CT study of a young man demonstrating normal global stress and rest flow. The coronary reserve is normal.

acquired immunodeficiency syndrome, and vascular graft infection. The role of CT during integrated PET CT imaging in the diagnosis of these conditions may range between CT for anatomical correlation and attenuation correction to non attenuation corrected fused images. In some condition, informations obtained from CT which may be classical and pathognomonic can be an important adjunct features in deciding clinical management.

For example, PET using ^{18}F-FDG appears to be a highly sensitive method in detecting infective foci in the bone. Histologically, the ^{18}F-FDG avidity defines the area of fibroblast proliferation and neovascularisation with mononuclear cell infiltration at the granulation tissue formation whereby these cells utilises most of their energy from the trapped ^{18}F-FDG for cells metabolism [63-65]FDG-PET is sensitive than the standalone CT in delineating evidence of implant infection (Figure 10)

However, since artefact through beam hardening effect of X-ray from CT scan during PET-CT study can significantly obscure the underlying pathology, often non attenuation corrected images are being the standard reference in making clinical decision for major interventional procedure. Thus, a combined PET-CT study can be a very useful modality in solving painful hip problem in a patient with hip prosthesis.

18F-FDG PET-CT can also be a useful technique in ruling out infection in critically ill patients under Intensive Care Unit (ICU) management. Study has shown that a normal scan exclude prolonged use of antibiotic in these patients [66]. Combined CT and PET have also been

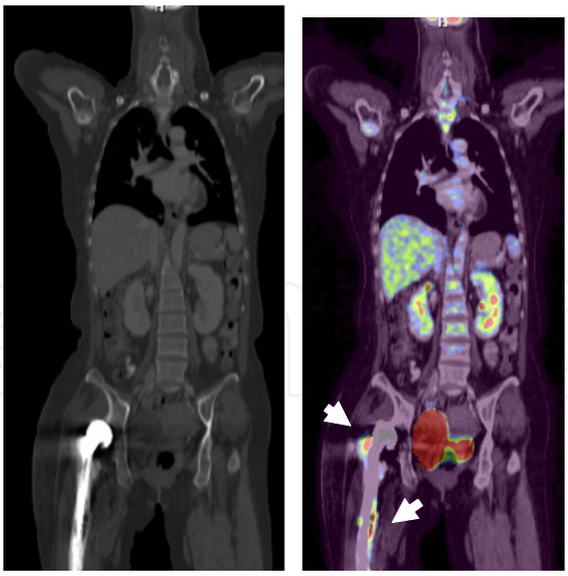

Figure 10. Coronal CT (left panel) is insensitive in delineating implant infection as the FDG PET-CT (right panel) is clearly showing increased FDG uptake along the implant denoting underlying infection (arrow heads).

reported to be useful in detecting vascular prosthesis infection. The presence of infection in such cases usually in elderly, will justify for removal of infected prosthesis. More recently, Rudd et al disclosed the capability of 18F-FDG-PET-CT in identifying and quantifying vascular inflammation within atherosclerotic plaques [67].These vulnerable plagues carry high risk of auto detachment causing embolisation and ischaemic infarct to vital organs increasing the risk for cerebral vascular accident and ischaemic heart disease (Figure 11). Positive correlation between FDG uptake measurements in the left anterior descending artery with high risk factors of coronary artery diseases has been established [68].

The scope of FDG PET-CT study is widest in cancer imaging leading to increasing application of this powerful modality into clinical practice. There has been significant evidence showing non exclusivity of FDG as a tumor marker observed with increase FDG uptake seen in a wide range of infection and inflammatory conditions[69]. Examples are chronic granulomatous infections like sarcoidoses, infections by tuberculosis, fungal infection like aspergillosis and narcoidoses which are known to demonstrate high FDG uptake. Although they can jeopardize the accuracy of integrated imaging interpretation in malignancy, their high standardized uptake value (SUV) during semiquantification on FDG PET-CT can be exploited and utilized as an important localizing tool for guided biopsy and potentially useful for navigating response to treatment [70].

8. FDG PET-CT in pre-clinical application

PET/SPECT neuroreceptor and metabolic imaging, as well as conventional and functional MR imaging, MR spectroscopy, optical imaging, and other techniques, is utilized almost routinely to help establish proof of- mechanism studies for new drugs, especially at the interface between

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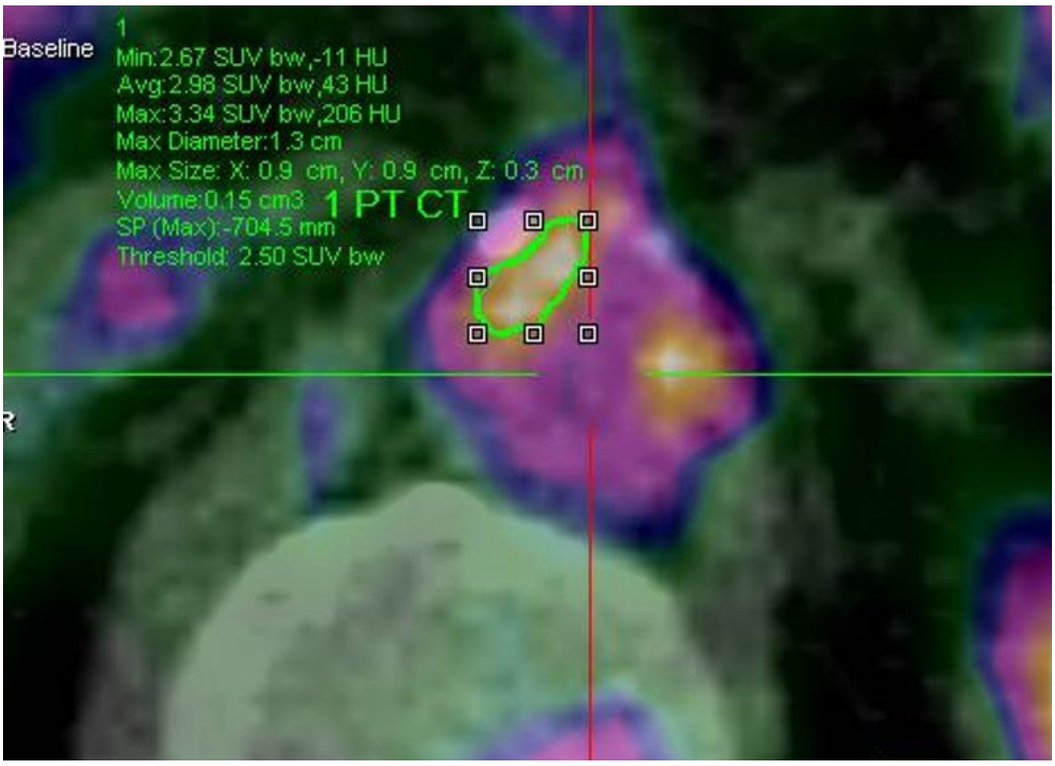

Figure 11. Cross sectional image of abdominal aorta demonstrating vulnerable plague at 11 o'clock (SUVmax of 3.3) and 3 o'clock position. The green and red cursors are shown to be crossing the centre of the aorta

preclinical and early phase 1 studies. In particular the use of FDG as a PET probe, its SUVmax values have been shown to correlate with histologic grade in heterogeneous series of bone and soft-tissue sarcomas [71]. The potential for molecular imaging in small animals to increase knowledge of drug effects in models of human cancer has been recognized around the world. This has been embraced as a means of decreasing the time taken to indentify agents that merit clinical trial and to decrease the cost of drug development [72]. The ability to extrapolate from animals to human studies makes PET a logical technique for both pre-clinical testing of new therapeutic drugs and for the validation of new tracers that might be relevant to the evaluation of human diseases. Manipulation of cells and tissues to produce animal models that mimic human diseases provides a useful system to test new tracers. At a pragmatic level, a short feedback loops between studies in mice and then in man is important. While unrestrained proliferation has been described as a hallmark of cancer and is a target of several targeted anti-cancer therapeutics, due to differences in blood thymidine levels and in the metabolism of PET probe which look at cell proliferation i.e. Fluorothymidine (FLT), both uptake and excretion of this tracer show significant differences in biodistribution in different species.

9. FDG PET-CT in non-clinical application

The development of imaging technologies, including hybrid systems allow the evaluation of gene expression in various cancers. The underlying original genetic problems of cancer can be

monitored by PET using radiolabeled metabolic substances including glucose, amino acids or nucleotides. Sometimes, molecular imaging means genetic imaging or molecular-genetic imaging in which the assessment is based on the reporter genes and labeled antisense oligonucleotide probes [73].

Radiolabeled antisense oligonucleotide probes have been applied to image endogenous gene expression at the transcription level [74]. In diagnostic radiology, CT and ultrasonography (US) have been examined as means of molecular-genetic imaging. In PET, dopamine 2 receptor (D_2R) gene is used as an imaging reporter gene, because of the availability of the well established radiolabeled probe ^{18}F-fluoroethlspiperone (FESP) [75]. Moreover, Furukawa et al. [76] have designed a reporter gene imaging system based on ^{18}F-labeed estradiol and human estrogen receptor ligand (hERL) binding domain in access of various tissues for gene therapy monitoring.

Several researchers have investigated the use of γ-emitters for molecular imaging [77, 78]; examples include the somatostatin receptor (SSTr) 2 (SSTr2) gene and ^{111}Inoctreotide [79], the norepinephrine transporter gene and ^{131}I-labeled metaiodobenzylguanidine (^{131}I-MIBG) [80], sodium/iodide symporter (NIS) gene and radioiodines or ^{99m}Tc-pertechnetate [33, 34]. Jacobs et al. [81] demonstrated the first human PET image of HSV1-tk gene expression in a glioma patient.

10. Molecular imaging: Future perspective

Molecular imaging is now being accepted by many (physicians) as an important platform in translating genetic defect through aberrant protein function and cellular transformation and development. Nevertheless, the sensitivity of molecular imaging techniques is varied depending on the type of radiopharmaceutical marker used in signaling the biological processes. In particular, the use of FDG as a ligand PET-CT has many limitations. The most obvious example of this is in the brain where high glucose utilisation by the normal cerebral cortex can mask brain tumors, particularly those of well differentiated. In addition, some tumors with high metastatic potential can have relatively low FDG-uptake. Similarly, the specificity of FDG–PET is also imperfect with some benign conditions, particularly granulomatous lesions i.e. tuberculosis, having high FDG uptake. These very real limitations of FDG used in the molecular imaging technique have enticed the search for alternative radiotracers which signal different biological disease process. Several alternative PET-radiopharmaceuticals are currently being investigated, which have the potential to reveal the proliferation rate, oxygen utilization, drug resistance properties and the viability of the tumors. Examples of new PET tracers include fluoroethyltyrosine (FET) for brain tumor imaging; the proliferation marker 18F-fluorothymidine (FLT) to assess bone marrow reserves and the exploitation of dual tracer strategy i.e. FDG and 68 Ga DOTA –octreotate for staging and therapeutic response in neuroendocrine tumor would promise a more complete assessment of disease process and tumor biology. The choline analogue 18F-fluorocholine (FCH) for patients with rising prostate specific antigen levels would potentially have an impact on the management strategy and thus

improve the overall patient survival. It is likely that the continuing success of molecular imaging will rest on the future development of more disease specific ligand or tracer, used in specific combination to answer the important clinical question.

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