Title: A physiological study comparing hyperpolarised carbon-13 labelled pyruvate (^{13}C-pyruvate) metabolism and sodium MRI in prostate cancer and normal prostate tissue

Short Title: MISSION-Prostate (**M**olecular **I**maging and **S**pectroscopy with **S**table **I**sotopes in **O**ncology and **N**eurology – Imaging metabolism in **prostate**)

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1. Study Synopsis

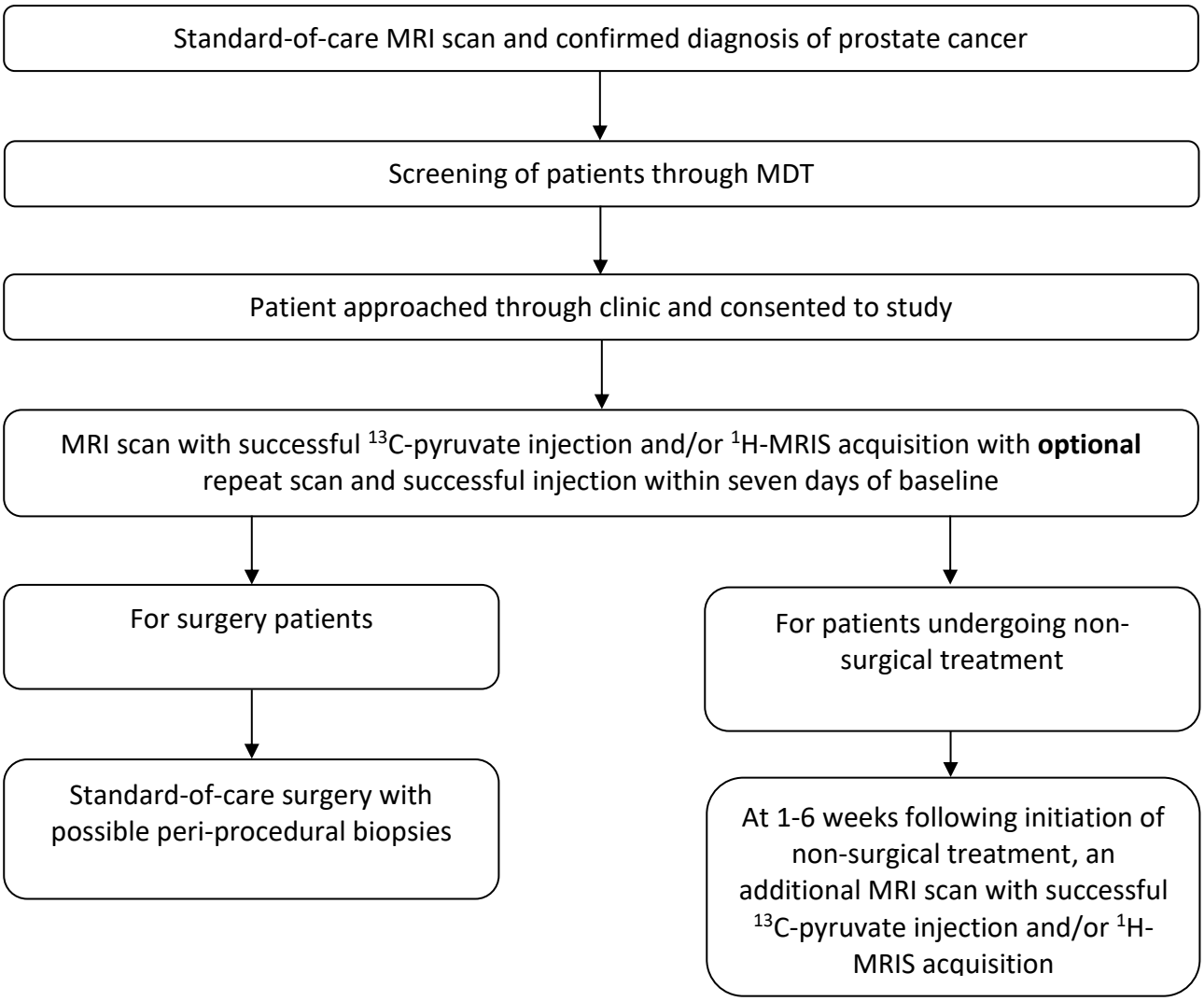
Study Title: *A physiological study comparing hyperpolarised carbon-13 labelled pyruvate (^{13}C-pyruvate) metabolism and sodium MRI in prostate cancer and normal prostate tissue*
Medical condition or disease under investigation: Prostate Cancer
Hypotheses: 1. Hyperpolarised ^{13}C-lactate forms in prostate tumours after the intravenous injection of hyperpolarised ^{13}C-pyruvate, and that this can be detected with ^{13}C-Magnetic Resonance Spectroscopic Imaging (MRSI). 2. Alterations in ^{23}Na-Magnetic Resonance Imaging (MRI) signal will correlate with the presence of prostate tumours, as a measure of underlying changes in tissue structure. 3. Downstream metabolites of pyruvate in prostate tumours will be visualised using proton (^{1}H) MRSI.
Background: Prostate cancer is the most common male malignancy in the UK. Current standard of care diagnostic imaging has limitations in its ability to accurately diagnose and risk-stratify prostate cancer patients to appropriate management. Developing a non-invasive test that probes the molecular signature of prostate cancer has the potential to significantly improve patient outcome. MRI can be used to detect many other nuclei other than standard hydrogen (proton) nuclei, including sodium (^{23}Na) and carbon (^{13}C). Cancers are known to metabolise glucose into pyruvate and then to lactate through the Warburg effect. The level of lactate is therefore higher in tumours than in healthy tissue. The imaging of pyruvate and lactate can thus be used to probe metabolism in cancerous tissue. The molecules pyruvate and lactate are detectable with MRI when labelled with ^{13}C, and this detection may be greatly enhanced through a process known as hyperpolarisation. Hyperpolarisation of ^{13}C can increase the signal-to-noise ratio of images by more than 10,000-fold. Many vital cellular processes and biological reactions depend on the maintenance of a low intracellular and high extracellular sodium concentration. Changes in tissue sodium have been shown to occur in a wide range of disease processes including inflammation, ischaemia and in several tumours. Therefore, studying the sodium levels in prostate cancer could provide complementary information to traditional MRI. As a potential addition to standard MRI, multi-nuclear MR imaging techniques could be used in the future to reduce the need for unnecessary prostate biopsies, improve the targeting of biopsies and staging of the disease, as well as a tool for early and specific detection of successful treatment response to therapy.

Primary objectives: 1. To understand the biological basis of signal generation by imaging the metabolism of ^{13}C-pyruvate and ^{13}C-lactate using hyperpolarised magnetic resonance spectroscopic imaging in patients with prostate tumours and studying how the image findings relate to histology, biochemistry and genetics (somatic mutations) within the tissue. 2. To image the distribution of tissue sodium within prostate cancer, normal prostate, and surrounding tissues. 3. To investigate the ability of alternative magnetic resonance spectroscopic imaging techniques, such as ^{1}H-MRSI, to image the metabolism of pyruvate and its derivatives within prostate cancer, normal prostate, and the surrounding tissues. *Secondary objectives*: 1. To determine the acquisition windows which provide the optimal hyperpolarised ^{13}C-pyruvate and ^{13}C-lactate signal-to-noise ratios (SNR). 2. To examine correlations between venous blood pyruvate, lactate, LDH and the MR signal, and the acquired dynamic ^{13}C-pyruvate/^{13}C-lactate MRS(I) data. 3. To determine whether ^{23}Na-MRI signal correlates to tumour grade
Study Design: This is a physiological study to assess the metabolism of pyruvate and the spatial distribution of sodium in patients with prostate cancer. It is a single site study to be carried out at the Addenbrooke's Hospital site. 1. Participants will be recruited through multidisciplinary team meetings and clinics. 2. Research study performed including proton MRI, ^{23}Na-MRI, and hyperpolarised ^{13}C-MRSI study performed. This will include the intravenous injection of hyperpolarised ^{13}C-pyruvate or ^{1}H-MRSI. 3. A subset of patients will undergo an optional repeat hyperpolarised ^{13}C-MRSI within seven days of baseline imaging to assess for reproducibility of the imaging test. 4. Patients undergo surgery (where applicable) as part of standard-of-care. Alternatively, if patient is not a surgical candidate the patient will undertake targeted biopsy. 5. Where possible, peri-procedural biopsies will be performed to obtain tissue for biochemical and histological analysis. To reduce the number of biopsies a patient receives, we will ask the patient to consent to an additional biopsy core for research use being taken at the standard-of-care biopsy timepoint. 6. Completion of standard-of-care (i.e. prostatectomy or end of treatment) marks the end of patient involvement in the study. 7. Standard-of-care histopathological assessment with be performed on the biopsy specimen. In addition, immunohistochemistry and other analytical tests may be performed on the biopsy specimen to assess for tissue biochemistry and metabolism.
Intervention(s): Patients will undergo a single MRI study lasting approximately one hour, including placement of two endorectal coils. A subset of patients will undergo a repeat study. The study will necessitate one intravenous cannula for venous access and an intravenous injection of hyperpolarised ^{13}C-pyruvate Alternatively, patients may undergo a ^{1}H-MRSI scan only without an endorectal coil and intravenous cannula.

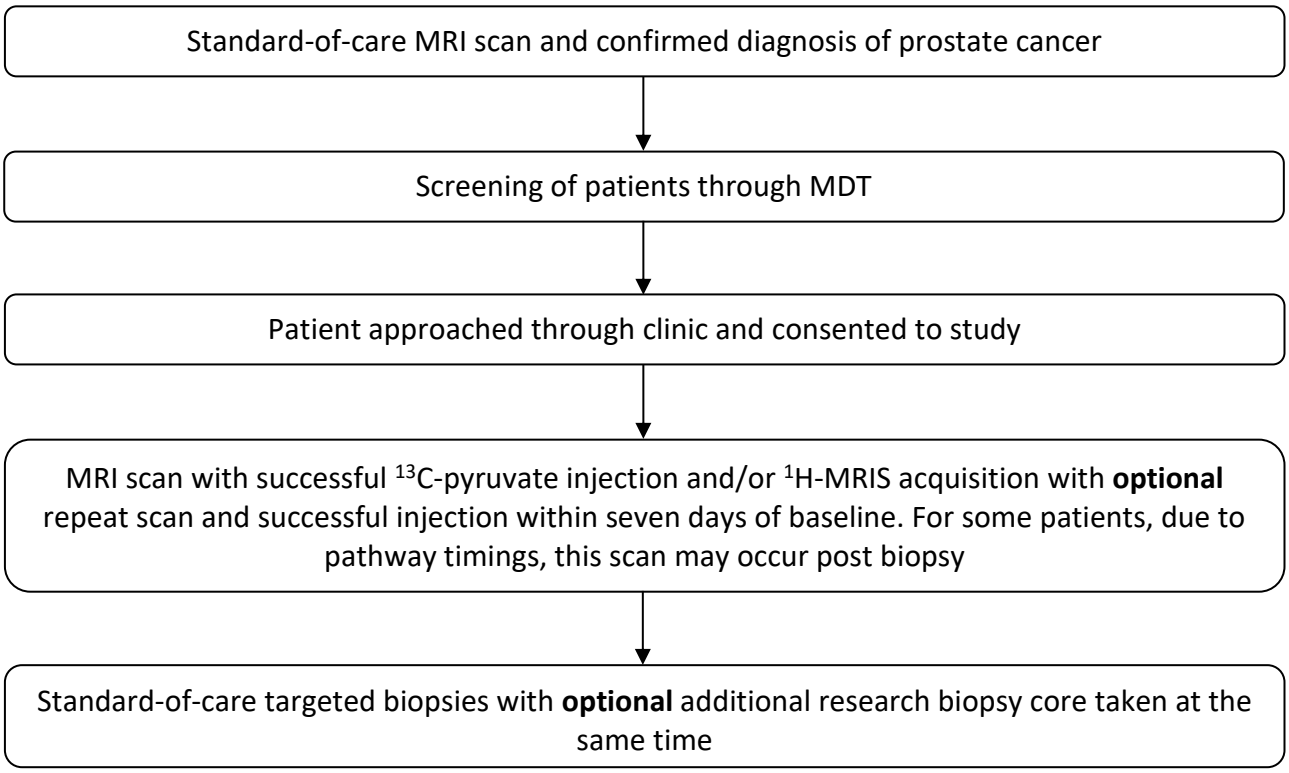
Planned Study Period: Patients will be enrolled in the study for 12 months after final ^{13}C-pyruvate injection.
Sample Size: 75 male patients with pathologically or imaging confirmed prostate cancer will undertake MRI scan and successful ^{13}C-pyruvate injection. A subset of these patients will be asked to undertake an **optional** repeatability scan and injection. No patient will be given more than four ^{13}C injections.

2. Study Flow Chart

For surgery and non-surgical treatment patients



For targeted biopsy patients



3. Background

3.1 Overview of prostate cancer

Prostate cancer is the leading male cancer in the UK with over 40,000 diagnoses annually and this incidence continue to rise [1]. However, while 1 in 8 men will be diagnosed with prostate cancer, only 3% of men will die from the disease, highlighting the indolent nature of many prostate cancers. Identifying aggressive prostate cancer and differentiating this from benign disease or more indolent tumours that do not require treatment is one of the major challenges in current urological practice.

3.2 Magnetic resonance imaging of prostate cancer

Magnetic Resonance Imaging (MRI) is routinely used to image suspected prostate cancer, but has limitations for tumour detection, with sensitivity and specificity of the technique ranging from 22%–85% to 50%–99%, respectively, depending on the composition of the study population and technical factors [2]. Standard clinical MRI provides information about the distribution of water molecules and is termed proton or ^{1}H-MRI. So called "multi-parametric" MRI (mp-MRI), incorporating multi-planar T_2-weighted anatomical imaging, and functional imaging, remains the modality of choice for tumour localisation. The functional sequences include: diffusion weighted (DWI) MR imaging (a technique to measure how water moves through a tissue), dynamic contrast-enhanced (DCE) MRI (measuring how the contrast freely passes into and out from "leaky" blood vessels in tumour), and proton spectroscopy (^{1}H-MRSI) to look at metabolite concentrations. Many of these, particularly DWI and DCE-MRI, are used in routine clinical practice. Although ^{1}H-MRSI has the potential to characterise tumour metabolism, it suffers from poor signal strength due to the low concentration of magnetic resonance active nuclei in metabolites that are of clinical interest limiting its use in the clinic [3].

3.3 Multi-Nuclear Imaging Techniques

MRI can be used to detect many other nuclei other than hydrogen. The images produced from these different nuclei (known generically as X-nuclei MRI) allow for other physical and metabolic processes to be studied in the human body, and two of these will be explored in this study.

3.4 Carbon-13 (^{13}C) MRI

3.4.1 The Warburg Effect

In 1956, the German scientist and physician Otto Warburg postulated that as part of their malignant transformation, cancer cells undergo a change in metabolism whereby to keep up with the energy demands of rapid growth there is a large increase in the rate of glycolysis and the production of pyruvate [4, 5]. He went on to show that in cancers there is a rise in the conversion of pyruvate to lactate which is much greater than would be expected as a result of faster aerobic glycolysis alone, even in the abundant presence of oxygen.

3.4.2 ^{13}C-MRI Dynamic Nuclear Polarisation

Endogenous carbon containing molecules are at a much lower concentration in the body compared to hydrogen concentration in water and fat. Furthermore, only 1.1% of natural abundance is detectable with MRI in the form of carbon-13. A method to increase the MR signal for metabolic imaging is hyperpolarisation. The term hyperpolarisation refers to an array of techniques all designed to increase the proportion of nuclei aligned with the main MR magnetic field.

Recent advances in a type of hyperpolarisation known as dynamic nuclear polarisation (DNP) may now offer a means to overcome the signal strength limitation of MR molecular imaging. DNP requires that the sample to be imaged is cooled to close to absolute zero and irradiated with microwave radiation. The microwave radiation transfers the spins from surrounding electrons to the chosen atomic nuclei thereby increasing the polarisation levels of the nuclei. It has been demonstrated that the MR signal-to-noise ratio of carbon-13 can be increased more than 10,000-fold and the sample could subsequently be dissolved into the liquid form so that it may be injected into a patient while maintaining hyperpolarisation levels [6]. This technique is sufficient to allow the spatial distribution of the injected molecule to be imaged as well as the metabolites formed from it, such as pyruvate.

The technique of hyperpolarised carbon-13 has recently been translated into human imaging using a prototype device and a single human study has been performed in prostate cancer in the University of California in San Francisco [7]. Over the last four years we have been developing this technique for human use in Cambridge with substantial investment from the Wellcome Trust, Cancer Research UK and the Cambridge Cancer Centre. We will use a hyperpolariser sited next to a clinical MRI system in Addenbrooke's hospital or at the Wolfson Brain Imaging Centre, Department of Neuroscience, University of Cambridge: these will be two of only a small number of sites in the world with this capability.

3.5 Sodium (^{23}Na) MRI

Sodium-MRI is a relatively new technique which aims to image this vital intra- and extracellular ion. Many vital cellular processes and interactions in excitable tissues depend on the maintenance of a low intracellular and high extracellular sodium concentration. This gradient is maintained by the transmembrane sodium-potassium pump, powered by ATP. If the supply of ATP is insufficient due to impaired cellular energy metabolism, or if the cell membrane integrity is disrupted, the intracellular sodium concentration will rise. Changes in tissue sodium have been shown to occur in a wide range of disease processes including inflammation, ischaemia and in several tumours. Therefore, studying the sodium levels in prostate cancer could provide complementary information to traditional MRI.

There are a number of reasons why tumours will demonstrate a high tissue sodium concentration (TSC). Proliferating cells have high intracellular sodium content secondary to increased activity of the Na+/H+ exchanger in the presence of reduced pH secondary to hypoxia and increased lactate [8, 9]. In addition, extracellular sodium will increase due to tumour neovascularisation and an increase in the tumour interstitial space [10]. Thus, increases in both intracellular sodium concentration and extracellular volume are contributing to an increase in tissue sodium.

^{23}Na produces the second strongest MRI signal among all nuclei present in biological tissues, making ^{23}Na-MRI feasible. However, the *in vivo* signal is 22,000-fold lower than that from protons and therefore ^{23}Na-MRI is challenging. This has been partly overcome by new techniques and higher-field strength magnets, allowing acquisition in a reasonable time (10 to 15 minutes) with a resolution of a few millimetres [11]. This now makes ^{23}Na-MRI a viable addition to existing ^{1}H-MRI protocols, rather than only being an option for studies on tolerant healthy volunteers.

Previous ^{23}Na-MRI studies on the prostate are limited. The only published ^{23}Na-MRI study of the prostate is by Hausmann *et al* [14], who imaged eight healthy volunteers using a sodium-tuned (cardiac) body coil, and demonstrated the prostate and its different departments were identifiable. To date, there have been no ^{23}Na-MRI studies imaging prostate tumours in patients. Furthermore, the signal-to-noise ratio when imaging the prostate with ^{1}H-MRI is greatly improved by use of an endorectal coil rather than body coil [15, 16] and we will apply this approach in this study.

4. Study Conduct

The study will be conducted in compliance with the current protocol, research governance, GCP and the applicable regulatory requirements. This study will be also carried out in accordance with the World Medical Association (WMA) Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989), South Africa (1996) and Scotland (2000) amendments.

5. Hypothesis of the study

The study will assess novel imaging techniques to study tissue structure and metabolism within prostate tumours. In particular, it will assess the distribution of tissue sodium and the physiological metabolism of a glucose breakdown product, pyruvate.

6. Objectives of the Study

6.1 Primary Objectives

1. To understand the biological basis of signal generation by imaging the metabolism of ^{13}C-pyruvate and ^{13}C-lactate using hyperpolarised magnetic resonance spectroscopic imaging in patients with prostate tumours and studying how the image findings relate to histology, biochemistry and genetics (somatic mutations) within the tissue.
2. To image the distribution of tissue sodium within prostate cancer, normal prostate, and surrounding tissues.

To investigate the ability of alternative magnetic resonance spectroscopic imaging techniques, such as ^{1}H-MRSI, to image the metabolism of pyruvate and its derivatives within prostate cancer, normal prostate, and surrounding tissues.

6.2 Secondary Objectives

1. To determine the acquisition windows which provide the optimal hyperpolarised ^{13}C-pyruvate and ^{13}C-lactate signal-to-noise ratios (SNR).
2. To examine correlations between venous blood pyruvate, lactate, LDH and the MR signal, and the acquired dynamic ^{13}C-pyruvate/^{13}C-lactate MRS(I) data.
3. To determine whether ^{23}Na-MRI signal correlates to tumour grade.

7. Study Design

This is a physiological study to assess the metabolism of pyruvate and the spatial distribution of sodium in patients with prostate cancer prior to treatment with prostatectomy and nonsurgical treatments. It is a single site study, imaging for which will be undertaken at the MRIS unit and the Wolfson Brain Imaging Centre, both located at the Addenbrooke's Hospital site.

7.1 Subjects

Suitable patients will be identified at the specialist multidisciplinary uro-oncology meeting, where management plans for all prostate cancer patients are discussed. Men eligible for the study will be approached to ask if they would be willing to participate. Patients will have an opportunity to read a full information sheet and written informed consent will be obtained following a sufficient cooling off period (minimum 24 h). Men who agree to participate will be invited for a research specific MRI examination.

7.1.1 Inclusion criteria

- Men aged > 18 years
- For surgery and non-surgical treatment patients, biopsy-proven intermediate risk or high risk prostate cancer (**Appendix 1**), with a clinical treatment plan
- Previous diagnostic clinical MRI demonstrates a visible tumour

7.1.2 Exclusion criteria

- Treatment for prostate cancer prior to first planned ^{13}C-pyruvate MRI scan
- Clinical contraindication to MRI
- Renal impairment as defined by a GFR <30 ml/min

7.2 Statistical considerations and patient number

For the purpose of this pilot study, with the primary objective of assessing the clinical feasibility of the MRI techniques, insufficient prior knowledge is available to perform a formal sample size calculation. The defined sample size has been determined based on the below statistical calculation and pragmatic considerations of the anticipated recruitment rates.

Study statistician: Dr Wendi Qian, Cambridge clinical trials unit (CCTU) Senior Statistician (Cancer Theme), University of Cambridge. 01223 256363, wendi.qian@nhs.net

7.3 Study Duration

The study duration is currently due to complete by 31-Mar-2026, however, study recruitment will be reviewed and this may be amended as necessary.

7.4 MR Imaging

All participants will undergo a research MRI either at the MRIS unit at Addenbrooke's Hospital or the Wolfson Brain Imaging Centre, University of Cambridge. The MRI examinations will be performed on a 3.0 T MR scanner. The sequences will include standard proton MRI, ^{23}Na-MRI, ^{13}C-MRSI, and ^{1}H-MRSI. Standard sequences and ^{1}H-MRSI will be acquired using the body coil, the ^{23}Na-MRI and ^{13}C-MRSI sequences will be acquired using separate endorectal coils. In some case for technical reasons not all sequences may be performed, and only one endorectal coil will be necessary; patients are also free to refuse the second coil if they find the first uncomfortable. The MRI scanning time will last approximately one hour.

The proton MRI will be similar to the MRI undertaken in the hospital setting as part of standard practice in the diagnosis of prostate cancer and will include the use of gadolinium contrast. ^{13}C-MRI will be performed after injection of hyperpolarised ^{13}C-pyruvate solution.

Within seven days after initial imaging a sub-set of patients will be asked to undergo an **optional** repeat baseline proton and/or ^{13}C-MRSI again. Such repeat testing is necessary to assess the reproducibility of images produced by this new imaging technique.

Throughout this study images will be reviewed by a radiologist and where appropriate the clinical teams will be informed of the results from the proton imaging. ^{23}Na-MRI, ^{13}C-MRSI and/or ^{1}H-MRSI on the other hand has not previously been sufficiently studied in prostate cancer and so the significance of findings from these imaging techniques is not known, the results will therefore not be disclosed to the participants or their clinicians.

In order to quantify sodium concentration, it is necessary to image calibration markers of known sodium concentration within the imaged field of view. We will place up to four tubes containing a sodium solution outside of the patient.

7.5 Surgery

Surgical patients meeting the inclusion criteria will proceed to surgery. Standard-of-care clinical pathway will not be altered as a result of the imaging and surgery will not be delayed by the study imaging.

7.6 Targeted biopsy

Patients undergoing targeted biopsy may have their research MRI scans either prior to or post targeted biopsy. This is due to the potential short cancer pathway for prostate cancer patients and the logistics of organising the research MRI scan. Standard-of-care clinical pathway will not be altered or delayed as a result of the imaging.

7.7 Non-surgical treatment

Patients with advanced tumours undergoing non-surgical treatments will have their baseline research MRI scan prior to commencement of treatment and at 1-6 weeks following initiation of treatment will have a post treatment research MRI scan. Standard-of-care clinical pathway will not be altered or delayed as a result of the imaging.

7.8 Histopathological evaluation

Standard-of-care histopathological assessment, in addition, immunohistochemistry and other analytical tests will be performed on the prostatectomy or biopsy specimens to assess biochemistry and metabolism.

Where possible, peri-procedural biopsies will be performed on the fresh tissue.

The gold standard for tumour localisation will be histology. Depending on the management of the patient this may be whole-mount histopathology sections of the *ex vivo* prostate following surgery, or from biopsy cores obtained by either a transrectal or transperineal approach. This will be dictated by the standard clinical pathway of each individual patient and this will in no way be influenced by the current study.

7.9 End of study

For surgical patients, completion of surgery marks the end of participants' involvement in the study. For targeted biopsy patients, either having targeted biopsy or research MRI scan (whichever comes last) marks the end of participants' involvement in the study. For non-surgical treatment patients, completion of post-treatment research MRI scan marks the end of participants' involvement in the study.

All participants will return to having their regular standard-of-care imaging and clinical management following end of their involvement in this research study.

8. Evaluation of Endpoints

8.1 Image comparison

The comparison of proton, ^{23}Na and ^{13}C images will be performed as a reader study where experienced radiologists will be asked to comment on the presence of lesions and their visibility.

8.2 Correlation of histology with biochemical parameters

We will look at how differences in images relate to biochemical and metabolic markers, gene expression and histology to tell if the imaging gives an accurate representation of histological tissue type and its biochemical properties. Histology will be from prostatectomy or biopsy specimens.

^{13}C signal intensity will be compared with tissue characteristics including carbonic anhydrase IX, CD31, Hypoxia-Inducible Factor-1α (HIF-1α), Ki67, monocarboxylic acid (MCT1/4) transporters, LDH expression and lactate/pyruvate levels. These will be exploratory comparisons given the small sample size. Immunohistochemistry results will likely have to be converted into semi-quantitative data using an appropriate density measurement of staining. The appropriateness of this type of analysis can only be confirmed however when data is actually collected.

9. Additional patient interventions compared to standard care and risks

- Additional patient travel time
- Research MRI study, scan time of approximately one hour
- Second research MRI study lasting approximately one hour in a subset of patients
- The study will necessitate the placement of an intravenous cannula for venous access
- The study will necessitate the placement of up to two endorectal coils.

Placing a cannula into a vein can cause some discomfort and very occasionally can lead to infection, but this is highly unlikely in the short time it will be in place. Some people can get bruising at the site where the cannula is inserted. This procedure is performed regularly in the hospital and is generally very safe. The cannula will be inserted just before the scan and will be removed immediately afterwards.

Injection of a Gadolinium-based MRI contrast agent can rarely induce an allergic reaction. Although it is extremely unlikely that an allergic reaction or other side effect will occur, there are facilities in place within the MRI unit and within the hospital to deal with them.

Some people (less than 5%) find the MR system claustrophobic. MR radiographers conducting the scans constantly monitor patients and can stop the scan if necessary.

The placement of an endorectal coil can be uncomfortable. The study will necessitate the placement of up to two endorectal coils (for ^{23}Na and ^{13}C imaging, respectively). A disposable cover will be placed over the coil. During insertion of the endorectal coil, pressure is felt within the rectum, which is often similar to that experienced during a digital rectal exam. Endorectal coils are commonly used routinely as standard of care for diagnostic imaging of the prostate in centres around the world. The coil will be sited by an experienced doctor within the research team, and removed immediately after the examination.

10. Data Handling

Data will be securely stored using password-protected storage media, in addition to password-protected servers. Patient lists will be stored securely in a locked facility in the Department of Radiology. This will all be carried out as per trust policy. In accordance with local guidance, the data will be stored securely for up to 10 years following the end of the study.

11. Confidentiality

All study images will be stored on an internal DICOM server (used for all Radiology research studies). Any analysis will only be performed on anonymised images. The participants will be identified by a study specific participants number and/or code in any database. The name and any other identifying detail will not be included in any study data electronic file.

Images acquired at the Wolfson Brain Imaging centre will be stored in non-anonymised form on encrypted servers at the University of Cambridge and may be transferred to the NHS for clinical purposes.

Research study team members listed on the study delegation log with responsibilities to handle study data will be able to access, process, analyse and report the study data. Researchers will be trained in handling the patient data and data anonymisation process. Anonymised data may be shared with academic and industry collaborators as noted in the PIS. Appropriate patient consent will be sought.

12. Ethical Agreement and Insurance

Ethical permission is being sought from the Cambridgeshire South Research Ethics Committee. Insurance will be provided by the NHS insurance scheme. The study design is covered by University of Cambridge clinical study insurance.

13. Sponsorship and Finance

The study is jointly sponsored by grants from the Evelyn Trust, Prostate Cancer UK and Cancer Research UK.

14. Patient remuneration

Participants will be remunerated for reasonable expenses incurred because of participation in this study (for example travel, parking).

15. References

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Appendix 1

DEFINITION OF RISK STRATIFICATION FOR MEN WITH LOCALISED PROSTATE CANCER.
(AUA guidelines 2007)

Low risk: PSA ≤10 ng/mL and a Gleason score of six or less and clinical stage T1c or T2a

Intermediate risk: PSA >10 to 20 ng/mL or a Gleason score of seven or clinical stage T2b but not qualifying for high risk

High risk: PSA >20 ng/mL or a Gleason score of eight to 10 or clinical stage T2c* and greater

***T2c**: the tumour is in both lobes but within the prostatic capsule