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Point of View

Positron emission tomography (PET) in diagnostic oncology: is it a necessary tool today?

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I have been asked to address this question as a clinical oncologist running a programme developing PET methodology to provide novel *in vivo* molecular imaging for translatory research in oncology. It is from this prospective that I consider the question of whether PET is a necessary tool in 'diagnostic' oncology.

1. What PET really is

Positron emission tomography (PET) uses radionuclides to label molecules which then can be imaged in man providing quantitative kinetic information. The inherent sensitivity and specificity of PET methodology is the most important strength of the technique [1]. PET can image molecular interactions and pathways, providing quantitative kinetic information down to the sub picomolar level. While it lacks the spatial resolution of magnetic resonance imaging (MRI) or computed tomography (CT), it is unrivalled in specificity and kinetic sensitivity. It has a huge future in oncological translation research [2].

Internationally a clinical need has been recognised to determine mechanisms of action and efficacy of anticancer therapy. Molecular imaging using PET is being developed to assess such *in vivo* pharmacokinetics and pharmacodynamics. However, few groups internationally currently have the range of expertise in radiochemistry, data analysis, bio-mathematical modelling and kinetic analysis to advance and exploit the technique for these purposes, so progress has been slow. Thus, whilst the technique is maturing and showing its worth as a research tool in neurology and psychiatry, it is still in its infancy in oncology.

2. What many clinicians think PET is

The vast majority of work that has been performed in PET in oncology has been simple static ^{18}[F]-fluorodeoxyglucose (FDG) imaging. This is because this is an available tracer and is methodology looking for an application. So far most of the oncology community sees and understands PET as a technique providing static ^{18}[F]-FDG images of tumours. The method is being promoted by the nuclear medicine community to oncologists for diagnostic imaging and staging. We are shown nuclear medicine 'hot spots' rather than kinetic molecular information. This is equivalent to having a Rolls-Royce (PET) and not only keeping it in the garage but keeping the doors shut as well (hot spots).

The argument about the future of PET in oncology has been discussed elsewhere [2]. However, we are discussing here not the value of PET in translational research, but whether ^{18}[F]-FDG static imaging is a necessary tool today in diagnostic oncology.

3. ^{18}[F]-FDG PET in diagnostic oncology

FDG is an analogue of glucose which is labelled with fluorine-18, a medium-lived positron emitter ($t_{1/2} = 109$ min). ^{18}[F]-FDG can be distributed to many centres from central sources and used in nuclear medicine departments. It can be imaged with a PET camera and shows preferential uptake of ^{18}[F]-FDG in tumours [3]. This is currently thought to be mainly due to the overexpression of GLUT-1 receptors on tumour cells [4]. There are, however, interpretation problems [5] and most significantly, ^{18}[F]-FDG is taken up in macrophages and so areas of inflammation can give false-positives.

There are a number of areas where ^{18}[F]-FDG PET's use has been promoted in diagnosis oncology.

3.1. Diagnosis of malignancy

The amount of ^{18}[F]-FDG uptake in peripheral lung lesions has been shown to discriminate tumours from benign lesions, the malignant lesions showing an

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increased uptake [6]. With experienced PET groups, several thoracic surgeons will now remove or leave peripheral lung lesions without a diagnostic biopsy based on the data from ^{18}[F]-FDG PET alone. Some thoracic surgeons will, therefore, argue this is a necessary tool. This has yet to be challenged medico-legally. As fine needle aspiration diagnosis becomes safer, the balance may swing and the diagnostic certainty of tissue diagnosis may outweigh the 80–90% certainty of the PET diagnosis. In no other situation has diagnosis using PET shown such certainty, allowing biopsies to be avoided. So currently, in a vast majority of cancers we still require tissue diagnosis. With the development of invasive radiology for histological assessment, plasma analysis using molecular biology techniques to look for other markers of malignancy, PET as a 80–90% accurate tool for diagnosis may become less important.

3.2. Staging

^{18}[F]-FDG PET has been used for loco-regional staging with some success [7,8]. Whole body PET imaging has been developed over the last few years [9]. A 'soft tissue bone scan' is produced by imaging of the whole body. Studies are suggesting that metastatic disease can be picked up that is missed by conventional imaging [10]. Oncological staging using ^{18}[F]-FDG is being promoted in a number of countries. However, it should be used as an adjuvant for the current, more standard staging and imaging methods. It will take a number of good, long-term clinical studies to define its role either for reclassifying staging or for seeking occult malignancies. It is difficult to predict if developments in standard imaging for staging such as CT and MRI will outstrip any possible advantages of whole body ^{18}[F]-FDG PET with its inherent false-positive and false-negative rates. In addition, from a wider perspective, with current therapies, there are only a limited number of oncology situations where additional imaging to increase the percentage chance of finding metastatic disease will affect the treatment decisions and/or treatment outcome.

3.3. Assessment of response to therapy

Some centres are developing PET to assess functional responses in tumours. This may provide additional clinical information such as assessing subclinical response or response where no volume change is anticipated, for example, following cytostatic therapy. ^{18}[F]-FDG uptake is broadly proportional to cell number and so a metabolic response marker could be useful. However, methodological developments in this area are still required before this can be considered as a standard technique. One of the areas of contention is the detail with which one performs the ^{18}[F]-FDG measurement. Clinically a quantitative measure of change will be far more useful than a non-quantitative one. The EORTC PET Study Group has recently produced guidelines for the use of ^{18}[F]-FDG to assess response [11].

4. Arguments for ^{18}[F]-FDG PET in diagnostic oncology

The advantages of ^{18}[F]-FDG diagnostic PET to individual patients currently may be restricted to those in whom a biopsy or an operation may be avoided. If healthcare systems nationally continue to fund this indication then we will acquire much information which will help nuclear medicine doctors develop expertise for PET imaging and promote the technology. In principle, in oncology, we should be moving from anatomical imaging to combined anatomical and functional imaging. It is only by using the technology that it can develop.

5. Arguments against ^{18}[F]-FDG PET in diagnostic oncology

Currently, ^{18}[F]-FDG to diagnose or stage tumours provides supplementary information. In a financially restricted healthcare system one may not be able to justify its use. There has been an explosion of ^{18}[F]-FDG imaging for tumours over the last 5–10 years. There is a perception by nuclear medicine PET doctors that oncologists want to see more tumours. Unfortunately this exposes a basic misunderstanding of cancer biology and therapy which should not be perpetuated in the oncological field or in the radiological community. Our priority is not diagnosis of more tumours, but more effective treatment. If we are sold a technique where we see more tumours, then this only moves us a small way forward.

6. Threats to PET oncology development from its sole use in diagnosis

1. The oncologists' introduction to PET is currently through static imaging. This hides the unique opportunity that PET provides. Very few oncologists have a working knowledge of PET methodology and only a handful of oncologists around the world have a good knowledge of the area and access to PET methodology groups. PET has a huge future, but its development requires advances in methodology to answer specific oncological questions. This will only occur if PET oncological programmes are led in a clinical and scientific oncological direction. Until oncologists help lead PET oncology programmes, it will be difficult

to prioritise the methodology for the oncology community.
2. There is a limited expertise in many countries for PET in oncology. If the available expertise is all directed to diagnostic work then little will be available for what is required outside this field. In this regard, PET for diagnosis is really a deviation and not a major advance.
3. PET may promise too much too soon. Few physicians and scientists outside the PET area have been given the opportunity to grasp just how complex PET methodology can be. Imaging science comprehensively deals with the specificity of the tracer molecules, data requisition, bio-mathematical models and is a science in its own right.
4. Bad science. Image assessment can be too subjective. PET is a unique tool for oncological translational research. However, we need more methodological developments to address the questions we need answering. We do not need to simplify the methodology and then try and find applications for a watered down subjective imaging technique.

7. What is needed for PET oncology to develop

We need more oncologists, basic scientists, drug development scientists and discoverers involved in the molecular imaging PET field. We do not have a critical mass or anywhere near the number of applications groups internationally. Until we convince clinical oncologists that basic science in PET in oncology has a long-term scientific future then they will not get involved. The PET community needs to appreciate that the clinical use of diagnostic ^{18}[F]-FDG PET for detecting metastatic disease may have a place, but may be of only limited value in the future. The big challenge is what we do with cancer, i.e. therapy. Here diagnostic PET units could make a significant contribution by using PET to produce a high sensitivity objective measure of functional response. Research PET units need to develop molecular imaging methodology for *in vivo* pharmacokinetics, investigation of *in vivo* mechanisms of action and specific pharmacodynamic endpoints. For this we need to move away from ^{18}[F]-FDG and develop more specific tracers.

8. Conclusion

PET in diagnostic oncology is a relatively, but not absolutely, necessary tool today. However, we will not be able to justify its long-term use as a diagnostic tool using ^{18}[F]-FDG alone or using just static information. There is a huge future for PET in oncology. We need to develop PET methodology in order to answer the important questions in oncology that cannot be answered in any other way. For that we need more specific tracers and more emphasis on kinetic molecular imaging.

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