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Opinion Open Access

Molecular Imaging: Unlocking The Potential for Personalised Cancer Therapy

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Opinion

There has been an explosive growth in the interest as well as applications of medical imaging technologies in clinical oncology over the past few decades. However, we in the field of molecular imaging realize that the truly transformative power of imaging in the clinical management of cancer patients lies ahead. As of now, medical imaging is at a cross roads of sorts with molecularly targeted imaging agents broadly expanding the limited capabilities of conventional anatomical imaging methods.

The versatility of Molecular imaging allows clinicians to not only see where a tumor is located in the body, but also to visualize the expression and activity of specific molecules (e.g., proteases and protein kinases) and biological processes (e.g., apoptosis, angiogenesis, and metastasis) that influence tumor behavior and/or response to therapy. Such diverse and hitherto unavailable information has, as expected had a major impact on cancer detection, individualized treatment, and drug development, as well as our understanding of how cancer arises and behave differently in people.

Such crucial advances in understanding the molecular biology of cancer, and the ability to translate these advances into therapeutic approaches, have led to a host of new targets and new drugs for anticancer therapy. With the new mantra of "personalized cancer care regimens" treatments are becoming more individualized and there is an increasing need to characterize tumors and identify therapeutic targets, in order to select the therapy that's most likely to successfully treat an individual patient's cancer.

Be it targeted loco-regional therapy, such as surgery and radiotherapy, as well as targeted systemic therapies, such as endocrine treatments for breast cancer, or receptor based therapies for lung and renal cancers for example, personalized treatment protocols is the way forward. Thus far, tumor characterization has been in the domain of *in vitro* assays and pathological evaluation of tumor biopsy material. Now, with the development of molecular/receptor/antibody and biochemical probes along with technical advances in functional and molecular imaging , the foundation for testing imaging as a cancer bio marker; namely, to help direct cancer treatment in a way that is complementary to plans based on tissue- and blood-based bio markers has been laid.

In fact, molecular imaging has already been serving as a cancer bio marker and guiding cancer therapy in clinical practice, and some of the implications that are praise worthy are :

(1) Prognosis: The imaging bio marker can help determine the aggressiveness of the tumor and thereby infer the likelihood of disease progression and cancer-related patient death. This information can help guide how aggressive the treatment should be.

(2) Prediction: The imaging bio marker can help identify the presence or absence of therapeutic targets and therefore direct the patient to the therapy that is most likely to be effective. Imaging can also help identify factors likely to mediate resistance to particular forms of treatment.

(3) Response: Functional and molecular imaging can measure therapeutic response at a much earlier time point than standard anatomic imaging. In addition, imaging the tumor's *in vivo* response to treatment may better predict the outcome in relation to important endpoints, such as disease-free and overall survival.

(4) Biology: Molecular imaging provides a unique tool for characterizing the *in vivo* biology of cancer and its response to treatment. It may offer insights into factors that determine why some patients will response to specific anti-cancer treatments, while other apparently similar patients do not.

(5) Targeted therapy: Molecular imaging probes identify the presence of certain molecular pathways or receptors in the tumor, which can then be utilized for therapy by linking with radioactive isotopes, an idea which has recently gained significant momentum in the name of THERANOSTICS.

The important thing to be noted is that, this type of molecular approach differs from the standard paradigm for cancer imaging, which has largely focused on detection and staging. These imaging probes used for detection must have reliably higher uptake in tumors compared to normal tissue and hence the probes vary from tumor to tumor. As a corollary, even the absence of a particular feature – for example, tumor receptor expression – may be equally, if not more, important than its presence to predict aggressiveness or a failure of standard treatment regimens.

Thus molecular imaging, if it is to be used as a cancer bio marker must be able to go beyond simply detecting the tumor, to quantify tumor in vivo biology across a range of values. In essence, the probe should have the ability to localize and characterize tumors at the same time. Multimodality images techniques such as PET/CT, or pairs of imaging procedures – for example, using multiple PET imaging procedures with different probes – may prove especially important for bio marker imaging. However it is important to note that, the implementation of molecular imaging as a bio marker in cancer clinical trials and clinical therapy will require efforts to develop rigorous, but clinically feasible, approaches for multimodality imaging and standardized image acquisition and analysis protocols.

Some of the niche areas which have already shown promise are highlighted below. As this article is not meant for an exclusive oncology community, the details and patient profiles have not been included.

Prognosticating Cancer

A number of studies across a variety of tumor types have shown that rates of tumor glucose metabolism, reflected by PET imaging of ^{18}F-fluorodeoxyglucose (FDG) uptake, are highly predictive of patient outcomes such as progression-free and overall survival.

The mechanisms underlying these findings are incompletely understood and likely complex. They include the association of increased glycolysis with other factors that are predictive of patient outcome, such as indices of cellular proliferation. They may also reflect a cellular stress reaction, also seen in normal non-tumor tissues, that enhances cellular survival and may mitigate the effectiveness of cytotoxic treatments. One of the simplest scenarios, in which FDG-PET is used to determine prognosis in clinical practice is the case of iodine-refractory thyroid cancer. Here, the absence of FDG uptake indicates a quite favorable prognosis that often directs the patient away from further treatment in favor of close observation. On the other hand, the presence of FDG uptake in refractory thyroid cancer identifies a relatively lethal form of the disease, indicating that further therapeutic intervention is warranted.

Predicting Response to Therapy: Identifying Therapeutic Targets with Imaging

Though complementary to biopsy and *in vitro* assay at present, imaging has significant advantages in identifying therapeutic targets. Primarily it has the ability to characterize the entire body's disease burden (versus a small biopsied sample of the tumor), measure the heterogeneity of the target within or across disease sites, and also measure the effect of treatment on the target during follow up.

One example is the use of ^{18}F-fluoroestradiol (FES) PET to image regional Estrogen Receptor (ER) expression. Studies have shown that the level of FES uptake in breast cancer predicts the likelihood of response to endocrine therapy. This is akin to current clinical practice, which measures ER expression on biopsy material to make treatment selections. Imaging may be particularly helpful in recurrent or metastatic disease, where biopsy can be challenging.

Another example is PET hypoxia imaging, using compounds such as ^{18}F-fluoromisonidazole (FMISO). PET hypoxia imaging may be particularly important in radiotherapy treatment planning where it is likely that hypoxic regions will need different dosing schemes, given the well-documented association between hypoxia and radio resistance.

Therapeutic Response Assessment and *In Vivo* Sensitivity

A decline in cellular proliferation in a tumor mass is an early event that indicates successful cancer treatment. Work demonstrating the efficacy of ^{11}C-thmyidine PET (which images cellular proliferation) for early response evaluation led a number of investigators to develop thymidine analogues that can be labeled with ^{18}F for PET imaging, making them practical for more routine clinical use [1].

The most promising to date is ^{18}F-fluorthymidine (FLT), which has undergone preliminary evaluation in patients. Early studies support serial FLT as a robust indicator of early response, including response to agents that work primarily as cytostatic (versus cytotoxic) therapy. This is a highly promising area of investigation, and multicentre trials of FLT-PET to measure early therapeutic response are underway.

[^{18}F]fluorodeoxyglucose was used recently to demonstrate the rapid response of gastrointestinal tumours to imatinib mesylate (Glivec) [2]. PET can also be used to measure specific biological endpoints that are directly relevant to a particular molecular target. For example, use of ^{124}I anti-erbB2 antibodies to detect over-expression of the *ErbB2* gene [3] can identify patients suitable for therapy with the anti-erbB2 antibody Herceptin, which is used in the treatment of breast cancer. In an interesting recent application, PET was used to show that the thymidylate synthase inhibitor AG337 was able to increase the tumor uptake of [^{11}C]thymidine [4]. This increased uptake measures the salvage pathway for thymidine and provides a PD endpoint that demonstrates thymidylate synthase inhibition by the drug.

Cancer Biology

The ability to measure *in vivo* cancer biology during treatment provides a unique opportunity to gain insights into factors underlying response and resistance. One interesting finding has been the association between mismatches in tumor metabolism and perfusion, and resistance to therapy.

For several tumor types, investigators have shown that tumours that have high rates of glucose metabolism relative to blood flow are less likely to respond to treatment, and that patients with tumours displaying such characteristics are more likely to have disease relapse. Identification of flow-metabolism mismatch as a marker of therapeutic resistance suggests the need for further studies to understand underlying mechanisms, and may identify alternative targets in tumours that are resistant to standard treatments.

Another illuminative example is that of Hsp90, a molecular chaperone that has recently emerged as a new target for anticancer therapies. It is responsible for folding, stability and function of a range of oncogenic client proteins and the inhibition of a single target, Hsp90, has the potential to affect multiple oncogenic pathways [5]. Radiolabelled choline has been used to study alterations in choline metabolism in treated tumour cells, establishing the potential for the use of PET-detected [^{11}C]choline to study the PD effects of 17AAG in tumours in the clinic [6].

Translating Diagnostic Probes in to Vectors for Targeted Therapy

As an extension to the above mentioned uses, we are presently trying to create probes which can also be coupled to therapeutic radioactive isotopes, thereby selectively targeting the expression of a particular receptor or biochemical pathway inside the patient's body. The biggest advantage is that this type of therapy can selectively kill cancer cells and spare normal or non-target cells. This would enable us to deliver a very high dose of radiation with minimal side effects; which is actually one of the major draw backs when compared with convention chemotherapy or external beam radio therapy. Furthermore, considerable effort is going into the development of reporter gene readouts used with PET to study the efficiency of gene expression following gene therapy [7]. For example, the herpes simplex

virus enzyme thymidine kinase, when expressed in transfected mammalian cells, converts PET substrates into a detectable form that can be imaged as an indicator of gene transfer efficiency [8].

As it is still early days, these promising studies and applications will have to be validated in larger, multicentre trials. A very significant potential contribution, which has not gained momentum, is to evaluate potential new drugs both for *in vivo* targeting as well as assessing response. Molecular imaging technologies that monitor biological processes and/or measure levels of targeted macromolecules can contribute significantly to preclinical and clinical drug evaluation. In conclusion, there should be a concerted and networked effort to integrate molecular imaging into the drug development process and clinical oncological decision making. Promising early results encourage and support these efforts and suggest considerable promise for molecular imaging in this role in the future.

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