Review Article

Clinical PET Imaging – An Asian Perspective

CL Ho,[1] *MBBS (HK), MSc (Stanford), DABNM*

Abstract

Positron emission tomography (PET) has entered a new phase of development since a major technological breakthrough in 2000. Combined with computed tomography (CT), the second-generation PET-CT scanner is now able to obtain both functional and anatomical information of the whole body from a single study. Its application in oncology has become one of the standard imaging modalities in diagnosis, staging and monitoring therapeutic efficacy. It is well known that the Asian and Western populations have their own characteristic disease spectrum and cancer incidence. Although changes in diet and life-style have narrowed the differences in the last decade, there remains moderate divergence and disparities in cancer pattern and priority of resource allocation in different countries. It is known that F-18 fluorodeoxyglucose (FDG) is the most widely used radiopharmaceutical in PET imaging and it has been confirmed valuable in a variety of cancer types such as lung, colorectum, oesophagus, head and neck (including nasopharyngeal carcinoma), breast, pancreas, lymphoma, melanoma, cholangiocarcinoma and many types of sarcoma. Some cancer types, however, are less sensitive to FDG-PET detection and these include hepatocellular carcinoma, urological carcinoma, gastric malignancy, mucinous and clear-cell gastrointestinal tumours, neuroendocrine tumours and well-differentiated thyroid cancers. Some of these less sensitive cancer types are more prevalent in the Asian population than the Euro-American population and are, therefore, more frequently encountered as false negative cases in FDG-PET imaging. On the other hand, Asian countries are more prevalent in diseases such as tuberculosis and the chance of having false positive FDG-PET cases is higher than the Euro-American countries in the evaluation of lung and other cancers. From the Asian perspective, we are more susceptible to having a higher chance of both false negative and false positive FDG-PET cases. Thus, there is a stronger emphasis of research on new drugs to overcome the limitations of FDG. The use of PET imaging as a diagnostic tool has gained wide acceptance in Asia during the past few years and its clinical utility is expected to continue to rise. More research on other PET radiopharmaceuticals should therefore be given a higher priority along side with the maturation of scanning technology.

Ann Acad Med Singapore 2004;33:155-65

Key words: Asia, PET-CT, Positron emission tomography (PET), Prevalence, Radio-pharmaceuticals

Introduction

Positron emission tomography (PET) is distinct from other imaging modalities in its ability to probe the physiology and biochemistry of normal and abnormal tissues. It is based on the same principle of tracer kinetics used in conventional nuclear medicine. The tracer, technically a "radiopharmaceutical", is the functional molecule (a probe) that measures a designated biochemical process already known in living systems. The "positron" is the labelling material that renders the molecule detectable and quantifiable. As the name implies, positron is a positive electron emitted by the decay of a positron-emitting element generated by the cyclotron. The advantage of using positron as the labelling agent lies in its high-energy gamma wave characteristic and its coincidence mode of emission. Energy loss due to body tissue attenuation can be accurately corrected and both dynamic and static imaging can be quantified. PET is the term for the imaging technology; a full description should specify which radiopharmaceutical is being used. Currently, the most widely used molecule is ^{18}F-fluorodeoxyglucose (FDG). FDG is actively transported into any living cells (normal or abnormal) just like an

[1] Director, Department of Nuclear Medicine & Positron Emission Tomography
   Hong Kong Sanatorium & Hospital, Hong Kong, SAR China
Address for Reprints: Dr Garrett CL Ho, Department of Nuclear Medicine & Positron Emission Tomography, Hong Kong Sanatorium & Hospital, 2 Village Road, Happy Valley, Hong Kong, SAR China.
Email: garrettho@hksh.com

ordinary glucose molecule. It is then phosphorylated by the hexokinase enzyme, the first and key reaction of glycolysis, and is "metabolically trapped". Therefore, FDG-PET measures cellular glycolysis, which theoretically reflects cellular proliferation, growth and cell type dedifferentiation. Obviously, this represents an oversimplification of tumour kinetics. Nonetheless, FDG is at present the most widely accepted biochemical tracer proven useful in detecting abnormal cellular metabolism. Besides FDG, there is now a large amount of research data on the use of other functional molecules in the evaluation of other biochemical paths of tumour kinetics. [11]C is another positron-emitting element, which is of unlimited potential in labelling various organic, physiological molecules. For example, ^{11}C methionine PET measures tissue amino acid metabolism and is useful in many forms of primary brain tumour, particularly glioma. [11]C choline PET measures membrane phospholipid metabolism and ^{11}C acetate PET measures fatty acid synthesis, both without urinary excretion and therefore facilitate evaluation of tumours of the urological and gynaecological systems. [11]C acetate PET has also been found valuable in liver malignancies. Various peptides and receptor agents have been evaluated for their application in mapping functional brain pathology and neuroendocrine properties.

PET Services in Asia

FDG-PET imaging is broadly classified into oncologic and non-oncologic applications (Tables 1 and 2). The spectrum of disease prevalence, medical referral system and socio-economic condition of the community generally prescribe the utilisation pattern of this imaging modality. In oncologic applications, FDG-PET has been proven particularly valuable in cancer of the lung, colorectum, oesophagus, head and neck, breast, lymphoma and melanoma. It is also very useful to look for a possible primary malignancy in the investigation of a metastatic lymph node of unknown origin. In monitoring therapeutic efficacy, it is a highly sensitive tool for the assessment of response to the treatment regimen (chemotherapy or radiation therapy); besides, it also has a unique characteristic in predicting prognosis. In non-oncologic applications, PET has been the gold standard to differentiate viable/hibernating myocardium from non-viable infarcts in patients with coronary artery disease. It provides functional information on a variety of neurological disorders such as dementia of Alzheimer and non-Alzheimer types, Parkinson's disease and epilepsy. Its non-specific nature of accretion in sites of inflammation and infection renders it useful in the investigation of fever of unknown origin and certain autoimmune disease.

As of 2003, PET service is available in more than 30 medical centres in Japan, 25 in China, 12 in Taiwan, 10 in

Table 1. Common Oncologic Indications of FDG-PET in Asia

Strong indications for FDG-PET
- Lung cancer staging (non-small cell lung carcinoma)
- Differentiation of benign and malignant lung or mediastinal masses (evaluation of indeterminate solitary pulmonary nodules)
- Lymphoma staging and recurrence
- Staging and detection of colorectal cancer recurrence
- Tumours of the head and neck staging and recurrence
- Breast cancer staging and restaging for locoregional, recurrence or metastasis
- Staging of oesophageal carcinoma (more accurate preoperative identification of stage IV disease and lymph node specificity)
- Melanoma staging
- Assessment of post-treatment efficacy
- Confirmation of other types of suspected cancer recurrence particularly when conventional anatomical imaging modalities are indeterminate or negative but with clinical suspicion (lymphoma, lung cancer, nasopharyngeal carcinoma and other head and neck tumours, musculoskeletal tumours, ovarian carcinoma, esophageal carcinoma)
- Investigation of tumour of unknown primary (e.g., a metastatic lymph node in the head and neck region)

Relative indications for FDG-PET
- Evaluation of neoadjuvant therapy and prediction of resistance
- Evaluation of indeterminate pancreatic masses and suspected metastases
- Evaluation of breast lumps when mammography screening is indeterminate or in case of dense breasts or when biopsy is risky
- Differentiation of infiltration/recurrence from radiation scarring in breast cancer patients with indeterminate axillary lumps
- Early prediction of hormonal therapy response in metastatic breast cancer
- Diagnosis of ovarian cancer when CA 125 is not elevated but anatomical imaging is suspicious, or vice versa, and if confirmed, staging
- Differentiation of brain tumour recurrence from therapy necrosis
- Restaging of previously treated follicular cell origin thyroid cancer with an elevated or rising serum thyroglobulin (greater than 10 ng/mL) and a negative iodine-131 whole-body scan
- Musculoskeletal tumours staging
- Neuroendocrine tumours

Tumours with low FDG-PET sensitivity (requiring other PET radiopharmaceuticals)
- Urological tumours
- Hepatocellular carcinoma
- Tumours of signet ring or mucinous clear cell pathology

Table 2. Common Non-oncologic Indications of FDG-PET in Asia

Non-oncologic indications for FDG-PET
- Post-traumatic brain syndrome
- Dementia: Alzheimer's disease, Pick's disease
- Epilepsy: search for epileptogenic foci
- Viability study in myocardial infarction
- Fever of unknown origin

South Korea, 4 in Hong Kong, 3 in Singapore and 1 in Philippines. Since the introduction of PET-CT hybrid scanning technology in 2000, PET imaging has entered the second phase of development in centres with pre-existing

PET facilities. At the same time, a number of new PET imaging facilities have been established. The provision of a clear anatomical roadmap for the functional aspect of pathology has increased the accuracy of disease localisation when compared with the old PET-alone imaging technique of the past. On the other hand, the inclusion of functional information to a confirmed or suspected structural abnormality has led to greater accurate diagnosis, staging and treatment planning.

The following discussion is largely based on the author's personal experience of practice in the Asian locality and only the essential entities are discussed.

Oncology

Lung Cancer in General

To date, there should be indisputable data that FDG-PET offers a highly accurate evaluation of lymph node involvement, as well as intrapulmonary and extrapulmonary metastasis in lung malignancy.[1-3] FDG-PET is able to evaluate the primary lesion, mediastinal lymphadenopathy and distant metastasis in a single scanning procedure. PET has been shown to have a weighted average sensitivity of 88% and specificity of 93% in the study of nodal disease (versus 63% and 80%, respectively, for CT).[4,5] In most cases, it is not difficult to categorise disease status as being operable or inoperable (stage IIIb and above) as the accuracy of FDG-PET in assessing nodal status is near that of mediastinoscopy. Moreover, PET is able to reveal more than 10% of the patients with distant metastasis not evident on CT.[6,7] In some cases where the tumour is in close proximity to the large vessels, pericardium, or oesophagus, T4 disease cannot be definitively excluded and the same difficulty can be accounted by high-resolution CT or MR even with cardiac-cycle gating technique. Whether PET-CT has any additional value is not known and requires more detailed evaluation. In the presence of pleural effusion, cytology of the pleural fluid or pleural biopsy may sometimes be necessary to exclude metastatic pleural involvement if no conclusive evidence is found on PET-CT. From an Asian perspective, the role of PET will continue to expand in staging, although its role in primary diagnosis can never preclude the need to obtain tissue diagnosis.

The other useful aspect of FDG-PET imaging is its application in monitoring treatment response in lung cancer and its ability to differentiate scarring from recurrence after therapy. It is estimated that about 1/3 of patients undergoing therapy may show an apparent increase or no change in tumour volume on radiographical imaging due to non-specific changes around the tumour.[8] These cases, however, show decreased tumour FDG uptake and should not be treated as non-responders to therapy based on anatomical information alone. On the other hand, if FDG intensity and functional tumour size (total lesion glycolysis) are not decreased in the course of treatment, change of therapeutic regimen should be considered.

Benign versus Malignant Lung Nodules

In the differentiation of benign and malignant solitary lung nodules, FDG-PET has been proven extremely useful in the Western population. Both sensitivity and specificity are >90%.[1-3] However, in Asia, its accuracy is hampered by the prevalence of pulmonary tuberculosis (TB). Some tuberculomas may have a very high FDG utilisation rate that is almost indistinguishable from malignancy either by visual assessment or by semiquantitative evaluation with the calculation of standard uptake value (SUV) (Fig. 1). The false positive rate is, therefore, presumably higher in this locality despite the fact that imaging pattern recognition and complementary radiological information may sometimes be helpful. Pulmonary TB can sometimes be a great mimic to lung cancer. What truly complicates the issue is the co-existence of TB and lung cancer. Bronchogenic carcinoma may be masked by pulmonary TB, or vice versa. The incidence of TB in lung cancer is about 0.7% to 4% while the incidence of lung cancer in TB is about 2%.[9,10] Therefore, even in the presence of a positive culture or staining result for acid fast bacilli, a more detailed histopathological work-up is necessary to rule out malignancy in case both PET and CT show a high index of suspicion. In the presence of co-existing TB, lung cancer staging by PET or CT can be erroneous. Follow-up imaging after anti-TB treatment is always warranted. In case of increase in lesion size or dissatisfactory progress after institution of anti-TB treatment, further investigation for concomitant/occult malignancy must be considered.

Other false positive reasons include active granulomatous lesions arising from coccidioidomycosis, aspergillosis and histoplasmosis. At the current time of writing, no reliable methods exist in the literature to accurately differentiate lung cancer from TB, although some small series in the literature[11] advocate that ^{11}C acetate or ^{11}C choline imaging may be helpful (the data could not be reproduced with a high level of reliability based on the author's experience). However, the true negative rate remains unchanged. Further research on labelling anti-TB medications may likely have a potential role in detecting and monitoring TB lesions. It is known that small lesions may be subjected to partial volume averaging effects and some very low-grade lesions, such as bronchoalveolar carcinoma, may occasionally be missed. These constitute the few percent of false negative cases in FDG-PET evaluation of lung lesions in patients without a known history of malignancy. In cases where a known (non-lung) primary malignancy is already present, the evaluation of lung metastasis by FDG-PET should be individually studied according to the type of cancer involved.

Lymphoma

The most common imaging method for staging malignant lymphoma was CT in the era of Gallium-67 imaging. In the last few years, multicentre trials and large study series have suggested an incremental accuracy of FDG-PET in primary staging of this disease entity.[12-14] Figure 2 shows a typical case of diffuse lymphoma involvement. The data is based on a combination of biopsy, comparative anatomical imaging and clinical follow-up. The reported FDG-PET sensitivities for Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL) range from 78% to 100%, and specificities from 90% to 100%. However, what is the implication of such information to the oncologists?

The treatment of HD is predominantly based on stage, but the treatment for NHL also includes a consideration for the "grading" of the disease.

The role of PET in low-grade NHL and high-grade NHL is believed to be less important than in intermediate-grade NHL. Low-grade NHL usually has an indolent course, presents late, and has a low curing rate. FDG-PET may have a low uptake and, therefore, may not accurately reflect the true therapeutic response. The only possible role of FDG-PET in this group is to confirm early stage I disease so that local radiation may be considered. High-grade NHL usually requires no radiation because aggressive chemotherapy would have immediately been given due to the poor prognosis if untreated. The main role of PET in high-grade NHL is to ascertain an effective chemo-regimen in the presence of residual masses seen on CT. In intermediate-grade NHL, PET is useful to identify 3 groups of patients: (1) the patients with early-stage non-bulky disease who may benefit from an abbreviated course of combination chemotherapy and radiation; (2) the patients with bulky disease to define the radiation boundary; (3) those with advanced non-bulky disease (including extra-nodal and small-nodal disease) for a longer duration of chemotherapy without radiation.

The role of PET in HD is more important because its treatment is mostly stage-based and its avidity for FDG is less variable. PET can identify the early-stage patients who may benefit from an abbreviated course of chemotherapy plus involved-field radiotherapy, or those with advanced stage diseases that require a longer chemotherapeutic regimen without radiation. For the recurrent HD patients determined by PET to be just one-site relapse above the diaphragm, radiotherapy alone may be instituted, as opposed to the option of high-dose chemotherapy with stem-cell transplant for the advanced-stage patients.

Therefore, PET-CT has a potential role to become the gold standard in the imaging of lymphoma because its combined function-and-anatomy capability is able to help the oncologists to stratify patients into subtypes, so that the most appropriate treatment option may be identified.

Colorectal Cancer

Colorectal malignancy is one of the top 3 cancer incidences in both Western and Asian countries. It is known that about 25% to 40% of colorectal cancer patients develop a recurrence within 2 years of tumour resection.[15] Increasing evidence suggests that resection of early recurrent colorectal carcinoma my lead to prolonged survival and cure.[16] FDG-PET is now the most widely used and clinically accepted means of early detection of colorectal cancer recurrence. It is especially useful in the abdomen when the post-surgical and post-irradiated abdomen can be difficult for CT evaluation.[17] Whether CEA has been a reliable marker of tumour activity or not, FDG-PET has been proven more sensitive and specific than conventional imaging methods. Considering tumour detection accuracy, the positive and negative predictive values of FDG-PET are all above 90% when compared with the average values of 60% to 70% by CT, as reported in large study series in the literature.[18] One of the advantages of PET-CT is its ability to identify sites of potential false positives, such as physiologic activities, thus increasing detection accuracy.

Its incremental value in affecting patient management is recognised in terms of categorising and subdividing patients for different treatment modalities and in predicting as well as monitoring the progress of radiotherapy and chemotherapy. PET has been shown to affect 20% to 40% of clinical management by sparing laparotomy in cases of multifocal metastasis, validating surgical resection by excluding sites of false positives or including sites of true positives for a single operative removal (Fig. 3) (changing treatment modality, modifying the intended treatment and changing stage).[19] These roles are expected to grow and become a standard procedure when PET services become commonly available.

Head and Neck Cancer

There has been a significant amount of data published in the literature in the past few years on the use of FDG-PET in head and neck cancer imaging, as well as its role in treatment response and detection of recurrence. Nodal staging (N) has been studied most thoroughly. Most of the reported cases showed that FDG-PET sensitivity and specificity are either better than or equivalent to CT/MR imaging. Tumour staging (T), however, showed no real advantage, except in the search for an unknown primary in the presence of a positive neck node (25% to 30% positive rate of detection). In the detection of recurrence after therapy, most data showed statistically significant advantage.

Two diseases of our major concern are nasopharyngeal

carcinoma (NPC) in Southeast Asia and oral cavity tumours (OCT) in the Indian subcontinent. NPC has a high association with Epstein-Barr virus (EBV) infection and OCT is suspected to have a dietary influence (spicy food and chewing cigarette and betel nuts). Data from Taiwan showed a high sensitivity and specificity of >90% in FDG-PET evaluation of suspected NPC recurrence 4 months after radiation therapy,[20] and high accuracy of FDG-PET in detecting recurrence when indeterminate MR findings are present.[21]

In the detection of recurrence, physical examination alone has a low yield because the post-irradiated neck is indurated. Diagnosis of lymph node recurrence may have a low detection accuracy for CT or MR imaging after surgery and/or irradiation. PET has been found to be extremely useful for detection of NPC recurrence both in the primary site and metastatic sites. Another study reported that 28% of NPC patients with suspected neck nodes were upstaged by FDG-PET relative to conventional CT findings.[22] In radiotherapy (RT) planning, software fusion imaging (PET and CT/MR) has been shown by Japanese researchers to play a role in normal tissue sparing, particularly the parotid glands, during conformal RT in the determination of gross tumour volume and clinical target volume.[23] Based on hardware fusion technology, PET-CT is expected to provide a more precise definition of the pathological boundaries of locoregional disease in addition to outlining the target areas for prophylactic irradiation. As an imaging tool that can offer higher accuracy in staging, detection of recurrence, monitoring of (chemoradiation) therapy and a combined functional-anatomical mapping guide for NPC and other head and neck tumours, the role of PET-CT will likely be the investigation of choice in the future (Fig. 4).

Cancer of Unknown Primary

FDG-PET is a valuable diagnostic tool in patients with cancer of unknown primary. The ability of PET to localise a primary malignancy in the presence of a metastatic pathology is reported to range from 20% to 50% (average ~30%).[24-29] These studies and local data include cases such as occult lung cancer, breast cancer, NPC, laryngeal carcinoma, salivary gland tumour, thyroid cancer, colorectal carcinoma, ovarian carcinoma and Merkel cell carcinoma. The initial presentations include, amongst others, a metastatic lymph node in the neck, supraclavicular fossa or groin, a malignant skin nodule, an axillary node with negative mammogram and clinical examination, a lung or brain biopsy of adenocarcinoma. The role of FDG-PET is 3-fold: to suggest a location to perform a biopsy; to avoid unnecessary invasive procedures in high-risk patients; and to perform an overall staging at the same time of evaluating other sites of metastases. As the data also implies, even in

those cases with negative FDG-PET findings, the chance of a good prognosis is reasonably high after appropriate treatment of the metastatic cancer. Long-term follow-up is needed to determine if any of these negative cases could continue to lead a favourable outcome. With the emergence of PET-CT, a clear advantage is that the location for biopsy can be more precise and the error arising from sampling error can be minimised.

Oesophageal Carcinoma

In the evaluation of oesophageal carcinoma, FDG-PET is more accurate than CT and comparable to endoscopic sonogram (ES) in the detection of nodal metastasis (both individual nodal groups and N staging evaluation). In the literature, the merit of FDG-PET studies in preoperative staging was at once controversial. Recent studies comprising of extensive lymph node dissection along with oesophageal resection in patients with oesophageal squamous cell carcinoma had an accuracy of 83% in FDG-PET, 60% in CT, and 58% in ES for N staging.[30] In individual nodal metastasis, FDG-PET had a sensitivity of 57%, specificity of 97%, versus 18% and 99% for CT, respectively. Some studies reported a lower accuracy of FDG-PET relative to ES, but the studies were performed on *en bloc* specimens instead of intraoperative lymph node dissection.[31,32] These studies also had a higher percentage of gastro-oesophageal tumour localisation and sample selection appears to be biased towards those cases with less lymph node involvement (cases with more extensive lymph node metastasis were excluded from operation in these studies). More clinical comparison is required to confirm the role and incremental value of FDG-PET in preoperative staging. Nevertheless, FDG-PET has been proven useful in the evaluation of distant metastasis and recurrence.

Breast Cancer

Physical examination and mammography continue to be the primary means of detecting breast masses and identifying those suspicious for malignancy, with biopsy being the standard procedure in confirming malignancy. In patients for whom mammography is less effective, such as those with radiodense breasts, implants or potential lobular cancers poorly visualised on mammography, PET plays an important role in lesion localisation. Likewise, in patients for whom mammograms are not definitive or when biopsy is risky, such as those with postoperative scarring or those with suspected recurrence/disease near a breast implant, PET may be effective in distinguishing malignant from benign processes. The application of PET in evaluating breast cancer has focused primarily on determining the extent of disease at initial diagnosis, staging, and in monitoring the effectiveness of therapy. Thus far, the best sensitivity for imaging primary breast tumours is 92%, with a specificity
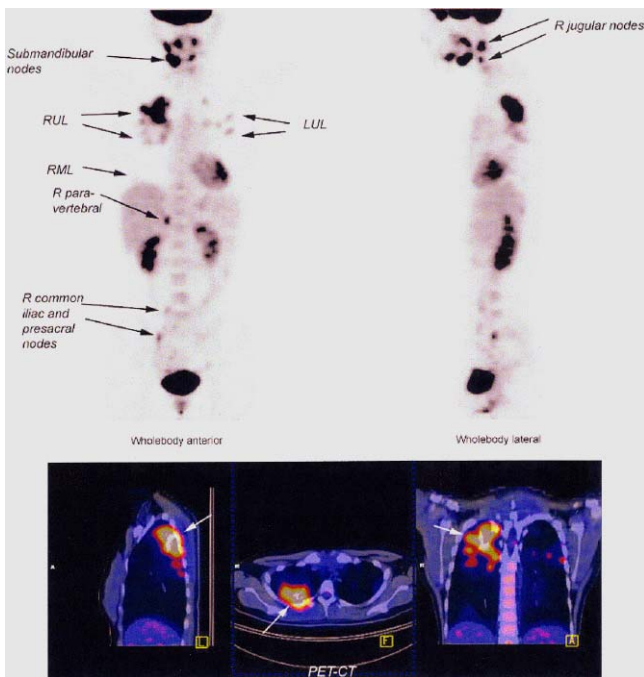
Fig. 1. Pulmonary TB is a great mimic to lung cancer. (Top) Wholebody 3D reconstructed FDG-PET showing primary TB with multiple lymph node dissemination. (Bottom) PET-CT of the same patient showing a large tuberculoma in the RUL. RUL: right upper lobe; LUL: left upper lobe

Fig. 2. FDG-PET of an advanced lymphoma shows multifocal nodal disease on both sides of diaphragm with extranodal involvement of liver and bone. CMN: celiac-mesenteric node; HN: hilar node; JDN: jugulodigastric node; PAN: pre-auricular node; RPN: retropharyngeal node; SCFN: supraclavicular node; SCN: subcarinal node; TS: thoracic spine metastases.
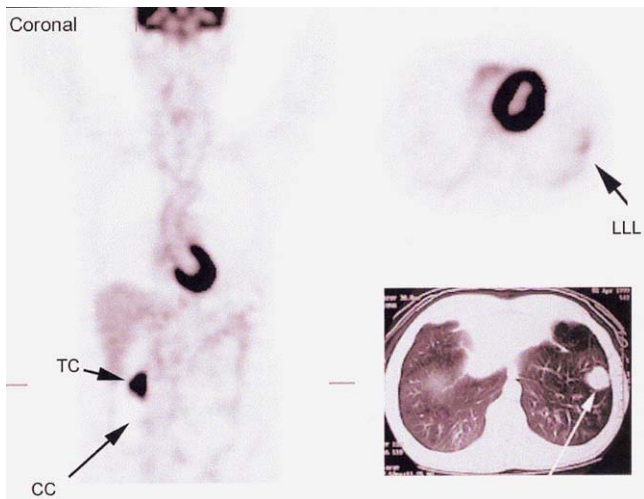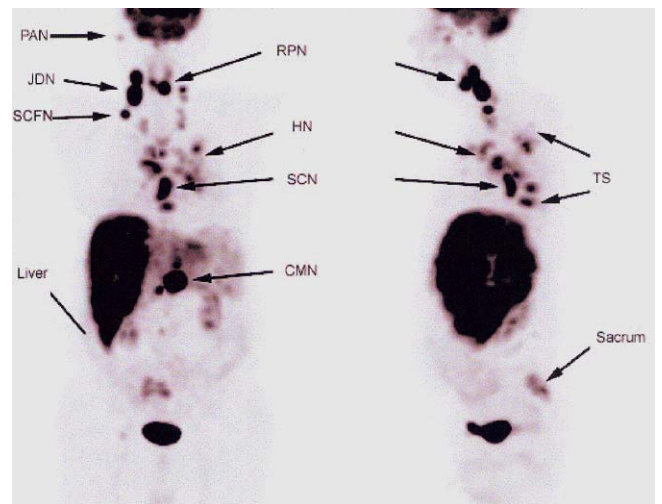

Fig. 3. FDG-PET shows a malignant colonic tumour in a patient being referred for evaluation of chemotherapeutic efficacy initially treated as primary adenocarcinoma of lung in the left lower lobe (LLL). The real primary is in the ascending colon. TC: tumour in colon; CC: caecum.
(Bottom right) CT of thorax shows the original LLL tumour before chemotherapy.
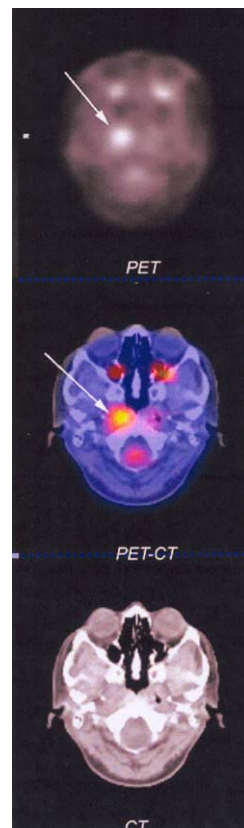

Fig. 4. A patient had borderline elevation of Epstein-Barr virus titre, a normal nasoscopy and negative biopsy. PET-CT showed abnormal focal metabolism in the right posterior wall of nasopharynx and obliteration of right lateral pharyngeal space. Note symmetrical mucosal lining on CT. The tumour was submucosal and repeated biopsy confirmed nasopharyngeal carcinoma.
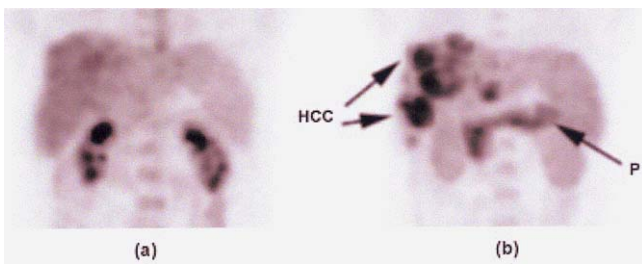
Fig. 5. Multifocal well-differentiated hepatocellular carcinomas (HCCs) are seen in both lobes of liver on ¹¹C acetate PET (b) but are only faintly seen or not visualised on FDG-PET (a). Normal pancreas (P) shows physiologically intense ¹¹C acetate metabolism.
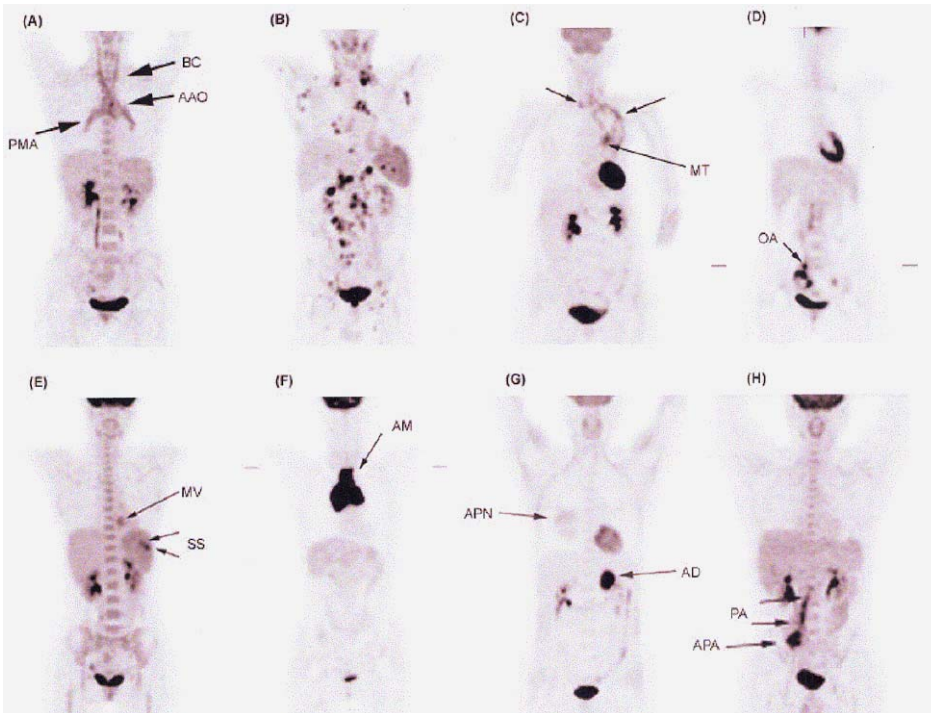

Fig. 6. FDG-PET in 8 patients referred for investigation of pyrexia of unknown origin: (A) Takayasu's disease with aortic arch arteritis (AAO) extending to the brachiocephalics (BC) and pulmonary arteries (PMA); (B) angioimmunoblastic lymphoproliferative disorder with entensive lymph node involvement; (C) pulmonary mycetoma (MT); (D) ovarian abscess (OA); (E) subacute bacterial endocarditis in the mitral valve (MV) and septic loculations in the spleen (SS); (F) non-Hodgkin's lymphoma in the anterior mediastinum (AM); (G) phaeochromocytoma in the left adrenal gland (AD) with resolving aspiration pneumonia (APN) as a result of bronchoscopy; and (H) appendiceal abscess (APA) tracking up to form psoas abscess (PA).

of 97% and an accuracy of 92%. In the axilla, sensitivity, specificity and accuracy are lower: 82%, 95%, and 90%, respectively.[33-35]

In Asia, the incidence of breast malignancy is increasing[36] and the frequency of recurrent breast cancer is expected to be increasing as well. Conventional follow-up tests include serum tumour marker (CA 15.3 and CEA) determination. Many of these patients have asymptomatic, isolated elevation of tumour markers but otherwise they may not have any clinical or instrumental signs of relapses. Recent studies have explored the role of PET in these patients. A sensitivity of 92%, specificity of 75% and an overall accuracy of 87% have been reported.[37] As early detection of recurrence improves survival, the inclusion of PET as an indication in the follow-up protocol may warrant serious consideration.

PET is also useful for monitoring response to radiation treatment or combination chemohormonal therapy. Dehdashti el al[38] demonstrated that a metabolic flare by FDG-PET and the degree of oestrogen receptor (ER) blockade by F-18 estradiol PET (FES-PET) early after institution of tamoxifen treatment appear to predict the responsiveness to anti-oestrogen therapy in patients with ER-positive metastatic breast cancer. Quantitative and/or semi-quantitative FDG-PET yields valuable information on prognosis and response to therapy in a timely fashion.

Preliminary studies have indicated that serial assessment of tumour metabolism by FDG-PET during the early phase of an effective chemohormonotherapy may predict subsequent response to such therapy.[38,39]

Pancreatic Cancer

Although pancreatic cancer is not one of the top 10 prevalent cancers in most Asian countries, it has been one of the leading causes of cancer deaths in the past few years. The statistics reflects the poor prognostic characteristics of this tumour and is partially secondary to the insidious nature of this tumour and its difficulty in diagnosis. Most patients have locally advanced or metastatic disease at the time of presentation. CT has a high sensitivity (71% to 95%) in detection of focal or diffuse pancreatic masses.[40] However, the differentiation of pancreatic cancer from focal pancreatitis remains a diagnostic problem since the later can have a CT appearance that is indistinguishable from that of malignancy. FDG-PET has been demonstrated useful in cases where clinical and CT findings are indeterminate, and where distant metastasis needs to be excluded before attempting extensive surgery.

Metastatic Thyroid Cancer

FDG-PET has been used for the detection of Hurtle cell carcinoma, medullary carcinoma and undifferentiated or anaplastic carcinoma of the thyroid. In the detection of metastatic well-differentiated papillary and follicular carcinoma, the sensitivity for detection is in the range of 50% to 78%, and specificity, 90% to 100% (versus 42% to 62% and 95% to 99% by radioactive I-131).[41] However, the combined sensitivity of both FDG-PET and I-131 imaging is 86% to 100%. This suggests that the low sensitivities of both FDG-PET and I-131 may be due to the complementary nature of these 2 radiopharmaceuticals. It is hypothesised that iodine metabolism is present in most well-differentiated thyroid cancer cells and FDG metabolism in less differentiated cell types. It is reported that FDG is more sensitive in detecting cervical metastasis and less so in lung metastasis than I-131.[42] Data in the literature and local experience suggest that cell type differentiation may be a more important factor. It is recommended that I-131 under TSH-stimulated state should be the conventional follow-up imaging modality of choice. In case of elevated thyroglobulin with negative I-131 findings, or when there is clinical suspicion even in a negative thyroglobulin status, FDG-PET imaging is indicated (although recently, redifferentiation of the cancer cells by using 13-cis-retinoic acid has been tried).[43,44]

Urological Tumours

The detection of urological tumours (prostate carcinoma, renal cell carcinoma and bladder carcinoma) is compromised by the presence of urinary FDG activities in the outflow system. In some cases, the small size of early and low-grade prostate malignant nodules is below the resolution of the PET scanner. FDG-PET is not a recommended investigation for primary tumour determination, although metastases and locoregional recurrence from these tumours can be effectively revealed by FDG-PET. Imaging accuracy may be improved by bladder catheterisation or post-diuretic delayed imaging. Recent PET imaging with ^{11}C acetate and ^{11}C choline have been found useful in these tumours because these tracers have no urinary excretion and the tumour-to-background ratio is higher than that of FDG.[45-48] In many Asian countries, the incidence of prostate malignancy has an upward trend, similar to the incidence of breast cancer in females. The need for other PET tracers will continue to rise.

Hepatocellular Carcinoma (HCC)

HCC is one of the leading cancers in many Asian countries and is ranked even higher in the list of cancer deaths in the last few years. However, it is reported that 30% to 50% of primary HCC are not FDG-avid or are only mildly avid.[49] The reason is that there is an abundant amount of the enzyme glucose-6-phosphatase in the normal liver and in certain types of HCC. This leads to dephosphorylation of FDG-6-phosphate and "leakage" of FDG back to the circulation. Recent research has found encouraging results in the use of ^{11}C acetate to assess the kinetics and uptake characteristics of fatty acid synthesis in these tumours. It was found that ^{11}C acetate and FDG are complementary to each other in the detection of HCC.[50] The individual tracer avidity depends on the differentiation of the HCC cell types. Well-differentiated HCC tends to show negative uptake on FDG-PET but positive uptake on ^{11}C acetate (Fig. 5). Poorly-differentiated HCC demonstrates a reverse uptake pattern using these 2 tracers. Moderately-differentiated HCC may show uptake of both tracers either in the same or different parts of the tumour. In this study, all the HCC lesions missed by FDG (false negative) are detected by ^{11}C acetate. This PET tracer may function as a complement to FDG in the detection of HCC and characterise the molecular aspect of tumour cell differentiation. In conjunction with FDG, dual tracer evaluation may provide valuable information to the differential diagnosis in the evaluation of liver masses.

The drawback of all ^{11}C products is the need for an on-site cyclotron because of the short half-life of 20 minutes. However, it is still possible to deliver 1 or 2 doses of these short-acting radiopharmaceuticals in some cities in Asia such as Hong Kong and Singapore because a satellite hospital may be within a short driving distance from the

cyclotron and PET radiopharmacy.

Tumours of Clear Cell (Signet Ring, Mucinous Cell) Pathology

Some studies have shown a positive correlation between tumour FDG uptake and cellularity and a negative correlation with the amount of mucin.[51] The amount of FDG uptake may be very low in hypocellular tumours and tumours with abundant mucin. We also observe that FDG-PET has a fair sensitivity in primary tumours with signet ring pathology and in tumours that are lipid-rich (such as liposarcoma with a high lipomatous content), secretory, or histiocytoid. Knowledge of the limitation of this tracer is important to avoid false negative detection, even with the use of PET-CT.

Non-Oncology

FDG-PET in the Investigation of Pyrexia of Unknown Origin

One disease category where the "disadvantage" of FDG-PET can become an "advantage" is the non-specific accretion of infective/inflammatory lesions for FDG. Except for TB, many infective/inflammatory lesions have a maximum SUV <2.5, and the pattern of involvement usually gives clues to differentiate an infective/inflammatory cause from real malignancy. From past experience with request for evaluation of pyrexia of unknown origin (PUO), about 20% to 30% of these cases showed positive findings which were later confirmed by surgery, biopsy or clinical follow-up. These cases include occult lung cancer, pulmonary and peritoneal TB, arteritis, phaeo-chromocytoma, ruptured appendicitis, Castleman's disease, mixed connective tissue disease, diffuse carcinomatosis of unknown primary and treated subacute endocarditis with distant sources of infection (Fig. 6). In about 70% of the requested cases for investigation of PUO, the nature of fever remains obscure. However, clinical follow-up has a high probability of spontaneous resolution of fever in some of these patients. It appears that a negative FDG-PET may also have a reasonably favourable prognosis. Stumpe et al[52] demonstrated 96% sensitivity in using FDG-PET for detection of soft tissue infection. The specificity was variable, 70% to 90%, due to the presence of multi-focal and multi-organ infectious sites in some cases, which were difficult to report on a lesion basis or body region basis.

Myocardial Viability

FDG-PET remains the gold standard for assessing myocardial viability in cardiac patients with fixed perfusion abnormalities and a history of infarct. The literature reports a variable range of accuracies (sensitivity ranging from 70% to 100% and specificity ranging from 30% to 90%) on the ability of PET to predict improvement in function after revascularisation.[53] This high variation can be attributed to a combination of differences in imaging equipment, perfusion tracers, metabolic status, data analysis and interpretation of results. There is a need to standardise the imaging protocol and methodology. With the use of PET-CT, the evaluation of the heart becomes another great challenge. Theoretically, the motion of the heart renders attenuation correction inaccurate. However, after a reasonable number of clinical trial and follow-up, assessment of myocardial viability with attenuation correction appears technically valid. This is presumably related to averaging effects. However, further confirmation requires a larger scale of clinical trial and technical support. Currently, there is lack of commercial software support for PET-CT gated acquisition, quantitative analysis, attenuation correction and graphical display for evaluation of myocardial viability. Therefore, all these factors point to the need for technical improvement.

Conclusion

The above discussion summarises some selective indications for PET in disease management and its merits and limitations when applied to the specific disease spectrum in Asia. FDG is far from being a universal tracer; yet its simplicity is also a beauty in the art of medical imaging. There are many other PET radiopharmaceuticals that are currently being researched for their usefulness in probing various aspects of disease kinetics. In the past few years, PET has gone through a cycle of practical trial in many Asian countries. The most often question posed in the past was whether PET could have an incremental value over other conventional imaging modalities. A direct statistical comparison between anatomical imaging and functional imaging is not always possible since their principles and mechanisms of disease detection are so different (although this is the only objective way to express scientific data). With the emergence of PET-CT, the discussion on the difference between functional/molecular imaging and anatomical imaging becomes irrelevant because they are clearly complementary. Co-registration of functional and anatomical images has become the main stream of medical imaging. With the understanding of individual disease prevalence in Asia and its detection accuracy by PET as discussed above, it can be easily perceived that the future of PET rests on a joint effort of radiopharmaceutical research and sharing of experience. When the cost-effectiveness of PET imaging becomes optimised, and the development of even faster scanners in the near future, PET-CT imaging is expected to reach a utility level as common as any imaging modality in Asia.

REFERENCES

1. Lowe VJ, Fletcher JW, Gobar L, Lawson M, Kirchner P, Valk P, et al. Prospective investigation of positron emission tomography in lung nodules. J Clin Oncol 1998;16:1075-84.

2. Gupta NC, Maloof J, Gunel E. Probability of malignancy in solitary pulmonary nodules using fluorine-18-FDG and PET. J Nucl Med 1996;37:943-8.

3. Bury T, Dowlati A, Paulus P, Corhay JL, Benoit T, Kayembe JM, et al. Evaluation of the solitary pulmonary nodule by positron emission tomography imaging. Eur Respir J 1996;9:410-4.

4. Bury T, Paulus P, Dowlati A, Corhay JL, Weber T, Ghaye B, et al. Staging of the mediastinum: value of positron emission tomography imaging in non-small cell lung cancer. Eur Respir J 1996;9:2560-4.

5. Guhlmann A, Storck M, Kotzerke J, Moog F, Sunder-Plassmann L, Reske SN. Lymph node staging in non-small cell lung cancer: evaluation by [18F]FDG positron emission tomography (PET). Thorax 1997;52: 438-41.

6. Lewis P, Griffin S, Marsden P, Gee T, Nunan T, Malsey M, et al. Whole-body F-18 fluorodeoxyglucose positron emission tomography in preoperative evaluation of lung cancer. Lancet 1994;344:1265-6.

7. Valk PE, Pounds TR, Hopkins DM, Haseman MK, Hofer GA, Greiss HB, et al. Staging non-small cell lung cancer by whole-body positron emission tomographic imaging. Ann Thorac Surg 1995;60: 1573-82.

8. Strauss LG, Conti PS. The applications of PET in clinical oncology. J Nucl Med 1991;32:623-50.

9. Kurasawa T. The coexistence of pulmonary tuberculosis and lung cancer [Japanese]. Nippon Rinsho 1998;56:3167-70.

10. Kim YI, Goo JM, Kim HY, Song JW, Im JG. Coexisting bronchogenic carcinoma and pulmonary tuberculosis in the same lobe: radiologic findings and clinical significance. Korean J Radiol 2001;2:138-44.

11. Liu RS, Feng HR, Chang CF, Liao CP, Yeh SQ, SH. Combined F-18 FDG and ^{11}C acetate PET imaging in diagnosis of pulmonary tuberculosis. J Nucl Med 2002;43:127P.

12. Hoh CK, Glaspy J, Rosen P, Dahlbom M, Lee SJ, Kunkel L, et al. Whole-body FDG-PET imaging for staging of Hodgkin's disease and lymphoma. J Nucl Med 1997;38:343-8.

13. Moog F, Bangerter M, Diederichs CG, Guhlmann A, Kotzerke J, Merkle E, et al. Lymphoma: role of whole-body 2-deoxy-2-[F-18]fluoro-D-glucose (FDG) PET in nodal staging. Radiology 1997;203:795-800.

14. Zinzani PL, Chierichetti F, Zompatori M, Tani M, Stefoni V, Garraffa G, et al. Advantages of positron emission tomography (PET) with respect to computed tomography in the follow-up of lymphoma patients with abdominal presentation. Leuk Lymphoma 2002;43:1239-43.

15. Pilipshen SJ, Heilweil M, Quan SH, Sternberg SS, Enker WE. Patterns of pelvic recurrence following definitive resections of rectal cancer. Cancer 1984;53:1354-62.

16. Valk PE, Abella-Columna E, Haseman MK, Pounds TR, Tesar RD, Myers RW, et al. Whole-body PET imaging with [18F]fluorodeoxyglucose in management of recurrent colorectal cancer. Arch Surg 1999;134: 503-13.

17. Schiepers C, Penninckx F, De Vadder N, Merckx E, Mortelmans L, Bormans G, et al. Contribution of PET in the diagnosis of recurrent colorectal cancer: comparison with conventional imaging. Eur J Surg Oncol 1995;21:517-22.

18. Akhurst T, Larson SM. Positron emission tomography imaging of colorectal cancer. Semin Oncol 1999;26:577-83.

19. Meta J, Seltzer M, Schiepers C, Silverman DH, Ariannejad M, Gambhir SS, et al. Impact of 18F-FDG PET on managing patients with colorectal cancer: the referring physician's perspective. J Nucl Med 2001;42: 586-90.

20. Kao CH, ChangLai SP, Chieng PU, Yen RF, Yen TC. Detection of recurrent or persistent nasopharyngeal carcinomas after radiotherapy with 18-fluoro-2-deoxyglucose positron emission tomography and comparison with computed tomography. J Clin Oncol 1998;16:3550-5.

21. Tsai MH, Shiau YC, Kao CH, Shen YY, Lin CC, Lee CC. Detection of recurrent nasopharyngeal carcinomas with positron emission tomography using 18-fluoro-2-deoxyglucose in patients with indeterminate magnetic resonance imaging findings after radiotherapy. J Cancer Res Clin Oncol 2002;128:279-82.

22. Kao CH, Hsieh JF, Tsai SC, Ho YJ, Yen RF, ChangLai SP, et al. Comparison of 18-fluoro-2-deoxyglucose positron emission tomography and computed tomography in detection of cervical lymph node metastases of nasopharyngeal carcinoma. Ann Otol Rhinol Laryngol 2000;109: 1130-4.

23. Nishioka T, Shiga T, Shirato H, Tsukamoto E, Tsuchiya K, Kato T, et al. Image fusion between 18FDG-PET and MRI/CT for radiotherapy planning of oropharyngeal and nasopharyngeal carcinomas. Int J Radiat Oncol Biol Phys 2002;53:1051-7.

24. Bohuslavizki KH, Klutmann S, Kroger S, Sonnemann U, Buchert R, Werner JA, et al. FDG PET detection of unknown primary tumors. J Nucl Med 2000;41:816-22.

25. Sheikholeslam-zadeh R, Choufani G, Goldman S, Hassid S. Unknown primary detected by FDG-PET. A review of the present indications of FDG-PET in head and neck cancers. Acta Otorhinolaryngol Belg 2002;56:77-82.

26. Regelink G, Brouwer J, de Bree R, Pruim J, van der Laan B F, Vaalburg W, et al. Detection of unknown primary tumours and distant metastases in patients with cervical metastases: value of FDG-PET versus conventional modalities. Eur J Nucl Med Mol Imaging 2002;29: 1024-30.

27. Johansen J, Eigtved A, Buchwald C, Theilgaard S A, Hansen H S. Implication of 18F-fluoro-2-deoxy-D-glucose positron emission tomography on management of carcinoma of unknown primary in the head and neck: a Danish cohort study. Laryngoscope 2002;112:2009-14.

28. Esik O, Szentirmay Z, Marian T, Kasler M, Agoston P, Lengyel E, et al. PET scan and double-independent pathologic investigations effectively support the detection of occult primary tumors. [Hungarian] Orv Hetil 2002;143:1262-5.

29. Rades D, Kuhnel G, Wildfang I, Borner AR, Schmoll HJ, Knapp W. Localised disease in cancer of unknown primary (CUP): the value of positron emission tomography (PET) for individual therapeutic management. Ann Oncol 2001;12:1605-9.

30. Choi JY, Lee KH, Shim YM, Lee KS, Kim JJ, Kim SE, et al. Improved detection of individual nodal involvement in squamous cell carcinoma of the esophagus by FDG PET. J Nucl Med 2000;41:808-15.

31. Flanagan FL, Dehdashti F, Siegel BA, Trask DD, Sundaresan SR, Patterson GA, et al. Staging of esophageal cancer with 18F-fluoro-deoxyglucose positron emission tomography. AJR Am J Roentgenol 1997;168:417-24.

32. Rice TW. Clinical staging of esophageal carcinoma. CT, EUS, and PET. Chest Surg Clin N Am 2000;10:471-85.

33. Avril N, Bense S, Ziegler SI, Dose J, Weber W, Laubenbacher C, et al. Breast imaging with fluorine-18-FDG PET: quantitative image analysis. J Nucl Med 1997;38:1186-91.

34. Crippa F, Agresti R, Seregni E, Greco M, Pascali C, Bogni A, et al. Prospective evaluation of fluorine-18-FDG PET in presurgical staging of the axilla in breast cancer. J Nucl Med 1998;39:4-8.

35. Hoh C K, Schiepers C. 18-FDG imaging in breast cancer. Semin Nucl Med 1999;29:49-56.

36. Chia KS, Lee JJ, Wong JL, Gao W, Lee HP, Shanmugaratnam K. Cancer incidence in Singapore, 1998 to 1999. Ann Acad Med Singapore 2002;31:745-50.

37. Suarez M, Perez-Castejon MJ, Jimenez A, Domper M, Ruiz G, Montz R, et al. Early diagnosis of recurrent breast cancer with FDG-PET in patients with progressive elevation of serum tumor markers. Q J Nucl Med 2002;46:113-21.

38. Dehdashti F, Flanagan FL, Mortimer JE, Katzenellenbogen JA, Welch

MJ, Siegel BA. Positron emission tomographic assessment of "metabolic flare" to predict response of metastatic breast cancer to antiestrogen therapy. Eur J Nucl Med 1999;26:51-6.

39. Wahl RL, Zasadny K, Helvie M, Hutchins GD, Weber B, Cody R. Metabolic monitoring of breast cancer chemohormonotherapy using positron emission tomography: initial evaluation. J Clin Oncol 1993;11:2101-11.

40. Ho CL, Dehdashti F, Griffeth LK, Buse PE, Balfe DM, Siegel BA. FDG-PET evaluation of indeterminate pancreatic masses. J Comput Assist Tomogr 1996;20:363-9.

41. Feine U, Lietzenmayer R, Hanke JP, Held J, Wohrle H, Muller-Schauenburg W. Fluorine-18-FDG and iodine-131-iodide uptake in thyroid cancer. J Nucl Med 1996;37:1468-72.

42. Wong CO, Dworkin HJ. Role of FDG PET in metastatic thyroid cancer. J Nucl Med 1999;40:993-4.

43. Simon D, Korber C, Krausch M, Segering J, Groth P, Gorges R, et al. Clinical impact of retinoids in redifferentiation therapy of advanced thyroid cancer: final results of a pilot study. Eur J Nucl Med Mol Imaging 2002;29:775-82.

44. Gruning T, Tiepolt C, Zophel K, Bredow J, Kropp J, Franke WG. Retinoic acid for redifferentiation of thyroid cancer – does it hold its promise? Eur J Endocrinol 2003;148:395-402.

45. Shreve P, Chiao PC, Humes HD, Schwaiger M, Gross MD. Carbon-11-acetate PET imaging in renal disease. J Nucl Med 1995;36:1595-601.

46. Fricke E, Machtens S, Hofmann M, Van Den Hoff J, Bergh S, Brunkhorst T, et al. Positron emission tomography with (11)C-acetate and (18)F-FDG in prostate cancer patients. Eur J Nucl Med Mol Imaging 2003;30:607-11.

47. Hautzel H, Muller-Mattheis V, Herzog H, Roden W, Coenen HH, Ackermann R, et al. The (11C) acetate positron emission tomography in prostatic carcinoma. New prospects in metabolic imaging [German]. Urologe A 2002;41:569-76.

48. Oyama N, Miller TR, Dehdashti F, Siegel BA, Fischer KC, Michalski JM, et al. [11]C acetate PET imaging of prostate cancer: detection of recurrent disease at PSA relapse. J Nucl Med 2003;44:549-55.

49. Okazumi S, Isono K, Enomoto K, Kikuchi T, Ozaki M, Yamamoto H, et al. Evaluation of liver tumors using fluorine-18-fluorodeoxyglucose PET: characterization of tumuor and assessment of effect of treatment. J Nucl Med 1992;33:333-9.

50. Ho CL, Yu SC, Yeung DW. 11C-acetate PET imaging in hepatocellular carcinoma and other liver masses. J Nucl Med 2003;44:213-21.

51. Berger KL, Nicholson SA, Dehdashti F, Siegel BA. FDG PET evaluation of mucinous neoplasms: correlation of FDG uptake with histopathologic features. AJR Am J Roentgenol 2000;174:1005-8.

52. Stumpe KD, Dazzi H, Schaffner A, von Schulthess GK. Infection imaging using whole-body FDG-PET. Eur J Nucl Med 2000;27:822-32.

53. Knuuti J, Schelbert HR, Bax JJ. The need for standardisation of cardiac FDG PET imaging in the evaluation of myocardial viability in patients with chronic ischaemic left ventricular dysfunction. Eur J Nucl Med Mol Imaging 2002;29:1257-66.