Combined Positron-emission Tomography–Computed Tomography: Merging Form with Function

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ABSTRACT

Combined positron-emission tomography–computed tomography is becoming a widely used imaging technique in nuclear medicine and nuclear radiology. Its unique dual functional-anatomical imaging capacity is highly complementary to conventional imaging, and it has become an integral part of the multidisciplinary clinical management of cancer in Hong Kong. The clinical value, efficacy, limitations, and cost-effectiveness of this technology are important pieces of information for referring physicians. This article briefly describes the basis of positron-emission tomography and combined positron-emission tomography–computed tomography, and reviews the current consensus on their clinical application in the diagnosis and treatment of cancer patients.

Key Words: Fluorodeoxyglucose F18; Neoplasm staging; Radionuclide imaging; Tomography, X-ray computed

INTRODUCTION

Combined positron-emission tomography (PET)–computed tomography (CT) is now possible with the recently introduced combined PET/CT scanner, and it has swept the medical field worldwide as a state-of-the-art imaging modality. Originally designed for oncological surveillance, the PET/CT scanner integrates functional and anatomical imaging, and it has created a rapid growth in the clinical demand for PET/CT imaging. In addition to offering anatomical imaging modalities, PET/CT assesses physiology and biochemistry. The PET/CT scanner thus has the potential of allowing earlier, more sensitive detection of disease.

WHAT IS PET/CT?

Janus: the Roman God with 2 Heads

In explaining what PET/CT is, we can refer to Janus: an ancient Roman god who is commonly depicted with 2 faces to represent contemplation on the happenings of the past while looking forward to the new. Similarly, the 2 ‘heads’ of the integrated PET/CT scanner offer the combined advantages of PET and CT.

PET is a quantitative method of determining the location of positron-emitting isotopes at a particular time. The method provides quantitative in vivo measurement of functional processes of the body with a spatial resolution that is superior to that of other imaging techniques used in nuclear medicine. In conjunction with CT, optimal interpretation can be made by coregistering structural and functional information. The combined PET/CT scanner is a single machine with the hardware combination of a dedicated PET scanner and a high-end CT scanner. This ultrafast multidetector provides rapid attenuation-correction with good imaging statistics, and eliminates the need to replace rod sources. It also shows excellent anatomical alignment and image coregistration, thereby enhancing the detectability of lesions in physiological images.1 CT images either must be of diagnostic quality or must be used solely for the purpose of anatomical location and attenuation-correction.

There is some controversy regarding the need for iodinated contrast agent in CT. At our institution, we have elected to add ‘diagnostic’ CT acquisition when clinically indicated after a standard PET/CT study. Since the introduction of the first PET/CT scanner in 1998, many...
studies have been conducted to explore the clinical roles of PET/CT in patient treatment and outcome. PET/CT is more effective than conventional anatomical imaging or PET alone in locating lesions and detecting abnormal uptake. The hybrid imaging method has been shown to lead to considerable change in impression in 20% of oncological cases, to affect treatment in 14% patients with cancer, and to improve specificity of lesion detection. Nonetheless, coregistration can lead to imaging errors owing to mismatches in PET and CT data sets. Mismatch is more pronounced at lung bases, the lung periphery, and the liver dome because of non-synchronous respiratory motion.

2-Fluoro-2-deoxy-D-glucose

2-Fluoro-2-deoxy-D-glucose (FDG) labelled with fluorine 18 has already been dubbed the “molecule of the century” and is the most widely used PET agent. The radioactive fluorine molecule in FDG replaces a hydroxyl (-OH) group of glucose and is produced in a cyclotron through the proton bombardment of oxygen 18–labelled water. FDG is a glucose analogue that competes with glucose in glycolysis after facilitated transport into normal and tumour cells. The phosphorylated form of FDG, however, is not further metabolised. It also has a low membrane permeability; hence, it becomes trapped and accumulates within cells with low concentrations of glucose-6-phosphatase, such as tumour cells, where they emit positrons that are detected by PET. Various types of tumours have increased metabolic rates and increased glycolysis compared with normal cells. The subsequent increased glucose or FDG uptake is related in part to an increased number of glucose transporter proteins at the cell membrane (mainly, but not exclusively, the GluT1 molecule).

‘SUV’: Standardised Uptake Value or Silly Unreliable Value?
The standardised uptake value (SUV) is defined as the tissue concentration of tracer, as measured by a PET scanner, divided by the activity injected per unit of body weight. The SUV is used to standardise and quantify regional tracer activity, and is calculated with the following formula:

\[ \text{SUV} = \frac{\text{FDG}_{\text{region}}}{(\text{FDG}_{\text{dose}}/\text{WT})} \]

where
- \( \text{FDG}_{\text{region}} \) = (decay-corrected) regional tissue activity concentration
- \( \text{FDG}_{\text{dose}} \) = injected tracer dose (decay-corrected)
- WT = body weight (in kg)

The main problem with the SUV is that it is subject to too many variables that are not controlled or even taken into account in most studies. SUV may be varied in different populations because SUV is normalised to body weight and, therefore, depends on the patient sample. SUV also depends on the time of calculation and glucose levels.

Furthermore, the calculated SUV may be slightly higher when using CT attenuation-correction than when using no correction, and caution should be taken when comparing data between CT and separate transmission scans.

SUV can be used as an aid but does not appear to perform better than an experienced reader to differentiate between tumour and non-tumour uptake. SUV is useful when pre- and post-therapy scans are compared. It appears to be an independent prognostic sign to monitor therapy. More meticulous quantitative measurements, including simplified kinetic analysis, Patlak graphical analysis, and even kinetic modelling, have been mentioned in the literature, but they are not commonly applied in routine clinical practice.

Is PET/CT Safe?
There is no absolute contraindication for the use of PET/CT, but special caution should be taken for patients with diabetes mellitus or a history of allergy. Taking a pertinent clinical history, including information about pregnancy, breastfeeding, diabetes mellitus, and allergies to iodine-based CT contrast agents, is vital for appropriate patient preparation. This preparation involves modifying fluid intake, diet, drug treatment, and other factors. If the patient has diabetes mellitus, a diet and exercise regimen should be started and glucose levels should be monitored.
PET/CT imaging should observe the ‘ALARA’ (as low as reasonably achievable) principle to decrease radiation exposure. The effective dose for the patient in each whole-body PET/CT examination is 15 to 25 mSv. A dose of 3 to 15 mSv is attributable to CT radiation, whereas a dose of 9 to 10 mSv is due to PET using 10 mCi FDG. The mean individual natural radiation dose in Hong Kong is approximately 2.8 mSv per year.

The urinary bladder wall receives the largest doses of radiation, followed by the myocardium. Patients should be encouraged to drink fluids and repeatedly empty their bladder after the study to decrease the radiation dose to the bladder. The excess risk of lifetime fatal cancer is exceedingly small and is usually more than offset by the benefit gained from the PET/CT examination.

CLINICAL APPLICATIONS OF FDG-PET/CT

Differences exist between the East and West in disease spectrum and cancer pattern. Asian countries see a greater prevalence than western countries in certain neoplasms — namely, hepatocellular carcinoma, urological carcinoma, gastric cancer, mucinous and clear-cell gastrointestinal tumours, neuroendocrine tumours, and well-differentiated thyroid cancer. These tumours are relatively low in FDG avidity. The whole-body approach used in PET/CT imaging allows broad coverage of the multiple organs, systems, and soft tissues, thereby allowing detection of skeletal disease without the need for a separate bone scan. This advantage makes whole-body PET/CT preferable to targeted examinations such as magnetic resonance imaging and CT.

Lung Cancer

Lung cancer is the leading cause of cancer death in Hong Kong. Solitary pulmonary nodule is usually identified on chest radiographs that are obtained as a part of a routine check-up or preoperative evaluation. Many studies have demonstrated the usefulness of PET in characterising pulmonary nodules. The reported sensitivity and specificity of PET in differentiating benign and malignant lesions have been uniformly high. Sensitivity, specificity, and accuracy have been reported to range from 82% to 100%, 75% to 100%, and 79% to 94%, respectively.

PET/CT is a cost-effective means of assessing solitary pulmonary nodule and of staging non–small-cell lung cancer. Most primary and metastatic diseases in the lung will be positive on the FDG-PET/CT scan (Figure 1). Sensitivity and specificity are both about 90% (versus 60% for CT alone). However, most primary pulmonary carcinoid tumours and some bronchoalveolar carcinomas have low FDG avidity. PET/CT is helpful to locate FDG-avid lesions in the mediastinum, as well as to locate chest wall abnormalities. The method can differentiate atelectasis and scars from viable tumours and can usually distinguish adrenal metastasis from benign conditions.

FDG-PET and FDG-PET/CT are more cost-effective than CT alone in health management. Notably, the prognostic value of PET imaging is its improvement in the detection rates of local and distant metastases in patients with non–small-cell lung carcinoma, compared with those of CT alone. Furthermore, compared with CT, PET/CT shows an improvement in the diagnostic accuracy of the staging of non–small-cell lung cancer. In one study, FDG-PET imaging changed or influenced management decisions in 67% of patients with non–small-cell lung cancer. Tumour FDG uptake, as measured by SUV and the tumour size, can indicate prognosis in non–small-cell lung cancer.

However, most granulomatous processes, including tuberculosis and acute infections, are FDG-avid and can hence yield false-positive results. Postsurgical or postradiation changes can have high FDG activity for 6 weeks. Therefore, caution should be taken when interpreting PET or PET/CT images, particularly in our locality, where tuberculosis is still common.

Current data suggest that once PET/CT becomes more widely available, it will be the preferred approach for determining the stage of disease in non–small-cell lung cancer. PET/CT better assesses the status of disease and stratifies prognosis than does conventional staging, and it may become the new standard approach to imaging in patients with lung cancers. PET/CT may also be an important modality for directing radiotherapy of lung cancer in the near future.

Colorectal Carcinoma

Accurate non-invasive detection of inoperable disease plays a pivotal role in selecting patients who would benefit from surgery. In comparison with PET alone, PET/CT has greater diagnostic value in terms of enhanced lesion characterisation (30%), better location (25%), and improvement in TNM staging (by 78% to 89%). Although the sensitivity of PET and PET/CT in
detecting primary colonic carcinoma is high, the 2 methods perform poorly in defining regional lymph node involvement. But they have a higher sensitivity and specificity than CT alone for the detection of hepatic metastasis.\textsuperscript{22,23} False-positive results can be due to abscesses, fistulas, diverticulitis, and, occasionally, adenomatous polyps. Many studies have demonstrated a strong role for PET or PET/CT in identifying recurrences of colorectal cancer (Figure 2).\textsuperscript{24-27} The sensitivity of PET or PET/CT is about 90% and the specificity is greater than 70%, which are both higher than values for CT. A high rate of false-negative findings has been reported for mucinous or clear-cell adenocarcinoma, as well as for small (<1 cm) necrotic lesions.\textsuperscript{25} The accuracy of PET or PET/CT is 90% to 95% in differentiating postoperative changes from local recurrence. For the detection of extrahepatic metastasis, the sensitivity of PET/CT is better than that of CT alone; PET is particularly helpful for identifying lesions in the abdomen, retroperitoneum, and pelvis. The specificity of PET is also greater than that of CT at all sites except the retroperitoneum. PET results have been shown to change the surgical management in 28% of patients and to help avoid unnecessary surgery in about 67% of patients.\textsuperscript{27} At present, PET/CT is particularly indicated in the following situations:

\textbf{Figure 1.} Axial positron-emission tomography (PET)–computed tomography (CT) images of a patient with non–small-cell carcinoma. A large primary tumour in the right lung is visible in the (a) CT image (white arrow), (b) attenuation-corrected fluorodeoxyglucose (FDG)-PET image (black arrow), (c) fused PET/CT image (open arrow), and (d) non-attenuation-corrected FDG-PET image (the small arrow indicates a necrotic centre of low FDG metabolism).
(1) When there is a rising serum carcinoembryonic antigen level in the absence of a known cause;
(2) When there is an equivocal structural lesion without a clear explanation;
(3) As a screening technique before curative resection of a recurrent tumour;
(4) To differentiate post-treatment changes from recurrent or residual disease; and
(5) To monitor therapy, such as radiotherapy and chemotherapy, as well as regional treatment such as chemoembolisation and cryosurgery.28,29

**Other Gastrointestinal Tumours**

**Oesophageal Carcinomas**
In Hong Kong, many patients undergoing surgery for oesophageal cancers are found to have occult metastasis. Frequent diagnosis at advanced-stage (III or IV) disease leads to poor patient survival. PET/CT can characterise equivocal lesions through anatomical imaging: it can improve N and M staging by detecting unsuspected metastases and prevent unnecessary surgery that carries high morbidity and mortality.30,31 In addition, FDG can predict histological response during induction therapy, which is critical in identifying surgical candidates.32 Finally, the response of neoadjuvant chemoradiation therapy, as assessed by serial FDG-PET, is strongly correlated with the pathological response and survival in locally advanced oesophageal tumours.33

**Hepatocellular Carcinoma**
The accumulation of FDG in hepatocellular carcinoma is variable owing to varying degrees of glucose-6-phosphatase activity in this tumour. Approximately 50% to 60% of these tumours are FDG-avid, whereas 40% to 50% yield false-negative results on PET imaging.34 Therefore, FDG-PET or PET/CT is not recommended
for the evaluation of focal lesions in patients with chronic hepatitis, or for hepatocellular carcinoma screening in a population at high risk for this cancer. Carbon 11–tagged acetate has been advocated as one of the dual PET tracers for hepatocellular carcinoma. For patients with FDG-avid hepatocellular carcinoma, PET/CT imaging may be helpful for staging and monitoring therapy.

**Cholangiocarcinoma**

PET/CT shows high sensitivity (70%) for the detection and location of nodular-type cholangiocarcinoma. It can detect unsuspected metastases and aid in monitoring therapy in patients with nodular cholangiocarcinoma. PET/CT shows poor sensitivity for the detection of infiltrating cholangiocarcinoma. Small ampullary carcinoma and mucinous cholangiocarcinoma can also yield false-negative results. False-positive results can be caused by inflammatory changes secondary to the presence of a biliary stent, a hepatic abscess, cholangitis, or cholecystitis.

**Pancreatic Carcinoma**

FDG-PET/CT imaging is superior to conventional morphological imaging for the detection of pancreatic cancer. PET/CT is particularly helpful for diagnosis in patients with suspected pancreatic cancer when CT has failed to identify a mass or when fine-needle biopsies are non-diagnostic. PET/CT has a particularly important role in diagnosis, TNM staging, and therapy monitoring among patients with pancreatic carcinoma. In view of the probable decreased sensitivity of the combined method when used among patients with hyperglycaemia, image acquisition should be performed under controlled metabolic conditions and in the absence of acute inflammatory abdominal disease, such as pancreatitis, stenting, or cholangitis. Endocrine pancreatic tumours, such as islet cell tumours, are usually negative for FDG uptake.

**Breast Cancer**

Breast cancer is one of the main causes of cancer death among women in Hong Kong. Since 1994, the breast has been the leading site for new cancers, primarily among women in the 40- to 64-year age group. Surgical management has become progressively more non-invasive and less surgically radical. Early detection and intervention remains the key to the successful reduction in patient morbidity and mortality.

Because of the limitations of PET and PET/CT to detect small cancers, PET/CT is not recommended for screening or routinely evaluating primary breast tumours. Nonetheless, PET and PET/CT allow accurate detection of breast cancer, with a sensitivity of 64% to 96%, specificity of 73% to 100%, and accuracy of 70% to 79%. The 2 methods are particularly useful in screening high-risk patients with dense breasts or after augmentation-mammoplasty. When staging early-stage breast cancer, FDG-PET cannot detect microscopic metastasis or determine the number of axillary nodes involved; these shortcomings mean that 5% to 20% patients have understaged disease and the prognostic value is lost. Therefore, location and biopsy of the sentinel node remain the method of choice to obviate more radical lymph node dissection. Lymphoscintigraphy and gamma probe detection of the sentinel node have been shown to be reliable and reproducible in identifying the diseased lymphatic drainage. However, PET or PET/CT still has an important role in investigating patients who have inner-quadrant breast lesions, which may affect the internal mammary chains, or when other imaging results seem equivocal. To stage locally advanced breast tumours that have a high incidence of metastases, PET or PET/CT is recommended. The 2 methods have been advocated as the main techniques to replace multiple modalities for restaging and monitoring therapy in local advanced and metastatic breast disease when a change in treatment is contemplated.

**Head and Neck Tumours**

Nasopharyngeal carcinoma is a common cancer in Hong Kong, China, Taiwan, and Singapore. The incidence among Chinese populations is 30 times that among Caucasians. Squamous-cell cancers form the vast majority of the extracranial head and neck malignancy (Figure 3). In contrast, non-squamous tumours of the extracranial head and neck comprise only less than 5% of all head and neck malignancies. Recent evidence shows that PET/CT imaging in patients with head and neck cancer improves the anatomical location of abnormalities and decreases equivocal findings on PET imaging. In one study, there was a change of patient care in 18% of patients following PET/CT. PET imaging is widely accepted as the imaging modality for the staging and follow-up of squamous-cell cancers. In comparison with anatomical imaging modalities, PET and PET/CT imaging are more accurate for the detection of neck nodal metastases and recurrent disease. The accuracy of PET imaging is superior to that of CT or magnetic resonance imaging.
As the specificity (91%) and positive predictive value (86%) of PET imaging are high, a positive PET/CT image indicates the need for neck dissection. PET/CT is useful for the detection of neck nodal metastases that have an unknown origin. In patients with recurrent head and neck carcinoma, PET and PET/CT imaging also have prognostic value.\textsuperscript{9,45,48,49}

There is variable diagnostic accuracy of PET imaging in detecting different types of non-squamous tumour of the extracranial head and neck. Preliminary results show that PET has a high sensitivity for detecting malignant salivary gland tumours. PET is also sensitive in detecting recurrent or residual well-differentiated follicular thyroid cancer, particularly Hürthle cell carcinomas that are negative on an iodine-131 scan. FDG-avid thyroid cancers have a poorer prognosis than FDG-negative tumours. Initial studies of FDG-PET show promise for imaging adenoid cystic carcinomas, sarcomas, and regional nodal metastases from melanomas.\textsuperscript{50}

**Lymphoma**

FDG uptake seems to correlate with cellular proliferation of lymphoma. In untreated lymphomas, the degree of FDG uptake is more severe in high-grade lymphomas than in low-grade disease. An unexpected sudden increase in FDG uptake in part or all of the known disease sites that may be enlarging in size during follow-up according to CT suggests transformation to a higher-grade tumour. PET/CT is recommended for staging lymphoma in addition to other conventional staging modalities, because it can detect additional nodal

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**Figure 3.** Images of multiple nodal metastases from squamous-cell carcinoma of the head and neck. Major areas of focally increased fluorodeoxyglucose metabolism (black arrows) correspond well to cervical sites of nodal recurrence. The maximum-intensity projection image (white arrow, bottom right) conveniently allows observation of the whole patient.
and extranodal lymphomatous lesions. The combined method can also assess bone marrow involvement, even if bone marrow biopsy results are negative. During chemotherapy, PET can identify the responders early in the course of treatment, thereby allowing appropriate alterations to be made in the chemotherapy regimen. Furthermore, PET or PET/CT can differentiate scars from persistent or recurrent tumours in residual masses after therapy and can allow improved discrimination of rebound thymic hyperplasia from viable lymphoma. Given the high incidence of lymphoma among HIV-positive patients, PET or PET/CT has an important role in differentiating lymphoma from toxoplasmosis in HIV-positive patients with cerebral lesions.

Because of the superior resolution of PET or PET/CT images compared with those obtained by gallium scintigraphy, PET or PET/CT is becoming the preferred method of evaluating patients with lymphoma. It is important to note that a negative PET or PET/CT scan does not exclude residual microscopic disease, and that chemotherapy with or without radiation should be completed as planned on the basis of histology and stage. PET and PET/CT are useful in staging and restaging disease, monitoring therapy, and detecting recurrence among patients with lymphoma. These methods allow good prediction of relapse before stem cell transplantation. A survey-based study shows that FDG-PET contributes to changes in clinical management in more than 40% of patients.

Genitourinary Tumours

FDG is excreted by the kidneys, and the high concentration of FDG in the urine obscures visualisation of structures adjacent to the collecting system and the bladder. FDG accumulates in most renal cancers and bladder carcinomas. High-grade tumours appear to have greater FDG uptake than do low-grade tumours. PET/CT is promising as a method of staging disease and monitoring therapy among patients with renal cell carcinomas that have a high FDG uptake. For prostatic cancer, however, both the primary tumour and pelvic lymph nodes are difficult to image because of the proximity of the bladder. In addition, uptake appears relatively low in prostatic cancer. Relatively high FDG uptake in benign prostatic hypertrophy increases the difficulty of differentiating benign from malignant prostatic lesions on PET/CT. In testicular cancer, PET/CT has a higher diagnostic accuracy than CT for staging and restaging, and should be the modality of choice for the assessment of a residual mass following chemotherapy. FDG-PET has also shown potential in cervical cancer imaging. PET/CT may offer benefits by way of the selection of appropriate recurrent cervical cancer patients for salvage therapy. For ovarian tumours, the role of PET/CT is still under investigation, but initial results are encouraging.

Future Role in Oncology

Thanks to advancements in technology and hybrid scanner design, new PET/CT scanners are more cost-effective and reliable than PET alone or the novel prototype. New applications, such as dynamic whole-body scans and the use of new PET tracers, including short-lived radioisotopes (e.g., carbon 11), are expected to be more readily available.

CONCLUSION

PET/CT is an advanced imaging technique that permits almost synchronous image acquisition and exact coregistration of anatomical and metabolic data. PET/CT is more effective than either PET alone or anatomical imaging in the precise location of neoplastic lesions. By playing a crucial role, not only in the detection and staging of cancer, but also in the design and monitoring of therapies, PET/CT will have a major impact on patient care, survival, and quality of life.

REFERENCES

1. Townsend DW, Carney JPJ, Yap JT, Hall NC. PET/CT today and tomorrow. J Nucl Med 2004;45(Suppl):4S-14S.
Combined Positron-emission Tomography—Computed Tomography


1139-1143.


63. Townsend DW, Beyer T. A combined PET/CT scanner: the path to true image fusion. Br J Radiol 2002;75(Suppl):24S-30S.

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