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PET Scanning in Oncology

C.B.J.H. Wilson

INTRODUCTION

POSITRON EMISSION tomography (PET) is a non-invasive imaging technique that allows the study of tissue function. Unlike X-ray computerised axial tomography (CT) or magnetic resonance imaging (MRI) that provide anatomical information, PET offers *in vivo* insight into tumour biology and metabolism.

PET, although requiring appreciable facilities and resources, is the most advanced methodology for effecting tracer studies in humans. Gamma-ray (positron-emitting) radioisotopes are used to label biochemicals or pharmaceuticals of interest, which are then introduced into the body and their spatial distribution measured by external radiation detectors. The images thus obtained can be considered as *in vivo* autoradiographs.

PET is a sensitive method and can measure as low as picomolar concentrations of tracer. The resolution of modern scanners is in the order of 4–7 mm. (These are the two main advantages of PET over magnetic resonance spectroscopy.) In view of the low concentrations of radioisotope used, and the short half life, radiation doses to the subject being studied are minimal.

If the biological fate of the tracer is known, kinetic models can be designed and used to provide quantative values of the biological function being traced (e.g. glucose uptake). For this it is usually necessary to measure both the tissue activity (via PET) and the blood activity as a function of time.

Although PET can be used as a simple imaging device for diagnosis, the aim is to measure biological differences between tumour and normal tissue.

This information can then be used to predict malignant grade, to select the appropriate therapy, or exploit it for therapeutic gain. Furthermore it may also provide an early and accurate assessment of the efficacy of a particular treatment regime.

THE PET SCANNER

Positron emitting radioisotopes are used. These are proton rich and decay with the release of a positron (a positively charged electron). This positron travels a short distance before combining with an electron to form a burst of radiation in the form of two 511 keV photons emitted at 180° to each other. This is known as annihilation radiation. By encircling the subject with a ring of radiation detectors, it is possible to record these pairs of photons of similar energy emerging from the body in opposite directions, using coincidence circuitry (Fig. 1).

The radionucleides that are most commonly used to label biochemicals along with their half life and present application are given in Table 1. Principal among these are $^{15}O_2$, $^{13}N_2$, and ^{11}C, which although having short half lives, are the longest lived gamma ray emitting forms of these basic biological elements. There is no suitable positron emitting isotope of hydrogen but ^{18}F is used as a labelling substitute. With the short lived isotopes (e.g. $^{15}O_2$) an on site cyclotron becomes necessary, but with the longer lived tracers (e.g. ^{18}F), it is possible to carry out studies

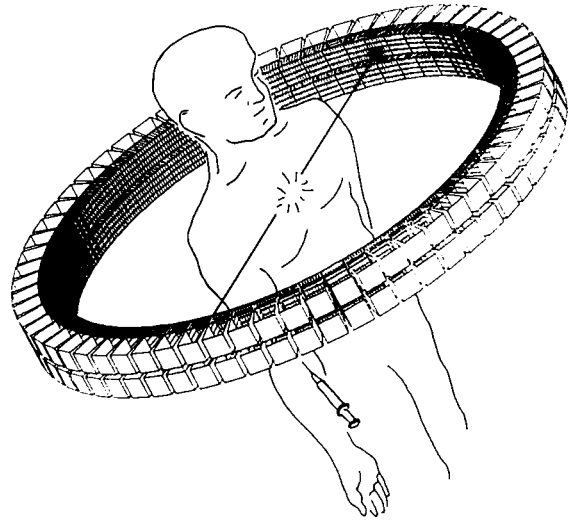

Fig. 1. Following the capture of a positron by an electron, two photons of 511 keV are emitted at 180° to each other. The coincidental events are registered by opposite detectors.

Table 1.

Radionucleide	Half life	Application
$^{15}O_2$	2 min	
$C^{15}O_2$, $H_2^{15}O$		Blood flow
$^{15}O_2$		Oxygen metabolism
$C^{15}O$		Blood volume
^{11}C	20 min	
^{11}C methionine		amino acid uptake
^{11}C glucose		glucose utilisation
^{11}C drugs		Drug uptake e.g. carmustine
^{11}C raclopride		Dopamine receptor
^{11}C somatostatin		Somatostatin receptor
^{11}C thymidine		Proliferation
^{18}F	110 min	
^{18}F deoxyglucose		Glucose utilisation
^{18}F deoxyuridine		Pyrimidine uptake
^{18}F fluorouracil		Drug uptake
^{18}F misonidazole		Hypoxic cell sensitisers
^{18}F oestradiol		Oestrogen receptors in breast
^{68}Ga	68 min	
^{68}Ga EDTA		Blood brain barrier
$^{13}N_2$	10 min	
$^{13}NH_3$		Blood flow
^{124}I	4 days	Monoclonal antibodies
		Iodine therapy dosimetry

Correspondence to C.B.J.H. Wilson, Department of Radiotherapy, Royal Marsden Hospital, Downs Road, Sutton, Surrey SM2 5PT, U.K.
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as long as the camera is within about 2 h travelling time from a cyclotron.

With these isotopes the scope for labelling biomolecules and pharmaceuticals is immense. However, to realise this, innovative and fast radiochemical procedures are needed to provide enough labelled compound to give meaningful results.

APPLICATION

Oncological studies have concentrated on the measurement of tumour blood flow and energy metabolism using kinetic models originally developed for normal tissue, notably brain. This explains the neurological bias of the early studies on tumours. More recent studies have examined differing tumour types with emphasis on the measurement of tumour proliferation, drug uptake and receptor studies.

Regional blood flow and tissue oxygenation are important factors that are thought to influence a tumour's response to radiotherapy and hyperthermia. Tissue perfusion is also of major importance for the delivery of chemotherapeutic agents and monoclonal antibodies. Tumour perfusion and oxygen metabolism has been measured using $^{15}O_2$ in brain and breast tumours [1]. A higher blood flow was seen in tumours and only a modest demand for oxygen. This data argues against the presence of significant hypoxic tissue in tumours. However imaging of hypoxia in human tumours has been suggested using ^{18}F-misonidazole [2]. Interestingly there is no apparent correlation between tumour perfusion and monoclonal antibodies uptake in breast cancer [3] ^{18}F-fluorodeoxyglucose (FDG), an analogue of glucose, is the most widely used tracer in oncological studies. FDG is transported across the cell membrane similarly to glucose and phosphorylated to FDG-6-phosphate (FDG-6P). Because of the modification of the molecule at the second carbon position, the FDG-6P cannot be catabolised further. In addition, in normal brain and experimental tumours, the concentration of the dephosphorylating enzyme (glucose-6-phosphatase) is low, so that FDG-6P becomes metabolically trapped and accumulates in the tissue at a rate proportional to glucose utilisation.

A wide range of animal and human tumours have been shown to have a high FDG uptake [4]. In brain tumours, Di Chiro and coworkers [5] have found the PET-FDG method 'extremely useful in patient management' in more than 350 patients. Its principal clinical uses are (a) grading of tumour (b) establishing prognostic criteria (c) differentiating between tumour recurrence and radiation necrosis (d) diagnosis of grade change. Tumours of high grade and worse prognosis appear to have higher FDG uptake [6] (Fig. 2) although these findings have not been universal [7]. In differentiating between tumour recurrence and radiation necrosis, it has been documented that regions with reduced FDG uptake and CT enhancement represented radionecrosis whilst lesions that enhance on CT and show high FDG uptake imply tumour recurrence.

Similarly FDG has been used successfully to image a wide range of human tumours: head and neck, lung, breast, colorectal, lymphoma, melanoma and musculoskeletal [8]. Although tumours may be successfully differentiated from normal tissue or fibrosis, there is no clear relationship between FDG uptake and proliferation rate. It would appear that the signal principally reflects enhanced glucose transport that may be secondary to *ras* oncogene activation [9].

Aminoacid metabolism has been studied principally using ^{11}C-methionine, as a marker of protein synthesis and an indirect marker of tumour proliferation. The low utilisation of normal brain provides a sharp contrast to the marked uptake seen both

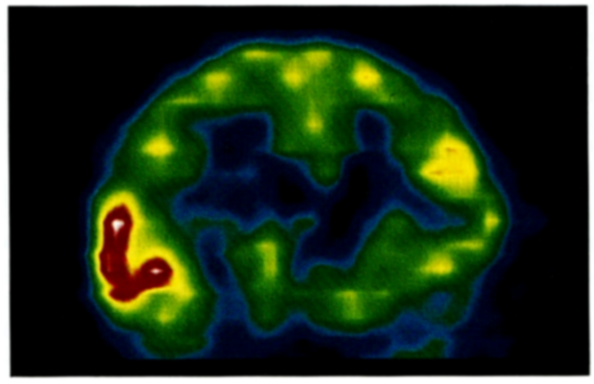

Fig. 2. 18F-fluorodeoxyglucose scan of a high grade glioma. In the coronal plane increased uptake is seen in the tumour in the right temporal lobe.

in low and high grade tumours and enables accurate deliniation of the growing tumour edge [10]. Methionine has been shown to be especially useful in the clinical evaluation of pituitary adenomas [11]. It has been used successfully to predict tumour response prior to clinical improvement and in some cases to tailor therapy appropriately. The results are impressive and indicate how the metabolic imaging of PET can successfully antipicate treatment outcome.

The uptake of methionine in other tumour types is being evaluated. Lung tumours have been clearly visualised using ^{11}C-methionine and viable areas differentiated from necrosis [12]. It would seem that methionine may be more sensitive than FDG in the mediastinum, but in view of its high uptake in the pancreas and liver, the reverse would be true for the abdomen.

Although the metabolic markers FDG and methionine are clinically useful in the detection of tumours, a marker specific for tumour proliferation remains the main objective. Developments in cancer therapy have been directed towards combatting tumour proliferation. An *in vivo*, non invasive and repeatable measure of proliferation would be of major importance prognostically and for the scheduling and monitoring of treatment. It would be especially valuable in the evaluation of new therapies.

Thymidine would be expected to be the most effective tracer. However the presence of numerous metabolites poses problems in attempting to quantify *de novo* DNA synthesis. ^{11}C-methylthymidine uptake has been measured using PET in 10 patients with non Hodgkin lymphoma [13], and a good correlation was obtained with histology. However this does not necessarily imply DNA synthetic rate, as much of the signal may be secondary to intratumoural metabolites. A novel labelling of thymidine within the ring leads to fewer metabolites [14], and within the first hour up to 80% of the thymidine is incorporated into DNA [15]. Several groups are currently investigating this new tracer.

Although PET would seem the ideal modality for the evaluation of drug uptake, surprisingly few studies have been performed. The most important determinant of cytotoxic effect is the product of drug concentration at the tumour site and time. In practice this is rarely, if ever, measured and can only be estimated from plasma levels and clearance studies. The kinetic behaviour of ^{11}C-carmustine has been investigated as a means of measuring the level of carmustine in gliomas [16]. Studies from the Heidelberg group on ^{18}F-5-fluorouracil (5FU) distribution in colorectal primaries and liver secondaries have confirmed the generally poor uptake of this drug [8]. A close correlation was seen

between tumour response and uptake. This method would appear suitable for the selection of patients who are likely to respond to 5FU chemotherapy and for determining the optimal scheduling of the drug. Similarly accurate dosimetry for targeted therapy may be determined using longer lived isotopes such as ^{124}I for thyroid cancer [17] and labeled monoclonal antibodies [3]. Receptor studies are still in their infancy. Several ligands have been developed for the potential quantification of oestrogen and progestogen receptors. ^{18}F-fluorooestradiol has been studied in 13 patients with breast cancer [18]. The PET images demonstrated excellent uptake of the oestrogen analogue at sites of primary carcinoma and metastases. A good correlation was found between the uptake and oestrogen receptor concentration measured *in vitro*. Progestogen ligands are under study. Dopaminergic receptor binding sites have been demonstrated in pituitary adenomas, using ^{11}C-raclopride. During treatment with bromocriptine, receptor down regulation has been observed [19]. The use of receptor studies for the monitoring of treatment response, especially to hormone therapy, is becoming a real possibility.

CONCLUSION

The main limitation of PET at present is cost and hence general availability. There are only a handful of centres in Europe engaged in oncological studies.

Clinically PET has been shown to be diagnostically useful in a wide range of tumours, using the metabolic tracers FDG and methionine. In time such qualitative scans may become as routine as bone scans. However for the present time, PET remains a research tool. A marker specific for proliferation is needed. This would be especially important for the early assessment of new therapies, and the selection of patients for accelerated treatments.

Moreover PET would seem the ideal modality for measuring drug uptake within tumours. Using this tracer technique, phase I and II studies could be short-circuited, enabling the rapid assessment and development of new pharmaceuticals. It would also help to optimise the scheduling and delivery of known agents, and determine dosimetry for targeted therapy. A European cooperative programme intergrating the expertise of the PET centres and research groups with the pharmaceutical industry would seem to be the answer.

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