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The spectrum of medical imaging

T. Jones*

University of Manchester, Christie Hospital Wilmslow Road, Withington, Manchester M20 4BX, UK

1. Introduction

When reading the material presented in this Special Issue of the *European Journal of Cancer* on Functional Imaging in Oncology, it is important to appreciate that the term medical imaging is a receptacle into which a wide range of techniques and their applications are placed. This can be confusing to the non-imaging specialist such as the oncologist for which this issue of the journal is intended to inform. While oncologists will be fully familiar with the selection of imaging modalities for locating tumours, the field of functional imaging is far less established and hence the need for this Special Issue.

This brief paper draws attention to the parameters that define the spectrum of medical imaging [1]. In order to help resolve what the distinctions between the various modalities for functional imaging are, it is appropriate to group them according to their: specificity, sensitivity, spatial and temporal resolution and ability to quantify the recorded images. The following should serve to help the reader identify the strengths and weaknesses of the functional imaging modalities presented within this issue. Indications are given as to where functional imaging can be used in oncology, especially for research. While it is clear that there are appreciable differences between what the various imaging technologies can provide, there is also scope for symbiosis between the respective methodologies.

2. Specificity

With medical imaging having been dominated by X-ray radiography, specificity has, in the main, been limited to imaging changes in tissue density which, it is inferred, result from disturbances in function. Within a similar theme, the use of magnetic resonance imaging (MRI) to detect disturbances of function rests on changes in proton density and magnetic spin relaxation times which are characteristic of the environment of the diseased tissue. The imaging of specific physical movements, e.g. blood flow, cardiac contractility, diffusion, leakage, lung ventilation, gastric motility, etc., represent functional imaging within main stream clinical radiology as covered by ultrasound, MRI and X-ray computed tomography (CT).

The more specific forms of functional imaging stem from detecting molecular interactions and pathways, which constitute biochemical, physiological and pharmacological processes. The key is being able to image the regional tissue levels of a specific molecule, the concentration and time course of which relate directly to the tissue's biochemistry or pharmacology. In recent years, in an attempt to make the clear distinction between this and less chemically specific forms of imaging, the term Molecular Imaging has been adopted, within which modalities such as positron emission tomography (PET), single photon emission tomography (SPET), magnetic resonance spectroscopy (MRS) and Luminescence imaging reside.

3. Sensitivity

For each of the modalities that offer a means for imaging function, their usefulness needs to be weighted by the sensitivity they have for recording their respective signals. Here, there are extremes at either ends of the spectrum of medical imaging:

The high photon flux used in X-ray CT provides for low statistical variance and hence the ability to detect the subtle differences in tissue density brought about by functional changes. Also for MRI, where the response is proportional to proton density and the environment which affect its magnetic spin, the high water content of tissue provides for a strong inherent signal enabling the

* Tel.: +44-161-446-8003; fax: +44-161-446-8111.
E-mail address: anne.mason@christie-tr.nwest.nhs.uk (T. Jones).

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resolution of small differences in hydrogen concentrations and its environment.

For imaging with radio labelled tracers of biochemical pathways or ligands for molecular interactions, the signals are clean since there are no background contributions. This results in high sensitivity determined primarily by the accumulated counting statistics, which in turn are limited by the amounts of radioactivity that can be administered to a subject. The electronic collimation offered through coincidence recording used in PET provides for a large acceptance angle and hence the capture of a significant proportion of the photons emitted from the radioactive disintegrations. As a result, PET has a sensitivity advantage over single photon detection, SPET, where physical collimation is necessary.

4. Spatial and temporal resolution

There is a considerable range of spatial resolutions realisable within the spectrum of medical imaging. They range from fractions of a millimetre in MRI to millimetres in MRS, PET and SPET. When considering the importance of the spatial resolution offered by an imaging modality, the key issue is that of signal cross-talk between normal and cancerous tissues.

The temporal resolution of the modality is important when kinetic data need to be recorded to derive: rate constants, turnovers, exchange rates and responses to stimuli. The key issue here is: does the imaging modality have the sensitivity to record, within the individual imaging time frames, the statistics needed to derive data that are of sufficient quality for the required kinetic analysis?

5. Quantification

This is the ability to convert the signals recorded within the picture elements of the image into standard or universal units. Where imaging is used for detecting focal lesions, their presence and location is the principal concern and not a quantitative measure of the focal signal. However, it is necessary to quantify where there is a need to objectively document change from the normal or over time. It is further needed in order to obtain absolute values of the functional parameters being imaged. This is important in order that the derived information can be communicated to, understood and appreciated by the clinical scientific community. Here, universal units are needed so that the data contained within the image elements can be processed to derive physiological or pharmacological parameters from the raw images. Practically, this requires quantitative transformations of raw image data through either region of interest analyses, but ideally into parametric images that still retain the original spatial resolution of the recorded images.

Transforming the image data into standard units requires that there is a means for normalising for procedural and patient variability introduced into the image. Examples include ratioing MRS spectral peaks to each other, correcting the radioactive signal recorded within the tissues to the amount of radioisotope administered and the patient's body weight.

To derive universal units, the data processing, where possible, needs to be to be taken a stage further than that of deriving standard units. Inevitably, it means introducing a calibration procedure to derive absolute values of, for example, tissue radioactive concentrations or density.

Over the last 10 to 15 years, a quantitative approach has been introduced which has gained widespread application to localising and defining the statistical significance of focal changes in function between parametric or semi-parametric images. This, to some extent has removed the need to make quantitative transforms of the image data and the segregation associated with how well the image data can be quantified. Statistical Parametric Mapping (SPM) [2] is an example of this approach. It rests on defining, for all the picture elements within the image data-sets, the global variance upon which focal changes that are statistically significant from this variance are identified.

6. Applications of modalities within the spectrum of medical imaging to oncology

In order to build on the described components that need to be considered when selecting a functional imaging modality, the following attempts to point to where on the spectrum one needs to focus when addressing certain investigative questions.

7. Development of novel treatments

The major issues facing oncology rest on the introduction of treatments based on novel therapeutic targets. The central questions where functional imaging can help in such developments rest on deriving 'proof of principle'. This includes pharmacokinetic (time course of the novel compound in the tumour and normal tissues) and pharmacodynamic (functional response of the tumour and normal tissues) measurements. Hence, from the oncologist's point of view and for a given therapeutic strategy, the following are examples of questions to be asked of the imaging methodologies:

- Is it possible to quantitatively image, in the tumour, the therapeutic target and changes therein, during and following therapy, using a tracer or ligand that is specific for that target?
- Is it possible to quantitatively image the concentrations of the anticancer agent within the tumour and normal tissues?
- Can a metabolic measurement be made to assess the tumour and normal tissue response to the anticancer agent? Ideally, the parameter imaged should relate directly to the metabolic pathway associated with the drug's site of action or downstream from it.
- Is it possible to quantitatively image a physiological response to an anticancer agent? An example here is to monitor the effect of antivascular agents by imaging changes in tumour blood flow.
- Will the spatial resolution allow the distinction between neoplastic and normal tissue to the extent that the latter's contribution to the tumour data is minimal?
- For those functional measurements which require kinetic data, is the temporal resolution and sensitivity of the imaging modality sufficient to be able to record accurate time course image data?

This checklist focuses on the cutting edge of anticancer treatments and, in such a context, would justify the exploitation of the more exotic ends of the imaging spectrum. This is especially the case if functional imaging can be used to provide endpoints for what are very expensive clinical trials.

8. Tumour physiology and metabolism

There are other applications of functional imaging in oncology that would benefit from a similar inquiry of what the imaging spectrum can provide. These include how to use functional imaging for more academic studies of the physiology and metabolism of human tumours.

9. Patient care

Much of what has been discussed centres on using functional imaging for research. However, it is inevitable, given enough activity and challenging the strengths of the respective methodologies within the medical imaging spectrum, that such technologies will migrate into the clinical care arena. In particular, through more specific measurements of tumour function, it should be possible to use changes therein as a means for monitoring the efficacy of an individual patient's treatment.

10. Cross-fertilisation between imaging modalities

The theme of this paper has been to bring to the attention of the oncologists the possibilities offered through the spectrum of functional imaging and to encourage them to select from this menu. There is a growing awareness that the strengths of one imaging modality can be usefully used to complement that of another. For example, high spatial resolution anatomical images from X-ray CT are being superimposed on metabolic images obtained with PET [3].

While encouraging the oncologist to challenge the possibilities offered within the spectrum of medical imaging, one is fully aware as to how immature many of the modalities are in their functional applications. To help advance this, attention is drawn to the growing interest in small animal imaging [4]. This provides a means to refine imaging protocols and paradigms to be used in patients which, when extended to data analysis, will provide for confirmation of data interpretation through *ex-vivo* assays of tumour and normal tissues.

11. Conclusion

An attempt has been made to crystallise the issues that need to be considered when proposing to use functional imaging in oncology. Details of the imaging modalities have not been discussed as they are covered in depth in the respective chapters. It is hoped that the oncologist will have gained some insight into the range of functional entities that can be considered and areas for their application. What is now required are commitments from this medical profession to ask relevant questions of functional imaging in order to realise the potential it has to help advance cancer treatments. This is needed in order to capitalise on an underexploited area for oncology. It is also needed to bring the additional commitment and stimulus to develop and refine the underlying methodologies, within the context of their applications.

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