Received:
08 September 2017

Revised:
13 December 2017

Accepted:
19 December 2017

<https://doi.org/10.1259/bjr.20170688>

Cite this article as:

Zaccagna F, Grist JT, Deen SS, Woitek R, Lechermann LMT, McLean MA, et al. Hyperpolarized carbon-13 magnetic resonance spectroscopic imaging: a clinical tool for studying tumour metabolism. *Br J Radiol* 2018; **91**: 20170688.

REVIEW ARTICLE

Hyperpolarized carbon-13 magnetic resonance spectroscopic imaging: a clinical tool for studying tumour metabolism

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ABSTRACT

Glucose metabolism in tumours is reprogrammed away from oxidative metabolism, even in the presence of oxygen. Non-invasive imaging techniques can probe these alterations in cancer metabolism providing tools to detect tumours and their response to therapy. Although Positron Emission Tomography with (¹⁸F)2-fluoro-2-deoxy-D-glucose (¹⁸F-FDG PET) is an established clinical tool to probe cancer metabolism, it has poor spatial resolution and soft tissue contrast, utilizes ionizing radiation and only probes glucose uptake and phosphorylation and not further downstream metabolism. Magnetic Resonance Spectroscopy (MRS) has the capability to non-invasively detect and distinguish molecules within tissue but has low sensitivity and can only detect selected nuclei. Dynamic Nuclear Polarization (DNP) is a technique which greatly increases the signal-to-noise ratio (SNR) achieved with MR by significantly increasing nuclear spin polarization and this method has now been translated into human imaging. This review provides a brief overview of this process, also termed Hyperpolarized Carbon-13 Magnetic Resonance Spectroscopic Imaging (HP ¹³C-MRSI), its applications in preclinical imaging, an outline of the current human trials that are ongoing, as well as future potential applications in oncology.

INTRODUCTION

Tumours metabolize glucose very differently from normal tissue, generating lactate even in the presence of oxygen, a process known as the Warburg effect.¹ Other metabolic pathways, such as amino acid utilization and fatty acid synthesis, are also reprogrammed in tumours compared to normal tissue.^{2–4} A number of non-invasive imaging methods have been used to probe these alterations in cancer metabolism. This review will describe a new technique for studying this metabolism termed Hyperpolarized Carbon-13 Magnetic Resonance Spectroscopic Imaging (HP ¹³C-MRSI).⁵

Positron Emission Tomography (PET) is an extremely sensitive technique for studying molecular processes without disrupting normal physiology, with tracer detection in the nano- to picomolar range.^{6,7} PET imaging in conjunction with (¹⁸F)2-fluoro-2-deoxy-D-glucose (¹⁸F-FDG), is an established clinical tool to probe altered

glucose metabolism in cancer patients.⁸ Whole body ¹⁸F-FDG PET is superior to standard CT for the assessment of tumour stage in many malignancies;⁹ however, it is limited by a relatively low clinical spatial resolution (of the order of 5 mm), poor soft tissue contrast, exposure of patients to ionizing radiation and the inability to discriminate between different metabolites or the compartment from which the signal arises e.g. extracellular vs intracellular.^{10,11}

Magnetic Resonance Spectroscopy (MRS) may also play a useful role in probing cancer metabolism by detecting the resonant frequencies of nuclei within distinct molecules (such as that of hydrogen, ¹H, or protons); therefore it can be used to non-invasively discriminate between metabolites.^{12,13} However, in comparison to PET, MR is a very insensitive technique utilizing only a small number of the available nuclei to generate an image or spectrum. At clinical field strengths, only a few of the available hydrogen nuclei in every million are used to generate these images.^{14,15}

This low sensitivity is due to the low polarization of the nuclei at thermal equilibrium and consequently, only molecules at relatively high concentration can be probed with MRS. Despite the great potential of MRS as a tool to study biochemistry *in vivo*, it is not used routinely in the clinic due to both the low spatial and molecular sensitivity of the technique, and difficulty in subsequent data interpretation.^{10,13}

Dynamic Nuclear Polarization (DNP) is a technique based in solid state physics which greatly increases the signal-to-noise ratio (SNR) achieved on MR by significantly increasing the polarization of nuclear spins and therefore enabling a much larger proportion of them to be utilized for imaging.¹⁶ In 2003, DNP was combined with an efficient method to transfer the substrate from the solid (~1 K) to liquid (~300 K) state, a process which is now known as "Dissolution DNP". This technique opened up new possibilities for the method to be translated into biological systems such as cell studies and *in vivo* animal imaging.¹⁷ The technique, termed HP ¹³C-MRSI MRSI, has now been translated into humans.¹⁸ This review provides a brief overview of the technique, its applications in preclinical imaging, an outline of the current human trials that are ongoing as well as future potential applications.

MR SPECTROSCOPY AND THE BENEFITS OF METABOLIC IMAGING WITH MRI

Conventional ¹H-MRI largely measures the spatial distribution of water and fat molecules within tissue and has led to many clinical applications in neurological, cardiac and oncological imaging.^{19–21} MR can also be used to provide information on the nature of other molecules by utilizing the property of chemical shift to discriminate the resonant frequency of protons. MRS has been used to detect the steady state levels of diverse molecules including lactate, N-acetylaspartate (NAA) and glutamate.^{12,13}

An alternative approach to the steady state measurement of tissue metabolites, is to probe dynamic changes in metabolites during enzymatic reactions, which can be assessed through the exogenous administration of labelled metabolites. A physiologically-active substrate labelled with a nucleus that can be detected with MRI, allows spectral discrimination between the substrate and its subsequent downstream metabolic products; when applied to imaging, it allows the spatial distribution of both the substrate and the product to be detected. However, MRS requires long acquisition times which in turn makes it difficult to discriminate rapid changes in real-time metabolism *in vivo*. ¹³C is ideal for labelling endogenous metabolic molecules which are mostly carbon based, as its low natural abundance (1.1%) results in a low level of background noise. ¹³C-MRS acquisition from either a single voxel or a small number of voxels has been used to successfully analyse many physiological processes in organs such as in the brain, as well as pathological processes including cancer.^{22–24} Although ¹³C-MRS has been used to detect early changes in cancer metabolism as a biomarker for response to treatment,²³ its utility is limited by very low SNR as well as poor temporal and spatial resolution. Therefore the increase in SNR afforded by DNP has opened up the possibility of applying ¹³C-MRS in new ways, allowing for rapid acquisition of imaging to probe real-time metabolism.^{17,25}

There are several methods that have been described for increasing nuclear polarization and generically they are termed hyperpolarization techniques; *e.g.* there are a number of approaches for the hyperpolarization of gases used in ventilation imaging.^{26–28} DNP was first postulated as a hyperpolarization method by Overhauser in 1953,¹⁶ and has now been applied to ¹³C-labelled physiologically substrates which are rapidly transported and metabolized by the cells. To facilitate the process, labelled molecules are mixed with a free-radical containing agent, frozen in a glass state and then cooled to approximately 1 Kelvin in a magnetic field *e.g.* 3.35 or 5 T. At these extreme physical conditions the electron pool in the free-radical becomes fully polarized and the transfer of polarization from the electron pool to the nuclear pool is facilitated by microwave irradiation. Increasing the polarization to levels required for *in vivo* imaging takes approximately 2 hours and following this the sample is removed from the field and quickly dissolved with superheated water.^{29,30} This hyperpolarized sample has an increase in signal of 10,000 to 100,000-fold and can be used to probe the real-time dynamics of enzymatic activity *in vitro* in cell culture or *in vivo* in animal models, using rapid spectroscopy or imaging.^{31–34} The term spectroscopic imaging is used where spectra are acquired from multiple voxels to generate an image of the metabolic distribution across the tissue.

One of the challenges of the technique is that the signal from the hyperpolarized carbon is very transient and decays with a half-life that is commonly 20–30 s *in vivo*; therefore, perfusion, transport and metabolism must occur during approximately 5 half-lives or 2–3 min. This limits the number of *in vivo* molecules and reactions that can be probed with the technique and necessitates very rapid and efficient imaging strategies.

Preclinical imaging

To date, [^{1-¹³C}]pyruvate has been the most widely used metabolite for hyperpolarized ¹³C MRSI, due to its relatively long polarization half-life (the time it takes for a compound to lose half of its initial hyperpolarized signal), rapid distribution and uptake, and the central role it plays in many metabolic pathways (Figure 1).^{35,36} Pyruvate is at an important metabolic crossroad between the formation of lactate on one hand, and entry into the tricarboxylic acid (TCA) cycle with the formation of carbon dioxide on the other.

In cancer, the ¹³C label on (1-¹³C)pyruvate is predominantly exchanged to (1-¹³C)lactate via the enzyme lactate dehydrogenase (LDH) but some will also be exchanged to (1-¹³C)alanine via alanine aminotransferase (ALT), or irreversibly converted to ¹³CO₂ via pyruvate dehydrogenase (PDH).³³ The production of lactate in tumour tissue, even in the presence of oxygen, is termed the "Warburg effect" and has been observed using HP ¹³C-MRSI in a variety of preclinical cancer models. There is evidence that the labelling of lactate correlates with tumour grade, with higher lactate labelling present in more aggressive tumours.^{1,37} HP ¹³C-MRSI has also been used to demonstrate a consistent decrease in the ¹³C exchange between (1-¹³C)pyruvate and (1-¹³C)lactate during tumour responses, regardless of treatment type in various *in vitro* and *in vivo* models, with changes seen as early as 24 h after the initiation of therapy, and sometimes earlier than conventional imaging modalities such as diffusion-weighted imaging.^{34,38–42} HP

Figure 1. Diagram showing the metabolic fate of glucose and pyruvate. ALT, alanine transaminase; AST, aspartate transaminase; CA, carbonic anhydrase; CAT, carnitine acyltransferase; CS, citrate synthase; FH, fumarate hydratase; GLDH, glutamate dehydrogenase; IDH, isocitrate dehydrogenase; LDH, lactate dehydrogenase; MDH, malate dehydrogenase; OGDC, oxoglutarate (α -ketoglutarate) dehydrogenase complex; PC, pyruvate carboxylase; PDH, pyruvate dehydrogenase; SCS, succinyl coenzyme A synthetase; SDH, succinate dehydrogenase (part of succinate-coenzyme Q reductase). Pyruvate, lactate and fumarate have been highlighted in bold.

^{13}C -MRSI may also have a role in the early detection of preneoplastic changes, as demonstrated in a pancreatic model evaluating LDH activity with increased HP ^{13}C label exchange between ^{13}C -pyruvate and endogenous lactate present with the onset of neoplastic transformation.⁴³

TRANSLATION INTO HUMAN IMAGING

The first human study using HP ^{13}C -MRSI was completed in 2013 at the University of California San Francisco.¹⁸ This study demonstrated the safety and feasibility of HP ^{13}C -MRSI with (1- ^{13}C) pyruvate in 31 male subjects with biopsy-proven prostate cancer. Patients were injected with hyperpolarized ^{13}C -pyruvate. Signals

from pyruvate and lactate were observed in the vasculature, tumour and normal prostate at the three dose levels considered (0.14, 0.28 and 0.43 ml kg⁻¹ actual body weight of 230 mm pyruvate solution) and uptake in the prostate was observed approximately 20 s after injection. A few mild adverse events such as dysgeusia (5/31 patients) were reported but none of them were considered to be dose-limiting toxicities. Two single events of dizziness and Grade 2 diarrhoea reported in the Phase 2 component were attributed to concomitant medications. The highest dose tested, 0.43 ml kg⁻¹ of ^{13}C -pyruvate solution, showed the highest SNR for ^{13}C -pyruvate as expected. The study also demonstrated an elevated ^{13}C -lactate/ ^{13}C -pyruvate ratio on HP ^{13}C -MRSI in one patient where no

Figure 2. Hyperpolarized pyruvate metabolism in human prostate cancer. Images from a patient with bilateral biopsy-proven Gleason Grade 3 + 3 prostate cancer. (a) Axial T_2 weighted image and (b) apparent diffusion coefficient (ADC) map showing a peripheral zone tumour (arrows). (c) False colour metabolic map superimposed over the proton image showing voxels with an elevated ratio of hyperpolarized ($1\text{-}^{13}\text{C}$)lactate/($1\text{-}^{13}\text{C}$)pyruvate bilaterally in the prostate and highlighted in pink, obtained after administration of hyperpolarized ($1\text{-}^{13}\text{C}$)pyruvate. Adapted from Nelson et al¹⁸ with permission.

abnormality was detectable on conventional ^1H -MRI; this patient was subsequently shown to have a biopsy-proven low-grade tumour (Figure 2). The study concluded that the data confirmed both the safety of the agent and that an elevated ^{13}C -lactate/ ^{13}C -pyruvate may be seen in regions that were otherwise undetectable with standard methods, opening up the possibility of using metabolic imaging to detect occult tumours.

This initial study required a sterile room for the production and hyperpolarization of the ^{13}C pyruvate prior to dissolution and injection. Wider application of the technology was made possible by the design of a new platform which utilizes an integral, disposable and sterile fluid path or pharmacy kit (Figure 3).²⁹ The SPINlab hyperpolarizer, produced by GE Healthcare, uses a closed-cycle cryogenic system and has multisample capability (Figure 4). The pharmacy kit is prefilled and sealed in a sterile environment, before being transferred to the clinical hyperpolarizer, thus enabling the hyperpolarization of a pyruvate sample within a routine clinical environment such as a radiology department, whilst maintaining the sample sterility. Filled pharmacy kits can either be used on the day of production or stored frozen depending on the method that is used.

Clinical imaging studies

There are currently six sites that have undertaken clinical imaging with the technique, although several other facilities will commence human imaging in the near future. Current studies in human HP ^{13}C -MRSI research are exploring pyruvate metabolism in a number of organs such as the brain, heart, liver and breast and in a variety of disease processes. Several of these studies are evaluating HP ^{13}C -MRSI derived biomarkers in addition to tissue samples in order to understand and validate the biophysical nature of signal generation with HP ^{13}C -MRSI. Another important aim is to establish the reproducibility and repeatability of the technique.

A significant objective of the current clinical studies is to investigate HP ^{13}C -MRSI as an imaging biomarker of early treatment response. Many of these studies are being run in parallel with other conventional imaging tests for measuring

treatment response, as well as functional MR imaging techniques, such as dynamic contrast-enhanced MRI. Changes in tumour metabolism in response to therapy have been shown to occur before anatomical changes can be detected and potentially could be earlier than functional imaging alterations. The use of the technique as a response biomarker has been demonstrated in several animal studies and is now being translated to humans (Figure 5).^{34,39,42,44} An exciting area for future research is how changes in metabolism measured by HP ^{13}C -MRSI following treatment relate to circulating tumour biomarkers such as cell-free DNA,^{45,46} as this would increase the ability to non-invasively interrogate tumour activity and responses to therapies, and spare patients the complications associated with serial biopsies. Potentially, HP ^{13}C -MRSI may provide a specific pharmacodynamic downstream imaging biomarker of both conventional and novel agents, and could also be used to detect early changes following therapy which are predictive of long-term response. This could therefore provide a novel non-invasive precision medicine approach to drug development, permitting early cessation of ineffective drugs and providing a cost saving in terms of patient time and toxicities.

THE FUTURE OF THE TECHNIQUE

MRI hardware developments for hyperpolarization Despite the large increase in SNR that is generated by DNP, both the hardware and acquisition sequences required have to be optimized to avail of this increased signal. Dedicated ^{13}C coils are needed for the technology; current research being undertaken aims to optimize coil design and pulse sequences to maximize the signal acquired. For example, the use of multiple-channel coil arrays can enable parallel imaging techniques to accelerate acquisition while retaining sensitivity.⁴⁷ Calibrationless methods have been shown to overcome the limitations of the short-lived hyperpolarized species in this context.⁴⁸

There have been several different imaging schemes proposed for the acquisition of hyperpolarized ^{13}C data.⁴⁹⁻⁵¹ A key component of most sequences is the use of single shot, multiple time point acquisition to acquire dynamic, 0-specific data.⁵¹

Figure 3. Pharmacy kit for clinical polarization. The kit contains pyruvate sealed within a closed sterile environment. The kit includes: a sample vial, the concentric tube assembly, the multiposition inlet/outlet valve, a syringe for dissolution medium, a filter and a receiver unit. EPA, electron paramagnetic agent; QC, quality control.

The differences mainly involve encoding efficiency, gradient demand and artefact behaviour: non-Cartesian trajectories are more efficient but are prone to artefacts.⁵⁰ The choice of the optimal sequence depends on the spatial and temporal resolution desired and the number of different chemical species to be resolved. Future developments in this area will involve assessing and improving intersite reproducibility of the data acquisition methods.

Pharmacy requirements and developments in formulation

The current approach for the consumables for the clinical polarizer requires a local sterile production facility to fill pharmacy kits which can be costly to establish. A more practical approach may be the development of a large, centralized, filling facility where pharmacy kits could be frozen and transported to other sites. There are a number of country-specific regulatory issues that need to be addressed for the production and

transport of these filled pharmacy kits at each site which needs to be considered before developing a programme of research locally.

If hyperpolarized ^{13}C -MRSI is to be more widely used, it needs to be accessible for non-specialist centres. To improve availability, there is ongoing research in the area of long-lived polarized states and transport of pre-polarized molecules. Although this area is still in the early stages of development and some way from clinical translation, it could potentially open up the possibility of hyperpolarizing molecules centrally and transporting them to the imaging site without the need for a local polarizer.

New hyperpolarized tracers

Hyperpolarized ^{13}C -labelled tracers offer unique opportunities to probe many metabolic pathways. Although many hyperpolarized tracers have been developed, very few have the

Figure 4. (a) Schematic of cryostat, magnet and sorption pump. The 3.35 T magnet is located within a helium-filled cryostat and suspended within an external vacuum vessel. Reproduced from Ardenkjaer-Larsen *et al*²⁹ with permission. (b) Photograph of the SPINlab Diamond Polarizer for clinical use in Cambridge (GE Healthcare). This clinical SPINlab uses a 5T magnet.

Figure 5. ^{13}C spectroscopic imaging of a murine lymphoma tumour before and after drug treatment. Colour maps representing ($1\text{-}^{13}\text{C}$)lactate and ($1\text{-}^{13}\text{C}$)pyruvate peak intensities obtained from ^{13}C chemical-shift imaging in the same mouse before and after treatment with the chemotherapeutic agent etoposide. The proton greyscale images define the tumour margins (indicated in white). Reproduced from Day *et al*³⁴ with permission.

Table 1. Some of the hyperpolarized tracers with clinical potential which are currently being investigated and their biological relevance

Tracer name	Biological relevance
(1- ^{13}C)pyruvate	LDH and PDH activity
(2- ^{13}C)pyruvate	LDH, PDH, TCA activity
(1- ^{13}C)lactate	LDH activity
(1- ^{13}C)acetate	TCA activity and fatty acid oxidation
(1- ^{13}C)glutamine	Glutaminolysis
(^{13}C)urea	Tissue perfusion
(1,4- $^{13}\text{C}_2$)fumarate	Cellular necrosis

LDH, lactate dehydrogenase; PDH, pyruvate dehydrogenase; TCA, tricarboxylic acid;

necessary biological, chemical and physical properties required for successful translation into human imaging. Table 1 summarizes some of the tracers which have clinical potential and provide biologically useful information. As discussed above, (1- ^{13}C)pyruvate has been used to probe LDH and PDH activity and similarly, (1- ^{13}C)lactate can be used to probe LDH; however, (1- ^{13}C)pyruvate cannot be used to probe the tricarboxylic acid (TCA) cycle as the label is not incorporated into acetyl CoA.⁵² (1- ^{13}C)pyruvate oxidation mediated by PDH releases the hyperpolarized ^{13}C as $^{13}\text{CO}_2$ and therefore the production of acetyl CoA and incorporation into the Krebs cycle cannot be studied. In contrast, (2- ^{13}C)pyruvate allows downstream metabolites such as acetyl carnitine, citrate and glutamate to be detected.^{53,54} (2- ^{13}C)pyruvate can assess metabolism in tissues where PDH activity is high such as the heart, by probing oxidative metabolism through the Krebs cycle rather than anaerobic glycolysis and lactate formation.⁵⁴

^{13}C -Urea has been utilized to probe tissue perfusion but unlike conventional perfusion tracers, is a small endogenous molecule.^{55,56} A number of potential issues have been identified with gadolinium-based contrast agents recently such as accumulation in the brain with repeated use,^{57,58} consequently, hyperpolarized urea may provide an alternative method to image tissue perfusion with a physiologically relevant molecule.⁵² ^{13}C -Urea could also be used to study tissue oxygenation as has been shown in both the healthy and diabetic rat kidney.^{59,60}

Hyperpolarized (1,4- $^{13}\text{C}_2$) fumarate has been proposed as a positive contrast agent for detecting successful treatment response and tissue necrosis. (1,4- $^{13}\text{C}_2$) fumarate is exchanged to (1,4- $^{13}\text{C}_2$) malate in the presence of the enzyme fumarase. The intracellular enzyme is released into the extracellular space following necrosis allowing enzymatic conversion of fumarate to malate (Figure 6).⁶¹ This has been demonstrated in tumours and in acute kidney injury.³¹

One important advantage of HP ^{13}C -MRSI over PET imaging is that it allows multiple probes to be injected either sequentially or simultaneously so that several metabolic pathways can be studied at a single time point. Although dual PET probe injection has also been undertaken, the modelling required to differentiate these probes is complicated by perfusion, metabolism and excretion and is often impractical; furthermore, conversion into metabolic products cannot be detected.⁶² In comparison, HP ^{13}C -MRSI has the advantage of discriminating probes and their metabolites by virtue of differences in chemical shift: therefore, metabolism of molecules injected simultaneously can be directly compared. This has been demonstrated in several preclinical models and has the potential to be applied to humans in the future.³⁸

Figure 6. Transverse images from (a) untreated and (b) etoposide-treated mice with implanted lymphoma tumours. The ^1H image shows the anatomical location of the tumour, outlined in white. The false-colour maps superimposed on the proton images demonstrate the spatial distribution of the total hyperpolarized ^{13}C malate and ^{13}C fumarate signals. The colour scale indicates the relative signal intensity compared with the maximum intensity in each image. Reproduced from Gallagher et al⁶¹ with permission.

Image analysis and quantification

Robust quantification of HP ^{13}C -MRSI will be important for the repeatability and reproducibility of the technique. Given that the technique probes exchange or flux between two metabolic pools, there are many analogies between the approaches taken for HP ^{13}C -MRSI and those used in PET and dynamic contrast-enhanced MRI. Several methods have been proposed to reliably and reproducibly quantify the pyruvate-lactate exchange reaction: kinetic parameters can be fitted to model-based approaches such as the two-site exchange model which are the most accurate; simpler model-free approaches such as the area under the curve of the lactate-to-pyruvate ratio and the lactate time-to-peak may adequately represent the reaction and may be more suitable for widespread clinical use.^{34,63,64} Further challenges of the technique include the segmentation of tumour from normal tissue which is compounded by the low resolution and SNR of the data. However, by fully utilizing the five-dimensional nature of HP ^{13}C MRSI—including spatial, temporal and spectral information—segmenting areas of high metabolic exchange from low exchange can be greatly facilitated and these approaches could be used for automated and reproducible delineation of tumour regions in the future.⁶⁵

Hyperpolarized ^{13}C -MRSI with PET/MRI

Since its introduction in clinical practice, PET/CT has found many clinical applications due to the combination of metabolic (PET) and anatomical (CT) information.⁶⁶ ^{18}F -FDG PET/CT is a powerful tool for staging and treatment response monitoring in a wide range of cancers such as lung cancer and lymphoma.^{8,67} The recent creation of hybrid systems combining PET and MRI have capitalized on the inherent advantages of MRI over CT such as the lack of ionizing radiation, functional imaging capabilities, spectroscopy and improved soft-tissue contrast.^{11,68} Several clinical applications have been proposed for PET/MRI^{69,70}: in oncology, examples include head and neck cancers, liver tumours and pelvic malignancies which may significantly benefit from the hybrid approach due to improvements in co-registration and reduction in movement artefact.^{71–75} PET/MRI has also demonstrated potential in organs such as the lung where traditionally MRI has only had a limited role, highlighting the potential of the combination of those two techniques.^{76–78}

PET/MRI could provide a powerful tool for imaging tumour metabolism. While ^{18}F -FDG is a highly sensitive measure of metabolism and has many applications, it simply measures glucose uptake and phosphorylation and therefore provides only an indirect measure of the Warburg effect.^{79–81} In contrast, hyperpolarized ^{13}C -MRSI is capable of monitoring the uptake of ^{13}C -pyruvate and its conversion into ^{13}C -lactate (or ^{13}C -alanine and ^{13}C -bicarbonate) enabling real-time *in vivo* imaging of metabolism and a more direct measure of the Warburg effect.^{82–84} Combining PET/MRI with ^{13}C -MRSI provides the opportunity to study cancer metabolism in conjunction with other MR measures of tumour structure, function and heterogeneity.⁸⁵ A recent study reported the simultaneous acquisition of ^{18}F -FDG PET and ^{13}C -MRSI

using a PET/MRI system in 10 dogs.⁸⁶ This demonstrated that, although there is a strong correlation between uptake of FDG and pyruvate conversion to lactate, there are areas of mismatch between the two techniques confirming the potential added value of combining the two techniques.^{86,87} A wide range of tracers in addition to ^{18}F -FDG could be used with this combined hyperpolarized ^{13}C -MRSI/PET approach such as the amino acid analogues ^{11}C -methyl-L-methionine (MET) and O-[2-(^{18}F)fluoroethyl]-L-tyrosine (FET) in brain tumours for diagnosis and therapy assessment.⁸⁸ This combination could be important in the management of some cancers, and certain population groups where longitudinal monitoring is required or where dose reduction is important such as children or females of reproductive age.⁸⁶ The technique will be translated into humans shortly.

As HP ^{13}C -MRSI is in its infancy and rapidly evolving, the projected long-term costs of the technology are difficult to accurately evaluate. Hardware costs will reduce in time if there is increased demand for hyperpolarization approaches. The authors believe that in the future the costs for undertaking such studies could be similar to those currently for PET imaging. These costs could be defrayed by the clinical benefits and treatment cost savings if the technique is shown to have unique applications, particularly if ineffective but expensive therapies can be discontinued. Given that MRI is more widely available than PET in most hospitals, HP ^{13}C -MRSI could become an important additional clinical tool if unique applications are revealed.

CONCLUSION

HP ^{13}C -MRSI can be used to probe tissue metabolism non-invasively *in vivo*. This may have important implications for the management of cancer patients in the future. Combined with conventional imaging tools, it may increase the accuracy of cancer staging, be used to target biopsies, help to distinguish highly aggressive from less aggressive disease and to demonstrate tumour heterogeneity. An important application for HP ^{13}C -MRSI is the detection of early changes in metabolic activity allowing for a rapid assessment of the therapeutic response to specific drugs and informing the clinical management in a faster and individualized fashion. While it is likely to remain a research tool for the foreseeable future, such an approach could have important implications for the personalized management of cancer in the future.

FUNDING

This work has been funded by Cancer Research UK (CRUK; C19212/A16628) and the CRUK & Engineering and Physical Sciences Research Council (EPSRC) Cancer Imaging Centre in Cambridge and Manchester (RQAG/052). Additional support has been provided by the CRUK Cambridge Centre, the National Institute of Health Research (NIHR) Cambridge Biomedical Research Centre, the Wellcome Trust, the Medical Research Council, MS Society, The Gates Cambridge Trust, the Austrian Science Fund (FWF, J4025-B26) and Addenbrooke's Charitable Trust.

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