From a Personal Point of View

The role of molecular imaging in personalised medicine is set to become far more prominent, especially in the field of oncology, with a wealth of techniques available to researchers and diagnosticians

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Worldwide cancer incidence is progressing rapidly with a strong impact on global society. Currently, WHO estimates that cancer associated mortality will increase by 51 per cent by 2030, leading to hundreds of billions of dollars in healthcare costs in western Europe alone. Forty per cent of these costs will have to be covered directly by healthcare systems to provide treatment and care for patients. On the other hand, medical cures in oncology remain inefficient, with a mean positive response rate of less than 20 per cent. New targeted therapies are expected to enhance cure rates, but this will strongly depend on the ability to select responsive patients at an earlier stage.

The development of biomarkers will improve the dynamics of personalised medicine and fill the unsatisfied needs in oncology for patient selection and prediction of therapeutic response. Molecular imaging enables a non-invasive quantification of specifically designed biomarkers. Among these imaging technologies, positron emission tomography (PET) is the most sensitive method that can be applied to quantify small molecules. However, the lack of a diversity of radiotracers and their often low specificity limits its use in clinical applications.

The introduction of new treatments requires that patients are specifically stratified and monitored to assess their response to the treatment. Co-development of specific biomarkers, as well as new tools for medical imaging, is a prerequisite to fully benefit from the progress taking place in targeted therapies. In addition, selecting the right drug for patients at an early stage in the process will be the only way to justify the high costs of the new targeted treatments.

A biomarker is an objectively measurable parameter; an indicator of a normal biological process, a pathological process or the pharmacological response to therapeutic intervention. Specific biomarkers have the potential to allow:

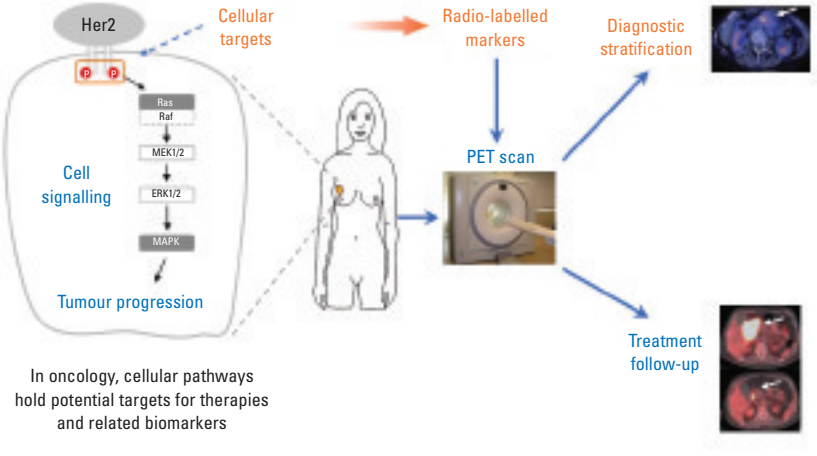
- Stratification of patients; namely the identification of subsets of patients that are 'responders' to treatment (efficacy or tolerance)
- Rationalisation of combination therapy
- Assessment of the effectiveness of treatment
- Accelerated development of new molecules

PET Technology Application and Radiotracer Use in Oncology

Unlike structural imaging, which allows morphological analysis of the organs, functional imaging provides information on the workings of the human physiology. These technologies include PET and single photon emission computed tomography (SPECT), which are used regularly by nuclear medicine services. These technologies are also grouped under the term 'molecular imaging' as they allow the visualising of processes at the cellular or molecular level (both disease mechanisms and specific biological targets).

At present, PET scans are approved for the monitoring and diagnosis of many cancers (see Table 1, page 50). The scans show strong application growth, despite the availability of only a single radiotracer, [^{18}F]-2-fluoro-2-deoxy-D-glucose ([^{18}F]-FDG).

Figure 1: Principles of PET biomarkers



In oncology, cellular pathways hold potential targets for therapies and related biomarkers

At least nine Phase 3 studies are now underway for additional PET applications in oncology (various forms of lymphoma, brain tumours, colorectal cancer, prostate cancer and so on) (1). To date, 101 PET radiotracers were tested in humans according to the Molecular Imaging and Contrast Agent Database (MICAD), which lists all imaging products marketed or under development. However, few have reached an advanced stage of development.

Figure 2: PET biomarker application

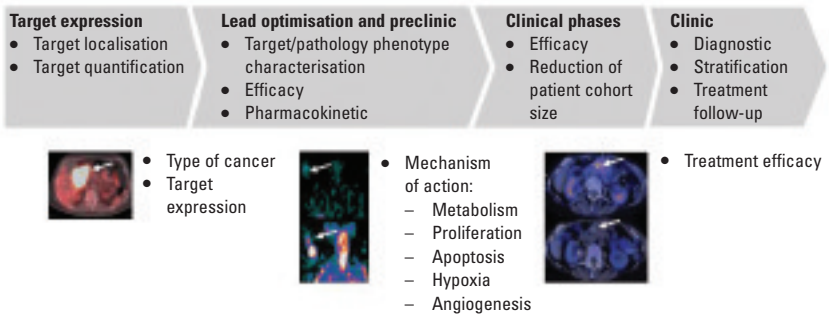


Table 1: Approved applications of ^{18}FDG in oncology in the US

Type of cancer	Diagnosis	Definition of tumour stage	Treatment monitoring
Breast		✓	✓
Cervical		✓	
Colorectal	✓	✓	
Oesophagus	✓	✓	
Head and neck	✓	✓	
Lung (NSCLC)	✓	✓	
Lymphoma	✓	✓	
Melanoma	✓	✓	
Pulmonary nodule	✓		
Thyroid		✓	

Source: Fass, Molecular Oncology, 2008

Table 2: Characteristics of radiotracers currently in clinical development in oncology

Radiotracers	Development phase	Cancer	Clinical trial start	Country	Clinical trial
^{18}F-DOPA	Phase 2	Thyroid	2007	France	NCT00647140
	Phase 0	Brain (children)	2007	US	NCT00556153
^{68}Ga-DOTANOC	Phase 0	Neuroendocrine	2008	Israel	NCT00569738
^{18}FDHT	Phase 0	Prostate	2003	US	NCT00588185
^{11}C-acetate	Phase 1/2	Prostate	2008	US	NCT00771550
	Phase 0	Prostate	2005	US	NCT00392938
	Phase 0	Divers	2008	Israel	NCT00687778
^{11}C-methionine	Phase 0	Multiple	2005 (done)	US	NCT00139204
	Phase 2/3	Prostate	1997	US	NCT00002981
^{18}F- or ^{11}C-choline	Phase 0	Prostate	2008	Israel	NCT00706212
	Phase 2	Prostate	2008	Denmark	NCT00670527
	Phase 3	Prostate	2007	Germany	NCT00520546

Source: ClinicalTrials.gov

Fluorodeoxyglucose (^{18}FDG)

The only currently authorised clinical PET radiotracer is ^{18}FDG. Its major clinical application concerns oncology, but indications in cardiac imaging and imaging of dementia also exist, and are currently being developed for this tracer. ^{18}FDG is a marker of metabolism, as it is a glucose analogue that cannot be fully metabolised by cells. It is therefore accumulated by those cells that have a high glycolytic activity, as is frequently the case for cancer cells. ^{18}FDG thus reveals all cells with high glucose consumption, including healthy ones such as brain or immune cells. However, the tracer has a number of limitations, particularly in terms of disease indication and specificity. It does not detect all cancers and is unable to achieve a full primary staging of metastases.

Emerging Radiotracers

Among the new PET radiotracers, the one that is most advanced in clinical oncology is fluorothymidine (^{18}FLT), but it has not yet received marketing approval. This tracer is currently in Phase 3 for monitoring breast cancer and is also being tested in Phase 2 studies for several other oncology applications (including lung, colon, head and neck cancers). Its uptake mechanism depends on the synthesis of DNA, a biological process that is characteristic of dividing cells. Preclinical studies have shown a clear relationship between the accumulation of ^{18}FLT and levels of tumour proliferation, although the mechanisms of DNA repair have to be taken into account and may complicate the interpretation. Several clinical studies suggest a good specificity for tumour cells, but with a sensitivity that is lower than that of ^{18}FDG.

^{18}FLT could answer questions that are insufficiently addressed by ^{18}FDG, such as the characterisation of tumours in terms of aggressiveness and prognosis. It might be able to differentiate malignant and benign tumours and could provide an *in vivo* mapping of tumour proliferation which, when used with other evidence, including biological information, could allow the development of a therapeutic strategy. A very important aspect – for both the patient and from an economic perspective – is the evaluation of the effectiveness of anti-tumour treatment, especially the early assessment after the first or second course of chemotherapy. This would allow a rapid change of treatment in case of inefficiency. Early assessment of chemotherapy

efficacy could represent the primary indication of ^{18}FLT, complementing rather than competing with current indications of ^{18}FDG. The future of ^{18}FLT will most likely be in the pre-therapeutic prognostic characterisation, rather than in the diagnosis and staging of tumours.

Other radiotracers that are most advanced in the oncology field were reviewed by Pantaleo *et al* (2) (see Table 2, page 50) and these include:

- ^{18}F-DOPA
- Radiotracers targeting somatostatin receptors, such as the ^{68}Ga, ^{68}Ga-DOTATOC and DOTANOC
- Labelled hormone analogues such as fluorodihydrotestosterone (^{18}FDHT) for prostate cancer and fluoroestradiol (^{18}FES) for breast cancer
- ^{11}C-choline
- ^{11}C-acetate
- ^{11}C-methionine

^{18}F-DOPA targets the dopamine system and was initially developed for the study of Parkinson's disease, although its applications in oncology are being evaluated.

The radiotracers specific to somatostatin receptors (^{68}Ga-DOTATOC, ^{68}Ga-DOTANOC and other derivatives of somatostatin) may be useful for diagnosis and the detection of neuroendocrine tumours.

The radiotracers labelled with carbon-11 for which development is well advanced (^{11}C-choline, ^{11}C-acetate and ^{11}C-methionine) are markers of metabolism. However, these molecules have an important drawback: ^{11}C has a very short half-life of 20 minutes (compared to nearly two hours for ^{18}F). Their use is therefore restricted to hospitals with a nearby cyclotron for the production of this radioisotope.

Other radiotracers based on monoclonal antibodies with grafted radioisotopes are also currently in development, such as ^{89}Zr-cetuximab or ^{64}Cu-trastuzumab. Although very specific, these tracers do have disadvantages, as the labelling of high molecular weight antibodies is complex; they can be degraded in the liver and their radioactivity may remain present for too long.

Moreover, tracer products that compete for the same molecular target as the therapeutic agent might be difficult to apply in a clinical setting, due to the increased complexity in treatment monitoring. Their application is limited to acting primarily as a companion biomarker to identify the levels of presence of the target. With regards to the cost/benefit ratio for routine use, this type of PET radiotracers may not be competitive when compared to *ex vivo* tests.

Key Unmet Needs in Oncology and PET Imaging

The lack of sufficient therapeutic and diagnostic tools represents a major unmet need in oncology today. Current treatments are often ineffective and can cause significant side effects. Early detection and surgery remain the best therapeutic factors for many cancer types. The correct diagnosis and stratification of patients remains a difficult task. In order to ensure proper use, targeted therapies require a precise diagnosis to determine if the therapeutic target is hyperactivated (such as Her2 in breast cancer) in order to predict whether the treatment will be effective. Currently, only

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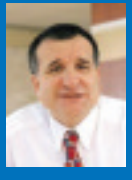

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three diagnostic tests are required by the FDA for the use of a drug (Herceptin, Erbitux and Sprycel) and a dozen other theranostic combinations (biomarker/drug) are available. However, no predictive test is available for commonly used therapies such as Avastin. There is no rationale to know *a priori* whether this therapy will be effective. The monitoring of treatment efficacy in real-time is still in its infancy; the use of PET in the clinical monitoring of treatment is permitted only for breast cancer in the US.

The application of PET imaging in oncology is still limited due to the emerging nature of this technology. Only one radiopharmaceutical, ^{18}FDG, is currently routinely authorised and while useful for many applications, there remains a large number of cases where it cannot be used. ^{18}FDG does not identify all types of cancers and is not precise enough to detect small primary tumours for two main reasons: its low specificity due to frequent false positives, especially in cases of inflammation or benign tumours; and its low sensitivity for tumours with low glycolytic activity, such as carcinoid tumours. Moreover, ^{18}FDG does not track early treatment after radiotherapy or surgery, critical to the development of personalised medicine, as there is a bias induced by inflammation due to treatment. The use of ^{18}FDG can also lead to misinterpretation of results, for example there may be a decrease in glucose uptake without inducing apoptosis in the case of treatment of GIST with Gleevec; or cancer cells may increase their capture of FDG after treatment (in the case of inflammation and hormonal therapy, for example). Other PET radiotracers highlighting the cell metabolism have similar issues to ^{18}FDG, including not being specific to tumour cells and having limited application to certain types of tumours. In the near future, PET biomarkers will most likely be dedicated to specific cancer indications and, with regard to the cost of their development, the challenge will be to find a large market application.

Conclusion

Due to the limited number of available radiotracers, PET imaging is currently seen mainly as a metabolic imaging tool with limited applications. New radiotracers will push their use much further and reveal the full potential of PET imaging. The ultimate goal is to exhibit and quantify a specific cellular process or a type of targets (such as kinases) that are closely related to tumour progression and carcinogenesis, leading to truly targeted molecular imaging. The development of new, more specific tracers is a prerequisite for the use of PET as the technology of choice for diagnostic molecular imaging. For commercial feasibility, development needs to focus on radiotracers that can potentially be used for various cancers (or various targeted therapies), which will significantly increase their market potential and make it worthwhile for imaging diagnostic companies to invest further in this field.

The development of PET radiotracers is booming because of their potential as 'surrogate endpoints' for drug trials. However, regulations for clinical trials of radiopharmaceuticals are not yet unified on a European level, and are currently based on several recommendations and guidelines of the EMA, and on domestic regulations for clinical trials in individual countries (3,4). In particular, the concept of microdosing in clinical studies is not fully or clearly described in the guidelines, and will require validation with the National Committees on Ethics and other health authorities. In order to assess new PET radiotracers and their benefits towards novel treatment evaluation, methodologies will have to be developed that allow the combination of the radiotracer and the targeted therapy under development to be included in the same clinical trials.

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