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The Role of Imaging Techniques in the Development of Novel Pharmaceuticals using Oncology as an Example

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Abstract

Imaging is a platform technology that can be used in most or all therapeutic areas. Applying imaging within a specific scientific field requires both expertise in the physiology and pharmacology of the disease, as well as an understanding of the imaging modality being used. Information must be obtained on both the effect of the drug on the body and the effect of the body on the drug. Imaging techniques are powerful tools in this field and can be used at different stages of drug development. Education is required as to how imaging can be applied within a therapeutic area to achieve research goals more efficiently and effectively. Imaging emerged in the field of oncology as a clinical tool to evaluate the presence of tumours and approximate tumour size. While clinical imaging equipment can be used on laboratory animals, sufficient interest in research using imaging technology grew and led to the development and optimisation of machines for small animal imaging. As the technology expanded, investigators began to use imaging to evaluate efficacy of novel drug therapies. The recent emerging interest in biomarkers has led to the application of imaging to understand drug mechanisms and predict efficacy. These experimental uses are now feeding back into the clinic and being applied in human patients.

Introduction

Within oncology, imaging emerged as a clinical tool to evaluate the presence of tumours and approximate tumour size. While clinical imaging equipment can be used on laboratory animals, interest in research using imaging technology grew and led to the development of machines for small animal imaging. As the technology expanded, investigators began to use imaging to evaluate efficacy of novel drug therapies.

Imaging is a value-added study endpoint:

- Enables visualisation and analysis of hard to measure states
- Translational method – can validate intended clinical imaging strategies
- Provides multiple simultaneous analyses
- Provides longitudinal data
- Increases detail/resolution
- Reduces animal numbers, sampling and analysis time
- Can shorten studies and lower research costs

How is imaging used in oncology studies?

Imaging can be used to measure tumour size regardless of location, but is most useful and necessary as an endpoint using orthotopic or metastatic models. Imaging can be used to both visualise tumours and quantify their size when implanted into internal body organs – such as the brain, liver or lungs – in animals. Imaging can also be used to track cells that are injected systemically – which is critical for the investigation and understanding of the metastatic spread of cancer. Imaging can also be used to evaluate how different regions of a tumour respond to therapy. Since tumours themselves are highly heterogeneous, not all regions will respond to drug in the same way or at all. It is possible for one region of the tumour to be non-responsive to drug while the rest of the tumour shrinks or dies. This detail is lost without the resolution provided by imaging. Lastly, imaging can be used as a target-based biomarker, in that it can indicate if a specific cellular mechanism or physiologic process is being affected by treatment.

The use of imaging in oncology is gaining increasing recognition within the field and the number of publications discussing imaging has been growing exponentially since the mid-1990's (see Figure 1).

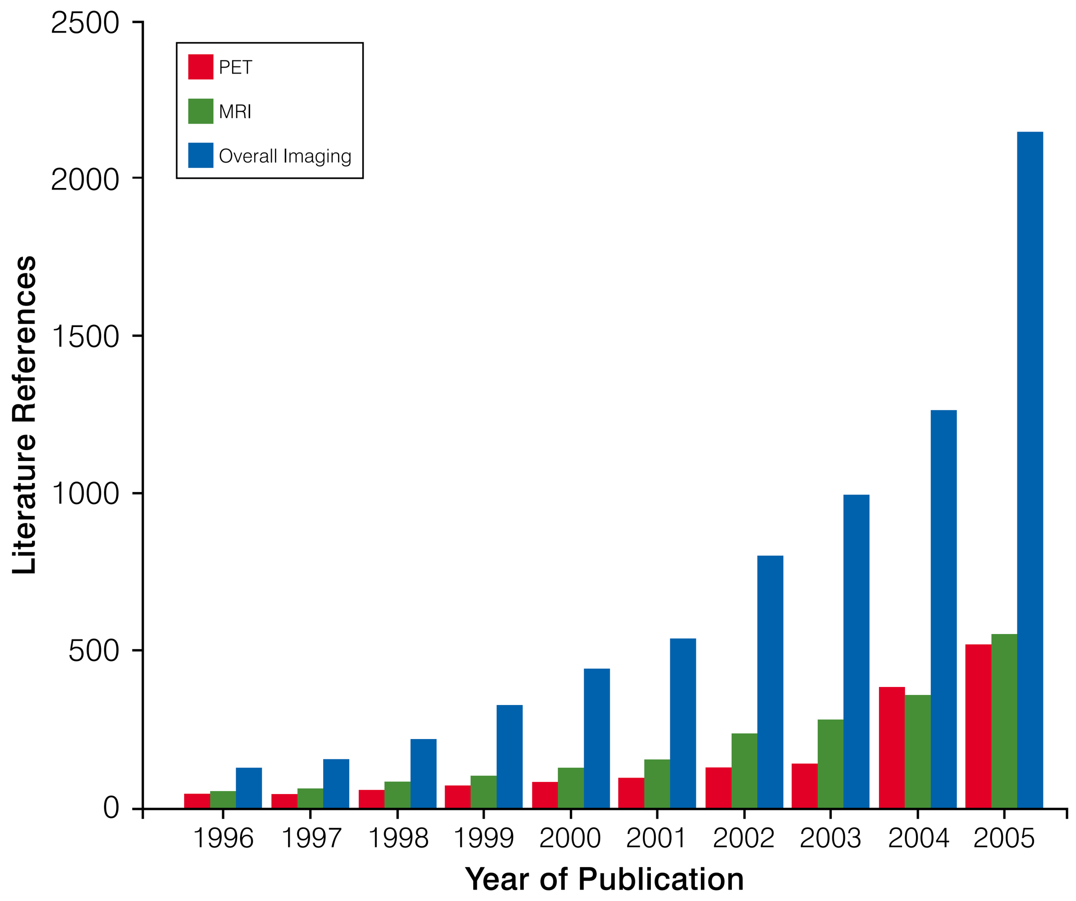

Figure 1. Imaging is an Emerging Technology in Oncology

MRI essentially measures the mobility of water or other contrast agents under high magnetic fields, allowing tissues with different compositions to be distinguished from one another. Dynamic Contrast Enhancement, or DCE-MRI, can be used to measure vascularity using an intravenously injected contrast agent. MRI can therefore be used to track tumour size (see Figure 2) and vascularity and can also be used to evaluate tumour heterogeneity in response to treatment.

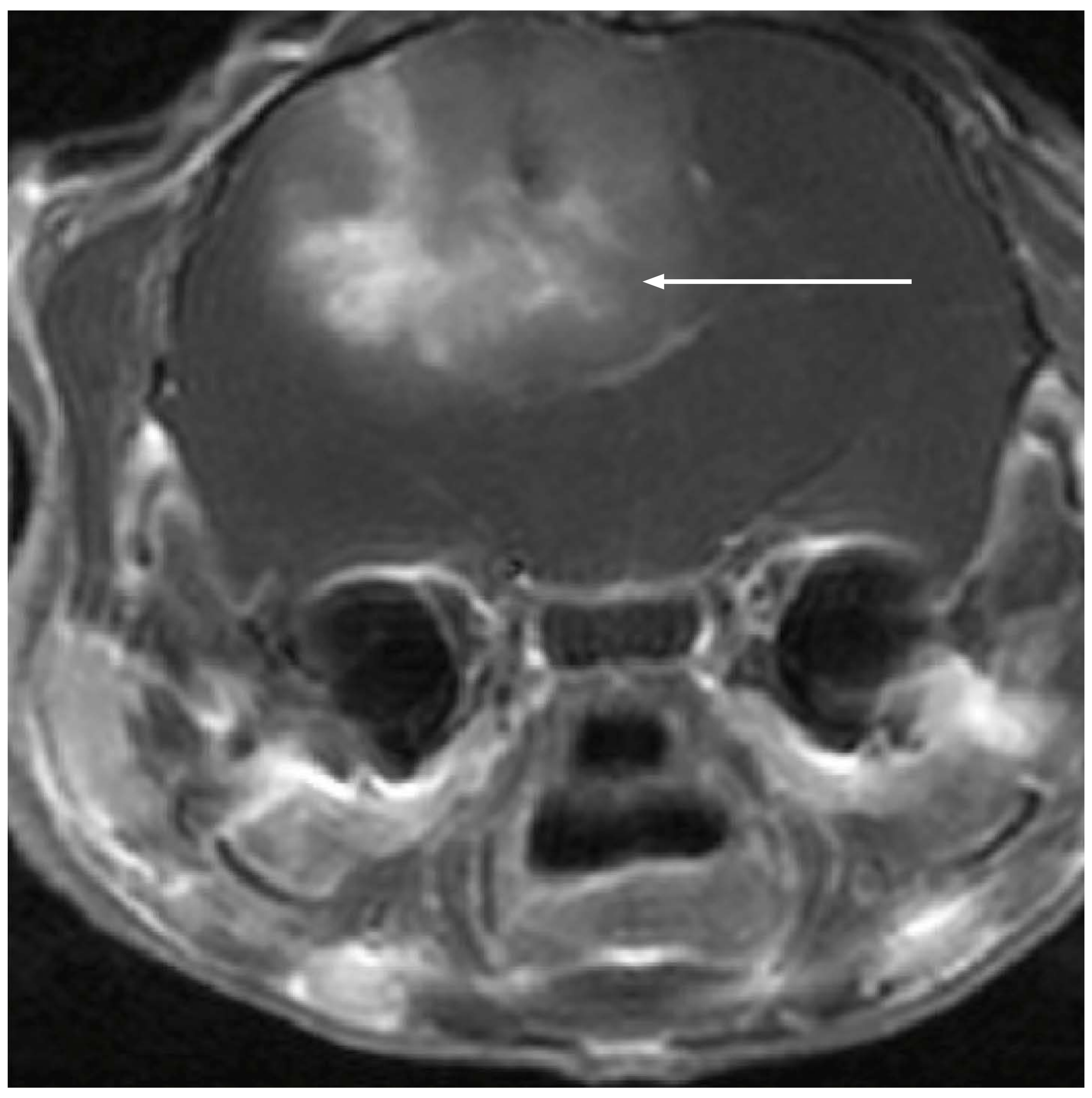

Figure 2. Small tumour detectable in the brain by Anatomic MRI after intracranial injection of D54 glioma cells

Positron emission tomography, or PET, measures emission of positrons from radioactive tracers and provides 3-dimensional images of distribution of these tracers within the tissues or region of interest. The most common tracer used is ^{18}F-fluoro-deoxyglucose, or FDG, which is essentially a glucose analogue that is taken up by tumours in part due to their high metabolic rate and provides a measure of cell metabolism (see Figure 3).

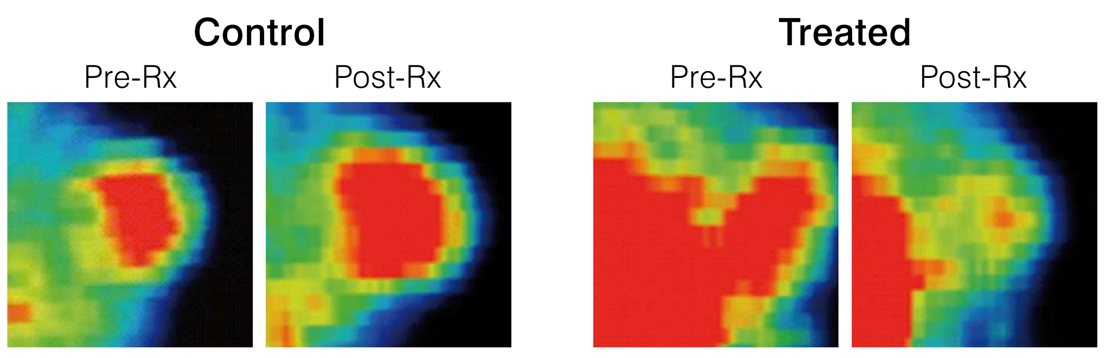

Figure 3. PET images of ^{18}-FDG uptake by subcutaneous Colo-205 xenografts demonstrating tumour response to paclitaxel therapy after 3 days of treatment

PET imaging can also be performed in conjunction with CT. In this case, the PET image is overlaid on top of the CT image, which can provide useful anatomic landmarks to locate tumours (see Figure 4).

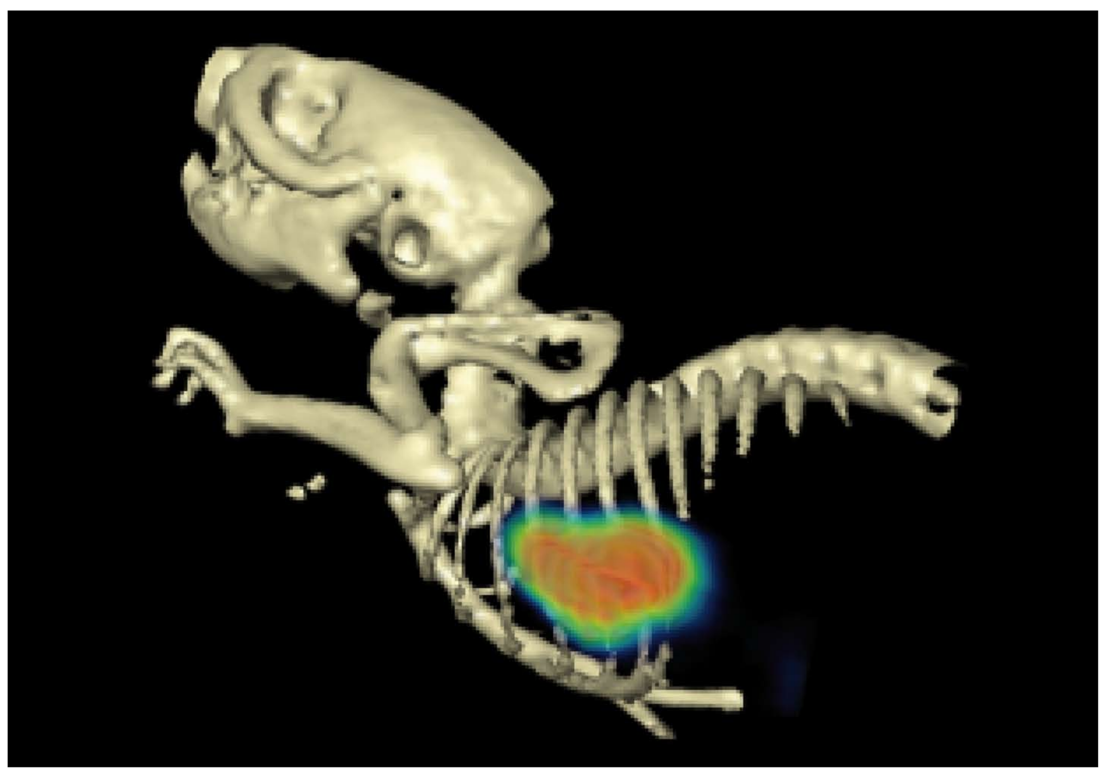

Figure 4. CT-PET images showing anatomic location of a subcutaneous tumour

These techniques provide data in living subjects. The main disadvantage of these is the poor resolution. QWBA provides this function (see Figure 5) and allows quantification of drug-related radioactivity in different regions of the tumour and systemic tissues. The disadvantages of QWBA are that it requires a radiolabelled test item and cannot provide longitudinal data.

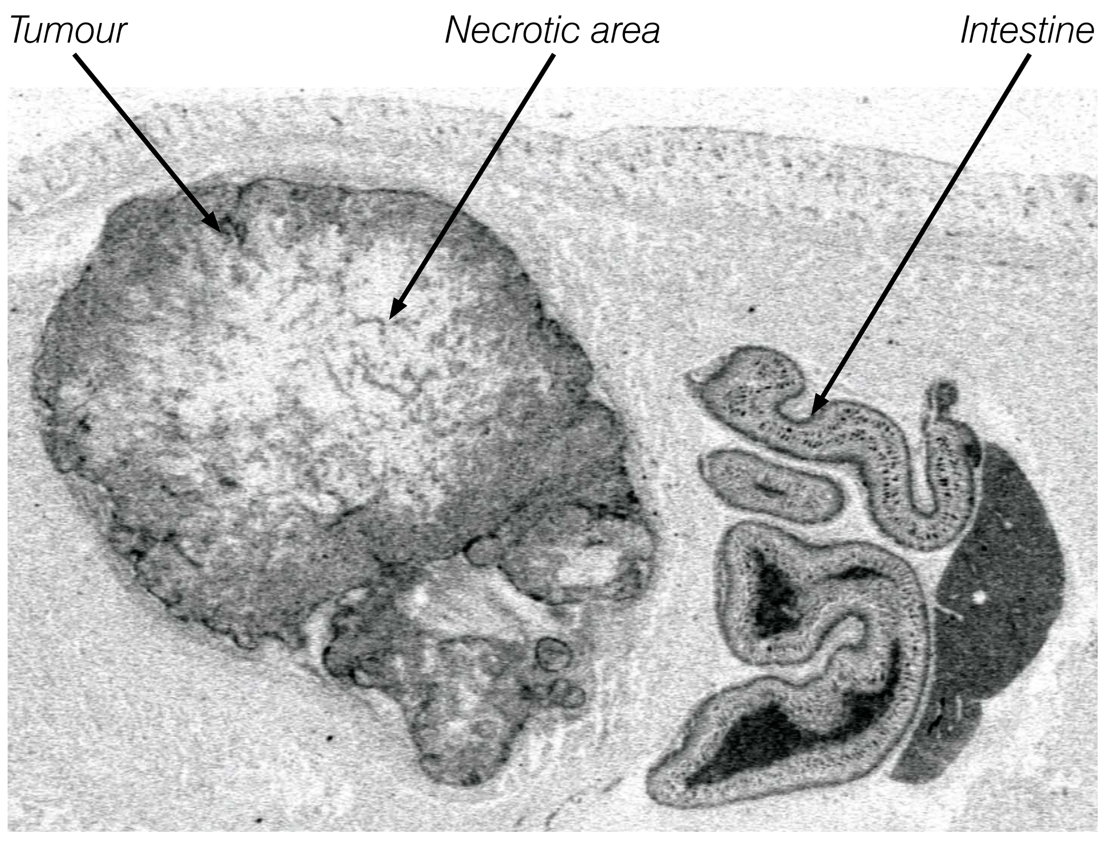

Figure 5. QWBA visualises targeting of tumours and allows quantification of drug delivery

Selecting imaging approach

The choice of imaging technique used depends on the specific scientific question being asked. Different imaging modalities measure fundamentally different things and need to be interpreted differently depending on the approach. Other factors include the spatial resolution and throughput of the instrument.

Summary

Charles River has become the leading CRO in the application of state-of-the-art imaging technologies to aid in the discovery of novel therapies.

- Cancer (primary focus)
- Inflammation
- Cardiovascular (expanding)
- Metabolic Diseases (diabetes)

Charles River is developing new relevant discovery technologies to speed the transition of therapeutics to clinical trials.

The overall goal is to provide clients with a quantitative correlation of drug-induced target modulation with efficacy and PK parameters.

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