The promise of multiparametric imaging in oncology: how do we move forward?

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Background

With the introduction of combined imaging modalities including PET/CT and more recently PET/MRI, there is strong interest in utilizing these independent modalities in a synergistic way. Up to now the field of multiparametric imaging research has mainly been driven by the MRI community. MRI offers the possibility of acquiring different sequences to visualize diverse properties of tissues (e.g. ADC mapping, T1/T2-weighted images). In the recent issues of *EJNMMI* there are several research papers looking into the topic of multiparametric imaging in a variety of cancer types using combined nuclear medicine imaging techniques with a different number of tracers together with advanced MR or CT imaging equipment [1–5]. Besides MRI, other drivers beneficial for multiparametric imaging are the increased number of standardization procedures that are being rolled out. For PET [6] and also MRI [7], standardization (or harmonization) procedures are currently in place or being developed. These procedures should remove some of the uncertainties and difficulties that multicentre trials face in quantitative analysis and allow more robust quantitative imaging-derived parameters [8].

A multitude of imaging techniques are currently available for visualizing tumour morphology and biology in vivo. CT

and MRI both provide morphological information. Biological processes that are dysregulated in cancer cells and distinguish malignant tissue from healthy tissue can be visualized using nuclear medicine-based techniques, MRI and CT. For many years, PET tracers looked at general features of tumours or normal tissues. Such a general approach includes the use of FDG, that is for imaging the classical marker of ATP-independent GLUT-mediated deoxyglucose uptake which is often upregulated in tumours. FDG uptake is commonly considered an indicator of “metabolism” although it reflects only a small part of the metabolic process. Another tumour hallmark that can be visualized using PET imaging is the activity of thymidine kinase 1, an enzyme involved in DNA synthesis, as a surrogate for most cell proliferation. Fluorothymidine (FLT) is the most studied tracer for this purpose.

Most solid tumours are, in addition, characterized by a low oxygen levels, i.e. hypoxia. Frequently used hypoxia PET tracers, based on 2-nitroimidazoles (e.g. FMISO, FAZA, HX4), visualize increased reductase activity in cells with insufficient oxygen, but do not show the molecular consequences of hypoxia. The chaotic and poor vasculature of tumours is often inadequate and results in diffusion-limited or perfusion-limited hypoxia. Dynamic contrast-enhanced CT or MRI (DCE CT/MRI) allows investigation of the vasculature (e.g. tumour permeability and blood flow) typically following injection of a contrast agent over time as it passes through the tumour blood vessels. Diffusion-weighted MRI (DWI MRI) facilitates mapping of diffusion patterns of water molecules, a characteristic related to cellular density. These advanced MRI techniques have a role in the standard guidelines for distinguishing malignant involvement from benign conditions, for instance in prostate cancer and pleural mesothelioma [9, 10]. Novel PET tracers have been developed for specific receptor imaging, including PET-labelled drugs. Examples include ¹⁸F-erlotinib, ⁸⁹Zr-bevacizumab, ⁸⁹Zr-trastuzumab and

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^{68}Ga -PSMA. The last of these is increasingly used in oncology as it may lead to treatment changes [11].

Even though a wide range of imaging techniques are available, not many functional imaging markers have gained wide acceptance in standard practice, except FDG. Of all imaging techniques no single imaging modality or tracer is ideal for answering all questions, and multimodality imaging needs to be individually tailored to the specific research or clinical question.

How to move forward

It has been recognized for a long time that tumours are frequently heterogeneous in their presentation and behaviour. Multiparametric imaging allows investigation of this heterogeneity in a comprehensive way. Subvolumes with distinct properties inside tumours can now be identified. For example, information on perfusion in subvolumes combined with hypoxia imaging might reveal differences between perfusion-limited hypoxia and intrinsic tumour hypoxia [12–14], or may explain the lack of accessibility of a receptor on the tumour cell to a targeted agent.

The large amount of information we currently can gather from these advanced imaging techniques is undoubtedly interesting. However, the next question is how to identify which biological processes are relevant, how these processes influence patient prognosis and finally how to individualize treatment based on this information. We envisage two distinct strategies to move forward.

Strategy 1: The agnostic data-driven approach

A way to link imaging studies to a clinically relevant outcome is through so-called ‘pattern-of-relapse’ studies. Such studies allow correlation of imaging features with the patient or tumour outcome (e.g. recurrence location) using follow-up imaging of various lesions [15–18]. Another imaging approach is to validate the imaging characteristics with biological properties in the surgical specimen [19–22]. This data-driven approach is attractive because no complete molecular knowledge is needed: the observations drive the identification of treatment-resistant areas in a pragmatic, agnostic way.

The drawback is clearly that no further biological precision can be obtained easily. Another down-side of this approach is its data-driven nature: many patients need to be imaged before these patterns-of-relapse can be accurately quantified, especially when these features divide the cohort into smaller subgroups. Few data are available. Furthermore, a comprehensive understanding of the combined imaging modalities is essential. All imaging modalities have their own inherent uncertainties, e.g. artefacts on MRI, limited resolution of PET, uncertainties in kinetic modelling with DCE CT/MRI. These

uncertainties with the individual imaging modalities together with registration effects could explain why correlations found between imaging modalities at the tumour and sub-tumour levels are no longer present at the voxel level. For example, a few years ago, a simulation study showed blurring of the underlying pathology because of the limited resolution of PET scanners [23].

One possible way to integrate multiparametric imaging in treatment individualization is by using radiotherapy ‘dose painting’. The radiation dose can be intensified or de-escalated for different tumour regions according to the expected treatment sensitivity derived from imaging data to improve local tumour control without increasing toxicity. Several clinical trials are looking into this approach, and treatment personalization can be performed at different levels; ranging from the subvolume level to the very fine voxel level [24–26]. In analogy to the pattern-of-relapse approach, dose painting requires detailed analysis to find dose–response relationships between functional imaging, underlying pathology and outcome to design appropriate clinical trials.

Strategy 2: Biology-driven approach

Present guidelines were written for a defined population, typically derived from phase III clinical trials. As subgroups become smaller eventually coming down to a personalized approach, the agnostic data-driven approach is no longer possible. Moreover, as all individuals and their disease are unique, so also, at the extreme, will all tumours and even all tumour cells be found to be unique [27]. Tailoring a treatment for each cell and particularly proving that the outcome in the patient was due to this intervention would be impossible.

However, there is also an opportunity for molecular imaging in this area. It is possible to individualize the treatment by knowing more precisely the main molecular characteristics of a tumour that are distributed in a more or less homogeneous way throughout the tumour. A classical example is the exon 19 or 21 mutation of the EGFR gene in adenocarcinoma of the lung. Although eventually resistance will occur in all patients, at the start the mutations are found in nearly all tumour cells and are spread homogeneously throughout the tumour [28]. However, before the tumour increases in size, it shows increasing inhomogeneity that can be visualized [29]. Therefore, before classical “disease progression” occurs, more precise imaging will identify patients who may be switched to an alternative therapy. It is expected that the combination of molecular knowledge underpinning the biology of the tumour and specific probes or image analyses will be an integral part of precision medicine. Multiparametric imaging might facilitate this approach by enabling the selection of the appropriate molecular imaging tools that quantify tumour properties or stratify patients. A recent example from the preclinical arena for precision medicine is hypoxia-activated prodrugs that only

show efficacy in hypoxic tumours [30]. Molecular imaging using hypoxia PET tracers could allow identification of those patients who would benefit from these drugs. This approach may be necessary for the more specific drugs being developed whose cost restricts their use to patients who will benefit.

A possible downside of this approach is that because the biology of tumours is complex it might be difficult to select the appropriate imaging technique to define the optimal treatment. As mentioned above, tumour cells will typically develop resistance against a single treatment and different pathways will be activated.

The future of imaging for precision medicine

The two strategies above both have their advantages and disadvantages and are most likely complementary. Both require reliable and more robust imaging biomarkers, standardization, validated end-points, genetic information, and more sophisticated trial designs. An important question will be how to implement these more advanced imaging approaches in clinical routine taking into account their availability and logistic considerations. Patient stratification and treatment monitoring will certainly be crucial steps for precision medicine in which imaging may play a major role.

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Compliance with ethical standards

Conflicts of interest None.

Ethical approval This article does not describe any studies with human participants or animals performed by any of the authors.

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