Revolutionary impact of PET and PET-CT on the day-to-day practice of medicine and its great potential for improving future health care*

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Abstract

In this communication, we present an overview of the impact and advantages of PET and PET-CT fusion imaging in the practice of medicine. We also discuss the evolution of this promising molecular imaging technique since its inception and the future prospects of the combined structure-function approach. Superior contrast resolution, accurate quantification and above all optimal image quality aid in improved diagnosis of many serious disorders including cancer. We speculate that this powerful imaging approach will almost completely replace most other conventional methods in the future. Currently, 18\(^{\text{F}}\)-fluorodeoxyglucose (FDG) is the main radiopharmaceutical employed for PET studies around the globe. With the availability of high quality PET images on a routine basis in most centres around the world and the likelihood that several other useful PET tracers will be approved in the near future for routine clinical applications, this technique will likely become essential in almost any medical disorder.

Key words: PET, PET-CT, 18\(^{\text{F}}\)-fluorodeoxyglucose

Introduction

One of the most remarkable events in the history of medicine was the discovery of the X-ray by Roentgen in 1895. This was subsequently enhanced by the introduction of CT in 1973 by Sir Godfrey Hounsfield with significant improvement in the sensitivity and specificity of structural imaging in medicine [1–3]. The introduction of MR imaging added another major dimension to the armamentarium available to the radiologist [4–7]. However, these powerful structural imaging techniques have poor sensitivity for early disease and suffer from major limitations for the assessment of early therapeutic response, which is of pivotal importance in the practice of oncology. In most settings, if there is minimal or no response, then there is no benefit from the continued administration of toxic and expensive treatment. The shortcomings of anatomical imaging also apply to the accurate staging of many malignancies and the early detection of recurrence of cancer following therapeutic interventions. Therefore, imaging methods that allow accurate assessment of disease activity at any stage of the disease are essential for optimal management of cancer patients.

Functional imaging with radiotracers is primarily based upon one or more of the following three approaches:

- Imaging physiological processes such as blood flow to an organ or diseased tissue;
- Visualizing ongoing biochemical and metabolic activities in the normal and abnormal tissues;
- Utilizing established pharmacological methodologies for diagnostic purposes and for developing new drugs.

However, alterations in the metabolic and biochemical path-
ways may not always translate into physiological changes, such as disrupted blood flow to the diseased site, early in the course of the disease. This is a major disadvantage of conventional nuclear medicine techniques as well as dynamic contrast-enhanced CT and functional MR imaging, which rely upon measuring physiological parameters for assessing organ function or pathological states. In addition, despite their superior sensitivity over structural imaging, conventional functional imaging modalities lack the specificity and precision that are achievable with techniques based on biochemical and pharmacological principles.

On the other hand, the functional imaging developed in the past three decades allows imaging at the molecular and cellular levels and has proven to be extremely sensitive and quite specific for assessing disease activity in several important clinical disorders [8]. The target sites for these probes encompass a wide variety of cell surface receptors, transporters, intracellular enzymes, and messenger RNA. The source of the signal detected by these techniques could originate directly from the molecule or from its surrogates [9]. Functional MRI allows the assessment of regional physiological and metabolic activity and the detection of parameters such as alterations in cerebral blood flow and perfusion to an organ or diseased tissue [10–13]. However, the MR contrast agents that target specific molecular sites such as cell receptors or enzymes have proven to be relatively insensitive for detecting adequate signals from tracer concentrations of these diagnostic compounds. Recently, NMR spectroscopic studies have shown that choline phospholipid metabolism is altered in cancer, especially in prostate and brain tumours, as well as in breast cancer [14]. This modality has been shown to be useful for characterizing many central nervous system disorders, such as multiple sclerosis, Parkinson’s disease, and Alzheimer’s disease [15, 16]. The use of optical imaging as a molecular probe has been of considerable interest, but a major deficiency of this approach is the inability to visualize structures deeper than a few centimetres from the surface [17]. Presently, optical imaging is being investigated for visualizing breast cancer [18, 19], for monitoring stroke [20, 21], the imaging of lymph nodes [22], and in detecting disease processes near the endothelial surface in the airways and gastrointestinal tract [23].

Positron emission tomography (PET) with FDG and other tracers has overcome many of the shortcomings associated with the competing modalities. Several newer positron-emitting radionuclides such as technetium-94 (94mTc), 68-Gallium (68Ga), and copper-64 (64Cu), labelled to the appropriate compounds, are expected to be useful for diagnostic purposes and may further expand the domain of PET for functional studies [24]. This paper reviews the current and future potential applications of this technology in the practice of medicine.

The fluorodeoxyglucose (FDG) technique was introduced in 1976 by investigators at the University of Pennsylvania, and the effectiveness of this modality as a molecular probe has been effectively demonstrated in the investigation of a multitude of serious disorders [25]. This agent was initially proposed as a novel tracer to determine regional brain function in normal physiological states and in neuropsychiatric disorders [26]. The critical role of PET imaging with FDG and with certain other tracers in the management of many diseases has now been well established. In addition, exciting areas of research currently include imaging of gene expression [27, 28] and molecular targeting techniques that are being adopted for the development of new drugs [29, 30].

FDG-PET has been applied successfully to a number of neurological disorders. The kinetics of hexokinase are altered in patients with seizures [31], which affects FDG activity in the seizure foci, forming the basis for using FDG-PET in localizing the seizure focus. FDG-PET imaging is effective in localizing seizure foci in the temporal lobe for surgical interventions [32], and has a sensitivity of 85% to 90% [32]. The seizure focus appears hypometabolic in the interictal state when anatomic images appear normal [33–35]. However, in longstanding seizure disorders, a certain degree of atrophy may eventually be detectable by MR imaging [36–38]. In Alzheimer’s disease, FDG-PET imaging appears critical for identifying patients in whom the disease process is subtle, and before structural alterations have occurred; thus, modern treatments may be more successful [32, 39–52] (Figure 1). Several drugs designed to augment acetylcholine levels in the brain, a substrate whose deficiency has been implicated in the cognitive dysfunctions of this disorder, are more effective in the early stages of Alzheimer’s disease. Extrapyramidal disorders including Parkinson’s disease can

Figure 1AB. Brain PET with FDG. Example of a scan of patient with Alzheimer’s disease (A) and in a normal subject (B): evidence of reduced metabolism at bilateral parietal and temporal regions in the former. Reprinted with permission from Leadership Medica for Alavi et al.
be accurately diagnosed with radiopharmaceuticals such as fluorine-18-6-fluoro-L-dopa (F-DOPA) or radiopharmaceuticals that bind to the dopamine transporter sites and therefore allow the detection of the degree of loss of presynaptic dopaminergic neurons [53–55]. Promising results have been obtained in the assessment of regional and global dysfunction in head injuries [56, 57], frontal lobe dementia [49, 58], and Huntington’s disease [59–61] using FDG-PET.

FDG-PET imaging is extremely useful in the management of a wide array of malignancies [62–87], where it has become essential in disease staging, monitoring response to treatment, planning and choosing appropriate therapies, detecting recurrence, and predicting prognosis (Figures 2–10). FDG-PET/CT is now of central importance in the staging of several malignancies including lung, head and neck, breast, cervical, oesophageal and colorectal cancers, melanoma, and lymphoma because of its sensitivity in detecting nodal and distant metastatic disease and due to its high specificity compared to structural imaging alone [62–87]. PET-CT is now regarded by many as the “one-stop-shop” for many malignancies where the coregistered structural and metabolic images allow for accurate localization and characterization of sites of disease.

FDG-PET imaging appears to be essential for the detection of the sites of infection and inflammation [90, 91]. Orthopaedic infections, particularly those related to implanted prostheses [92–94] and osteomyelitis [95–97], can be detected by FDG-PET imaging, and based on recent studies it may become the study of choice for many malignancies where the coregistered structural and metabolic images allow for accurate localization and characterization of sites of disease.

The use of FDG-PET imaging is considered the standard approach for determining myocardial viability. 82Rb shows great promise in detecting changes in myocardial perfusion [113]. FDG is taken up in atherosclerotic vessels [114]. There is evidence that the uptake is mainly located in the intima and probably represents high metabolic activity in macrophages, which are abundant in atherosclerotic plaques [114] as well as thromboses and clots. Integrated PET/CT has great potential as it provides an opportunity to delineate the anatomical extent (CT coronary angiography) and physiological as well as metabolic severity of coronary artery disease (ischaemic burden) in a single setting.

PET imaging with [18F]fluoride may soon replace conventional bone imaging with 99mTc-labelled methylene diphosphonate (or similar compounds), which utilize non-tomographic scanning techniques. Tomographic images with PET have substantially higher resolution and therefore provide superior sensitivity and specificity than conventional planar and even SPECT techniques. The accelerated utilization of thymidine in malignant cells because of enhanced DNA synthesis can be detected by either 11C- [117, 118] or 18F-labelled [119–121] thymidine radiotracers as evidence for cellular proliferation. So far, the most promising agent appears to be 30-deoxy-30-[18F]fluorothymidine (FLT) [122–124], which may be of value in determining early response to therapy, because cytotoxic chemotherapeutic agents affect cell division earlier and to a greater extent than glucose metabolism. FLT may be favourable for imaging brain metastases because of its low physiological uptake in grey matter [123].

Numerous reports have described the usefulness of multiple promising compounds in animal and human studies for detecting hypoxia in certain malignancies. For instance, [18F]fluoromisonidazole (FMISO) [126, 127], [60Cu]diacetyl-bis(N(4)-methylthiosemicarbazone) (60Cu-ATSM) [128], 2-(2-nitrimidazo-1[H]-yl)-N-(3-[18F]fluoropropyl)acetamide ([18F]EF1) [129],
**Figure 3.** FDG-PET in a case of carcinoma ovary, post surgery and post chemotherapy, which had a significant recent rise of serum tumour marker (CA-125). CT abdomen demonstrated solitary hepatic lesion. FDG-PET demonstrated extensive omental involvement, multiple metastatic nodes in the mediastinum and left supraclavicular nodes accounting for the rise of CA-125. Reprinted with permission from Leadership Medica for Alavi et al.

**Figure 5.** Whole body FDG-PET in a diagnosed patient of primitive neuro-ectodermal tumour of the right proximal femur at diagnosis. Note the widespread irregular FDG uptake in the skeleton, suggesting bone marrow involvement in addition to the avid FDG uptake in the primary. Bone scan shows disease only when there is cortical involvement and is negative when there is only marrow involvement. Reprinted with permission from Leadership Medica for Alavi et al.

**Figure 4.** Whole body 18F FDG PET carried out for rising CEA levels in a patient with colorectal carcinoma. The 3D image shows extensive metastases in the chest, spine, pelvis and an inguinal node. Post treatment rise of serum tumour marker level in ovarian and colorectal carcinoma has been one of the major indications for whole body PET/CT study in these malignancies. Reprinted with permission from Leadership Medica for Alavi et al.

and [2-(2-nitro-1[H]-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl)-acetamide] ([18F]EF5) [130]. In assessing hypoxia, FMISO, an analogue of 2-nitroimidazole, seems to be a poor choice because its uptake is low in hypoxic cells and because it clears slowly from the normal tissues [127]. 60Cu-ATSM is proposed to overcome these difficulties and may prove to be effective for this purpose [128]. However, EF-5 may be superior to these tracers and become the standard choice in the future. Labelling annexin V with 18F may permit imaging apoptosis by PET and substantially improve the quality of scans obtained by 99mTc-labelled annexin V. Quantitative imaging of angiogenesis using peptides containing RGD sequence with affinity to vβ3 radiolabelled with 18F [131–135] has the potential to become an important tool in assessing cancer in its various stages. We expect that future agents for pretreatment targeting will be synthesized using positron-emitting radionuclides such as 18F (as a surrogate for 11C) and 86Y (as a surrogate for 90Y) for optimal visualization of the targeting sites in B-cell non-Hodgkin’s lymphomas [136, 137]. Similarly, peptides such as octreotide labelled with positron-emitting radionuclides, e.g. 64Cu-labeled octreotide [138] and gallium-68 (68Ga)-labelled octreotide analogues [139, 140], will be routinely employed for imaging neuroendocrine tumours, which yield substantially superior image quality compared with either planar or SPECT images with indium-111 (111In)-labelled compounds [138, 140, 141] (Figure 11). Studies suggest that 11C-labeled acetate or 15C- or 18F-labelled amino acids such as choline are useful and will be valuable in examining patients with prostate cancer [144–148] (Figure 12). Labelled hormones such as 18F-labelled
Figure 6. FDG-PET in a case of sacral chordoma, post surgery and radiotherapy. CT and MRI were inconclusive on the nature of the soft tissue at the primary site. Patient had low backache. FDG-PET demonstrates avid uptake in the mass suggesting active tumour tissue at that site. Reprinted with permission from Leadership Medica for Alavi et al.

Figure 7. A 39-year-old male, diagnosed with a case of inoperable rectal GIST, was referred for disease evaluation. CT scan of the abdomen had shown a 6 × 7 × 8 cm homogeneous mass involving the right lateral aspect of the rectum with luminal compromise and infiltration of the ipsilateral seminal vesicle and the prostate. Biopsy proved this to be a malignant GIST of the rectum with a mitotic count of 10/50 HPF and no evidence of necrosis. Pre treatment whole body FDG PET shows a fair sized focus of avid FDG uptake in the rectal primary. Note the avidity and pattern of FDG uptake corresponding to the high mitotic count observed in histopathology without any evidence of necrosis. Reprinted with permission from Elsevier Inc. for Basu et al. [156].

Figure 8. Post 1-month Imatinib treatment FDG PET shows a near total resolution of the uptake except a tiny focus of viable disease in the primary region. Reprinted with permission from Elsevier Inc. for Basu et al. [156].
oestrogen analogues have been used for assessing breast cancer response to tamoxifen therapy [149, 150]. Similar findings have been observed regarding the efficacy of imaging with $^{18}$F-labelled male hormone for the assessment of hormone therapy in prostate cancer [151]. In the area of oncology and neurop-harmacology, PET studies have great promise in aiding novel drug development. FLT-PET to monitor the preclinical testing of histone deacetylase inhibitors (HDACI) and FDG-PET as the surrogate marker for early response evaluation with Imatinib mesylate are two examples of this promising application. By targeting SSTR using octreotide and analogues labelled with a positron-emitting radionuclide, several PET imaging agents have been developed for neuroendocrine tumours and are being tested in several centres across the world for diagnostic and therapeutic purposes. The development of $^{68}$Ga-DOTA labelled somatostatin analogues has been the key to this success (Figure 13). Parallel to this, F-DOPA PET has emerged as a new diagnostic tool for the imaging of various neuroendocrine tumours and has demonstrated its utility in carcinoid tumours and in differentiating between focal and diffuse disease in hyperinsulinism of the newborn that has significantly changed the management in these disorders (Figure 14, 15).

Currently, FDG stands out as the most effective positron imaging radiopharmaceutical, accounting for more than 95% of PET imaging procedures performed around the world, and is utilized for the assessment of central nervous system disorders, malignant diseases, and myocardial viability, as well as the detection of infection and inflammation (Figure 16). In addition, there is potential for FDG-PET in the assessment of thrombosis and atherosclerosis, muscle spasm, and motility disorders and in examining voluntary and smooth muscle-related disorders. The expanding list of indications for FDG-PET demonstrates that it is a nonspecific

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**Figure 9AB.** Whole body FDG-PET. A — baseline MIP (upper panel) and limited post-furosemide MIP (lower panel). B — coronal images showing a curvilinear area of intense FDG uptake at the skull base posteriorly on the right side (SB). In addition, FDG-PET revealed symptomatically silent abnormal disease foci (arrows) in the right adrenal gland (AD) (which were clearer in the repeat post furosemide abdominal scan done on the same day), subcutaneous nodule on the right arm (SQ), mediastinum (M), and the right iliac bone (IB). The subcutaneous nodule was hitherto unknown and was serendipitously discovered by FDG-PET, and on biopsy turned out to be a metastatic deposit. Reprinted with permission from Elsevier Inc. for Basu et al. [156].
Several groups have attempted to improve the specificity of this tracer by imaging the sites of abnormality at dual time points following its administration [76, 152, 153]. In addition, combined PET/CT scanners that operate as a single unit are currently replacing the conventional dedicated PET scanners in most centres and provide more specificity to the diagnosis.

The unprecedented impact of FDG-PET imaging on the daily practice of medicine has substantially improved healthcare throughout the world. FDG-PET methodology has clearly demonstrated the extraordinary power of PET in medicine. This has led to the development of many novel radiotracers that have been designed to explore new diagnostic and therapeutic domains. We therefore expect that molecular imaging with PET will play an increasingly central role in research and in the optimal management of patients with many disorders [154, 155]. This will include diagnosing pathological processes at the molecular level and individualizing treatment for these patients.
Figure 13. 36-year-old male presented with multiple lesions on ultrasonography of the abdomen suggesting multiple liver metastases. $^{68}$Ga-DOTA-TOC scan demonstrated primary in duodenum with multiple liver metastases. FDG-PET was normal in this patient. Biopsy was suggestive of neuroendocrine tumour of GIT. Reprinted with permission from Elsevier Inc for Basu et al. [156].

Figure 14. A FDOPA image of the abdomen of a child with hyperinsulinism shows intense focal uptake in the head of the pancreas while the rest of the gland is not visualized. This is a typical pattern for focal disease in a child in whom it is curable by surgery. Reprinted with permission from Elsevier Inc for Basu et al. [157].

Figure 15. The image shown above reveals generalized uptake in the entire gland and is consistent with diffuse hyperinsulinism. This pattern usually requires near total resection of the gland for palliative purposes. Reprinted with permission from Elsevier Inc for Basu et al. [157].
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References


Figure 16. This figure shows significant uptake in the distal ileum, which extends to the cecal region which is mildly active (long arrow). This image clearly demonstrates the high sensitivity of this technique in detecting regional inflammation. Interestingly, there is a serendipitous finding in the right lower lung field, which represents bronchopneumonia (short arrow). This inflammatory process became symptomatic the day after the PET/CT study was acquired Reprinted with permission from Elsevier Inc for Basu et al. [157].


61. Kuwert T, Lange HW, Langen KJ, Herzog H, Aulich A, Feinendegen LE. Cerebral glucose consumption measured by PET in patients with...


121. Wagner M, Zeltz U, Buck A et al. [18F]fluoro-30-deoxy-30-fluorothymino-


141. Ogawa T, Shishido F, Kanno I et al. Cerebral glioma: evaluation with
methionine PET [comment]. Radiology 1993; 186: 45–53.


