Research Protocol

Version 1.1

04.02.2022

The use of PET-MRI scans in radiotherapy planning of patients with head and neck cancer: A single centre pilot study

Contents

Abbreviations:

AE – Adverse event

CT – Computed Tomography

CTV – Clinical Target Volume

GCP – Good Clinical Practice

GTV – Gross Tumour Volume

IMRT – Intensity Modulated RadioTherapy

MDT – Multi-Disciplinary Team

MRI – Magnetic Resonance Imaging

NCI – CTCAE-National Cancer Institute Common Terminology Criteria for Adverse Events

NCRI – National Cancer Research Institute

PET – Positron Emission Tomography

RCR – Royal College of Radiologists

SAE – Serious Adverse event

STH – Sheffield Teaching Hospitals

SUSAR – Suspected unexpected serious adverse event

UKIO – The United Kingdom Imaging & Oncology

Section 1 - Project details

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1.2 Sponsor details

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1.3 Project title

The use of PET-MRI scans in radiotherapy planning of patients with head and neck cancer: A single centre pilot study

This is a pilot study to assess whether patients with head and neck cancer can tolerate a PET-MRI scan whilst immobilised in a thermoplastic shell that replicates their treatment position during radiotherapy and to assess whether it can improve accuracy in radiotherapy planning.

1.4 STH Project Reference number

STH 21185

1.5 Protocol version number and date

Version 1.1, 04.02.2022

1.6 Signatures of chief investigator and sponsor

…….. ……

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Principal Investigator

…….. ……

Professor Simon Heller 04/02/2022
R&D Director

1.7 IRAS number: 286722

1.8 Phase of trial

Not applicable.

1.9 STH Directorate affiliation

Specialised cancer services directorate

Section 2 – Research question(s)

The primary research question to be answered in this project is “Are patients with locally-advanced head and neck cancer able to tolerate a PET-MRI scan when they are immobilised in a radiotherapy treatment shell?” This will be assessed by measuring the proportion of patients that complete the full scanning protocol and by obtaining participant feedback on their experience of completing the scan.

The secondary question is “Can a PET-MRI scan fused with a planning CT scan improve the accuracy in radiotherapy planning of patients with head and neck cancer? Accuracy will be assessed by:

1. Comparing the radiotherapy target volumes and radiotherapy plans with and without the use of a PET-MRI scan.

2. Comparing inter- and intra-observer variability in treatment contours with and without the use of a PET-MRI scan within and between oncologists and implications of that.

Section 3 – Abstract

Patients with head and neck cancers are often treated with radiotherapy. The overall aim of treatment is to cure the cancer whilst minimizing its side effects. These cancers are usually close to the surrounding vital organs which are often affected by the radiotherapy. This can cause side effects such as a dry mouth or swallowing difficulties. Improving the accuracy of radiotherapy planning could help reduce side effects and improve quality of life post-treatment.

To design this treatment, patients undergo a “planning CT scan”, a computed tomography scan. This is obtained while the patient’s head and shoulders are held in position by a custom-made thermoplastic shell. The shell is necessary to ensure that the patient is in exactly the same position every time a dose of radiation is given.

The most important step in planning this treatment is accurately identifying the cancer and the surrounding normal tissues. This is to work out exactly which areas need to be treated and which areas need to be avoided. This is done on the planning CT scan. During diagnosis of cancer, patients undergo other imaging including an MRI (Magnetic Resonance Imaging) scan and a PET-CT(Positron Emission Tomography CT) scan . These are the best imaging modalities for head and neck cancer and feed into the process of identifying cancer accurately. It would be better from a radiotherapy planning perspective if these scans are acquired in the same position as the ‘planning CT scan’.

A PET-MRI scan is a combined MRI and PET scan, which is a new technology available in Sheffield. The current project aims to determine whether patients with head and neck cancers can tolerate an additional ‘PET-MRI’ scan with immobilisation similar to that used during the radiotherapy planning process and to assess if this additional scan helps in improving accuracy in radiotherapy planning.

Section 4 – Aim of the study

This is a pilot study to investigate the use of PET-MRI scanning in patients with locally-advanced head and neck cancer in radiotherapy treatment planning. The specific objectives are:

Primary objective:

To assess the proportion of patients completing the full PET-MRI scans when they are immobilised in a radiotherapy treatment shell. For patients that do not complete the full scanning protocol, we would determine how long they remain within the scanner.

Subjective assessment of tolerability to the scan, will be determined using a patient tolerability questionnaire (Appendix 1).

Secondary objective:

The secondary objective is to obtain pilot data on assessing the impact of the additional PET-MRI scan on the precision of radiotherapy planning. This will be assessed by comparing the radiotherapy target volumes and treatment plans with and without the use of PET-MRI scan. These tests will be conducted retrospectively and thus will not have any impact on patients' flow through to treatment or their standard care.

Exploratory objective:

To assess whether PET-MRI scanning adds benefit to cancer patient's diagnostic investigations.

Section 5 –Background

5.1 Clinical and Scientific Relevance:

Over the last 20 years, curative treatment of cancers of the head and neck has gradually evolved, particularly for cancers that arise in the pharynx/throat. There has been a progressive reduction in the proportion of patients that have surgery, and a concomitant increase in the proportion receiving radical (curative) chemo/radiotherapy (radiotherapy with or without concurrent chemotherapy). This is because function (speech and swallowing) is generally better preserved for chemo/radiotherapy compared to surgery and surgery and chemo/radiotherapy have similar cure rates[1].

The overall aim of chemo/radiotherapy treatment is to maintain a high chance of curing a patient's cancer, while at the same time minimising side-effects and maximising longer-term function. All locally-advanced head and neck cancers are in close proximity to vital structures ('organs at risk'), and these structures are often affected by radiotherapy. Frequent long-term side-effects include dry mouth, when the salivary glands are in the radiotherapy treatment fields, and difficulty swallowing due to scarring of the muscles of the pharynx/oesophagus. Technological developments, including Intensity Modulated Radiotherapy (IMRT), have improved the precision of radiotherapy treatment planning, leading to significantly reduced long-term side effects[2]. Further research strategies to improve outcomes are based on improving the accuracy of 'target delineation' which is a critical step in radiotherapy planning. This step includes identifying the gross tumour as well as the surrounding normal structures on scans with high accuracy. Interventions that can improve precision in this process could lead to changes in the overall volume of tissue treated and reduce the overall dose of radiation to surrounding normal structures which could translate to reduced side effects.

Radiotherapy involves delivering high energy X-rays to the primary tumour, nodal metastases as well as the draining lymph nodes which may be at risk of microscopic i.e. subclinical disease, with the objective of killing all of the cancer cells. For patients with head and neck cancers, this treatment is generally given as fractions (doses) of radiation five days a week for six to seven weeks. In order to deliver the radiotherapy

to the same site over 30-35 treatment sessions, the patient position must be consistent and accurately reproduced at each treatment session. This is achieved by using a thermoplastic shell that holds the patient's head and shoulders in position and is secured to the treatment table. Patients undergo a computed tomography (CT) scan wearing the thermoplastic shell which enables a virtual simulation of the treatment. Critically, the planning CT scan is obtained in the same position and using similar immobilisation as the radiotherapy treatment itself.

The most important step in radiotherapt planning is 'target delineation', the process of accurately defining the cancer and nearby normal organs on this planning scan. This dictates the volume of tissue that receives radiation. Other diagnostic scans such as magnetic resonance imaging (MRI) and positron emission tomography CT (PET-CT) scans feed into the target delineation process as oncologists use these images as a guide, but ultimately the contouring and treatment planning is done on the CT planning scan.

Once the gross tumour is contoured, oncologists use a margin to create a clinical target volume. This margin is to account for microscopic spread of cancer cells. Using a smaller margin to set the clinical target volume will reduce the radiation to the surrounding normal structures and eventually can translate into reduced side effects. But the gross tumour volume must be identified accurately to avoid the risk of under-dosing the tumour[3].

5.2 Scientific Justification

MRI is the imaging modality of choice for staging of malignant tumours of the head and neck because of its superior soft tissue detail compared to other modalities[4]. Patients with advanced-stage disease (e.g. T4 tumours or N3 nodal disease) should also have a PET-CT to exclude distant metastatic disease and help guide the decision-making process regarding treatment intent, resectability etc[5]. These scans are performed without patients being in the radiotherapy treatment position, which can then cause difficulties in localisation and using this information to aid target delineation. There is evidence that fusion of the planning CT scan with MRI or PET-CT images can improve the accuracy of radiotherapy planning/contouring and this

accuracy is enhanced if the MRI or PET-CT scans are acquired in the radiotherapy treatment position[6,7].

Combining the superior anatomical image quality of an MRI scan with the functional images of a PET scan in a single scanner is a recent development in imaging technology that may provide a more accurate delineation of locally-advanced head and neck cancers. PET-MRI is superior to PET-CT for local staging of nasopharyngeal cancer and differentiated thyroid cancer[8,9], with several small studies demonstrating the added value of PET-MRI in head and neck squamous cancer[10,11]. PET-MRI is not currently in routine clinical use, in part because of access, but it has the potential to transform future patient care. A new University of Sheffield PET-MRI scanner has been installed in 2020. Weston Park Cancer Centre has a national reputation of providing high quality clinical care for patients with head and neck cancer and is one of the top recruiters to UK-wide clinical trials (PET-Neck, De-Escalate, ART-DECO, DARS NIMRAD, COMPARE). The service is enhanced by wider multidisciplinary expertise: excellence in diagnostic radiology and state-of-the-art multimodality image co-registration techniques that have been tested and applied in numerous structural and functional MRI and CT studies[12,13]. Using PET-MRI to aid radiotherapy planning has not been evaluated anywhere in the world. Therefore, the new PET-MRI scanner in Sheffield represents a 'window of opportunity' to exploit such technology and would place Sheffield at the forefront of UK research in this area.

The current study will test the feasibility of PET-MRI in the setting of radiotherapy planning. Pilot data to assess and measure the variance in radiotherapy planning will also be obtained, and would be used to design a larger study if the feasibility was confirmed.

5.3 Potential benefit to patients

The current project is a feasibility study to confirm that PET-MRI scans with immobilisation in a radiotherapy shell are tolerated by head and neck cancer patients. At this stage, it is of no direct benefit to patients enrolled on the study, but, if successful, will provide important pilot data that could be used to plan a larger study in the future.

We do not anticipate that the PET-MRI scan will add any new diagnostic information as all recruited patients would have had similar imaging (MRI and PET-CT) already at the time of diagnosis. However, this is an additional and advanced imaging technique where the PET-MR images are reported by an appropriately-trained radiologist. If there is any significant change that could have an impact on a patient's cancer treatment, this will be communicated to the patient by their Oncologist.

Gaining qualitative perspectives of the participant's experience of undertaking a PET-MRI scan will allow the project team to gain valuable insight into potential barriers that could influence the implementation of this imaging modality into standard clinical practice. This will help the team to develop supportive services which will help future patients to successfully complete the scan as part of their routine standard care. Subsequently, this could provide a long term benefit to future patients by providing them with access to a technology that can potentially aid in improving the precision of radiotherapy planning. This can, in turn, have a positive impact on overall outcomes from cancer treatment; in terms of curing cancer as well as reducing side effects.

Section 6 – Plan of Investigation

6.1 Methodology

The current study is a feasibility study of whether patients with locally-advanced head and neck cancer can tolerate PET-MRI scanning whilst being immobilised in a radiotherapy shell. The primary objective will be the assessment of the proportion of patients that complete the full scanning protocol (estimated duration 20-30 minutes). For patients that fail to tolerate the full scan, their duration within the scanning environment will be determined as it may be possible to shorten the MRI component of the scan, thus reducing the scan duration. All recruited patients will have had a staging MRI scan, a CT scan of the chest and upper abdomen as well as PET-CT as part of their investigations for cancer diagnosis which means they have successfully completed the standard scanning protocols for MRI or PET, including the standard contrast agents used for these scans.

Patients that participate in the current study will have an extra PET-MRI scan, which will expose them to a small amount (4 – 6 mSv) of extra radiation.

This PET-MRI scan will be obtained while they are wearing the immobilisation shell. Enrolled patients would have had a trial run of wearing the same shell for their planning CT scan required as part of their standard care for radiotherapy planning. Planning CT scan is generally well tolerated and typically lasts 20 minutes which is relatively shorter compared to the time in the shell for a PET-MRI scan.

Potential obstacles to individual patients are their size (the magnet bore is 60cm which is further narrowed down due to the immobilisation equipment required and may influence who can be recruited), their comfort during the scan, as large upper aerodigestive tract tumours affect swallowing and cause coughing, all of which degrade the quality of the images as well as claustrophobia which may be worsened by the thermoplastic shell. A PET-MRI scan with immobilisation has not been tested before. However, researchers are aware that an MRI scan with similar immobilisation is tolerated by head and neck cancer patients and is in routine use in some radiotherapy centres in the UK to aid radiotherapy planning. Likewise, proton beam therapy which involves radiotherapy treatment with protons requires patients to remain in the immobilisation shell for a significantly longer period than the

conventional linac based planning and treatment. This reassures the study team that a PET-MRI scan with immobilisation in patients with head and neck cancer may be feasible despite the longer duration of the scan.

A subjective qualitative assessment of patient tolerability will be obtained using a patient questionnaire. On completion of the PET-MRI, participants will be asked to complete a bespoke questionnaire about their scan. The questionnaire has been developed by members of the project team and lay representatives (Appendix 1). It explores key elements of the scan process (e.g. patient positioning, the use of contrast agents etc.) identified by the literature base as areas which can act as barriers to successful completion by participants. The questionnaire is composed of a mix of binary (yes/no) Likert-scale and open-ended exploratory questions.

6.2 Summary of Study Design

This is a prospective study that aims to determine the feasibility of PET-MRI scanning of head and neck cancer patients that are immobilised in a radiotherapy treatment shell. It is estimated that ten patients will be recruited to the study. Patients will be registered into the study once they have given informed written consent. All patients who consent to study entry will undergo study screening to confirm eligibility. Patients who are ineligible following screening will not be considered as enrolled in the study and will receive treatment as per their usual clinical care.

6.3 Setting for the Project

Patients will initially have their management discussed through the STH central head and neck MDT. The study will be introduced to potentially eligible patients by oncologists when radical radiotherapy is recommended and recruitment to the study will be at Weston Park Cancer Centre, Sheffield. PET-MRI scans will be performed in the dedicated PET-MRI facility in Academic Radiology, Royal Hallamshire Hospital, Sheffield.

6.4 Participants

Patients with locally-advanced head and neck cancers who are fit for radical (curative) treatment. This is a single-centre study and we expect to recruit ten patients.

6.4.1 Inclusion criteria

To be eligible for inclusion, participants must meet the following criteria:

1. Aged 18 years or over
2. Able to give informed written consent.
3. New diagnosis of biopsy-proven head and neck cancer.
4. WHO performance status ≤ 2.
5. MDT-recommended treatment with radical radiotherapy, with or without concurrent systemic therapy.
6. MRI and PET-CT staging scans for diagnosis.

6.4.2 Exclusion criteria

1. Known intolerance/sensitivity to ^{18}F-2-deoxyglucose or gadolinium-containing contrast agents.
2. Claustrophobia or other contraindications to MRI.
3. Unable to pass through a 55 cm hula hoop.
4. Female patients that are pregnant or breastfeeding.
5. Unable to understand written or spoken English.
6. Patients not undergoing radical intent radiotherapy.
7. Patients with stage 4 or 5 chronic kidney disease or other biochemical abnormalities e.g. uncontrolled blood glucose levels which can have an impact on PET-MRI imaging or contrast administration.

In the last 12 months, 104 patients have been treated with radical radiotherapy (curative intent) for a newly-diagnosed head and neck cancer at Weston Park Cancer Centre, Sheffield. This equates to 8 new patients per month that are potentially eligible for recruitment. We anticipate 1 or 2 patients per month to participate in the study.

The patient population would include Sheffield as well as the peripheral cancer units of Chesterfield, Rotherham, Doncaster and Barnsley. Radiotherapy is planned and delivered centrally at Weston Park Cancer Centre for all patients.

6.5 Sample size

The current study is a feasibility study. We estimate that ten patients will be sufficient to determine whether PET-MRI in a radiotherapy immobilisation shell is tolerable to patients with locally-advanced head and neck cancer. A patient tolerability questionnaire obtained from the ten patients will provide subjective qualitative data from a patient's perspective. The retrospective analysis to achieve the secondary objective for patients who tolerate the scan will be used as pilot data to inform larger studies in the future if feasibility is successful.

6.6 Recruitment

Patients newly-diagnosed with head and neck cancer who had a PET-CT scan along with a staging MRI scan and CT chest/upper abdomen scans as part of their diagnosis and were recommended radical radiotherapy will be identified in the weekly central Sheffield Head and Neck MDT. Potentially eligible patients will be approached by their oncologist during an out-patient clinic prior to the radiotherapy planning process and the study discussed with them. Interested patients will be given a verbal explantion of the study and a Patient Information Sheet by an authorised trial clinician or research nurse (an individual on the delegation log). Following this, the patient will be given sufficient time (minimum 24 hours) before they are contacted and asked whether they wish to be considered for the study. If they wish to proceed, then they will be seen on their next hospital visit to give informed, written consent. The Principal Investigator or an authorised clinician on the delegation log will witness the patient's signature and countersign the consent form. Patients are free to withdraw their consent at any time without reason; this will not adversely affect their treatment. One copy of the signed consent form will be given to the patient, one kept in the hospital notes and one in the site file.

All staff involved in the consent procedure will have current Good Clinical Practice (GCP) training. In the unlikely event that the patient loses capacity after informed

consent and before the PET-MRI scan, then the patient will be withdrawn from the study in the interest of safety.

Screening logs will be kept for those patients who are given the patient information sheet and were eligible. This data will be considered by the Trial Management Group if there are difficulties in recruiting to the study.

6.7 Outcome Measures

6.7.1 Objectives and measurement

Primary objective

The primary outcome will be the proportion of patients that complete the PET-MRI scan as per protocol whilst immobilised in the radiotherapy treatment shell. For patients that do not complete the full scan, the duration of time in the scanner will be recorded as well as the reasons why they were unable to complete the scan. Patient tolerability questionnaire will provide this qualitative data.

Secondary objective

The secondary objective is to assess the impact of the additional PET-MRI scan on the precision of radiotherapy planning. These tests will be conducted retrospectively after conventional radiotherapy planning and do not interrupt a patient's flow through to treatment or their standard care.

<u>Co-registration of images for radiotherapy planning:</u>

A PET-MRI scan of each patient provides PET images that are inherently co-registered with MRI images. In order to achieve the secondary objectives, three categories of images are obtained for radiotherapy planning purposes by superimposing images from the PET-MRI scan on to the planning CT scan, a technique termed 'image registration'.

Category 1: Planning CT scan ("CT") with no fusion: this is standard practice

Category 2: Planning CT fused with MRI images from the PET-MRI scan ('CT-MRI')

Category 3: Planning CT fused with PET-MRI images ('CT-PET-MRI')

The secondary objectives are:

1. To compare the radiotherapy target volumes (GTV (gross tumour volume) and CTV (clinical target volume)) contoured in the three categories above (CT, CT-MRI and CT-PET-MRI images). A quantitative assessment will be done by measuring the volumes in three dimensions using Varian's External Beam Planning software in Aria. A qualitative analysis of the 3D dose distribution, comparison of target coverage, conformity, homogeneity and examination of specific dose/volume objectives of organs at risk will be done.

2. Assess inter- and intra-observer variability in treatment contours and precision of target delineation in the three categories above (CT, CT-MRI and CT-PET-MRI scans). This will be assessed using Dice Similarity Index and Hausdorff distance in the three categories.

Exploratory objective:

To assess whether PET-MRI scanning adds benefit to the cancer patient's diagnostic investigations. Clinical reports of the PET-MRI scan will be compared to reports from staging MRI and PET-CT scans to determine if any new diagnostic information is brought to light by PET-MRI.

6.8 Statistical/Qualitative analysis

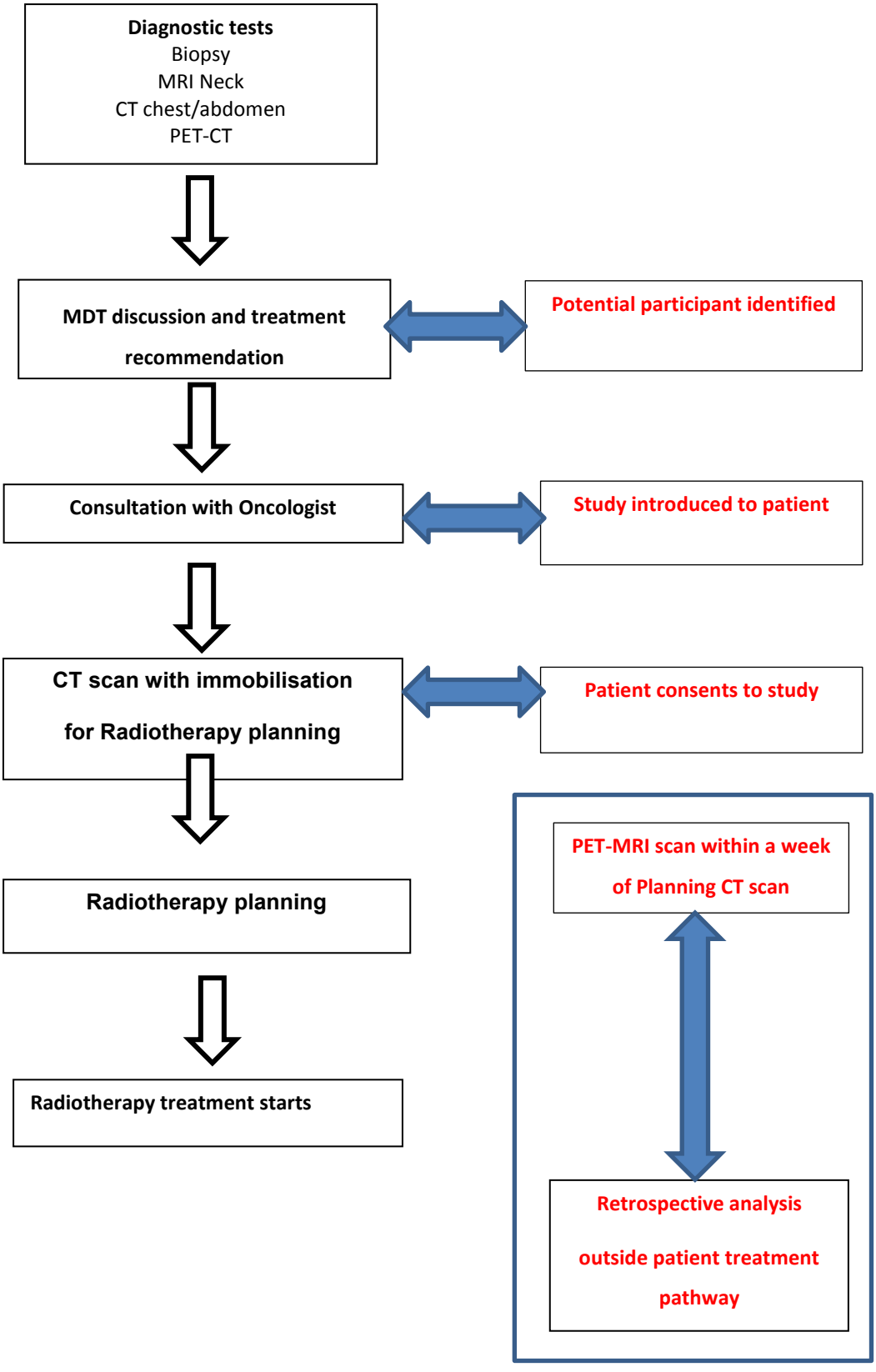
- The proportion of patients completing the PET-MRI scan will be recorded that will determine feasibility.
- All recruited patients are expected to complete a questionnaire which will provide a qualitative assessment. Statistical analysis will be completed on the binary and Likert scale questions. This process will allow the study team to identify any issues faced during the PET-MRI scan and thepercentage of participants who were affected by these. Thematic analysis will be completed on the open-ended questions. This will allow the project team to explore themes around patient experience, helping the team to understand how

patients may need to be supported during the scanning process if it is to become standard of care.

- As this is a pilot study with ten patients, we do not anticipate this analysis for secondary objectives to provide any statistically significant outcomes. But this will help to specify the kinds of analysis that are possible in a larger study and will also be used to calculate sample sizes.

6.9 Intervention

An illustration of the pathway of a patient that is enrolled in the study is shown in the following diagram. Study-specific events are indicated in **red**.



6.10 Safety Assessment

Patients that are enrolled in the study will have one additional diagnostic test compared to their normal standard of care, namely, a PET-MRI scan. Patients recruited to the study will have had a standard gadolinium-enhanced MRI scan of the neck as well as a whole-body PET-CT scan with radioactive glucose tracer during their diagnosis of cancer as standard of care a few weeks prior to recruitment into the study. Potential safety issues related to the additional PET-MRI scan are: (i) administration of the MRI contrast agent gadolinium; (ii) administration of radioactive ^{18}F-2-deoxyglucose; (iii) additional radiation exposure from ^{18}F-2-deoxyglucose.

6.10.1 Administration of Gadolinium

Chelates of the rare earth element gadolinium are used as contrast agents in MRI scans. They improve the conspicuity of abnormal tissue and are considered mandatory in staging head and neck cancers[14]. The current Gadolinium-based contrast agents on the market are considered to be safe: they have a very low rate of immediate adverse events (0.06 – 0.09%) and the incidence of acute severe reactions such as anaphylaxis is very rare (0.0025 – 0.005%[15];). A previous reaction to MRI contrast is an exclusion criterion (see section 6.4.2) and patients with a history of this will not be recruited. Gadolinium can be nephrotoxic when given in large volumes (30 mL) to patients with renal disease/renal impairment. For tumour enhancement in cancer staging 7.5 mL of the macrocylic chelate gadobutrol (Gadovist, Bayer; 1mmol/mL) is used in Sheffield Teaching Hospitals and this is safe. Linear chelate Gadolinium-containing agents have been associated with nephrogenic systemic fibrosis and there are also concerns regarding Gadolinium retention in the brain following repeated doses of linear chelates. These findings led the European Medicines Agency to suspend use of the linear chelates in 2017. The macrocyclic agents such as Gadobutrol are considered safe even in patients with severe chronic renal impairment[16]. Overall, there is considered to be no extra risk to patients from the MRI component of the PET-MRI scan.

6.10.2 Administration of ^{18}F-2-deoxyglucose

PET imaging in oncology is based on the increased uptake of glucose by cancer cells, which have more cell surface glucose transporter proteins and increased

intracellular glycolytic enzyme levels than normal cells. The increased glycolytic rate of cancer cells enables their detection with the fluorine-labelled analogue of glucose, ^{18}F-2-deoxyglucose. There are no safety concerns with the use of ^{18}F-2-deoxyglucose, which is in standard use for PET-CT scanning throughout the world.

6.10.3 Additional radiation exposure from ^{18}F-2-deoxyglucose

The radioactive isotope ^{18}F decays by positron emission, having a half-life of 110 min. For 'average' patients, this isotope has an effective radiation dose of 19 μSv/MBq[14], resulting in an exposure of about 4 – 6mSv from the typical 200 - 300 MBq of ^{18}F that is used in PET oncology imaging.

FDG dose reference levels				
Minimum ARSAC Dose Reference Level (DRL):	100MBq			
SPC DRL for GE710 Discovery scanner	**Weight**	**DRL**	**min/bed**	**Overlap**
	<115Kg	3.5MBq/Kg	2	23 (~50%)
	115-140Kg	400MBq	2.5	
	>140Kg		3	

This is a standard dose for a diagnostic PET scanning and used widely. Patients will be required to follow radiation protection advice after the scan which includes staying away from pregnant women and young children for about 8 hours while the radioactive tracer can still be in their system.

Patients have their contrast-enhanced radiotherapy planning CT scan as part of standard treatment before the PET-MRI scan. A minimum of 24 hours and maximum of 2 weeks will be maintained between the planning CT scan and the PET-MRI scan.

6.10.4 Adverse events

All Adverse Events (AEs), Serious Adverse Events (SAEs) and fatal or life-threatening suspected / unexpected serious adverse reactions (SUSARs) that occur during the study, either observed by the investigator or reported by participants, whether or not attributed to the study, will be reported to the DMEC in accordance with current GCP standards. SAEs and SUSARs, and deaths should be reported within 24 hours of becoming aware of the event.

We do not expect any persistent or prolonged adverse effects from the intervention. Participants are monitored for 30 days from recruitment to the study. Standard care involves regular assessments and ongoing treatment of cancer over the next 6-8 weeks and regular post treatment follow up thereafter. Any suspected adverse events from study intervention will be reported to the study team appropriately.

6.10.5 Definitions of Adverse Events

An adverse event(AE) is any untoward medical occurrence in a patient or clinical trial subject that does not necessarily have a causal relationship with this treatment and can include:

- Any unintentional, unfavourable clinical sign or symptom.
- Any new illness or disease or the deterioration of existing disease or illness.
- Any clinically relevant deterioration in any laboratory assessments or clinical tests.

All AEs judged by either the Investigator or the Sponsor as having a reasonable suspected causal relationship to the project will qualify as adverse reactions. The expression ‘reasonable causal relationship’ should convey that there are facts (evidence) or arguments to suggest a causal relationship.

A Serious Adverse Event (SAE) is defined in general as any untoward medical occurrence or effect that:

- Results in death.
- Is life threatening. The term life threatening refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability or incapacity.
- May jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

Clinical judgement must be exercised in deciding whether an SAE is serious in other situations. Important SAEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the participant may require

intervention to prevent one of the other outcomes listed in the definition above, must also be considered serious.

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is a Serious Adverse Reaction which also demonstrates the characteristics of being unexpected, the nature, seriousness, severity or outcome of which is not consistent with procedure.

6.10.6 Recording and Reporting Adverse Events

Information about adverse events, whether volunteered by the patient, discovered by investigator questioning or detected through physical examination, laboratory test or other investigation, will be collected and recorded on the relevant CRF. Adverse events will be collected for all participants from the time of written informed consent until 30 days after the PET-MRI scan. All AEs will be monitored until resolution, or if the AE is determined to be chronic, until a cause is identified. If an AE remains unresolved at the conclusion of the study, the investigator will make a clinical assessment about whether continued follow-up of the AE is warranted. The investigator will evaluate AEs for duration and intensity according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI-CTCAE).

The investigator will determine the relationship of the study treatment to an AE based on the following definitions:

- Not related - the AE is not related if the PET-MRI scan has not occurred or the occurrence of the AE is not reasonably related in time or the AE is considered unlikely to be related to the PET-MRI scan (i.e., there are no facts [evidence] or arguments to suggest a causal relationship).
- Possibly related - the PET-MRI scan and the AE are reasonably related in time and the AE could be explained equally well by factors or causes other than the PET-MRI scan.
- Probably related - the PET-MRI scan and the AE are reasonably related in time and the AE is more likely explained by the scan than by other factors or causes.

All Serious Adverse Event (SAE) will be reported within 24 hours of discovery to the Research Department by a member of the Research Team using the form provided by the Research Department.

6.11 Pregnancy

Patients that are pregnant cannot be recruited to the study as per the exclusion criteria (section 6.4.2).

6.12 Subject withdrawal, breaking the blind and trial stopping/discontinuation rules

Participants can withdraw from the study at any time. If a participant withdraws after giving written consent but before PET-MRI scanning, their scan will be cancelled. If a subject withdraws after the PET-MRI scan has been completed, their images will be retained and analysed for inclusion within the study.

This study does not involve blinding, so breaking the blind rules are not applicable for this study.

6.13 Instruments

6.13.1 PET-MRI scanner :

The new University of Sheffield PET-MRI scanner has been installed as per standard operating procedures.

6.13.2 Patient questionnaire (Appendix 1)

A Patient and public involvement(PPI) group was formed for the study at the time of applying for the SHC grant fund. Face validity was established by gaining feedback from key stake-holders including co-investigators and lay members of the project team. These experts were asked to evaluate whether the questions effectively captured and addressed the topic under investigation. The PPI group was consulted again and recommendations were incorporated.

The questionnaire was pilot tested by a subset of the studies' target population to explore any formatting or distribution issues which may influence the quality of returns and response rates.

As this is a feasibility study recruiting 10 patients, the above steps to validate the the questionnaire were agreed as adequate by the study team.

6.13.3 Screening and data collection tool (Appendix 2)

See appendix 2.

6.14 Quality control and Assurance

Induction: Induction to all members in the delegation log assisting in conducting this research study will be provided at a setup meeting before commencing recruitment into the study.

Quality assurance of documentation: The trial will be conducted in accordance with Good Clinical Practice standards.

Immobilisation equipment and PET-MRI scanner: The intervention in this study is the extra PET-MRI scan with immobilisation of head, neck and shoulders. PET-MRI scanning is still relatively a new technology in the NHS; national standardised protocols and quality assurance procedures are not currently available. Immobilisation is achieved using a custom made thermoplastic shell and an MRI compatible board to secure the shell to the scanner couch. This equipment is quite similar to the standard immobilisation used in radiotherapy planning for head and neck cancer.

Co-registration of PET-MRI images with planning CT images: Study team will use rigid registrations in Varian's ™ Image Registration software. A three point match will allow us to report an RMS value for each registration. The match quality will be assessed qualitatively using split window and blended views, and then approved by a clinician before being used for contouring.

Study QA team: This team includes co-investigators with expertise in multimodal image acquisition and co-registration of different imaging modalities. The team would facilitate transfer of confidential data between University of Sheffield Academic Radiology and Weston Park Cancer Centre radiotherapy departments. This team will also ensure accuracy of co-registration of PET-MRI scan images with the planning CT images.

6.15 Project Plan

This study will recruit 10 patients over a period of 12 months.

The project plan is:

Dec 2021: Obtain NHS REC approval, HRA Approval and Confirmation of Capacity and Capability from STH NHS FT

Obtain NHS REC approval and research governance approvals from NHS sites.

Feb 2022: First patient recruited

Feb 2023: Last patient recruited

Mar 2023- Feb 2024 : Data analysis, report writing & dissemination of results

Section 7 – Statistical opinion

With this type of feasibility study, it is not necessary to perform formal power calculations, and justification of the number of subjects to be enrolled is provided in section 6.5.

Section 8 – Project Management

A Steering Committee will manage the study and ensure that the project proceeds in a timely manner. It will comprise:

- Committee Chair
- A Head and Neck Clinical Oncologist with expertise in head and neck cancers
- A radiologist with expertise in reporting MRI scans
- A radiologist with expertise in reporting PET scans
- A medical physicist with expertise in engineering and clinical applications of MR imaging
- A Nuclear medicine scientist
- A radiotherapy dosimetrist with expertise in head and neck cancer radiotherapy planning
- A radiotherapy physicist with expertise in head and neck cancer radiotherapy planning

The Committee will:

- Ensure, monitor and if necessary, revise the strategy of the project
- Establish rules to run the project
- Resolve problems and difficulties
- Monitor costs
- The principal investigator will supervise, monitor and holds overall responsibility of the study

Communication between Committee members will be by email or telephone and face-to-face meetings will be held whenever needed at the following time-points:

- At the start of the study
- When the first participant has been scanned
- 2 monthly onthly until the study ends
- Ad-hoc if required

Section 9 – Expertise of the Researcher and Associated Team

The current project is a collaboration between Sheffield Teaching Hospitals and the University of Sheffield. The Principal applicant is Dr Satya Garikipati, who is a Consultant Clinical Oncologist at Weston Park Cancer Centre with a major clinical commitment to treating head and cancer patients. Dr Garikipati is the Site Lead for Head and Neck cancer services at Sheffield Teaching Hospitals, a member of the British Association of Head & Neck Oncologists and a Yorkshire Cancer Research connect NHS academy fellow. The wider head & neck oncology team at Weston Park Cancer Centre have a national reputation for providing high-quality clinical services to cancer patients and are one of the top UK recruiters to both national and international clinical trials in head & neck oncology (*e.g.* PET-Neck, De-Escalate, DARS, ART-DECO, NIMRAD, COMPARE). The Radiology team comprises a mixture of clinical consultants with expertise in head & neck imaging and PET imaging as well as expertise in imaging research, including translating basic science research into clinical use in the NHS. The combination of H&N specialist oncologists, radiologists, radiographers, dosimetrists and physicists (diagnostic/academic and radiotherapy) have participated in previous radiotherapy clinical trials in head & neck and are well versed in the practical issues of carrying out research projects that involve ionising radiation.

Section 10 – Ethical Issues

The trial will be taken through the appropriate ethical and regulatory authorities prior to opening. All patients will provide informed, written consent and can refuse to participate at any stage without giving a reason. All information collected during the trial will be kept strictly confidential. Data protection will comply with the 1998 Data Protection Act. Data will be stored electronically on NHS servers within Sheffield Teaching Hospitals that are protected by firewalls. All clinical data will be identified only by the allocated study number; signed consent forms with patients' names on will be stored securely separately.

The only ethical issue raised by this study is that participants would receive an extra small dose of radiation (from the PET component of the PET-MRI scan) that, at this stage, would not be of clinical benefit. This is a standard dose of radiation used for diagnostic scans. In the future, if the addition of a PET-MRI scan could improve the accuracy of patients' radiotherapy plans, the potential benefit in their overall cancer treatment is likely to outweigh the inconvenience from the small additional dose of radiation from a PET scan.

Section 11 – Involvement of Service Users

A patient and public involvement (PPI) group was formed at the time of submission of this research proposal for the Sheffield Hospitals Charity fund. Members of this group have been contacted again and feedback was obtained about the patient information sheet and patient tolerability questionnaire. Recommendations from feedback have been incorporated in these documents.

We also aim to involve this group to discuss results from the study and obtain their comments and recommendations for future of this project.

Section 12 – Methods for Disseminating Research Results

This is the first time such a feasibility study using PET-MRI is being conducted globally. If feasibility is demonstrated, the results may be disseminated by presentations and publication in a scientific/medical journal. We expect that the academic beneficiaries would include clinical oncologists, radiotherapy radiographers and radiotherapy physicists as well as diagnostic radiologists and physicists involved in head and neck cancer research. These groups will be engaged by presenting results obtained from this pilot study at national/international scientific conferences in Imaging and Oncology (e.g. NCRI, UKIO and RCR).

Section 13 – Strategy for taking the work forward if the research project is productive

If technically-feasible, further funding will be required to collect data that will inform a definitive future study. Potential funders are Yorkshire Cancer Research, Medical Research Council (Confidence in Concept scheme) and The National Institute for Health Research (Efficacy and Mechanism Evaluation programme).

Section 14 – Intellectual Property Arrangements

Sheffield Teaching Hospitals NHS Foundation Trust is the study sponsor. The University of Sheffield will have shared ownership of the intellectual property(IP) that results from the project. If commercially-exploitable findings result from the project, IP advice will be sought at an early stage. Intellectual property will be managed by Sheffield Teaching Hospitals NHS FT and the University of Sheffield Research departments as required by the project.

Section 15 – Costing the project

The total costs for the project are £53,899.

This is composed of the following:

Staff costs : £32,832

Non-staff costs: £6,642

Scanning costs: 14,425

Section 16 – Funding source

The project has been funded by Sheffield Hospitals Charity through the Specialised Cancer Services Research fund (2019 round; grant ref. 192035)

Section 17 – References

1. Kim Y-J & Lee R (2018) Surgery vs. radiotherapy for locally advanced hypopharyngeal cancer in the contemporary era: A population based study. *Cancer Med*. **7**: 5889-5900.

2. Nutting CM, Morden JP, Harrington KJ, Guerro Urbano T, Bhide SA, Clark C *et al*. (2011) Parotid -sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. *Lancet Oncol*. **12**: 127-136.

3. Grégoire V, Evans M, Le QT, Bourhis J, Budach V, Chen A *et al*. (2018) Delineation of the primary tumour clinical target volumes (CTV-P) in laryngeal, hypopharyngeal, oropharyngeal and oral cavity squamous cell carcinoma: AIRO, CACA, DAHANCA, EORTC, GEORCC, GORTEC, HKNPCSG, HNCIG, IAG-KHT, LPRHHT, NCIC CTG, NCRI, NRG Oncology, PHNS, SBRT, SOMERS, SRO, SSHNO, TROG consensus guidelines. *Radiother Oncol*. **126**: 3-24.

4. iRefer: Making the best use of Clinical Radiology (2017). Royal College of Radiologists, London, 8th ed.

5. Cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over (NG36) *NICE* (2018).

6. Chuter R, Prestwich R, Bird D, Scarsbrook A, Sykes J, Wislon D, Speight, R (2017). The use of deformable image registration to integrate diagnostic MRI into the radiotherapy planning pathway for head and neck cancer. *Radiother Oncol*. **122**: 229-235.

7. Paulino AC, Koshy M, Howell R, Schuster D, David LW (2005). Comparison of CT- and FDG-PET-defined gross tumor volume in intensity-modulated

radiotherapy for head-and-neck cancer. *Int J Radiat Oncol Biol Phys* **61**: 1385–92.

8. Chan S-C, Yeh C-H, Yen T-C, Ng S-H, Chang JT-C, Lin C-Y *et al.* (2018) Clinical utility of simultaneous whole body 18F-FDG PET/MRI as a single-step imaging modality in the staging of primary nasopharyngeal carcinoma. *Eur. J Nucl. Med. Mol. Imaging* **45**: 1297-1308.

9. Binse I, Poeppel TD, Ruhlmann M, Gomez B, Umutlu L, Bockisch A, Rosenbaum-Krumme SJ (2016) Imaging with ^{124}I in differentiated thyroid carcinoma: Is PET/MRI superior to PET/CT ? *Eur. J Nucl. Med. Mol. Imaging* **43**: 1011-11017.

10. Partovi S, Kohan A, Vercher-Conejero JL, Rubbert C, Margevicius S, Schlucter MD *et al.* (2014) Qualitative and quantitative performance of ^{18}F-FDG-PET/MRI versus ^{18}F-FDG-PET/CT in patients with head and neck cancer. *Am J Neuroradiol* **35**: 1970–1975.

11. Schaarschmidt BM, Heusch P, Buchbender C, Ruhlmann M, Bergmann C, Ruhlmann V *et al*. (2016) Locoregional tumour evaluation of squamous cell carcinoma in the head and neck area: a comparison between MRI, PET/CT and integrated PET/MRI. *Eur J Nucl Med Mol Imaging* **43**: 92–102.

12. B A Tahir, A J Swift, H Marshall et al(2014). A method for quantitative analysis of regional lung ventilation using deformable image registration of CT and hybrid hyperpolarized gas/1H MRIPhysics in medicine and biology 2014 Dec 7;59(23):7267-77.

13. B H Tahir, P J Hughes. S Robinson, M Q Hatton, J M Wild, R H Ireland (2018). Spatial Comparison of CT-Based Surrogates of Lung Ventilation With Hyperpolarized Helium-3 and Xenon-129 Gas MRI in Patients Undergoing Radiation Therapy International journal of radiation oncology 2018 Nov 15;102(4):1276-1286.

14. Olliff J, Richards P, Connor S, Wong WL, Beale T, Madani G. Head and Neck Cancers. In: Nicholoson T (ed). *Recommendations for cross-sectional imaging in cancer management*, Second edition. London: The Royal College of Radiologists, 2014.

15. The Royal College of Radiologists. *Guidance on gadolinium-based contrast agent administration to adult patients*. London: The Royal College of Radiologists, 2019.

16. The International Atomic Energy Agency. *Radiation Protection in newer medical imaging techniques: PET/CT.* Vienna: International Atomic Energy Agency, 2008.