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What does positron emission tomography offer oncology?

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Abstract

The origins of positron emission tomography (PET) date back 70 years. Since the 1970s, however, its use has increased exponentially in the fields of neurology, cardiology and oncology. [^{18}F]-Fluorodeoxyglucose (FDG) whole-body scanning is by far the most widely utilised and recognised application of PET in oncology. However, PET is a very versatile and powerful imaging modality capable of helping bridge the gap between the laboratory and the clinic. This article reviews the history and current applications of PET in oncology and then explores some of the newer applications and potential future uses of this versatile technology particularly in the area of cancer research.

Keywords: Positron emission tomography; Radionuclides; [^{18}F]-FDG

1. Positron emission tomography (PET)

Positron emission tomography (PET) is a sophisticated imaging technique that is able to detect, localise and quantitate radionuclides in the body non-invasively. PET utilises commonly radionuclides such as [^{15}O], [^{11}C], [^{18}F], [^{124}I] and incorporates them into molecules in a potentially huge range of compounds ranging from simple H_2O to complex pharmaceuticals. These compounds can then be used to image important physiological, biochemical and molecular processes at a level of sensitivity unmatched by other imaging techniques (see Fig. 1) [1].

2. History of PET in oncology

The beginning of the development of PET dates back to early this century when the theoretical physicist P. Dirac postulated the existence of positive electrons based on the equations of quantum mechanics and Einstein's theory of relativity [2]. C.D. Anderson subsequently proved Dirac's theory in 1932 when he observed experimentally that cosmic rays include particles with the mass of electrons, but with a positive charge [3]. These particles were called positrons. Around this time in Berkeley, California Ernest Lawrence and his team were developing the first cyclotron: two D-shaped magnets capable of accelerating particles to produce progressively higher energy protons and deuterons that could then bombard elements to explore the nature of the atomic nucleus [4]. The fusion of the theory and experimental observation led to the development of larger cyclotrons able to produce large quantities of artificial radioisotopes such as carbon-11, nitrogen-13, oxygen-15 and fluorine-18, isotopes that continue to form the backbone of medical PET imaging today.

Another step in the evolution of the PET scanner we know today was the development in the 1940s of a system for external measurement of radiotracers. Handheld Geiger–Muller counters were initially used to measure the rate of accumulation of radioactive iodine by the thyroid gland to help decide whether a thyroid nodule was benign or malignant [4]. An automated system of detector movement followed producing the first so-called 'scanner' [5]. It was not long before this was used to produce nuclear images of other organs and *in vivo* molecular imaging was born [4]. Multidetector systems were then developed culminating in the ring detector systems still used today.

The next major step in PET development for oncological use occurred in the 1970s. In 1948, Kety and

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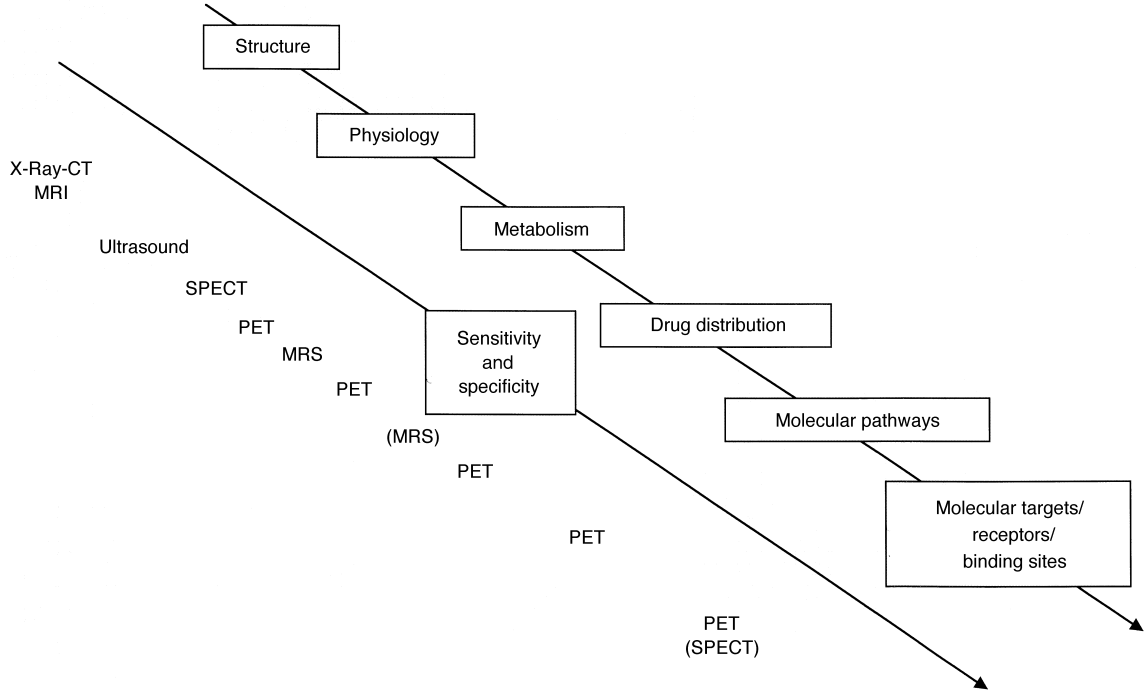

Fig. 1. The spectrum of medical imaging, which ranks the ability to image decreasing concentrations (sensitivity) of specific molecules (specificity). The spectrum covers a sensitivity range of 10^9 (millimolar to picomolar). CT, computed tomography; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; PET, positron emission tomography; SPECT, single photon emission computed tomography. Reproduced with permission [1].

Schmidt had used nitrous oxide to apply the Fick principle to measure cerebral blood flow and oxygen utilisation [6]. This method of measuring cerebral blood flow made it possible to determine in living persons the average rate of glucose use in the brain as a whole from measurements of blood flow and the arteriovenous difference in glucose levels and oxygen utilisation. In 1977, Sokoloff described the carbon-14 deoxyglucose method for measurement of local cerebral glucose utilisation [7]. This technique was subsequently adapted to use fluorine-18 deoxyglucose [8] and the [^{18}F]-fluorodeoxyglucose (FDG) scan for the measurement of glucose metabolism, *in vivo*, in humans was born.

3. Development and current status of [^{18}F]-FDG imaging

The use of FDG in PET is based on the Warburg's observation back in the 1930s that malignant tumours have an increased glycolytic rate [9]. FDG initially follows the same metabolic pathway as glucose. It is carried into the cell by endothelial glucose transports and is converted to FDG-6-phosphate. Unlike glucose, this is then trapped in the cell, where it accumulates at a rate proportional to glucose utilisation [10]. In the 1980s, a number of animal studies demonstrated an increased uptake of FDG in transplanted and spontaneous tumours [11–13]. Di Chiro and colleagues [14] was one of the first to show that FDG–PET could differentiate tumour recurrence from post-radiotherapy changes in the brain. With the development of the PET whole-body scanner, the range of applications of FDG expanded and its use is becoming more widespread in a number of clinical applications (Table 1). Some of these uses have been more extensively investigated and evaluated than others and there are many ongoing studies, not only in the clinical applications, but also in the refinement of the technique itself.

4. Future developments in the field of FDG–PET

One of the main criticisms of the clinical use of FDG–PET has been the lack of a standardised methodology in the data collection and analysis of scans. For example, there are several methods of evaluating whole-body FDG–PET scans: subjective, qualitative visual evaluation, a more time-consuming and costly method of quantitating the standard uptake value or SUV with Patlak analysis, a semi-quantitative method using an SUV curve, other kinetic parameters of glucose uptake such as Ki, the net influx constant, and Mrglu, the glucose metabolic rate. There is variation in the timing of scanning protocols and whether lean body mass or total body mass is used in the calculations of SUVs. Attempts are being made to standardise the methodology [46] and such efforts are essential in improving the quality and reliability of FDG–PET in the future.

An aspect of FDG–PET that is being increasingly studied is the use of this technique to assess response to treatment [10,47]. This has potential advantages for patient management and drug development. A paper by Brock and associates [38] performed FDG–PET measurements in brain tumours at 7 days after treatment and found that these results could predict ultimate clinical and radiological response recorded at 2 months. Another example is in the paralleling of phase I studies with [^{18}F]-FDG–PET, which may then be used to predict toxicity and tumour response at a preclinical level. This can then be used to facilitate effective drug development and in defining optimal drug scheduling and in the individualisation of therapy [10]. Recent European guidelines for the use of [^{18}F]-FDG for response assessment in oncology have been produced by the European Organization for Research and Treatment of Cancer (EORTC) PET study group [46].

[^{18}F]-FDG–PET continues to play an increasing part in the diagnosis and management of patients with cancer. In the USA for example, in lung cancer, [^{18}F]-FDG has become the standard investigation in the diagnosis of solitary lung nodules and in the pre-operative staging of lung carcinoma. Validation in other areas (see Table 1) will continue and it may become increasingly incorporated into patient management algorithms. Its relative place in diagnostics has been discussed elsewhere [48].

[^{18}F]-FDG has dominated the PET oncology field, but perhaps the greatest strength in PET is the ability to utilise many other radioisotopes; isotopes that can be incorporated into complex compounds and pharmaceuticals and used to investigate the biology of human cancers *in vivo* and the effects of various manipulations.

Table 1
A list of clinical applications where there is good evidence that [^{18}F]-FDG–PET improves the management of certain tumours

Clinical applications of FDG–PET	Tumours with evidence of benefit [Ref.]
Preoperative detection and staging of disease	Lung cancer [15–17] Breast cancer [18,19] Colorectal cancer [21,22] Melanoma [22,23] Head and neck cancer [24,25] Pancreatic cancer [26]
Detection of recurrence	Lymphoma [27] Head and neck cancer [28] Thyroid cancer [29,30]
Differentiation between recurrence and scarring post-treatment	Colorectal cancer [31,32] Brain tumours [33,34]
Evaluating response to treatment	Head and neck cancer [35–37] Brain tumours [38] Sarcoma [1,39] Breast cancer [40,41]
Determination of biopsy site	Head and neck cancer [42,43] Brain tumours [44,45]

FDG–PET, [^{18}F]-fluorodeoxyglucose positron emission tomography.

4.1. Tumour physiology

Measuring blood flow, blood volume and oxygen utilisation using ^{15}O-labelled $H_2{}^{15}O$ and $C^{15}O$ has been a mainstay of PET studies from the early years. Initially these were developed for brain studies [49,50] but the technique has subsequently been modified to measure blood flow and exchanging water space in breast tumours [51]. These techniques have a potentially important role in the development and assessment of new antivascular and antiangiogenic therapies targeting tumour vasculature that are being increasingly investigated.

5. Imaging of tumour metabolism

Tumours are characterised by abnormal growth and metabolism. However, [^{18}F]-FDG imaging is not completely specific for malignant tumours: inflammation, tuberculosis and certain non-malignant tumours have increased uptake. In an attempt to increase the specificity of PET in imaging cellular growth, other radiotracers were developed and are continuing to be developed. [^{11}C]-thymidine has been developed as a specific marker of DNA synthesis. Data from normal tissue models have shown correlation between [^{11}C]-thymidine uptake as determined by PET, DNA turnover in regenerating tissues and non-regenerating livers and cell proliferation [52,53]. Preliminary data suggest that [^{11}C]-thymidine uptake may provide a more direct and relevant *in vivo* measure of response in both tumours and normal tissue [54,55]. However, the rapid metabolism and accumulation of metabolites complicates the interpretation of [^{11}C]-thymidine scans. New tracers are being developed that enter the DNA synthetic pathway but are more stable to systemic degradation e.g. [^{18}F]-3′-deoxy-3′-fluorothymidine (FLT) [56] and bromine-76-bromodeoxyuridine [57].

Tracers of protein synthesis are also being developed as markers of biosynthesis [58]. [Methyl-[^{11}C]-methionine] is the most widely used amino acid radiopharmaceutical [59,60]. However, again their secondary metabolism [61] and dilution into unknown pool sizes of intracellular amino acids [58] makes their interpretation difficult.

A specific, easy to use marker of tumour growth would have an important role in the oncological use of PET [54]: It could be used to accurately assess early response and predict clinical outcome of treatment reducing the exposure to patients and the expense of ineffective treatments. It could be used to confirm com-

plete response to therapy. It could be used when carrying out trials of new treatments, schedules or combinations providing a quantitative measure of fractional cell kill. And it could be useful in assessing the *in vivo* response of normal tissue to therapy.

6. Tumour receptor imaging

The last 20 years have seen an exponential increase in our knowledge and understanding of tumour cell biology and molecular characteristics of tumours and tumorigenesis. Amongst this has been recognition that receptor and transport systems play an important part in tumour biology and are a potential target for future therapies. Radiopharmaceuticals that can assess such markers are being developed to aid diagnosis and therapeutic planning. Several fluorinated antioestrogens and anti-androgens have been labelled as PET-tracers and measurement of receptor concentrations made [62,63]. Oestrogen receptor (ER) status of breast tumours has prognostic implications and currently the method of assessing ER status is from biopsy specimens. To date, the use of PET constitutes the most reliable non-invasive method for assessing ER status [64]. An interesting development along this whole line uses ^{18}F-labelled and ^{131}I-labelled tamoxifen analogues to image ER-positive breast tumours [65]. The potential use of such ligands is to predict a patient's susceptibility to tamoxifen, determine the proportion of oestrogen receptors occupied by therapeutic drug and monitor the effectiveness of hormonal therapy on an ongoing basis [64]. Similar uses have been suggested for androgen receptor ligands in prostate cancer [66]. Potential targets in the future include other receptors that are becoming recognised as being important in oncology such as the vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), P-glycoprotein (Pgp), a plasma membrane transporter and other protein products encoded by multidrug resistant (MDR) genes are another potentially important area of PET research. These proteins reduce intracellular accumulation of cytotoxic agents and the efficacy of chemotherapy. A number of PET radiopharmaceuticals are being developed to investigate the process further and in conjunction with strategies to block expression or activity of these proteins to improve the efficacy of cytotoxic agents. These radiopharmaceuticals include Technetium-99m sestamibi which is a substrate for Pgp and has been used in clinical studies for tumour imaging, and to visualise blockade of Pgp-mediated transport after modulation of the Pgp pump [67]. ^{11}C-labelled drugs such as ^{11}C-verapamil and ^{11}C-daunorubicin [68] and ^{11}C-colchicine [69] have also been investigated and are additional tools for the quantification of Pgp-mediated transport with PET *in vivo*. A potential use of such agents would be to select patients who may benefit from the addition of Pgp modulators, which are being developed [70].

7. Tumour hypoxia

Hypoxia is present in almost all tumours *in vivo* [71]. It is one of the main causes of resistance to conventional radiotherapy and chemotherapy and hence an important factor to consider when investigating tumours and developing treatments. Tracers such as [^{18}F]-fluoromisonidazole already exist that can quantitate hypoxia in tumours using PET [71–73]. Newer, more sensitive agents are being developed [74] and have a potential role in the selection of patients for therapy with bioreductive agents, antiangiogenic agents, antivascular agents and hypoxia-targeted gene therapy [75].

8. Imaging gene expression

Gene therapy has been hailed as one of the next major developments in cancer therapeutics. It has not, as yet, translated into clinical application, but hopes are still high. PET could have a unique role to play in development and assessment. Most work to date has centred on gene therapy in tumours transduced with the herpes simplex virus type 1 thymidine kinase (*HSV1-tk*) suicide gene. The principle of suicide genes is that they mediate conversion of a prodrug only on reaching the site of its intended target [76]. In the case of *HSV1-tk* the prodrug is gancyclovir. Cells that express *HSV1-tk* are more susceptible to gancyclovir toxicity because they phosphorylate the drug, which then becomes trapped, additionally phosphorylated and incorporated into cellular DNA, leading to chain termination [64]. A number of analogues to gancyclovir that can be imaged by PET have been developed [77–79] and used to monitor gene expression in animals. In future, these will be developed for use in humans.

9. Drug development

A number of conventional cytotoxic agents have already been radiolabelled and have proved useful in investigating aspects of drug pharmacokinetics that cannot be measured in any other way. Conventional pharmacokinetic studies rely on inferring information on tissue levels from plasma measures. PET, however, can be used to directly measure the drug concentration in tissue. For example, [^{57}Co]-bleomycin has been used to produce tissue and plasma time–activity curves that have been used to determine tumour and normal tissue kinetics directly [80]. The distribution of [^{13}N]-cisplatin

[81], 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) and 2-chloroethyl-3-sarcosinamide-1-nitrosourea (SarCNU) [82] in brain tumours has been investigated. More complicated pharmacokinetic analyses have been performed with ^{18}F-labelled 5-fluorouracil. Not only has information been obtained on the pharmacokinetics of the drug in metastases and normal tissue [83], but this has been applied to predicting response to therapy [84,85]. [^{18}F]-5-FU can also be used to assess the effects of biochemical modulation of 5-FU [75,86] *in vivo* (see Fig. 2) [87].

There is unlimited potential for the investigation of drugs in oncology using such methods. What is needed and what will be developed are improvements in the whole radiolabelling process: basic radiochemistry, precursor synthesis, rapid radiolabelling, automation of radiosynthesis and analytical techniques [70].

10. Radioimmunotargeting and antibody imaging

Therapeutic monoclonal antibodies are establishing themselves in clinical practice and are having some success [88,89] particularly in the area of lymphoma and breast cancer. The high level of interest in such agents has led to recent advances in radioimmunotargeting. This involves the administration of nuclide-carrying antibody with a specific target that administers a low dose of radioactivity over a long period of time. Most radionuclides used in radioimmunotherapy have positron-emitting analogues, which can be used for PET imaging [90] and for performing dosimetry. With the expansion of this area of cancer therapeutics, PET will have an important role.

11. Summary

The remit of this article was to introduce the reader to some of the accomplishments of PET in the area of oncology and to look ahead to its future. Space does not allow a comprehensive review, but we have attempted to present a broad illustration of the many and varied uses of PET in the oncology field. Although FDG–PET is an important area, it does tend to dominate peoples' perception of PET. FDG–PET will continue to be used as a diagnostic tool and as an adjunct to the other imaging modalities. The real strength of PET, however, lies in its unique ability to quantitatively assess biochemical and physiological processes *in vivo*. The future of oncology lies in individualisation of therapy; being able to select the best treatment for an individual patient; being able to objectively assess response at an early stage; being able to assess normal tissue toxicities. It lies in more specific tumour targeting and improvements in delivery and scheduling of anticancer therapies. PET is a

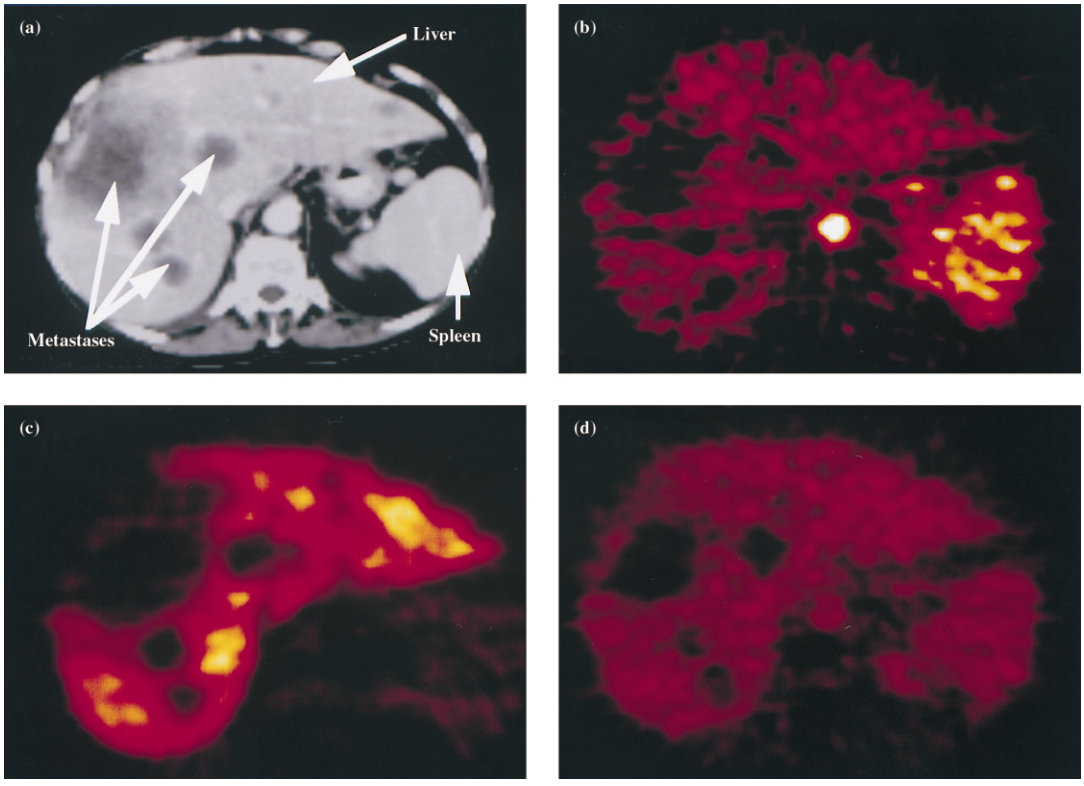

Fig. 2. Transabdominal computed tomography (a) and corresponding positron emission tomography (PET) blood flow (b) and PET [^{18}F]-fluorouracil images without eniluracil (c) and after eniluracil (d), showing liver, spleen and multiple hepatic metastases. Reproduced with permission [87].

valuable tool in all these areas and the future for PET in oncology, above all, looks healthy.

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