Pertanika J. Sci. & Technol. 23 (1): 1 - 12 (2015)

SCIENCE & TECHNOLOGY

Journal homepage: http://www.pertanika.upm.edu.my/

Review Article

Applications of ^{18}(F) FDG PET/CT in Oncology

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ABSTRACT

The escalating costs of conventional diagnostic technology in oncology have yet to obviate futile surgery intervention and the spiralling treatment cost. The evolution in engineering technology which looks at the correlation of the anatomy and the function of tumours i.e. Positron Emission Tomography-Computed Tomography (PET-CT) have impacted on the improved diagnostic accuracy and treatment in oncology. Clinical data have demonstrated that the information provided by PET/CT often changes patient management. This review addresses the value of PET-CT as a surrogate molecular marker in tumours and to discuss some issues in adopting PET/CT in routine daily practice as supported by the numbers of literature reviews of its application in oncology since it was first commercialized in 2001. The description of the technology used in multimodality imaging has gained encouraging interest among physicians, policy makers and insurance companies on the importance of the PET-CT, for which roles are not limited to the staging, disease prognostication and treatment monitoring with potential impact on treatment cost and justification of radiation safety for the patient. PET/CT is a useful tool in cancer investigation as evidenced by its role as a surrogate marker in underpinning the cellular reprogramming of different pathological entities.

Keywords: Casemix, PET/CT, oncology, image fusion, technology

Article history:
Received: 6 August 2012
Accepted: 21 May 2014

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INTRODUCTION

Most radiologic procedures i.e. Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) map the morphology of tumours with little or no information about their metabolism. Positron Emission Tomography (PET) employing 2-(fluorine-18)

ISSN: 0128-7680

fluoro-2-deoxy-D-glucose (FDG) is being gradually received as an important tool in providing qualitative and quantitative metabolic informations that is critical in influencing diagnosis and follow-up (Lau *et al*., 2006; Czernin, 2007). Radio-labelling of the PET tracer, the Flourine-18 (^{18}(F)) with FDG (glucose analogue) provides an accurate localisation of a cancerous biological target via signalling the intracellular glycolysis obtained by the co-registration of the PET and CT images (Antti, 2010). The value of combining the FDG-PET and the CT has improved the diagnostic accuracy in cancer at large (Fathinul, 2013a; Fathinul *et al*., 2013b; Nordin, 2012; Pfannenberg, 2007; Niikura *et al*., 2011). For the purpose of this review, we address the utility of FDG-PET CT as a useful imaging tool by highlighting its use in the field of oncology imaging.

Scanning Procedure

PET/CT equipped with a crystal detector arranged in a ring around the patient covering an extended 50cm to 70cm per field of view is the common prototype system in commercial use. Prior to undergoing a PET/CT examination, patients are required to fast for at least 6 hours and to avoid strenuous physical activities. After validating the desired venous glucose level (< 7.0mmol/L), patients are injected with approximately 10mCi 18F-FDG and are instructed to lie completely still in the first 60 minutes in a designated injection room. A CT scan is performed for the purpose of an attenuation correction to rescale the 511kV PET data. The PET emission acquisition is performed at approximately 3.0 minutes per bed position. PET, CT and fusion PET/CT images are displayed on a dedicated PET-CT display system for qualitative and semi-quantitative analysis (Ronald *et al*., 2010).

Flurodeoxyglucose (Fdg) as a Signaling Probe for PET/CT

One of the primary metabolic changes associated with proliferating tumour cells is induction of aerobic glycolysis. Glucose is a critical nutrient for proliferating cells (Lee *et al.*, 2009). Malignant cells have increased facilitated glucose transport and up regulation of hexokinase activity; hence, tumours can be identified by regions of increased glucose utilisation (Gatenby & Gillies, 2004). FDG is used to signal altered glucose metabolism in patients with malignancy. The focal area of abnormally increased FDG uptake is considered suspicious for malignant disease, particularly as metabolic changes which often precede the morphological changes are associated with disease (Wahl, 1991). Whole-body PET/CT has become the standard of care for cancer staging because of its high diagnostic accuracy and ability to provide a rapid survey for both regional and distant forms of metastatic disease (Czernin, 2007).

Qualitative and Semi-quantification of FDG Uptake

The uptake of 18F-FDG can be assessed by qualitative and semi-quantitative means; each has its advantages and limitations. Mannus *et al*. recommended a scheme on the visual interpretation of tumour response on PET (Fig.1, Table 1) (MacManus, 2003). Quantitative evaluation of FDG PET images provides quantitative data in the form of a standardised 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 tumour habitus within the body. This value normalises the tumor FDG uptake with the FDG injected activity and the body weight (Kim, 1994)

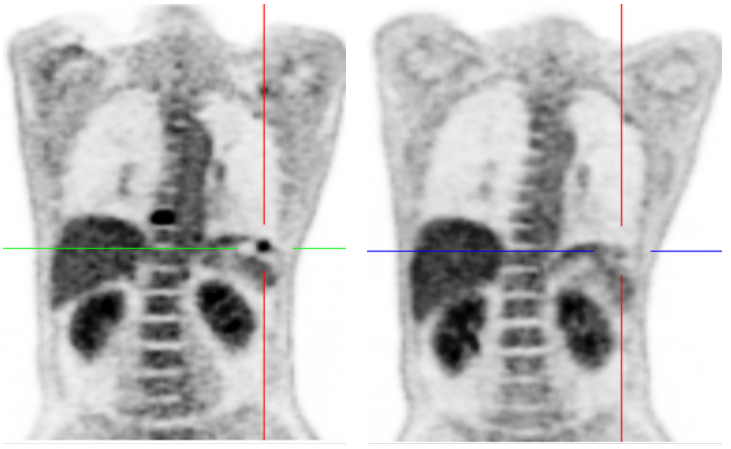

Fig.1: PET/CT treatment monitoring of a 60-year-old patient with left basal non-small lung carcinoma (NSCLC). The left panel: A coronal baseline PET image showing a 3.0 mm left FDG-avid lesion (SUV max: 7.56). The right panel: A coronal post-treatment PET image showing partial metabolic response of the left NSCLC lesion (SUV max: 3.17)

TABLE 1: Scheme Defining the Different Qualitative Assessment of the Disease Response as Evaluated on PET-CT (Macmanus, 2003)

Type of response	Description
Complete metabolic response (CMR)	-return of 18F-FDG uptake in previously documented lesions to a level of equivalent to or lower than the activity in normal tissue
Partial metabolic response (PMR) (Fig. 1)	-a significant visual reduction in 18F-FDG PET uptake in tumour sites on the visual analysis of a tumour in question but residual abnormalities suggesting malignancy
Progressive metabolic disease (PMD)	-an increase in the extent of metabolic abnormality favouring tumour growth or evidence of new sites of disease
Stable metabolic disease (SMD)	- no change

PET-CT and the Recist Criteria

The standalone structural imaging modality assessment of a small cancer lesion is devoid of information on the functional changes. The actual metabolic activity of a cancer is thence deemed as under evaluated in important parameters that influence successful treatment as cancer healing is confounded by area or fibrosis which mimic the viable cancer tissue. The use

of Response Evaluation Criteria in Solid Tumours (RECIST 1.1) to criteria in the assessment of a lesion does not represent the actual intracellular changes which lead many limitations in preparing a patient for an appropriate treatment strategy (Eisenhauera *et al*., 2009). An instance of this is a lymph node of size larger than 1 cm denoted as containing a tumour on the structural imaging, which always misleads the treating physician on the nodal staging on the TNM AJCC 6th edition (Yan-Ping *et al*., 2009). The most favourable index of the 18F-FDG PET/CT is that it is capable of exhibiting more rapid change in cellular metabolism than in tumour size (Stroobants *et al*., 2003). Functional information derived from PET is complementary to the high resolution structural imaging data available from such modalities as CT and MRI. Because of the limitations of CT scanning, PET/CT scanning may also have a role in response assessment after induction therapy prior to surgery, particularly for stage IIIA NSCLC. Choi *et al*. found that the residual metabolic rate of glucose (MRglc) as measured using FDG-PET was strongly correlated with response to preoperative chemoradiotherapy in locally advanced NSCLC as assessed by a pathological examination of a tumour obtained from a thoracotomy (Choi *et al*., 2002). Currently, the American College of Radiology Imaging Network 6668/RTOG 0235 trial is prospectively evaluating whether the primary tumour 18F-FDG SUVmax shortly after definitive chemoradiation can predict long-term survival in inoperable stage II or III NSCLC (Greene *et al*., 2002). In GIST, Choi *et al*. confirmed their previous observation that RECIST significantly underestimated tumour response. They suggested that a more than 10% decrease in one dimension of a cancer lesion on CT at 2 months after treatment is adequate to identify good responders to FDG-PET, and predicts a longer long-term prognosis (Haesun *et al*., 2007). The use of contrast-enhanced CT has enabled demonstration of tumour characteristics i.e. tumour density, enhancing tumour nodules and tumour vessels, in addition to tumour size. The additional information on the tumour enhancement on CT connotes that the outside dimensions of a tumour mass may not accurately reflect how active the tumour is and the decrease in tumour density of the responding tumours on CT is correlated with the development of tumour necrosis or cystic myxoid degeneration.

An evolving new guideline looking at the metabolic changes as a yardstick for post treatment evaluation of a solid tumour has been suggested i.e. PET assessment evaluation of a solid tumour (PERSIST). However, a lot more work on the factors that confound the parameters used before these new criteria are to be accepted given assessment on the metabolic changes require more parameters that need standardization (Richard *et al*., 2009). PERSIST, however, offers the potential to characterise the nature of tumour cells on the understanding of the alteration of their normal biochemical and biologic features. Thus, the information obtained is basically different from that alluded by anatomic imaging.

FDG PET/CT in Tumor Staging

Poor sensitivity of standalone CT, MRI and PET may lead to inaccurate staging of a tumour. Recent data, with regards to tumour staging, have shown that integrated PET/CT images are superior to PET images alone and PET and CT images viewed side by side (Kim, 1994). Contrasted CT technique used for the evaluation of equivocal PET results promises higher achievable diagnostic results in many tumours (Nordin, 2012), for instance, the prevalence

of brown fat FDG-accumulation in patient neuroendocrine tumour. The contrasted CT has a greater sensitivity in distinguishing an occult lesion given the raised lesion-to-background noise ratio (Yon, 2006; Pottgen, 2006). The impact of PET in detecting diffuse involvement of other organ systems as part of the metastatic spread or delineation of the subcentimetre focus of FDG-avidity has averted futile surgery and unnecessary treatment costs (Pottgen, 2006). In this regards, we observed the change in the patient management as a result of the up-staging of tumour by the PET-CT modality (Fathinul, 2011). In addition, the metabolic information on the PET image would facilitate the biopsy localisation of a lesion. This is supported by many published data on the improved diagnostic yield of biopsy employing PET/CT as compared to the conventional approach (Fathinul, 2011; Caroline, 2008). Subcentimeter metastatic lesions are better visualised on the PET/CT as compared to CT given the benefit of signalling glycolytic metabolism that has improved lesion detection at large (Fig.2) (Yoon, 2011).

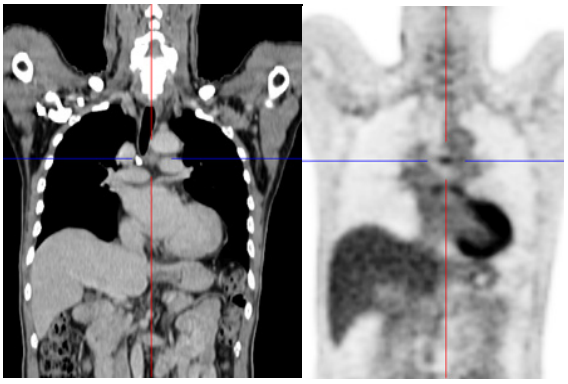

Fig.2: Example of discordant positron emission tomography (PET) and computed tomography (CT) results. CT (left) images of a mediastinal lymph node showing a subcentimeter lymph node. The corresponding PET image (right) exhibited an FDG-avid lymph node denoting the altered glucose metabolism suspicious for pathological lymph node. [Images courtesy of *Pusat Pengimejan Diagnostik Nuklear*]

The value of using PET/CT for patients undergoing restaging after treatment is equally apparent. It is now possible for this modality to distinguish between malignancy and post-therapeutic change (Van *et al.*, 2002). According to Selzner *et al*., combined PET/CT over scored standalone CT and PET in restaging tumours after years of disease-free survival, when the distorted anatomy may not be easily distinguished from the site of a tumour recurrence (Selzner *et al*., 2004). PET/CT has proven to be a very sensitive non-invasive staging technique and may even determine the exact location of a solitary lymph node particularly in evaluating the stage of non-small cell lung cancer (NSCLC), thus concluding the precise classification as N1 or N2 lymph node station based on classification by the American Joint Committee of Cancer (AJCC) (Asamura, 2000). Unsuspected extra thoracic soft tissue or skeletal metastases also may be revealed by PET/CT in cases where other imaging methods fail to demonstrate distant metastasis (Schoder, 2007).

FDG PET/CT Predicts Tumor Aggressiveness

In addition, the degree of metabolic defect via semi-quantitative analysis, SUV could predict tumour aggressiveness and overall patient survival as high SUV values correlate with poor disease prognosis (Yamada *et al*., 1992). We reported 23 patients with recurrent phaechromocytoma/paraganglioma, with regards to SUVmax evaluation on tumour aggressiveness; nine patients had local controls (34.1%) with mean progression-free survival (PFS) of 19.35±3.34 months with a significant number of patients with metastatic disease who had SUV > 9.2 as compared to the local disease group ($p<0.05$) (Fathinul *et al*., 2014). The prediction of tumour aggressiveness is important for tailoring a management plan obviating the risk of unnecessary treatment toxicity and to reduce the cost burden for patients. This is in line with many studies which demonstrated that the decrease of FDG uptake after a single infusion of chemotherapy was a predictor of eventual response to this regimen (Kostakoglu *et al*., 2002). On the other hand, no decrease of tumour FDG uptake after the first infusion was a predictor of non-response.

FDG PET/CT Alters the Management Plan

PET/CT changed the primary diagnosis in approximately 16% of cases, whereas PET/CT resulted in a change in staging and treatment plan in approximately 28% to 32% of the cases, respectively, and thus enabled the establishment of an appropriate scheme for disease response to treatment (Pottgen, 2006). Current procedures to monitor therapy using anatomical imaging modalities, such as CT, have a major setback given that functional changes often precede anatomical changes. A significant metabolic change can be established by comparing the standardised uptake values (SUV) from pre- and post-treatment scans, although such comparisons can only be made accurately on attenuation-corrected, quantitative PET images (Wahl, 1991). In our experience, we found that in a cohort of 23 patients with head and neck tumours, there were changes in the management plan in 58% of the patients being evaluated on the PET/CT as compared to CT-based staging (Fathinul, 2013a).

PET-CT in Radiation Oncology

The new approach of radiation therapy and intensity modulated radiation therapy necessitates more precise target volume definitions for dose-sparing of normal tissues. Traditionally, CT has been popular as a tool of choice for radiation therapy planning. Nevertheless, CT has been shown to have relatively low sensitivity and specificity for detecting tumour tissue (Gregoire, 2007). In a meta analysis for solid tumours, PET/CT imaging was found to have a better sensitivity of 92% and a specificity of 93% compared to 85% and 88% for PET and 64% and 83% for CT alone, respectively, and hence for the radiation treatment (Antoch, 2004). Tumour biology has been identified as an essential factor for effective dose delivery (Ling *et al*., 2000). With PET/ CT imaging the biological tumour volume allows the radiation dose to be modulated according to the distribution of the PET signal intensity within the tumour volume specifically (Ling *et al*., 2000; Schwartz *et al*., 2005). In addition, the PET-CT provides a single reproducible session for highly precise patient positioning during the imaging and

treatment sessions rendering an accurate tumour delineation and effective dose delivery over standalone PET and CT systems (Gilman, 2007). The proliferating tissue has increased FDG avidity although the radiation inflammatory effect may at times be misinterpreted as a true positive lesion (Figure 3). A recent review of PET/CT utilisation for radiotherapy planning in lung cancer showed differences in the range of 30% to 60% between PET-derived contours versus CT-only target volumes (Greco, 2007).

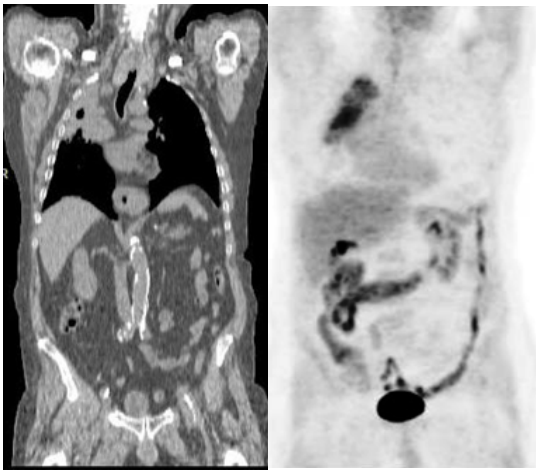

Fig.3: CT and PET coronal images; A 54-year-old man had completed radiotheraphy of the right lung for recurrent NSCLC. The images show typical dome-shape consolidative changes with increased FDG accumulation in radiation pneumonitis. (Images courtesy of Peter Mac Callum Centre)

PET/CT and the Radiation Risk

Most commonly, PET utilises ^{18}F-FDG as a radiotracer; the short half-life of 110 min reduces radiation exposure compared with other commonly used radionuclides such as ^{99m}Technetium (6 hours) or ^{201}Thallium (72 hours). It carries a low absorbed dose to the patient estimated at approximately 7 mSv. The radiation (X-rays) from our diagnostic CT protocol ranged from 8mSv to 16 mSv for a two-dedicated low tube current dose (35mAs) and the CARE Dose 4D (120kV). The 64-multislice CT technique was equipped with the dual focal spot that ensured more image yields without increase in the total radiation dose and the CARE dose 4D is capable of modulating tube current adaptation tailoring to the patient's size, for which features render an efficient effective patient dose of up to 20% as compared to the lower 16 multislice of the same kind (Zito, 2009). In general, the benefits of subjecting patients for the PET-CT outweigh the radiation risk as most information required for the staging of a tumour is available in a single session study. In a study by Hishar *et al*., the dose minimisation strategy on PET was adequate to yield a good PET-CT image without significant compromise (Hishar, 2014).

PET-CT and Economy

Despite increasing evidence supporting the accuracy of standalone imaging i.e. CT, MRI or PET, high cost and limited cost-effectiveness data have militated against funding for routine clinical use in many countries (Gambhir, 1996). There is now substantial evidence that PET/CT is an exceedingly accurate multimodality imaging in detecting malignant tissue and provides a higher specificity than conventional imaging (Michael *et al*., 2011; Ell, 2006). Precision in staging may avert futile surgery for which PET-CT has changed the management plan whilst providing additional clinical benefits to patients (Ell, 2006). Considering the median length of pre- and post-operative hospital stay, the cost of surgical resections and biopsies evaluated on PET-CT was found overall to be cost beneficial (Rohren, 2004). In Heinrich *et al*.'s trial on patients with pancreatic cancers who underwent PET-CT for disease staging, metastases were found in 16 patients with cancer initially deemed resectable, leading to different management and cost savings of USD 1,066 per patient (Heinrich *et al*., 2005). In the United States, the use of FDG PET scanning has been shown to be a cost-effective alternative to conventional imaging methods in the evaluation of non-small-cell lung cancer, and this led MEDICARE, an insurance provider, to reimburse patients for those indications (Dewan, 1995). In our initial experience in working with patients with cancers referred for staging, a remarkable change in management strategy reflected a potential reduction in the total costs incurred to be borne by the patients.

PET-CT Potential Pitfalls

As PET and CT are operated on a sequential basis, where co-registration of data obtained from both methods is deemed to some degradation artefacts. The use of contrasted CT in PET/CT; among other known artefacts the following were seen: banana lesion caused by diaphragmatic movement in the lower lung; breathing artefacts; patient motion; incidental metal device on the patient torso or FDG-RBC microembolus; leakage of FDG at the injection site or from the contaminated patient's gown after urine voiding; and pooling of intravenous contrast as source of false positive FDG-avidity were also observed as an attribute to the overestimation of the attenuation correction (Fathinul & Lau, 2009a; Fathinul & Lau, 2009b; William, 2007). Therefore, a careful instruction for PET/CT preparation and adoption of improved techniques during PET-CT i.e. gated respiration and improvement of the PET detector to facilitate image enhancement are urgently required.

CONCLUSION

A combined PET and CT scanner is a practical and effective approach in acquiring co-registered anatomical and functional images in a single scanning session. It denotes the new era in molecular imaging whereby advancement in science and technology has impacted the way physicians personalise treatment plans with more effective strategy and a cost effective package for the patient. Combined contrasted PET/CT imaging facilitates the separation of normal physiologic uptake from pathological tissue with a more favourable accuracy and, hence, helps reduce the incidence of false-positive and false-negative incidence.

ACKNOWLEDGEMENTS

This work was supported in part by the Research University Grant Scheme (RUGS), University Putra Malaysia.

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