Positron emission tomography (PET) in endocrine tumours

Positron emission tomography (PET) has many clinical applications in oncology, neurology and cardiology. PET is widely available in developed countries, and has also become available in a number of middle-income countries, including South Africa. Commonly used PET radionuclides include fluorine-18, carbon-11, nitrogen-13 and oxygen-15, which are commonly found in organic chemistry and biochemistry. Undoubtedly the most important radiopharmaceutical used in PET scanning at present is [F-18]-FDG, which accumulates in many tumour cells. FDG PET imaging has some specific uses in the evaluation of patients with endocrine tumours. These include the detection of recurrent differentiated thyroid carcinoma in patients with a rising thyroglobulin level and negative iodine scan, and cases of recurrent medullary thyroid carcinoma with rising calcitonin levels. In parathyroid adenoma, FDG PET appears useful in cases where conventional nuclear medicine imaging is negative. For adrenal masses, FDG PET appears to be a highly accurate tool to distinguish benign from malignant lesions. The role of FDG PET in phaeochromocytomas, carcinoids and endocrine pancreatic tumours is probably limited to those that are less well differentiated and metabolically active. However, a future role for PET imaging in the detection of endocrine tumours, using more specific substrates, appears very promising.

Positron emission tomography (PET) has been a research tool since the 1970s. Clinical applications today are primarily in the fields of oncology, neurology and cardiology. In the developed world a rapid expansion in PET facilities has taken place, owing to a dramatic increase in oncological indications since the 1990s. Today PET is widely available in developed countries and has also become available in a number of middle-income countries, including South Africa.

PET is an imaging technique that utilises isotopes known as positron emitters. Because these isotopes have an excess of protons, their nuclei undergo $\beta^+$ decay. This results in the release of a positron, the anti-matter equivalent of an electron, and a neutrino. The positron moves a short distance in tissue before undergoing mutual annihilation with a nearby electron. Based on the energy-mass formula $E = mc^2$, the energy of the two particles is converted into two 511 KeV gamma rays that are released in opposite directions (Fig. 1).

**Fig. 1.** A proton-rich nucleus (1) undergoes $\beta^+$ decay with the conversion of a proton into a neutron, and the release of a positron (2) and an antineutrino. The positron undergoes mutual annihilation with an electron, resulting in the release of two 511 keV gamma rays in opposite directions (3). A ring of detectors on a PET scanner is then able to detect the two gamma rays, allowing the in vivo position of the isotope to be determined (4). (From Atlas of Clinical Positron Emission Tomography, reproduced courtesy of Hodder Education.)
A PET camera is a device designed to locate the isotope in vivo by detecting these two gamma rays. The PET camera normally consists of a number of rings of detectors which are able to detect the two gamma rays simultaneously, thus positioning the source of the radio-isotope along a line between the two points of detection. The detection of millions of these events enables a three-dimensional image of the distribution of the radio-isotope in the body to be created.

A variety of ‘PET cameras’ exist. At the top end of the range are dedicated PET-computed tomography (CT) scanners, currently costing approximately R15 million. These machines combine a top-end PET scanner with a CT scanner. The CT scanner firstly enables the improved anatomical localisation of areas of radiopharmaceutical concentration, and secondly allows rapid attenuation correction of PET images, which significantly increases patient throughput.¹ The improved anatomical localisation of PET lesions can often enhance the specificity of the technique, for example by distinguishing between normal physiological uptake in certain structures and abnormal pathological uptake in others. PET-CT scanning is therefore not a CT scan with a new sophisticated contrast agent, but rather the addition of the CT results in some improvement in the specificity of the PET scanning, and significantly increases patient throughput. As a result of the advantages offered by PET-CT systems, there is no longer any development of stand-alone PET systems. At the other end of the spectrum is so-called ‘gamma camera-based PET’ where a conventional two- or three-headed gamma camera is modified for the detection of positron emitters. While there is a decrease in the sensitivity of these machines, they have been shown to be able to produce similar results to dedicated PET scanners for some malignancies.² Probably an even more important drawback of these machines, however, is the prolonged imaging time required for the majority of studies, resulting in severe limitations to patient throughput. With PET-CT systems becoming increasingly affordable, their future role is likely to be limited.

**PET radiopharmaceuticals**

Commonly used PET radionuclides include fluorine-18, carbon-11, nitrogen-13 and oxygen-15. In contrast to most radio-isotopes used in conventional nuclear medicine, such as Tc-99m and I-123, these elements are commonly found in organic chemistry and biochemistry, simplifying the chemical design of biological tracers incorporating these tracers. The 110-minute half-life of F-18 still makes it possible for radiopharmaceuticals such as [F-18]-fluoro-deoxy-glucose (FDG) to be prepared at one site and transported to a hospital located at a remote site for PET imaging. The other radionuclides mentioned above, however, with half-lives of 20, 10 and 2 minutes respectively for C-11, N-13 and O-15, are too short-lived for this to be possible. A PET facility with access to the full diversity of possible radiopharmaceuticals therefore requires an on-site cyclotron with automated radiochemistry facilities for their preparation.

Undoubtedly the most important radiopharmaceutical used in PET scanning at present is [F-18]-FDG. As early as the 1920s it was known that tumours utilise more glucose than normal tissue.³ The increased concentration of glucose transporter proteins and hexokinase enzymes results in a relatively increased accumulation of FDG in a large number of tumours.⁴ FDG differs chemically from glucose in the absence of an oxygen atom and the addition of a fluorine-18 atom in position 2. This not only makes it possible to detect the molecule with a PET camera, but also alters its biochemical handling in vivo. Similarly to glucose, FDG is taken up into cells and under the influence of hexokinase can be phosphorylated to FDG-6-P. Glucose-6-phosphate can however be metabolised whereas FDG-6-phosphate cannot, and it cannot be converted back to FDG and released from the cell. The chemistry of FDG therefore results in its accumulation and concentration, particularly in tumour cells rich in glucose transporters and hexokinase. Uptake of FDG is therefore a marker of increased glucose metabolism which in itself is relatively nonspecific, typically being present in areas of inflammation or neoplasia.

**Performing an FDG PET scan**

Patients are normally prepared for FDG scanning by a 6-hour fast before the study, to enhance the non-insulin-dependent uptake of glucose by tumour tissue. Patients are encouraged to drink plenty of fluids to ensure adequate hydration. Diabetics need to have their blood glucose levels well controlled, but ideally no insulin should be administered within 4 hours of the scan. FDG is administered intravenously, with a normal adult typically receiving a dose of about 370 MBq. The patient is then allowed to relax in a comfortable environment for the next 60 - 90 minutes. Patients are discouraged from talking or chewing within 30 minutes of the injection to minimise uptake in head and neck muscles. In some cases a muscle relaxant may be administered. Furosemide can be administered 15 minutes post-injection to encourage renal clearance. Normal biodistribution of FDG results in uptake in the brain, heart, liver, gastro-intestinal tract and urinary system, and in muscles (Fig. 2). Scans are normally performed on an outpatient basis, and patients are able to leave immediately once the imaging has been completed.
While FDG PET imaging has a well-established role in a number of oncological conditions, including non-small-cell lung carcinoma, lymphoma, colon carcinoma and melanoma, it is also worth while examining its role in endocrine tumours. Endocrine tumours can be regarded as differing from those arising from many tissue types in certain respects. Firstly, endocrine tumours are often benign. Secondly, these tumours often present relatively early owing to symptoms resulting from the over-secretion of hormone(s). Owing to the relatively low glucose metabolism of many of the well-differentiated endocrine tumours, they are not particularly FDG-avid. This and the nonspecific nature of FDG PET scanning frequently limits its role.

Many of these tumours, however, utilise specific substrates, expressing specific receptors and secreting specific hormones, which may render them particularly well suited for the development of more specific PET tracers in future.

Thyroid tumours

A thyroid adenoma is an unusual benign endocrine tumour in that it is relatively FDG-avid. However, this differs little from many malignant thyroid tumours, and FDG imaging is therefore of no value in distinguishing between the two. Conversely, in detecting a focal area of increased FDG uptake in the thyroid during PET scanning, up to 50% of these lesions have been found to be due to malignant disease. About 90% of thyroid malignancies are due to differentiated thyroid cancer — either follicular, papillary, or a mixture of the two. Of the remainder, roughly equal proportions are made up of medullary thyroid carcinoma, originating from thyroid C-cells, and anaplastic carcinoma. While FDG PET scanning has a sensitivity of about 75% for differentiated thyroid carcinoma as a whole, this is only 65% in cases that are positive on iodine scanning, but increases to about 85% in cases that are negative on iodine scanning.

FDG PET imaging has also been found to be useful for the detection of Hurthle cell carcinoma, a hypermetabolic variant of the follicular thyroid carcinoma that typically does not concentrate radio-iodine. For medullary thyroid carcinoma FDG PET scanning does not routinely play a role in staging or monitoring of patients; however, medullary thyroid carcinoma tends to be FDG-avid, and PET scanning is a useful tool for the localisation of the recurrent disease in patients with a rising calcitonin level on follow-up (Fig. 4).

Parathyroid tumours

Although the sensitivity of FDG PET to detect parathyroid adenomas is variable, work using carbon-11 methionine is very promising (Fig. 5). It is still preferable to use conventional nuclear medicine imaging.
imaging with Tc-99m methoxyisobutyl isonitrile (MIBI)-pertechnetate subtraction and washout studies for the localisation of these tumours, but PET imaging may have a role in cases where this is unsuccessful, including patients with previous neck explorations.

Parathyroid adenocarcinoma is a rare but potentially curable tumour. PET is most likely to be useful for tumour localisation in cases where other imaging is negative.

**Adrenal tumours**

The majority of adrenal tumours are metastatic. In most cases these metastases are highly FDG-avid. While effective CT and magnetic resonance imaging (MRI) techniques exist to distinguish benign from malignant adrenal masses, FDG PET also appears to be highly accurate in making this distinction. Primary adrenal cortical malignancies are very rare and literature on the use of PET is limited. There is, however, evidence that FDG PET can be useful to detect both primary cancer and metastatic disease.

Approximately 10% of phaeochromocytomas are malignant and 10% are bilateral. Both CT and meta-iodobenzylguanidine (MIBG) imaging have a sensitivity of about 90% for the detection of these tumours. MIBG is also particularly useful for the detection of bilateral and metastatic disease, and to predict the efficacy of I-131, MIBG therapy. The role of FDG PET imaging in phaeochromocytoma appears limited, although some FDG-positive, MIBG-negative cases have been reported. Studies using the more specific PET substrate F-18 dobutamine have revealed excellent results.

**Carcinoids and endocrine pancreatic tumours**

The majority of carcinoids and endocrine pancreatic tumours are benign and exhibit poor uptake of FDG. The role of functional imaging is largely reserved for In-111 octreotide, particularly with tumours not localised using anatomical imaging, or endoscopic or intra-operative ultrasound techniques. FDG PET may, however, have a place in the detection of poorly differentiated tumours, which are metabolically more active. Again, promising results have been shown with more specific substrates such as carbon [C-11]-5-hydroxytryptophan, which have been found to be highly sensitive.

**Pituitary tumours**

The role for FDG imaging in pituitary tumours appears limited. Macro-adenomas tend to be FDG-avid, but micro-adenomas are not normally detected. MRI imaging is therefore the gold standard to assess the primary tumours. Nevertheless, several receptor ligands under investigation in the research environment show promise for distinguishing tumour types, detecting viable tumour, identifying parasellar tumours, and assessing response to treatment.

**Conclusions**

FDG PET imaging has some specific uses in the evaluation of patients with endocrine tumours, in
particular, the detection of recurrent differentiated thyroid carcinoma in patients with a rising thyroglobulin and negative iodine scan, as well as in cases of recurrent medullary thyroid carcinoma with rising calcitonin levels.

In the case of parathyroid adenoma, FDG PET appears useful in cases where conventional nuclear medicine imaging is negative. For adrenal masses, FDG PET appears to be a highly accurate tool to distinguish benign from malignant lesions. It may also be useful in a subgroup of non-MIBG avid pheochromocytomas. Its role in carcinoids and endocrine pancreatic tumours appears limited to those that are less well differentiated and metabolically active.

A role for PET imaging in the detection of endocrine tumours, using more specific substrates, however appears very promising. This is not surprising given the often highly specific uptake of particular substrates by these tumours. Once these substrates become more widely available, it is likely that the role of PET imaging in the detection and localisation of endocrine tumours will expand.

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