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Editorial

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[F]-fluorode--oxyglucose (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[F]-fluorodeoxyglucose

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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 (^{94m}Tc), 68-Gallium (^{68}Ga), and copper-64 (^{64}Cu), 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

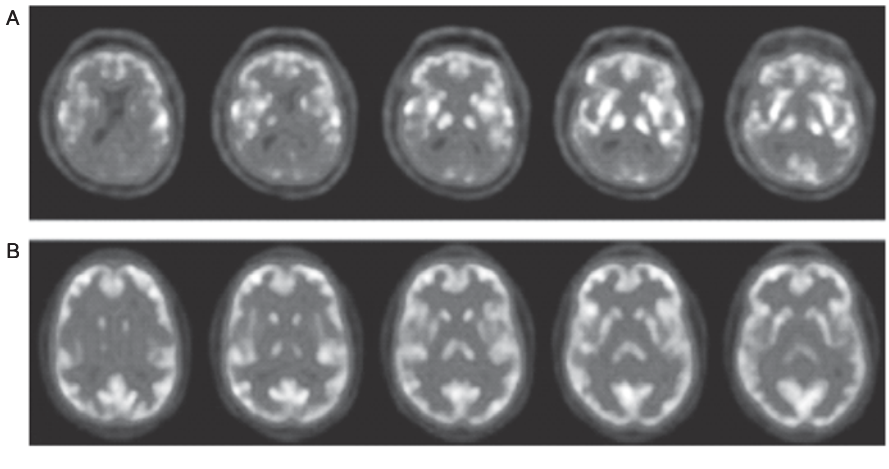

Figure 1AB. Brain PET with FDG. Example of a scan of patient with Alzheimer's disease (**A**) and in a normal subject (**B**): evidence of reduced metabolism at bilateral parietal and temporal regions in the former. Reprinted with permission from Leadership Medica for Alavi et al.

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 in such complicated and difficult clinical settings. FDG-PET is also being used to detect infection in soft tissues [98–101] and to identify sources of fevers of unknown origin [102–105]. Studies have reported success in detecting inflammatory processes in disorders such as regional ileitis [106], sarcoidosis [107–110], rheumatologic disease [111], and vasculitis [112].

The use of FDG-PET imaging is considered the standard approach for determining myocardial viability. ^{82}Rb 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 [^{18}F]fluoride may soon replace conventional bone imaging with ^{99m}Tc-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 ^{11}C- [117, 118] or ^{18}F-labelled [119–121] thymidine radiotracers as evidence for cellular proliferation. So far, the most promising agent appears to be 30-deoxy-30-[^{18}F]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, [^{18}F]fluoromisonida-zole (FMISO) [126, 127], [^{60}Cu]diacetyl-bis(N(4)-methylthiosemicarbazone) (^{60}Cu-ATSM) [128], 2-(2-nitroimidazol-1[H]-yl)-N-(3-[^{18}F]fluoropropyl)acetamide ([^{18}F]EF1) [129],

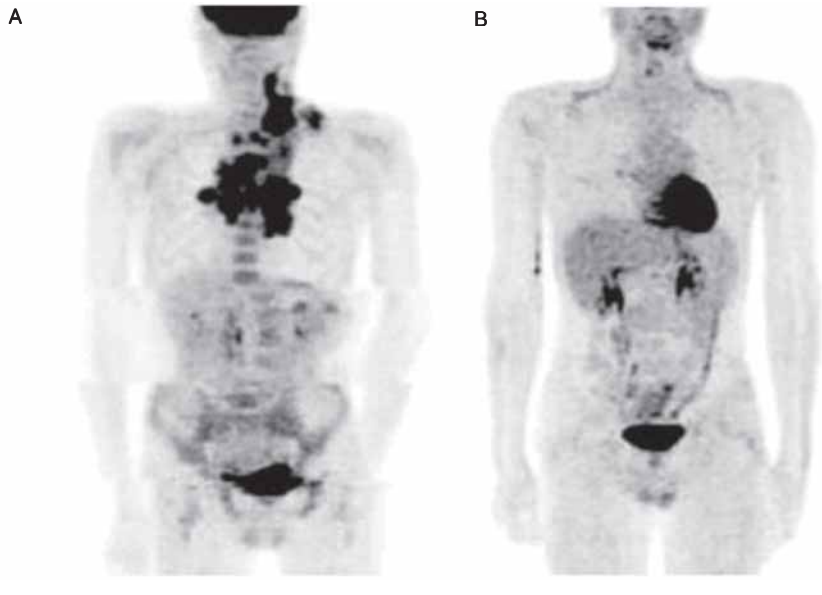

Figure 2AB. A patient of Hodgkin's lymphoma with bulky mediastinal disease (**A**); FDG-PET acquired after 3 cycles of chemotherapy, which demonstrated a complete response (**B**). A major role of FDG-PET is monitoring treatment response early in the course of therapy. Functional response with FDG-PET is usually observed ahead of anatomical response, and this has important implications for tailoring treatment regimen and further patient management. Reprinted with permission from Leadership Medica for Alavi et al.

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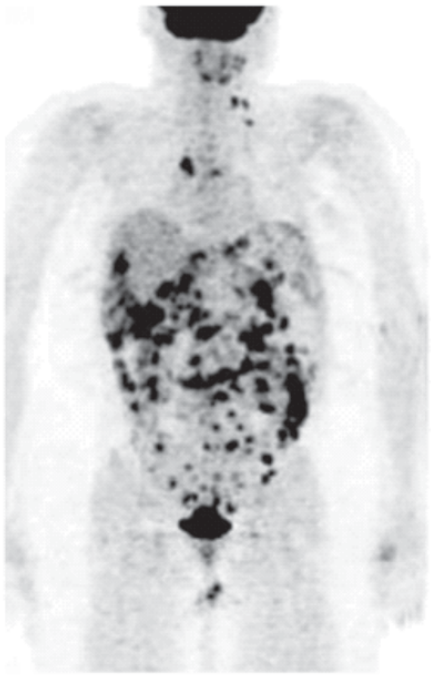

Figure 3. FDG-PET in a case of carcinoma ovary, post surgery and post chemotherapy, which had a significant recent rise of serum tumour marker (CA-125). CT abdomen demonstrated solitary hepatic lesion. FDG-PET demonstrated extensive omental involvement, multiple metastatic nodes in the mediastinum and left supraclavicular nodes accounting for the rise of CA-125. Reprinted with permission from Leadership Medica for Alavi et al.

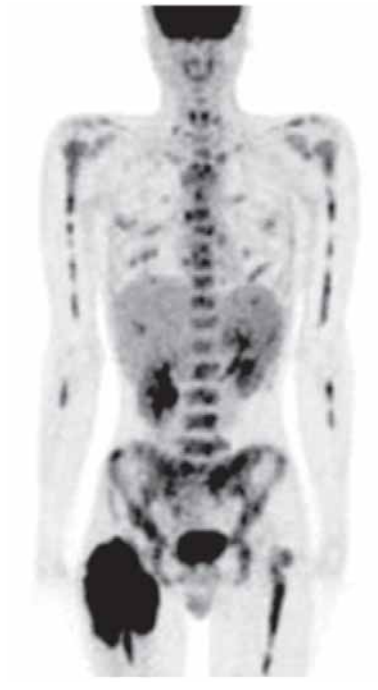

Figure 5. Whole body FDG-PET in a diagnosed patient of primitive neuroectodermal tumour of the right proximal femur at diagnosis. Note the widespread irregular FDG uptake in the skeleton, suggesting bone marrow involvement in addition to the avid FDG uptake in the primary. Bone scan shows disease only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

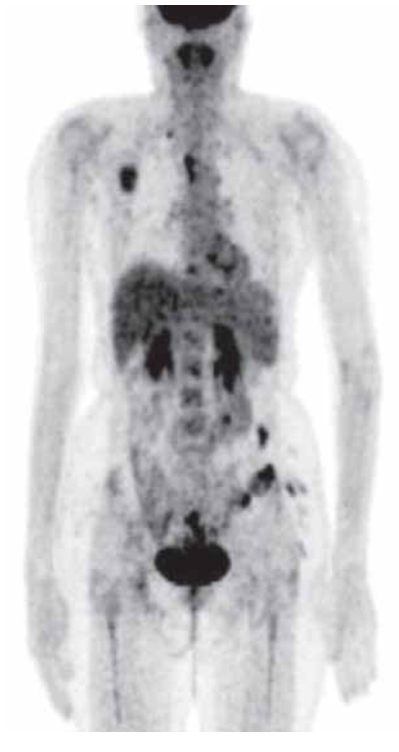

Figure 4. Whole body ^{18}F FDG PET carried out for rising CEA levels in a patient with colorectal carcinoma. The 3D image shows extensive metastases in the chest, spine, pelvis and an inguinal node. Post treatment rise of serum tumour marker level in ovarian and colorectal carcinoma has been one of 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] ([^{18}F]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]. ^{60}Cu-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 ^{18}F may permit imaging apoptosis by PET and substantially improve the quality of scans obtained by ^{99m}Tc-labelled annexin V. Quantitative imaging of angiogenesis using peptides containing RGD sequence with affinity to $\alpha V\beta 3$ 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 ^{124}I (as a surrogate for ^{131}I) and ^{86}Y (as a surrogate for ^{90}Y) 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. ^{64}Cu-labeled octreotide [138] and gallium-68 (^{68}Ga)-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 (^{111}In)-labelled compounds [138, 140, 141] (Figure 11). Studies suggest that ^{11}C-labeled acetate or ^{11}C- or ^{18}F-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 ^{18}F-labelled

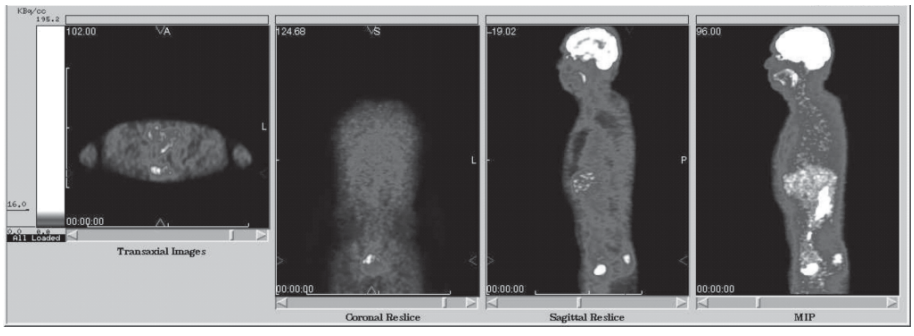

Figure 6. FDG-PET in a case of sacral chordoma, post surgery and radiotherapy. CT and MRI were inconclusive on the nature of the soft tissue at the primary site. Patient had low backache. FDG-PET demonstrates avid uptake in the mass suggesting active tumour tissue at that site. Reprinted with permission from Leadership Medica for Alavi et al.

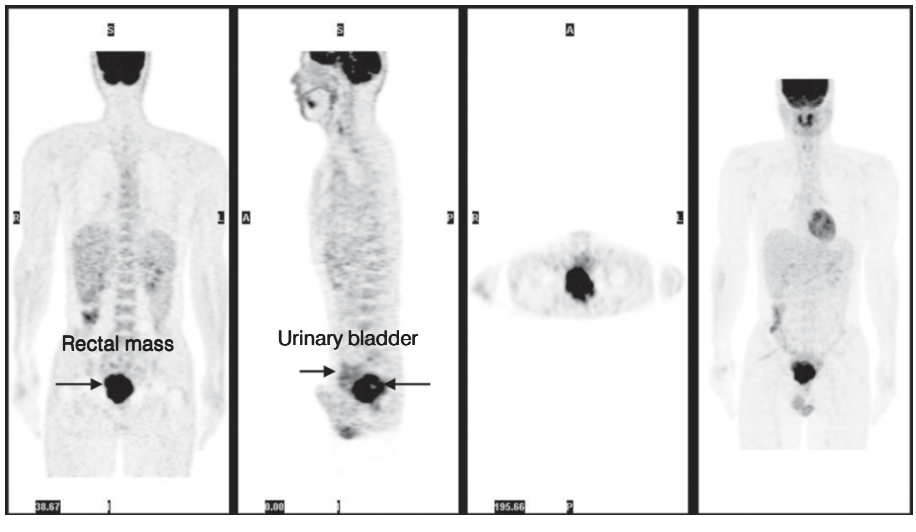

Figure 7. A 39-year-old male, diagnosed with a case of inoperable rectal GIST, was referred for disease evaluation. CT scan of the abdomen had shown a 6 × 7 × 8 cm homogeneous mass involving the right lateral aspect of the rectum with luminal compromise and infiltration of the ipsilateral seminal vesicle 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].

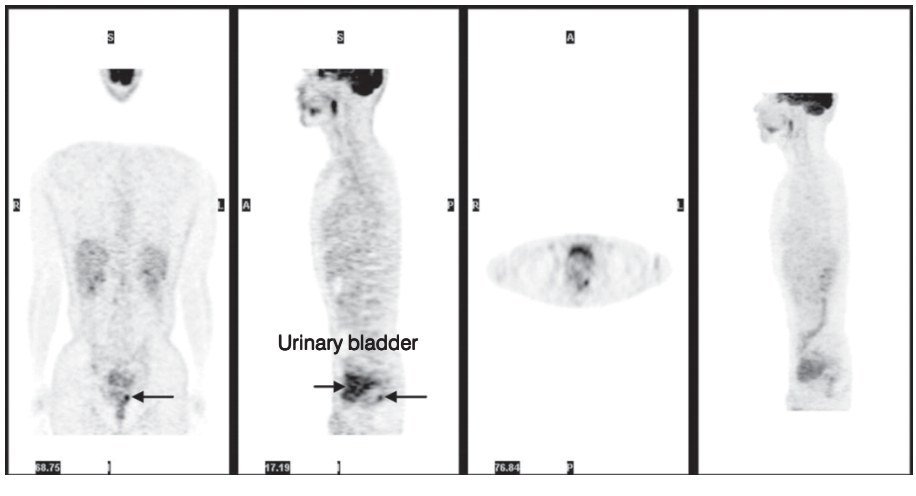

Figure 8. Post 1-month Imatinib treatment FDG PET shows a near total resolution of the uptake except a tiny focus of viable disease in the primary region. Reprinted with permission from Elsevier Inc. for Basu et al. [156].

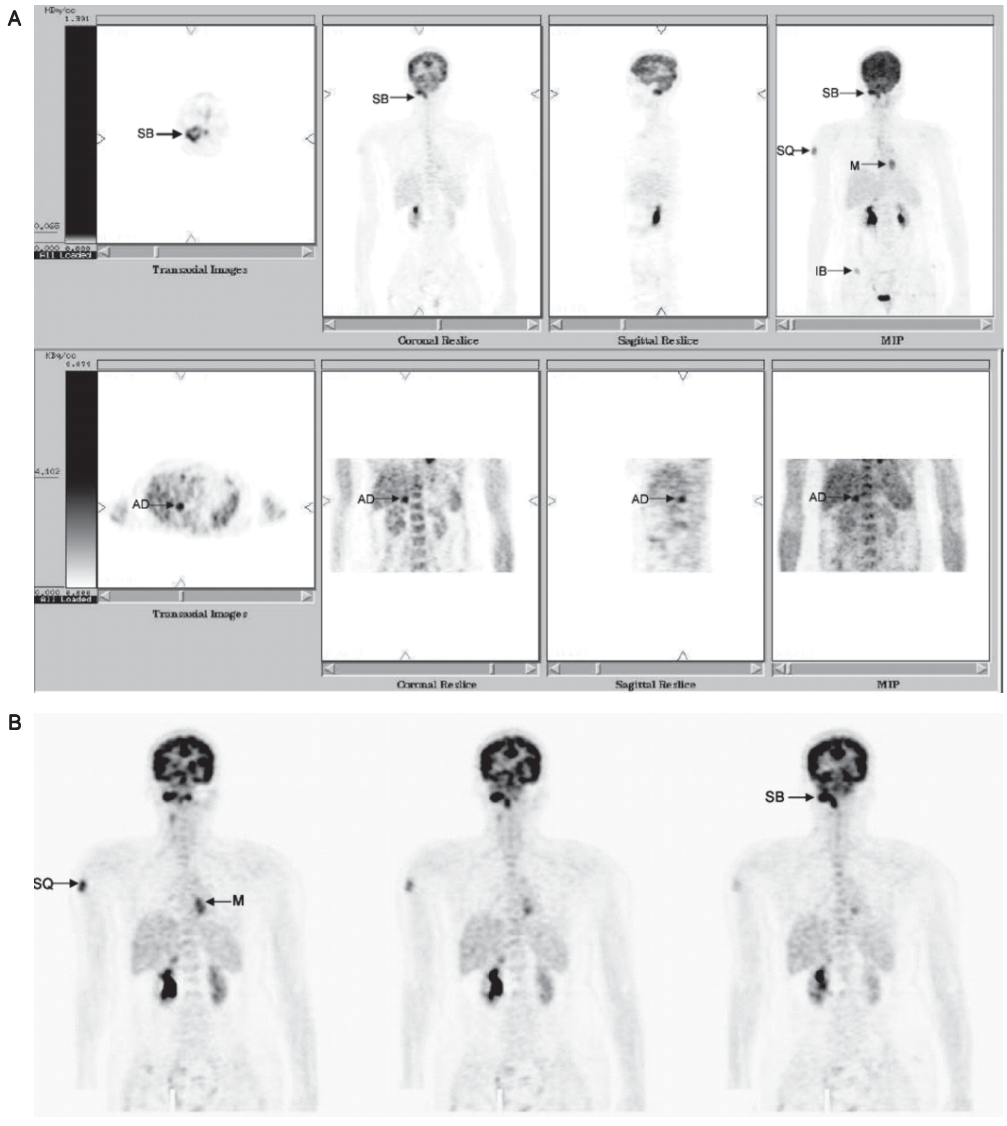

Figure 9AB. Whole body FDG-PET. **A** — baseline MIP (upper panel) and limited post-furosemide MIP (lower panel), **B** — coronal images showing a curvilinear area of intense FDG uptake at the skull base posteriorly on the right side (SB). In addition, FDG-PET revealed symptomatically silent abnormal 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].

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 neuropharmacology, 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

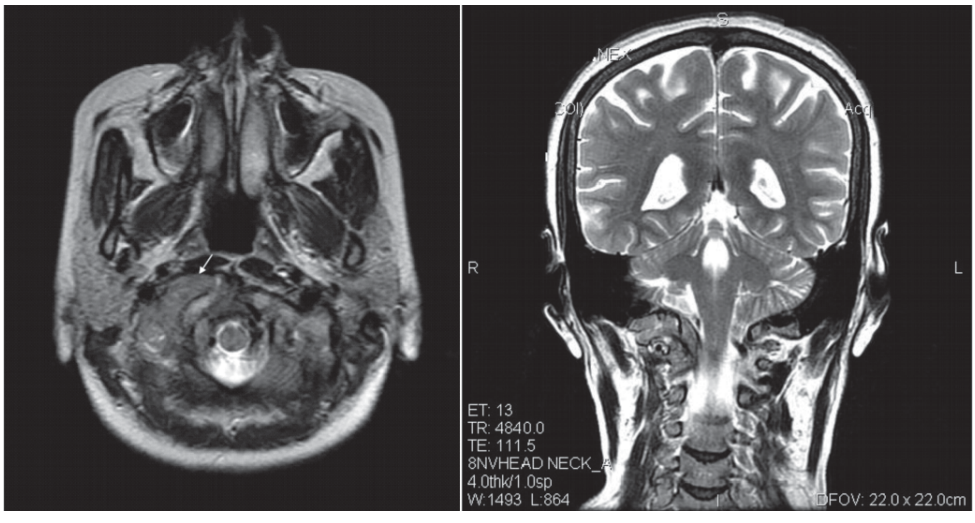

Figure 10. MRI of the brain (transaxial and coronal views) demonstrating 2 × 2 × 2 cm space occupying lesion with altered marrow signal intensity involving base of the skull on the right side, lying at the anterolateral aspect of foramen magnum involving right hypoglossal canal and adjacent jugular bulb. The lesion appeared hypointense on T1-weighted images, mildly hyperintense on T2-weighted images, and showed post contrast enhancement. Figure adapted and reproduced with permission from Elsevier Inc. for Basu S et al., Lancet Oncol 2006; 7: 610.

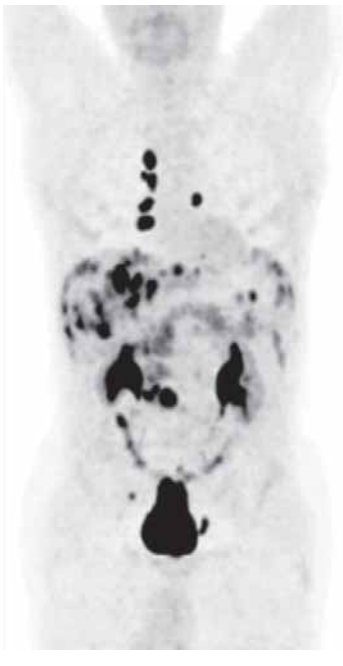

Figure 11. Evidence of ^{18}F FDOPA PET in neuroendocrine tumour. Evidence of abnormal uptake in several liver lesions, abdominal and thoracic lymph nodes, and in the peritoneal foci. Reprinted with permission from Leadership Medica for Alavi et al.

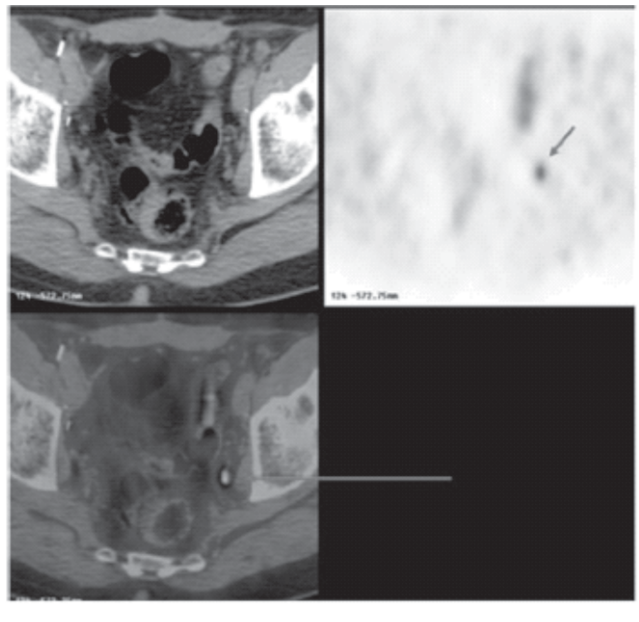

Figure 12. ^{11}C-choline PET in a patient previously treated with prostatectomy and radiation therapy, with recent increase of PSA (Jan 2006: 1.1 ng/ml and March 2006: 1.6 ng/ml). Bone scintigraphy negative. ^{11}C-choline PET shows recurrence in pelvic lymph nodes. Reprinted with permission from Leadership Medica for Alavi et al.

tracer. 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.

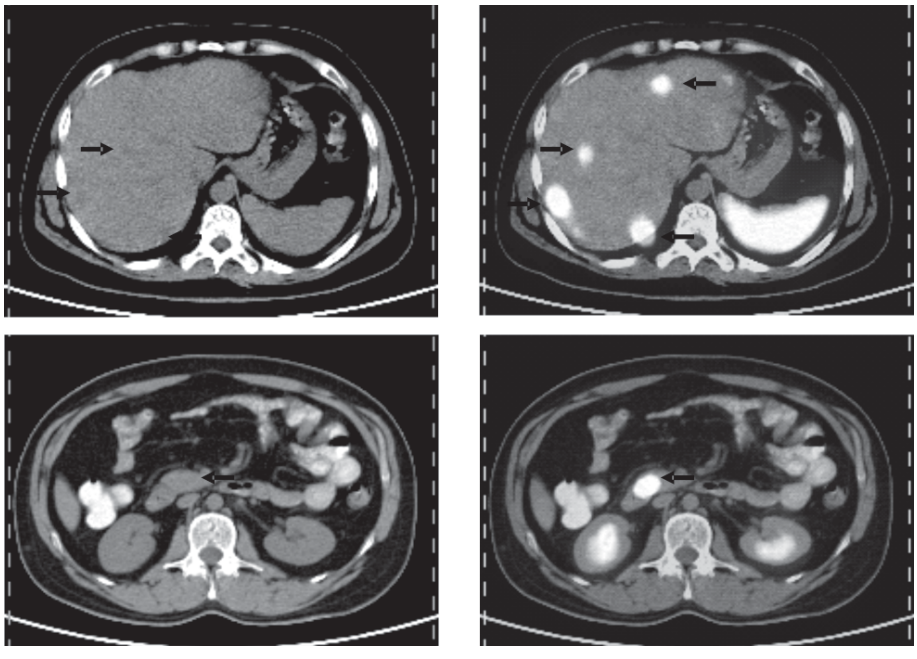

Figure 13. 36-year-old male presented with multiple lesion on ultrasonography of the abdomen suggesting multiple liver metastases. ^{68}Ga-DOTA-TOC scan demonstrated primary in duodenum with multiple liver metastases. FDG-PET was normal in this patient. Biopsy was suggestive of neuroendocrine tumour of GIT. Reprinted with permission from Elsevier Inc for Basu et al. [156].

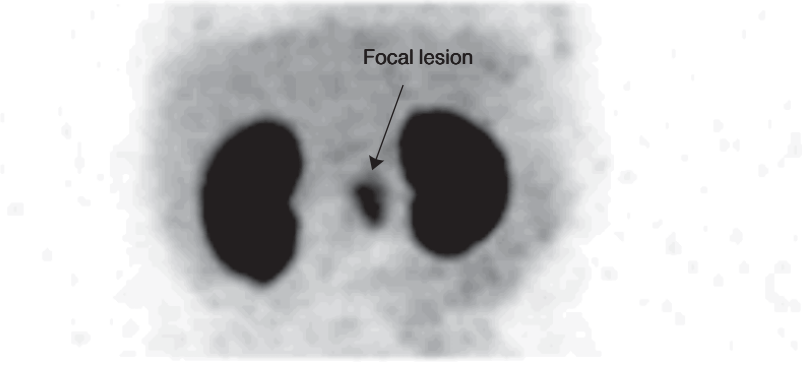

Figure 14. A FDOPA image of the abdomen of a child with hyperinsulinism shows intense focal uptake in the head of the pancreas while the rest of the gland is not visualized. This is a typical pattern for focal disease in a child in whom it is curable by surgery. Reprinted with permission from Elsevier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

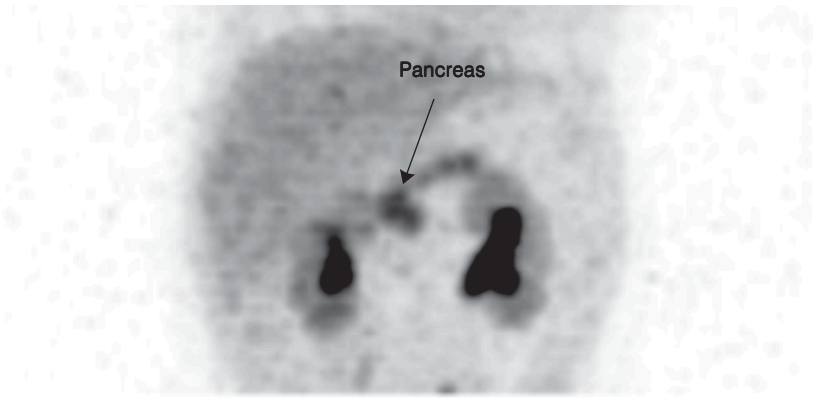

Figure 15. The image shown above reveals generalized uptake in the entire gland and is consistent with diffuse hyperinsulinism. This pattern usually requires near total resection of the gland for palliative purposes. Reprinted with permission from Elsevier Inc for Basu et al. [157].

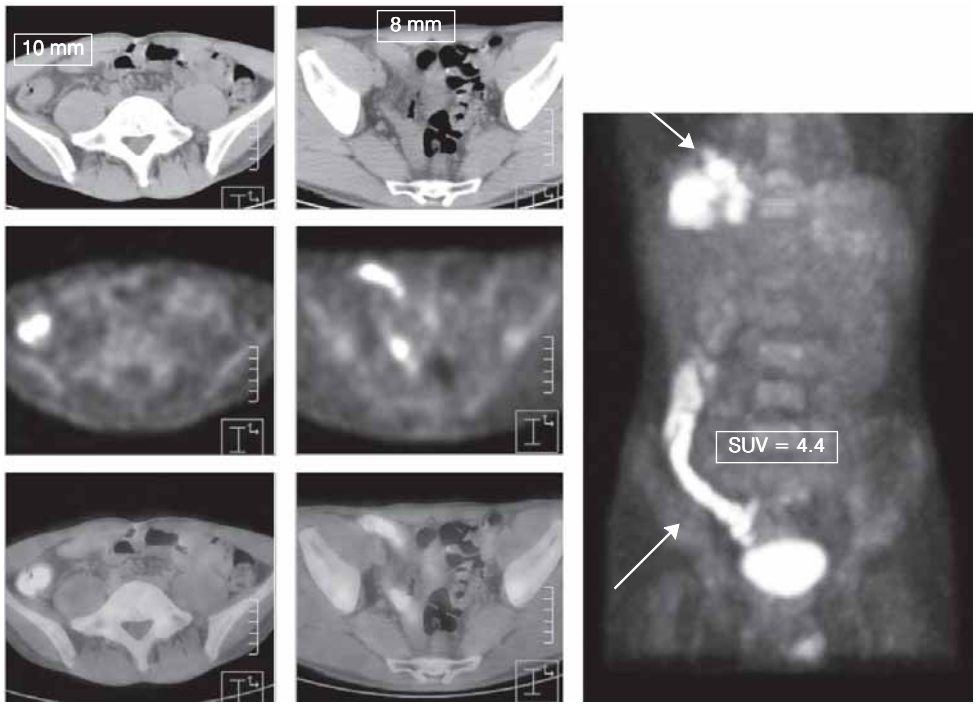

Figure 16. This figure shows significant uptake in the distal ileum, which extends to the cecal region which is mildly active (long arrow). This image clearly demonstrates the high sensitivity of this technique in detecting regional inflammation. Interestingly, there is a serendipitous finding in the 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].

*Adapted in part from *PET: a revolution in medical imaging*. Radiol Clin North Am 2004; 42: 983–1001 and Unparalleled Contribution of ^{18}F-FDG PET to Medicine Over 3 Decades. J Nucl Med 2008; 49: 17N–37N.

References

1. Schaner EG, Chang AE, Doppman JL, Conkle DM, Flye MW, Rosenberg SA. Comparison of computed and conventional whole lung tomography in detecting pulmonary nodules: a prospective radiologic-pathologic study. AJR Am J Roentgenol 1978; 131: 51–54.
2. Vanel D, Henry-Amar M, Lumbroso J et al. Pulmonary evaluation of patients with osteosarcoma: roles of standard radiography, tomography, CT, scintigraphy, and tomoscintigraphy. AJR Am J Roentgenol 1984; 143: 519–523.
3. Muhm JR, Brown LR, Crowe JK, Sheedy II PF, Hattery RR, Stephens DH. Comparison of whole lung tomography and computed tomography for detecting pulmonary nodules. AJR Am J Roentgenol 1978; 131: 981–984.
4. Crim JR, Cracchiolo A, Bassett LW, Seeger LL, Soma CA, Chatelaine A. Magnetic resonance imaging of the hindfoot. Foot Ankle 1989; 10: 1–7.
5. Hilpert PL, Friedman AC, Radecki PD et al. MRI of hemorrhagic renal cysts in polycystic kidney disease. AJR Am J Roentgenol 1986; 146: 1167–1172.
6. Semelka RC, Shoenut JP, Ascher SM et al. Solitary hepatic metastasis: comparison of dynamic contrast-enhanced CT and MR imaging with fat-suppressed T2-weighted, breath-hold T1-weighted FLASH, and dynamic gadolinium-enhanced FLASH sequences. J Magn Reson Imaging 1994; 4: 319–323.
7. Stark DD, Wittenberg J, Butch RJ, Ferrucci Jr JT. Hepatic metastases: randomized, controlled comparison of detection with MR imaging and CT. Radiology 1987; 165: 399–406.
8. Czernin J, Phelps ME. Positron emission tomography scanning: current and future applications. Annu Rev Med 2002; 53: 89–112.
9. Blasberg RG, Gelovani J. Molecular-genetic imaging: a nuclear medicine-based perspective. Mol Imaging 2002; 1: 280–300.
10. Johnson GA, Cofer GP, Fubara B, Gewalt SL, Hedlund LW, Maronpot RR. Magnetic resonance histology for morphologic phenotyping. J Magn Reson Imaging 2002; 16: 423–429.
11. Calautti C, Baron JC. Functional neuroimaging studies of motor recovery after stroke in adults: a review. Stroke 2003; 34: 1553–1566.
12. Hennig J, Speck O, Koch MA, Weiller C. Functional magnetic resonance imaging: a review of methodological aspects and clinical applications. J Magn Reson Imaging 2003; 18: 1–15.
13. Cohen M, Bookheimer S. Localization of brain function using magnetic resonance imaging. Tech Neurosci 1994; 17: 268–277.
14. Coakley FV, Qayyum A, Kurhanewicz J. Magnetic resonance imaging and spectroscopic imaging of prostate cancer. J Urol 2003; 170: S69––S75 [discussion, S75-S76].
15. Rovaris M, Rocca MA, Filippi M. Magnetic resonance-based techniques for the study and management of multiple sclerosis. Br Med Bull 2003; 65: 133–144.
16. Kantarci K, Jack Jr CR. Neuroimaging in Alzheimer disease: an evidence-based review. Neuroimaging Clin N Am 2003; 13: 197–209.
17. Bremer C, Ntziachristos V, Weissleder R. Optical based molecular imaging: contrast agents and potential medical applications. Eur Radiol 2003; 13: 231–43.
18. Ntziachristos V, Yodh AG, Schnall M, Chance B. Concurrent MRI and diffuse optical tomography of breast after indocyanine green enhancement. Proc Natl Acad Sci USA 2000; 97: 2767–2772.
19. Bremer C, Tung CH, Bogdanov Jr A, Weissleder R. Imaging of differential protease expression in breast cancers for detection of aggressive tumor phenotypes. Radiology 2002; 222: 814–818.

20. Kirkpatrick PJ, Lam J, Al-Rawi P, Smielewski P, Czosnyka M. Defining thresholds for critical ischemia by using near-infrared spectroscopy in the adult brain. J Neurosurg 1998; 89: 389–394.
21. Miyai I, Yagura H, Hatakenaka M, Oda I, Konishi I, Kubota K. Longitudinal optical imaging study for locomotor recovery after stroke. Stroke 2003; 34: 2866–2870.
22. Wunderbaldinger P, Turetschek K, Bremer C. Near-infrared fluorescence imaging of lymph nodes using a new enzyme sensing activatable macromolecular optical probe. Eur Radiol 2003; 13: 2206–2211.
23. Marten K, Bremer C, Khazaie K et al. Detection of dysplastic intestinal adenomas using enzyme-sensing molecular beacons in mice. Gastroenterology 2002; 122: 406–414.
24. Dearling JL, Lewis JS, Mullen GE, Rae MT, Zweit J, Blower PJ. Design of hypoxia-targeting radiopharmaceuticals: selective uptake of copper-64 complexes in hypoxic cells in vitro. Eur J Nucl Med 1998; 25: 788–792.
25. Alavi A, Reivich M. The conception of FDG-PET imaging. Semin Nucl Med 2003; 32: 58–81.
26. Alavi A, Hirsch LJ. Studies of central nervous system disorders with single photon emission computed tomography and positron emission tomography: evolution over the past 2 decades. Semin Nucl Med 1991; 21: 58–81.
27. Blasberg R. PET imaging of gene expression. Eur J Cancer 2002; 38: 2137–2146.
28. Gambhir SS, Barrio JR, Herschman HR, Phelps ME. Assays for noninvasive imaging of reporter gene expression. Nucl Med Biol 1999; 26: 481–490.
29. Cherry SR. Fundamentals of positron emission tomography and applications in preclinical drug development. J Clin Pharmacol 2001; 41: 482–491.
30. Vaalburg W, Hendrikse NH, de Vries EF. Drug development, radiolabelled drugs and PET. Ann Med 1999; 31: 432–437.
31. Bachelard HS, Thompson MF, Polkey CE. Kinetic properties of hexokinase in resected temporal lobes of patients with drug-resistant epilepsy. Epilepsia 1975; 16: 431–437.
32. Newberg A, Alavi A, Reivich M. Determination of regional cerebral function with FDG-PET imaging in neuropsychiatric disorders. Semin Nucl Med 2002; 32: 13–34.
33. Engel Jr J, Kuhl DE, Phelps ME, Rausch R, Nuwer M. Local cerebral metabolism during partial seizures. Neurology 1983; 33: 400–413.
34. Theodore WH, Newmark ME, Sato S et al. [18F]Fluorodeoxyglucose positron emission tomography in refractory complex partial seizures. Ann Neurol 1983; 14: 429–437.
35. Barrington SF, Koutroumanidis M, Agathonikou A et al. Clinical value of "'ictal"' FDG-positron emission tomography and the routine use of simultaneous scalp EEG studies in patients with intractable partial epilepsies. Epilepsia 1998; 39: 753–766.
36. Moran NF, Lemieux L, Kitchen ND, Fish DR, Shorvon SD. Extrahippocampal temporal lobe atrophy in temporal lobe epilepsy and mesial temporal sclerosis. Brain 2001; 124: 167–175.
37. Kobayashi E, D'Agostino MD, Lopes-Cendes I, Berkovic SF, Li ML, Andermann E, et al. Hippocampal atrophy and T2-weighted signal changes in familial mesial temporal lobe epilepsy. Neurology 2003; 60: 405–409.
38. Meyer PT, Cortes-Blanco A, Pourdehnad M, Levy-Reis I, Desiderio L, Jang S, et al. Inter-modality comparisons of seizure focus lateralization in complex partial seizures. Eur J Nucl Med 2001; 28: 1529–1540.
39. Imbimbo BP, Martelli P, Troetel WM, Lucchelli F, Lucca U, Thal LJ. Efficacy and safety of eptastigmine for the treatment of patients with Alzheimer's disease. Neurology 1999; 52: 700–708.
40. Morris JC, Cyrus PA, Orazem J et al. Metrifonate benefits cognitive, behavioral, and global function in patients with Alzheimer's disease [comment]. Neurology 1998; 50: 1222–1230.
41. Knapp MJ, Knopman DS, Solomon PR, Pendlebury WW, Davis CS, Gracon SI. A 30-week randomized controlled trial of high-dose tacrine in patients with Alzheimer's disease. The Tacrine Study Group. JAMA 1994; 271: 985–991.
42. Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Donepezil Study Group [comment]. Neurology 1998; 50: 136–145.
43. Rosler M, Anand R, Cicin-Sain A et al. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial [comment][erratum appears in BMJ 2001; 16; 322(7300): 1456]. BMJ 1999; 318: 633–638.
44. Kuhl DE, Metter EJ, Riege WH. Patterns of local cerebral glucose utilization determined in Parkinson's disease by the [18F] fluorodeoxyglucose method. Ann Neurol 1984; 15: 419–424.
45. Ishii K. Clinical application of positron emission tomography for diagnosis of dementia. Ann Nucl Med 2002; 16: 515–525.
46. Alavi A, Dann R, Chawluk J, Alavi J, Kushner M, Reivich M. Positron emission tomography imaging of regional cerebral glucose metabolism. Semin Nucl Med 1986; 16: 2–34.
47. Salmon E, Sadzot B, Maquet P et al. Differential diagnosis of Alzheimer's disease with PET. J Nucl Med 1994; 35: 391–398.
48. Van Heertum RL, Tikofsky RS. Positron emission tomography and single-photon emission computed tomography brain imaging in the evaluation of dementia. Semin Nucl Med 2003; 33: 77–85.
49. Silverman DH, Small GW, Chang CY et al. Positron emission tomography in evaluation of dementia: regional brain metabolism and long-term outcome. JAMA 2001; 286: 2120–2127.
50. Herholz K, Salmon E, Perani D et al. Discrimination between Alzheimer dementia and controls by automated analysis of multicenter FDG PET. Neuroimage 2002; 17: 302–316.
51. Alavi A, Clark C, Fazekas F. Cerebral ischemia and Alzheimer's disease: critical role of PET and implications for therapeutic intervention. J Nucl Med 1998; 39: 1363–1365.
52. Alavi A, Newberg AB, Souder E, Berlin JA. Quantitative analysis of PET and MRI data in normal aging and Alzheimer's disease: atrophy weighted total brain metabolism and absolute whole brain metabolism as reliable discriminators. J Nucl Med 1993; 34: 1681–1687.
53. Davis MR, Votaw JR, Bremner JD et al. Initial human PET imaging studies with the dopamine transporter ligand 18FFECNT. J Nucl Med 2003; 44: 855–861.
54. Vingerhoets FJ, Schulzer M, Ruth TJ, Holden JE, Snow BJ. Reproducibility and discriminating ability of fluorine-18 -6-fluoro-L-dopa PET in Parkinson's disease. J Nucl Med 1996; 37: 421–426.
55. Huang WS, Chiang YH, Lin JC, Chou YH, Cheng CY, Liu RS. Crossover study of (99m)Tc-TRODAT-1 SPECT and (18)F-FDOPA PET in Parkinson's disease patients. J Nucl Med 2003; 44: 999–1005.
56. Alavi A, Newberg AB. Metabolic consequences of acute brain trauma: is there a role for PET? J Nucl Med 1996; 37: 1170–1172.
57. Newberg AB, Alavi A. Neuroimaging in patients with head injury. Semin Nucl Med 2003; 33: 136–147.
58. Newberg A, Cotter A, Udeshi M, Alavi A, Clark C.A metabolic imaging severity rating scale for the assessment of cognitive impairment. Clin Nucl Med 2003; 28: 565–570.
59. Mazziotta JC, Phelps ME, Pahl JJ et al. Reduced cerebral glucose metabolism in asymptomatic subjects at risk for Huntington's disease. N Engl J Med 1987; 316: 357–362.
60. Kuhl DE, Phelps ME, Markham CH, Metter EJ, Riege WH, Winter J. Cerebral metabolism and atrophy in Huntington's disease determined by18FDG and computed tomographic scan. Ann Neurol 1982; 12: 425––434.
61. Kuwert T, Lange HW, Langen KJ, Herzog H, Aulich A, Feinendegen LE. Cerebral glucose consumption measured by PET in patients with

and without psychiatric symptoms of Huntington's disease. Psychiatry Res 1989; 29: 361–362.
62. Hustinx R, Benard F, Alavi A. Whole-body FDGPET imaging in the management of patients with cancer. Semin Nucl Med 2002; 32: 35–46.
63. Wahl RL, Hawkins RA, Larson SM et al. Proceedings of a National Cancer Institute workshop: PET in oncology — a clinical research agenda. Radiology 1994; 193: 604–606.
64. Rigo P, Paulus P, Kaschten BJ et al. Oncological applications of positron emission tomography with fluorine-18 fluorodeoxyglucose. Eur J Nucl Med 1996; 23: 1641–1674.
65. Bar-Shalom R, Valdivia AY, Blaufox MD. PET imaging in oncology. Semin Nucl Med 2000; 30: 150–185.
66. Bury T, Dowlati A, Paulus P, Hustinx R, Radermecker M, Rigo P. Staging of non-small-cell lung cancer by whole-body fluorine-18 deoxyglucose positron emission tomography. Eur J Nucl Med 1996; 23: 204–206.
67. Albes JM, Lietzenmayer R, Schott U, Schulen E, Wehrmann M, Ziemer G. Improvement of non-small cell lung cancer staging by means of positron emission tomography. Thorac Cardiovasc Surg 1999; 47: 42–47.
68. Coleman RE. PET in lung cancer. J Nucl Med 1999; 40: 814–820.
69. Wahl RL. Current status of PET in breast cancer imaging, staging, and therapy. Semin Roentgenol 2001; 36: 250–260.
70. Zhuang H, Sinha P, Pourdehnad M, Duarte PS, Yamamoto AJ, Alavi A. The role of positron emission tomography with fluorine-18-deoxyglucose in identifying colorectal cancer metastases to liver. Nucl Med-Commun 2000; 21: 793–798.
71. Bohuslavizki KH, Klutmann S, Sonnemann U et al. [F-18 FDG PET for detection of occult primary tumor in patients with lymphatic metastases of the neck region].Laryngorhinootologie 1999; 78: 445–449.
72. Bohuslavizki KH, Klutmann S, Kroger S et al. FDG PET detection of unknown primary tumors. J Nucl Med 2000; 41: 816–822.
73. Braams JW, Pruim J, Kole AC et al. Detection of unknown primary head and neck tumors by positron emission tomography. Int J Oral Maxillofac Surg 1997; 26: 112–115.
74. Lassen U, Daugaard G, Eigtved A, Damgaard K, Friberg L. 18F-FDG whole body positron emission tomography (PET) in patients with unknown primary tumours (UPT). Eur J Cancer 1999; 35: 1076–1082.
75. Kole AC, Nieweg OE, Pruim J et al. Detection of unknown occult primary tumors using positron emission tomography. Cancer 1998; 82: 1160–1166.
76. Hustinx R, Smith RJ, Benard F et al. Dual time pointfluorine-18 fluorodeoxyglucose positron emission tomography: a potential method to differentiate malignancy from inflammation and normal tissue in the head and neck. Eur J Nucl Med 1999; 26: 1345–1348.
77. Keyes JW JR, Watson Jr NE, Williams III DW, Greven KM, McGuirt WF. FDG PET in head and neck cancer. AJR Am J Roentgenol 1997; 169: 1663–1669.
78. Weihrauch MR, Re D, Bischoff S et al. Whole-body positron emission tomography using 18F-fluorodeoxyglucose for initial staging of patients with Hodgkin's disease. Ann Hematol 2002; 81: 20–25.
79. Delbeke D, Vitola JV, Sandler MP et al. Staging recurrent metastatic colorectal carcinoma with PET. J Nucl Med 1997; 38: 1196–1201.
80. Flamen P, Hoekstra OS, Homans F et al. Unexplained rising carcinoembryonic antigen (CEA) in the postoperative surveillance of colorectal cancer: the utility of positron emission tomography (PET). Eur J Cancer 2001; 37: 862–869.
81. Flanagan FL, Dehdashti F, Ogunbiyi OA, Kodner IJ, Siegel BA. Utility of FDG-PET for investigating unexplained plasma CEA elevation in patients with colorectal cancer [comment]. Ann Surg 1998; 227: 319–323.
82. Moertel CG, Fleming TR, Macdonald JS, Haller DG, Laurie JA, Tangen C. An evaluation of the carcinoembryonic antigen (CEA) test for monitoring patients with resected colon cancer. JAMA 1993; 270: 943–947.
83. Vitola JV, Delbeke D, Meranze SG, Mazer MJ, Pinson CW. Positron emission tomography with F-18-fluorodeoxyglucose to evaluate the results of hepatic chemoembolization. Cancer 1996; 78: 2216–2222.
84. Stumpe KD, Urbinelli M, Steinert HC, Glanzmann C, Buck A, von Schulthess GK. Whole-body positron emission tomography using fluorodeoxyglucose for staging of lymphoma: effectiveness and comparison with computed tomography. Eur J Nucl Med 1998; 25: 721–728.
85. Weber WA, Ott K, Becker K et al. Prediction of response to preoperative chemotherapy in adenocarcinomas of the esophagogastric junction by metabolic imaging. J Clin Oncol 2001; 19: 3058–3065.
86. Findlay M, Young H, Cunningham D et al. Noninvasive monitoring of tumor metabolism using fluorodeoxyglucose and positron emission tomography in colorectal cancer liver metastases: correlation with tumor response to fluorouracil. J Clin Oncol 1996; 14: 700–708.
87. Demetri GD, von Mehren M, Blanke CD et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 2002; 347: 472–480.
88. Kubota R, Kubota K, Yamada S, Tada M, Ido T, Tamahashi N. Microautoradiographic study for the differentiation of intratumoral macrophages, granulation tissues and cancer cells by the dynamics of fluorine-18-fluorodeoxyglucose uptake. J Nucl Med 1994; 35: 104–112.
89. Schuster DP, Kozlowski J, Hogue L, Ferkol TW. Imaging lung inflammation in a murine model of Pseudomonas infection: a positron emission tomography study. Exp Lung Res 2003; 29: 45-57.
90. Basu S, Chryssikos T, Moghadam-Kia S, Zhuang H, Torigian DA, Alavi A. Positron emission tomography as a diagnostic tool in infection: present role and future possibilities. Semin Nucl Med. 2009; 39: 36–51.
91. Basu S, Zhuang H, Torigian DA, Rosenbaum J, Chen W, Alavi A. Functional imaging of inflammatory diseases using nuclear medicine techniques. Semin Nucl Med. 2009; 39: 124–145.
92. Manthey N, Reinhard P, Moog F, Knesewitsch P, Hahn K, Tatsch K. The use of [18 F]Fluorodeoxyglucose positron emission tomography to differentiate between synovitis, loosening and infection of hip and knee prostheses. Nucl Med Commun 2002; 23: 645–653.
93. Zhuang H, Duarte PS, Pourdehnad M et al. The promising role of 18FFDG PET in detecting infected lower limb prosthesis implants. J Nucl Med 2001; 42: 44–48.
94. Vanquickenborne B, Maes A, Nuyts J et al. The value of (18)FDGPET for the detection of infected hip prosthesis. Eur J Nucl Med Mol Imaging 2003; 30: 705–715.
95. Zhuang H, Duarte PS, Pourdehand M, Shnier D, Alavi A. Exclusion of chronic osteomyelitis with F-18 fluorodeoxyglucose positron emission tomographic imaging. Clin Nucl Med 2000; 25: 281–284.
96. Guhlmann A, Brecht-Krauss D, Suger G et al. Fluorine-18-FDG PET and technetium-99m antigranulocyte antibody scintigraphy in chronic osteomyelitis. J Nucl Med 1998; 39: 2145–2152.
97. Kalicke T, Schmitz A, Risse JH et al. Fluorine-18 fluorodeoxyglucose PET in infectious bone diseases: results of histologically confirmed cases. Eur J Nucl Med 2000; 27: 524–528.
98. Bakheet SMB, Powe J, Kandil A, Ezzat A, Rostom A, Amartey J. F-18FDG uptake in breast infection and inflammation. Clin Nucl Med 2000; 25: 100–103.
99. Kao CH. Ring-like FDG uptake in acute cholecystitis. Clin Nucl Med 2003; 28: 162–163.
100. Krupnick AS, Lombardi JV, Engels FH et al. 18-fluorodeoxyglucose positron emission tomography as a novel imaging tool for the diagnosis of aortoenteric fistula and aortic graft infection-a case report. Vasc Endovasc Surg 2003; 37: 363–366.
101. Yu JQ, Kung JW, Potenta S, Xiu Y, Alavi A, ZhuangH. Chronic cholecystitis detected by FDG-PET. Clin Nucl Med 2004; 29: 496–497.
102. Blockmans D, Knockaert D, Maes A et al. Clinical value of [(18)F]fluoro-

deoxyglucose positron emission tomography for patients with fever of unknown origin. Clin Infect Dis 2001; 32: 191–196.
103. Meller J, Altenvoerde G, Munzel U et al. Fever of unknown origin: prospective comparison of [18F]FDG imaging with a double-head coincidence camera and gallium-67 citrate SPET. Eur J Nucl Med 2000; 27: 1617–1625.
104. Lorenzen J, Buchert R, Bohuslavizki KH. Value of FDG PET in patients with fever of unknown origin. Nucl Med Commun 2001; 22: 779–783.
105. Bleeker-Rovers CP, de Kleijn E, Corstens FHM, van der Meer JWM, Oyen WJG. Clinical value of FDG PET in patients with fever of unknown origin and patients suspected of focal infection or inflammation. Eur J Nucl Med Mol Imaging 2004; 31: 29–37.
106. Neurath MF, Vehling D, Schunk K et al. Noninvasive assessment of Crohn's disease activity: a comparison of 18F-fluorodeoxyglucose positron emission tomography, hydromagnetic resonance imaging, and granulocyte scintigraphy with labeled antibodies. Am J Gastroenterol 2002; 97: 1978–1985.
107. Alavi A, Buchpiguel CA, Loessner A. Is there a role for FDG PET imaging in the management of patients with sarcoidosis? J Nucl Med 1994; 35: 1650–1652.
108. Lewis PJ, Salama A. Uptake of fluorine-18-fluorodeoxyglucose in sarcoidosis. J Nucl Med 1994; 35: 1647–1649.
109. Ludwig V, Fordice S, Lamar R, Martin WH, Delbeke D. Unsuspected skeletal sarcoidosis mimicking metastatic disease on FDG positron emission tomography and bone scintigraphy. Clin Nucl Med 2003; 28: 176–179.
110. Yasuda S, Shohtsu A, Ide M et al. High fluorine-18 labeled deoxyglucose uptake in sarcoidosis. Clin Nucl Med 1996; 21: 983–984.
111. Polisson RP, Schoenberg OI, Fischman A et al. Use of magnetic resonance imaging and positron emission tomography in the assessment of synovial volume and glucose metabolism in patients with rheumatoid arthritis. Arthritis Rheum 1995; 38: 819–825.
112. Hara M, Goodman PC, Leder RA. FDG-PET finding in early-phase Takayasu arteritis. J Comput Assist Tomogr 1999; 23: 16–18.
113. deKemp R, Ruddy T, Hewitt T, Dalipaj M, Beanlands R. Detection of serial changes in absolute myocardial perfusion with 82Rb PET. J Nucl Med 2000; 41: 1426–1435.
114. Yun M, Jang S, Cucchiara A, Newberg AB, Alavi A. 18F FDG uptake in the large arteries: a correlation study with the atherogenic risk factors. Semin Nucl Med 2002; 32: 70–76.
115. Blake GM, Park-Holohan SJ, Cook GJ, Fogelman I. Quantitative studies of bone with the use of 18Ffluoride and 99mTc-methylene diphosphonate. Semin Nucl Med 2001; 31: 28–49.
116. Hoegerle S, Juengling F, Otte A, Altehoefer C, Moser EA, Nitzsche EU. Combined FDG and [F-18] fluoride whole-body PET: a feasible two-in-one approach to cancer imaging? Radiology 1998; 209: 253–258.
117. van Eijkeren ME, Thierens H, Seuntjens J, Goethals P, Lemahieu I, Strijckmans K. Kinetics of [methyl-11C]thymidine in patients with squamous cell carcinoma of the head and neck. Acta Oncol 1996; 35: 737–741.
118. Vander Borght T, Labar D, Pauwels S, Lambotte L. Production of [2-11C]thymidine for quantification of cellular proliferation with PET. Int J Rad Appl Instrum [A] 1991; 42: 103–104.
119. Barthel H, Cleij MC, Collingridge DR et al. 30-deoxy-30-[18F]fluorothymidine as a new marker for monitoring tumor response to antiproliferative therapy in vivo with positron emission tomography. Cancer Res 2003; 63: 3791–3798.
120. Buck AK, Schirrmeister H, Hetzel M et al. 3-deoxy-3-[(18)F] fluorothymidine-positron emission tomography for noninvasive assessment of proliferation in pulmonary nodules. Cancer Res 2002; 62: 3331–3334.
121. Wagner M, Seitz U, Buck A et al. 30-[18F]fluoro-30-deoxythymidine([18F]-FLT) as positron emission tomography tracer for imaging proliferation in a murine B-cell lymphoma model and in the human disease. Cancer Res 2003; 63: 2681–2687.
122. Shields AF, Grierson JR, Dohmen BM et al. Imaging proliferation in vivo with [F-18]FLT and positron emission tomography. Nat Med 1998; 4: 1334–1336.
123. Dittmann H, Dohmen BM, Paulsen F et al. F-18 FLT PET for diagnosis and staging of thoracic tumours. Eur J Nucl Med Mol Imaging 2003; 30: 1407–1412.
124. Cobben DCP, Elsinga PH, Suurmeijer AJH et al. Detection and grading of soft tissue sarcomas of the extremities with F-18-30-fluoro-30--deoxy-L-thymidine. Clin Cancer Res 2004; 10: 1685–1690.
125. Halter G, Buck AK, Schirrmeister H et al. F-18 3-deoxy-30- fluorothymidine positron emission tomography: alternative or diagnostic adjunct to 2-F-18-fluoro-2-deoxy-D-glucose positron emission tomography in the workup of suspicious central focal lesions? J Thorac Cardiovas Surg 2004; 127: 1093–1099.
126. Koh WJ, Bergman KS, Rasey JS et al. Evaluation of oxygenation status during fractionated radiotherapy in human nonsmall cell lung cancers using [F-18]fluoromisonidazole positron emission tomography. Int J Radiat Oncol Biol Phys 1995; 33: 391–398.
127. Nunn A, Linder K, Strauss HW. Nitroimidazoles and imaging hypoxia. Eur J Nucl Med 1995; 22: 265–280.
128. Fujibayashi Y, Taniuchi H, Yonekura Y, Ohtani H, Konishi J, Yokoyama A. Copper-62-ATSM: a new hypoxia imaging agent with high membrane permeability and low redox potential. J Nucl Med 1997; 38: 1155––1160.
129. Evans SM, Kachur AV, Shiue CY et al. Noninvasive detection of tumor hypoxia using the 2-nitroimidazole [18F]EF1. J Nucl Med 2000; 41: 327–336.
130. Dolbier Jr WR, Li AR, Koch CJ, Shiue CY, Kachur AV. [18F]-EF5, a marker for PET detection of hypoxia: synthesis of precursor and a new fluorination procedure. Appl Radiat Isot 2001; 54: 73–80.
131. Blankenberg FG, Strauss HW. Nuclear medicine applications in molecular imaging. J Magn Reson Imaging 2002; 16: 352–361.
132. Eliceiri BP, Cheresh DA. The role of alpha V integrins during angiogenesis: insights into potential mechanisms of action and clinical development. J Clin Invest 1999; 103: 1227–1230.
133. Cheresh DA. Structure, function and biological properties of integrin alpha V beta3 on human melanoma cells. Cancer Metastasis Rev 1991; 10: 3–10.
134. Haubner R, Wester HJ, Weber WA et al. Noninvasive imaging of alpha(V)beta3 integrin expression using 18F-labeled RGD-containing glycopeptide and positron emission tomography. Cancer Res 2001; 61: 1781–1785.
135. Haubner R, Wester HJ, Burkhart F et al. Glycosylated RGD-containing peptides: tracer for tumor targeting and angiogenesis imaging with improved biokinetics. J Nucl Med 2001; 42: 326–336.
136. Kaminski MS, Zelenetz AD, Press OW et al. Pivotal study of iodine I 131 tositumomab for chemotherapy-refractory low-grade or transformed low-grade B-cell non-Hodgkin's lymphomas. J Clin Oncol 2001; 19: 3918–3928.
137. Witzig TE, Gordon LI, Cabanillas F et al. Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. J Clin Oncol 2002; 20: 2453–2463.
138. Anderson CJ, Connett JM, Schwarz SW et al. Copper-64-labeled antibodies for PET imaging. J Nucl Med 1992; 33: 1685–1691.
139. Hofmann M, Maecke H, Borner R et al. Biokinetics and imaging with the somatostatin receptor PET radioligand (68)Ga-DOTATOC: preliminary data. Eur J Nucl Med 2001; 28: 1751–1757.
140. Henze M, Schuhmacher J, Hipp P et al. PET imaging of somatostatin receptors using. J Nucl Med 2001; 42: 1053–1056.
141. Ogawa T, Shishido F, Kanno I et al. Cerebral glioma: evaluation with

methionine PET [comment]. Radiology 1993; 186: 45–53.
142. Wester HJ, Schottelius M, Scheidhauer K et al. PET imaging of somatostatin receptors: design, synthesis and preclinical evaluation of a novel 18F-labelled, carbohydrated analogue of octreotide. Eur J Nucl Med Mol Imaging 2003; 30: 117–122.
143. Jager PL, Vaalburg W, Pruim J, de Vries EG, Langen KJ, Piers DA. Radiolabeled amino acids: basic aspects and clinical applications in oncology. J Nucl Med 2001; 42: 432–445.
144. Hara T, Kosaka N, Kishi H. PET imaging of prostate cancer using carbon-11-choline. J Nucl Med 1998; 39: 990–995.
145. Kotzerke J, Prang J, Neumaier B et al. Experience with carbon-11 choline positron emission tomography in prostate carcinoma. Eur J Nucl Med 2000; 27: 1415–1419.
146. Price DT, Coleman RE, Liao RP, Robertson CN, Polascik TJ, DeGrado TR. Comparison of [18F]fluorocholine and [18 F]fluorodeoxyglucose for positron emission tomography of androgen dependent and androgen independent prostate cancer. J Urol 2002; 168: 273–280.
147. Dimitrakopoulou-Strauss A, Strauss LG. PET imaging of prostate cancer with 11C-acetate. J Nucl Med 2003; 44: 556–558.
148. Oyama N, Akino H, Kanamaru H et al. 11C-acetate PET imaging of prostate cancer. J Nucl Med 2002; 43: 181–186.
149. Mortimer JE, Dehdashti F, Siegel BA, Katzenellenbogen JA, Fracasso P, Welch MJ. Positron emission tomography with 2-[18F]fluoro-2-deoxy--D-glucose and 16-alpha-[18F]fluoro-17-beta-estradiol in breast cancer: correlation with estrogen receptor status and response to systematic therapy. Clin Cancer Res 1996; 2: 933–939.
150. Dehdashti F, Mortimer JE, Siegel BA et al. Positron tomographic assessment of estrogen receptors in breast cancer: comparison with FDG-PET and in vitro receptor assays. J Nucl Med 1995; 36: 1766––1774.
151. Gambhir SS. Molecular imaging of cancer with positron emission tomography. Nat Rev Cancer 2002; 2: 683–693.
152. Zhuang H, Pourdehnad M, Lambright ES et al. Dual time point F-18-FDG PET imaging for differentiating malignant from inflammatory processes. J Nucl Med 2001; 42: 1412–1417.
153. Conrad GR, Sinha P. Narrow time-window dual-point F-18-FDG PET for the diagnosis of thoracic malignancy. Nucl Med Commun 2003; 24: 1129–1137.
154. Basu S, Alavi A. Unparalleled contribution of 18F-FDG PET to medicine over 3 decades. J Nucl Med 2008; 49: 17N-21N, 37N.
155. Alavi A, Lakhani P, Mavi A, Kung JW, Zhuang H. PET: a revolution in medical imaging. Radiol Clin North Am 2004; 42: 983–1001.
156. Basu S, Kumar R, Rubello D, Fanti S, Alavi A. PET Imaging in Neuroendocrine tumors: Current status and future prospects. Minerva Endocrinol 2008; 33: 257–275.
157. Basu S, Torigian D, Alavi A. The role of modern molecular imaging techniques in gastroenterology. Gastroenterology 2008; 135: 1055––1061.