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Current Perspective

# Clinical molecular imaging with positron emission tomography

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ABSTRACT

Molecular imaging allows for the in vivo evaluation of targeted molecules and biological processes in man. Positron emission tomography (PET) is a highly sensitive and quantitative molecular imaging modality, whose utility in clinical and experimental medicine is increasing by the day. In this article, the principles of PET and its currently accepted applications in oncology, such as cancer staging, treatment response assessment and as a prognostic marker are reviewed. Further, the evolving role of PET in areas of oncology such as radiotherapy treatment planning, anti-cancer drug development and the evaluation of patho-physiological processes which drive a cell into neoplastic activity is discussed.



## 1. Introduction

Scientific advances in imaging in the latter half of the twentieth century have made it possible to perform clinical imaging of molecular structures within the body. These imaging modalities, such as positron emission tomography (PET), allow *in vivo* assessment of radiolabelled molecules, by detection of emitted radiation from the body. PET is a highly sensitive and quantitative nuclear imaging modality that has been used widely to clinically image a number of molecules, ranging from physiological compounds such as water[1] to therapeutic substances such as anti-cancer agents.[2] Although other imaging methods, such as functional magnetic resonance imaging (MRI) and functional computerised tomography (CT), also provide functional imaging data, such as changes in perfusion, based on surrogate changes in intravenous contrast dynamics, these modalities do not image specific molecules and are not be discussed in this review. This review discusses the principles of PET imaging, followed by molecules that have been clinically imaged with PET, their current applications (Table 1) and the future prospects for clinical molecular imaging.

## 2. Positron emission tomography (PET)

PET imaging is based on coincidence detection of two simultaneously emitted photons, which occurs when a positron annihilates after combination with an electron. Positron

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**Table 1 – Some of the molecules imaged clinically with PET and their applications**

| Radiolabelled molecule | Process monitored | Applications |
|---|---|---|
| Fluorodeoxyglucose (FDG) | Glucose metabolism | Staging and diagnosis of cancer[20,22]<br>Radiotherapy treatment planning[41]<br>Response marker and prognostic evaluation[23,25,26,30,31] |
| [$^{18}$F]3′-deoxy-3′fluorothymidine (FLT) | Proliferation | Response marker and prognostic evaluation[12] |
| Water | Blood flow | Tissue blood flow[2]<br>Pharmacodynamic evaluation[1] |
| N-[2-(dimethylamino)ethyl]acridine-4-carboxamide (DACA) | Drug pharmacology | Normal tissue and tumour pharmacology[15] |
| Temozolomide | Drug pharmacology | Normal tissue and tumour pharmacology[16] |
| 5-fluorouracil | Drug pharmacology | Normal tissue and tumour pharmacology[2] |
| Misonidazole | Hypoxia | Assessment of tissue and tumour hypoxia[46] |
| Methionine | Amino acid uptake | Radiotherapy treatment planning[42] |

emitting isotopes are produced in a cyclotron and can be chemically linked to a probe molecule and injected intravenously into a patient. The single emitted positrons in the body combine with an electron, resulting in the annihilation of the positron and electron with all the mass being converted into electromagnetic radiation. In order to conserve energy and linear momentum, the electromagnetic radiation appears in the form of two photons of equal energy (511 keV; equal to the rest mass energy of the electron and positron), which are emitted at 180° to each other. The emitted photons are detected by a technique known as coincidence detection, whereby a coincident signal is transmitted when two scintillation detectors separated by 180° are stimulated simultaneously. This fundamental physics forms the basis of dynamic detection and three-dimensional localisation of PET. The emission of positrons from the compound follows its behaviour within the body; hence PET can provide unique functional imaging data, not available with other modalities. Moreover, the ability to correct for attenuation of radiation by body tissue and the highly sensitive nature of PET technology makes it possible for accurate quantification of the radiolabelled compound to picogram amounts. The recent introduction of PET/CT, in which the technologies of PET and spiral CT have been combined in a single multimodality detection instrument, has aided significantly in the exact localisation of radiotracer uptake.[3] One limitation of PET is the inability to distinguish between the chemical species attached to the radionuclide. The inherently low spatial resolution of PET, which is in the 3–5 mm range is due to several factors, including non-collinearity of the annihilation photons, i.e. photons do not emit exactly at 180° as a result of residual momentum at annihilation and the small but finite range of positron travel in the body prior to annihilation.

Molecular imaging with PET is based on the tracer principle. A tracer is a substance that follows or traces the path or behaviour of a substance that is being investigated. For PET, a very small amount of the molecule of interest is radiolabelled with the positron emitting isotope, when it is called a radiotracer. In an ideal tracer, any isotope effect should be negligible or at least quantitatively predictable and the mass of the tracer should be small compared with the mass of the endogenous substance being traced. Therefore, it is essential that molecules of high specific activity (activity/mole) are radio-synthesised, and this requires expert radiochemical input. In contrast to a true tracer, which is identical to the natural substance, an analogue tracer is a compound that possesses many of the properties and is related in a known and predictable manner to the natural compound that it is meant to trace. The *in vivo* uptake and behaviour of the radiotracer in the body can be assessed by several methods, ranging from simple non-quantitative methods, such as visual inspection to semi-quantitative and quantitative methods. Semi-quantitative methods such as standardised uptake values (SUV) measure radiotracer uptake at a certain time point after injection of the radiotracer, while quantitative methods, such as graphical and compartmental analytical methods involve complex modelling procedures and usually require arterial, venous or arterialised venous blood sampling. Modelling methodologies could also be either model led compartmental techniques or data-led methods such as spectral analysis,[4] where limited *a priori* assumptions are required for modelling purposes.

Since a number of commonly occurring elements, such as carbon, oxygen and nitrogen, have positron-emitting radionuclides, the stable nuclides of these elements can be potentially replaced by their positron emitting counterparts in a number of compounds and evaluated using PET. Fluorine-18, a commonly used radionuclide is used to replace fluorine present in compounds of interest, such as 5-fluorouracil (5FU), and can also be used to replace hydrogen atoms of which it is isoteric, or hydroxyl groups of which it is isoelectronic. The short half-lifes of the positron emitting nuclides (half-life of oxygen-15, nitrogen-13, and carbon-11 are 2, 10 and 20 min, respectively), necessitating an on-site cyclotron, together with complex radiosynthetic processes has so far limited the number of radiotracers evaluated with PET. However, radiosynthesis of tracers with isotopes of longer half-life such as fluorine-18 (half-life 110 min) and Iodine-124 (half-life 4.2 d) may preclude the necessity for an on-site cyclotron, and advances in radiochemistry may permit a greater number of radiotracers to be evaluated by PET.

## 3. Radiolabelled molecules evaluated with PET

### 3.1. *Fluorodeoxyglucose (FDG)*

The molecule that has been most often imaged with PET is the fluorine-18 radiolabelled glucose analogue tracer

fluorodeoxyglucose (FDG), which was developed to image glucose metabolism. FDG initially follows the same metabolic pathway as glucose and is carried into the cell by glucose transporters. However, unlike glucose which is rapidly metabolised to carbon dioxide and water, FDG undergoes phosphorylation and accumulates at a rate proportional to glucose utilisation and is trapped in the cells. Cancer cells are known to have higher rates of glucose uptake than normal cells, and this is attributed to a number of mechanisms, including overexpression of glucose transporters and the transcription factor hypoxia inducible factor-1, which regulates genes involved in glycolysis.[5] The measurement of glucose metabolism as a surrogate marker of tumour activity and cell number has been utilised for a number of applications in cancer management, including cancer staging, response assessment, prognostic evaluation and radiotherapy treatment planning.

### 3.2. [$^{18}$F]3′-deoxy-3′fluorothymidine (FLT)

The low or variable glycolytic activity of some tumour types has limited the utility of FDG-PET in tumours, such as hepatocellular carcinoma[6] and primary prostatic cancer.[7] Furthermore, physiological uptake in the brain, accumulation in inflammatory diseases, confounding effects of tissue inflammation on FDG uptake soon after radiotherapy, non-specific bowel uptake and urinary excretion of FDG may limit tumour detection and/or cause false positive findings. Therefore, other PET markers, especially those targeting proliferation such as [$^{11}$C]thymidine[8] and its analogue [$^{18}$F]3′-deoxy-3′fluorothymidine (FLT)[9] have been evaluated. FLT, a promising PET marker for proliferation is taken up by proliferating cancer cells by thymidine kinase (TK-1) and trapped intracellularly.[10] FLT uptake reflects proliferation, but incorporation of FLT into DNA is negligible[11] and is therefore an indirect tracer of proliferation. Initial clinical studies have also demonstrated that [$^{18}$F]FLT was more sensitive than [$^{18}$F]FDG to image recurrent high-grade brain tumours, correlated better with Ki-67 values, and was a more powerful predictor of tumour progression and survival.[12]

### 3.3. Water

The most often used tracer to measure *in vivo* blood flow using PET is oxygen-15 radiolabelled water ([$^{15}$O]$H_2O$). Its uptake is proportional to blood flow and is nearly freely diffusible, therefore satisfying criteria for a good blood flow tracer. In addition, radiolabelled water is biologically inert, chemically stable, with no physiological effects and its short-half life allows rapid and repeatable studies to be performed. Tissue perfusion has been evaluated as a surrogate for drug delivery and a pharmacodynamic marker.[1,2]

### 3.4. Therapeutic anti-cancer agents

A number of cytotoxic agents[13] have been radiolabelled and tissue and tumour pharmacokinetics of these agents have been assessed using PET. These include *N*-[2-(dimethylamino)ethyl]acridine-4-carboxamide (DACA),[14,15] temozolomide,[16] 5-FU,[2] cisplatin[17] and tamoxifen.[18]

## 4. Current applications of PET

### 4.1. Staging and diagnosis

Of all its applications, the utility of FDG as a staging and diagnostic tool in cancer has increased exponentially over the last several years and is routinely used in a number of centres worldwide. FDG-PET has an overall average sensitivity of 84% (based on >18,000 patient studies) and a specificity of 88% (based on >14,000 patient studies) in cancer.[19] Although it has also been used for diagnosis in those settings where FDG-PET results can replace invasive diagnostic procedures or can inform the anatomical location of procedures to be done, FDG-PET is preferentially used to stage (rather than diagnose) a number of tumours including melanoma, lymphoma, oesophageal, lung and colorectal cancers. The value of FDG-PET in the pre-operative staging in non-small cell lung cancer (NSCLC) has been underlined by level one evidence that shows a reduction in the need for unnecessary thoracotomies in one out of five patients who had a pre-operative FDG-PET scan.[20] FDG-PET has also found particular utility in detecting distant metastases and metastatic disease in lymph nodes that appear normal on CT scan.[21] After treatment, FDG-PET is valuable for restaging and is used in this setting to detect recurrent or residual disease or to determine the extent of a known recurrence.[22]

### 4.2. Response assessment and prognostic evaluation

Structural changes in tumour volume are used as a prospective endpoint to assess drug activity in phase II studies and as a surrogate endpoint for other measures of clinical benefit such as disease-free and overall survival in the more definitive phase III clinical trials. Additionally, volume changes serve as an important guide for the clinician and patient in decisions regarding continuation of therapy in routine practice. Since changes in tumour function, such as glucose metabolism, may predate volume changes in responding tumours (Fig. 1), FDG-PET has the potential to monitor and assess therapy. The advent of cytostatic agents has also introduced new challenges in the assessment of tumour response, as these agents may not necessarily lead to tumour shrinkage. In patients with gastrointestinal stromal tumours (GIST) treated with the cytostatic agent imatinib,[23] FDG-PET responses predicted subsequent computed tomography responses and the value of FDG-PET in response assessment in GISTs has been recognised.[24]

Several studies have evaluated the utility of FDG-PET for early response evaluation during treatment. These studies in a variety of tumours such as lymphomas,[25] oesophageal cancer,[26] gastric cancer,[27] head and neck[28] and lung cancer[29] have demonstrated that early metabolic responders have a longer survival. Such a prognostic estimation by metabolic imaging is akin to the similar prognostic significance of a pathological response that is usually obtained after treatment and could serve as a guide for modification of therapy. Early identification of non-responding patients therefore has the potential to alter therapy and reduce the costs and side-effects of ineffective therapy. In addition to early response evaluation, metabolic imaging can also serve as a pharmaco-

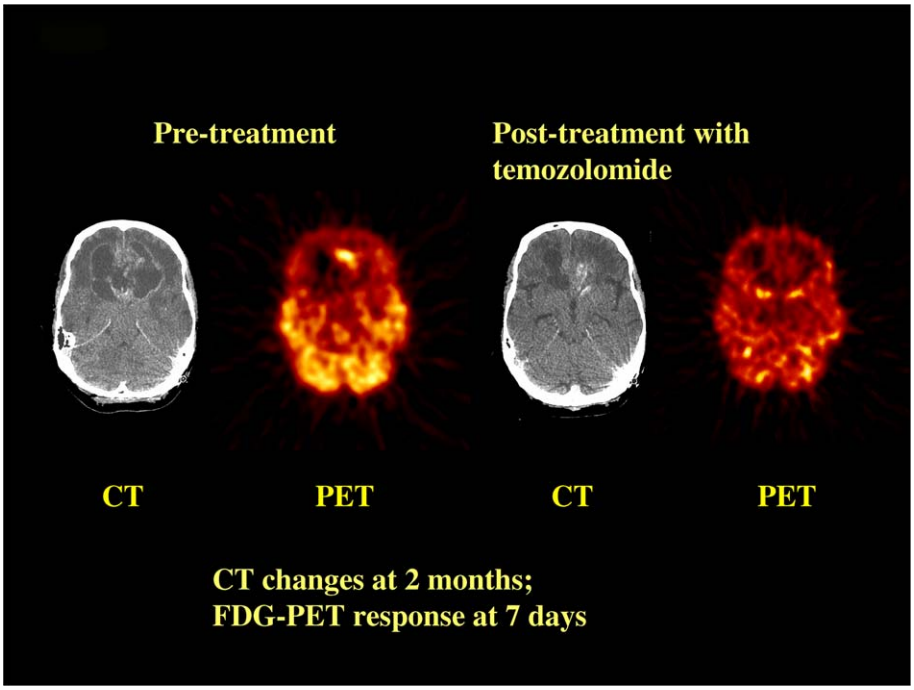


**Fig. 1 – Response to temozolomide in patients with high-grade glioma. Early positron emission tomography (PET) response at 7 days, compared with computed tomography (CT) response at 2 months.[50]**

dynamic endpoint in drug development, especially in studies with newer target-directed agents, where higher doses may not necessarily be better and an optimal therapeutic dose may exist. This will also prevent an erroneous rejection of certain agents, where a functional response may be observed in the absence anatomical shrinkage of tumours.

FDG-PET has also been used for response assessment after completion of therapy. This is especially important in malignant lymphomas, where anatomical imaging after completion of therapy often reveals residual masses that could represent either persistent disease or fibrotic tissue. Identification of residual disease after chemotherapy could influence further treatment options, including the need for consolidation radiotherapy. Several studies have demonstrated that persistent or increased focal FDG uptake in initially involved tumour sites in patients with Hodgkin's disease or non-Hodgkin's lymphoma is highly predictive for residual or recurrent disease and associated with a poor outcome.[30–32] A retrospective analysis in patients with non-Hodgkin's lymphoma has underlined the supplementary value of PET to international workshop criteria based response assessment.[33] Additionally, the poor prognostic relevance of residual FDG uptake after completion of treatment has been confirmed in a number of tumour types including sarcomas[34] and oesophageal,[35] lung,[36] head and neck[37] and cervical carcinomas.[38]

### 4.3. *Radiotherapy treatment planning (RTP)*

The diagnostic potential of FDG-PET together with its ability to differentiate malignant from non-malignant tissue has been utilised in RTP. Since, the aim of RTP is to treat the tumour together with areas of potential microscopic spread, minimising dose to uninvolved organs, integration of PET in the RTP process could potentially increase the therapeutic index of radiotherapy (Fig. 2). In addition, information on the biological tumour phenotype, such as extent of hypoxia, gene expression, angiogenesis and apoptosis, could potentially aid in the derivation of a biological target volume with individual areas being targeted with intensity modulated radiotherapy (IMRT) to obtain a biological dose distribution or 'dose painting'. Tumours may also be imaged throughout radiotherapy to assess re-oxygenation or accelerated repopulation, which may have an impact on choice of adjuvant treatment. However, a number of potential inaccuracies associated with PET, such as increased FDG uptake by inflammatory processes, the inability to provide information on microscopic disease, inclusion of patient motion during PET acquisition, the dynamic nature of biological target volumes and difficulties with visual delineation of the tumour volume edges should be taken account of during RTP.

The role PET in RTP has been evaluated in a number of tumours. In patients with lung cancer, integration of FDG-PET in the RTP process can detect lymph node involvement[39] and differentiate malignant tissue from atelectasis.[40] Several studies have also demonstrated a significant impact on the delineated target volume after the integration of FDG-PET in RTP in patients with lung cancer.[41] In head-and-neck cancer, where FDG-PET could be superior to structural imaging in the differentiation of viable tumour tissue after treatment and in the detection of lymph node metastases and unknown primary cancer, the value of FDG-PET for RTP is still under investigation.[41] In gliomas, where radiolabelled amino acids are avidly taken up by glioma cells, methionine-PET helps to define the tumour volume and differentiate tumour from normal tissue. An improvement in survival has been observed in patients with recurrent high grade gliomas, re-irradiated

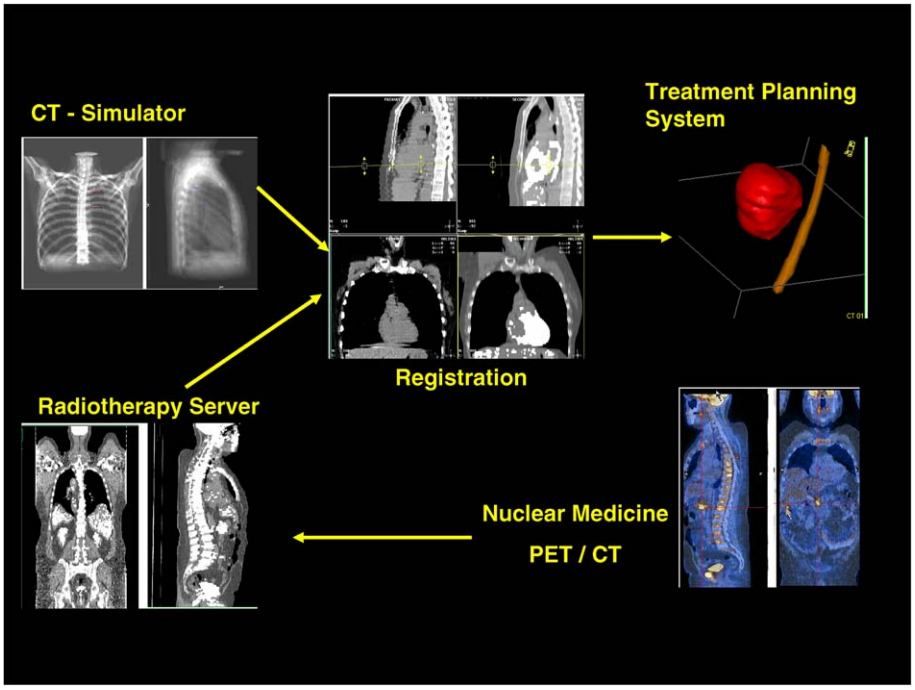


**Fig. 2 – Utility of PET in radiotherapy treatment planning process. As an example the imaged PET/CT dataset is transferred to the radiotherapy planning system and registered manually to the CT simulator dataset. Target volumes are defined on the combined images to generate a plan for radiotherapy treatment. (Courtesy: Dr. I. Rosenberg, University College Hospital, London).**

using methionine-PET in the treatment planning, in comparison with patients planned on MRI/CT images alone.[42] In prostatic cancer, where the utility of FDG-PET is limited, other PET markers such as choline and acetate are currently under investigation.[41] Finally, the real impact of RTP modification based on PET can only be determined by experimental and clinical evidence and detailed cost–benefit analyses.

### 4.4. *Anti-cancer drug development*

In addition to its potential role in the development of biological agents discussed earlier, PET can provide information on *in vivo* normal tissue and tumour pharmacology, which so far has relied on surrogate information obtained from body fluids. Such an understanding of both the drug's behaviour within the body (pharmacokinetics) and its effects (pharmacodynamics) could also aid in rational modifications to the drug development processes and hence save time. Moreover, hypothesis-testing clinical-trial designs can be used, allowing early proof-of-principle studies showing mechanism of action, which could be obtained during drug development. A number of PET patho-physiologic markers such as $[^{15}O]H_2O$ and $[^{18}F]$FDG have already been adopted as PET pharmacodynamic markers and used in the evaluation of anti-neoplastic agents.

#### 4.4.1. *Pharmacokinetic evaluation*

PET has been used to evaluate the early development of the anti-cancer agent DACA, a topoisomerase I and II inhibitor, prior to conventional phase I study (pre-phase I) setting in humans and in conjunction with phase I and II studies. Pre-phase I studies at 1/1000th levels of the phase I DACA starting dose and phase I pharmacokinetic studies during a 3 h and a 120 h infusion were performed with carbon-11 radiolabelled DACA.[14,15] These studies predicted potential myocardial toxicity as evidenced by saturation at phase I doses compared with pre-phase I doses,[15] although preclinical studies demonstrated a dose-limiting neurotoxicity.[43] PET-DACA studies with the 120 h infusion did not demonstrate saturable uptake in tumours although maximum tolerated doses in plasma were reached, which was likely to predict lack of efficacy of the agent.[14] These studies predicted drug efficacy and toxicity early during drug development that was not possible by other means.

Pharmacokinetic evaluation of temozolomide, an alkylating agent structurally related to dacarbazine has also provided valuable information. Temozolomide is a pro-drug that is stable in an acidic environment, which was postulated to become active in an alkaline pH.[44] This pH dependent activity allows for oral administration of temozolomide and it is hypothesised temozolomide targets tumours, where it undergoes ring opening and becomes active. Using a strategy of labelling temozolomide in two different positions with carbon-11 and performing paired studies in patients with gliomas, the pharmacokinetics of temozolomide were evaluated. Although exposure to temozolomide was higher in tumour than in the normal brain, there was no difference in ring opening in tumours compared with normal tissue, implying that activation did not preferentially occur in tumours compared with normal tissue.[16] Currently, temozolomide is the fastest growing drug in the treatment of brain tumours.

#### 4.4.2. *Pharmacodynamic evaluation*

PET can be used to evaluate a number of pharmacodynamic endpoints, which may either be true endpoint or a validated surrogate endpoint. In a phase I study of combretastatin, a tubulin-binding anti-vascular agent, tumour and normal tissue perfusion were assessed with [$^{15}$O]$H_2O$-PET at 30 min and 24 h after drug administration.[1] Tissue and tumour perfusion decreased with increasing doses, with tumour perfusion decreasing above a threshold dose of 52 mg/m$^2$. In contrast to normal tissue perfusion, which was reversed at 24 h, tumour perfusion continued to be suppressed. Such data indicates how PET imaging can provide insights for timing of drug administration. PET studies have also confirmed a pharmacodynamic relationship between dose and efficacy. In a study of labelled 5-FU in patients with metastases from colorectal cancer, a higher 5-FU-tumour uptake (SUV), was associated with longer survival.[45]

#### 4.4.3. *Proof-of-principle studies*

In the development of anti-cancer agents, hypothesis-confirming, proof-of-principle studies are sought at an early stage. As an example, the utility of PET in such proof-of-principle studies is illustrated for eniluracil, which is an inactivator of dihydropyrimidine dehydrogenase (DPD), the primary degradative enzyme of 5-FU. Inactivation of DPD would prevent the catabolism of 5-FU and channel 5-FU to its active anabolites. PET studies were based on the hypothesis that inactivation of DPD by eniluracil would result in a substantial decrease in uptake of the [$^{18}$F] radiolabelled tracer consisting of 5-FU and metabolites by the liver, which is the primary site of 5-FU catabolism by DPD. 5-FU pharmacokinetics evaluated prior to and after administration of eniluracil demonstrated a significant decrease in hepatic uptake and exposure to the radiotracer. In addition, a decrease in renal exposure with an absence of primary catabolite, fluoro-beta alanine (FBAL) in urine confirmed the mechanism of action of eniluracil.[2] The non-visualisation of radiotracer in the gallbladder after eniluracil demonstrated the absence of FBAL-conjugates after DPD inactivation.

### 4.5. *Evaluation of patho-physiology*

The relative lack of understanding of the underlying patho-physiological processes which drive a cell into neoplastic activity and poor knowledge on the specific differences between normal and cancer cells makes rational therapy development particularly difficult. PET, being a functional imaging modality can play an important role in the elucidation of patho-physiological processes. Such an understanding of the underlying disease processes would in turn potentially lead to rational drug discovery and aid in the manipulation of cancer therapy. Already, a number of patho-physiological PET markers, such as radiolabelled water (tissue perfusion), FDG (glucose metabolism)[13] and fluoro-misonidazole (hypoxia)[46] have already been adopted for clinical use and further PET markers to evaluate apoptosis,[47] angiogenesis[48] and gene expression[49] are undergoing animal studies.

It can be envisaged that for newer drugs, an imaging paradigm will be developed early during therapy development ensuring that the degree of modulation of PET probes in rodent tumours (which is associated with activity) is achieved in humans. The availability of new cameras designed for animal PET studies with high sensitivity and resolutions of less than 1 mm will greatly aid in the evaluation of such PET probes in animal models, prior to clinical use. It is envisaged that once the novel PET markers are validated they would be clinically evaluated in order to develop novel therapies and to consolidate and rationalise our current treatment strategies.

## 5. Conclusion

Molecular imaging with PET is a multidisciplinary field, necessitating close collaboration between oncologists, physicists, radio-pharmacists, and the pharmaceutical industry. Already, PET has had a significant impact in the field of oncology as a staging and diagnostic tool and its role in response assessment and prognostic evaluation is expanding. The potential of PET to influence cancer therapy is significant and its role in RTP and anti-cancer drug development is being increasingly recognised. The introduction of PET/CT, together with ongoing developments in the fields of cancer biology, radiochemistry and instrumental physics, is certain to fuel further developments in the field of molecular imaging. Its role in oncology is likely to increase further as knowledge of the underlying patho-physiology processes that drive a cell into neoplastic activity increases, which in turn can be aided by PET.

## Conflict of interest statement

None declared.

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