18F-FDGPET-CT is a Useful Molecular Marker in Cancer Biology

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1 Introduction

Positron emission tomography (PET) is being increasingly used for diagnosis, staging, and follow-up of various malignancies. It has been studied in the evaluation of various tumours including but not limited to non–small cell lung carcinoma, lymphoma, melanoma, breast cancer, and colorectal cancer (Vesselle *et al*., 2000; Kostakoglu *et al*., 2003). Conventional imaging modalities i.e. computed tomography (CT) have stood across the decades complementing physicians in formulating diagnosis and strategizing treatment planning. The escalating costs of the conventional diagnostic methods in oncology have yet eschewed the futile surgical interventions and the spiraling treatment cost. The evolution in engineering technology which look at the correlation of the anatomy and the function of tumour i.e. PET-CT have impacted on the improved diagnostic accuracy and treatment in oncology. In most of the techniques used worldwide is the non-invasive diagnostic imaging tool using radiolabeled glucose analog, Fluorodeoxyglucose (FDG), to the Fluorine-18 (^{18}(F)) of the PET-CT, (Table 1, Figure 1). The innovation of combining both PET & CT modalities has impacted in the improved accuracy of its application in oncology by co-registering the disease anatomy and its function. The use of PET-CT technique has received global acceptance for its superb efficacy in sufficing the management in oncology which in turn help improve the mortality and morbidity of the cancer-burdened patients. Given the known natural behaviours of tumours, 18F-FDG accumulation in tumours is used as index of increased glucose metabolism and as a marker of tumour viability for which, the degree of 18F-FDG uptake usually reflects tumour aggressiveness. Such knowledge will allow more effective treatment adoption in the setting of the individual patient's genetic makeup and disease process.

Properties (^{18}F)	Quantification
Radiation	Gamma: 511 keV
Gamma constant	1.879E-04 mSv/hr at 1 meter (Shlein *et al,* Eds. 1998)
Half life($T_{1/2}$)	Physical ($T_{1/2}$): 1.83 hours[2] (Delacroix *et al*, 1998)

Table 1: Physical Properties of Fluorine-18 (^{18}F)

2 PET-CT

PET-CT is a rapidly developing imaging tool, with a clinical role that now exceeds 15 years (Wood KA *et al*., 2007). The efficacy of PET CT routine to provide unique additional information, increase accuracy of interpretation and to acquire complementary information accounted as a powerful technique in multimodality imaging. PET CT requires a positron emitter radionuclide produce at the end of the bombardment from cyclotron before it is sent to a synthesis module for production of radioactive tracer. The PET-CT is a dual- modality imaging tool which uses a various ligands as a tagged pharmaceutical substance whilst allowing both functional and structural changes of an abnormal metabolic tissue to be imaged contemporaneously. PET is a non-invasive diagnostic tool that provides tomographic images and quantitative parameters of perfusion, cell viability, proliferation and/or metabolic activity of tissues. Therefore, FDG PET can reveal the presence of a tumour when conventional morphological diagnostic modalities (i.e. X-ray, CT, MRI and ultrasound) do not yet detect any evident lesions. The most commonly used

radioactive tracer in PET-CT routine is the glucose derivative, 2-(^{18}F) fluoro-2-eoxy-D-glucose or commercially known as 18F-FDG. PET scanner could only detect positron emitters. The collision between a positron and an electron resulted in annihilation and creates gamma ray energy of 511 keV to be given on both sides and hence detected by the scanner (Figure 1).

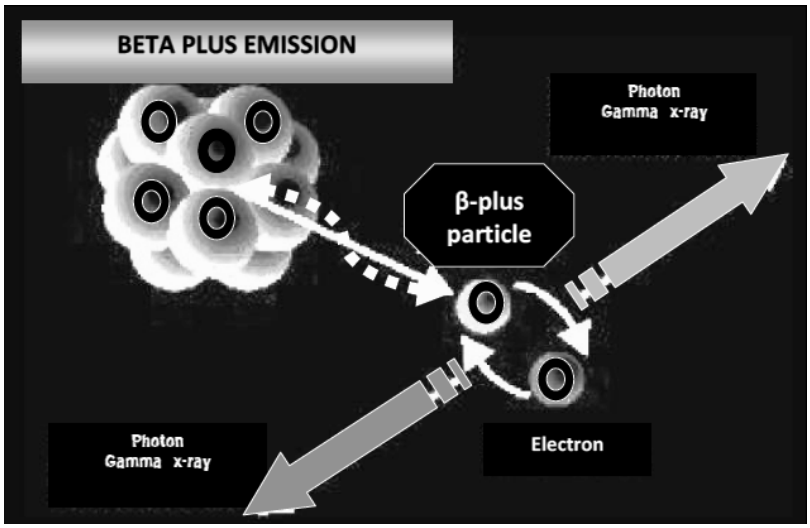

Figure 1: Detection of a gamma energy of 511 keV on the PET scanner detector by 18F.

In recent technology, most of the configuration of the detector is in full rings configuration (Figure 2) with the BGO (bismuth germinate), LSO (lutetium oxyorthosilicate) and LYSO (Cerium-doped lutetium yttrium orthosilicate) are being the most common scintillators used. Properties of different scintillatormodels used in PET scanner are shown in Table 2.

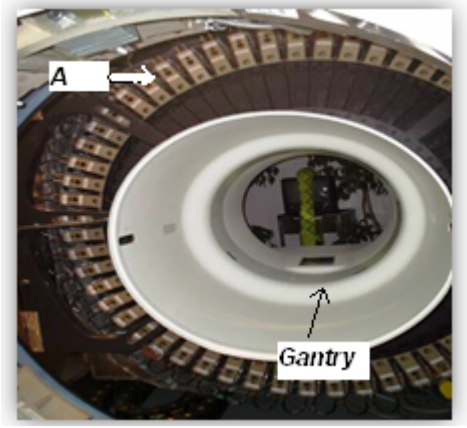

Figure 2: Block detector (A) with full ring configuration mode

	Density (g/cc)	Z	Decay Time (ns)	Light Yield (% NaI)	Attenuation Length (mm)
Na(TI)	3.67	51	230	100	30
BGO	7.13	75	300	15	11
LSO	7.40	66	47	75	12
GSO	6.70	59	43	22	15
LYSO	7.30	64	50	75	87

Table 2: Scintillators used in PET scanner, Note: BGO (bismuth germinate), LSO (lutetium oxyorthosilicate) and LYSO (Cerium-doped lutetium yttrium orthosilicate)

Computed tomography (CT) imaging provides high quality images which reproduce transverse cross sections of the body. The introduction of multi slice scanners (8-slice, 16-slice and 64-slice) provides resolution and allows gated cardiac imaging. Over few years, the technologists had came out with the hybrid PET CT which is able to provide accurate diagnosis by using data from CT for attenuation correction.

3 ^{18}F-FDG

FDG is an analog of glucose and is taken up by living cells via the first stages of normal glucose pathway (Figure 3). The rationale behind its use as a tracer for cancer diagnosis depends on an increased glycolytic activity in neoplastic cells. Glucose as an essential element in living cells for baseline metabolism is taken into the cells by phosphorylation process and converted into energy through the Krebs Cycle. Similarly, the rate of FDG uptake is also proportion to the rate of tissue metabolism. In vivo, intense uptake and metabolism of FDG 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 (Warburg O., 1956). This is the basic principle underlying the value of molecular imaging using FDG as a metabolic probe. Since its ability to signify the metabolic pathway of various pathological tissues in specific critical diseases, FDG is an invaluable biomarker in molecular imaging. For example, the alteration of the glucose metabolism in cancer requires further understanding of what are the molecular mechanisms that underpin metabolic reprogramming. These mechanisms are complex and involve adaptive responses to the tumour microenvironment, such as hypoxia, or mutations in enzymes or oncogenes that control cell metabolism. Genetic alteration, peptide receptors, surface proteins, somatostatin receptors are all related in the establishment of malignant disease.

FDG will be accumulated in a high metabolic-affinity tissue of cancer cells (Figure 4). Tumour tissue contains an increased amount of glucose transporter protein i.e. transcription of GLUT 1 and GLUT 3 together with the presence of a highly active hexokinase isoform. This certainly helps to enhance the FDG uptake in the tumour. In addition, relative hypoxia, which often occurs in tumour masses, may activate the metabolic steps in the anaerobic glycolytic pathway and enhance FDG uptake (Minn *et* al., 1996). FDG is trapped into the cancer cells due to their high glycolytic activity and excreted from the body through the renal system, which is unable to reabsorb the tracer. A 30-60 minute interval between FDG administration and image scan is usually enough to obtain a good tumour/background ratio of the

tracer. The cell alterations related to neoplastic transformation are associated with functional impairments that are discernible before structural alterations occur.

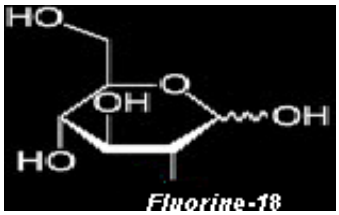

Figure 3: 18F-FDG: Chemically, it is 2-deoxy-2-(18F) fluoro-D-glucose, a glucose analog, with the positron-emitting radioactive isotope fluorine-18 substituted for the normal hydroxyl group at the 2' position in the glucose molecule.

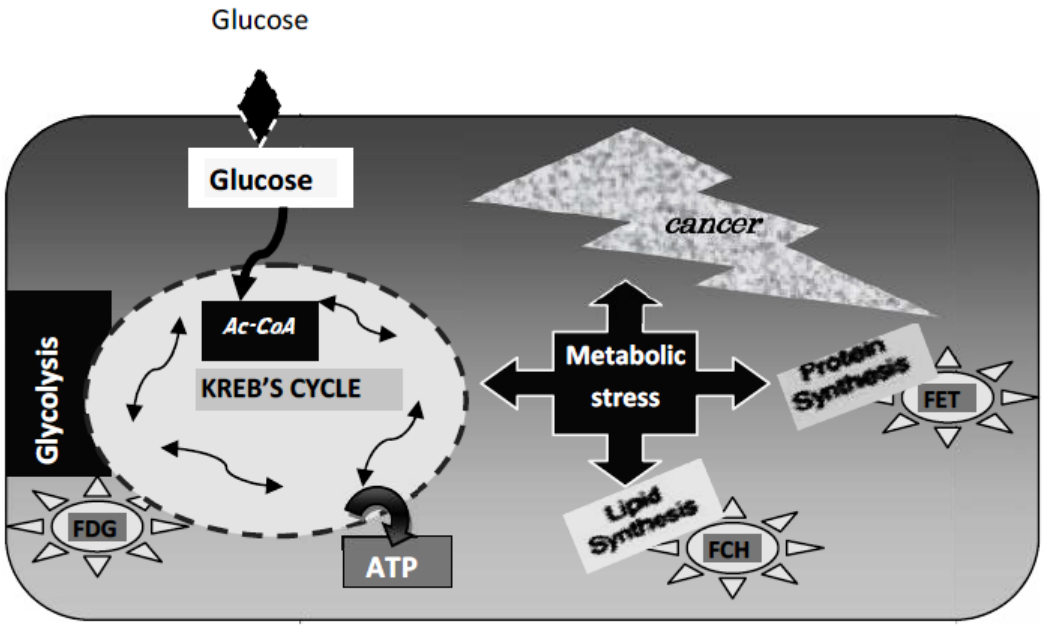

Figure 4: The kinetics of the FDG tracers is similar to glucose. It passes through cell membranes other than brain-blood barrier and is phosphorylated intracellularly in a process analogous to the glucose. The phosphorylized FDG compound does not enter in the Krebs cycle, thence it is effectively trapped in normal cells. As a result of cancer-induced altered metabolism, the normal cell undergoes a metabolic stress which underpins major cellular reprogramming i.e. an increased glucose metabolism, protein synthesis and cell membrane synthesis.Metabolic stress induces lipid synthesis and the protein anabolism which can be signaledby FCH and FET respectively. Note: Ac-CoA; acetyl-coenzyme, ATP; adenosine triphosphate; FDG;18F-Fluorodeoxyglucose (Weber *et al*., 2000); (^{18}F) fluoroethyltyrosine (FET), 18F-fluorocholine (FCH) (Yavin., 1976).

FDG uptake in tumours correlates with tumour growth and viability, so the PET scan and the possible metabolic quantification may provide useful information about tumour characterization, patient prognosis, and monitoring of the response to anticancer therapy. At present there is considerable evidence that the application of FDG-PET is becoming more and more widespread for the diagnostic assessment of patients with suspected malignancies, in tumour staging, and in therapy monitoring (Kostakoglu *et al*., 2003).

FDG has a pre-eminent role at present by virtue of a better predictive value for detecting most cancer types than conventional structural imaging standards. Although it has been demonstrated repeatedly that the degree of disturbance of glucose metabolism in individual tumours, it carries independent prognostic information (Rodney *et al*., 2007). It has been reported that prognostic factors can be identified by immunohistochemical staining of tumour tissue. However, biopsy samples do not represent the genetic information or protein expression of the entire tumour(Lee *et al*., 2008). Additionally, accumulating data suggested that FDG PET may serve as a non-invasive method, which can indirectly measure the expression of various biologic markers of tumour aggressiveness. Therefore, the standardized uptake value (SUV) which represents the integration of FDG activity in tissue of the total injected 18 F FDG may become one of the potential prognostic factors (Figure 5). Patients with high concentrations of tumour cells or highly metabolic tumour cells would be expected to have poorer prognosis (Huang SC., 2000). At present, besides providing useful diagnostic information regarding pre-treatment staging and post-treatment follow-up, intensity of FDG uptake is emerging as a valuable predictive factor regarding treatment outcome (Spiro *et al*., 2008).

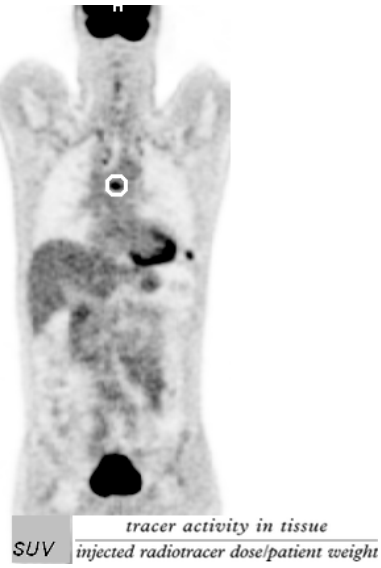

Figure 5*:* The SUV (white circle) represents an activity of the tissue tracer accumulation in microcuries per gram, injected radiotracer dose is in millicuries, and patient weight is in kilograms (Image Courtesy by PusatPengimejanDiagnostikNuklear, UPM)

The SUV is a semiquantitative assessment of the radiotracer uptake from a static PET image. The SUV of a tissue can be depicted as the minimum, maximum or mean in the region of interest. The mean SUV is the mathematical mean of all the pixels in the region of interest, whereas the minimum and maximum SUV are values of the pixel with the lowest and highest SUV, respectively. We rely on visual inspection and use SUV in assessing questionable lesions or in the follow-up of FDG-avid masses. Typically, malignant tumours have an SUV of greater than 2.5–3.0, whereas normal tissues such as the liver, lung, and marrow have SUVs ranging from 0.5 to 2.5. The SUV of a tissue can be depicted as the minimum, maximum or mean in the region of interest. This value normalizes the tumour FDG uptake with the FDG injected activity and the body weight (Kim *et al*., 1994).

The degree of tumour uptake of FDG on PET as assessed by the SUV has shown to be an independent prognostic factor in nasopharyngeal carcinoma (NPC) and other tumours (Chan *et al*., 2009). There have been many published reports that signify tumour burden as reflected by the volume of tumour tissue demonstrating increased FDG uptake on PET, or metabolic tumour volume (MTV), is a novel potential prognostic factor (Lee *et al*., 2007). Reduction in FDG uptake has been shown to correlate with reduction in viable cell numbers, to precede lesion shrinkage in the setting of conventional cytotoxic therapies and to provide useful prognostic information (Minn *et al*., 1997; Fukunaga *et al*., 1998; Vesselle *et al*., 2000)

The use of FDG as a tool in molecular imaging technique i.e.PET-CT has some limitations. The most obvious example of this is in the brain where high glucose utilization by the normal cerebral cortex can mask brain tumours, particularly those of lower grade. Several alternative PET-radiopharmaceuticals are currently being investigated, both preclinical and in early clinical trials, which have the potential to reveal the proliferation rate, oxygen utilization, drug resistance properties and the viability of the tumours.

Lack of uptake in the human brain is a major potential advantage of radiolabeled amino acids compared to FDG. Enhanced protein synthesis is also an important biological characteristic of malignant tissues. As a proof of principle, (^{18}F) fluoroethyltyrosine (FET) appears a promising candidate. Preliminary studies of the FET in brain tumour evaluation appear promising (Weber *et al*., 2000). 18F-fluorocholine (FCH), as a precursor for the biosynthesis of cellular membrane phospholipids (i.e. phosphatidylcholine), represents specific PET tracers capable of marking out membrane metabolism and turnover. Choline is transported into mammalian cells and then phosphorylated by choline kinase. Phosphorylcholine is subsequently integrated into phophatidylcholine, a major membrane phospholipids (Yavin, 1976; Yorek *et al*., 1986**)**.

The increased uptake of choline by malignant cells is believed to result from up-regulation of choline kinase in cancer cells (Katz-BrullR & Degani, 1996; Ramirez de Molina *et al*., 2002). These processes are both known to be increased in tumour cells **(**Podo, 1999). For many tumour types, choline-PET is reported to be a good diagnostic technique, although in practice its clinical value is mainly limited to prostate cancer (Figure 4) **(**Hara *et al*., (1997)**)**.

4 ^{18}(F)FDG PET-CT in genetic mutation of cancer

18F-FDGResearcher found that there is a positive correlation between tumour18F-FDG uptake and tumour aggressiveness in a variety of tumours (Oshida *et al.,* 1998). The glucose transporter 1 (GLUT1) is

most circulated isoform of glucose transporter (GLUT) in human body (Zhao and Keating, 2007). The minor variance of the DNA sequence due to mutation such as single-nucleotide polymorphism (SNP) may influence the development of certain diseases or the response to pathogens, drugs or other agents. SNP of the GLUT1 gene have been shown to link with the risk of diabetic nephropathy (Hodgkinson *et al.,* 2001; Ng *et al.,* 2002), vascular calcifications (Rufino *et al.,* 2008) and renal carcinoma (Page *et al.,* 2005). 18F-FDGWolf *et al.* (2004) has demonstrated the 18F-FDG uptake in breast cancer for SNP of vascular endothelial growth factor (VEGF) gene. VEGF is known to have predominant role in tumour angiogenesis. On the other hand, SNPs of non-protein-coding regions such as micro-RNA that contributed to the splicing of genes, binding of transcription factors may influence the 18F-FDG uptake. PVEGF and SNP are examples of procto-ongene which are activated in oncogenesis rendering potential association with the degree of an altered glucose metabolism as orchestrated by glucose transporter genes i.e. Glut 1 or Glut 3 (Brown *et* al., 1996; Hamada *et al.,* 2008; Westerterp *et al.,* 2008). In addition, 18F-FDG PET has been shown to be useful in the diagnosis and staging of non-small cell lung cancer (NSCLC) (Downey *et al.*, 2004; Cho *et al.,* 2011). Researchers have suggested that the standardized uptake value (SUV), a quantitative measurement of 18F-FDG uptake on PET (Thie, 2004), is link with outcomes in patients with NSCLC (Vansteenkiste *et al.,* 1999; Sasaki *et al.,* 2005; Al-Sarraf *et al.,* 2008; Goodgame *et al.*, 2008; Berghmans *et al.,* 2008).

5 FDG PET-CT and cancer biology

Oncology is a vital stream of medical field whereby cancer is a known burden to the patients nationwide. Across the world, many renowned institutions have already engaged researchers and fund raising programs to reduce the burden of the cancer survivors and hence the improvement of the total quality of life. These are achieved by invigorating new molecular imaging techniques in the cancer diagnosis and the discovery of new drugs in cancer treatment. In oncogenesis, normal cells grow in an abnormal pattern. At cellular level, various altered behaviours are expressed by the abnormal cells which include excessive cellular proliferation, uncoordinated growth and tissue invasion. These are achieved when regulatory genes at molecular levels have reprogrammed to the metabolic stress induced in cells with resultant altered DNA and altered cellular programs. The mitosis and protein synthesis are disturbed activating the pro-oncogene and inactivation of tumour suppressor genes. An increased in cellular metabolism cells forming a basis for molecular probe employing PET-CT in signaling cellular reprogramming in tumour tissue (Figure 4) (Yavin, 1976). Aside from increased glucose metabolism, cancer cells also show increased amino acid metabolism, nucleoside metabolism by rate of proliferation, and lipid metabolism in which FDG PET imaging might be impaired (Figure 6).

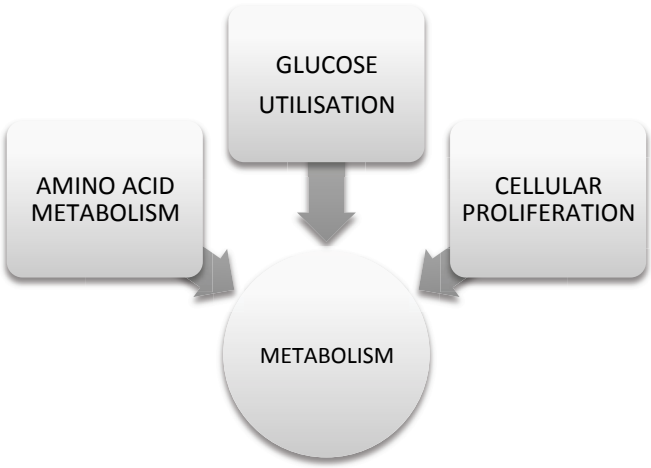

Figure 6: Main factors that influence the in-vivo altered cancer metabolism

5.1 Head & Neck Tumour

Most types of the head and neck tumour, have altered glycolytic metabolism, leading to high FDG-avidity. Several authors have reported the use of FDG PET scanning in cancer of the head and neck, both in the setting of primary staging and evaluation of patients after primary therapy, suggesting significantly higher accuracy than conventional evaluation. The common tumour of this category is nasopharyngeal carcinoma (NPC). All NPC cases were regrouped into two histological types according to the WHO 1991 classification, namely keratinising squamous cell carcinoma (equivalent to WHO Type I) and non-keratinising carcinoma (pooling together WHO Type II non-keratinising and Type III undifferentiated carcinoma in the old terminology (Shanmugaratnam & Sobin, 1991). Types II (non-keratinising squamous cell carcinoma) and III (undifferentiated carcinoma) are more common, carry a more favourable prognosis and are more sensitive to radiotherapy. Types are important as it is associated with treatment efficacy and response. It is a radio and chemo-sensitive tumour which has good prognosis when its clinical course could be interrupted and intervened early by means of imaging technique. This is the yardstick in the evaluation of a small lymph nodes which in the primary presentation setting, there has been a tendency to use PET primarily in cases with equivocal findings after conventional evaluation. With regards to head and neck tumour, PET imaging has also emerged as a sensitive technique in detecting clinically occult metastatic disease, retropharyngeal lymph nodes or small volume lesions (Table 3). Liu *et al* showed PET as being more sensitive in detecting skeletal metastases compared to skeletal scintigraphy (70% compared with 37%) in 30 of 202 patients. (Liu *et al*., 2006).

Nonetheless, the superiority of PET-CT to whole-body MRI in overall Tumour-Node-Metastasis (TNM) staging supports the usefulness of 18F-FDGPET-CT as a possible first-line modality for whole-body tumour staging (Antoch *et al.*, 2003). The SUV is not associated with the clinical staging of NPC, but is correlated to the T staging of NPC. Though irrelevant to the N staging of NPC, the SUV is correlated to the size of the lymph nodes, and also related to the degree of differentiation of NPC (Wen-Shan *et al*., 2012).

18F-FDGPET-CT	Limitation of morphological imaging
Provide both structural and functional information of tumours	Limited to structural information
Alters tumour staging (Patrick *et al*.,2006)	Underestimate the preliminary staging
Sensitive in localizing deep seated tumour and small lymph node involvement	Limited information on structural changes
Good for treatment monitoring based on the functional metabolic changes	Limited to structural changes (Akram AI – Ibraheem *et al*., 2009)

Table 3: Factors which favour the superiority of the 18 (F) FDGPET-CT as compared to the structural imaging.

5.2 Gastric Tumour

Most of the published studies on assessing therapy response in gastric cancer have been performed with 18F-FDG PET. With the advent of PET-CT, which allows one to combine the structural information provided by helical CT with molecular imaging by PET, an almost simultaneous assessment of tumour morphology and metabolism over time has become possible (Gebski *et al*., 2007). 18F-FDG PET has shown promising results in assessing response to therapy and tumour control and in prognosis in gastrointestinal cancer (Gebski *et al*., 2007). Among these, assessment of early response to therapy has gained importance because it implies clinical consequences in the diagnostic management of patients. Changes in regional tumour metabolism may precede changes detectable by structural imaging (Weber & Figlin, 2007).

Prospective study of 44 patients with locally advanced gastric cancer demonstrated that FDG PET can correctly predict the response to therapy early, after initiation of chemotherapy, and the metabolic response was also predictive of survival. The metabolic response as measured after 14 days from chemotherapy was correlated with both the pathologic response (in 29 of 35 patients) and the overall survival (Birchmeier *et al*., 2003). Many published series had denoted a significantly lower survival rate in patients with high FDG uptake by tumours (Mochiki *et al*., 2004; Ott *et al*., 2003). A metabolic response in FDG-PET was significantly correlated with subsequent histologic tumour regression as well as with patient survival (Mochiki *et al*., 2004). Our group had performed study on the cohort of 18patients with esophageal cancer (F Fathinul *et al*., 2012). These patients underwent FDG PET-CT from 2010-2011 with the mean follow-up of 7.5 months. There were stratified into those who had low SUVmax and high SUVmax group using a cut-off value of 5.5 and the presence of FDG-avid lymph nodes. An SUV_{max} of> 5.5 in the primary tumour (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 (Table 4).

In the era of targeted molecular therapy, tumour response assessment with FDG PET has already proven invaluable in monitoring the therapeutic effect such as imatinib (tyrosine kinase inhibitor) on gastrointestinal stromal tumours (GIST) (Figure 7). A key molecular driver of these tumours is mutation of the C-KIT oncogene leading to constitutive activation of signaling pathways involved in cell growth, survival and proliferation. Imatinib normalises the enhanced activity of the glucose transporter genes by this tumours and as a result, glucose metabolism returns to normal level within days of commencing treatment. Therefore, normalisation of FDG uptake provides a reliable guide to the effectiveness of

imatinib long before measurable tumour response criteria i.e. RECIST are satisfied. (Van den Abbeele *et al*., 2007).

Variable	Hazard ratio	95% CI	*P*–value
Size primary cut-off (4.5cm)	0.042	0.001 ± 1.509	0.083
SUV-avid lymph node	20.830	2.061 ± 210.496	0.010
SUVmax cut-off (5.5)	58.650	1.426 ± 2412.701	0.032
Sex	0.517	0.083 ± 3.202	0.478

Table 4: Multivariate Cox proportional hazards regression model (n=18) F Fathinul *et al*., 2012

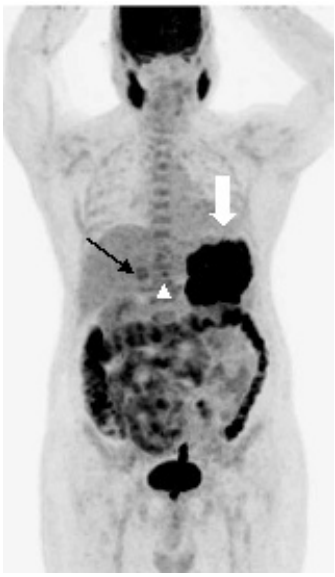

Figure 7: 45 year-old man with GIST tumour (large white arrow). Coronal multiple image projection (MIP) PET image showing FDG-avid tumour in the gaster with an altered lymph node metabolism (arrow head) and a liver metastasis (long arrow). Information on the morphological imaging i.e. CT was inadequately localized the small involvement of the lymph node (image is not shown)(Image Courtesy by PusatPengimejanDiagnostikNuklear, UPM)

5.3 Sarcoma

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 (Kole *et al*., 1997; Lucas *et al*., 1998; Johnson *et al*., 2003). In sarcoma, the demand of oxygen for ubiquitous tumour cells has resulted in insufficient to supply adequate perfusion and the consequent tumour hypoxia has profound consequences for cancer therapy, because hypoxic cells are both radio and chemo-resistant. At cellular level, the hypoxic tissues ignite the switch of the Krebs cycle metabolism to glycolysis. Several studies have demonstrated that 18F-FDG uptake is an indirect reflection of tumour hypoxia (Dierckx &

van de Wiele, 2008). In this regards, the hypoxic tissue does not accumulate FDG which serves as a vital marker or indicator for poor treatment response utilizing the routine chemotherapy treatment. Special radiotherapy techniques or targeted therapy that are active in a hypoxic environment, offer the potential for improving treatment outcomes for patients with hypoxic cell components within their tumours.

There are substantial differences in FDG uptake values between low- and high-grade bone and soft-tissue sarcomas (Figure 8) (Griffeth *et al*., 1992; Lucas *et al*., 1999; Schwarzbach *et al*., 2000). Uptake values of FDG have been shown to correlate with histologic grade in heterogeneous series of bone and soft-tissue sarcomas (Figure 7) (Ioannidis *et al*., 2004). PET-CT can help improve the localization of tumours and the accuracy of staging in patients with bone and soft-tissue sarcoma (Bar-Shalom *et al*., 2003).

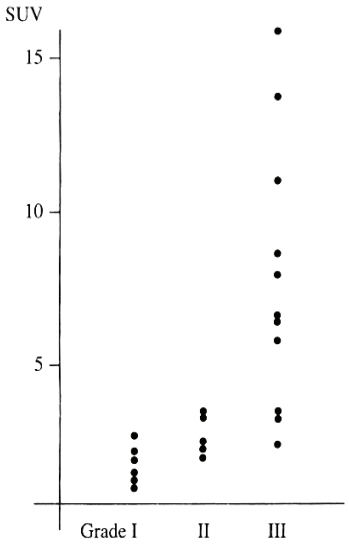

Figure 8: SUVmax quantification versus histological grade of soft tissue sarcoma (Folpe *et al*., 2000)

5.4 Neuroendocrine tumour

Metabolic heterogeneity is common in neuroendocrine tumours, and lesions in the same patient that appear identical on CT often demonstrate quite different molecular imaging characteristics. In particular, a chromaffin-derived tumour pheochromocytoma/paraganglioma (PCC/PGL), interestingly, these tumour deposits are probably less differentiated as they usually display enhanced glucose metabolic activity on FDG scanning.18F-FDG PET has proved to be an effective tool in the localization of metastatic paraganglioma and as compared with other imaging modalities alone, 18F-FDG provides additional information in patients with metastatic and multifocal forms of pheochromocytoma (Heaney *et al*.,2008; Taieb *et al*,. 2009 ; Zelinka *et al*., 2008). Most pheochromocytomas accumulate FDG. Uptake is found in a greater percentage of malignant than benign pheochromocytomas (Zelinka *et al*., 2008). FDG PET is especially useful in defining the distribution of those pheochromocytomas that fail to concentrate MIBG (metaiodobenzylguanidine) (Shulkin *et al*., 1993). This information is crucial for treatment planning because tumour deposits that demonstrate low uptake of somatostatin radiotracers do not respond to radionuclide therapy.

In patients with SDHB-associated PCC/PGL (potentially malignant) FDG PET has 97%–100% sensitivity in localising tumour lesions whereas the sensitivity of (^{123}I) Metaiodobenzylguanidine (MIBG) is 65% – 80% (Shulkin *et al*., 1993; Timmers *et al*., 2009; Zoran Erlic *et al*., 2009). The sensitivity of (^{123}I) MIBG is 83% – 100% versus 77% – 90% of (^{131}I) MIBG (sensitivity is lower for extra-adrenal and/or metastatic disease) their specificity is 95% – 100% (Shulkin *et al*., 1993; Shapiro *et al*., 2001)

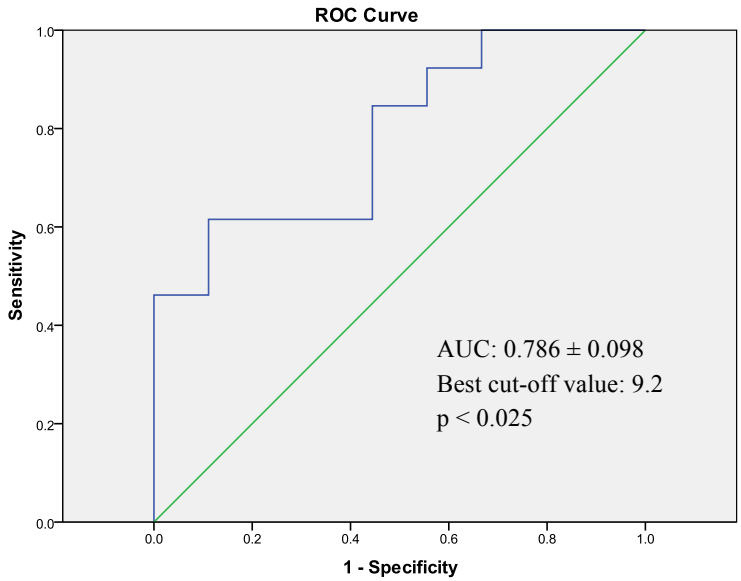

Figure 9: Receiver-operating-characteristic curve of SUVmax in predicting patient who had PCC/PGL recurrent. Sensitivity and specificity obtained using best cut-off value were 61.5% and 77.7%, respectively. AUC= area under the curve. (Fathinul *et al*, 2011)

Our group hasstudies 23 patients with (PCC/PGL) who underwent FDG PET-CT study when tumour recurrence occurred (Fathinul *et al*, 2011). The clinical risk factors of sex, serum catecholamine, tumour type, tumour SUVmax, maximum tumour size (cm), 2.0cm<size<2.0cm were evaluated for the predictors of disease end-points using the Chi-Square and Fischer's Exact tests (Table 5). We found a promising role of the semi-quantitative value of SUVmax in predicting the malignant potential of the tumour when a cut-off value of SUVmax of 9.2 was used (Figure 9). In this cohort of patient, we found that more patients with SUVmax of more than 9.2 have metastatic lesion as compared to those with local disease only (Table 5). Our result suggested that patients with metastatic disease and high malignant potential have altered tumour glycolysis as quantified by SUVmax reveals. This explains that the altered glycolysis in those with metastasis has likely undergone de-differentiation hence the SUV is much higher.

Factor	No of Patients		*p*-value
	Local control (n = 9)	Metastasis (n = 14)	
PCC/PGL Tumour SUVmax			*0.003
<9.2	9	6	
>9.2	0	8	
Tumour size			*0.04
<2.0cm	9	9	
>2.0cm	0	5	
Serum catecholamine			0.18
positive	2	12	
negative	7	2	

Table 5: Outcomes according to the tumour risk factors; SUVmax, tumour size and serum catecholamines. Fathinul *et al*., (2011). *Fischer's Exact Test, significant level (p<0.05)

5.5 Lung cancers

Lung cancer is a worldwide leading cause of cancer related death. It is challenging for the radiologist to provide accurate staging using conventional morphological imaging modalities. FDG PET CT has been reported to provide improved accuracy over conventional imaging modalities in staging, restaging, predicting and prognosis of lung cancer patient. In view, the revised TNM staging system for lung cancer is expected to improve the outcome of lung cancer patients. Despite detail assessment on tumour size, pleural involvement, nodule classifications, local and distant metastases in the new improved revised system, 'skip metastatic' phenomenon may be missed. In addition, incidental pulmonary nodules can complicate scan interpretation whether these are synchronous multiple primary lesions, metastases or benign lesions. The location of these nodules identified on multi-detector computed tomography (MDCT) can serve as a good clinical clue to which entity does it belong to. The work up to exclude a second primary is an important task as the objective of treatment is to cure whenever possible. Although FDG PET CT has a high negative predictive value in excluding nodal disease and highly accurate in detecting metastatic disease, the limitation in PET camera resolution may falsely under stage small size metastatic nodes. Subcentimeter malignant nodules are subjected to false negative results whereas some FDG-avid lesions on PET are of false positive nature (Fathinul Fikri & Lau, 2010). While normal FDG uptake pattern may cause false negative interpretation of solitary brain metastases, contrasted CT or MR is the method of choice in determining the role of surgical resection as a method of treatment in these types of patients.

Optimizing imaging information acquired from both systems in an integrated synchronized study is one option to reduce the false interpretation of PET CT findings. Contrast enhanced PET CT study provide a new avenue in differentiating high T-staging and may be useful in discriminating invasive disease by preservation of fat plane. On genomic aspect, Huang *et al*. (2010) suggested that higher 18F-FDG from epidermal growth factor receptor (EGFR) mutation among Asian patients with advanced lung adenocarcinoma. Choi *et al.* (2012) concluded in their studies, lower 18F-FDG uptakes of primary tumours was associated with an in-frame deletion of axon 19 in patients with NSCLC. Even though genetic test are the gold standard, 18F-FDG uptakes may provide useful information and essential when a genetic assessment is not feasible.

Although FDG is a useful marker in molecular imaging of lung cancer patients, radiologists must understand in detail the pitfalls and disadvantage of this imaging system in order to optimize their clinical role and contribution to treatment and outcome in lung cancer patients.

6 Conclusion

A combined PET and contrasted CT scanner is a practical and effective approach to acquiring co-registered anatomical and functional images in a single scanning session. In particular, its utility in oncologic imaging has impacted the way physicians personalizing treatment to each of the cancer type. The 18F-FDG-PET-CT imaging facilitates the separation of normal physiologic uptake from a pathological tissue with a much favorable accuracy and hence help reduce the incidence of false-positive and false-negative incidence. In a nutshell, FDG-PET CT technology has become a vital tool in cancer diagnostic frontier.

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