Spotlight

PET or MRI to improve response evaluation in clinical trials?

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For more on the **use of PET-guided treatment in lymphoma** see **Articles** *Lancet* 2018; **390:** 2790–802

For more on the **use of PET to predict response in breast cancer** see **Articles** *Lancet Oncol* 2014; **15:** 1493–1502

For more on **PERCIST** see *Radiology* 2016; **280:** 576–84

For more on **immuno-PET assessment of response** see *Nat Med* 2018; **24:** 1852–58

Opening opinion: PET

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PET is an imaging technique providing three-dimensional depiction and (semi-)quantification of the regional distribution of radiopharmaceuticals, with very high sensitivity (picomolar range) and spatial resolution up to 4 mm. PET radiopharmaceuticals are designed to target molecular or biological processes relevant to cancer. Contemporary PET scanners are coupled with CT or MRI scanners for hybrid imaging to enhance the precise anatomical location of tracer accumulation. Tracer uptake can be assessed visually or semi-quantitatively.

For assessment of cancer therapy, the most studied and clinically used tracer is 2-[^{18}F]fluoro-2-deoxy-D-glucose (^{18}F-FDG), which accumulates in cancer cells in phosphorylated form due to the Warburg effect. Compared with more conventional imaging, baseline ^{18}F-FDG PET allows CT, ultrasound, and bone scintigraphy whole-body tumour imaging, with detection of malignancy in normal-sized lymph nodes, bone, and bone marrow without morphological changes. One of the key strengths of ^{18}F-FDG PET to assess therapy response is that changes in glucose metabolism after chemotherapy, radiotherapy, or chemoradiotherapy precede, in many tumour types, morphological changes depicted on CT or conventional MRI. Another key strength is the lack of signal in normal lymph nodes, whereas diffusion-weighted MRI has high signal in normal lymph nodes and, therefore, relies on increases in size.

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Significant visual or semi-quantitative decline in FDG uptake can be seen after 1–3 weeks of therapy, with a size reduction of less than 10% on CT and a decline in FDG uptake seen as early as 1–3 weeks after treatment initiation, when tumour size reductions would be less than 10% by CT or anatomical MRI. This feature allows, in principle, early changes to therapy dose if an insufficient effect on the tumour is seen within weeks of the start of therapy. In residual masses or consolidations after chemotherapy or stereotactic body radiotherapy, absence of ^{18}F-FDG uptake is strongly associated with tumour control. The concept of PET-guided treatment has been validated in randomised phase 3 trials in lymphoma, where interim PET is used to either change or escalate ineffective treatments or to de-escalate treatment in early responders. In solid tumours, PET-based identification of metabolic non-responders and subsequent therapy intensification has yielded promising results—eg, increasing the pathological complete response in breast cancer. The main advantages of PET are its capacitiy to assess the total body in a short scan time, making it ideally suited in the metastatic setting and in induction therapy before major surgery, where detection of novel metastatic disease is of utmost importance.

Owing to the very high contrast between tumour and non-tumour tissue in PET and recent advances in image analysis software, it is feasible to calculate the total volume and tracer uptake of all FDG-avid tumour lesions within a patient, known as metabolic tumour volume (MTV) and total lesion glycolysis (TLG), respectively. These metrics provide information on all malignant lesions within a patient with good intraobserver and interobserver agreement, avoiding the need to define target and non-target lesions as is done in the Response Evaluation Criteria in Solid Tumors (RECIST) framework. Differences in baseline MTV are prognostic in many cancer types, including non-Hodgkin lymphoma, myeloma, and non-small-cell lung cancer. Therapy-induced changes in these so-called volumetric PET parameters can predict prognosis after therapy better than conventional PET uptake in gastric, colorectal, and oesophageal cancer. It is expected that volumetric total tumour burden determination will become a new standard in therapy assessment in the next decade and inclusion of these metrics in clinical trials is warranted.

Quantitative response criteria for PET have been put forward by the European Organisation for the Research and Treatment of Cancer (EORTC) Imaging Group, and in the recently updated PET Response Criteria in Solid Tumors

(PERCIST), together with frameworks for multicentre cross-calibration in clinical trials. These criteria are based on the reproducibility of ^{18}F-FDG PET measurements, discriminating therapy-induced changes from repeatability variation. The PERCIST framework provides more guidance on the number of lesions, their delineation, the definition of target lesion, and reporting. The key parameter is the change in lean body mass corrected SUV_{peak}, the highest average uptake in a 1 cm^3 sphere within the tumour. Prospective trials have shown high concordance between EORTC and PERCIST criteria, showing the robustness of metabolic response evaluation. This consistency is a strength compared with MRI, where obtaining homogenous data from machines from different vendors and different magnet strengths can be a challenge.

Many other tracers are available for tumour detection by PET and have been shown to be of value for response assessment—eg, prostate specific membrane antigen (PSMA)-ligands and radiolabeled amino acids for brain tumours. A current active area of research focuses on PET imaging of immune therapy receptivity at baseline (eg, PD-L1 tracers) or a signature of immune activation (eg, tracers binding to CD8). It is expected that response criteria will also be developed for these PET tracers. Molecular imaging of receptiveness to immunotherapy or its effectiveness is within clinical reach and this would be a key distinctive benefit of PET over MRI, for which no molecular probes are in current clinical use and that assesses only changes in aspecific parameters, such as size, perfusion, and diffusion restriction. Preliminary data for PD-L1 show better outcome prediction of immuno-PET than standard immunohistochemical analysis.

In summary, PET allows rapid, reproducible, quantitative whole body molecular assessment of total tumour burden, with tracers that show proncounced changes in uptake early within the course of therapy (^{18}F-FDG); it provides a unique non-invasive assessment plaform of targets relevant for many cancer types, including key molecules of the immune system.

Counter-opinion: MRI

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Imaging is a critical component of drug development and provides evidence of novel drug antitumour activity. Response Evaluation Criteria in Solid Tumors (RECIST), using either CT or anatomical MRI, is the standard for response evaluation in clinical trials. RECIST only considers changes in tumour size and was developed based on studies of cytotoxic chemotherapy. With the advent of new therapeutic strategies, such as targeted therapies and immunotherapies, specific imaging response evaluation approaches are necessary. In the era of personalised cancer care, the traditional one-treatment-fits-all approach has evolved towards pursuing individualised treatment decisions based on validated biomarkers. Similarly, the development of new imaging biomarkers, matching functional imaging assays to tumour types, and drug mechanisms of action can accelerate drug development; precision imaging contributes to the pursuit of precision medicine.

Novel functional MRI techniques allow for non-invasive prediction and quantification of treatment response, going beyond anatomical features for response evaluation. The involvement of imaging specialists in clinical trial design and development is necessary for maximising the potential of different imaging modalities, including MRI, for patient stratification and response assessment.

Diffusion-weighted MRI is used to study the movement of water molecules within a tissue and provides information on tissue cellularity. In response to treatment, a decrease in cellularity results in increased water molecule diffusivity and, consequently, increased apparent diffusion coefficient values. Changes in tumour cellularity occur before changes in tumour size are visible; hence, diffusion-weighted MRI can offer earlier readouts for antitumour activity endpoints in clinical trials. Quantifying decreases in tumour cellularity by diffusion-weighted MRI has great potential for capturing true responses to immunotherapy, thus overcoming the problem of pseudoprogression when using sole size-based criteria. Evaluating changes in whole-body diffusion-weighted MRI is also a reliable tool for assessing responses in bone metastases for which there are no validated response criteria either by CT, bone scintigraphy, or PET. This advantage is relevant for drug development in prostate and breast cancer or in multiple myeloma, in which metastatic disease can be confined to the skeleton.

Functional MRI can also assess antitumour activity and optimise patient selection for clinical trials of antiangiogenic drugs. These therapies produce clinical benefits via tumour vasculature but often do not result in changes in tumour size. Tumour vascularity can be evaluated by intravoxel incoherent motion from diffusion-weighted MRI, without intravenous contrast administration, and perfusion MRI sequences, such as dynamic contrast enhancement. Vessels are more abundant and permeable in tumours than in normal tissues, which can be quantified using different MRI parameters, such as the transfer constant (Ktrans) or blood volume. Elevated baseline Ktrans is a predictive marker for favourable responses to antiangiogenic treatments in renal and colorectal cancer. Early changes in dynamic contrast enhancement MRI parameters are good indicators of response to sorafenib in renal and hepatocellular carcinomas. Perfusion MRI techniques are already being used in clinical practice; however, no vasculature-specific ligands for PET imaging have been validated.

For more on **biomarkers for individualised cancer treatment** see *Nat Rev Cancer* 2010; **10:** 514–23.

For more on **novel tools for image analysis** see *Nat Rev Clin Oncol* 2017; **14:** 749–62.

For more on the **study of olaparib in prostate cancer** see *Cancer Discov* 2017; **7:** 1006–17.

Although, in general, PET is the technique of choice for molecular imaging, MRI spectroscopy provides a non-invasive alternative (ie, not using ionising radiation) to study certain metabolites and monitor changes within tissues in conjunction with treatment. MRI spectroscopy offers a range of opportunities for pharmacodynamic studies in early clinical trials. 1H-MRI spectroscopy can also be used to study tumours based on choline-containing compounds, which are abundant in cell membranes. Monitoring variability in the amount of choline within a tissue reflects tumour cellularity changes in response to treatments in prostate, breast, and brain tumours.

MRI also presents a higher spatial anatomical resolution than PET scans. Tumours are spatially heterogeneous and evolve over time in response to treatment selective pressures. Whole-body MRI is feasible in relatively short times (30–40 min for whole-body MRI scan, including anatomical and functional sequences), and it is easy to implement at most MRI units. Accounting for this higher spatial resolution and with the advent of novel computational analysis tools, whole-body MRI allows for the evaluation of intra-patient and intra-tumour heterogeneity. In a clinical trial of the PARP inhibitor, olaparib, in metastatic prostate cancer, diffusion-weighted MRI guided the identification of relapse foci within bone metastases, revealing emerging mutations as mechanisms of resistance. Together, these features could aid drug development, assess intra-patient differential responses, and guide biopsies for studying resistance mechanisms and identify putative predictive biomarkers for more efficient clinical trials.

Finally, MRI does not use ionising radiation so, unlike CT or PET scans, it is an ideal assay for clinical trials in paediatric tumours or specific populations with contraindications to radiotherapy, such as pregnant women.

In summary, multi-parametric MRI offers the opportunity for early and accurate imaging compared with standard PET imaging in some settings. However, we can use different MRI and PET techniques as tools for precision medicine depending on the tumour type and the mechanism of action of the tested drug. One technique might present advantages over the other as a predictive biomarker or response endpoint in clinical trials. Advances in both MRI and PET can accelerate drug development by tailoring imaging assessment in clinical trials to tumour type and drug mechanism of action. In the future, hybrid PET–MRI imaging will open new horizons in imaging by using a combination of molecular, functional, and anatomical information.

Digital Oncology

Medical crowdfunding to access CAR T-cell therapy

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For more on the **costs of CAR T-cell therapies** see *JAMA Oncol* 2018; **4:** 994–96

For more on **side effects associated with CAR T-cell therapy** see *Cell Gene Ther Insights* 2018; **4:** 295–307

For more on **crowdfunding for medical treatment** see *JAMA* 2017; **317:** 1623–24 and *Soc Sci Med* 2017; **187:** 233–42

US Food and Drug Administration (FDA) approval of two chimeric antigen receptor T (CAR T) cell therapies —tisagenlecleucel and axicabtagene ciloleucel—in 2017 offered new therapeutic options to paediatric patients with relapsed or refractory acute lymphoblastic leukaemia and adult patients with relapsed or refractory diffuse large B-cell lymphoma. These therapies, which have now been approved by regulatory bodies around the world, provide hope to patients who have few other available options, but these therapies raise important ethical concerns. These concerns are driven by the extraordinarily high costs of these therapies—either US$475 000 for paediatric patients with acute lymphoblastic leukaemia or $373 000 for adult patients with diffuse large B-cell lymphoma, for the drug product alone in the USA—and the associated costs and their serious side-effects. CAR T-cell therapies were developed and approved at a time when patients were increasingly turning to crowdfunding to raise funds to pay for medical expenses and gain access to established or unproven medical interventions, yet little is known about patients' use of crowdfunding to access CAR T-cell therapy. We sought to understand whether and why patients were using crowdfunding to raise money to access CAR T-cell therapies, either during clinical development or after regulatory approval.

We systematically searched GoFundMe, the most popular crowdfunding website, for English-language campaigns related to CAR T-cell therapy. We searched three times over a 15-day period between Oct 21, 2018, and Nov 3, 2018, using keyword searches for "'CAR-T", "cancer", and "chimeric," and the trade names for the first two CAR T-cell therapies: "Yescarta" and "Kymriah". We reviewed each search result to assess if the campaign met our inclusion criteria (ie, the campaign sought to raise funds for a specific patient or group of patients to receive CAR T-cell therapy). We found 143 distinct campaigns and coded each campaign to identify key characteristics. Objective measures (ie, goal amount, amount raised, number of donations, number of Facebook shares, campaign state date, patient diagnosis, patient sex, and patient age <18 years) were assessed by a single coder, while more subjective measures (ie, reasons for campaign, explanation of CAR T-cell therapy, link to learn more about therapy, discussion of risks, and discussion of success rates) were independently assessed by two coders. Disagreements were discussed and resolved by consensus. Monetary values were converted to US dollars using exchange rates determined on Nov 3, 2018.