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ARTICLE

The role of PET in monitoring therapy

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Abstract

Positron emission tomography (PET) is being increasingly used for the evaluation of patients with known or suspected cancer at all phases of the management process from diagnosis, through staging to follow-up after treatment. The role of PET in therapeutic monitoring is expanding rapidly due to its ability to provide earlier and more robust identification of non-responders than provided by conventional non-invasive imaging approaches. PET can thereby potentially provide important benefits to the individual patient by allowing an earlier change to alternative treatments that may be more efficacious or by avoiding the unnecessary toxicity related to ineffective therapy. As therapies become ever more expensive, this could also produce cost savings because of earlier termination of ineffective treatment. Conversely, PET may demonstrate important biological effects despite a lack of apparent morphological response and therefore prevent premature withdrawal of effective therapies. Globally, the vast majority of therapeutic monitoring studies use the glucose analogue, fluorine-18 fluorodeoxyglucose (FDG) but new tracers such as fluorine-18 fluorothymidine (FLT) also offer promise for this application. In this review, the potential benefits and limitations of FDG PET are discussed along with suggestions regarding the most practical methodologies for response evaluation using this modality.

Keywords: *Therapeutic response; fluorine-18 fluorodeoxyglucose (FDG); drug development; fluorine-18 fluorothymidine (FLT).*

Introduction

Modern oncology is moving towards individualised cancer care which recognises that unique host and tumoral factors are likely to determine outcomes of treatment in any individual patient. Differential responses between individuals are likely to relate to biological factors that go well beyond variability in the bioavailability and metabolism of drugs. For example, development of clonal heterogeneity due to the intrinsic genomic instability could lead to differential therapeutic response in different lesions within any given individual. Similarly, micro-environmental factors may even alter the biological response characteristics of cancer cells within lesions. Thus, evaluation of therapeutic response must be able to assess the majority of sites of disease and to differentiate, reliably and early in treatment, responding from non-responding cell populations.

Monitoring response to cancer therapy has two important roles. First and most importantly, it is used to help clinicians determine the need for ongoing treatment in any individual patient and to guide what that treatment should be. Second, it is often used as an end-point to determine the efficacy of new cancer therapies in clinical trials. This role is becoming more important in drug development and has important implications for public health as the cost of developing new drugs continues to increase. In order to be a valid instrument for use in drug development, any therapeutic monitoring technique must be demonstrated to be a powerful surrogate for more important, but often more costly to obtain, measures of outcome including survival.

There are many potential methods for therapeutic monitoring. The least invasive and most widely accessible of these include measurement of tumour markers in blood or other body tissues. While these tests

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can be very helpful for tumours that excrete a tumour marker, this is neither universal nor necessarily specific. For modern biological therapies, biopsy evaluation of target modification, often termed biomarker analysis, is becoming more sophisticated but is invasive and potentially prone to sampling errors. Neither approach can characterise the location and extent of residual disease or the presence of heterogeneity within or between cancer lesions. Therefore, in clinical practice, imaging plays a fundamental role in therapeutic response assessment. Traditionally this has been based on changes in the dimensions of lesions as measured by structural imaging techniques like CT, ultrasound, X-ray or MRI. The most recent iteration of the methodology to be used for defining response of tumours to treatment is the so-called RECIST (Response Evaluation Criteria in Solid Tumors) criteria[1].

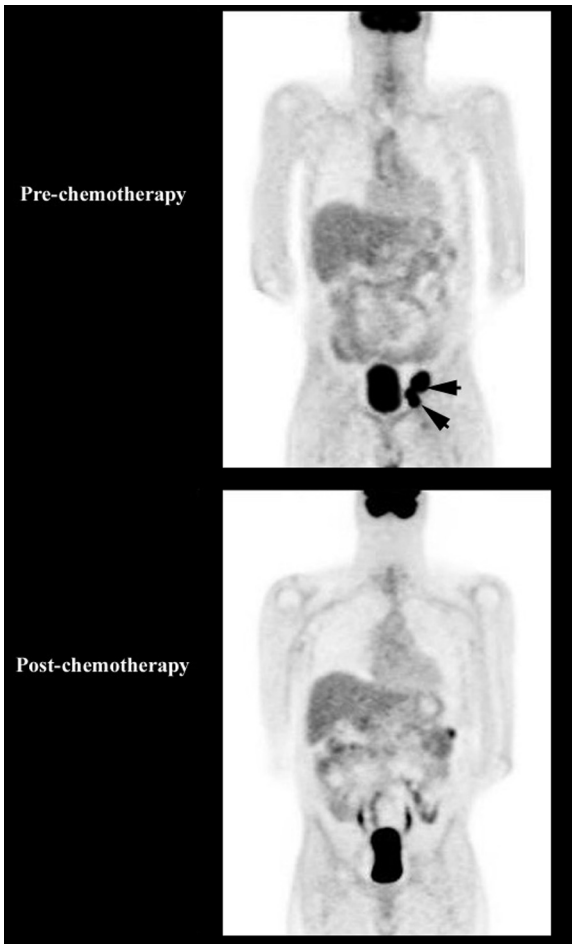

Figure 1 **On baseline PET scanning of a patient with widely metastatic malignant melanoma obtained before planned chemotherapy (above) a representative coronal image plane demonstrates foci of intense uptake in the left external iliac nodal stations (arrows) and at other sites not displayed in this plane. The iliac nodes measured up to 15 mm. Following three cycles of chemotherapy there was no change in the CT appearances but PET suggested a complete metabolic response (below). While cure is unlikely in this clinical setting, a favourable metabolic response encouraged ongoing therapy and may have prognostic implications. Normalisation of the images on hepatic activity enables qualitative evaluation of response.**

While the requirement for only uni-dimensional measurement has improved the simplicity of response assessment, changes in lesion size are relatively slow to occur, particularly when cancer lesions contain a pre-existing fibrotic or necrotic component. Secondary fibrotic changes in soft tissues adjacent to tumour sites as a result of radiotherapy or surgery may also complicate evaluation of therapeutic response. Furthermore, some disease processes heal by fibrosis leaving a significant residual mass, thereby limiting categorisation of a complete response. These limitations may lead to continuation of treatment for longer than necessary or to an unnecessary change in therapy. Conversely, structures such as lymph nodes that return to normal size with treatment may still harbour disease and hence partial responses may appear to be complete. This may lead to premature cessation of treatment. Similarly, when metastatic sites have normal appearances on CT, it is not possible to recognise disease regression.

One of the major advantages of PET compared to structural imaging techniques is that metabolic changes tend to occur more rapidly than regression of structural changes. Preliminary studies reported more than 10 years ago demonstrated that reduced FDG uptake in breast cancer preceded and predicted morphological response to chemohormonotherapy[2]. Since then numerous other studies have demonstrated that reduction in FDG uptake correlates with subsequent clinical and radiological response. However, metabolic changes can occur independent of structural imaging regression (Fig. 1). Recently, rapid reduction of FDG uptake in gastro-intestinal stromal tumours (GIST) following treatment with imatinib, an agent that blocks the c-kit oncogene product, has been demonstrated within 48 h of commencing treatment[3], well before any radiologic changes would be expected. Indeed, even in the absence of CT regression an ongoing metabolic response has proven a robust predictor of ongoing clinical response (Fig. 2). Similarly, despite radiologic response, ongoing metabolic abnormality is generally indicative of residual tumour and warrants ongoing treatment, if not necessarily a change in therapeutic approach (Fig. 3). The increasing body of evidence in support of the utility of FDG PET for evaluation of therapeutic response has led to recommendations for its wider use and attempts to codify response categories[4].

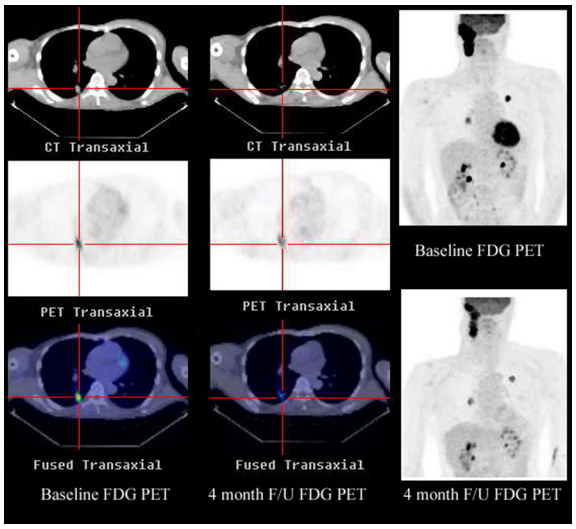

Figure 2 **Despite a very favourable response in lung lesions between baseline (left upper) and follow-up (middle upper) CT scans, FDG PET (middle centre) demonstrated ongoing metabolic abnormality consistent with only a partial metabolic response. Fused PET/CT images (left and middle lower) potentially enable partial volume correction. Baseline (right upper) and post-treatment (right lower) maximum intensity projection (MIP) images also revealed minimal metabolic response despite a clinical reduction in the size of cervical lymph nodes.**

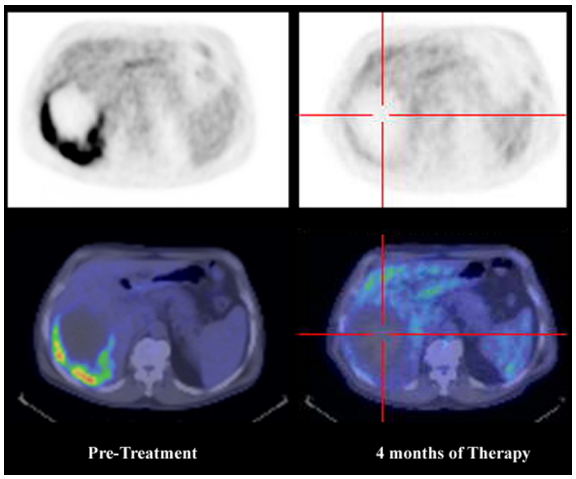

Figure 3 **Representative, co-registered FDG PET images (above) and fused PET/CT images (below) in the transaxial plane are demonstrated from a patient with a large, centrally necrotic GIST tumour at baseline (left) and 4 months after commencing imatinib (Glivec) (right). The hypermetabolic rim of the tumour had demonstrated a marked reduction in uptake within 1 week of commencing therapy (not shown) but the hypodense lesion on CT had increased slightly in size on follow-up. An ongoing metabolic response allowed the patient to remain on therapy with ongoing symptomatic benefit.**

What is a 'metabolic response'?

To differentiate between the morphological changes used as markers of therapeutic response based on conventional imaging, the changes occurring on PET in response to treatment are often referred to as a 'metabolic response'. Currently, this term is most often used to denote a qualitative or measured change in FDG uptake in tumoral sites. Rather than predefining criteria of response based on an ultimate FDG signal level after treatment or a given percentage change between the baseline and follow-up studies, most publications have used post hoc determination of the percentage change in the quantitative and semi-quantitative measures of FDG uptake to optimise the predictive accuracy of FDG PET for subsequent therapeutic response as subsequently documented by structural imaging, clinical examination findings or survival. A further significant variable in the methodology has been the temporal relationship of the response assessment to therapy delivery. As a consequence, the criteria for dichotomising patients into responders and non-responders have varied considerably with respect to both the definition of response used, and the percentage reduction in the measured parameter that is deemed to represent a given response category. In an attempt to achieve a consensus position, the European Organization for Research and Treatment of Cancer (EORTC) has promulgated guidelines for the methodology of performing serial FDG PET evaluations and for the standardisation of metabolic response categorisation[4]. While such attempts to simplify the process of metabolic response assessment are laudable, this approach has many limitations. For example, while a reduction in FDG uptake in lesions is usually seen in responding lesions, in some situations a transient increase or 'metabolic flare' may be predictive of subsequent clinical benefit. This has recently been described in the setting of introduction of tamoxifen in metastatic breast cancer[5]. This may reflect a partial agonist effect of the treatment drug on oestrogen receptor-positive cells or increased energy utilisation related to induction of apoptotic pathways. *In vitro* data suggest that a transient increase in FDG uptake can also occur following exposure of cells to radiation[6]. These factors suggest that the timing of the follow-up scan may be critical to characterisation of response, and may also be therapy specific. For example, while early reduction in FDG is typically seen in responding patients within studies using chemotherapy, a lack of significant change on FDG PET early following external beam radiotherapy has been described to have an imperfect negative predictive value for subsequent clinical response[7].

Methodological issues

The methods that have been used to assess metabolic response have varied in complexity from simple quali-

tative comparison of baseline and post-treatment scans to fully quantitative evaluation approaches involving arterial blood sampling, prolonged dynamic imaging and complex compartmental modelling. These techniques have different strengths and limitations.

Qualitative reporting of metabolic response

Despite its simplicity, the subjectivity of qualitative reporting has been seen as a limitation. While a 'complete metabolic response' is likely to be fairly consistently applied between individual reporting physicians and between institutions when there is a normalisation of the PET scan appearances, an inflammatory response to therapy can limit the number of patients achieving such a designation[8]. Although these inflammatory changes often have a different distribution that residual tumour[9], they can pose interpretative difficulties, particularly for less experienced PET readers. When the scan appearances do not return to normal, the methodology used to define a qualitatively incomplete metabolic response remains poorly defined at this time. As with any qualitative analysis of digital data, consistent display of the PET images is critical if reproducible results are to be obtained. Just as it would be inappropriate to evaluate a lung lesion by CT using lung windows on one occasion and using mediastinal soft tissue windows on another, it is also inappropriate to use inconsistent thresholding of PET images. One approach to standardisation is to display the baseline and post-treatment scans on a scale based on the standardised uptake value (SUV). The SUV is a parameter that corrects absolute radioactivity per gram of tissue for the amount of radioactivity administered, radioactive decay and the size of the individual[10]. Assuming a uniform distribution of radiotracer throughout the body and no elimination except by radioactive decay, the SUV in all tissues would be unity. However, due to excretion of radiotracer from the body and active accumulation of activity by other tissues, the measured SUV in different tissues can vary significantly. Organs like the brain and liver which actively take up FDG, even under fasting conditions, tend to have SUV measurements considerably above 1.0 while tissues like the lung and adipose tissue that have minimal use of glucose per gram of tissue have very low SUV recordings. Most cancers have a SUV of greater than one, and often much greater. There are some practitioners who believe that a cut-off SUV of around 2.5 is useful to separate benign from malignant processes but some tumours can have a SUV of less than 2.5 while many active inflammatory processes have SUV values higher than this (Fig. 4).

An alternative to using a SUV-calibrated scale is to normalise the two sets of images so that the intensity of a reference tissue on each scan is adjusted to the same grey or colour scale level. This can be done using visual cues or through software techniques. For qualitative analysis we normalise co-registered baseline and follow-up FDG PET scans using the liver as the reference tissue, reasoning that, apart from the brain and, variably, the heart, hepatic tissue has the highest normal soft tissue uptake of FDG under fasting conditions. Using a linear grey scale, the liver is set in the middle of the 256-level grey scale (mid-grey) (Fig. 1). For fused PET/CT images we use a rainbow colour scale for the PET data with the liver set at the interface between blue and green. Using these guidelines the intensity of tissues such as mediastinal blood pool, and bone marrow can be reproducibly compared to hepatic activity and the relative intensity of tumour deposits can also be appreciated between studies.

In our facility we have developed and use a standardised nomenclature for qualitative reporting of serial FDG PET scans in therapeutic monitoring that can be applied to all tumour types. In our schema, a complete metabolic response (CMR) is defined as a return of FDG uptake in previously documented lesions to a level equivalent to, or less than, residual radioactivity in normal tissues within the organ in question. A partial metabolic response (PMR) constitutes a significant reduction in FDG uptake in tumour sites based on visual inspection of appropriately displayed comparative images. Stable metabolic disease (SMD) and progressive metabolic disease (PMD) are defined respectively by a lack of change, or an increase in the intensity and extent of metabolic abnormality in a pattern consistent with tumour growth. We have reported that powerful prognostic stratification is provided using this schema for the evaluation of therapeutic response to radical radiotherapy in patients with non-small cell lung cancer (NSCLC) when patients are imaged 4–12 weeks after radiotherapy[11]. The frequency and prognostic value of a CMR are likely to be influenced by the responsiveness of the tumour to treatment, the biological aggressiveness of the disease process and the timing of the follow-up scan after treatment. While patients with a complete metabolic response will not necessarily be cured, it is likely that the majority of those patients who achieve a durable remission of cancer will come from this group of patients. Supporting this, the prognostic value of a complete metabolic response on qualitative evaluation of FDG PET after completion of chemotherapy has also been demonstrated in lymphoma[12].

Quantitative and semi-quantitative analysis of therapeutic response

The earlier that FDG PET scanning is performed during therapy, the lower the likelihood that the metabolic signal from remaining viable cancer cells will reduce to a level where it is undetectable or that qualitative progression will have occurred. Therefore, partial metabolic responses or stable disease have predominated in many FDG PET therapeutic monitoring trials, particularly those involving chemotherapy. Where abnormal radiotracer uptake remains in a lesion, determination of the degree

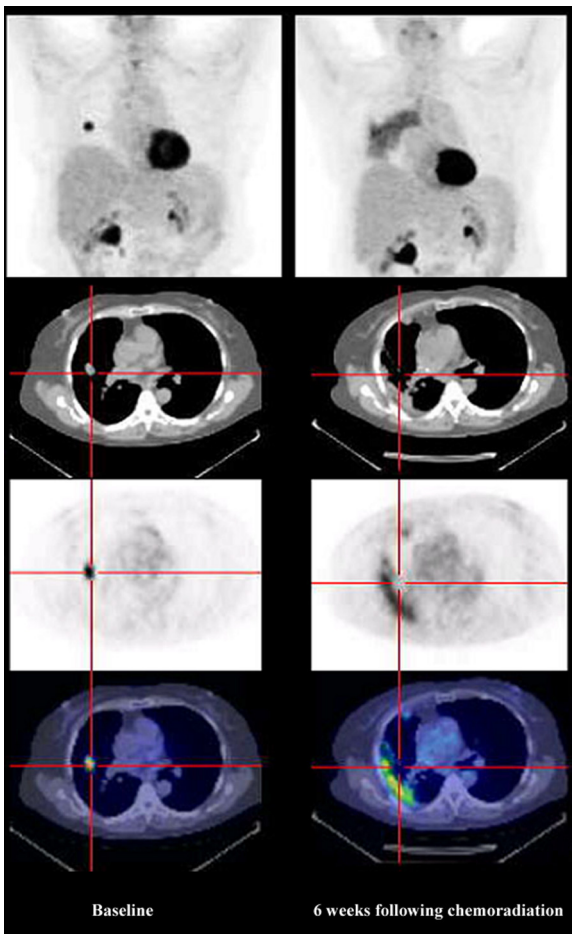

Figure 4 **Maximum intensity projection (MIP) images (above) of the baseline (left) and follow-up (right) FDG PET studies demonstrate a change in the distribution of metabolic abnormality from focal uptake related to a known non-small cell lung cancer to a geographic pattern consistent with radiation pneumonitis within a radiation portal. The reference transaxial CT images at the level of the primary tumour in the right mid-zone (upper) demonstrate almost complete resolution of the primary lesion but progressive pleurally based changes. Corresponding transaxial PET (middle right) and PET/CT fused (lower right) images following treatment demonstrate no uptake in the primary tumour site but increased activity related to the radiographic abnormality. Based on the pattern of abnormality, no further treatment was given. Although progressive radiation fibrosis of the lung was observed, no local recurrence has been confirmed. The SUV in the presumed area of pneumonitis was similar to that recorded for the primary tumour at baseline demonstrating the limitations of relying purely on semi-quantitative measures to differentiate between benign and malignant processes.**

to which it has reduced may have therapeutic and prognostic implications. In such cases, measurement of lesion radiotracer uptake may provide more objective evaluation than qualitative assessment. There are a number of techniques by which FDG uptake can be measured in tumour sites. These vary in complexity and reproducibility and, as yet, there is no consensus on the most appropriate method.

Using the exquisite sensitivity of PET for the measurement of radioactivity in both the blood and tissue over time, it is possible to use tracer kinetic models to quantify biochemical processes *in vivo*. Such approaches have provided unique insights into the mechanism of many diseases and continue to offer great potential in basic science applications of this technology[13]. However, tracer kinetic modelling involves assumptions that may not necessarily be valid in cancer cells[14] and represents a technically and computationally complex technique that is not easily implemented in clinical practice. For oncological applications the major impediment to the routine application of quantitative measurement of glucose metabolic rates is the need to perform single bed-position dynamic imaging for an hour or more. This limits evaluation to 10–25 cm of the body, depending on the axial field of the scanner used and negates the whole body screening advantages of modern PET scanners or necessitates an additional whole body study be performed after completion of the dynamic scan. This significantly decreases throughput of patients and thereby increases the cost of PET. Furthermore, where differential responses may occur in various tumour sites, it is not possible to prospectively identify which target lesion might be best for quantitative evaluation. Nevertheless, there have been numerous studies that have used quantitative measurement of glucose metabolic response that have demonstrated that FDG PET performed early during therapy can predict subsequent morphological response. Serial calculation of SUV calculations or tumour to background ratios (TBR) can be applied to whole body images and provide a more practical option. Again, there are numerous studies demonstrating that a reduction in these semi-quantitative parameters is predictive of a subsequent morphological response[4].

Validation of metabolic response as a surrogate for therapeutic response

Having recognised the significant limitations of morphological imaging in assessing therapeutic response, the demonstration that an early FDG reduction correlates well with subsequent reduction in tumour dimensions is not sufficient to validate PET as a therapeutic monitoring tool. Many authors have therefore sought to validate metabolic response by comparison with subsequent evaluation of pathological response. While this may appear to be an objective method of validation, it is only pertinent to those patients who come to surgery or biopsy, and may be subject to sampling

error. Since many patients now receive chemotherapy or radiotherapy alone or in combination as part or all of their cancer therapy, pathological validation of therapeutic response is often not feasible. This poses significant problems for the evaluation of the clinical efficacy of PET as a therapeutic monitoring tool[15]. Furthermore, the presence of apparently viable cells in a pathological specimen after treatment with radiotherapy may not necessarily indicate that these cells have long-term clonogenic potential. In a study of patients who underwent surgery after a negative PET scan following radiotherapy for head and neck cancer, there was a significant false negative rate but this was not mirrored by a high relapse rate in patients who were managed conservatively without surgery[16]. Accordingly, it is likely that PET will only be a worthwhile technique for therapy response monitoring if it provides a more robust and practical surrogate for outcomes such as progression free or overall survival. While preliminary results are encouraging, further studies evaluating the prognostic significance of metabolic response results are required.

The potential advantages of PET/CT

The whole body screening capability of PET enables discordant responses to be readily apparent. Furthermore, PET is not limited to 'measurable' lesions in the manner that CT or MRI are. By demonstrating differential metabolic responses, PET, particularly when performed on current generation combined PET/CT scanner, allows biopsy to be guided to areas of suspected viable tumour[17]. While improving the ability to confirm residual disease, this technique also offers the potential to assay the genomic features of poorly responding sites. This may provide insights into mechanisms of treatment resistance and thereby identify new therapeutic approaches. By demonstrating the presence of significant non-viable components prior to treatment, PET/CT should also improve assessment of the reduction in disease bulk with neoadjuvant therapies (Fig. 3). The marrying of structural and functional information ought also to allow superior sensitivity for residual small volume disease by allowing corrections to be made for partial volume effects. For example, faint residual uptake in a tiny lung nodule that was previously intense on the baseline evaluation is likely to reflect residual tumour, whereas uptake of similar intensity through a sizeable residual mass in the lung is likely to purely reflect normal soft tissue activity.

Alternative tracers

One of the major limitations of FDG PET is the relative non-specificity of increased glucose metabolism for malignancy. There are many active inflammatory diseases and some aggressive benign tumours that can have high FDG-avidity. PET tracers that demonstrate an increased rate of cellular proliferation are likely to be particularly helpful in the setting of therapeutic monitoring since they are less likely to be taken up in inflammatory conditions. The search for proliferation markers has been active with most attention to thymidine analogues. Although C-11 thymidine has been synthesised and used to evaluate the proliferative rate of tumours, the short physical half-life of C-11 and the metabolic degradation of the radiotracer limits its clinical application. To date, the most promising of proliferation tracer for clinical application appears to be [^{18}F]fluorothymidine (FLT)[18,19]. Automated synthesis units are now commercially available for this agent. There is good evidence that FLT uptake is closely correlated with cellular proliferation with correlation between the intensity of uptake as measured by SUV with proliferation indices such as Ki-67 staining in suspected lung cancer lesions undergoing resection[20]. Thus, FLT is an exciting tracer for therapeutic monitoring, particularly for therapies that may have a tumoristatic rather than tumoricidal mode of action. A range of other PET tracers are available that may have relevance to therapeutic monitoring[21]. For example, demonstration that tumour hypoxia, as imaged by fluorine-18 fluoromisonidazole (FMISO) PET, is present in the majority of locally advanced head and neck cancers[22], suggests that follow-up scans may be useful to assess the utility of targeted therapy with the hypoxic cytotoxin tirapazamine.

Conclusion

PET is already an important technique for assessment of therapeutic response. Improvements in PET methodology, its wider availability and development of better tracers will likely increase the proportion of studies that are performed for the purpose of determining ongoing treatment strategies. There is also a growing awareness of the potential of PET to provide a clearer idea of the relative efficacies of competing therapies, well before such information could be obtained from therapeutic trials using conventional monitoring strategies. Accordingly, the pharmaceutical industry and regulators are developing strategies for incorporating PET into drug development.

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