Development and Validation of a Tumour Oxygenation Monitoring Probe

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Sponsor

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

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This protocol describes the Development and Validation of a Tumour Oxygenation Monitoring Probe. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the UK Policy Frame Work for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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GLOSSARY OF ABBREVIATIONS

BOLD-MRI	Blood Oxygen Level Dependant- Magnetic Resonance Image
DICOM	Digital Imaging Communications in Medicine
DRS	Diffuse Reflectance Spectroscopy
ICHNT	Imperial College NHS Trust
HIF	Hypoxia Inducible Factor
pCR	Pathological Complete Response
PET-FDG	Positron Emission Tomography - Fluorodeoxyglucose
STL	Standard Tessellation Language
TAM	Tumour Associated Macrophage

KEYWORDS
Tumour, Oxygenation, Sensor, Diffuse Reflectance Spectroscopy

STUDY SUMMARY

TITLE	Development and Validation of a Tumour Oxygenation Monitoring Probe
DESIGN	Tumour oxygenation sensor validation using 3D-Printed tissue phantoms
AIMS	To design and validate a novel tumour oxygenation monitoring probe which may be used to monitor response to therapies in cancer, using 3D-printed phantoms
OUTCOME MEASURES	Correlation of sensor oxygenation measurements as compared to gold-standard oxygenation measurements in phantom tissue models
POPULATION	3D printed tissue phantoms, based upon breast and rectal cancer MRIs
ELIGIBILITY	20 Anonymised pre-treatment MRI scans for patients with locally advanced rectal cancer (10 scans) and breast cancer (10 scans) MRIs from patients younger than 18 years of age, or older than 99 years of age will be excluded. MRIs from patient who did not go on to receive neoadjuvant therapy will be excluded
DURATION	1 Year

1. INTRODUCTION

1.1 BACKGROUND

1.1.1 Tumour Oxygenation

Tissue hypoxia is a common feature of most solid tumours. More than a just simple outstripping of vascular supply, tumour hypoxia results in complex interplay that affects malignant cellular function and the tumour microenvironment. Tumour hypoxia drives a selective pressure towards adaptations for increased cell survival and proliferation as well as angiogenesis. These adaptations are mediated primarily through the Hypoxia Inducible Factors (HIFs): transcription factors that respond to cellular hypoxia through expression of genes responsible for a diverse array of functions including inflammatory cell recruitment, angiogenesis and cell survival. Similarly, hypoxia alters the tumour microenvironment: necrosis attracts tumour associated macrophages (TAMs) and cancer associated fibroblasts, both of which are associated with increased mitogenic and metastatic potential. Angiogenesis in response to tumour hypoxia results in dysfunctional and permeable vessels that provide a route for metastasis.

Tumour hypoxia is chemo- and radio-protective. A wealth of evidence has contributed to the development of the oxygen fixation hypothesis: an understanding that molecular oxygen is a necessary requirement for the mechanistic action of ionizing radiation. Oxygen is required for the generation of free radicals during ionization, and to establish breakages in DNA. Hypoxia is similarly associated with decreased responsiveness to chemotherapy: hypoxia induces changes which reduce susceptibility to DNA damage and induces cell cycle arrest, while localized hypoperfusion reduces chemotherapeutic delivery.

Tumour hypoxia ultimately results in more aggressive tumours with increased metastatic potential and resistance to therapies.

1.1.2 Current Methods of Tissue Oxygenation Monitoring

The potential role for tissue oxygenation monitoring to assist in prognostication, guide treatment decisions and assess responses has driven the need for improved means of assessing tumour oxygenation. The ideal solution would provide accurate, quantitative and continuous assessment of tumour oxygenation, accounting for spatial variation within the tumour.

Eppendorf electrodes provide direct and accurate measurements of tumour oxygenation. However, the invasive nature limits them to superficial tumours, and while providing quantitative assessment of tumour oxygenation, it does not provide a spatial representation of tumour oxygenation.

Positron Emission Tomography with fluorodeoxyglucose (PET-FDG) or oxygen sensitizers such as Fluoromisonidazole or Copper-diacetylbis(4-methylthiosemicarbazonato) provides an indirect spatial representation of tumour oxygenation. It is, however, not quantitative and requires the administration of radioactive isotopes.

Blood Oxygen Level Dependent Magnetic Resonance Imaging (BOLD-MRI) utilises differences in magnetic nature of oxy and deoxyhaemoglobin to provide an indirect assessment of tissue oxygenation. BOLD-MRI detailed spatial assessment of tumour tissue oxygenation without need for agents or isotopes. However, it only provides a snap-shot non-quantitative assessment of tumour oxygenation.

1.1.3 Clinical Paradigms for Tumour Oxygenation Monitoring

Continuous tumour oxygenation assessment is likely to be a valuable adjunct in the management of many cancers. Two paradigms that demonstrate its potential include neoadjuvant chemoradiotherapy for locally advance rectal cancer, and neoadjuvant therapy for breast cancer.

Rectal Cancer:
The addition of neoadjuvant chemoradiotherapy to transanal mesorectal excision marked a significant advance in the management of locally advanced rectal cancer. 50.4 Gray of external beam radiotherapy given over 28 fractions in conjunction with chemotherapy reduces the risk of circumferential involvement at surgery and improves overall survival. However, the response rates are highly variable, and as low as 30%. The potential benefit is balanced significant costs, with 18% of patients suffering from grade III/IV toxicities. Continuous oxygenation monitoring could provide a useful adjunct in the monitoring of neoadjuvant chemotherapy, potentially allowing for personalisation of management.

Breast Cancer:
Neoadjuvant therapy in breast cancer is used to reduce tumour size, which may convert inoperable tumours to operable ones, allow for breast conserving therapy, and in some cases result in a complete pathological response (pCR). Endocrine therapies, tyrosine kinase inhibitor, and chemotherapy are given alone, or in combination for up to 6 months before surgery. MRI is the preferred modality for assessing response to neoadjuvant therapy and surgical planning, particularly with regards to breast-conserving therapy. However, the diagnostic accuracy of MRI is only 70% and is particularly confounded in cancers with areas of fibrosis. Continuous tumour oxygenation monitoring has the potential to monitor response to neoadjuvant therapy for breast cancer and may provide a valuable adjunct in surgical planning.

1.1.4 Tissue Oxygenation Monitoring Using Diffuse Reflectance Spectroscopy
Diffuse reflectance spectroscopy can measure the oxygenation status tissue due to the differing absorbance profiles of oxygenated and deoxygenated haemoglobin (Figure 1A). DRS is well suited to oxygenation monitoring as it provides oxygenation measurements that are dynamic (real-time), spatially accurate and quantifiable. Furthermore, it has the potential to be miniaturized into an implantable device.

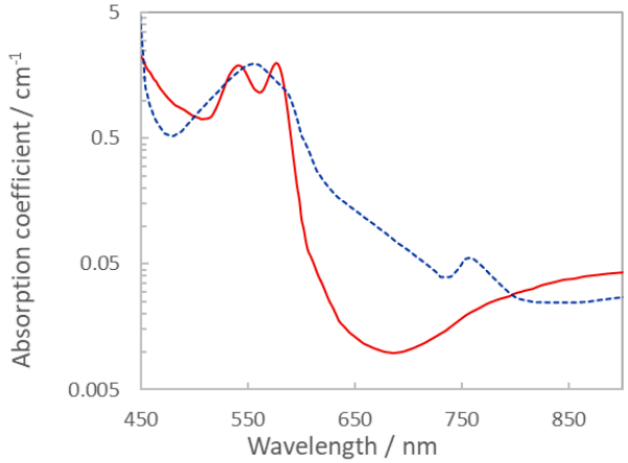

Figure 1: Optical absorbance of oxygenated and deoxygenated haemoglobin.

1.1.5 A Novel Tumour Oxygenation Monitor using DRS
Tumour oxygenation monitoring has the potential to provide valuable insights into tumour prognostication and management. The Institute for Global Health Innovation plans to develop an implantable tumour oxygenation sensor, providing a novel modality for tumour assessment and

monitoring. This research describes the development and validation of oxygenation sensing probe (Figure 2). Successful development and validation of the probe will be followed by future research to miniaturise and incorporate the technology into an implantable device.

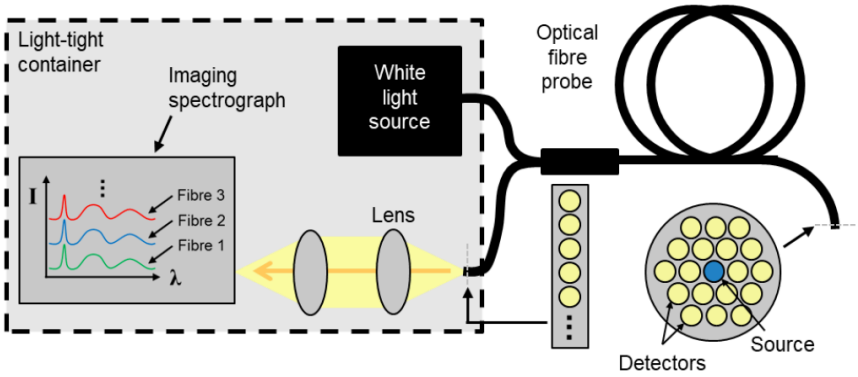

Figure 2: A tumour oxygenation monitoring probe using diffuse reflectance spectroscopy.

1.2 RATIONALE FOR CURRENT STUDY

Overall Research Hypothesis:

- Dynamic tumour oxygenation monitoring can predict treatment response in chemoradiotherapy for rectal and breast cancer.

Current Research Hypothesis:

- A novel-designed tumour oxygenation monitor, utilising diffuse reflectance spectroscopy, can provide accurate tissue oxygenation assessment in tumour phantom models.

2. STUDY OBJECTIVES

Primary Objective:

- To develop and validate a novel tumour oxygenation monitoring probe which may be used to monitor response to therapies in cancer, using 3D-printed phantoms.

Secondary Objectives:

- Define the correlation between sensor-derived oxygenation measurements and Gold-standard measured oxygenation in 3D-printed tissue phantoms
- Define the spatial resolution of the sensor oxygenation measurements

3. STUDY DESIGN

3.1 Anonymised MRIs

Anonymised MRIs representative of the chosen breast and rectal clinical paradigms will be used to ensure the generalisability of this research.

MRI DICOM files will be provided by Imperial College NHS Trust Department (ICHNT) of Radiology. The raw DICOM files will be anonymised by the Department of Radiology prior to being received by the research team. The research team will never have access to identifiable information of the MRIs. The MRIs will be stored on a password protected encrypted hard drive.

10 Breast MRIs will be identified by Professor Deborah Cunningham (consultant radiologist specialising in breast malignancy at ICHNT) from previous breast multidisciplinary meetings. The MRIs will be segmented by Dr Simon Dryden (and verified by Prof Cunningham) using slicer (slicer.org) open-source software to delineate malignant tissue.

10 Breast MRIs will be identified by Dr Lesley Honeyfield (consultant radiologist specialising in gastrointestinal malignancy at ICHNT) from previous GI multidisciplinary meetings. The MRIs will be segmented by Dr Simon Dryden (and verified by Prof Honeyfield) using slicer (slicer.org) open-source software to delineate malignant tissue.

3.2 TOAST++ Simulations

The TOAST++ framework is software which models the diffuse light transport in tissue, which first requires a Finite Element Mesh of the target issue [8]. These meshes will be constructed based upon the requested anonymised MRI segmentations. Optical signals will be simulated for a variety of sensor/probe/implant designs for a range of tissue parameters, based on scattering and absorption values from the literature [9]. These simulations will be used to initially verify the extent of sensitive volume within the tumours, allowing for optimisation of the sensor-detector spacing. Then hypoxic regions will be simulated based on distributions from the literature and any potential candidates from the MRIs. These simulations will demonstrate the sensitivity of the sensor to changes in oxygenation.

3.3 3D-Printing of Phantoms

Prototype sensor designs will be verified in experiments using phantoms with realistic geometry, based on the same meshes of the MRI segmentations used simulations. The tissue phantoms will be 3D printed tissue phantoms will be produced according to the methodology described by *Dempsey et al*. First the tumour segmentations will be converted to 3D surfaces in standard tessellation language (STL) file format. The phantoms will be printed using a Formlabs 3D printer, using resin containing titanium oxide and near-infrared (NIR) dye (Projet 900NP) so as to mimic tissue absorption and scattering properties.

3.4 Sensor Measurement Collection

Measurements of oxygenation within the 3D printed phantoms will first be performed using a benchtop spectrometer to provide a “gold standard”. This benchtop system allows for measurements with a high spectral resolution over a broad spectral range, whereas the sensor by necessity is targeted at key wavelengths (Figure 1). The results of these experiments will assess the suitability of the sensor design for monitoring oxygenation in tumours.

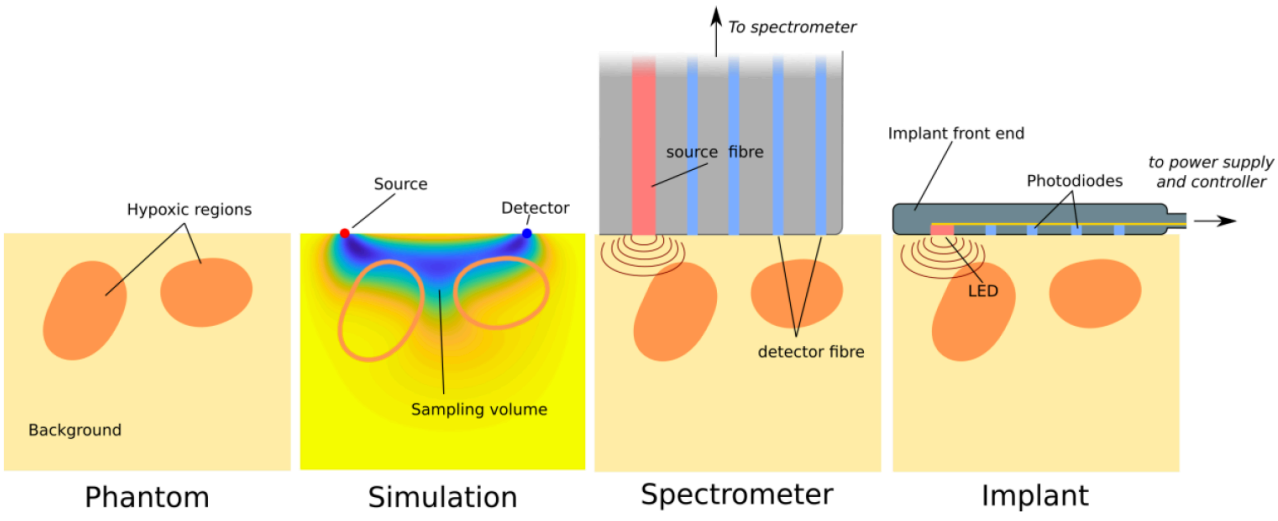

Figure 3: Schematic demonstrating a 3D printed phantom, TOAST++ simulation, novel monitoring probe and future miniaturised device (left to right)

3.5 Statistical Analysis
The fraction of the volume of the tumour to which the sensor is sensitive will be expressed as a % of the total volume, and the fraction for each tumour will be expressed as a mean+SD summary statistic.

4. PARTICIPANT ENTRY

4.1 INCLUSION CRITERIA
10 Breast MRIs from patients identified from multidisciplinary team meeting (MDT) records who went on to have neoadjuvant chemo and hormonal therapy for locally advanced breast cancer. The MRIs will be anonymised by the care team before being made available to the research team.

10 Rectal MRIs from patients identified from MDT records who went on to have neoadjuvant radiotherapy for locally advanced rectal cancer. The MRIs will be anonymised by the care team before being made available to the research team.

4.2 EXCLUSION CRITERIA
MRIs from patients under the age of 18, or older than 99 years old will be excluded.

MRIs from patients who did not receive neoadjuvant therapy for cancer will be excluded.

5. REGULATORY ISSUES

5.1 ETHICS APPROVAL
The Study Coordination Centre has obtained approval from the Health Regulator Authority (HRA). The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

5.2 CONFIDENTIALITY
MRIs will be anonymised by the ICHNT Department of Radiology prior to transfer of data to the research team. The research team will never have access to personal identifiable information.

The Chief Investigator will preserve the confidentiality of retrospective data used in the study and is registered under the Data Protection Act.

5.3 INDEMNITY
Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

5.4 SPONSOR
Imperial College London will act as the main Sponsor for this study.

5.5 FUNDING
The Biomedical Research Council are funding this study

5.6 AUDITS

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Framework for Health and Social Care Research.

6. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated by Dr Simon Dryden.

7. PUBLICATION POLICY

It is intended a peer-reviewed paper describing the development and validation of the tumour oxygenation sensor

The peer reviewed paper will be published in line with Imperial College London's open access policy.

8. REFERENCES

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