Mri-only treAtmeNT planning for Anal and Rectal cAncer radiotherapY (MANTA-RAY)

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Submitted in accordance with the requirements for the degree of

Doctor of Philosophy

The University of Leeds

School of Medicine

May 2021

The candidate confirms that the work submitted is his own, except where work which has formed part of jointly authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

Chapter 2 is based on work from the jointly authored publication: Bird D, Henry AM, Sebag Montefiore D, Buckley DL, Al-Qaisieh B, Speight R. A Systematic Review of the Clinical Implementation of Pelvic Magnetic Resonance Imaging–Only Planning for External Beam Radiation Therapy. Int J Radiat Oncol Biol Phys [Internet]. 2019;105(3):479–92. Available from: https://doi.org/10.1016/j.ijrobp.2019.06.2530 David Bird was responsible for conducting the systematic review including data collation, analysis, writing the paper and responding to reviewers comments. All co-authors reviewed the paper and provided feedback on written drafts.

Chapter 3 is based on work from the jointly authored publication: Bird D, Nix MG, McCallum H, Teo M, Gilbert A, Casanova N, Cooper R, Buckley DL, Sebag-Montefiore D, Speight R, Al-Qaisieh B and Henry AM, Multicentre, deep learning, synthetic-CT generation for ano-rectal MR-only radiotherapy treatment planning. Radiother Oncol [Internet]. 2021 Mar;156:23–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S016781402031197X. David Bird was responsible for patient recruitment, the methodology and analysis including the synthetic-CT validation, writing the paper and responding to reviewers comments. MG Nix was responsible for the synthetic-CT cGAN model generation, training the model, generating the testing synthetic-CT datasets and writing the description of the cGAN model in the paper. H McCallum was responsible for the anonymisation and transfer of patient data from the Northern Centre for Cancer Care. M Teo, A Gilbert, N Casanova and R Cooper supported patient recruitment. All co-authors reviewed the paper and provided feedback on written drafts and the final paper.

Chapter 4 is based on work from the jointly authored publication: Bird D, Beasley M, Nix MG, Tyyger M, McCallum H, Teo M, Casanova N, Cooper R, Gilbert A, Buckley, DL, Sebag-Montefiore D, Speight R, Henry AM and Al-Qaisieh B, Patient position verification in magnetic-resonance imaging only radiotherapy of anal and rectal cancers. Physics and Imaging in Radiation Oncology. 2021. Available from: https://doi.org/10.1016/j.phro.2021.07.005. David Bird was responsible for patient recruitment, the methodology and analysis, writing the paper and responding to reviewers comments. M Beasley and M Tyyger supported the import of synthetic-CT and MRI into

the XVI software. MG Nix was responsible for the generation of the synthetic-CT data. M Teo, A Gilbert, N Casanova and R Cooper supported patient recruitment. All co-authors reviewed the paper and provided feedback on written drafts and the final paper.

Chapter 5 is based on work from the jointly authored publication: Bird D, Nix MG, McCallum H, Teo M, Gilbert A, Casanova N, Cooper R, Buckley DL, Sebag-Montefiore D, Speight R, Al-Qaisieh B and Henry AM, The benefit of MR-only radiotherapy treatment planning for anal and rectal cancers: A planning study. Journal of Applied Clinical Medical Physics. 2021 Oct. Available from: https://doi.org/10.1002/acm2.13423. David Bird was responsible for patient recruitment, the methodology and analysis, writing the paper and responding to reviewers comments. MG Nix was responsible for the generation of the synthetic-CT data used in this study. M Teo, A Gilbert, N Casanova and R Cooper supported patient recruitment. A Gilbert, N Casanova and R Cooper were responsible for MRI gross tumour volume contouring. All co-authors reviewed the paper and provided feedback on written drafts and the final paper.

Chapter 6 is based on work from the jointly authored publication: Assessing the patient experience of anal and rectal cancer MR simulation for radiotherapy treatment planning, Bird D, Pearce S, Teo M, Gilbert A, Casanova N, Cooper R, Burnett C, Sebag-Montefiore D, Speight R, Henry AM and Al-Qaisieh B, Journal of Radiotherapy In Practice, 1-6, 2021, DOI: 10.1017/S1460396921000261. David Bird was responsible for patient recruitment, the methodology and writing the paper. S Pearce was responsible for analysing the questionnaire responses. M Teo, A Gilbert, N Casanova and R Cooper supported patient recruitment. All co-authors reviewed the paper and provided feedback on written drafts and the final paper.

Acknowledgements

This doctoral research was funded by a National Institute for Health Research clinical doctoral research fellowship. This PhD thesis presents independent research funded by the National Institute for Health Research. The views expressed are those of the author and not necessarily those of the National Health Service, the National Institute for Health Research or the Department of Health and Social Care.

My PhD was supported from the beginning by the Leeds Cancer Centre and particularly Vivian Cosgrove and the radiotherapy physics department. Thank you for your vision and support, as without it I'd not have been successful in my PhD fellowship application or the research that has followed.

Many people at the Leeds Cancer Centre and beyond have provided professional and personal support that has made this work possible including; radiotherapy physicists; Sarah Wright, Marcus Tyyger, Helen Baines, Dave Paynter, Sinead Pearce and J.J. Wyatt (Northern Centre for Cancer Care), MRI physicists; Dan Wilson and David Broadbent; dosimetrists, Laura Dowsett, Lynn Aspin, Christopher Lee and Jo Davis; research radiographers, Carole Burnett, Matthew Beasley, Pam Shuttleworth, Louise Loughman, Sharon Fernandez; clinical oncologists, Paul Hatfield, Michelle Kwok-Williams and Mohan Hingorani; radiologist; Peter Brown; radiotherapy and diagnostic radiographers, Helen Shepherd, Jo Dooling, Julie Towse, Cat Buchan, Craig Shepherd, Brett Crabtree; statisticians, Eleanor Hudson and Sarah Brown (Leeds Clinical Trials Unit). To all of you, thank you for your hard work and support.

I am particularly grateful to Rachel Cooper, Alexandra Gilbert, Nathalie Casanova and Mark Teo for their help and support with recruiting study participants, contouring and offering their guidance for all things clinical. Thank you.

I would like to acknowledge the help of my research collaborators Mike Nix and Hazel McCallum. Mike, without your involvement my work wouldn't have been achievable and so for your

friendship and support I am deeply grateful. Hazel, thank you for supporting this study with your advice and the data sharing which facilitated this work.

To my NIHR mentor, Ellen Donovan, your words of wisdom and encouragement have meant a great deal to me, thank you. To my NIHR friend, Claire Mills, it's some journey we're on - keep going! Thank you for your friendship.

To my supervision team; Ann Henry, Richard Speight, Bashar Al-Qaisieh, David Sebag-Montefiore and David Buckley, thank you for your support throughout this PhD, it has been greatly appreciated. Ann, thank you for your guidance and advice throughout which has always helped to move the research forward.

Richard and Bash, I owe you both a great deal. Without your support I'd never have even considered applying for my fellowship, let alone completing it. I will always be extremely grateful for your friendship and support which has been integral to the successes we've achieved together.

To my friends and family; Jack, Vicki and Howard, Mum and Dad, Aren, Simeon, Nigel and Vivienne. Thank you for indulging me! Your encouragement and friendship have always been important to me. You don't have to read this thesis, I promise.

Pippa, Reuben, Ezra and Amalie, my PhD is dedicated to you. Pippa, you alone understand the scale of the challenges that have been faced, the hard work that's been put in and the joy that's been found. Reuben, Ezra and Amalie, this book is what all those meetings on my computer have been about! Your love keeps me going. Birds fly together.

Abstract

Introduction: A barrier to the widespread clinical implementation of magnetic resonance imaging (MRI)-only radiotherapy planning for pelvic sites is the limited assessment in the literature demonstrating technical achievability and benefit. The MRI-only treatment planning for anal and rectal cancer radiotherapy (MANTA-RAY) study aimed to validate synthetic-CT (computed tomography) model generation accuracy, show the viability of cone beam CT (CBCT) patient positioning using synthetic-CT and MRI as a reference image, assess the patient experience of radiotherapy MRI scans and quantify potential clinical benefits of MRI-only patient treatments for anal and rectal cancer sites.

Methods: The MANTA-RAY study recruited 46 patients with anal and rectal cancers who received radiotherapy CT and MRI scans after informed consent. A deep learning synthetic-CT model was trained and validated in terms of dosimetric calculation accuracy. Differences in CBCT patient position registration accuracy were assessed when using synthetic-CT and MRI as the reference images. The patient experience of the MRI simulation was assessed. A planning study quantified the differences between MRI- and CT-only planned treatments.

Results: The synthetic-CT model had excellent dosimetric accuracy (planning target volume (PTV) D95% dose difference to CT = 0.1%). MRI and synthetic-CT reference images had systematic differences to CT in all translational and rotational dimensions of <1 mm and <0.5 °. The radiotherapy MRI patient experience was found to be better or similar to the CT experience for the majority of respondents. MRI-only target volume delineations resulted in statistically significant GTV (gross tumour volume) and primary PTV volume reductions and treatment plan dose reductions to healthy organs compared with CT-only plans.

Conclusions: These findings provide evidence that MRI-only treatment planning for anal and rectal cancers is technically achievable and accurate, can be clinically implemented without detrimentally affecting the patient pathway and could lead to improved patient outcomes if organ dose reductions translate into less treatment related toxicity.

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Abbreviations

2D - 2 dimensional

3D - 3 dimensional

ACR - American College of Radiology

CBCT - cone-beam computed tomography

CE - Conformitè Europëenne

cGAN - conditional generative adversial networks

CINAHL - Cumulative Index of Nursing and Allied Health Literature

COVID - Coronavirus disease

CT - computed tomography

CTV - clinical target volume

DICOM - Digital Imaging and Communications in Medicine

DIR - deformable image registration

DRR - digitally reconstructed radiograph

DVH - dose volume histogram

EBRT - external beam radiotherapy

FFF - flattening filter free

FU - Fluorouracil

GE - general electric

GPU - Graphics Processing Unit

GTV - gross tumour volume

HRA - health research authority

HU - Hounsfield Unit

IPEM - Institute of Physics and Engineering in Medicine

ISRCTN - International Standard Randomised Controlled Trial Number

LCC - Leeds Cancer Centre

LME - linear mixed effect

MAE - mean absolute error

MANTA-RAY - MRI-only treatment planning for anal and rectal cancer radiotherapy

ME - mean error

MR - magnetic resonance

MRCAT - Magnetic Resonance for Calculating ATtenuation

MRI - magnetic resonance imaging

MV - megavoltage

NCCC - Northern Centre for Cancer Care

NHS - National Health Service

NIHR - National Institute for Health Research

OAR - organ at risk

PACS - picture archiving and communication system

PET - position emission tomography

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PTV - planning target volume

PTVE - elective PTV

REC - research ethics committee

RF - radiofrequency

RIR - rigid image registration

SD - standard deviation

SE - spin echo

SPACE - sampling perfection with application of optimised contrasts using different flip angle evolution

STATA - statistics and data

TE - echo time

TPS - treatment planning system

TR - repetition time

TV - target volume

UK - United Kingdom

USA - United States of America

UTE - ultrashort echo time

VIBE - Volumetric interpolated breath-hold examination

VMAT - volumetric modulated arc therapy

XVI - X-ray Volumetric Imaging

Chapter 1 Introduction

1.1 Opening statement

This research study is focussed on the development, feasibility and potential benefit of magnetic resonance imaging (MRI)-only planning (the use of MRI alone to plan radiotherapy treatments) for anal and rectal cancers. It aims to address the key questions which limit the opportunity for widespread clinical implementation of this new technique including; assessing the dosimetric accuracy of synthetic-CT (computed tomography) scans; the accuracy of patient positioning with MRI-only reference imaging; the potential benefit of MRI-only planning to patient treatments and the impact of radiotherapy MRI on patient experience. It also assesses the progress of MRI-only clinical implementation in the pelvis through a systematic review of the literature. The overall hypothesis of this study is that MRI-only planning for anal and rectal cancers is technically achievable, clinically implementable and improves patient radiotherapy treatments.

MRI is known to have significantly improved soft tissue contrast compared to CT. This is beneficial for radiotherapy target volume delineation as it allows clinicians to visualise tumours more accurately (1,2). The introduction of MRI-based planning has the potential to improve target delineation accuracy and pathway efficiency (3). However, MRI-only planning requires accurate electron density information to be calculated from the MRI voxel information, acceptable levels of geometric distortion and the replacement of CT within the patient positioning treatment pathway. MRI-only planning has been clinically introduced for localised prostate-only cancer treatments (from here onwards referred to as prostate cancer treatments) but little assessment has been undertaken for anal and rectal cancers.

A conventional pathway to plan radiotherapy treatments begins with the acquisition of a CT scan of the patient in the treatment position so that an oncologist can delineate the target volumes and healthy tissues surrounding them. From this, a treatment plan can be produced. The CT scan provides the patient electron density information required to calculate radiation dose and as a consequence, historically, radiotherapy treatment pathways are optimised for use with CT as the primary modality. Therefore MRI-only planning requires the generation of patient electron density information from the MRI scan, a “synthetic-CT”, to allow radiotherapy treatment planning to

occur. CT scans are also used for positioning patients for treatment through their use as reference images to validate the patient position prior to treatment delivery. Consequently, the change in imaging modality from CT to MRI or synthetic-CT needs to be investigated to assess the risk of introducing accuracy errors into the patient positioning pathway. In addition, as with any new technique, to allow its widespread implementation, scientific evidence is required demonstrating that it improves patient treatments whether through improved patient outcomes or more efficient pathways with equivalent outcomes.

In this chapter, MRI-only radiotherapy treatment planning for anal and rectal cancers is introduced in the context of radiotherapy treatment pathways, including highlighting the role and wider use of MRI in the treatment pathway. The rationale for, and challenges facing, the development of MRI-only treatments for anal and rectal cancers is discussed, including comparison to the more developed and now clinically introduced MRI-only treatment planning technique for prostate treatments. A project overview is provided including the overall hypothesis and aims of the study, the structure of the thesis, the description of each study phase and the justification of the importance of the research.

1.2 Radiotherapy

There are approximately 367,000 new cases of cancer diagnosed annually in the UK (4). Radiotherapy has a key role in the treatment of cancer, alongside surgery and chemotherapy. While currently 27 % of patients diagnosed with cancer in the UK have radiotherapy as part of their primary treatment (5), it is estimated approximately 50 % of cancer patients would benefit from radiotherapy (6). Radiotherapy can be used curatively as a standalone (radical) treatment or in combination with other treatments such as chemotherapy (adjuvant) or prior to/post-surgery (neo-adjuvant/adjuvant) (7). Radiotherapy can also be used as a palliative treatment to relieve pain or side-effects (8).

One form of external beam radiotherapy is the targeted delivery of high energy X-rays produced and delivered through a medical linear accelerator (linac) into a patient's body, with the aim to eradicate cancerous cells (9). This radiation deposits energy, "radiation dose", into both healthy and cancerous cells, where the higher the dose deposited in a cell corresponds to the higher the

likelihood of cell death. The aim of radiotherapy is to treat patients by delivering radiation to cells in their body, maximising the delivery of the prescribed dose to the target cancer cells. In radical treatments, radiotherapy often aims to control the proliferation of the cancer cells. For many radiotherapy treatments a secondary aim is to deliver the required radiation dose, while minimising the dose to surrounding healthy tissues (10). This is because healthy tissue and organ cell death leads to organ and tissue damage which can result in acute and/or chronic toxicities (side effects of radiotherapy due to radiation damage to healthy organs or tissues) or death.

Radiotherapy is delivered incrementally through a number of treatments known as fractions which are typically spaced a day apart. Fractionation (the use of multiple fractions) benefits patients by reducing the damage sustained to healthy tissues as they can repair at a faster rate than cancerous cells in between treatments, reducing the organ damage and resultant treatment side-effects (11). A wide range of cancers are treated using external beam radiotherapy, including brain, head and neck, breast, thoracic, abdominal and pelvic cancers with dose and fractionations and delivery techniques varying depending on the cancer (12).

1.3 Anal and rectal cancers

Rectal cancer is a common cancer in the UK with 14,000 cases diagnosed annually (13). Conversely, anal cancer is much rarer in the UK, with only 1,300 cases diagnosed annually (14). Radiotherapy plays a significant role in the treatment of both cancers. For rectal cancers, radiotherapy is utilised as a neo-adjuvant treatment, to shrink the cancerous tissues prior to surgical resection (15) with standard dose and fractionations including 45 Gy in 25 fractions for high risk patients (with adjuvant capecitabine chemotherapy) or 25 Gy in 5 fractions for intermediate risk patients or patients not fit for chemotherapy (16,17). For anal cancers, radiotherapy is predominantly used as a radical treatment in combination with fluoropyrimidine (5-fluorouracil or capecitabine) and mitomycin chemotherapy treatments (18) with standard dose and fractionations including 53.2 or 50.4 Gy in 28 fractions dependant on nodal involvement. Dose escalation to the primary tumour volume is being investigated through clinical trials for both cancer sites (19–21). Because the survival rate of anal and rectal cancer patients treated with potentially curative radiotherapy is 50-80 % at five

years (22,23), many patients experience long term radiotherapy toxicities due to radiation damage to surrounding normal tissues. Therefore there are two broad aims of radiotherapy research for anal and rectal cancers; 1) treatment improvements to increase patient survival rates and 2) treatment improvements to reduce the treatment toxicities and therefore improve patient's post-treatment quality of life.

The location of the anus and rectum in the pelvis means that the bladder, sexual organs, bowels and pelvic bones are in close proximity to or within, the treatment target volumes and as a consequence result in severe toxicities due to radiotherapy treatments. These have been shown to include; gastrointestinal, genitourinary and dermatological toxicities which can result in delayed or early curtailed treatment, reducing the survival outcome for these patients, or persistent long term post-treatment toxicities, where patients have greatly reduced quality of life (24–27). Consequently, one method for improving the long-term quality of life for cancer survivors is to improve treatment outcomes, through reducing the dose delivered to healthy tissues, and therefore reduce treatment toxicities.

1.4 Radiotherapy clinical pathway

1.4.1 Planning CT scan

The radiotherapy treatment pathway begins with the patient receiving a CT scan in the radiotherapy treatment position (a planning CT scan). For anal and rectal cancer patients, the treatment position at the Leeds Cancer Centre (LCC) involves the patient lying on a flat top couch in a supine position with the following immobilisation devices situated around them; a pro-step foot positioning device (28) and site specific (anus or rectum) knee block, where the anus knee block pulls the knees together and the rectum knee block holds the legs parallel to each other. The devices are indexed to the flat treatment couch to ensure the position is reproducible. Changes in position of a patient's internal anatomy due to changes in bladder filling are managed through a drinking protocol which aims to ensure a reproducibly "full" bladder. For example, at the LCC the rectum cancer drinking protocol is 3 cups of water over the 30 minutes prior to CT scanning. This treatment position is assumed for all clinical radiotherapy scans and appointments with the aim that an identical position is assumed for each appointment.

The planning CT scan generates images of the inside of a patient's body by passing a narrow beam of X-rays through the patient. The tissues within the body attenuate the radiation beam and the residual remaining radiation is measured as it exits the patient (29). By delivering this narrow beam of radiation in a rotating manner over 360 ° around the patient, a map of the amount of attenuation within the body can be created. By using computational techniques such as filtered back projection, this attenuation map can be transformed into an image of the anatomy of the body, where the intensity of each voxel is measured in Hounsfield Units (HU). HU is the measure of the radiation attenuation co-efficient of a specific tissue relative to the radiation attenuation co-efficient of water. HU is approximately proportional to tissue electron density which is required to calculate the deposition of radiation dose in the body. As such, radiotherapy centres use the planning CT scan in combination with an empirically measured calibration curve which accurately relates HU to electron density to provide the anatomical and electron density information required for dose calculation and radiotherapy treatment planning (9). Each rotation around the body produces an image of a number of "slices" of the body, with each slice for radiotherapy purposes being typically 2 mm thick along the superior-inferior axis. By moving the patient through the scanner on the scanning couch, sufficient slices of patient anatomy can be produced to allow the planning of a radiotherapy treatment (29).

After the CT scan has been acquired, the radiotherapy target volumes and healthy organs at risk (OARs) are delineated (30). OARs are specific organ or tissues that clinicians have identified as being at risk of toxicities due to radiation damage incurred by the treatment, and as a consequence the dose delivered to them needs to be limited. Radiotherapy target volumes can be defined in three categories as seen in Figure 1-1. A gross tumour volume (GTV) is the visible macroscopic tumour. A clinical target volume (CTV) is the extent of the microscopic, non-visible, cancerous cells and therefore includes all the tissue that the radiotherapy treatment is aiming to ensure the prescribed radiation dose is delivered to. A planning target volume (PTV) is the CTV plus a margin that takes into account all the uncertainties in the planning and delivery of the radiotherapy treatment. The magnitude of the margin depends on the size of the uncertainties to ensure that the CTV receives the prescription dose when treatment is delivered (31). One of the sources of uncertainty in the treatment pathway is the poor soft-tissue contrast of CT scans which limits the ability to distinguish between different tissues, including the difference between healthy and tumour tissue (2). This adds uncertainty to the process of accurately delineating radiotherapy

target volumes and can particularly be a challenge when delineating the GTV. The poor visualisation of soft tissues on CT can lead to larger GTVs, CTVs and PTVs being delineated to ensure that all cancerous tissues are treated. This can result in more healthy tissue being irradiated that necessary (over-treatment), potentially leading to greater treatment toxicities (32).

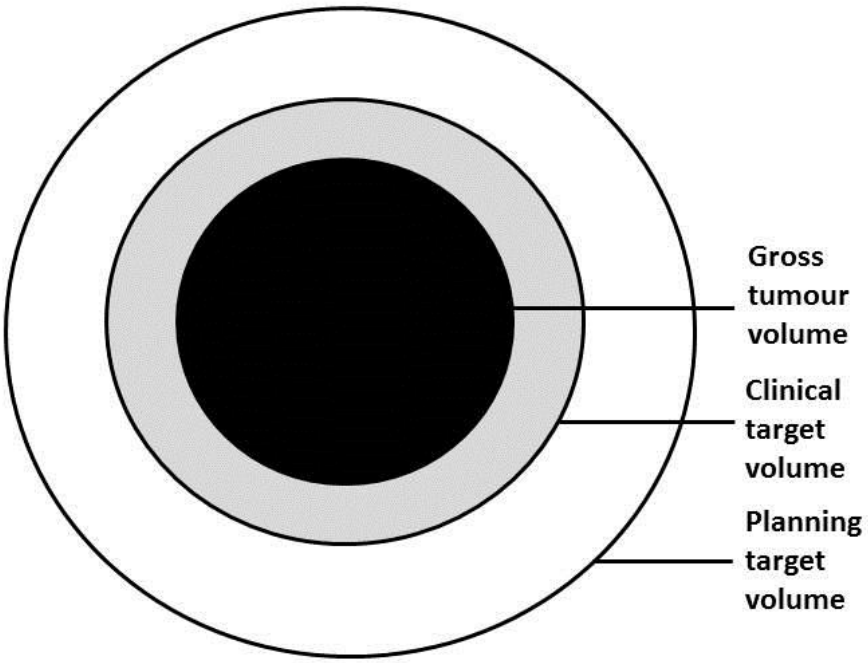

Figure 1-1. Radiotherapy planning volumes, including the gross tumour volume (GTV), clinical target volume (CTV) and planning target volume (PTV), replicated from ICRU 50 (31).

1.4.2 Radiotherapy treatment planning

Treatment planning systems (TPS) are used to calculate the deposition of radiation dose in the body. Treatment plans are optimised to deliver the prescription dose to the target volumes while minimising the dose to OARs in close proximity. Radiotherapy treatments have developed considerably in the last 10 years at which time 3D conformal planning techniques were commonly used (where a limited number of shaped but static beams are aimed at the tumour target at angles chosen to reduce OAR doses). State of the art treatments now use volumetric modulated arc therapy (VMAT) techniques, where radiation is delivered while the beam is rotated up to

360 ° around the patient and the shape of each beam is also continually adjusted (33). VMAT is beneficial because it provides greater control over where the radiation dose is deposited in healthy tissue, allowing greater sparing of OARs. These technological developments in TPS and linac machines (34,35), have allowed highly complex radiation distributions to be planned and delivered. This has resulted in the ability to deliver dose precisely to the target volumes and greatly improve the sparing of the healthy tissues resulting in reduced patient toxicities (33).

Because of these treatment delivery improvements, it is widely recognised that the greatest current challenge to providing radiotherapy treatments is the accurate visualisation of cancerous tissues (32). Inaccuracy in target definition can lead to geographic misses, where cancerous tissues are not included in the treatment volume, or over-treatment, where healthy tissue is unnecessarily included in the target volume (36). Geographic misses reduce the likelihood of successful treatment (limiting survival rates) while over-treatment leads to greater organ doses which can lead to greater toxicities for patients (37). One method of improving target volume definition and therefore reducing the risk of geographic misses or over-treatment is to use more accurate imaging techniques such as MRI to improve the clinician's abilities to accurately define radiotherapy target volumes (38).

1.4.3 Treatment delivery

After treatments have been planned, they are delivered by the linac treatment machine to the patient on the treatment couch as seen in Figure 1-2. To ensure the accurate delivery of radiation, it is vital that the patient is positioned as they were for their planning CT scan. Therefore, once the patient is set up on the treatment couch, the verification of their position is undertaken.

There are multiple methods for verifying that the patient position is acceptable for treatment. Cone-beam CT (CBCT) scans are used for the majority of treatments worldwide, using a CBCT scanner which is attached to the linac (39,40). However other simpler methods are also available such as measuring the distance from the linac focal spot to the patient skin surface or 2-dimensional megavoltage (MV) imaging which allows images to be acquired from the linac beam itself. CBCT scanners acquire 3-dimensional CT scans with the patient in the treatment position and facilitate accurate patient positioning. A CBCT scan, unlike a conventional CT scan which

delivers a narrow fan-beam of radiation, delivers a cone shaped beam of radiation through the patient. As its beam is much wider in the longitudinal direction, it can collect all the attenuation information required to produce an image of the patient's body with only a single rotation around the body (9). The CBCT technique is used because of the mechanics of the linac head rotation which mean the rotation around the patient is significantly slower than that of a conventional CT scanner. The disadvantage of a CBCT scan is that while the image is similar to a CT scan, in that it produces an image of the X-ray attenuation within a patient's body, it has more artefacts and generally poorer image quality which means tissues, organs and target volumes are less easily visible compared to CT(40). However, the image quality is optimised to ensure it is sufficient for use in verifying the patient position in comparison to the planning CT.

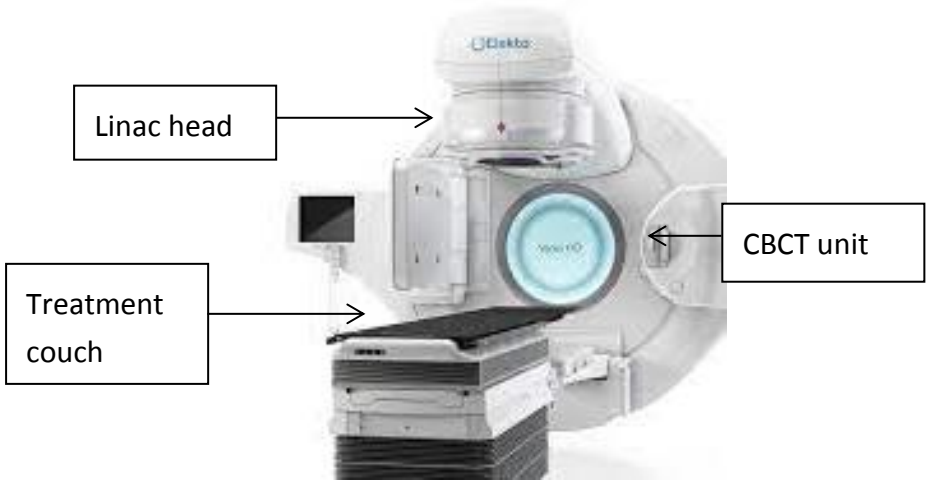

Figure 1-2. An Elekta AB Versa HD medical linac, treatment couch and CBCT unit (41).

The CBCT scan that is acquired on the treatment couch is rigidly registered to the planning CT scan. This allows the patient's position to be adjusted so it matches the planning CT prior to the treatment being delivered (40). Once the patient is acceptably positioned, where the machine-delivered high dose irradiated volume is correctly aligned with the patient target, the treatment is delivered. The positioning process can be challenging due to daily changes in a patient's body position and shape, both internal and external. This can result in accepting small positional changes which are accounted for by the PTV margin. Rigid registration can be undertaken between the reference image and CBCT using up to 6 degrees of freedom, although routinely only

translations and not rotations are corrected for. CBCT scans are also used to assess whether patient anatomy in the treatment region has changed from the time of the planning CT scan, either through weight gain/loss, tumour growth/shrinkage or internal anatomical changes such as bladder or bowel filling or organ motion. This is because changes in patient anatomy can mean that the treatment dose distribution calculated during the treatment planning stage, from the planning CT scan, is no longer an accurate representation of the radiation dose being delivered to the patient. In this case a new planning CT and treatment plan is required.

For anal and rectal cancers, CBCT position verification is carried out at the LCC either using daily CBCT imaging with on-line corrections before each treatment or an off-line imaging protocol. Using an off-line protocol, CBCT imaging is undertaken for the first 3 to 5 fractions of a patient's treatment and weekly throughout the treatment to ensure the treatment is being delivered correctly. In the event of positioning issues being identified and corrected, further CBCTs are acquired. An off-line protocol balances resources, the number of patients requiring treatment each day and the need to minimise excess dose accumulation within the patient with the more resource intensive daily on-line protocol. As a consequence the planning CT scan is used to support accurate patient positioning for the duration of treatment.

1.5 MRI

MRI scans can be used to improve the visualisation of tumours within the radiotherapy treatment pathway as MRI scans have significantly better soft-tissue contrast compared to CT scans. This allows the more accurate visualisation and consequent delineation of tissues, including target volumes (42).

Inside an MRI scanner is a high strength, typically 1.5 or 3 tesla (T), uniform magnetic field, running along the axis of the scanner bore, i.e. longitudinally along the patient. This is known as the Bo field. When the human body is placed within a uniform magnetic field, the magnetic moments (spins) associated with the hydrogen atoms within the body interact with the magnetic field. This leads to a small net magnetisation in the direction of the magnetic field which is known as the longitudinal magnetisation (as it is parallel to the magnetic field). When a second smaller magnetic field, oscillating at an appropriate (resonant) radiofrequency (an excitation RF pulse), is

applied in the transverse plane, the direction of the magnetisation can be moved until it is perpendicular to the direction of the longitudinal magnetic field. This is known as transverse magnetisation. When the RF pulse is removed the spins “relax”, returning back to their original longitudinal magnetised state. This relaxation releases energy in the form of an RF signal.

Magnetisation in both the longitudinal and transverse planes relaxes back to its original state at different rates. These are defined by the T1 and T2 relaxation constants, where T1 and T2 are the times for the spins to return to 63 % of their initial longitudinal magnetisation and reduce to 37 % of their maximum transverse magnetisation, respectively. T1 and T2 times differ depending on the specific chemical/molecular environment and hence on the individual tissues that the hydrogen atoms reside in and it’s these differences that give MRI its soft-tissue contrast.

After the excitation RF pulse ends, as the transverse and longitudinal magnetisations relax, an MRI sequence specifies the length of time before it measures the signal. The time between the generation of transverse magnetisation and signal measurement is called the echo time (TE). An MRI sequence also specifies the length of time between successive excitation RF pulses, the repetition time (TR). By adjusting the TE and TR times of the sequence, the difference in the signal from tissues with differing relaxation constants can be altered, therefore adjusting the MRI contrast. This allows sequences to intensify or subdue specific tissue image intensities. Different categories of MRI sequences refer to how the relaxing magnetisation is manipulated to create different tissue contrast. For example, a T2 weighted sequence is one that emphasises the signal differences in tissues caused by their T2 transverse magnetisation relaxation rate (43), and typically have TR times greater than T1 relaxation constants and TE times approximately similar to the T2 relaxation constants.

Figure 1-3 shows how T1 and T2 weighted images exploit tissue T1 and T2 properties to generate image contrast. For a T2 weighted image, the longer TR time means that all tissue longitudinal magnetisation has had sufficient time to return to its equilibrium state, such that there is no difference (given the same proton densities) in longitudinal magnetisation between them. The longer TE time means that sufficient transverse relaxation has occurred to ensure the difference in the transverse magnetisation between tissues with short and long T2 relaxation rates is maximised and this is what produces the contrast between tissues.

Examples of T1 and T2 weighted sequences used in radiotherapy are the T1 VIBE (volumetric interpolated breathhold examination) Dixon and T2- SPACE (sampling perfection with application

of optimised contrasts using different flip angle evolution) sequences. T1 VIBE Dixon is a fast 3D T1 weighted gradient echo sequence which is designed to produce maps of water and fat content in the body. T2-SPACE is a 3D T2 weighted turbo spin echo sequence (developed by Siemens but known as VISTA or CUBE when using Philips or GE (General Electric) scanners) which produces good anatomical detail and highlights abnormal tumour tissue (44,45). The T2-SPACE sequence uses multiple echoes to achieve a fast image acquisition.

To produce images, the position of the measured signal components within the body needs to be known. This is achieved by encoding the in-plane (x and y direction) and longitudinal slice (z direction) tissue positions into the signal through the use of magnetic field gradients (46). The gradients result in each location in the body having a unique signal in terms of its frequency and phase (47). The measured signal can then be decoded to identify each voxel's individual signal intensity. Fundamentally MRI signal intensity is a product of the relaxation rate of excited hydrogen atoms within tissues, and not related to tissue attenuation properties or tissue electron density which is required for radiation dose calculation (43).

A challenging aspect of MRI is the potential for geometric distortions, whether system- or patient-induced. System distortions are caused by inhomogeneities in the static magnetic field and non-linearities in the gradient fields, whereas patient-induced distortions are caused by perturbations of the magnetic field induced by the presence of the patient's tissue in the field. Geometric distortions are caused by these changes in magnetic field strength because the MRI signal spatial location is encoded using the magnetic field gradients. These differences in the magnetic field, from the expected field strength, cause the signal location to be incorrectly interpreted during the decoding process and therefore cause the geometric distortion to occur. Geometric distortions can be managed through hardware and software correction methods, and particularly through MRI sequence parameter selection, for example using high receiver bandwidths (43).

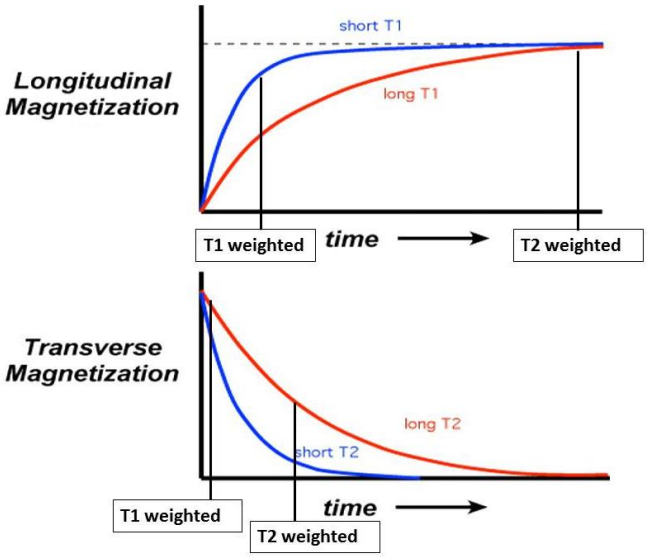

Figure 1-3. The longitudinal and transverse relaxation over time for two tissues which have short (blue) and long (red) T1 and T2 relaxation constants respectively. The black lines show the signal measurement time and respective residual magnetisation differences for T1 and T2 weighted images.

1.6 The use of MRI in the radiotherapy planning pathway

Within cancer care, MRI is routinely preferred to CT in the staging of tumours as it allows the better identification of tumour tissue compared to normal tissues (48). Within the pelvis, for anal and rectal cancers, it is T2 weighted MRI sequences that are primarily used for tumour identification (44,45).

The purpose of a diagnostic MRI scan is very different to its purpose for radiotherapy treatment guidance. For diagnostic scans the identification, location and approximate size of the tumour is established compared to radiotherapy where the aim is to visualise and delineate the tumour's precise size, shape and location. This means diagnostic and radiotherapy scans are optimised differently with diagnostic scans optimised to maximise the contrast between healthy and diseased tissue. Often this can result in a large scan slice thickness (to increase the signal to noise ratio) and spacing and with some geometric distortion being accepted. Conversely radiotherapy scans are optimised such that geometric distortions are minimised**,** with equal slice thickness and spacing comparable to CT (often ≤2 mm), and, with the exception of brain scans, the patient must

be set up in the radiotherapy treatment position (49). Consequently it is difficult for the majority of diagnostic MRI scans to be co-registered to the planning CT (1). This means it is common that diagnostic MRIs are instead viewed side-by-side with the planning CT by clinicians to help delineate treatment volumes, despite this limiting the benefit of MRI.

1.7 Radiotherapy MRI scans in CT-MRI pathways

Radiotherapy MRI scans are MRI scans that have been acquired specifically for radiotherapy treatment purposes, therefore meeting all the requirements discussed above (49,50). Radiotherapy MRI scans are used in conjunction with CT scans through co-registration (known as CT-MRI pathways). By acquiring the CT and MRI scans in the same treatment position, through the use of immobilisation devices, and in the case of pelvic cancers bladder filling protocols, co-registration is possible where a rigid or deformable registration aligns the MRI with the CT. Immobilisation devices which are indexed to the scanner couch can be manufactured such that they are equivalent on CT and MRI scanners. In addition, to prevent the MRI receiver coils deforming the patient surface, coil bridges can be used which elevate the coils away from the patient's skin.

The registration between the MRI and CT allows the target volumes to be delineated on the MRI scan and transferred to the CT where the treatment is planned as the CT is still required for dose calculation and CBCT registration (51). This has the benefit of allowing the soft-tissue contrast of MRI to be used in conjunction with the patient electron density information from the CT (2,52). While radiotherapy MRI scans are becoming more prevalent in radiotherapy centres, there are a number of limitations preventing their comprehensive use.

A practical challenge associated with radiotherapy MRI scans is their dependence on MRI scanning capacity. Radiotherapy MRI scans can be undertaken on diagnostic MRI scanners with bespoke equipment additions (unless investigating the brain where additions are not required) or with dedicated radiotherapy MRI scanners. For example, in 2018, in the UK only two radiotherapy centres had dedicated MRI scanners, with the majority of centres having more limited access through diagnostic MRI departments. Obtaining MRI provision for radiotherapy MRI scans is difficult due to the cost of purchasing scanning time, dedicated MRI equipment

and the requirement for experienced personnel to commission and manage MRI radiotherapy services (49). It is interesting to note that the use of MRI scans in radiotherapy varies substantially across Europe, where for example countries such as Denmark and Sweden have high radiotherapy MRI provision (53) whilst in the UK radiotherapy MRI provision is limited to a few cancer sites and centres (54). This is indicative that further evidence demonstrating the benefit of radiotherapy MRI scans is required to support the further growth and more uniform provision of radiotherapy MRI access across the globe.

As well as the practical issue of MRI provision, the main source of error associated with radiotherapy MRI scans in a CT-MRI pathway is the requirement to co-register CT and MRI datasets, although geometric distortions can also introduce significant uncertainties if not properly managed through the optimisation of the MRI sequence (2).

The co-registration process is reliant on patient data being acquired in an identical position for both their CT and MRI scans with any differences in the region of interest introducing registration errors between the CT and MRI. Sources of registration errors can be external, such as variations in patient set up between scans for example differences in the patients position on the scanning couch, or internal such as organ or breathing motion and physiological variation in bladder or bowel filling (51,55). Registration errors have been shown to add systematic uncertainties in target volume delineations of approximately 2 mm for prostate and rectal cancers (56–58) and therefore registration accuracy limits the ability of radiotherapy MRI to improve the target delineation process.

1.8 Image registration

Image registration is used within radiotherapy to align two image datasets through a geometric transformation (51). This transformation works to optimally relate identical points between the two images. Typically the image registration process keeps one dataset stationary (the primary dataset) and adjusts the position of the other dataset (the secondary dataset) to find its optimum position relative to the primary dataset. Image registration can be undertaken globally, including the whole image in the optimisation, or locally including only a specific region of interest. Registrations can also be manually undertaken by an operator, who adjusts the alignment based

on their own judgement of the spatial relationship between the primary and secondary datasets, or automatically by an algorithm, which optimises the registration through calculating the similarity between the datasets (49). In clinical practice, registrations often include a combination of automatic and manual registration methods.

There are two types of registration method, rigid image registration (RIR) and deformable image registration (DIR). RIR is when the transformation preserves all distances within an image set. RIR therefore can include translations and rotations of the secondary image, but not shearing or scaling. DIR is when the secondary image can also be "deformed" such that distances within an image set are not maintained. This allows the image to be manipulated through scaling and shearing both globally and locally as well as through translations and rotations (51).

RIR is most successful when there has been a rigid offset of the patient anatomy, but no changes in shape or size, and relies on the difference in patient positioning being very small or negligible. For example where CT and MRI scans of the head have been acquired on the same day, the brain is a good candidate for RIR as it is rigidly constrained within the skull, and so the spatial relationship linking the brain position on the CT and MRI can be determined purely through translations and rotations (49). However, the greater the patient positional difference between two scans, the less likely it will be that a RIR will achieve a high quality registration and the misalignment between anatomy and therefore registration error will increase. For example, the liver is a highly deformable organ and even when CT and MRI scans are acquired on the same day, the process of moving a patient on and off scanner beds can cause the shape of the liver to change. Whilst within the pelvis, bladder and rectal filling can also deform the internal patient anatomy over short time periods. In these cases, DIR can be used to change the shape of the patient anatomy within the secondary dataset, to match that of the primary dataset. RIR has the benefit of maintaining geometric fidelity and anatomical accuracy, where neither dataset is manipulated. This means users can have confidence that the visualised anatomy does represent the patient's anatomy on both scans. Conversely, while DIR has the benefit of being able to remove misalignments of the anatomy through deforming patient anatomy, it also can introduce errors into the pathway by applying deformations that do not accurately represent the patient anatomy. Therefore when image registration is taking place, it is important to assess the quality of the registration to ensure it is suitable for use (49,51).

It is a significant challenge to adequately assess the accuracy of image registration, whether RIR or DIR. Two commonly applied methods are; visual qualitative assessment and target registration errors. Visual qualitative assessment is most commonly used, where the fusion of the registered datasets is visually assessed by an experienced operator. It relies on the clinical knowledge of the assessor to determine whether the registration is sufficiently accurate for clinical use in the region of interest. Visual qualitative assessment can easily detect gross registration errors, but more subtle mis-registrations can be challenging to detect and it does not provide a quantitative measure of accuracy. Target registration error (TRE) is the offset in distance between known anatomical landmarks on the CT and MRI scan, where a perfect image registration would have a TRE of 0 mm. However, it requires accurate placement of the landmark positioning in clearly identifiable matching positions on both datasets, which can be difficult to achieve (49,51).

Within this study, visual qualitative assessment is utilised in combination with local and global RIR and DIR to align CT and MRI datasets. Further information regarding the methods used can be found in each individual chapter.

1.9 MRI-only radiotherapy treatment planning

MRI-only radiotherapy treatment planning is the use of an MRI scan alone to plan a radiotherapy treatment without a planning CT being acquired for use at any stage of the treatment pathway. The issues of MRI scanner provision and co-registration uncertainties give strength to the rationale that MRI-only treatment planning would be beneficial to the treatment planning pathway compared to a CT-MRI pathway because it would result in significant resource efficiency, removing the need for both a CT and MRI scan, as well as removing co-registration errors between scans (1,3). Compared to a CT-only pathway, MRI-only has the significant benefit of introducing MRI soft-tissue contrast to the pathway without the additional costs and inaccuracies introduced when moving from a CT-only to a CT-MRI pathway.

There are a number of other benefits to MRI-only planning; it could allow treatments to be refined further if delineation uncertainty and registration error was no longer the limiting treatment improvement factor and it removes the radiation dose that patients receive when undergoing a CT scan (1–3,59). In addition MRI-only planning facilitates other benefits of MRI

in radiotherapy which include; reducing clinician inter-observer delineation inconsistency (15) and enabling improved access to functional imaging.

However, the variation in radiotherapy MRI provision also makes the assessment of MRI-only pathways challenging because there are multiple standard pathways with which to compare. While some countries within Europe have extensive MRI provision, many countries do not, and so the question of whether to compare MRI-only to CT-only or CT-MRI pathways is unclear (53). Comparing MRI-only to CT-MRI is a comparison of the most advanced current radiotherapy treatment to the new intervention, but the counter argument to this is that further evidence is needed to demonstrate that all radiotherapy centres should be utilising radiotherapy MRI, and therefore the more important assessment is to compare MRI-only to CT-only with the aim of showing that MRI-only techniques are worth the investment to move away from CT-only pathways.

Until recently, MRI-only planning was unfeasible due to three significant technical barriers; 1) that MRI scans do not provide the patient electron density information required to calculate radiation dose, 2) the lack of knowledge regarding non-CT reference images for CBCT patient position verification and 3) that MRI distortions prevented the acquisition of geometrically accurate images (59–61). However, technological developments have improved MRI distortion levels, and solutions to the lack of patient electron density information are now a commercial reality, known as “synthetic”-CTs. Synthetic-CT scans generate the CT information from an MRI scan, providing the patient HU, and therefore electron density, information required for dose calculation. Synthetic-CTs also have the potential to be a replacement reference image for CBCT verification (62,63). The introduction of synthetic-CT allows the soft-tissue contrast benefit from MRI to be used for target volume delineation and the radiation dose to be calculated from the synthetic-CT.

1.10 Synthetic-CT generation

The generation of synthetic-CT data from MRI data is challenging due to the inherent differences in the information displayed in CT and MRI images. This is because MRI signal intensity has no relation to electron density and there is no relationship with CT signal intensity without further

information. CT voxel HU intensity is approximately proportional to electron density, where high electron density tissues such as bone have high HU signal intensity, low electron densities such as air or bowel gas have low HU signal intensity and tissues with electron densities in between these two extremes have proportionally representative values. In comparison, MRI voxel intensity varies depending on the acquired sequence and can result in dense tissues having high or low signal intensities. Particularly relevant when comparing CT and MRI is the challenge of cortical bone which has very fast relaxation constants (64). As a consequence, in many standard MRI scans cortical bone is represented with low or zero signal intensity, which is the same or very similar to the signal from air and is in marked contrast to CT where it is has a high HU signal intensity.

There are multiple methods in the literature for producing synthetic-CT scans. Two systematic reviews (62,63) investigated the development of synthetic-CT generation techniques which can be categorised into bulk density, atlas and voxel-based methods.

Bulk density assignment methods are the simplest, where different tissues are separated on MRI through assessing their signal intensities and assigned a mean HU or electron density value for that tissue class. In some cases, positional filters can also be used to separate different anatomical classes that have similar signal intensities (63).

Atlas based methods use paired CT and MRI datasets where patients are in the same treatment position. The datasets are combined into an atlas or multiple atlases, and in combination with mathematical functions which compare the differences between the incoming MRI and the atlases, determine an averaged or optimal MRI, and consequent synthetic-CT that best matches the incoming MRI (63).

Voxel based methods generate a synthetic-CT directly from the MRI voxel intensities on a voxel by voxel basis. These are the most complex methods for generation, but have the potential to most accurately depict individual patient anatomy as they involve less generalisation (63). A challenge for these methods is that different tissues can have the same signal intensities depending on the MRI sequence used, so methods of accounting for this are required. This can mean acquiring multiple MRI scans, or using positional voxel information in addition to intensity information. A recent development in voxel based methods is the use of machine learning models, for example conditional generative adversial networks (cGANs) (65), which can handle the complexity of the MRI to CT intensity and positional relationships when trained on a specific MRI sequence. cGANs are a form of deep learning computational modelling, which uses neural

networks to develop a relationship between a set of input and output images, such that an unseen input image can be transformed into an output image using this relationship (66).

Commercial pelvis and brain synthetic-CT solutions are now available from Philips, Siemens Healthineers and Spectronic Medical (67–70). Initially each pelvis solution was for prostate treatments only, but have been developed such that recently they became clinically available for all sites in the pelvis.

Initial prostate-only models methodologies were as follows: Philips and Siemens synthetic CT generation models use a T1 VIBE Dixon sequence which produces four images from one sequence acquisition; fat and water, in-phase and opposed phase (67,69). Each model uses a form of bulk density assignment to categorise tissues by their water and fat content and then assign pre-determined HU values to each tissue category. After the initial bulk density assignment, Siemens use an atlas model to render pelvic bones onto the image (69). In comparison, Philips first segment the bone, and then categorise the soft tissues (67). Within the pelvis, as it is recognised that T2 MRI sequences are optimal for visualising tumours (15,45), both Philips and Siemens synthetic-CT algorithms also require a T2 sequence to be acquired to allow target volume delineation. Spectronic Medical's synthetic-CT generation model uses a T2-SPACE sequence to produce synthetic CTs (68), initially with an atlas methodology. However, as previously discussed, these models have been updated and now include the whole pelvis (67,69,70). Detailed information regarding the updated methodologies is not currently publically available for Spectronic Medical and Siemens Healthineers models although Spectronic Medical have stated that their updated model is based on a deep learning neural network which is trained on a database of paired CT and MRI sequences and therefore is a complex voxel based methodology (70). The Philips MRCAT (Magnetic Resonance for Calculating Attenuation) pelvis model is fundamentally similar to their prostate-only model, with the addition of continuous HU assignment spectra for both soft-tissue and bone classifications. This continuous assignment means that rather than assigning a single bulk HU to each classification, a range of HU values is applied which improves the accuracy of HU assignment (71).

Although these commercial products are available, the level of independent validation seen in the literature for each solution is limited primarily to prostate cancer treatments (72,73). It is this development and initial validation on prostate cancer sites which is why the clinical implementation of MRI-only treatment planning has been seen first for prostate treatments.

1.11 Clinical implementation of MRI-only

Worldwide, prostate cancer treatments were chosen as one of the first sites for developing synthetic-CT generation methods due to the relative simplicity of radiotherapy treatments in comparison to other cancer sites. The pelvis is a preferable body area, as the abdomen and thorax have the challenge of breathing motion on MRI scans to contend with and the head and neck has substantial amounts of small bones which are difficult to visualise on MRI. In addition these body regions also have to contend with the challenge of distinguishing lung and/or air from bone which can be difficult on MRI. Within the pelvis, prostate treatments were the best candidate for development for several reasons. Firstly, prostate treatments often follow a CT-MRI pathway, which means that ample data was available for use in development. In addition, prostate treatments have a small, locally defined treatment volume around the prostate, which has a relatively stable position within the body. Prostate treatments are also single sex, meaning that the anatomy seen within the scans is less varied than for dual-sex cancers. The complexity of the treatment is also limited, where radical prostate treatment target volumes include the prostate and seminal vesicles with a PTV around them. Finally a common method of patient position verification for prostate treatments is the use of fiducial markers (74), which can be localised using 2D image matching rather than requiring 3D CBCT position verification. This allows prostate MRI-only to be clinically implemented without 3D CBCT positional verification, as is the standard pathway for anal and rectal cancers, which requires the use of MRI or synthetic-CT data as a reference image for positional verification.

With the arrival of CE marked commercial synthetic-CT products, prostate MRI-only treatments have begun to be clinically delivered in specialist centres (75). However, it is unclear how broadly MRI-only planning for prostate treatments has been validated in the clinic and whether its implementation will translate into widespread use for prostates or to other treatment sites.

1.12 Anal and rectal cancer MRI-only treatment planning

Building on previous work within the pelvis, the next logical sites for MRI-only treatment development are anal and rectal cancers due to their similarity to prostate treatments in terms of

their anatomical location. However the translation of technology is non-trivial as there are a number of differences between them that increases the complexity of undertaking MRI-only planning for these sites.

The obvious anatomical difference from prostate cancer is that anal and rectal cancers can affect both male and female patients, meaning that female anatomy also needs to be assessed and validated in synthetic-CT models. There are a number of differences between male and female anatomy that could have an impact on synthetic-CT generation. Firstly, the pelvic bones have differences in terms of structure, position and weight, where female pelvis's are wider, thinner and less dense (76), secondly, there are the obvious differences in soft-tissue sexual organs such as the uterus and vagina, and thirdly, due to the different organs, the position of organs in the pelvis are subtly different. All these anatomical changes can impact the ability of synthetic-CT models to correctly generate synthetic-CT datasets for female pelvic anatomy depending on the model's generation method.

As well as healthy organ anatomical differences, there are significant differences in the position and size of anal and rectal target volumes compared to prostate treatments. Figure 1-4 shows the sagittal slice of prostate, anus and rectum treatment planning CTs with their treatment PTVs, where it can be seen the prostate treatment PTVs are significantly smaller than those for anal and rectal treatments. This is partially due to anal and rectal treatments both including elective anatomically defined CTVs which are delineated independently to the tumour volume (19,20). Commonly anal and rectal target volumes can therefore include anatomy starting with the anal canal and continuing superiorly to the L5 vertebrae or further in cases with significant spread of nodal disease. This makes the size of anal and rectal target volumes significantly larger than prostate target volumes. Therefore accurate dose calculation needs to extent throughout the whole pelvis for anal and rectal cancers, unlike for prostates where only a fixed subsection of the pelvis needs accurate dosimetry.

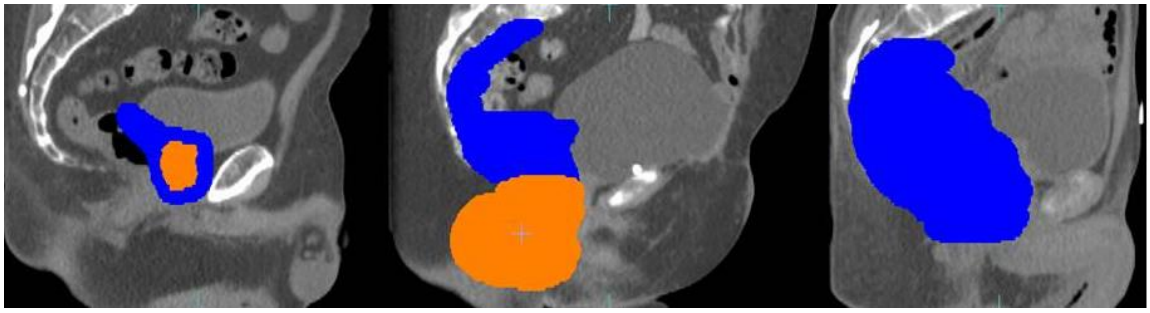

Figure 1-4. A prostate (left), anus (middle) and rectum (right) cancer patient's PTVs visualised on a sagittal slice of their planning CT scans, where high dose PTVs (60 Gy for prostate and 53.2 Gy for anus) are depicted in orange and the lower dose PTVs (50 Gy for prostate, 40 Gy for anus and 45 Gy for rectum) are depicted in blue.

These differences in cancer site compared to the prostate also impact the treatment pathway in terms of patient positioning verification. Unlike prostates which can use 2D image matching with gold fiducial markers for treatment positioning, anal and rectal cancers rely on soft-tissue registration between the reference image and CBCT to accurately position patients and so these sites cannot rely on the semi-automatic, independent of reference modality, registration process of prostate fiducial marker matching.

While synthetic-CT accuracy has been well investigated for prostate cancers, for anal cancers there are no assessments in the literature and for rectal cancers only six studies (with patient numbers between 5 and 20) had been undertaken prior to February 2021 (77–82). The dosimetric accuracy results were promising, but no firm conclusions in terms of generalisable cohort validation were possible due to the limited patient numbers and low inclusion of female patient data (<10).

Similarly, only two studies (with patient numbers of 7 and 10) have assessed rectal cancer CBCT treatment position registrations and focussed on synthetic-CT vs. CT, with no assessment of MRI as a reference image (55,77). This is similar to prostate treatments however, as prostate CBCT treatment position verification is often undertaken with fiducial markers and so the assessment of soft-tissue registration accuracy has been limited (73,78,83–86).

In addition to these technical challenges, a key question facing MRI-only planning is that of its added benefit to radiotherapy treatments. As previously discussed, it's well established that MRI has improved soft-tissue contrast to CT and that some centres utilise MRI already within CT-MRI

pathways (53). However many centres do not, and the onus is on those developing MRI within radiotherapy to provide sufficient evidence that MRI, in a CT-MRI or MRI-only pathway, quantitatively improves patient treatments. This evidence could be in terms of improved consistency in delineation, improved treatment plans with respect to target coverage and OAR sparing or patient outcomes in terms of survival and/or toxicities. Diagnostic studies for prostate, anal and rectal cancers have shown reductions in GTV of approximately 18 cc in each cancer site respectively (87–89) when delineated on MRI compared to CT. In addition prostate MRI-only treatment outcomes have been assessed by the first centre in the world to treat patients (75). However, no evidence has been presented quantitatively to show the hypothesised changes to treatment volumes impact final treatment PTVs, and therefore treatment plans and patient outcomes, for anal and rectal cancers.

1.13 Study overview

1.13.1 Overall hypothesis and study focus

The overall hypothesis of this study is that MRI-only planning for anal and rectal cancers is technically achievable, clinically implementable and improves patient radiotherapy treatments.

A systematic review of the clinical implementation of pelvic MRI-only treatment planning was carried out at the outset of this study (see Chapter 2), with the aim to identify and understand the remaining challenges that centres are encountering in the clinical implementation of MRI-only planning in the pelvis, as well as highlight the progress that had been made. These findings were used to inform the design of the further phases of this research which addressed the overall hypothesis of the study.

To be technically achievable, synthetic-CT datasets for anal and rectal cancer sites need to be generated, which cover a sufficient field of view for treatment planning purposes, and validated to show their dosimetric accuracy. Here it is hypothesised that the use of a deep learning, cGAN model can produce dosimetrically accurate synthetic-CT datasets which are generalisable for the whole patient cohort, including male and female patients.

To be clinically implementable, the reference planning MRI or synthetic-CT scan needs to be useable as the reference image for CBCT registrations within the radiotherapy treatment pathway. The impact of changing the reference modality in terms of CBCT registration accuracy needs to be quantified. Here it is hypothesised that MRI and synthetic-CT datasets can be used with the clinical CBCT registration software, X-ray Volumetric Imaging (XVI) (version 5.1, Elekta AB**,** Stockholm, Sweden), and soft-tissue matching, without quantitatively reducing the accuracy of the registrations. Also of importance to the clinical implementation of MRI pathways into radiotherapy departments is the patient experience of radiotherapy MRI in comparison to a routine CT-only clinical pathway. Here it is hypothesised that the patient experience of a radiotherapy MRI scan would differ from the planning CT scan due to the difference in scanning environment, but that opportunities to improve experience through specific radiotherapy MRI pathway optimisation may be identifiable.

While there are many potential benefits of using MRI-only planning for anal and rectal cancers, here it is hypothesised that MRI-only planning quantitatively improves radiotherapy treatments by reducing the volumes of treatment target volumes and that these target changes result in treatment plan improvements, specifically through reduced doses to OARs when target volume coverage is maintained.

1.13.2 Study phases

The MRI-only treatment planning for anal and rectal cancer radiotherapy (MANTA-RAY) study is a National Institute for Health Research (NIHR) funded research study (ISRCTN (International Standard Randomised Controlled Trial Number) registry number: ISRCTN82734641) which was developed for this PhD and comprises the research component of my NIHR doctoral fellowship. It investigates the challenges associated with the clinical implementation of MRI-only planning for anal and rectal radiotherapy treatments, as discussed below.

The MANTA-RAY study was comprised of four phases, which ran concurrently. Figure 1-5 shows the workflow of the study. During the study set up, prior to patient recruitment, a systematic review was carried out investigating the clinical implementation of MRI-only planning in the literature, the results of which were used to inform the following study phases. The systematic

review is discussed in Chapter 2. Total recruitment aimed to include 60 anal and rectal cancer patients, 30 male and 30 female, including 30 anal and 30 rectal cancers. Participation entailed the use of a patient's clinical radiotherapy data from their routine CT-only treatment pathway, a research-only radiotherapy MRI scan and the completion of a patient experience questionnaire after their radiotherapy MRI. Phase 1 investigated the dosimetric accuracy of synthetic-CTs from a deep learning model and is discussed in Chapter 3. The deep learning model required additional patient data for training and testing purposes, this data (from 37 rectal cancer patients) was acquired through a collaboration with the Northern Centre for Cancer Care (NCCC). Phase 2 assessed the impact of using MRI or synthetic-CT as the CBCT reference image on treatment registrations and is discussed in **Error! Reference source not found.**. Phase 3 assessed the impact f MRI-only planning, compared to CT-only planning, on treatment target volumes and treatment plan doses to OARs if target coverage is maintained and is discussed in Chapter 5. Phase 4 assessed the patient experience of radiotherapy MRI compared to planning CT and is discussed in Chapter 6.

1.13.3 The importance and contribution of the MANTA-RAY study

This study focusses on the key challenges which face MRI-only planning for anal and rectal cancer sites with the aim of furthering its development and providing evidence that its introduction is both clinically feasible and beneficial for patients.

MRI-only planning has considerable potential to improve patient treatments for a wide variety of treatment sites and its initial technical feasibility has been shown for prostate cancer treatments. However there are unknowns regarding whether its achievability can be translated to more complex treatment sites and if so whether it provides sufficient benefit to warrant its widespread implementation. The research presented here provides an important stepping stone in the development of MRI-only planning by assessing treatment sites which, whilst similar to prostates in location, have increased challenges associated with them. This work, in the context of MRI-only planning development, is therefore situated between the thorough initial exploration of MRI-only techniques for prostate treatments, and the future aim of developing its widespread implementation across all clinical sites that may benefit from it.

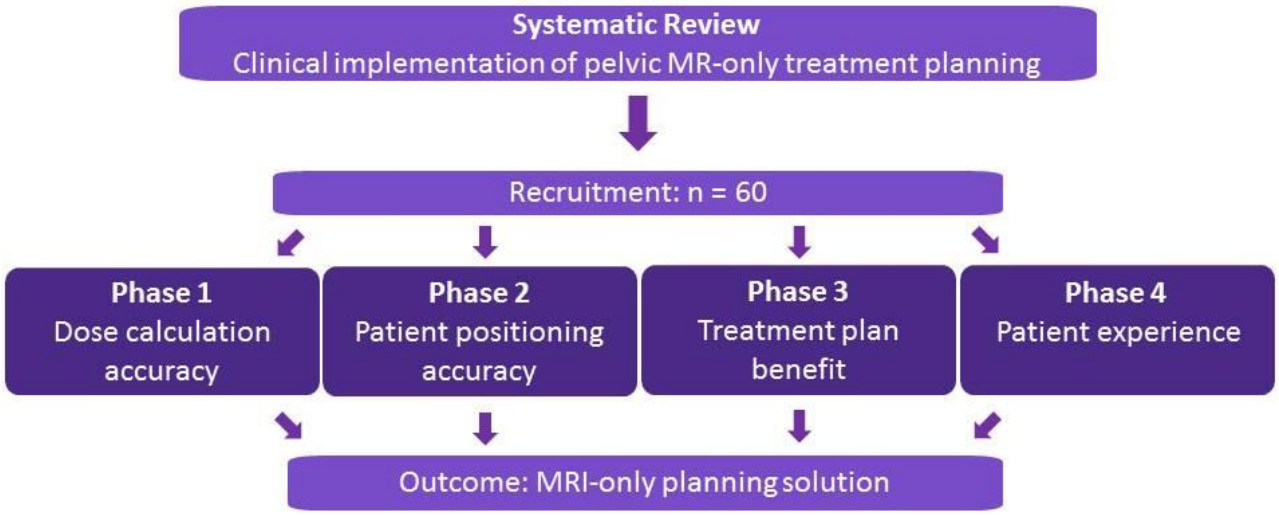

Figure 1-5 The MANTA-RAY study workflow including; the systematic review, participant recruitment and the four research phases.

The challenges assessed here; synthetic-CT dosimetric accuracy, patient treatment position verification using MRI and synthetic-CT as a reference image, the patient experience of radiotherapy MRI scans and the benefit of using MRI-only planning are fundamental questions that require greater evidence in the literature to enable its widespread use. Similarly the systematic review synthesises evidence to further inform and support the development of MRI-only planning, especially for centres not at the forefront of MRI innovation within radiotherapy.

Phases 1 and 2, synthetic-CT validation and MRI/synthetic-CT reference imaging, are the first such investigations for anal cancers and T2 SPACE MRI sequences, and one of the largest and most comprehensive investigations for rectal cancers in the literature. The assessment of T2-SPACE sequences is beneficial as the majority of clinically available synthetic-CT model validation studies use T1 VIBE Dixon sequences and as such the findings support the feasibility and benefits of this alternative scan approach. Similarly both phases have important findings which further the evidence in the wider community regarding the direction that synthetic-CT generation and reference imaging should follow, specifically through demonstrating that deep learning cGAN architecture allows the generation of a synthetic-CT model which is robust to varying input data, and also that the challenge of using MRI data as a CBCT reference image includes the need for greater vendor investment.

Phase 3, the assessment of MRI-only treatment planning changes, provides novel evidence that quantitatively demonstrates the benefit of radiotherapy MRI (through an MRI-only comparison) in the pre-treatment pathway for anal and rectal cancers. This evidence is important in the development of MRI-only treatment planning as a new technique but also in the wider introduction of MRI in the treatment pathway which requires further evidence to accelerate and successfully embed itself into the global radiotherapy community. This is also the first such investigation of its kind in the literature for anal and rectal cancers and highlights that MRI-only treatment planning does quantitatively reduce doses to OARs as well as significantly reduce target volumes.

The patient experience study, phase 4, highlights the challenge of introducing MRI into the radiotherapy treatment pathway, for centres unfamiliar with radiotherapy MRI, which differs from a diagnostic setting in terms of its requirements. The assessment of patient radiotherapy MRI experiences is very limited in the literature, with only one previous study which assessed lung cancer radiotherapy MRI. The patient experience study broadens the understanding of patient experience of radiotherapy MRI scans with concrete suggestions focussing on patient comfort.

1.14 Study methods

1.14.1 Regulatory and ethical approval

A health research authority (HRA) and research ethics committee (REC) application was prepared and submitted in July 2018. The application requested approval for recruiting anal and rectal cancer patients for an additional research-only radiotherapy MRI scan, with the inclusion of a Buscopan injection to minimise peristaltic motion during the scan. HRA and REC approval (reference: 18/LO/1298) was gained in August 2018. Local regulatory and ethical approval was gained in September 2018, relating to the capability and capacity of Leeds Teaching Hospitals NHS Trust for undertaking the study. The study was opened for recruitment on 28th September 2018.

1.14.2 Patient recruitment

Patients being treated at the LCC were recruited from the standard treatment pathway for curative chemo-radiation (anal cancers) or neo-adjuvant radiotherapy (rectal cancers), with participation in this study having no impact on their treatment. Inclusion criteria included; patients suitable for this treatment pathway as the standard of care, older than 18 years of age and who have provided written informed consent. Exclusion criteria included; patients with medical contra-indications to MRI such as pacemakers and patients with extreme claustrophobia.

46 patients were recruited to take part in this study at the LCC, 29 rectal cancer patients (15 male, 14 female) and 17 anal cancer patients (9 male, 8 female) including providing written informed consent. While this study aimed to recruit 60 patients; recruitment was curtailed in March 2020 due to the COVID-19 pandemic.

David Bird (DB) was responsible for patient recruitment in his role as a clinical scientist and as the principal investigator of the MANTA-RAY study. The recruitment process was as follows, where "(DB)" signifies where the task was carried out by David Bird. Eligible patients were identified through screening of consultant oncologist pre-treatment patient clinic lists (DB). Consultant clinical oncologists initially approached eligible patients. If the patient was interested, further information regarding the trial was provided in written form and verbally discussed (DB). Patients who chose to participate in the study were consented to take part a minimum of 24 hours after they were initially approached (DB). Each participant's research-only MRI scan was booked through liaising with the pre-treatment simulation radiographers (DB). Table 1-1 shows the patient demographics of participants of the MANTA-RAY study, recruited at the LCC.

Data was acquired from the collaborating partners, the NCCC, included the clinical radiotherapy planning data for 37 rectal cancer patients. Patient target outlining protocols for the NCCC data matched the LCC outlining protocols. This data was acquired to support the training and validation of the deep learning synthetic-CT model (chapter 3), where the CT and MRI data for 26 patients were used for training the synthetic-CT model, and CT, MRI and clinical target volumes for 15 patients were used for validating the synthetic-CT model. Further details of the collaboration are in section 1.14.7 Data sharing collaboration.

Patient Demographics		Disease Site	
		Anus	Rectum
Mean Age (Range)		63 (46-76)	63 (37-78)
Sex (number of patients)	Male	9	15
	Female	8	14
T stage (number of patients)	1	2	1
	2	5	11
	3	9	16
	4	1	1
N stage (number of patients)	0	8	8
	1	5	16
	2	4	5
Treatment schedule (number of patients)	53.2 Gy in 28#	8	-
	50.4 Gy in 28#	7	-
	25 Gy in 5#	-	7
	45 Gy in 25#	-	22
Mean days between CT and MRI (Range)		20.5 (0-43)	11.9 (0-30)
MRI scan date relative to patient treatment (number of patients)	CT & MRI same day	1	8
	Pre-treatment	6	15
	Within first 5 fractions	3	8
	Within first 10 fractions	7	4
	Within first 15 fractions	1	2

Table 1-1. Patient demographics for MANTA-RAY patients recruited at the LCC.

1.14.3 Clinical data acquisition

Planning CT scans were acquired in the radiotherapy treatment position following local bladder filling and immobilisation clinical protocols. Scanning parameters can be seen in Table 1-2. Patients were set up on a flat couch with immobilisation devices including a Prostep ankle stock (Elekta) and a site specific knee block. Bladder filling aimed to result in patients having a full bladder with 3 cups of water consumed over 30 minutes prior to the scan. No rectal filling protocols were used for participants in this study.

Clinical target volumes and OARs (for rectum; bladder and bowel cavity, for anus; small bowel, bladder, femoral heads and genitalia) were delineated on the CT as per the LCC's standard treatment protocol (defined in section 5.3.2) for each patient's routine treatment prior to being utilised for this study. Consultant clinical oncologists delineated the treatment target volumes and

the bowel cavity, small bowel and genitalia OARs, while all other OARs were delineated by experienced dosimetrists according to local clinical protocols.

There are differences in the local target volume delineation protocols (defined in section 5.3.2) between anal and rectal cancers, although both sites are delineated on CT scans alone with no MRI co-registration.

For anal cancers, GTV is defined as the macroscopic primary tumour, while nodal tumours are defined as GTVN. CTVA is defined as the GTV + 1 cm or 1.5 cm (depending on T-stage) extended to include the whole anal canal, CTVN is GTVN + 0.5 cm and CTVE is an elective anatomically defined treatment volume which includes a combination of the mesorectal, bilateral inguinal, internal and external iliac and presacral nodes. PTV definitions include PTVA (CTVA + 1 cm), PTVN (CTVN + 0.5 cm) and PTVE (CTVE + 0.5 cm). For rectal cancers, GTV is defined as the macroscopic primary tumour extended to the whole lumen and identified nodal tumours. CTVA is defined as the GTV + 1 cm, CTVB is an elective anatomically defined treatment volume including a combination of the mesorectum, pre-sacral, internal iliac and pelvic side-wall nodes and CTVF is the combination of CTVA and CTVB. The PTV is defined as CTVF + 1.5 cm anteriorly and 1 cm in all other directions.

The clinical delineation protocol for rectal cancers was amended when MRI GTVs were delineated for the planning study in Chapter 5, where MRI GTVs were defined as the macroscopic tumour and nodal tumours only without an expansion to the whole lumen as for CT. This change was possible due to the improved visibility on MRI compared to CT which reduced the uncertainty regarding the macroscopic GTV position considerably. An alternative option would have been to use the same delineation protocol for CT and MRI, however, that would have negated the benefit of using MRI and its superior soft-tissue contrast and here the aim was to establish how using MRI changed our ability to visualise target volumes, including the GTV.

1.14.4 Radiotherapy MRI scans

The MRI scan was acquired in the same radiotherapy treatment position as each patient's planning CT including matched bladder filling and immobilisation. T2-SPACE sequence parameters can be

seen in Table 1-2. Coil bridges were used to rest the coils on, preventing patient surface deformation. The whole patient external contour was included in the axial field of view.

The radiotherapy MRI scan protocol at the LCC was set up by MRI clinical scientists; Dan Wilson and David Broadbent, with the T2-SPACE sequence set up from previous work which had included the optimisation of the sequence to limit geometric distortion to acceptable levels. The T2-SPACE sequence was chosen as the synthetic-CT generation scan due to its use for synthetic-CT generation by Spectronic Medical's commercial synthetic-CT solution and the NCCC. The T2-SPACE sequence was also assessed for tumour visualisation purposes with consultant lower GI (gastrointestinal) radiologists and was determined to be appropriate for synthetic-CT generation and target volume and OAR delineation. For the T2-SPACE sequence to be sufficient for radiotherapy planning purposes, its field of view was required to cover all necessary anatomy in the superior-inferior plane as well as the whole patient body in the axial plane. A sample of 40 previous anal and rectal cancer patients was assessed to establish the required scan lengths for these patients, with the finding that the maximum required scan length was 35cm - ensuring coverage from 2cm inferior of the inferior edge of the patient's genitalia up to the L2/3 vertebra interface for patients with extensive disease. However, the maximum superior-inferior distance of the SPACE sequence was approximately 27 cm. Therefore a T2-SPACE scan protocol was developed where two overlapping SPACE sequences were acquired as a "set and go" protocol to cover the required FoV and then "stitched" together to create one composite scan. Scans were reviewed visually at the time of acquisition and if patient motion was identified, the scans were reacquired.

T2-SPACE MRI scan acquisition time varied depending on superior-inferior scan length with a mean of 5 minutes 20 seconds per acquisition. Research MRI scans were scheduled for a time when the patient had a clinic appointment prior to or during their first two weeks of treatment. The mean time between CT and MR data acquisition undertaken at the LCC was20.5 days (range: 0 to 43 days) for anal cancer patients and 11.9 days (range: 0 to 30 days) for rectum cancer patients.

1.14.5 Treatment delivery imaging

Patient CBCT scans were acquired prior to treatment as part of the routine clinical protocol for patient treatment position verification using the XVI CBCT system.

1.14.6 LCC data pre-processing

Planning CT, clinical target volume and OAR contours, patient treatment CBCTs and the research radiotherapy MRI scan were collected for each patient recruited from LCC. All data was de-identified prior to use. Planning CT, clinical delineations (target volumes and OARs) and the radiotherapy MRI scan were imported into the RayStation treatment planning system (Version 9B, RaySearch Laboratories, Stockholm, Sweden). The planning CT and MRI were then rigidly registered within RayStation using a mutual information algorithm with registrations visually assessed by an experienced image registration physicist (David Bird) to ensure suitability. Following pre-processing the patient data was ready for use in the following study phases.

		NCCC	LCC
MR	Make & Model	Siemens Espree 1.5 T	Siemens Aera 1.5 T
	Sequence	3D T2-SPACE	3D T2-SPACE
	Resolution	1.4x1.4x1.5 mm	0.9 x0.9 x1.5 mm
	Refocusing Flip Angle (°)	160	160
	TR (ms)	1500	1600
	TE (ms)	211	211
	Bandwidth (Hz/px)	600	545
	Echo train length	105	134
	Field of View (Superior-Inferior)	216 mm	Inferior: 2 cm inferior of genitalia Superior: superior aspect of L5 vertebra or greater as required
CT	Field of View (Axial)	450x450 mm^2	450x450 mm^2
	Make & Model	Siemens Sensation Open	Philips Brilliance Big Bore
	Resolution	1.1x1.1x3 mm	1.2x1.2x2 mm
	kVp (kV)	120	120
	X-ray Tube Current (mAs)	122	135

Table 1-2. The CT and radiotherapy MRI scan parameters for patients at the LCC and the NCCC.

1.14.7 Data sharing collaboration

A data sharing collaboration was agreed with the NCCC, meeting NHS data protection requirements. The NCCC shared additional de-identified patient treatment scan data for 37 rectal cancer patients (CT and radiotherapy MRI scans and clinical delineations), sufficiently similar to the data to be prospectively acquired within this study for use in the generation and validation of a synthetic-CT deep learning cGAN model (phase 1, chapter 3). The NCCC data sharing agreement has HRA and REC approval through the AMIRA study (REF 16-YH-0295) which includes the sharing

of routinely-collected anonymised, radiotherapy planning data. This data includes CT and MRI scans from the NCCC to the LCC for the purposes of developing and validating a synthetic-CT model. It is this data that was shared with the LCC for use within Chapter 3. The AMIRA study was a research collaboration set up to investigate MRI-only planning for pelvic and brain cancers and the MANTA-RAY study sits within this wider study as it investigates anal and rectal cancers. The REC application form explicitly stated: “In patients from Freeman Hospital Newcastle upon Tyne, MR scanning is already established as standard of care in radiotherapy planning. Many historical images are available and as many of these patients will have died from their cancer it would not be possible to gain consent. The research team in the Freeman have discussed the project and have agreement from their local Information Governance Team that anonymised images can be transferred to Leeds Teaching Hospitals NHS Trust. No patient identifiable information will be shared.” In addition Cauldicott approval was gained within the LCC for the collection and processing of de-identified patient data from other NHS Trusts.

The NCCC planning CT and MRI scans were acquired with parameters seen in table 1, with matched bladder filling and immobilisation in the radiotherapy treatment position. Unlike the LCC scans, NCCC radiotherapy MRI scans were acquired for clinical delineation purposes. MRI scans were acquired within 2 days of the planning CT, prior to target volume delineations taking place. The T2-SPACE MRI scan was a single acquisition centred on the rectal cancer GTV in the superior-inferior direction.

Routine clinical delineations (target volumes and OARs) delineated using NCCC local clinical protocols were also collected. The target volume delineation protocols matched those of the LCC and were used in chapter 3 for the synthetic-CT validation. All retrospectively collected NCCC data was de-identified prior to being provided to LCC for use in this study.

1.15 Chapter overview

Chapter 2 discusses the systematic review of the clinical implementation of pelvic MRI-only planning. This work has been published in the International Journal of Radiation Oncology, Biology and Physics (90).

Chapter 3 discusses the anal and rectal cancer synthetic-CT dosimetric accuracy assessment. This work has been published in the journal Radiotherapy and Oncology (91).

Chapter 4 discusses the assessment of MRI-only CBCT positional verification using MRI or synthetic-CT as the reference image. This work has been published in the journal Physics and Imaging in Radiation Oncology (92).

Chapter 5 discusses the assessment of treatment changes for anal and rectal MRI-only radiotherapy. This work has been published in the Journal of Applied Clinical Medical Physics (93).

Chapter 6 discusses the patient experience of radiotherapy MRI scans. This work has been published in the Journal of Radiotherapy in Practice (94).

Chapter 7 discusses the whole body of work, including the key findings, implications for clinical practice and future work.

Chapters 2-6 are reproductions of the published journal articles which are referenced above. Minor edits to the published versions have been included here, such as edits of typing errors and requested wording changes. For each chapter, where additional information has been requested, a further appendix section has been included.

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Chapter 2 A systematic review of the clinical implementation of pelvic magnetic resonance imaging (MR)-only external beam radiation therapy

2.1 Abstract

The use of magnetic resonance imaging (MRI) scans alone for radiotherapy treatment planning (MR-only planning) has been highlighted as one method of improving patient outcomes. Recent technological advances have meant that introducing MR-only planning to the clinic is now becoming a reality, with several specialist radiotherapy clinics treating patients with this technique. As such, substantial efforts are being made to introduce this technique into widespread clinical implementation.

A systematic review of publications investigating the clinical implementation of pelvic MR-only radiotherapy treatment planning was undertaken following the PRISMA guidelines. The Medline, Embase, Scopus, Science Direct, CINAHL and Web of Science databases were searched (timespan: all years to 2nd January 2019). Twenty six articles met the inclusion criteria. The studies were grouped into the following categories: 1. MR acquisition and synthetic-CT generation verification, 2. MR distortion quantification and phantom development, 3. Clinical validation of patient treatment positioning in an MR-only workflow and 4. MR-only commissioning processes.

Key conclusions from this review are: i) MR-only planning has been clinically implemented for prostate cancer treatments; ii) A substantial amount of work remains to translate MR-only planning into widespread clinical implementation for all pelvic sites; iii) MR scanner distortions are no longer a barrier to MR-only planning; however they must be managed appropriately; iv) MR-only based patient positioning verification shows promise, however limited evidence is reported in the literature and further investigation is required; and v) a number of MR-only commissioning processes have been reported which can aid centres as they undertake local commissioning, however this needs to be formalised in guidance from national bodies.

2.2 Introduction

One of greatest challenges remaining in radiotherapy is considered to be improving the accuracy of treatment volume delineations (1). Further reducing the uncertainty in delineation could lead to improved patient outcomes either by reducing treatment volumes, allowing a reduction in treatment related toxicities (2, 3) or reducing the risk of geographic misses thereby improving local control and potentially overall survival rates. The use of magnetic resonance imaging (MRI) scans alone for radiotherapy treatment planning (MR-only planning) has been highlighted as one method of potentially improving target volume delineation accuracy (4-6). This is due to MRI's improved soft tissue contrast compared to computed tomography (CT) as well as the potential to utilise the other benefits of MRI, such as functional imaging (5).

Recent technological advances have meant that introducing MR-only planning to the clinic is now becoming a reality (5, 7). Hardware and software developments have improved the geometric distortion inherent within MR images to levels that are acceptable for radiotherapy treatment planning (8), and substantial progress has been made in acquiring electron density information from MRI data alone through synthetic-CT generation methods (4, 9). The field of synthetic CT generation has been reviewed (4, 9) and commercial solutions are available, including several prostate solutions and, recently released, a solution for the whole pelvis (10, 11, 12). Consequently, MR-only treatments are now being carried out by specialist radiotherapy clinics, and over time are likely to move to more widespread clinical implementation.

This systematic review assesses the literature surrounding the clinical implementation of pelvic MR-only radiotherapy treatment planning with the aim of detailing and discussing the breadth of work which has been undertaken. This review only considers work which has been published in relation to MR-only planning for pelvic external beam radiotherapy.

2.3 Method

A systematic review of publications investigating the clinical implementation of pelvic MR-only external beam radiotherapy treatment planning was carried out using the PRISMA guidelines (13).

The Medline, Embase, Scopus, Science Direct, CINAHL and Web of Science databases were searched with a time span of: all years to 2nd January 2019 (for Medline and Embase this corresponded to “Week 3 December 2018” and “Week 52 2018” respectively) using the search protocols seen in Supplementary information. Articles were included that referred to “MR-only” or “synthetic-CT” and “radiotherapy” or synonyms of these terms in their title or abstract. These deliberately broad search criteria were used to minimise the risk of relevant studies not being identified. The search results for each database were combined and duplicates were removed. The remaining results were screened from their titles for eligibility. Primary screening included only search results that were related to the use of MRI in radiotherapy for cancer treatment. Secondary screening included only articles related to the clinical implementation of MR-only external beam radiotherapy treatment planning for pelvic cancer sites. Articles focussing on: the general use of MRI in radiotherapy, MRI in brachytherapy, synthetic-CT model generation techniques, target volume delineation using MRI, MR image registration, PET-MRI in radiotherapy, MRI safety, MR-only contouring and MR-only fiducial marker identification were excluded. Articles regarding synthetic-CT model generation techniques were specifically excluded due to the rationale that they were recently appraised in the literature within two review articles (4, 9), and that this review is focussed on the clinical implementation, rather than technique development, aspect of MR-only planning. Conference proceedings were excluded due to their large number and variable information provision which made their inclusion unbeneficial. A backwards citation search of the remaining eligible studies was undertaken. The included studies were categorised according to their focus. For each category key findings from each study were included in a data table.

2.4 Results

The database search results can be seen in Figure 2-1. The combined database search resulted in 2024 records, with 1066 remaining after duplicate removal. After primary screening, 535 records remained. After secondary screening, 71 studies remained. After further review, 49 studies were removed, 44 conference abstracts and 5 studies which did not meet the eligibility criteria. This left 22 studies to which the citation search added 4 studies. Therefore 26 studies were included in this systematic review. The categories and number of excluded articles can be seen in Table 2-1.

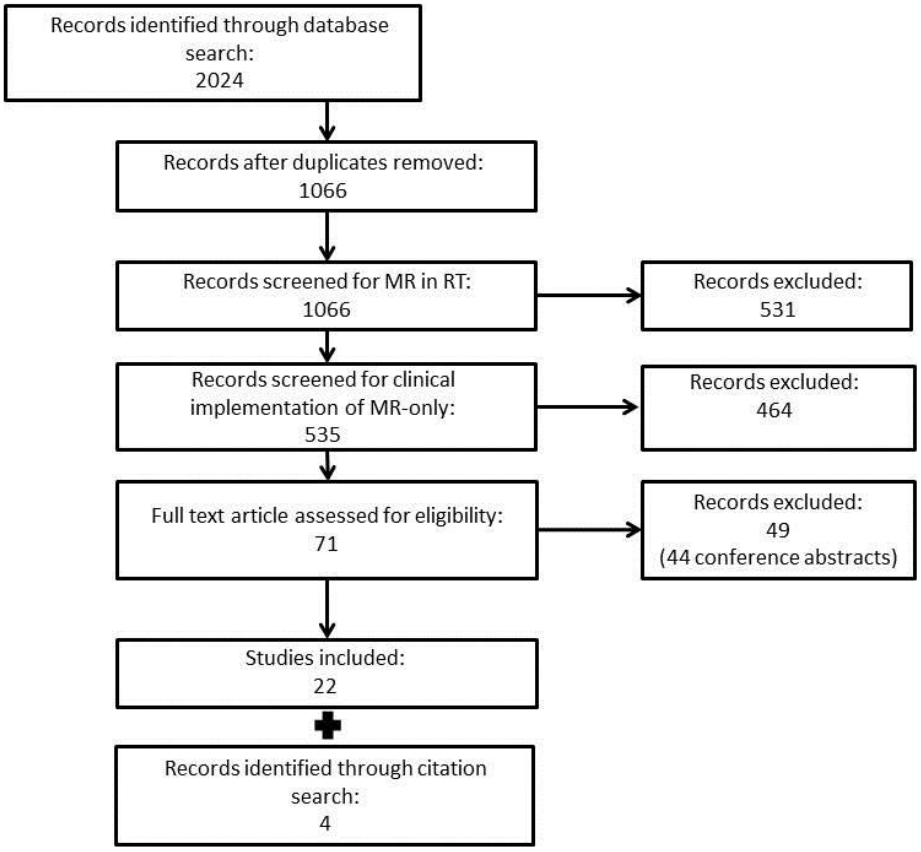

Figure 2-1. Flowchart of the systematic review process, including the number of studies included in this review.

Included studies were organised into one or more of the following categories for review: 1. MR acquisition and synthetic-CT generation verification, 2. MR distortion quantification and phantom development, 3. Clinical validation of patient treatment positioning in an MR-only workflow and 4. MR-only commissioning processes. These four categories will be discussed in more detail below.

2.4.1 MR acquisition and synthetic-CT generation verification

The systematic review identified 9 studies investigating MR acquisition or synthetic-CT generation verification (6, 14-21). A key summary of study results can be found in Table 2-2.

Primary screening - reasons for exclusion	**No. of Articles**
Not related to cancer treatment	65
Not related to radiotherapy cancer treatment	301
Not related to the use of MR in radiotherapy cancer treatment	165
Total	**531**
Secondary screening - reasons for exclusion	
General use of MRI	115
Other site synthetic-CT generation technique	98
Brain synthetic-CT generation technique	65
Brachytherapy/Gammaknife	48
Prostate synthetic-CT generation technique	43
MR delineation	33
MR image registration	12
Proton/Ion synthetic-CT generation technique	12
Other	10
MR-only contouring	7
MR-only fiducial marker identification	7
PET-MR	7
UTE synthetic-CT generation techniques	5
MR safety	2
Total	**464**
Tertiary Screening - reasons for exclusion	
Conference abstracts	44
MR-only review articles	3
Synthetic-CT model development studies	2
Total	**49**

Table 2-1. Categories and number of articles excluded from this review after primary, secondary and tertiary screening.

Author	Year	sCT technique	No. Patients in Study	MR acquisitions	MR Scanner & Magnet strength	MR-only treated patients	sCT success rate (%)	Other key information
Christiansen (16)	2017	Philips - MRCAT	30	T1 mDIXON	Philips Ingenia 1.5 T	1	97 (29/30)	1. MR synthetic-CT generation failed in 1 case, reason unknown. 2. Dosimetric accuracy for gamma analysis of 2%2mm - median 100% in all structures. 3. Rectal gas found to be main contributor to dosimetric errors.
Kemppainen (19)	2017	Philips - MRCAT	5*	T1 mDIXON	Philips Ingenia 1.5 T	X	X	*Only prostate patient data from study included. 1. Mean dosimetric accuracy (prostate patients) for 2%/2mm and 1%/1mm gamma analysis of 100% and 99.2% respectively within PTV. 2. Mean relative dose difference of 0.7% in PTV and <1.2% in OARs.
Maspero (21)	2017	Philips - MRCAT	14	T1 mDIXON	Philips Ingenia 3 T	X	X	1. Mean relative dose difference between CT and sCT found to be 0.3% within the CTV and 0.04% within the whole body.
Persson (6)	2017	Spectronics Medical - MRIPlanner	170	T2 SPACE	GE Discovery 3 T GE Signa 3 T Siemens Area 1.5 T Siemens Skyra 3 T	X	85 (145/170)	1. Patient MR acquisition issues (# of patients): distortion correction turned off (12), whole body not included in FoV (4), insufficient superior-inferior coverage (2), hip prosthesis patients (2), extreme rectum change between CT & MR (1). 2. Mean dosimetric deviations of less than 0.3% for all targets and organs. 3. Multi-centred (4 centres) study found insignificant differences found between range of treatment techniques, planning systems, prescribed doses, calculation models and target volumes.
Tyagi (17)	2017	Philips - MRCAT	48	T1 mDIXON	Philips Ingenia 3 T	42	87.5 (42/48)	1. Patient MR acquisition issues (# of patients): hip prosthesis patients (4), large patient exceeded MRCAT size limitations (2). 2. Dedicated software utilised for contouring workflow. MR sequence blurring impacted 2D DRR fiducial marker identification in 2 patient cases. 3. MRCAT failure modes: i) presence of hip prosthesis, ii) significant bone disease in pelvis, iii) significant discrepancies from the bone model boundary conditions, iv) patient size exceeds 50cm left-right or 30cm

								anterior-posterior. 4. Time saving of ~15 minutes using MR-only simulation compared to CT-MR simulation, further 15 minute saving estimated in the future if logistic challenges resolved.
Tyagi (18)	2017	Philips - MRCAT	25	T1 mDIXON	Philips Ingenia 3 T	X	X	1. Mean relative dose difference between sCT & CT <0.5%.
Wyatt (20)	2017	Dowling (40)	21	T2 SPACE	Philips Magneto Espree 1.5 T	X	54* (21/37)	*Retrospective data collection. 1. Patient dataset exclusions (# of patients): required patient body outside of MR FoV (13), hip prostheses (2), gross patient motion (1). 2. Dosimetric accuracy for 2%2mm gamma analysis: mean 98.9%, minimum 97.6%, and maximum 99.5% in all structures.
Kerkmeijer (15)	2018	Philips - MRCAT	Not known	T1 mDIXON	Philips - unknown	Yes, number unknown	Not known	1. Inclusion criteria: fiducial markers present in prostate. 2. Exclusion criteria: hip prostheses and contra-indications for MRI.
Tenhunen (14)	2018	Korhonen (39)	250	T1 mDIXON	GE Optima - 1.5 T	125	92 (184/200)	1. Patient MR acquisition issues (# of patients): gold markers not identifiable (8), hip prosthesis related distortions (5), obesity (2), motion (1). 2. CT vs MR-only patient treatment outcomes: PSA & acute toxicities results showed no significant differences between pathways. 3. Noted lack of support of MR-only workflow from technical software, including planning systems.

Table 2-2. Summary of the key results from the MR acquisition and synthetic-CT generation verification studies, where "No. patients in Study" refers to the total number of patients recruited for MR-only investigations, "MR-only treated patients" refers to the number of patients planned and treated using the MR-only technique and "sCT success rate" refers to the percentage of patients for whom a useable sCT was generated.

All studies reported results relating to prostate cancer treatment planning. Studies reporting synthetic-CT dosimetric accuracy findings were included where they were validating previously reported synthetic-CT generation models as part of clinical implementation, rather than as part of the development of a synthetic-CT model.

Tenhunen (14), Kerkmeijer (15), Christiansen (16) and Tyagi (17) reported treating patients using an MR-only pathway, with the number of patients treated ranging from 125 (Tenhunen (14)) to 1 (Christiansen (16)). Tenhunen (14) also reported the MR-only patient cohort's initial clinical response in terms of early response PSA and acute toxicity follow ups.

Persson (6), Tenhunen (14) and Tyagi (17) reported their experiences of prospectively acquiring MR data for MR-only treatment planning in terms of their MR scan success rates and the issues that prevented successful scanning. In Persson's (6) case, this was from a multi-centre research-only study for commissioning purposes, while Tenhunen (14) and Tyagi (17) experiences were from treating their first MR-only patients. Wyatt (20) reported MR scan success rates from retrospectively assessed MR data, while Christiansen (16) reported synthetic-CT generation success rate but did not discuss issues regarding MR acquisition. In describing their clinical workflow for MR-only planning, Tyagi (17) also reported a time saving when using an MR-only vs. CT-MR based workflow.

Persson (6), Christiansen (16), Tyagi (18), Kemppainen (19), Wyatt (20) and Maspero (21) reported validating the dosimetric accuracy of their respectively chosen synthetic-CT solution in a clinical environment, as required for commissioning MR-only planning.

2.4.2 MR distortion quantification and phantom development

The systematic review identified 13 studies investigating MR distortion quantification methods and/or phantom development (18, 19, 22-32). A key summary of study results can be found in Table 2-3.

Price (22), Huang (23), Walker (24), Sun (25) and Cunningham (26) developed phantoms for use in measuring geometric distortions or end-to-end testing the MR-only pathway. Huang (23), Price (22) and Walker (24) developed large field of view (FoV) phantoms for assessing system (Bo)

distortions and characterised their respective MR scanner distortions. Price (22) and Huang (23) assessed the set up reproducibility of their phantoms using CT scan testing methods while Walker (24) assessed the impact of a continuous moving-table acquisition method on measured distortions with 0, 1.1 and 2 mm/s table speeds.

Sun (25) and Cunningham (26) developed anthropomorphic pelvic shaped phantoms for measuring system and patient-induced susceptibility distortions and/or end-to-end testing of the MR-only pathway. Both phantom designs were based on prostate patient anatomical sizes. Sun's (25) phantom had 2 designs, for end-to-end testing or geometric distortion assessment respectively. Cunningham's (26) phantom was designed such that it could simulate patient bladder and rectal filling for end-to-end testing, including dosimetric verification of treatment plans.

Tyagi (18), Kemppainen (19), Gustafsson (27), Glide-Hurst (28) and Adjeiwaah (29) investigated the impact of MR scanner distortions on patient treatments by applying measured or simulated distortions to patient treatment plans. Kemppainen (19) and Gustafsson (27) measured system-induced geometric distortions using large FoV phantoms for 15 and 10 patients respectively. Tyagi (18), Kemppainen (19), and Glide-Hurst (28) measured patient-induced susceptibility geometric distortions for 20, 4 and 9 patients respectively with Glide-Hurst (28) assessing distortions for different patient bladder filling states and scanner magnet strengths. Adjeiwaah (29) assessed the impact of MRI scanner distortions, including measured Bo system distortions and simulated patient-induced susceptibility distortions, for 17 patients.

Wyatt (30) evaluated the repeatability and set-up sensitivity of the commercially available GRADE (Spectronics Medical AB, Helsingborg, Sweden), large FoV distortion phantom. The distortion measurement repeatability was assessed for inter- and intra-scanning session variability. The set-up sensitivity of the phantom was investigated by deliberately scanning the phantom with a 1 mm offset and 1 ° rotation and assessing distortion variations.

Torfeh (31) and Price (32) characterised their MR scanner system and gradient non-linearity distortions respectively over large FoVs as required for MR-only planning. Torfeh (31) assessed the impact of manufacturer 2D and 3D distortion correction algorithms on clinically used radiotherapy sequences. Price (32) characterised and minimised inherent 2D and 3D large FoV gradient nonlinearity distortions using post-processing techniques.

Author	Year	Phantom & software	Phantom Shape (cm x cm x cm)	MR Scanner & Magnet strength	Other key information
Price (32)	2015	Philips temporal GNL phantom In-house 3D distortion phantom, In-house software	2D: 36x43x2 3D: 46.5x35x16.8	Philips Panorama 1 T	1. Gradient nonlinearity distortions found to be stable over 6 month time period. 2. Vendor 3D distortion corrections maintained <1mm distortion up to 9.5cm from isocentre. 3. Post processing corrected distortions <1mm for large FoVs up to 25cm from isocentre. 4. Author notes significant inherent gradient nonlinearity distortions may be a specific feature of open bore MR scanners, rather than cylindrical scanners, due to shorter gradient coils.
Sun (25)	2015	Self-developed pelvic-shape phantoms & software	25x40x26	Siemens Skyra 3 T	1. Phantom internal details: spherical and cylindrical inserts representing prostate, rectum bladder and femoral heads based on average of 39 prostate patients or 11 plastic grid sheets. 2. Maximum distortion across phantom with 3D correction found to be 1.7mm (75% quartile 0.54mm). 3. Phantom end to end testing found mean dose difference of 1.1cGy between CT and MR.
Walker (24)	2015	Self-developed large FoV phantom & software	Max: 50x50x51.3	Siemens Skyra 3 T	1. Maximum 3D distortion correction distortion was 4.08mm for a 2mm spin echo (SE) sequence. 2. Within 152mm of isocentre for 2mm SE with 3D distortion correction, distortion was ≤2mm. 3. For the continuous moving-table mode, 1.1mm/s was found to have the least distortion with a maximum of 4.4mm and a distance of 140mm within which the distortion was less than 2mm.
Huang (23)	2016	Self-developed large FoV phantom & software	46.5x35x16.8	Siemens Skyra 3 T	1. Mean Bo distortion of <1mm found within a radius of 15cm from the isocentre.
Torfeh (31)	2016	GE Large FoV phantom and in-house software	50x50x50	GE MR-Sim 1.5 T	1. In-house software validated with a mean distortion error of 0.15mm. 2. Mean Bo distortion both in-plane and through plane found to be <2mm within a radius of 25cm when manufacturer 2D and 3D distortion applied as recommended. 3. Without distortion correction, the size of distortions made use for radiotherapy purposes unachievable.
Gustafsson (27)	2017	Spectronics Large FoV GRADE phantom &	50.2x40.4x53.4	GE Discovery 3 T	1. Mean and maximum distortions measured to be <0.5mm and <12.6mm respectively. 2. Maximum distortions measured were: 0.43mm at <100mm, 0.82mm at 100-150mm, 1.85mm at 150-200mm and 7.9 at 200-250mm, increasing with radial distance from isocentre.

		software			3. Structure deformation was minimal with mean magnitude 0.01mm for internal structures and <0.33mm for the full body contour. The mean percentage dose difference was +/-0.02%.
Kemppainen (19)	2017	Large FoV phantom & software – Unknown origin	Minimum: 37.5x 37.5x45.5	Philips Ingenia 1.5 T	1. Mean system distortion of <1mm measured within all PTVs with mean maximum distortion within patient body contours of <2mm. 2. Impact of geometric distortion on dose calculation accuracy found to be <0.2% for all PTVs, with mean patient-induced distortions were <1mm in all cases.
Price (22)	2017	Self-developed large FoV phantom in-house software	Max: 55x55x45	Philips Panorama 1 T Philips Ingenia 1.5 T Philips Ingenia 3 T	1. Phantom modular to allow variation in set up for different scanners. 2. Set-up reproducibility measured to be 0.1, 0 and -0.6mm respectively in X, Y and Z directions with negligible rotations. 3. Distortion <1mm within 100mm radially to isocentre.
Tyagi (18)	2017	X	X	Philips Ingenia 3 T	1. Mean patient-induced susceptibility geometric distortion of -0.07 (range -0.73 to -0.56) and -0.2mm (range: -0.62 to -0.35mm) within the outer body and prostate respectively.
Adjeiwaah (29)	2018	Spectronics phantom & software	35.1x47x45.1	GE Signa 3 T	1. For sequences of bandwidths of 122Hz, 244Hz and 388Hz, system distortions were <3.19mm, <2.52mm and <2.08mm within a radial distance of 25cm from the isocentre and the patient-induced distortions were <5.8mm, <2.9mm and <1.5mm respectively. 2. Dosimetric analysis found a mean dose difference of <0.5% was found between distorted and undistorted treatment plans. 3. Higher bandwidth sequences are recommended to minimise distortion effects.
Cunningham (26)	2018	Self-developed male pelvic-shape phantom	23x38.1x Unknown	Not applicable	1. External and internal organ shapes based on data from 19 prostate cancer patients. 2. Internal structure: pelvic bone anatomy, prostate, urethra, and fillable bladder and rectum. 3. Modular changes are possible to accommodate dosimetry inserts or organ changes. 4. Phantom able to accurately and reproducibly simulate rectum and bladder filling and to dosimetrically verify treatment plans, with an assessment plan found to have a dose difference of 1.5% between the calculated and measured doses.

Glide-Hurst (28)	2018	X	X	Philips Panorama 1 T Philips Achieva 1.5 T Philips Ingenia 3	1. Empty, partially full and full bladder states investigated over ~45 minute scanning session. 2. Patient-induced susceptibility distortions were small with <2% of prostate & seminal vesicles voxels distorted by >0.5mm and all bladder voxels distorted by <1mm. 3. A significant change in rectal gas seen to increase distortion.
Wyatt (30)	2018	Spectronics Large FoV GRADE phantom & software	50.2x40.4x53.4	Siemens Magnetom Espree 1.5 T Siemens Prisma 3 T GE Signa PET-MR 3 T	1. Bo distortion measurements for intra- and inter- scanning sessions were repeatable. 2. Mean range of measurement for all scanners and sequences less than 1mm, maximum ranges 2.9mm and 2.6mm for 1.5T and 3T scanners. 3. Phantom found to be relatively sensitive to large set up errors ~1mm translation or 1º rotation.

Table 2-3. Summary of the key results from the MR distortion quantification and phantom development studies.

2.4.3 Clinical validation of patient treatment positioning in an MR-only workflow

The systematic review identified 3 papers investigating the clinical validation of patient treatment positioning verification (18, 33, 34). A key summary of study results can be found in Table 2-4. These studies have been included because they are reporting patient treatment positioning verification results for previously reported MR-only treatment synthetic-CT models as part of clinical implementation.

Tyagi (18), Kemppainen (33) and Korhonen (34) evaluated the accuracy of synthetic-CTs as digitally reconstructed radiograph (DRRs) reference images for treatment positional verification using orthogonal planar images (Tyagi (18), Kemppainen (33) and Korhonen (34)) and/or cone-beam CT (CBCT) (Tyagi (18) and Korhonen (34)). Tyagi (18) and Kemppainen (33) investigated the Philips MRCAT synthetic-CT solution. Kemppainen's (33) DRR analysis included inter- and intra-observer variability, separating the variability into systematic and random error contributions and compared the total geometric accuracy to a reference of 2 mm error from CT to MR registration. Tyagi's (18) CBCT analysis was based on fiducial marker 3D CBCTs, where 5 CBCTs were included for registration per patient.

Korhonen's (34) DRR analysis included inter-observer variability and investigated the use of both the synthetic-CT and MR images as reference images for CBCT registration. CBCT registrations were undertaken using Elekta X-ray volume imaging (XVI) software (Elekta AB, Stockholm, Sweden) for 5 patients, for 10 CBCTs for each patient (50 CBCT registrations per reference modality).

Author	Year	sCT technique	No. of Patients	DRR/ CBCT	2D method	CBCT method	Inter/ Intra-observer	Other key information	
Korhonen (34)	2015	Korhonen (39)	DRR - 5, CBCT - 5	DRR & CBCT	Manual - bony registration	Automatic - bony & grey-value, 3D and 6D registration	DRR Inter-observer: 10	CBCT (max. diff.)	Grey value method Bone method
									sCT vs CT - 2mm (3D), and 1.7mm, 1.1° (6D) MR vs CT - 4mm (3D), and 3.5mm, 1.6° (6D) sCT vs CT - 1.6mm, and 1.3° (6D)
								DRR	Heterogeneous sCT vs CT - manual registration errors were highest in the PA direction with mean differences of -0.3 ±1m and 0.3 ±1.7mm for kV and MV acquired positional images respectively
Tyagi (18)	2017	Philips MR-CAT	DRR – 20, CBCT - 5	DRR & CBCT	Manual - fiducial marker registration	Manual - fiducial marker registration	X	CBCT (mean diff.)	sCT vs CT: <1±0.79mm, <1±0.89mm, <0.5±0.85mm for LR, AP and SI directions respectively.
								Other information	1. Individual registration differences were observed up to 2mm in some fractions with larger variations in prostate rotation.
								DRR (mean diff.)	sCT vs CT: 0.3mm, 0.3mm and 0.6mm in the lateral, vertical and longitudinal directions respectively.
Kemppainen (33)	2018	Philips MR-CAT	20	DRR	Manual - bony registration	X	Inter-observer: 5, Intra-observer: 3	DRR (mean diff.)	sCT vs CT: -0.5mm, +0.1mm and +0.1mm in the vertical, longitudinal and lateral directions
								Other information	1. Repeatability coefficients were 2.1mm vs 2.6mm, 1.4mm vs 2.1mm and 1.2mm vs 1.4mm in vertical, longitudinal and lateral directions between CT and sCT respectively. 2. Significant increase in intra-observer variability found for vertical, longitudinal and lateral directions, however magnitude was less than 0.5mm in all directions. 3. MRCAT has positive effect on total geometric accuracy compared to 2mm registration error of CT-MR pathway.

Table 2-4. Summary of the key results from the clinical validation of patient treatment positioning in MR-only workflow studies.

2.4.4 MR-only commissioning processes

The systematic review identified 6 papers investigating MR-only commissioning processes (15, 21, 35-38). A key summary of study results can be found in Table 2-5.

Kerkmeijer (15), Kapanen (35) and Kim (36) reported experiences related to commissioning an MR-only pathway. Kerkmeijer (15) and Kapanen (35) utilised their experiences of commissioning an MR-only pathway and an MR simulator respectively to present recommendations for clinically commissioning an MR-only pathway including proposing quality assurance testing and associated levels of acceptability with individual pathway components. Kim (36) used a failure mode and effects analysis methodology to systematically assess the risks, and their frequency, severity and detectability, of an MR-only planning pathway compared to CT-MR based pathway. This included mapping the respective elements required for a MR-only pathway, their risks and associated mitigation strategies.

Maspero (21) and Korsholm (37) reported synthetic-CT accuracy assessment methodologies. Maspero (21) quantified the confounding factors in MR-only dose calculation accuracy assessments for prostate cancer patients, including inter-scan differences (set-up and positioning differences, MR-related geometric inaccuracy and registration errors), synthetic-CT generation and electron density conversion errors. Korsholm (37) developed a statistical approach to evaluating the significance of errors introduced by MR-only planning compared to CT-based planning, with the criterion that 95% of patients should have an uncertainty in dose calculation within 2% of the CT dose for relevant structures.

Palmer (38) developed and validated a quality assurance procedure for assessing synthetic-CT clinical feasibility using kV-CBCT, where CBCT scans were used to recalculate the synthetic-CT treatment plan as a check of its dose calculation accuracy.

Author	Year	No. of Patients in study	Other key information
Kapanen (35)	2013	X	1. Proposed calibration and testing procedures for verification of the treatment isocentre position, geometric accuracy, and other basic QA with an ACR phantom.
Korsholm (37)	2014	21	1. A statistical model approach to assessing the accuracy of synthetic-CT calculation was utilised where the criteria of accuracy was considered to be 95% of patients having an uncertainty in dose calculation within the PTV within 2% of the CT dose.
Maspero (21)	2017	14	1. For electron density conversion, synthetic-CT generation and inter-scan difference, average dose difference in the CTV of: 0.7±0.2%, 0.16±0.13% and 0.01±0.35% and in the whole body of: 0.1±0.03%, -0.03±0.02% and 0±0.06% were found respectively.
Kerkmeijer (15)	2018	X	1. Recommended requirements for MRI-only radiotherapy clinical implementation including: geometric accuracy, treatment position MR acquisition, sCT generation, MRI-based OAR delineation and protocol optimisation and MRI-based treatment position verification.
Kim (36)	2018	X	1. Many processes and therefore failure modes are shared between CT-MR and MR-only workflows with the highest failure modes related to changes in target location due to internal anatomy changes, in these cases current mitigation processes were still valid. 2. The highest risk failure modes for the MR-only workflow alone related to the sCT generation process, including: inaccuracies in target delineation on MR images, insufficient management of patient- & system-level distortions, inaccurate bone volumes. 3. Mitigation strategies for failures include: sufficient staff training and a robust quality control/quality assurance programme.
Palmer (38)	2018	10	1. The CBCT system was stable over time in Hounsfield Units (HU) (standard deviation of <40HU) and the variation in HU between CT and CBCT was found to be minimal (<60HU). 2. A comparison of the dose distributions between sCT and CT compared to sCT and CBCT found mean dose differences for all metrics of ≤1%. 3. The CBCT system can be considered to be similar to a CT system and can be used as a clinically feasible QA procedure.

Table 2-5. Summary of the key results from the MR-only commissioning processes studies, where "No. patients in Study" refers to the total number of patients recruited for the MR-only investigations.

2.5 Discussion

A wide range of findings were reported within this systematic review and are discussed in further detail below. There are several key findings seen in the literature and these are highlighted here prior to being discussed in more detail below. These findings are: i) MR-only planning has been clinically implemented for prostate cancer treatments; ii) A substantial amount of work remains to translate MR-only planning into wide spread clinical implementation for all pelvic sites; iii) MR scanner distortions are no longer a barrier to MR-only planning; however they must be managed appropriately; iv) MR-only based patient positioning verification shows promise, however limited evidence is reported in the literature and further investigation is required; and v) a number of MR-only commissioning processes have been reported which can aid centres as they undertake local commissioning, however this needs to be formalised in guidance from national bodies.

As highlighted in four studies, prostate cancer patients were treated using an MR-only planning solution, showing that clinical implementation is achievable (14-17). It is interesting to note that all commissioning work identified in this review was also focussed on prostate treatments. This is a natural starting point for pelvic MR-only planning as other pelvic sites (rectum, bladder, anus, gynaecological) have a number of additional challenges associated with them including differences in male and female anatomy, significantly larger treatment volumes and non-fiducial marker based 3D imaging requirements which makes their implementation more complex. It is important to note that the majority of work discussed is translatable to other cancer sites; however it is clear that a significant amount of work remains to widen the implementation of MR-only planning to all pelvic cancer treatments.

This review identified 3 key areas which were investigated for clinical implementation purposes: MR acquisition and synthetic-CT generation verification; MR distortion quantification and phantom development; and clinical validation of patient treatment positioning in an MR-only workflow. In each, no major barriers to implementation were found while additionally a number of publications reported commissioning methodologies which will benefit the wider community by providing guidance for local centres to employ within their own MR-only clinical commissioning.

The first step to implementing a MR-only pathway is ensuring sufficient and suitable MR data acquisition is achieved. A high success rate of acquiring MRIs usable for synthetic-CT generation is key to the widespread implementation of MR-only techniques, as this will limit the need for additional CT scans. Persson (6), Tenhunen (14) and Tyagi (17) all described their success rates in prospective studies and categorised the identified issues related to scanning. As the scan success rates are similar (from 85-92%) this suggests that this is an achievable percentage in any centre, particularly as Persson's (6) study is a multi-centre study. The differences in success rate can be explained due the variations in study design. Persson's (6) exclusion criteria included patients with hip prostheses and operator error as valid reasons for an unsuccessful MRI scan while Tenhunen (14) and Tyagi (17) had no exclusion criteria. Wyatt (20) also analysed their successful scanning rate (54%), however their rate was severely impacted by a lack of scanning guidance for MR operators caused by the retrospective design of the study. However, it does still provide useful information regarding common issues with MR acquisition in this context. Centres should ensure that training from experienced personnel is provided for MR scan operators and consider methods to identify errors at the point of acquisition to ensure MR scan success. Tenhunen (14) and Tyagi (17) identified several patient and hardware/software related issues that also prevented successful MR-only planning and therefore required a percentage of patients to revert to a CT-MR based pathway. Although further development of MR-only solutions may lead to a reduction in patients requiring an additional CT scan, provision should still be made for CT-based planning to occur. In addition, these studies do not discuss patients who have contra-indications to MRI and therefore will always require a CT-only pathway.

Christiansen (16), did not report MR-acquisition success, but described their synthetic-CT generation failure rate, finding that 3% (1 of 30) synthetic-CT's failed to generate using the Philips MRCAT solution. This was considered to be due to the software's "sanity" check ability to prevent obviously erroneous synthetic-CT generation, although the exact cause was not established. This highlights that synthetic-CT generation methods require input data to follow clearly defined criteria to be successful, and it's a beneficial feature that the Philips MRCAT safe-guards against inappropriate data defined as including; large patient sizes, large disease sites (300mm or greater scan lengths) and hip prosthesis (17, 19). It is of note that Tyagi (17) didn't have any similar issues. This could have been due to a systematic difference in pathway, for example Tyagi's use of a specific mold for each patient to achieve a more robust patient position, or a non-systematic,

patient-specific, issue. This is another example of the variety of errors associated with an MR-only planning pathway that require careful assessment.

For acquired MR data to be clinical usable, its dosimetric accuracy needs to be robustly quantified as within acceptable limits. Dosimetric accuracy of prostate synthetic-CT solutions was investigated by the majority of studies and considered to be clinically acceptable in all cases. (6, 16, 18-21). The similar results of these studies, despite significant differences in study design including various synthetic-CT generation methods, shows that the dosimetric accuracy of synthetic-CT techniques is broadly reproducible across a wide range of clinical systems and techniques, including multiple commercial options available for prostates (10, 11). The presented studies also provide a suitable blueprint for centres wishing to begin clinical implementation of MR-only planning themselves regarding dosimetric accuracy assessment. These studies progress by firstly assessing dosimetric accuracy through research-only studies, followed by end-to end pathway testing and eventual implementation only when the local results provided sufficient confidence that the MR-only planning was sufficiently dosimetrically accurate to be used without CT for assurance.

In addition to dosimetric accuracy, another key criterion of useable MR data for MR-only treatment planning is that it is geometrically accurate. To be sufficiently confident of this for clinical implementation requires robust quality assurance techniques and phantoms as well as the characterisation of the MR image distortions. The reported studies focussed on designing suitable phantoms for either measuring geometric distortions or end-to-end testing the MR-only pathway (22-26), the quantification of distortions on patient data (18, 19, 27-29), or the reproducibility of distortion measurements (30) and provide information to aid distortion commissioning for an MR-only pathway.

Distortions within 1 T (22, 28, 32), 1.5 T (19, 22, 28, 30, 31) and 3 T scanners (18, 22-25, 27, 28, 30), from a range of manufacturers including Siemens (23-25, 30), Philips (18, 19, 22, 28, 32) and GE (27, 31), were measured within a satisfactory range for MR-only planning, considered to be 2mm (8). Unlike the other presented studies, Wyatt (30) and Price (32) suggested that the majority of distortions measured as part of their studies were larger than clinically acceptable for MR-only planning. However, both authors noted that their MR sequences were not optimised for clinical use as their acquired sequence bandwidths were insufficient to reduce distortion to within acceptable levels, where a minimum suitable bandwidth is considered to be 220Hz/pixel at 1.5T

and 440Hz/pixel at 3T. This is a timely reminder that scanners and clinically used scans require distortion characterisation to ensure they are suitable for use.

It is important that distortions are placed in context by evaluating their impact on patient treatments. A number of studies did this by assessing the impact of different distortions when applied to patient treatment plans with Kemppainen (19) and Gustafsson (27) assessing system distortions, Tyagi (18), Kemppainen (19) and Glide-Hurst (28) assessing patient-induced susceptibility distortions and Adjeiwaah (29) assessing both system and patient-induced susceptibility distortions. These results broadly showed that these distortions can be considered to have negligible impact on the patient plan, although their assessment and subsequent protocol optimisation is vital. Particularly this is true when regarding patient-induced distortions, as they cannot be corrected systematically as they vary between patients, however these studies give confidence that their impact can be quantified and/or negated for a range of scanners and magnet strengths. Similar investigations should form part of any centre's clinical implementation of MR-only planning to allow local distortion effects to be quantified and assessed as clinically significant or not. It is noted these studies were undertaken with low patient numbers (20 or less) and in none of the studies were distortions correlated with patient size. Because distortions increase with distance from the isocentre, their impact will increase with patient size. Without information relating to patient sizes therefore, it is not possible to assess whether the true impact of distortions on larger patients has been quantified. Potentially of more value to a commissioning centre would be to select a large range of patient sizes and quantify the impact of distortion as a function of patient size rather than attempt to establish the "average" patient size.

It is also to the wider radiotherapy community's benefit that self-developed phantom designs are detailed in the literature (22-26), which allows centres to replicate these phantoms. It was noticeable that for pelvic MR-only large FoV distortion measurements, these studies only used two commercially available phantoms, the Spectronics Medical's GRADE (27, 30) and GE's large FoV phantoms (31), with the remaining studies developing their own phantoms (22-26). However, it should be noted there are several other commercially available phantoms that have not been reported here including the Quasar MRID 3D, CIRS large FoV, Phantomlab MagPhan RT and Philips MRI distortion phantoms. It is possible that the use of these phantoms isn't reflected in this systematic review due to the search criteria focussing on MR-only clinical implementation

pathways, rather than CT-MR pathways. As such further comment on their potential benefit in this context is not possible.

Sun (25) and Cunningham's (26) anthropomorphic phantoms are a beneficial development in phantom design as they allow quantitative end-to-end testing, including dose measurements within the phantoms. Of interest is Cunningham's (26) phantom's ability to model physiologic changes in the bladder and rectum which will improve the commissioning process by allowing the impact of patient anatomical changes to be assessed in a quantitative and reproducible manner. Further development of anthropomorphic phantoms may increase their use in the quality assurance of MR-only planning as it develops as a clinical technique.

For MR-only planning to be implemented, MR data is required to be used for patient position verification purposes prior to treatment. Publications relating to its assessment as part of clinical implementation were limited however, with only Tyagi (18), Kemppainen (33) and Korhonen (34) assessing prostate patient treatment positioning accuracy. All three studies assessed digitally reconstructed radiograph (DRR) positioning with results showing broad agreement between the use of planning CT and synthetic-CT generated DRRs, providing confidence that synthetic-CT generated DRRs can produce clinically acceptable results. Korhonen (34) and Kemppainen (33) also investigated inter- and/or intra- observer variability for DRR registrations and found it to be clinically insignificant.

3D CBCT based patient treatment positioning was investigated using a manual fiducial marker registration (18) and the automatic bone and grey-value registration methods of Elekta's XVI system (34). It was shown that synthetic-CT to CBCT registrations were comparable to planning CT to CBCT registrations (mean differences <1mm) indicating that synthetic-CT datasets can replace CT datasets, for manual or automatic registrations, for patient treatment positioning. Tyagi (18) also noted that, anecdotally, clinicians were happy with the delineations of bladder and rectum on the synthetic-CT. It is interesting that the sCT to CT results varied between Korhonen (34) and Tyagi (18). This could be influenced by a number of factors, including: the difference in matching technique (automatic vs manual) or the inclusion of a patient mold within Tyagi's study to improve setup reproducibility.

MR to CBCT registrations were also assessed by Korhonen (34) but did not replicate the same level of similarity to planning CT to CBCT registrations as synthetic-CT to CBCT registrations. This is understandable as XVI uses a chamfer matching algorithm and is optimised for registering datasets

of the same modality, i.e. CT to CBCT and registrations may improve if more suitable mutual information algorithms were used. It's an indicator that CT images cannot be simply replaced with MR images and that further commercial support and investment in this field is required. In addition, it's important to note that although differences are seen between CT and MR registrations, from the data shown, neither CT nor MR can be determined as more accurate as there is no ground truth to compare to. It can only be determined that the registrations produce different results. To resolve which modality is more accurate, manual landmark evaluation can be used for an initial comparison, while a future potential solution would be to utilise an anthropomorphic phantom which could provide the required ground truth information. It can be hypothesised that it would be best to register MR to CBCT, rather than synthetic-CT to CBCT, as this would mean real, rather than synthesised, data was being used, theoretically improving the registration accuracy. These findings suggest that MR-only pathways exist which allow reproducible patient positioning verification to be carried out and these studies provide a suitable methodology for a centre looking to implement MR-only planning with respect to assessing patient treatment positioning accuracy and reproducibility.

A wide variety of processes and experiences relating to commissioning an MR-only pathway were reported for prostate treatments. Kerkmeijer's (15) and Kapanen's (35) experiences in terms of workflow, equipment and commissioning requirements provide substantial amounts of information which is particularly beneficial because these processes, within this early-phase of clinical implementation, are not well established. It is a challenging process to determine the commissioning and routine workflow to ensure the optimal performance and the highest quality of patient care and therefore more publications detailing individual centre's experiences, such as these, would be welcome until this technique is more firmly embedded in routine clinical practice or guidance documents are published. The information provided within Kim's publication (36) provides useful tools for identifying risks and highlighted many risks which will be shared between all MR-only pathways as well as also suggesting mitigation strategies to lessen their impact. That the greatest source of risk is the synthetic-CT generation process is not a surprising result; however the strength of this methodology is that it provides an overall framework for assessing, comparing and minimising risks. This allows the user to have confidence that their MR-only pathway is optimised to protect from errors as much as is reasonably practicable. In addition, as a process, it can be repeated over time to continually re-assess and fine-tune the pathway and is

also applicable to any future MR-only treatment sites in addition to prostate cancer which was presented here.

The quantification of the accuracy of a centre's local synthetic-CT generation technique is a key stage of commissioning an MR-only pathway and the studies by Maspero (21) and Korsholm (37) provide differing methods of undertaking this. It is interesting to see that Maspero (21) found that electron density conversion (from CT scan generated Hounsfield units to electron density via an electron density plotted curve) was the greatest confounding factor, followed by synthetic-CT generation (the assigning of Hounsfield units to MR scan voxels to produce the synthetic-CT). Inter-scan differences (set-up and positioning differences between CT & MR scans, MR geometric inaccuracy and CT-MR registration errors as required for comparison) produced almost a negligible difference in result. This suggests that the commissioning process should also focus on appropriate electron density curve calibration as a key part of the commissioning process.

Palmer's (38) presentation of a method of validating synthetic-CT generations using collected patient CBCT data provides a tool by which commissioning centres can ensure further confidence over the accuracy of their treatment planning pathway. As previously discussed by Kim (36), the generation of synthetic-CTs is a major risk in the MR-only pathway, the challenge of ensuring robust patient treatment on an individual basis is non-trivial. Palmer's method would directly allow a gross error check on the treatment plan which could highlight potential issues at the beginning of a patient's treatment. Palmer (38) noted however that further analysis of this technique would be beneficial as only simple errors were assessed within the validation presented and as a consequence its sensitivity to less noticeable errors is uncertain.

The studies identified here are a significant step towards widespread pelvic MR-only clinical implementation. However, there are several areas where further attention is required. As discussed previously, the translation of this technique to other clinical pelvic sites is a significant challenge which should not be underestimated. Several studies reported issues associated with processing data within MR-only pathways. This may be due to a lack of support for the MR-only workflow by radiotherapy vendors and clinical treatment planning software and further collaboration, investment or support from commercial companies would be beneficial. Unseen in the literature was a long timescale (≥1 year) Bo distortion evaluation study focussing on its impact on an MR-only pathway. Long timescale changes in Bo distortion could have a significant impact on resultant MR image geometric accuracy which would require correction to prevent the

translation of errors into the planning process. Such a study would demonstrate the reliability and reproducibility of scanner Bo distortion over time and therefore provide evidence for distortion quality assurance frequency recommendations. Patient treatment positioning verification within clinical implementation was only addressed in three studies, and while the results presented were encouraging and suggested that MR-only techniques can accurately be used for patient treatment positioning, there is plenty of evidence yet to gather. All these studies involved small cohorts of patients and used the synthetic-CT generation method of the Philips prostate MRCAT (11) or similar (39) which are not comparable to all methods of synthetic-CT generation. In addition, the majority of results were collected with manual registration techniques, whereas it is common in the clinic to use a manufacturer's automated or semi-automated technique and the impact of different clinical equipment and techniques, in larger patient cohorts, needs to be more widely investigated.

Despite the variety of publications related to MR-only commissioning and individual centres experiences, the radiotherapy community is so varied in term of equipment, resources and technique that there is significant scope for further experiences to be reported in the literature and consensus guidelines to be produced by early adopters and national bodies. There is also a substantial need for more studies to begin providing evidence of the benefit of using MR-only planning, for example that it has improved patient outcomes, or treatment pathway improvements.

2.6 Conclusion

MR-only planning has been clinically implemented for prostate treatments, however further research is required to develop MR-only planning for other pelvic sites. Particularly the accuracy of synthetic-CT generation models for female anatomy requires further reporting within the literature. MR scanner distortions are no longer a barrier to MR-only planning, although they must be appropriately managed, while MR data acquisition and synthetic-CT generation for prostate treatments have been shown to be sufficiently accurate for clinical use. The clinical implementation of MR-only patient treatment positioning verification remains under reported in the literature and requires substantial investigation to allow its widespread use. The range of

investigations reported here are a suitable starting point for radiotherapy centres aiming to clinically implement MR-only planning, however further evidence and regulation is required, including the publication of consensus guidelines from early adopters and/or governing bodies.

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2.8 Supplementary information

Search terms

The search criteria used for identifying papers for the review from the Medline, Embase, Scopus, Science Direct, CINAHL and Web of Science databases are as below.

Ovid Medline and Embase

1. exp Magnetic resonance imaging/

2. exp Radiotherapy/

3. (magnetic adj3 (only OR alone)).tw

4. (MR* adj1 (only OR alone)).tw

5. ((pseudo* OR synth* OR sub*) adj1 (CT OR comp*)).tw

6. 3 or 4 or 5

7. 1 and 2

8. 6 and 7

9. (radiother* or radi* therapy).tw

10. (treat* adj3 plan*).tw

11. 9 or 10

12. 6 or 11

13. (MR or MRI or Mag* res* im*).tw

14. 12 and 13

15 8 or 14

Scopus

1. (MR or MRI or (Magnetic resonance imaging)) pre/1 (only or alone)

2. (pseudo OR synthetic OR substitute) pre/1 (CT OR (computed tomography))

3. #1 or #2

4. Radiotherapy or (radiation pre/1 therapy)

5. #3 and #4

Science direct

1. (((MR or MRI or “Magnetic resonance imaging”) and (only OR alone)) OR ((pseudo OR synthetic OR substitute) and (CT OR “computed tomography”))) AND (radiotherapy OR “radiation therapy”)

Cinahl

1. (MR or MRI or (Magnetic resonance imaging)) W1 (only or alone)

2. (pseudo OR synthetic OR substitute)

3. (CT OR (computed tomography))

4. 2 and 3

5. 1 or 4

6. Radiotherapy or (radiation W1 therapy)

7. 5 and 6

Web of science

1. TS=((MR or MRI or ("Magnetic resonance imaging")) Near/1 (only or alone))
2. TS=((pseudo OR synthetic OR substitute) near/1 (CT OR ("computed tomography")))
3. 1 or 2
4. TS=(radiotherapy or (radiation AND therapy))
5. 3 and 4

2.9 Additional information

2.9.1 Methodology update

Further information regarding the systematic review methodology is as follows:

- The search was not restricted to English language papers only, however all search terms were in English so it is likely that non-English language papers would not have been identified.
- Screening and data extraction was undertaken by David Bird. All extraction and screening was undertaken as a single assessment with no repeat assessments by multiple observers.
- No risk of bias assessment was undertaken. Here a broader review of the information contained within each study was included, and as such including detailed information of the bias of each included paper was outside the scope of this study.

2.9.2 Systematic review update January 2019- April 2021

2.9.2.1 Findings

On 13th April 2021, the systematic review literature search was updated to include studies from 2019-current. Seventeen additional papers were identified which met the inclusion criteria as defined in chapter 2. Four studies investigated synthetic-CT dosimetric validation (1–4), three studies investigated MRI distortion quantification and phantom development (5–7), three investigated the clinical validation of patient treatment positioning in an MRI-only workflow (1,8,9) and eight investigated MRI-only commissioning processes (10–17). These studies predominantly focussed on prostate cancer MRI-only treatments and enhanced the knowledge of the clinical implementation of pelvic MRI-only planning in the literature. However, these studies did not change the key conclusions of the systematic review.

Kemppainen (1), Bratova (2) and Yu (4) presented studies which quantified the accuracy of the Philips MRCAT synthetic-CT solution for prostate, rectum and gynaecological cancer treatments, while Wyatt (3) investigated the use of the Spectronics Medical MRIPlanner synthetic-CT solution

for prostate cancer treatments with artificial hips. The findings of Kemppainen and Yu (1,4) are directly applicable to the work presented here in Chapter 3 as they included the assessment of the synthetic-CT accuracy of 15 and 43 rectal cancer patients respectively. Interesting both studies found the MRCAT solution had a mean PTV D95 dosimetric difference between sCT and CT of approximately 1% across the whole cohort, which is clinically acceptable but worse than our mean PTV D95% dose difference of 0.1%.

Rostami (7) evaluated a new large field of view phantom for geometric distortion assessment, Singhrao (6) presented a new anthropomorphic phantom capable of providing tissue-like image contrast on CT and MRI while Heikkinen (5) evaluated the long-term geometric accuracy stability of multiple MRI scanners.

Kemppainen (1), Brooks (8) and Kan (9) assessed the accuracy of CBCT soft tissue registrations using sCT (Kemppainen and Kan) and MRI (Brooks) as reference images, however no assessment was undertaken for anal or rectal cancers and so the relevance of these studies to the work presented in Chapter 4 is limited.

Hunter (12), Tyagi (13) and Ambolt (14) presented clinical experiences of large cohort studies which demonstrating the feasibility of the implementation of MRI-only planning for prostate treatments. Nejad-Davarani (10) assessed the uncertainties related to introducing MRI-only planning for prostate treatments, while Choi (11) and Walker (17) assessed the use of first fraction CBCT images as a patient specific sCT dosimetric accuracy quality assurance measure. Ilamurugu (15) quantified the registration errors associated with CT-MRI vs. MRI-only pathways for prostate treatments, while Bernstein (16) quantified the potential changes in PTV margins when utilising MRI-only vs. CT-MRI for recurrent gynaecological cancer treatments.

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Chapter 3 Multicentre, deep learning, synthetic-CT generation for ano-rectal MR-only radiotherapy treatment planning

3.1 Abstract

Background and purpose*:* Comprehensive dosimetric analysis is required prior to the clinical implementation of pelvic MR-only sites, other than prostate, due to the limited number of site specific synthetic-CT (sCT) dosimetric assessments in the literature. This study aims to provide a comprehensive assessment of a deep learning-based, conditional generative adversarial network (cGAN) model for a large ano-rectal cancer cohort. The following challenges were investigated; T2-SPACE MR sequences, patient data from multiple centres and the impact of sex and cancer site on sCT quality.

Method: RT treatment position CT and T2-SPACE MR scans, from two centres, were collected for 90 ano-rectal patients. A cGAN model trained using a focal loss function, was trained and tested on 46 and 44 CT-MR ano-rectal datasets, paired using deformable registration, respectively. VMAT plans were created on CT and recalculated on sCT. Dose differences and gamma indices assessed sCT dosimetric accuracy. A linear mixed effect (LME) model assessed the impact of centre, sex and cancer site.

Results: A mean PTV D95 % dose difference of 0.1 % (range: -0.5 % to 0.7 %) was found between CT and sCT. All gamma index (1 %/1 mm threshold) measurements were >99.0 %. The LME model found the impact of modality, cancer site, sex and centre was clinically insignificant (effect ranges: -0.4 % and 0.3 %). The mean dose difference for all OAR constraints was 0.1 %.

Conclusion: Focal loss cGAN models using T2-SPACE MR sequences from multiple centres can produce generalisable, dosimetrically accurate sCTs for ano-rectal cancers.

3.2 Introduction

The potential benefits of magnetic resonance (MR)-only radiotherapy treatment planning have been well documented, as has the need to generate synthetic-CT (sCT) datasets to allow treatment dose to be calculated (1,2). Commercial sCT solutions are available; however a recent systematic review found that comprehensive dosimetric analysis is required prior to the clinical implementation of pelvic MR-only sites, other than prostate, due to the limited number of site specific synthetic-CT dosimetric assessments in the literature (3).

For pelvic MR-only sites, rectum and anus cancer sites have increased complexity compared to prostate treatments as they include male and female anatomy, greater tumour position variation and larger treatment volumes. To our knowledge, no studies have assessed sCT dosimetric accuracy for anus treatments, while a small number of studies have assessed rectum sCTs using a mix of research and commercially available sCT solutions (4–9). All dosimetric results were found to be clinically acceptable, however these studies only assessed small, <12 (6–9), or medium, 15-20 (4,5), patient numbers and small numbers of female patients (range 0-9).

The majority of pelvic sCT methods, including commercial products such as the Philips (Philips Healthcare, Ohio, USA) MRCAT (10), use a T1 Dixon MR sequence as it provides good fat-muscle-bone contrast and all previously reported rectum sCT studies used this sequence. However because T2 sequences are optimal for ano-rectal GTV delineation (11–13), for a T1 Dixon sCT generation solution to be used clinically, a T2 sequence must also be acquired. Requiring a second sequence reduces scanning efficiency and can reduce the treatment accuracy by introducing inter-scan changes including; motion, anatomical changes and registration errors to the pathway. Ideally a single T2 sequence would be used for pelvic sCT generation and target volume and organ delineation, such as the T2-SPACE (Sampling Perfection with Application optimised Contrasts using different flip angle Evolution) sequence which is used within the Spectronic Medical AB (Helsingborg, Sweden) commercial prostate solution (14). Additionally, only one of these rectal sCT studies, Maspero (6), applies a deep learning approach to sCT generation which are hypothesised to provide more image contrast and detail within the sCT (15–17).

Here, we comprehensively assess a conditional generative adversarial network (cGAN) sCT model, with a focal loss function designed to enhance performance in the hard to predict bone region. Absolute and dosimetric performance of this cGAN sCT model is quantified for a large ano-rectal

cohort, to give confidence that ano-rectal sCT generation can be successful and is viable for clinical use, where clinical acceptability is considered to be a dosimetric difference of ±2% (18). This work addresses a number of challenges to sCT generation including; the use of a routine T2-SPACE MR sequence for sCT generation, the utilisation of patient data from multiple centres and the impact of male vs. female anatomy and of cancer site, anal vs. rectal, on the sCT output, whilst simultaneously addressing the persistent issue of poor cortical bone density estimation.

3.3 Method

3.3.1 Data acquisition

This study is part of a wider MR-only radiotherapy study: "Mri-only treAtmeNT planning for Anal and Rectal cAncer radiotherapY" (MANTA-RAY), research ethics committee (REC) reference: 18/LO/1298, ISRCTN Registry: ISRCTN82734641. Paired CT and MR datasets were collected from 90 ano-rectal patients (73 rectum, 17 anus and 54 male, 36 female) from two centres (37 from centre A, 53 from centre B) who were due to undergo radical VMAT external beam radiotherapy and had no contraindications to MRI. Exclusion criteria included patients with artificial hips, and contra-indications to MRI, and as a consequence 2 additional patients who had received MRIs were excluded from this study. Both scans were acquired in the radiotherapy treatment position with matched bladder filling and immobilisation. T2-SPACE MR scan acquisition time varied with scan length with a mean of 5 minutes 20 seconds per acquisition.

Radiotherapy planning CT scans and T2-SPACE MR scans were acquired at both centres with the parameters shown in Table 3-1. The mean time between CT and MR data acquisition was 7.9 days (range: 0 to 43 days) for all patients, 0.5 days (range: 0 to 1 days) for NCCC patients and 15.1 days (range: 0 to 43 days) for LCC patients. MR scans were scheduled for a time when the patient had a clinical appointment prior to or during their first two weeks of treatment.

Clinical target volumes and organs at risk (OARs) (rectum; bladder and bowel cavity, anus; small bowel, bladder, femoral heads and genitalia) were delineated on the CT as per our centre's standard treatment protocol for each patient's routine treatment prior to being utilised for this study.

		Centre A	Centre B
MR	Make & Model	Siemens Espree 1.5 T	Siemens Aera 1.5 T
	Sequence	3D	3D
	Resolution	1.4x1.4x1.5 mm	0.9 x0.9 x1.5 mm
	Refocusing Flip Angle (°)	160	160
	TR (ms)	1500	1600
	TE (ms)	211	211
	Bandwidth (Hz/px)	600	545
	Echo train length	105	134
	Field of View (Superior-Inferior)	216 mm	Inferior: 2 cm inferior of genitalia Superior: superior aspect of L5 vertebra or greater as required
	Field of View (Axial)	450x450 mm^2	450x450 mm^2
CT	Make & Model	Siemens Sensation Open	Philips Brilliance Big Bore
	Resolution	1.1x1.1x3 mm	1.2x1.2x2 mm
	kVp (kV)	120	120
	X-ray Tube Current (mAs)	122	135

Table 3-1. The MR and CT scan parameters for Centre A and centre B.

3.3.2 sCT model and pre-processing

The paired CT-MR datasets of 46 rectum patients were used to train the sCT model, 22 from centre A, 24 from centre B and 32 male, 14 female. The data was pre-processed by registering the MR to CT with a deformable registration, using patient external and bladder structures as "controlling ROIs", before being resampled to the CT frame of reference in Raystation 8b

(RaySearch Laboratories, Stockholm, Sweden). All CT & MR voxels outside the patient external contour were set to an intensity of -1024 and 0 respectively, using the patient external contour generated on each individual dataset. Only image slices with both CT and MR data were used to ensure the data was accurately paired. No gas within the patient external was masked on CT or MR in the training cohort.

The cGAN used a novel focal loss function and was trained for 170 epochs on a Tesla K-80 (Nvidia, California, USA) GPU including the use of augmentation. A fuller description of the cGAN model and rationale for its use can be seen in section 3.6 Supplementary information.

3.3.3 Test data

CT and MR data for 44 patients; 15 rectum from centre A (7 male, 8 female), 17 anus (9 male, 8 female) and 12 rectum (6 male, 6 female) from centre B, were used as test data. Test MR datasets were registered to the CT and masked using the same process as for the training data. Deformable registration was chosen for the test data as it removed the majority of inter-scan patient position differences between the CT and MR scans. The sCT data (DIR sCT) were generated using the model described above in section 3.2.2.

The DIR sCTs were imported into Raystation 8b and were rigidly registered to the CT. New patient external contours were generated for each sCT, all other target volumes and OARs were copied from the CT to the sCT, and as such they were identical on each dataset, using the standard tool within Raystation 8b. All bowel gas was masked for CT and sCT datasets at a threshold of -200 HU and set to water density (1 g/cm^3) to ensure consistency with the methodology of previous rectal sCT studies (4–6).

A second testing dataset was generated, where the MR data was registered rigidly, rather than using deformable registration as previously, to the CT data prior to sCT generation (RIR sCT). Masking was carried out using the rigidly registered MR patient external. Analysis was carried out on both datasets.

3.3.4 Assessing sCT quality

3.3.4.1 HU analysis

Hounsfield Unit (HU) accuracy was determined by computing the mean absolute error (MAE) and mean error (ME) in the (overlap) patient external volume and also in a region thresholded to > 150 HU on each CT dataset to represent bony anatomy. Thirteen patients with bowel CT contrast or metal implants of any type were excluded from this specific analysis.

3.3.4.2 Plan generation & dosimetric analysis

VMAT plans, following departmental clinical protocols, were created and optimised for each patient's CT scan, clinical treatment target volumes and OARs, in Raystation 8b, using the collapsed cone photon algorithm on a dose grid of 3x3x3 mm^3. Rectum plans were prescribed as either 45 Gy in 25 fractions or 25 Gy in 5 fractions to the PTV chosen according to their clinical treatment. Anus plans used a simultaneous integrated boost technique with 53.2 Gy and 40 Gy in 28 fractions prescribed to the primary and elective PTVs respectively. Each CT plan was subsequently recalculated, without reoptimisation, on the sCT.

Dosimetric differences between doses calculated on the CTs and sCTs were assessed through primary PTV dose statistics, D95%, D50% and D2%, for each plan. Global dose gamma index calculations between the CT and sCT were also performed for 3%/3 mm, 2%/2 mm and 1%/1 mm thresholds. The gamma indices were calculated using a region of interest defined as voxels within a dose threshold of 20% of the target prescription dose. For anus treatments, where an elective nodal PTV (PTVE) was also present and prescribed 40Gy, the PTVE D95% differences were also assessed as a further measure of accuracy.

OAR dose statistics were assessed for the 29 patients from centre B to establish the dosimetric accuracy of treatment plan calculations away from the primary PTV. Only patients from centre B were assessed as this ensured consistency in the approach, including scan field of view being sufficient for all OARs, and all OAR contours being delineated using the same clinical protocol. Assessed OARs were bladder and bowel cavity for rectum plans and bladder, small bowel, femoral

heads and genitalia for anus plans. The clinical protocol OAR constraint statistics were collected for CT and DIR sCT plans, the absolute differences were calculated between CT and sCT and compared as a percentage of the constraint tolerance level.

3.3.5 Statistical analysis

A linear mixed effect (LME) model was utilised to quantify the statistical significance of dosimetric differences and constrain the effect within 95% confidence intervals between modalities, CT and sCT. The model also allowed the quantification of dosimetric differences of secondary variables within the dataset including; treating centre, patient sex and cancer site. The LME model used: dose (normalised by prescription dose) as the dependant variable; modality, sex, treating centre, cancer site and dose statistic (D95 %, D50 %, D2 %) as fixed variables; and patient as a random variable.

3.3.6 Results

Figure 3-1 shows matched T2-SPACE MR (left), CT (middle) and sCT (right) slices from an anal cancer patient, where the CT and MR have been deformably registered prior to sCT generation.For DIR sCTs, mean ME of 0.4 (range: -7.8 to 12.4) HU was observed across the analysed cohort, with mean MAE of 35.1 (range: 27.2 to 40.3) HU. Bone showed a mean ME of -95.5 (range: -290 to -0.6) HU. For RIR sCT, mean MAE, ME, Bone MAE and Bone ME were 44.5, 0.8, 250.2 and -142.1 HU respectively.

Dosimetric DIR sCT results are shown in Table 3-2 and Figure 3-2. All dose differences were found to be less than ±0.8 % (Figure 3-2). All gamma indices at 1 %/1 mm were greater than 99.0 %. For anus treatments the mean dose difference for PTVE D95 % was 0.1 % (SD: 0.1 %, range: -0.1 % to 0.3 %). OAR dosimetric differences (Table 3-3) were found to be small with a mean difference of 0.1 %, (S.D: 0.6 %) of the constraint tolerances over all organ measures. The Rigid sCT mean dose

difference was similar to the DIR sCT mean dose difference (-0.1 % vs. 0.1 %), however considerably more variability was seen for Rigid sCTs.

	Number of Patients	Dose constraint	Dose difference (%) mean (S.D) [range]	Gamma Index - mean (S.D) [range] 3%/3 mm	2%/2 mm	1%/1 mm
All	44	D95 %	0.1 (0.2) [-0.5 to 0.7]	100 (0.1) [99.8 to 100]	99.8 (0.1) [99.3 to 100]	99.5 (0.2) [99.0 to 100]
		D50 %	0.1 (0.3) [-0.6 to 0.6]			
		D2 %	0.1 (0.3) [-0.6 to 0.7]			
Rectum	27	D95 %	0.1 (0.3) [-0.5 to 0.7]	100 (0.0) [99.8 to 100]	99.8 (0.1) [99.5 to 100]	99.5 (0.2) [99.0 to 100]
		D50 %	0.1 (0.3) [-0.6 to 0.6]			
		D2 %	0.1 (0.3) [-0.6 to 0.6]			
Anus	17	D95 %	0.1 (0.2) [-0.2 to 0.5]	99.9 (0.1) [99.8 to 100]	99.7 (0.2) [99.3 to 100]	99.4 (0.2) [99.0 to 99.9]
		D50 %	0.2 (0.2) [-0.2 to 0.5]			
		D2 %	0.1 (0.2) [-0.2 to 0.5]			
Male	22	D95 %	0.1 (0.2) [-0.2 to 0.5]	99.9 (0.1) [99.8 to 100]	99.8 (0.1) [99.5 to 100]	99.5 (0.2) [99.1 to 99.8]
		D50 %	0.1 (0.2) [-0.2 to 0.5]			
		D2 %	0.1 (0.2) [-0.2 to 0.4]			
Female	22	D95 %	0.1 (0.3) [-0.5 to 0.7]	100 (0.0) [99.8 to 100]	99.8 (0.2) [99.3 to 100]	99.4 (0.3) [99.0 to 100]
		D50 %	0.1 (0.3) [-0.6 to 0.6]			
		D2 %	0.1 (0.4) [-0.6 to 0.7]			

Table 3-2. DIR test data dose differences and gamma indices for DIR sCTs vs. CTs for all patients and sub-categories; cancer site and sex where dose differences are calculated as a percentage of the prescription dose.

The LME model found a 95 % confidence interval range in dose difference of 0.0 % to 0.2 % between CT and DIR sCT (Table 3-4). No significant differences in dose were found between treating centre, cancer site; anal or rectal, or sex, with the maximum effect sizes within 95 % confidence intervals showing no clinically significant differences (considered to be <±2 %) (18).

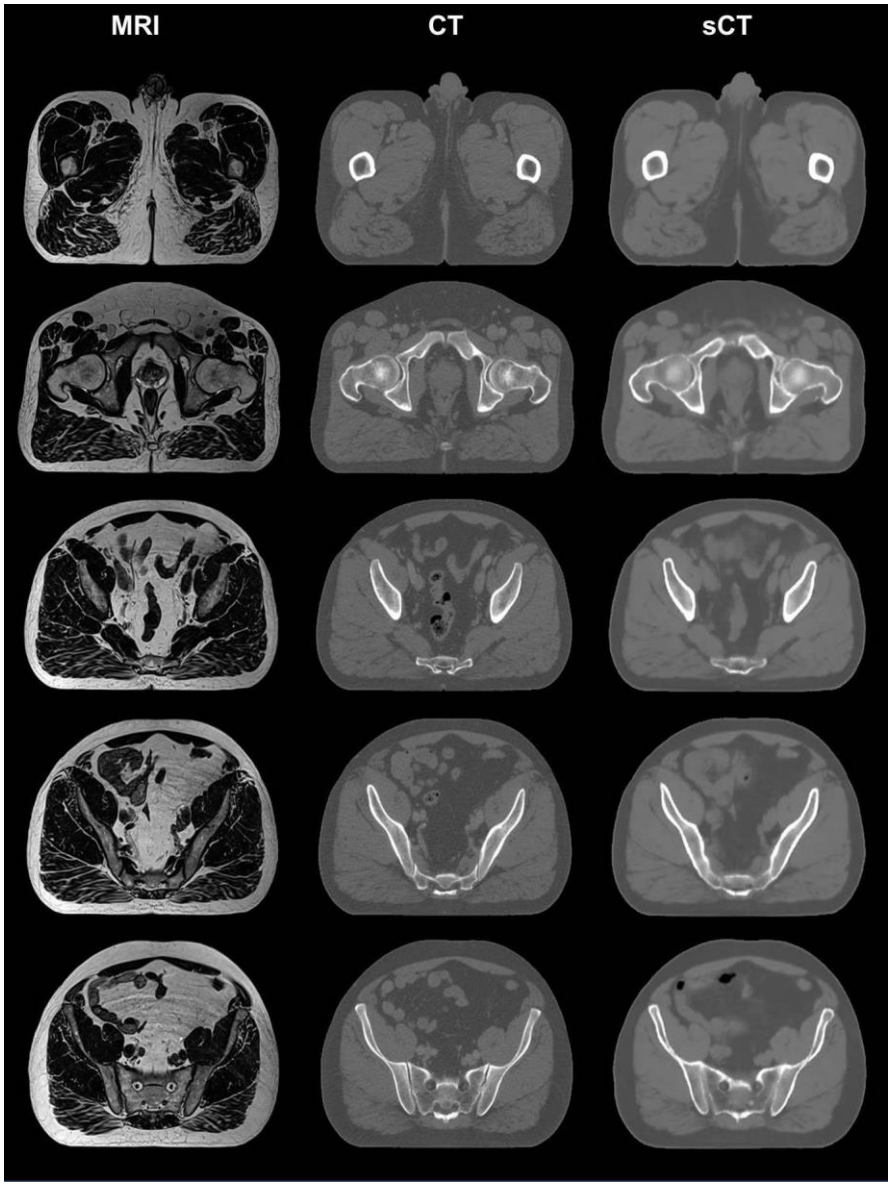

Figure 3-1. Matched T2-SPACE MR (left), CT (middle) and sCT (right) slices from an anal cancer patient, where the CT and MR have been deformably registered prior to sCT generation.

3.4 Discussion

This study is the first to assess sCT dosimetric accuracy for anal cancer treatments and is the largest known patient cohort for rectal cancer treatments. We found that focal loss driven cGAN-based sCT generation using T2-SPACE MR sequences for ano-rectal cancers achieved excellent sCT quality. Comparing the RIR sCT cGAN results from this study to Maspero et. al. (6), who achieved

MAE of 62 HU, our method shows an absolute improvement of ~18 HU. This represents a 40 % reduction in HU error across the cohort.

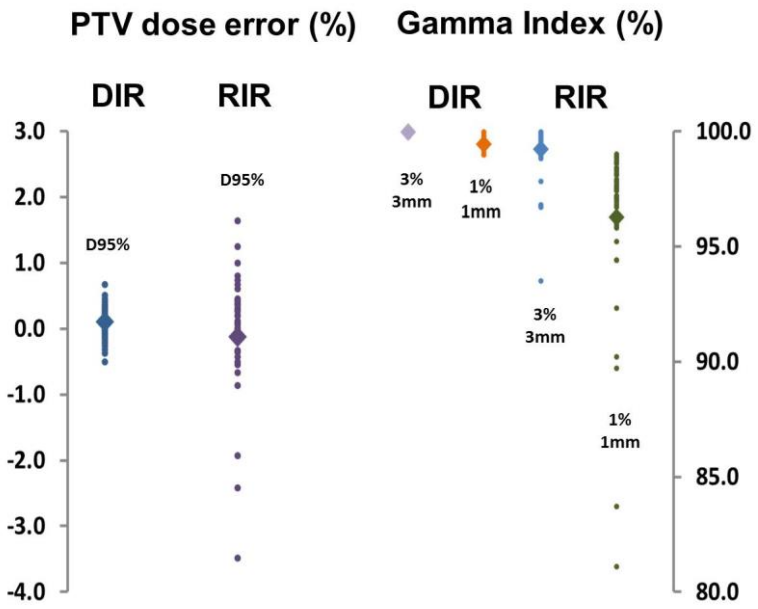

Figure 3-2. All (circle) and mean (diamond) PTV dose differences and gamma indices for the DIR and RIR sCTs, where dose differences are calculated as a percentage of the prescription dose.

The DIR sCT dosimetric differences to CT (mean +0.1 %) and gamma index analysis findings (all patients > 99.0 % at 1 %/1 mm threshold) show an excellent level of agreement. These results suggest the sCT solution is clinically acceptable, while the large testing cohort size supports confidence that this result is representative of the patient population. The LME model dosimetric difference effect size (0.1 %) is also in line with previously published studies (±0.3 %) (4–9). The dosimetric assessment of OAR constraints also found clinically acceptable agreement between sCT and CT (mean difference: 0.1 %) suggesting that clinically sufficient sCT dosimetric accuracy extends throughout the entire sCT dataset. These results are also in line with previously reported OAR dose statistics for rectum sCT datasets (mean dose difference: ~0.6 %) (5,8).

	OAR	Dose constraint	Tolerance	Dose difference (%) mean (S.D) [Range]
Rectum	Bowel Cavity	V30Gy/V18Gy	250cc	0.1 (0.4) [-0.5 to 1.0]
	Bladder	V35Gy/V21Gy	45%	0.0 (0.4) [-0.9 to 0.6]
Anus	Bladder	D35 %	45 Gy	0.1 (0.1) [-0.1 to 0.2]
	Small Bowel	D150 cc	50 Gy	0.3 (0.4) [-0.5 to 0.9]
	Femoral Heads	D35 %	40 Gy	0.0 (0.1) [-0.1 to 0.3]
	Genitalia	D50 %	35 Gy	0.0 (0.2) [-0.6 to 0.4]

Table 3-3. OAR relative dose differences between DIR sCT and CT plans for each organ constraint for each cancer site. Mean, S.D. and range are calculated as the difference between CT and sCT as a percentage of the constraint tolerance.

		95% confidence (%)	
	Dosimetric difference (%) (%)	Lower bound	Upper bound
Modality (CT vs. sCT)	0.1	0.0	0.2
Hospital (centre A vs centre B)	-0.1	-0.4	0.1
Site (rectal cancer vs anal cancer)	0	-0.2	0.3
Sex (male vs female)	0	-0.2	0.1

Table 3-4. Linear mixed effects model coefficients and 95% confidence intervals, where dose differences are calculated as a percentage of the prescription dose.

The assessment of rigidly registered sCTs to CT is a comparison of the “true” MR-only planning sCT, where no image augmentation has occurred, however it also introduces unpredictable inter-

scan patient body changes which will impact the dosimetric difference to CT. The mean sCT dose difference of -0.1 % vs. CT is more than clinically acceptable, but substantially greater range in the dose difference was seen compared to the DIR sCTs (Figure 3-2). This suggests the underlying systematic sCT to CT dose difference is similar to the DIR data, but being masked by the larger random error of these less similar datasets. This larger range of dosimetric difference across the rigid registration cohort can be explained by the time differences between CT and MR in the test cohort which can cause changes in patient anatomy. This was a limitation of the study that was required to enable successful data collection. A potential issue with using DIR datasets is that the deformable registration may mask an inherent lack of skin tissue visualisation, which can occur with MR sequences, by matching the CT and MR skin surfaces. This would result in any dosimetric differences caused by the inherent skin visualisation to not be represented in the DIR data. However, these differences would be represented in the RIR dataset results and we found the maximum systematic dosimetric impact between CT and MR was -0.1 %.

This study suggests that there is no detriment to the sCT image quality or dosimetric accuracy by using T2-SPACE sequences when used in combination with a focal loss GAN-based deep learning model. This is of benefit to improving the efficiency and accuracy of pelvic MR-only planning as it allows a single scan to be used for sCT generation and target volume and OAR delineation. Only using one sequence reduces MR scanning time, making the scan more tolerable for patients and reducing costs and eliminates systematic registration errors between multiple required MRI scans caused by patient position changes. Therefore it would be beneficial if more commercially available pelvic solutions utilised T2 sequences rather than T1 sequences for pelvic sCT generation.

The LME model allowed the assessment of the impact of using data from multiple centres by assessing the 95 % confidence interval values of the effect of the associated variables. The small range of effect (-0.4 to +0.1 %) between sCTs from centres A and B suggests our cGAN method is capable of producing a generalisable solution for use at multiple centres, in the case that some data from each centre is used in training data. Analogous to this is the situation where a single centre has data from multiple sources - for example multiple MR scanners all with slightly different sequence parameters. This is a beneficial feature as it could allow centres to pool data for sCT model generation making the generation of sCT models more feasible for smaller centres where the required data is harder to collect. We expected differences between sCTs from different centres due to differences in the input MR scans where there was a 3-fold scaling factor

and therefore quantisation differences in the low intensity areas of the images (air, bone and muscle) between MRs from centre A and centre B (a further description of the quantisation difference can be seen in appendix A). However, our results are evidence that this model can handle bimodal input data and produce consistent results.

GAN methods such as ours and Maspero (6) do not appear to provide a significant dosimetric improvement compared to other methods (4,5), however in this case it has allowed a more diverse, less-optimal dataset to be utilised to produce a robust, generalisable solution. The HU values of bone are significantly better represented with a focal loss cGAN. This improved bone representation may improve the use of sCTs for CBCT patient treatment positioning and it would be beneficial to investigate this further. A limitation of this study is the use of only one MRI vendor, although different scanner models, at both centres which limits the intensity variability between the matched sequences. It would be of benefit to assess this sCT generation model on a wider variety of input data, including more centres and scanner vendors as this would allow a greater assessment of the model's generalisability.

There are some limitations to generating sCT datasets using a cGAN as in this study, and these relate to training cohort requirements. Training cohorts need to be sufficiently large to produce generalisable and robust results and have accurate registration between CT and MR. This can mean a large cohort of patient data needs to be prospectively acquired which takes time. An additional limitation of cGANs is that once the model is trained, input data for generating sCTs is fixed such that parameters need to remain the same as for the training data. This requires users to be confident regarding their future cGAN model use and MR-only pathways prior to use.

This study shows that T2-SPACE MR sequences from multiple centres can produce generalisable, dosimetrically accurate, sCTs with low HU errors, for a large cohort of ano-rectal cancer patients and that a single T2 MR sequence can be used for both target and OAR delineation and sCT generation. Dosimetric differences were minimal and clinically insignificant for both PTVs and OARs. The model, which employed focal loss with a cGAN, proved robust to differences in input data such as treating centre, cancer site and patient sex.

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3.6 Supplementary information

3.6.1 cGAN model description

Building on the approach of Maspero et.al. (6), who repurposed the cGAN 'pix2pix' for sCT generation, we have optimised performance by replacing the purely convolutional patch discriminator architecture of pix2pix with a shallow (3 layer) U-net, allowing pixel-wise discrimination up to the input resolution for localised confidence assessment at imputation. In contrast to the usual adversarial approach, discriminator losses were trained against pixel wise absolute error for generated examples, allowing the discriminator to drive the generator only in regions of poor prediction quality. We have employed automated focal regression loss(19) for both the L1 generator loss and the adversarial losses, to further concentrate training on improving poorly predicted pixels.

Following hyper parameter tuning on a reserved subset of the training data, the final cGAN was trained for 170 epochs on a Tesla K-80 (Nvidia, California, USA) GPU, with 4995 individually paired slices per epoch and a batch size of 7 (GPU memory limited), with an input layer filter depth of 16, using the Adam optimiser with a batch-corrected learning rate of 0.0002, $\beta1=0.5$, $\beta2=0.999$ and dropout rate = 0.5. Data augmentation was performed by randomly cropping, left-right flipping and warping input and label data in a pairwise fashion. λ, the ratio of L1 to adversarial generator loss was optimised to 10 for the pixel-wise discriminator, in contrast to 100, as recommended for patch-GANs. The 16 filter input depth applies to both generator and discriminator, doubling on each of the first three convolutional layers to a maximum of 128 in the deepest layers of the generator bottleneck.

The decision to replace the 'patch' discriminator of pix2pix with a shallow U-net was made to overcome a limitation mentioned in the pix2pix paper, whereby local detail was improved by smaller patches up to a limit where pixel-level discriminators performed poorly. By encoding and decoding the image information via a U-net, we are able to produce pixel-resolution discriminator maps which accurately reflect poorly performing regions, improving e.g. bone detail, without inducing hallucinated details in other parts of the image.

The cGAN that our presented work was originally developed from (Pix2Pix) has an approximate ratio of 5:1 between the generator and discriminator which is somewhat reduced due to increased

discriminator complexity in our work. It is not generally necessary for the discriminator and generator to have similar numbers of parameters in a cGAN, but rather that the pixel and adversarial losses are balanced, which is achieved via the 'λparameter' for pix2pix and our network.

3.6.2 Rationale for choice of CT treatment plan dose grid

The dose grid of (3 mm x 3 mm x 3 mm) was chosen as it is the clinically used dose grid for ano-rectal treatments at the centres within this study and so it is the most clinically representative option.

Given the fixed nature of the treatment beam geometry for both scans, where positionally they are matched, we expected the gamma analysis to be dominated by dosimetric effects and dose grid resolution will have minimal impact.

3.6.3 Differences in MR scan intensities between centres A and B

There was a difference in input MR scan voxel intensities where there was a 3-fold scaling factor and subsequently quantisation differences in the low intensity areas of the images (air, bone and muscle) between MRs from centre A and centre B. Figure 3-3 shows two MR scans from two rectal cancer patients, one from centre A and one from centre B with the same window and levelling settings. It can be seen that there are clearly visible differences between the voxel intensities within these images. This can also be seen clearly in the histograms of each image.

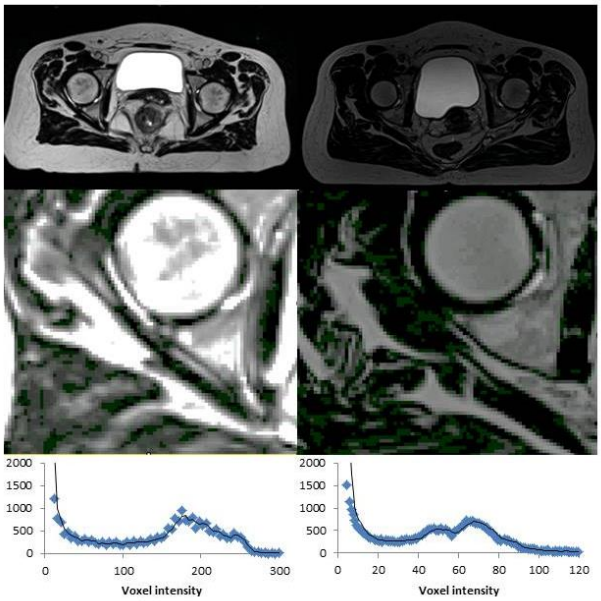

Figure 3-3. Examples of centre A (left) and centre B (right) MR scans with the same window and levelling preset and their intensity histograms, where top images are the full MR scan slice, middle are zoomed in on the bone, muscle interface and bottom are the histograms of the full images (top).

3.6.5 DIR and rigid sCTs

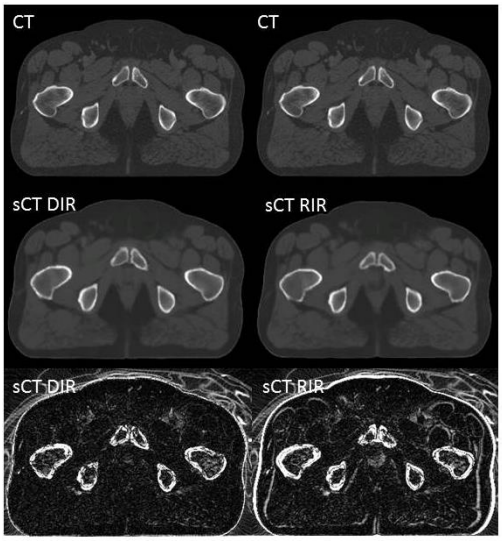

Figure 3-4. The CT (top) and DIR and RIR sCTs (middle) and their difference maps between the CT and respective sCTs (bottom) for a single anal cancer patient, with matched windowing and levelling for the CT, and sCTs and also for the difference maps.

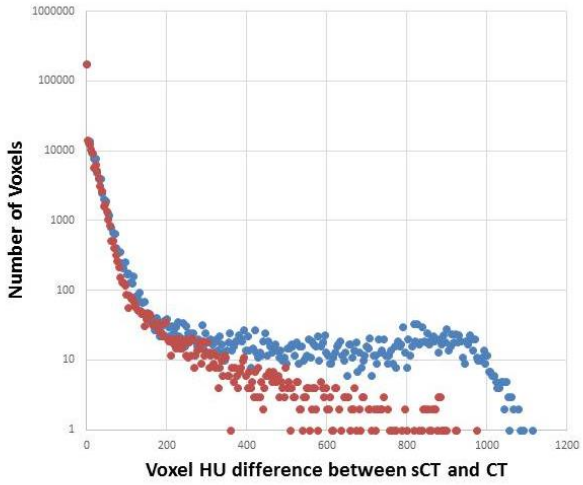

Figure 3-5. A histogram plot for the HU difference maps seen in Figure 3-4 for a DIR (red) and RIR (blue) sCT slice.

Figure 3-4 and Figure 3-5 show the difference in the DIR and RIR sCTs compared to CT. It is clear in the difference maps and HU voxel comparison that the RIR sCT has higher differences around the bony anatomy and also around the patient external where the alignment of the CT and RIR sCT is not as good as that for the DIR. It is also clear that there is still a difference in the bony anatomy position of the DIR sCT compared to CT, but it is smaller than for RIR sCTs. It is also noticeable that there is a small amount of misalignment within the soft tissues on the RIR sCT which isn't present for the DIR sCT. This example shows the improvement in positional matching between CT and MR that the deformable registration provides and why its use was beneficial to this study.

3.7 Additional information

3.7.1 Anal cancer elective PTV analysis

The anal cancer synthetic-CT dosimetric validation also included an assessment of the elective nodal PTV dose. These PTVs had a prescription dose of 40 Gy. Elective PTV dosimetric differences for the D95%, D50% and D2% dose levels between CT and synthetic-CT over the cohort of seventeen anal cancer patients were as follows: D95%; mean = +0.1 %, range = -0.1-0.3 %, D50%; mean = 0.2%, range = -0.1-0.3 %, D2%; mean = +0.1 %, range = -0.1-0.4 %.

This data was not included in the MLE modelling, however the results are in line with the primary PTV and OAR dose difference findings in the main chapter and indicate that the anal cancer synthetic-CT dosimetric accuracy extends throughout the elective PTV. This is corroborated by the gamma index analysis results seen in the main chapter where all 1%/1mm results were >99.0 % and includes the elective volume.

3.7.2 Basic description of the cGAN model architecture and explanation of its loss parameters

A separate paper describing the architecture of the model in greater detail is in preparation which will increase the understanding of the model in the literature.

A generative adversarial network (GAN) is a deep learning approach to creating data - in this case synthesising images. A GAN consists of two neural networks, a generator which creates the synthetic-CT and discriminator which assesses if the synthetic-CT is real or “fake”. GANs are described as adversarial because the generator and discriminator networks work against each other to improve the quality of the output synthetic-CT. The discriminator’s output assessment of real or fake is used to improve the generator’s synthetic-CT generation. This in turn makes it more difficult for the discriminator network to distinguish between real CTs and synthetic-CTs. This feedback cycle repeats until a stable synthetic-CT generation solution is produced, where the discriminator is unable to distinguish between real CTs and generated synthetic-CTs. It is possible to train a single generative network to create synthetic-CTs, in which case the generator can learn specific relationships between seen data. However, generators networks alone struggle to deal with unseen examples, and it is the discriminator that greatly improves a model’s ability to generalise to unseen data (1-2).

GANs use random input data to generate output data. This means there is no pixel to pixel relation between the inputted image and generated image. In the case of synthetic-CT image synthesis, this means a trained GAN would be able to generate synthetic-CTs but they would have no voxel-to-voxel paired relationship with the MRI - the anatomy would be “made up”, not representing the real MRI anatomy. A conditional GAN (cGAN), as used in this study, varies from a GAN in that it uses paired data and this is what makes it conditional. The model is trained on paired CT and MRI data which means that any generated synthetic-CTs include the anatomy that was found in the input MRI and there is a specific voxel-to-voxel relationship between the two datasets (1-2).

In neural networks, loss terms are used to quantify the difference between the expected and produced output data - in this case the real CT and the synthetic-CT. Loss terms are the metric which therefore influences the next iteration of the synthetic-CT generation, where the aim is to improve the synthetic-CT estimate by minimising the loss value (1-2). The cGAN used in this study has two loss terms, L1 loss and adversarial loss. L1 loss is calculated as the MAE between the synthetic-CT and real CT and the adversarial loss is a measure of whether the discriminator can determine the difference between the synthetic-CT and the CT. Within the cGAN model, all voxel values were normalised between 0 and 1 and so the L1 loss value could range between 0 and 2, with the larger the difference between synthetic-CT and CT indicating a larger L1 loss value. The

adversarial loss was a score of how realistic the synthetic-CT was compared to the CT, ranging from 0 (completely fake) to 1 (completely real).

These loss functions are combined to produce a total loss, where total loss = L1 loss+ adversarial loss. The total loss is used to optimise the synthetic-CT generation, where the generator aims to lower the total loss to a minimum. Therefore to ensure an optimised solution these two losses need to be balanced, so that the generator is impacted by both loss terms. In our cGAN, the experimental values for the L1 and adversarial losses were found to be approximately 0.05 and 0.5 respectively which is a significant imbalance. Therefore we introduced a λ factor, of approximately 10, which was a scalar for the L1 loss, to balance the L1 and adversarial losses within the total loss. Therefore the total loss = λ*L1 + adversarial loss.

A further factor which was optimised was the number of generator iterations per discriminator iteration. Here we amended the ratio from 5:1 which is commonly used in cGANs to approximately 1:1, as discussed in section 3.6.1 this was due to the complexity of the discriminator.

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Chapter 4 Patient position verification in magnetic-resonance imaging only radiotherapy of anal and rectal cancers

4.1 Abstract

Introduction: Magnetic resonance (MR)-only treatment pathways require either the MR-simulation or synthetic-computed tomography (sCT) as an alternative reference image for cone beam computed tomography (CBCT) patient position verification. This study assessed whether using T2 MR or sCT as CBCT reference images introduces systematic registration errors as compared to CT for anal and rectal cancers.

Methods: A total of 32 patients (18 rectum, 14 anus) received pre-treatment CT- and T2 MR-simulation. Routine treatment CBCTs were acquired. sCTs were generated using a validated research model. The local clinical registration protocol, using a grey-scale registration algorithm, was performed for 216 CBCTs using CT, MR and sCT as the reference image. Linear mixed effects modelling assessed systematic differences between modalities.

Results: Systematic translation and rotation differences to CT for MR were -0.3 to +0.3 mm and -0.1 to 0.4° for anal cancers and -0.4 to 0.0 mm and 0.0 to 0.1° for rectal cancers, and for sCT were -0.4 to +0.8 mm, -0.1 to 0.2° for anal cancers and -0.6 to +0.2 mm, -0.1 to +0.1° for rectal cancers.

Conclusions: T2 MR or sCT can successfully be used as reference images for anal and rectal cancer CBCT position verification with systematic differences to CT <±1 mm and <±0.5°. Clinical enabling of alternative modalities as reference images by vendors is required to reduce challenges associated with their use.

4.2 Introduction

The potential benefits of magnetic resonance (MR)-only radiotherapy treatment planning have been well documented, as has the need to generate synthetic computed tomography (sCT) datasets to allow treatment dose to be calculated (1–3). Standard radiotherapy pathways include cone beam computed tomography (CBCT) patient position verification using computed tomography (CT)-simulation as the reference image. Therefore MR-only treatment pathways must use either the MR-simulation or sCT instead. However, there is limited assessment within the current literature of CBCT registration accuracy (4) when using sCT or MR as the reference image, with the majority of those assessing prostate (5–10) CBCT patients, with Kemppainen (6) also assessing gynaecological patients. These assessments can be used as a bench mark level of acceptability for other pelvic sites with mean 3D translational differences between MR/sCT and CT of <±2 mm. However, rectum and anus cancer sites have increased complexity as compared to prostate treatments including; male and female anatomy, greater tumour position variation and larger treatment volumes (11). Additionally prostate CBCT registrations can be undertaken using fiducial markers, removing the need for soft tissue registration (12). The independent assessment of CBCT registrations for anal and rectal cancer sites is required prior to MR-only clinical implementation.

To the authors knowledge no studies have assessed CBCT patient positioning accuracy in a MR-only workflow for anal cancers, while two studies have assessed rectal cancer CBCT patient positioning using sCT, but not MR, as a reference image (13,14). Maspero et al and Tyyger et al assessed the use of sCTs generated by commercially available sCT models using clinically available CBCT positioning software for ten (seven male, three female) and seven (all male) rectal cancer patients respectively.. Their findings suggested that sCT could be utilised as a reference image for rectal CBCT registrations, with Maspero's (13) mean differences in translations and rotations when using sCT vs. CT <±1 mm and <±0.5 º respectively. However, Tyyger (14) also found gross misregistration occurred for three patients when using the sCT and both studies had limited patient numbers, including only 3 female patients.

Previously, we described the validation of a deep-learning based sCT model on a cohort of anal and rectal cancer patients using a T2 MR sequence with mean dosimetric difference to CT of 0.1% (range -0.5% to +0.7%) (11).

Here we aimed to assess whether using sCT or T2 MR scans as the reference image for CBCT patient position verification introduced systematic registration errors vs. CT. This assessment was for a cohort of thirty two anal and rectal cancer patients, using a soft tissue matching algorithm in clinically used patient positioning software.

4.3 Methods

4.3.1 Data collection

This study is part of a wider MR-only radiotherapy study: “Mri-only treAtmeNT planning for Anal and Rectal cAncer radiotherapy” (MANTA-RAY), research ethics committee reference: 18/LO/1298, ISRCTN Registry: ISRCTN82734641. This study included 32 ano-rectal patients (18 rectum and 14 anus; 16 male and 16 female; who underwent radical VMAT external beam radiotherapy. Dose, fractionation and the number of acquired CBCTs per patient group were as follows: anal cancer treatments; 53.2Gy in 28 fractions - 8 CBCTs (fractions 1-4 and 4 weekly scans), rectal cancer patients; 45Gy in 25 fractions - 7 CBCTs (fractions 1-4 and 3 weekly scans) and 25Gy in 5 fractions - 5 CBCTs (daily). Exclusion criteria included patients with contra-indications to MR.

All patients received planning CT, MR and routine CBCTs acquired in the radiotherapy treatment position with matched bladder filling and immobilisation protocols. Acquisition parameters are shown in Table 4-1. For the MR scan, coil bridges were used to keep the coils from deforming the patient skin position. Eight CBCTs were deleted from the clinical systems prior to collection for this study so could not be used in the analysis (one rectum CBCT and seven anus CBCTs from four patients).

MR	**Make & Model**	Siemens Aera 1.5 T
	Sequence	3D T2 SPACE
	Resolution	0.9 x0.9 x1.5 mm
	Refocusing Flip Angle (°)	160
	TR (ms)	1600
	TE (ms)	211
	Bandwidth (Hz/px)	545
	Echo train length	134
	Longitudinal scan length	Standard: 2cm inferior of genitalia to L5 vertebra Extended (if high nodal involvement): 2cm inferior of genitalia to L5 vertebra
	Field of View (Axial)	450x450 mm^2
CT	**Make & Model**	Philips Brilliance Big Bore
	Resolution	1.2x1.2x2 mm
	kVp (kV)	120
	X-ray Tube Current (mAs)	135
	Field of View (Axial)	450x450 mm^2
CBCT	**Make & Model**	Elekta XVI
	Resolution	1 x 1 x 1 mm
	kVp (kV)	120
	X-ray Tube Current (mAs)	32
	Field of View (Axial)	400 mm diameter

Table 4-1.The scan parameters for patient CT, MR and CBCT scans.

Mean time between planning CT and MR data acquisition for all anal and rectal cancer patients recruited at the LCC was 15.1 days (range: 0 to 43 days) as MR scans were for research purposes and scheduled for when the patient had a clinical appointment prior to or during their first two weeks of treatment. The T2-SPACE sequence was acquired in two linked acquisitions, with

positional matching and an overlap of 2 cm before being “stitched” together offline into a single sequence with no overlap. This ensured sufficient superior-inferior scan length to cover all the anatomy required for radiotherapy treatment planning, including target volumes and organs at risk (OARs).

4.3.2 Synthetic-CT generation

MR scans were rigidly registered to their paired CT datasets using the mutual information registration algorithm in Raystation 8b (RaySearch Laboratories, Stockholm, Sweden) and manually assessed to ensure accuracy. The rigidly registered MR was resampled to the CT frame of reference using Raystation 8b’s standard tri-linear resampling. An sCT scan was generated from each patient’s T2-SPACE MR scan using the deep learning based cGAN sCT model previously described (11). Figure 4-1 shows an example of an axial slice of the CT, MR, sCT and CBCT of a single anal cancer patient used for registration.

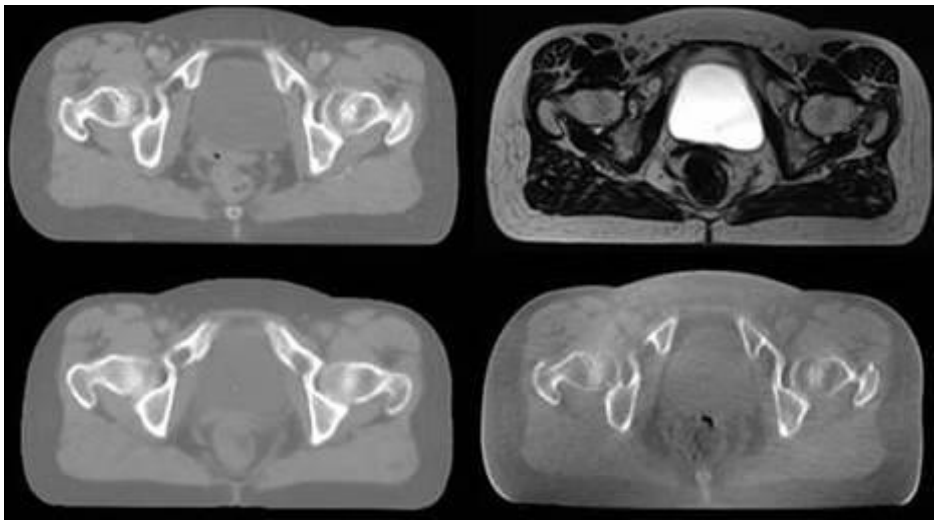

Figure 4-1. Example of an axial slice of a single anal cancer patient CT (top left), MR (top right), sCT (bottom left) and CBCT (bottom right) scan used for CBCT registrations.

4.3.3 Reference data preparation for CBCT matching

The CBCT registration software does not natively accept MR or sCT datasets as a reference image for CBCT registration and the sCT DICOM (Digital Imaging and Communications in Medicine) tags had to be generated to match the CT. The MR and sCT pixel data for each slice was transposed into the matching CT slice pixel DICOM file, with CT DICOM tags and in the CT frame of reference. This allowed the software to recognise the MR and sCT datasets as valid (CT) reference data. This also allowed their use in conjunction with each patient's original treatment structure set and treatment plan. For MR datasets, the "rescale intercept" DICOM header value was adjusted from -1024 to 0 to prevent the MR voxel intensity information being rescaled inappropriately during import.

This process ensured the 3 datasets; CT, sCT and MR, all in the same frame of reference were ready for import. The reference data scans were imported and all patient routine CBCTs were associated with each reference image scan independently. Correction reference points (the co-ordinates which translations and rotations are centred around) were set to the plan isocentre for each reference scan as per the departmental clinical protocol.

4.3.4 CBCT matching process

Each patient CBCT scan was registered to each reference scan (CT, MR and sCT) using the clinical matching protocol used in this centre as detailed below. The automated grey value registration algorithm (17) for translations and rotations was applied locally using a clinically relevant clip box, defined on the reference image using anatomical boundaries and PTV position. Clip box protocol parameters varied for anal and rectal cancers respectively according to local clinical protocol and can be seen in Table 4-2. Figure 4-2 shows examples of rectal and anal clip boxes. All registrations were undertaken by an experienced clinical scientist (DB) specialising in radiotherapy imaging. All patient CT registrations were undertaken first, followed by MR and then sCT, with a break of 2 days between any individual patient's CT, MR and sCT registrations being undertaken to reduce operator bias. As 208 registrations were therefore carried out between each individual patient's

CT, MR and sCT registrations, this was considered to be a sufficient gap to ensure no registration bias occurred through recollection of a patient's previous registrations.

Protocol	Dimension	Anatomy to Include	Anatomy to exclude
Anus	Left/Right	Pelvic cavity	Femoral Heads
	Ant/Post	Pubic symphysis	Sacrum
	Sup/Inf	PTV	Sacrum
Rectum	Left/Right	Pelvic cavity	Femoral Heads
	Ant/Post	Sacrum	Pubic symphysis
	Sup/Inf	Whole Sacrum & PTV	X
Extended clip box	Left/Right	Femoral Heads	X
	Ant/Post	Pubic symphysis and Sacrum	X
	Sup/Inf	Pubic symphysis and Sacrum	X

Table 4-2. XVI registration standard protocol clip box size parameters for anal and rectal cancer sites, and the large extended clip box.

After each automated registration was carried out, the operator undertook a visual assessment of the registration. In the event of gross errors, an extended clip box was used as described in Table 4-2 to provide the registration algorithm with additional information to use in the registration process. A simple assessment of intra-observer variability, the variability in one operator carrying out the clip box positioning and any resultant difference in automatic registration, was carried out by repeating the CT, sCT and MR to CBCT registrations for all CBCTs for one anus and one rectum patient (chosen at random) and calculating the variations in each translational and rotational plane between registration 1 and 2.

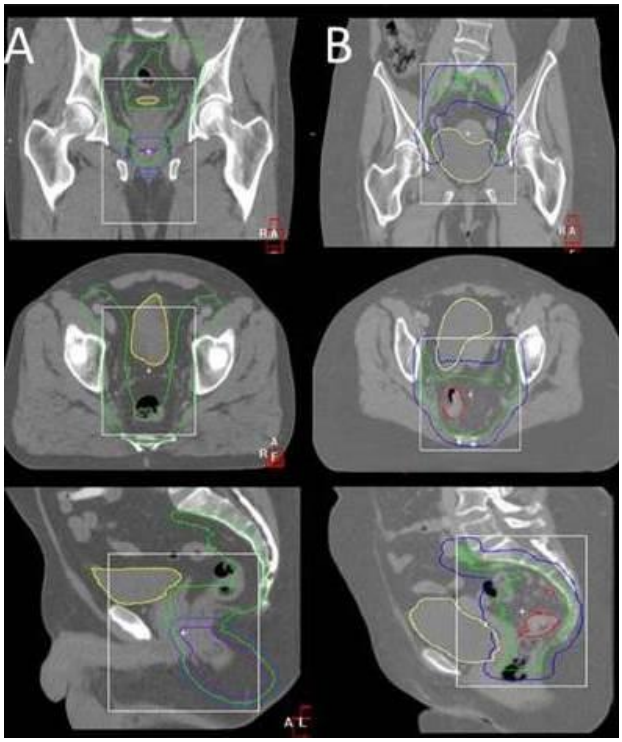

Figure 4-2. Example CBCT registration clip boxes for anal (A) and rectal (B) cancer sites respectively as positioned on a reference CT image.

4.3.5 Statistical analysis

Linear mixed effects (LME) models in STATA (StataCorp, 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC) were applied to the CBCT registration results to assess the effect of reference image (MR or sCT) on the CBCT registrations. MR and sCT were compared to CT which was assumed to be the gold standard as the current clinically used reference image. The LME models calculated the systematic difference in translations and rotations in terms of "effect size" - the systematic shift in each individual translational or rotational dimension from CT when the alternative reference image (MR or sCT) was used. Separate models were applied to anal and rectal cancers as well as for translations and rotations within each cancer site cohort. The LME models used translational distance or rotational angle as the dependent variable; reference image (CT, MR and sCT), dimension (x (left-right/rotation), y (anterior-posterior/pitch) and z(superior-inferior/yaw) and time point (fraction 1-4 or weekly) as fixed effect independent variables and patient as a random effect independent variable. The analysis assessed each translational or

rotational dimension separately by applying a contrast interaction between reference image and dimension variables within the model. The models also calculated 95% confidence intervals to provide an assessment of potential error in the systematic differences.

4.4 Results

The standard clip box protocol produced no gross registration errors for rectal cancer patients or anal cancer patients with sCT or CT reference images. However for 4 anal cancer patients (28% of anal cancer patients) where MR was used as the reference image, gross registration errors were detected. For these patients, 16/32 CBCT registrations (15% of the total anal cancer MR registrations) were affected. The use of the extended clip box protocol in these cases produced successful registrations with no gross errors.

For translations the systematic effect of using sCT and MR vs. CT were between -0.6 and 0.8 mm and -0.4 and 0.3 mm respectively. For rotations, the systematic effect of using either sCT or MR vs. CT was between -0.1 and 0.2^{o} and -0.1 and 0.4^{o} respectively. Maximum 95% confidence intervals were -1.2 and 1.5 mm and -0.5 and 0.7^{o} for translations and rotations respectively. Table 4-3 shows the results of the LME modelling and Figure 4-3 shows each individual CBCT registration difference of MR/sCT from CT and includes outlier differences in registrations of 4-6 mm.

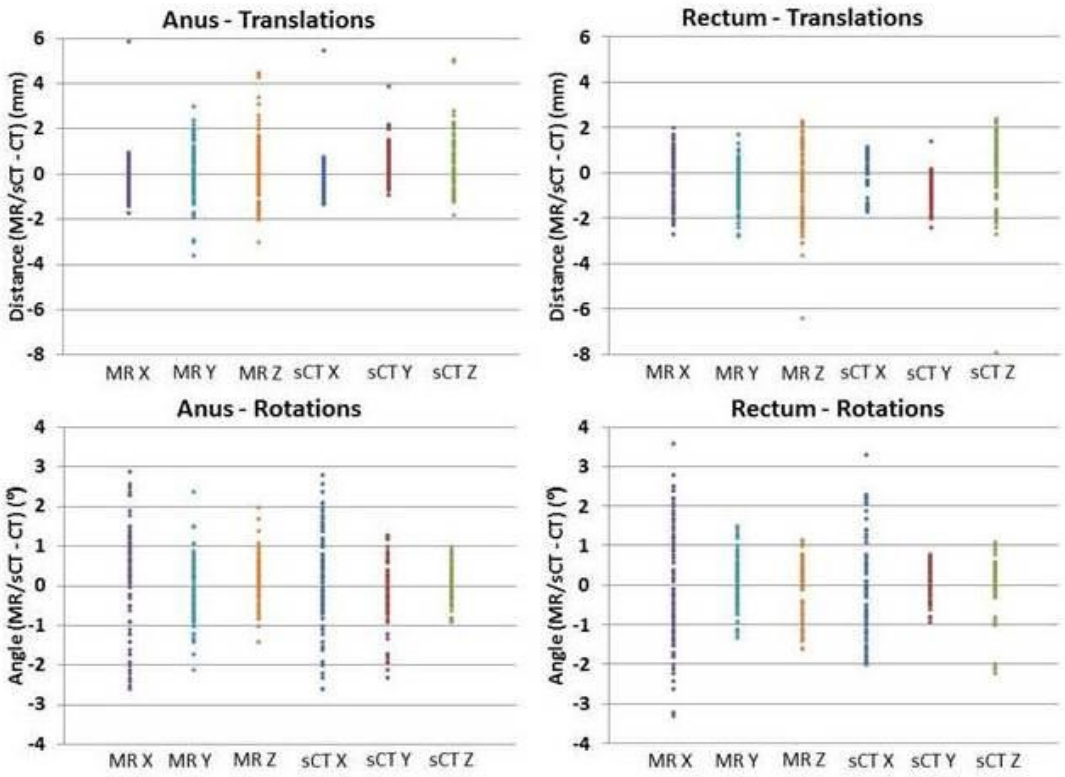

Figure 4-3. The translational and rotational (x (left-right/rotation), y (anterior-posterior/pitch) and z(superior-inferior/yaw)) MR and sCT CBCT registration differences to CT for anal and rectal cancer sites, where differences were calculated as the MR or sCT value minus the CT value.

Mean intra-observer variability for all CBCTs from a single anal cancer patient was found to be -0.1 mm and 0.1°, 0.1 mm and 0.0°, and 0.3 mm and 0.1° for CT, sCT and MR respectively. Mean intra-observer variability for all CBCTs from a single rectum patient was found to be 0.0 mm and 0.0° for CT, sCT and MR respectively.

4.5 Discussion

Standard anal and rectal radiotherapy pathways include CBCT patient position verification using CT-simulation as the reference image. The implementation of MR-only radiotherapy treatment pathways requires that either the MR-simulation or sCT is used for CBCT positional verification. Our findings suggest that MR or sCT can be used for CBCT patient positional verification within an

MR-only radiotherapy treatment planning pathway for anal and rectal cancers with minimal impact on registration accuracy.

	Reference image (vs. CT)	Dimension	Translations (mm)	Rotations (^{o})
			Effect size (95% confidence intervals)	Effect size (95% confidence intervals)
Anus	**MR**	x	-0.3 (-1.0 to 0.4)	0.4 (0.1 to 0.7)
		y	0.3 (-0.4 to 1.1)	-0.1 (-0.4 to 0.2)
		z	0.1 (-0.6 to 0.8)	0.1 (-0.2 to 0.5)
	sCT	x	-0.4 (-1.1 to 0.3)	0.2 (-0.1 to 0.5)
		y	0.8 (0.0 to 1.5)	-0.1 (-0.5 to 0.2)
		z	0.3 (-0.4 to 1.0)	0.1 (-0.3 to 0.4)
Rectum	**MR**	x	0.0 (-0.6 to 0.7)	0.0 (-0.4 to 0.4)
		y	-0.4 (-1.0 to 0.2)	0.1 (-0.3 to 0.5)
		z	-0.3 (-0.9 to 0.3)	0.0 (-0.4 to 0.4)
	sCT	x	-0.2 (-0.8 to 0.4)	-0.1 (-0.5 to 0.3)
		y	-0.6 (-1.2 to 0.0)	0.1 (-0.3 to 0.4)
		z	0.2 (-0.5 to 0.8)	0.0 (-0.4 to 0.3)

Table 4-3. The translational and rotational effect sizes and 95% confidence intervals from the linear mixed effects modelling for MR and synthetic-CT compared to CT for anal and rectal cancers respectively.

We found that a subset of MR anal cancer registrations failed to produce acceptable registrations with the standard clip box. It was notable that no issues occurred with any rectal cancer patients or sCT registrations. A possible cause is the combination of the smaller range of anatomy included in the anal cancer clip box and the use of MR .These gross errors were easily detected through operator registration checks which are always advised for an automated registration process, but

it does suggest that additional care is needed for MR registrations or adjustments to anus MR clip box clinical protocols are needed.

The argument in favour of using MR rather than sCT as a reference image includes firstly that MR data is the visualisation of “real” tissue, and secondly that a sCT is a representation of CT scan, there will be a loss of image quality and soft tissue detail compared to MR. However, counter-arguments include that using MR with improved soft-tissue contrast that is not present in the CBCT could lead to a false sense of improved accuracy. Furthermore, our findings suggest that using a deep-learning model generated sCT was preferrable as the systematic registration errors were no greater than for MR, and in addition resulted in no gross registration errors unlike for the MR datasets. A potential method to combine the benefits of both imaging modalities, would be to register based on the sCT but then inspect the quality of the registration using both the MRI and sCT datasets.

The challenge facing the use of MR or sCT as a reference image is that commercially available CBCT registration software are not CE marked for the use of reference images from different imaging modalities, and do not currently accept MR data without processing such as we did here. Although it is possible to utilise MR without vendor support it has complexities which require centres to accept greater risk attached to its use. Greater investment, support and development from commercial vendors would enable MR-only radiotherapy pathways to maximise their benefit and to continue to progress into clinical use. It is also the responsibility of radiotherapy centres to provide more evidence that further development is required and that utilising MR for positional registration is a safe and geometrically accurate option. The lack of vendor support will limit the global adoption of MR-only pathways beyond prostate (where setup can use fiducial markers) and brain (where inherent immobilisation can allow 2D position verification to be acceptable) as most other sites require 3D CBCT patient position verification.

Our results are in line with those in the literature, whether comparing against the baseline findings from prostate studies (5–9) or the more relevant rectum study findings of Maspero (13) and Tyyger (14). We found the systematic impact of sCT and MR on translations and rotations were <± 1 mm and <±0.5 ° which is similar to Maspero for sCT reference images. Therefore we can suggest that sCTs, whether generated from deep learning voxel based models such as ours or bulk density models, have similar results for CBCT position registrations. We extend this with our MR findings and a strength of this work is that it includes a larger patient cohort with an equal number of

female and male patients such that it more accurately represents the range of anatomy found within a clinical population. It should be noted that the rigid registrations undertaken in the data preparation had the potential to introduce systematic errors into this study, while these were minimised by the assessment of the registrations by an experienced clinical scientist (DB), it is likely some component of the residual systematic errors identified here are due registration error introduced at that point.

It can be seen from Figure 4-3 that despite the small systematic differences between reference image modalities, there was a large range of random differences between CT and MR/sCT and that there are some poor registration outliers. This is unlike Maspero, who found no sCT registrations had differences of >±2 mm and >±1.2° (13). One explanation is that the registration algorithm varied between our studies, where Maspero used a bony chamfer matching algorithm vs. the grey value algorithm used here which explains Maspero's lack of outlier registrations as bony matches are more reproducible. However, the range of registration errors seen in this study has most likely been caused by changes in patient position between CT and MR, which can occur over short time frames, but also would be exacerbated by our mean time between CT and MR scans of 15 days. This is also markedly different to Maspero, where all CT and MR datasets were acquired within 3 hours of each other which will have had an impact in limiting intra-patient anatomical changes between scans. This is a limitation of the study as it would have been preferable to limit CT & MR scanning to the same day; however this was not achievable in our data collection due to MR scanner availability.

This limitation increases the importance of using linear mixed effect modelling for analysing our data, as it can take into account the large random fluctuations to find the underlying systematic differences between reference images. An alternative option for mitigating the impact of the variation in patient position between the CT and MR/sCT data would have been to register the MR to the CT using a deformable registration, rather than a rigid registration. However this would have augmented the MR (and therefore also sCT) anatomy, potentially masking the systematic differences in registrations between MR/sCT and CT.

We carried out a simple assessment of intra-observer variability by repeating the CT, sCT and MR to CBCT registrations for all CBCTs for one anus and one rectum patient and found that the intra-observer variability was negligible for each reference image (CT, sCT and MR). This gives us confidence that further intra-observer variability measurement would not change our findings.

Here we did not assess manual registrations which were beyond the scope of this study, however it is reasonable to consider manual registrations to be more subjective than automatic registrations and further assessment would be beneficial.

This study found that the impact sCT or T2-SPACE MR sequences as reference images for CBCT registration resulted in minimal systematic differences compared to CT (<±1 mm and <±0.5 °), suggesting that from a treatment setup point of view MR-only radiotherapy can be considered as equivalent to CT-based radiotherapy. A remaining barrier to widespread clinical implementation is the clinical enabling of alternative modalities as reference images by vendors to reduce the challenges associated with their use.

4.6 References

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4.7 Additional information

This chapter focuses on the systematic differences in CBCT registration when using MRI or sCT compared to CT as the reference image. We have shown that MRI or sCT have acceptable overall accuracy, however the precision of using MRI or sCT has not been investigated. This is a limitation of this work because if MRI or sCT do not have acceptable levels of precision, then it is possible that the use of either modality could introduce unacceptable uncertainties for individual patients which could make their treatment with MRI-only patient positioning unsafe. While this work does not directly investigate the issue of precision, as part of the methodology, all registrations were assessed for gross registration errors. Our findings showed that there were few significant gross registration errors, which were all resolved with an extended clipbox and this suggests that the precision of using either MRI or sCT was sufficient to prevent significant individual patient errors. As discussed in section 4.5, there were a number of large differences in registration between CT and sCT/MRI. We attribute these to local internal patient position differences caused by the significant time difference between CT and MRI data acquisition. These differences make an assessment of the true precision of the registration algorithm challenging in this case.

In a clinical workflow, while initially patient positioning would be undertaken using the automated matching algorithm, an operator manual assessment and adjustment would also be undertaken which would further limit the possibility that unsafe patient position registrations would be carried out. This manual adjustment makes the assessment of precision based purely on the automatic registration algorithm less beneficial, and further work should assess both the accuracy and precision of multi-observer manual patient positioning registrations.

Chapter 5 The benefit of MR-only radiotherapy planning for anal and rectal cancers

5.1 Abstract

Introduction**:** Limited evidence exists showing the benefit of magnetic resonance (MR)-only radiotherapy treatment planning for anal and rectal cancers. This study aims to assess the impact of MR-only planning on target volumes (TV) and treatment plan doses to organs at risk (OARs) for anal and rectal cancers vs. a computed tomography (CT)-only pathway.

Materials and Methods: 46 patients (29 rectum and 17 anus) undergoing pre-operative or radical external beam radiotherapy, received CT and T2 MR simulation. TV and OARs were delineated on CT and MR and VMAT (volumetric arc therapy) treatment plans were optimised independently (53.2Gy/28 fractions for anus, 45Gy/25 fractions for rectum). Further treatment plans assessed gross tumour volume (GTV) dose escalation. Differences in TV volumes and OAR doses, in terms of Vx Gy (organ volume (%) receiving x dose (Gy)), were assessed.

Results: MR GTV and primary planning target volume (PTV) volumes systematically reduced by 13 cc and 98 cc (anus) and 44 cc and 109 cc (rectum) respectively compared to CT volumes. Statistically significant OAR dose reductions vs. CT were found for: bladder and uterus (rectum) and bladder, penile bulb, and genitalia (anus). With GTV boosting, further statistically significant dose reductions were found for: sigmoid, small bowel, vagina, and penile bulb (rectum) and vagina (anus).

Conclusion: Our findings provide evidence that the introduction of MR (whether through MR-only or CT-MR pathways) to radiotherapy treatment planning for anal and rectal cancers has the potential to improve treatments. MR related OAR dose reductions may translate into less treatment related toxicity for patients or greater ability to dose escalate.

5.2 Introduction

Magnetic resonance imaging (MR)-only radiotherapy treatment planning is the use of an MRI scan alone to plan radiotherapy treatments. These techniques require the generation of a "synthetic-CT" (computer generated) dataset as MRI does not directly provide the patient density information required to allow dose calculation that is usually obtained from CT (1–3). MR-only planning techniques have developed considerably in recent years, with commercial synthetic-CT (sCT) solutions now available and specialist centres treating prostate cancers (1–3). However, a remaining challenge to wide-spread adoption is the lack of evidence within the literature demonstrating the benefit of MR-only radiotherapy treatment planning to patients, in terms of improving treatments compared to standard pathways (1).

To the authors' knowledge, only one study has assessed the impact of MR-only radiotherapy treatment planning on patient outcomes, finding prostate treatment acute outcomes were similar to a CT-MR pathway (4). For anal and rectal cancers there is no evidence in the literature showing the benefit of MR-only radiotherapy treatment planning to patient treatments.

It is difficult to assess the benefit of MR-only radiotherapy treatment planning as standard pathways in routine clinical use include CT-only or CT-MR pre-treatment imaging. CT-only radiotherapy treatment planning pathways are common in many centres, for example in the UK, where dedicated radiotherapy MR provision is relatively scarce (5). However, where the MR simulation resources are available, CT-MR pathways are the preferred option (6). The central hypothesis for using MRI in the radiotherapy treatment planning process, whether in a CT-MR or MR-only pathway, is that the improved soft-tissue contrast of MR allows improved visualisation of tissues (7,8). For anal and rectal cancers it is hypothesised this could lead to the more accurate definition of tumours and therefore reduced radiotherapy target volumes. This is supported by diagnostic anal and rectal study findings of net reductions in tumour volume when delineated on MR vs. CT (9,10).

Comparing MR-only to CT-MR pathways there are a number of benefits which include; reduced CT scanning, streamlining clinical workflows, removing CT-MR registration uncertainties and the increased ease of introducing functional imaging (7,8,11). As well as the logistical and practical advantages, it is the removal of systematic CT-MR registration errors (12) which could further improve patient treatments.

Here we aim to quantify the impact of MR-only radiotherapy treatment planning on TVs and treatment plan doses to OARs for anal and rectal cancer treatments when compared to a routine CT-only simulation pathway. We hypothesise that reduced MR-only TVs should result in treatment plans with reduced organ at risk (OAR) doses if TV coverage is maintained. By comparing MR-only and CT-only pathways, we are assessing both the benefit of including MR in the treatment pathway, which is also true of a CT-MR pathway, and the benefit of removing CT-MR pathway registration uncertainties. We also hypothesise that GTV dose escalation planning (13–15), would enhance the benefit from MR-only vs. CT-only planning due to the reduced volume of GTVs delineated on MR vs. CT.

5.3 Methods

5.3.1 Data collection

This study recruited 46 patients with anal and rectal cancer from a single centre; 29 rectum and 17 anus; 24 male and 22 female, who were due to undergo pre-operative or radical VMAT (volumetric arc therapy) external beam radiotherapy. Exclusion criteria included patients with contra-indications to MR. Patient demographics and staging can be seen in Table 5-5 (5.7 Supplementary information). This study is part of a wider MR-only radiotherapy study: “Mri-only treAtmeNT planning for Anal and Rectal cAncer radiotherapY” (MANTA-RAY), research ethics committee (REC) reference: 18/LO/1298, ISRCTN Registry: ISRCTN82734641.

All patients received CT and T2-SPACE MR simulation in the radiotherapy treatment position with matched bladder filling and immobilisation protocols. For MR simulation, coil bridges were used to prevent the coils from deforming the patient skin position. The mean time between planning CT and MR data acquisition for all anal and rectal cancer patients recruited at the LCC was 15.1 days (range: 0 to 43 days) as MR simulation was for research purposes and scheduled for a time when the patient had a clinical appointment prior to or during their first two weeks of treatment. The timings of the MR scans can be seen in Table 5-5 (5.7 Supplementary information where in total 41 % of MR scans were acquired prior to treatment starting, 69 % were acquired by the end of week one of treatment (fraction 5) and 95 % were acquired by the end of week two of treatment

(fraction 10). MR scans were rigidly registered by an experienced clinical scientist (DB) specialising in image registration, focussing on the rectum and anal canal, to their paired CT datasets using the mutual information registration algorithm in Raystation 8b (RaySearch Laboratories, Stockholm, Sweden). MRs were resampled to the CT frame of reference using Raystation 8b's standard tri-linear resampling. A synthetic-CT (sCT) scan was generated from each patient's T2-SPACE MR scan using a deep learning based cGAN sCT model. The cGAN sCT model and the CT and MR acquisition parameters have been previously described in the literature (16).

5.3.2 Target volume and OAR delineation

All TVs (defined in Table 5-1) were delineated on CT and T2 MR simulation scans separately according to our centre's clinical protocol, apart from GTVBoost volumes which were chosen according to clinical trials assessing GTV dose escalation (13–15). All patients had diagnostic MR available and patients with anal cancer additionally had diagnostic PET-CT available to assist delineations through side-by-side comparisons to the planning scan as per our centre's clinical protocol. These diagnostic scans were unsuitable for registration and further use in the study due to their slice thickness and slice spacing which were not optimised for radiotherapy use.

CT TVs, as used for each patient's clinical treatment, were delineated by the treating consultant clinical oncologist. MR GTV delineations were undertaken by one of three consultant clinical oncologists specialising in anal and rectal cancer treatments with experience of interpreting T2 MR sequences for ano-rectal tumour delineations. MR GTVs were undertaken 2+ months after CT delineations to avoid potential recollection bias. All GTV delineations were undertaken using all clinically available information, apart from the other scan (CT or MRI). An experienced clinical scientist (DB) specialising in radiotherapy imaging created all other MR TVs through expansions and manual adjustments, all matching the CT clinical pathway (Table 5-1). For elective CTVs (rectum and anus) the CT CTV was rigidly transferred to the MR and manually adjusted to anatomical boundaries, accounting for anatomical changes between CT and MR, for example differences in the mesorectum boundary.

Anus		Rectum	
Target volume	**Definition**	**Target volume**	**Definition**
GTV	Macroscopic primary tumour only	GTV	CT: Macroscopic primary tumour extended to whole lumen and identified nodal tumours MR: Macroscopic primary tumour only
CTVA	T1/2: GTV + 1.0 cm enlarged to include the whole of the anal canal and external sphincters T3/4: GTV + 1.5 cm enlarged to include the whole of the anal canal and external sphincters	CTVA	GTV + 1.0 cm
		CTVB	Elective anatomically defined volume including the mesorectum, pre-sacral, internal iliac and pelvic side-wall nodes
PTVA	CTVA + 1.0 cm	CTVF	CTVA + CTVB
GTVBoost	GTV + 0.5 cm	PTV	CTVF + 1.5 cm (anterior) and 1 cm (all other directions)
GTVN	Identified nodal tumours	GTVBoost	GTV + 1.0 cm
CTVN	GTVN + 0.5 cm		
PTVN	CTVN + 0.5 cm		
CTVE	Elective anatomically defined volume including the mesorectal, bilateral inguinal, internal and external iliac nodes to 2cm above the lower border of sacroiliac joints, presacral nodes (or 1.5 cm superior from the most superior GTV)	X	
PTVE	CTVE + 0.5 cm		

Table 5-1. Target volume delineations and their definitions for anal and rectal cancers, including GTV (gross tumour volume), GTVN (nodal gross tumour volume), GTVBoost (boost gross tumour volume), CTVA (primary clinical target volume), CTVB/E (elective clinical target volume), CTVN (nodal clinical target volume), CTVF (final clinical target volume), PTV/PTVA (primary planning target volume), PTVN (nodal planning target volume) and PTVE (elective planning target volume).

OARs were delineated on CT and MR by experienced dosimetrists and included bladder, small bowel, sigmoid, penile bulb, vagina, uterus (rectum and anus), bowel cavity (rectum only), femoral heads and genitalia (anus only). All OARs were assessed and amended as required by an experienced clinical scientist (DB) to ensure accuracy. Genitalia OARs (delineated from anatomical landmarks) were delineated on CT and rigidly transferred to MR to ensure consistency. Penile bulb, vagina and uterus were delineated on MR and transferred to CT (rigid registration: penile bulb, deformable registration: vagina and uterus). These registrations were undertaken and

validated through visual assessment by an experienced physicist (DB) who specialises in MR-CT registrations. The decision to transfer the OARs from MR was made because of the poor visualisation of these OARs on CT. All MR TVs and OARs were rigidly transferred to the sCT from the MR to allow radiotherapy treatment planning to occur.

5.3.3 Target volume analysis

Volumetric and positional TV analyses were undertaken. The positional analysis compared the overlap of CT and MR volumes using sensitivity and specificity measures - the volume overlap between CT and MR contours, as a percentage of the volume of CT (sensitivity) or MR (specificity) respectively.

5.3.4 Radiotherapy treatment planning

VMAT plans were created and optimised for each patient's CT and sCT scan independently by a single experienced clinical scientist (DB) following the centre's clinical protocol. Plans were optimised for the delineated TVs and OARs, in Raystation 8b, using the collapsed cone photon algorithm on a dose grid of 3x3x3 mm^3 and beam arrangements seen in Table 5-6 (5.7 Supplementary information). Rectum plans were prescribed as 45 Gy in 25 fractions to the primary PTV and anus plans were prescribed to a three dose level technique with 53.2 Gy, 50.4 Gy and 40.0 Gy in 28 fractions to the primary, nodal and elective PTVs respectively (subsequently referred to as "standard" plans). To increase the homogeneity of prescription doses we opted to standardise the dose prescription for each cancer site (in practice some patients received 25Gy in 5 for rectal cancers and 50.4Gy for T1/2N0 anal cancers).

Dose escalation plans ("Boost" plans) were also generated to assess the impact of dose escalation to GTV-based ("GTVBoost") structures with 61.6 Gy and 55 Gy prescribed for anus and rectum respectively. GTVBoost prescription doses were chosen according to clinical trials assessing GTV dose escalation (13–15). Boost plans were created by copying each standard plan, adding optimisation constraints and objectives for the GTVBoost contour and re-optimising the plan. All

treatment plan optimisation parameters and clinical objectives can be seen in Table 5-7 and Table 5-8 (5.7 Supplementary information).

All plans were optimised to meet target coverage constraints while minimising OAR doses. To reduce uncertainty and operator variability, the planning protocol was adapted to include a high mandatory coverage goal for all PTVs, with the rationale that high target coverage prevents subjective, plan specific, local areas of poor PTV coverage within the plan objectives which may impact OAR dose reductions.

5.3.5 VMAT plan analysis

As all plans had strict TV coverage criteria, plan assessment focussed on the dosimetric differences to OARs when TV coverage was achieved. Each OAR was assessed in terms of the Vx (%), the volume of the organ as a percentage of the total organ volume, receiving x Gy in dose. DVH statistics were collected for 95, 90, 80, 70 and 60 % of the prescription dose for each standard plan and compared between CT and MR. These dose levels were chosen to allow a more comprehensive analysis of the dose-volume relationship for each OAR. Dose levels lower than 60% of the prescription dose were not assessed. For boost plans, DVH assessments focussed on the dose levels introduced by the GTVBoost prescription (52.25 Gy, 49.5 Gy and 45 Gy (rectum) and 58.5 Gy, 55.4 Gy and 53.2 Gy (anus)).

For standard and boost plans, collected DVH statistics were filtered such that if both the CT and MR DVH statistic (Vx) were ≤1% then the statistic was removed from the analysis. This removed cases where the TV and OAR were separated sufficiently that the OAR was not receiving that dose level on either plan. In all cases the femoral heads received a dose less than 60% of the prescription and consequently were removed from the analysis.

5.3.6 Statistical analysis

Linear mixed effects (LME) models in STATA (17) were applied to TV volume and OAR dose analyses to establish statistically significant differences in TVs and OAR doses attributable to the change in modality, CT and MR. Separate models were applied to each cancer site cohort (anus and rectum) and TV/OAR dose level individually. DVH statistic differences were only modelled if 5 or more patients' results were present. TV LME models used volume (cc) as the dependant variable, modality (CT and MR), sex (male and female) and staging (1, 2, 3 or 4) as fixed effects independent variables. The OAR dose LME models used DVH statistic, Vx, as the dependant variable, modality (CT and MR), sex (male and female) and organ volume as fixed effect independent variables. Patient was a random effect independent variable in all models. Organ volume was included to account for impact of variations in organ volume (for example the bladder) on the DVH statistics.

5.4 Results

Table 5-2 shows the MR TV volume differences vs. CT, their statistical significances and the positional overlap between MR and CT. TV comparisons for both anal and rectal cancers found a statistically significant systematic reduction in MR GTV (12.6 cc and 42.6 cc respectively), primary PTV (98.1 cc and 109.1 cc respectively) and GTVBoost (22.3 cc and 95.2 cc respectively) volumes compared to CT. Figure 5-1 shows box plots of the volumes of the anal and rectal radiotherapy target volumes on CT an MR. Figure 5-2 shows a visual example of the changes in GTV, CTVA and primary PTV between MR and CT for a single anus and rectum cancer case.

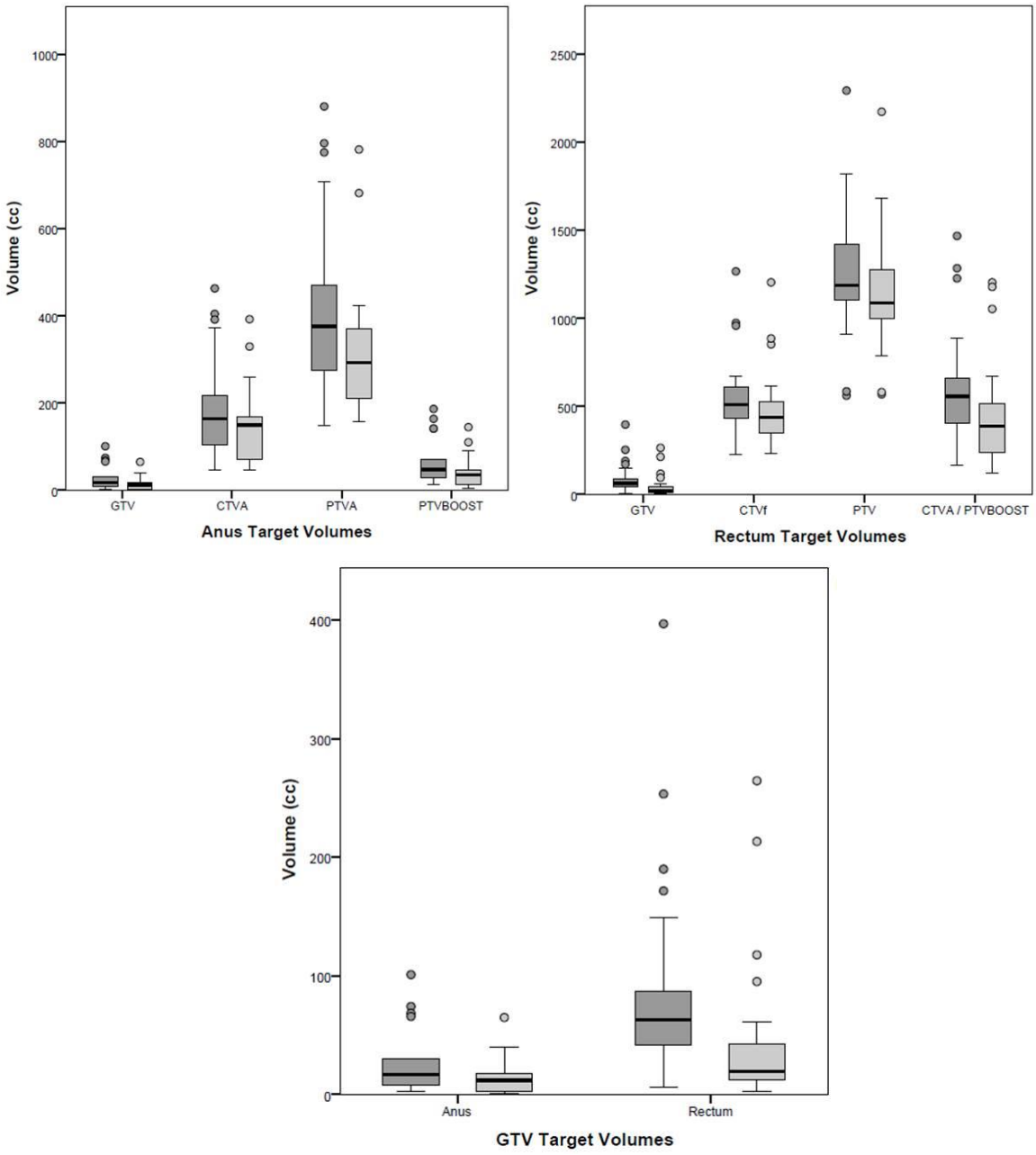

Figure 5-1. Box-plots comparing the volumes of treatment target volumes for anal cancers (top left), rectal cancers (top right) and all GTVs (bottom middle) on CT (dark grey) and MR (light grey) including the median, interquartile range and outlier values.

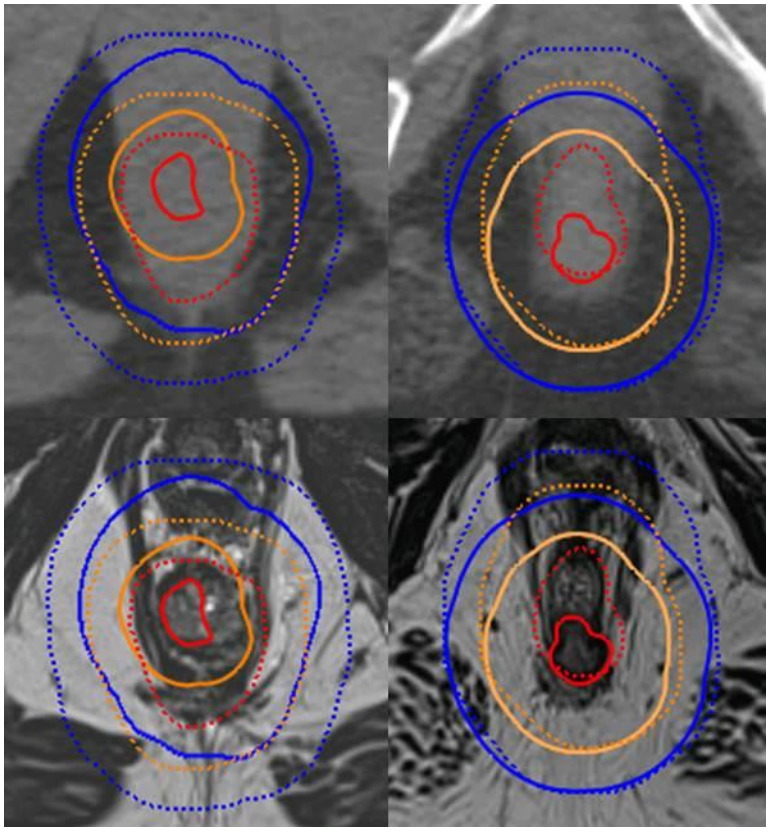

Figure 5-2. Comparison of anus (right) and rectum (left) cancer GTVs (red), CTVAs (orange) and primary PTVs (blue) for MR (bold) vs. CT (dotted) delineations on CT (top) and T2 SPACE MR (bottom) data sets.

Table 5-3 shows the dosimetric differences to OARs in standard plans between MR and CT. For anus plans, statistically significant dosimetric reductions were found on MR (vs. CT) plans for the bladder (3.8 % at V70%), penile bulb (~10 % across a range of V60-95%) and genitalia (~4 % across a range of V60-70%). Systematic dose reductions that had not reached statistical significance were also found for the vagina (~13 % across a range of V80-95%). For rectum plans, statistically significant dosimetric reductions were found on MR (vs. CT) plans for the bladder (~5 % across a range of V60-95%) and uterus (~13 % across a range of V60-95%). Systematic dose reductions that had not reached statistical significance were found for the penile bulb (~6 % across a range of V60-95%).

		MR volume effect size vs. CT (95% confidence intervals) (cc)	Mean Overlap	
			Sensitivity (% of CT)	Specificity (% of MR)
Rectum	GTV	**-43.6 (-54.8 to -32.5)**	36.4	93.7
	CTVA	**-95.2 (-116.3 to -74.3)**	57.8	95.2
	CTVB	**-11.7 (-17.1 to -6.3)**	94.5	97.6
	CTVF	**-66.0 (-80.7 to -51.4)**	85.7	98.3
	PTVA	**-109.1 (-131.1 to -87.2)**	90.3	99.0
	GTVBoost	**-95.2 (-116.3 to -74.3)**	57.8	95.2
Anus	GTV	**-12.6 (-19.5 to -5.7)**	32.5	80.3
	CTVA	**-47.7 (-72.4 to -22.9)**	66.0	87.1
	PTVA	**-98.1 (-146.1 to -50.1)**	72.4	92.0
	GTVN	-3.0 (-7.6 to 1.5)	53.5	73.0
	CTVN	-9.2 (-20.3 to 1.9)	70.7	84.5
	PTVN	**-24.5 (-47.0 to -2.1)**	74.4	91.9
	CTVE-all	**-35.0 (-56.6 to -13.4)**	89.8	94.7
	PTVE-all	**-106.8 (-144.7 to -68.9)**	88.1	94.2
	GTVBoost	**-22.3 (-33.7 to -10.9)**	46.9	81.8

Table 5-2. The MR TV differences in volume compared to CT and the mean sensitivity and specificity overlap for each target volume between MR and CT over the whole patient cohort, where effect size is the systematic difference between MR and CT volumes (a negative value indicates that MR is smaller than CT). Bold effect size values indicate statistically significant confidence intervals.

Standard Plans	Dose level	Anus		Rectum	
		Number of patients	Vx effect size (95% confidence intervals) (%)	Number of patients	Vx effect size (95% confidence intervals) (%)
Bladder	**V95%**	5	-1.1 (-3.6 to 1.4)	28	**-5.3 (-8.2 to -2.4)**
	V90%	5	-1.1 (-4.9 to 2.7)	28	**-5.4 (-8.3 to -2.5)**
	V80%	7	-0.6 (-5.6 to 4.4)	28	**-5.3 (-8.2 to -2.4)**
	V70%	17	**-3.8 (-6.4 to -1.2)**	28	**-5.2 (-8.2 to -2.3)**
	V60%	17	-4.1 (-8.6 to 0.3)	28	**-5.2 (-8.2 to -2.2)**
Small bowel	**V95%**	0	-	23	-1.0 (-5.4 to 3.4)
	V90%	1	-	23	-0.9 (-5.6 to 3.7)
	V80%	3	-	23	-0.9 (-5.6 to 3.7)
	V70%	13	2.0 (-2.0 to 5.9)	23	-0.8 (-6.1 to 4.4)
	V60%	14	5.0 (-0.7 to 10.7)	23	-0.8 (-6.7 to 5.0)
Sigmoid	**V95%**	2	-	29	-3.0 (-7.1 to 1.1)
	V90%	3	-	29	-2.7 (-6.9 to 1.5)
	V80%	5	-1.5 (-6.5 to 3.5)	29	-1.8 (-6.3 to 2.7)
	V70%	17	-2.7 (-9.6 to 4.3)	29	-1.0 (-5.7 to 3.7)
	V60%	17	-2.5 (-11.1 to 6.0)	29	-0.6 (-5.7 to 4.5)
Vagina	**V95%**	8	-12.5 (-29.2 to 4.2)	14	0.7 (-1.3 to 2.6)
	V90%	8	-12.9 (-28.9 to 3.2)	14	0.5 (-1.3 to 2.3)
	V80%	8	-16.0 (-33.4 to 1.4)	14	0.1 (-1.3 to 1.6)
	V70%	8	-3.5 (-7.7 to 0.7)	14	0.2 (-1.1 to 1.5)
	V60%	8	1.1 (-0.5 to 2.7)	14	0.7 (-0.7 to 2.1)
Uterus	**V95%**	2	-	13	**-15.9 (-24.4 to -7.4)**
	V90%	2	-	13	**-14.9 (-23.8 to -6.1)**
	V80%	3	-	13	**-13.8 (-22.6 to -4.9)**
	V70%	7	-10.4 (-27.3 to 6.6)	13	**-12.8 (-21.3 to -4.3)**
	V60%	7	2.6 (-24.3 to 29.6)	13	**-11.8 (-20.3 to -3.2)**
Penile Bulb	**V95%**	9	**-11.2 (19.9 to -2.5)**	6	-7.3 (-27.2 to 12.5)
	V90%	9	**-9.6 (-16.4 to -2.7)**	9	-5.4 (-18.4 to 7.6)
	V80%	9	**-8.3 (-15.5 to -1.2)**	9	-6.0 (-18.2 to 6.2)
	V70%	9	**-8.4 (-16.2 to -0.7)**	9	-7.3 (-18.8 to 4.2)
	V60%	9	**-8.8 (-16.8 to -0.7)**	10	-9.7 (-21.5 to 2.1)
Genitalia	**V95%**	5	-4.8 (-11.0 to 1.3)		
	V90%	5	-5.2 (-12.0 to 1.6)		
	V80%	6	-5.1 (-11.5 to 1.3)		-
	V70%	11	**-4.0 (-7.5 to -0.5)**		
	V60%	17	**-3.5 (-5.7 to -1.3)**		

Table 5-3. The MR dosimetric differences to OARs in standard plans for anal and rectal cancer treatments, where volume effect size is the systematic difference in volume of each organ receiving x Gy of dose on MR vs. CT (a negative value indicated a lower dose on MR compared to CT). Bold effect size values indicate statistically significant confidence intervals. "Number of patients" is the number of patients whose DVH statistics were >1% on both CT and MR and therefore included in the analysis.

Boost Plans	Anus			Rectum		
	Dose level	Number of patients	Vx Effect size (95% confidence intervals) (%)	Dose level	Number of patients	Vx effect size (95% confidence intervals) (%)
Bladder	V58.5	0	-	V52.25	11	-1.8 (-4.2 to 0.6)
	V55.4	0	-	V49.5	11	-3.0 (-6.1 to 0.1)
	V53.2	2	-	V45	27	**-4.6 (-7.6 to -1.7)**
Small	V58.5	0	-	V52.25	8	**-3.4 (5.9 to -0.8)**
bowel	V55.4	0	-	V49.5	8	**-3.6 (-6.7 to -0.5)**
	V53.2	0	-	V45	23	-1.0 (-3.9 to 1.9)
Sigmoid	V58.5	0	-	V52.25	16	**-6.4 (-9.1 to -3.7)**
	V55.4	0	-	V49.5	16	**-6.4 (-9.6 to -3.3)**
	V53.2	1	-	V45	29	**-4.6 (8.9 to -0.4)**
Vagina	V58.5	7	**-4.4 (-8.0 to -0.8)**	V52.25	13	**-13.6 (-26.3 to -0.9)**
	V55.4	7	-8.7 (-22.0 to 4.7)	V49.5	14	-6.9 (-17.1 to 3.2)
	V53.2	8	-11.1 (-28.3 to 6.0)	V45	14	-1.7 (-5.7 to 2.2)
Uterus	V58.5	0	-	V52.25	11	**-19.8 (-30.7 to -9.0)**
	V55.4	1	-	V49.5	12	**-21.9 (-32.7 to -11.2)**
	V53.2	2	-	V45	13	**-19.6 (-26.9 to - 12.3)**
Penile	V58.5	3	-	V52.25	3	-
Bulb	V55.4	7	-22.4 (-49.2 to 4.4)	V49.5	4	-
	V53.2	8	**-15.4 (-30.3 to -0.5)**	V45	6	**-11.5 (-34.3 to -11.3)**
Genitalia	V58.5	2	-			
	V55.4	3	-		-	
	V53.2	4	-			

Table 5-4. The MR dosimetric differences to OARs in boost plans for anal and rectal cancer treatments, where volume effect size is the systematic difference in volume of each organ receiving x Gy of dose on MR vs. CT (a negative value indicated a lower dose on MR compared to CT). Bold effect size values indicate statistically significant confidence intervals. "Number of patients" is the number of patients whose DVH statistics were <1% on both CT and MR and therefore included in the analysis.

Table 5-4 shows the dosimetric differences to organs in boost plans between CT and MR. For anus plans, statistically significant dosimetric reductions were found for the vagina (4.4 % at V58.5Gy) and penile bulb (15.4 % at V53.2Gy). For rectum boost plans, statistically significant dosimetric reductions were found for the bladder (4.6 % at V45Gy), small bowel (~3.5 % across a range of

V49.5-52.25Gy), sigmoid (~6 % across a range of V45-52.25Gy), vagina (13.6 % at V52.25Gy), uterus (~20 % across a range of V45-52.25Gy) and penile bulb (11.5 % at V45Gy).

5.5 Discussion

A challenge to widespread adoption of MR-only radiotherapy treatment planning is the lack of evidence within the literature demonstrating its benefit in terms of improving treatments. Here we provide evidence that utilising an MR-only radiotherapy pathway for anal and rectal cancers makes statistically significant changes to TV volumes and treatment plan OAR doses, in terms of reductions in volume (~100 cc for PTV/PTVA) and dose-volume parameters (5 to 20 %) compared to a CT-only pathway. These TV and treatment plan changes can be considered evidence of benefit, as smaller TVs result in less irradiated tissue, and lower normal tissue doses can be expected to lead to reduced organ toxicities (18). It is important to recognise that while we have compared an MR-only radiotherapy pathway to a CT-only pathway, many centres with radiotherapy MR provision employ a CT-MR pathway. Our findings are more difficult to apply to CT-MR pathways which, compared to MR-only, introduce co-registration errors. As such the treatment changes we present here would likely be smaller for a CT-MR pathway. However, our findings can also broadly be applied to MR-CT pathways and therefore add to a growing body of evidence that the introduction of MR can improve treatments, whether through MR-only or CT-MR pathways, which has not previously been shown in the literature in these terms.

Our findings showed that the improved soft tissue visualisation of MR translated into reduced TV volumes for both anal and rectal cancers. GTV volumes were reduced significantly as suggested by diagnostic CT vs. MR comparisons in the literature (9,10) and this translated through to reductions in primary PTV volumes. The resultant ~100 cc reduction in PTV volume is a significant amount of tissue which will be spared a high (prescription level) dose. Both cancer sites also saw significant reductions in anatomically defined CTVB/E volumes from CT to MR. A visual assessment of the CTVs showed that this was due to an improvement in tissue visualisation at the mesorectum anterior border, where it is difficult to define the mesorectum, vagina and seminal vesicle borders on CT. This soft-tissue contrast improvement has the potential to also improve clinician confidence, speed and inter-observer variability when delineating, although assessing this was

beyond the scope of this study. The GTVBoost volume reductions also add evidence that MR based radiotherapy treatment planning may have a greater impact on GTV boost treatments. Our positional differences between MR and CT delineated TVs showed the specificity of TVs (overlap as a percentage of the MR volume) was much higher than the sensitivity (overlap as a percentage of the CT volume), suggesting that MR volumes are not only smaller than CT, but also predominantly within the CT volumes which adds strength to the hypothesis that MR improves the visualisation of TVs. It is notable that our delineation protocol for rectum GTVs varied between CT and MR, where CT GTVs included the whole lumen but MR GTVs included the visible tumour only. This was due to the soft tissue contrast of MR enabling a systematic change in delineation protocol through improved visualisation and it is the impact of this improved visualisation that we have quantified here. This introduces a bias into the comparison, where it is expected that the GTV volume would reduce when delineated on MR compared to CT. However, here we have deliberately compared current clinical practice for a CT-only workflow to an MR-only workflow, where the lack of soft-tissue visualisation on CT necessitates the GTV including the whole lumen.

Our standard treatment plan analysis found statistically significant reductions in OAR doses for both cancer sites. This provides evidence that MR-only radiotherapy treatment planning makes a quantitatively significant improvement to treatment plans compared to CT-only pathways. The OAR dose changes that we saw here are logical. For standard plans we saw that the organs closest to the primary GTV - the sexual organs for anal cancers (19) and the bladder and uterus for rectum cancers - had statistically significant systematic dose reductions, whereas we saw no change to the small bowel dose which is predominantly the organ furthest from the GTV. There were also a number of organs that had systematic dose reductions that had not reached statistical significance. While less definitive, these findings should also be viewed positively and suggest that there may be additional benefit assessed in a larger cohort. Our dose escalation (boost) plan analysis also suggests that MR boost plans were able to improve the sparing of OARs very close to the primary GTV, for example the vagina and penile bulb for anal cancers, but that for rectal cancers there was a much wider dose reduction to the majority of OARs, including small bowel and sigmoid. This can be explained by the much larger GTVBoost volume for rectal cancers compared to anal cancers, the central position of the rectum in the pelvic cavity, and the differences in the elective CTV standard plan dose prescription between rectal and anal cancers.

There are limitations to this study. It is known that some tumour shrinkage occurs during treatment as shown by Van den Begin (20) who found for rectal cancers MRI GTVs vs. a pre-treatment baseline volume that tumour shrinkage of up to 10 % after 1 week (5 fractions) and 26 % after 2 weeks (10 fractions) can occur. Logistical challenges meant it was necessary to accept acquiring MR scans after patient treatments had started and this had the potential to bias our findings. However, to assess this we stratified our CT to MR GTV volume findings by MR acquisition date and found that for both anal and rectal cancers there was no correlation between MR scan timing and average GTV reduction vs. CT (pre-treatment = 53 % , week 1 = 44 % and week 2 = 56 %). It is possible that some component of the tumour reduction we identified here has been caused by treatment, however, the GTV reductions seen here are much larger than those demonstrated due to treatment by Van den Begin and consequently, it is more likely that the large reduction in GTV caused by improved MR tissue visualisation substantially outweighs the impact of treatment GTV changes.

It is possible that the OAR dose reductions found here may be insufficient to produce meaningful toxicity reductions. Future work would benefit from assessing the impact of these dose reductions on normal tissue complication probability for the organs highlighted here. However this is a non-trivial assessment to undertake and as such it was outside the scope of this study to assess dose-toxicity relationships. We also did not assess OAR changes in relation to the position of the tumour, however our use of filtering DVH statistics was designed to reduce the impact of this on our analysis. Further work would be beneficial to investigate whether it's possible to prospectively identify patients who would benefit most from MR-only planning, prior to simulation. A challenge with planning studies is ensuring that treatment plan differences are not due to inter-operator variability in delineations and planning. Here, there was the potential for inter-operator variability as the clinicians delineating GTVs differed between CT and MR. However, we aimed to avoid significant inter-operator variability through delineations being undertaken by experienced consultants, following our local clinical protocols with additional training, stricter planning constraints, and oversight by a single physicist for consistency. The simulation protocols also minimised our OAR volume differences and the uncertainty this can cause between CT and MR as seen in Table 5-9.

There is also an argument that reducing target volumes due to a change in imaging modality could have a negative effect on tumour control probability as our understanding of required treatment

dose levels stems from CT based targets and the reduction of the target volumes is in essence removing implicit margins caused by a lack of contrast on CT. This argument highlights the need for caution when assessing new techniques such as MR-only planning.

Our findings suggest that MR-only radiotherapy treatment planning can be considered to be an improvement in the personalisation of radiotherapy treatments, compared to CT-only, as it allows clearer visualisation of individual patient anatomy. Here we aimed to assess the impact of MR-only radiotherapy treatment planning on target volumes and treatment plan doses to OARs for anal and rectal cancers when compared to a routine CT-only pathway. Our findings provide evidence that MR-only radiotherapy treatment planning for anal and rectal cancers results in statistically significant reductions in TV volumes and reduced doses to a number of OARs. This suggests that patients could benefit from MR-only (or CT-MR) radiotherapy treatment planning with the potential for improved patient outcomes, if OAR dose reductions translate into less treatment related toxicity or support GTV dose escalation.

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5.7 Supplementary information

		Anus (total 17)	Rectum (total 29)
Age	**Mean (Range)**	63 (47 - 76)	63 (38 - 78)
Sex	**Male**	9	15
	Female	8	14
Staging	**T1**	2	1
	T2	5	11
	T3	9	16
	T4	1	1
MR scan acquired	**Pre-treatment**	6	13
	Fraction 1-5	4	9
	Fraction 6-10	6	6
	Fraction 11-13	1	1

Table 5-5. Anal and rectal cancer patient demographics

		Anus	Rectum
Modality		Photons	
Technique		VMAT	
Prescription type		"Average Dose"	
Isocentre Position		Centre of PTV	
Energy (MV)		6MV FFF	
Beam arrangement		360 º arc (starting at 180 º)	
Beam optimisation settings		Dual arc	
Standard Plan Prescription	PTV	53.2 Gy in 28 fractions	45 Gy in 25 fractions
	PTVN	50.4 Gy in 28 fractions	X
	PTVE	40 Gy in 28 fractions	X
Boost plan additional prescription	GTVBoost	61.6 Gy in 28 fractions	55 Gy in 25 fractions

Table 5-6. Treatment plan beam arrangement and prescription parameters for standard plans.

	Optimisation objectives					
	Rectum			Anus		
	Target volume/OAR	**Objective**	**Description**	**Target volume/OAR**	**Objective**	**Description**
Standard plan	**PTV**	Min Dose	45 Gy	**PTV**	Min Dose	53.2 Gy
		Uniform Dose	45 Gy		Uniform Dose	53.2 Gy
	Patient External	Dose Fall Off	High: 45 Gy, Low: 25 Gy, Distance: 1.5cm	**PTVN - PTV**	Min Dose	50.4 Gy
		Dose Fall Off	High: 25 Gy, Low: 0 Gy, Distance: 6.0cm		Uniform Dose	50.4 Gy
	Bladder-PTV	Max DVH	20.0 Gy to 30 %		Dose Fall Off	High: 53.2 Gy, Low: 50.4 Gy, Distance: 2.0 cm
	Bowel Cavity - PTV	Max DVH	20.0 Gy to 30 %	**PTVE - (PTV+PTVN)**	Min Dose	40 Gy
	Penile Bulb - PTV	Max DVH	20 Gy to 35 %		Dose Fall Off	High: 53.2 Gy, Low: 40.0 Gy, Distance: 2.0 cm
	Uterus - PTV	Max DVH	20 Gy to 35 %	**Patient External**	Dose Fall Off	High: 53.2 Gy, Low: 25 Gy, Distance: 1.5cm
	Vagina - PTV	Max DVH	20 Gy to 35 %		Dose Fall Off	High: 53.2 Gy, Low: 0 Gy, Distance: 6.0cm
				Bladder - PTVs	Max DVH	20 Gy to 35 %
				Small Bowel - PTVs	Max DVH	20 Gy to 35 %
				Femoral Heads - PTVs	Max DVH	20 Gy to 35 %
		X		**Genitalia - PTVs**	Max DVH	20 Gy to 35 %
				Penile Bulb - PTVs	Max DVH	20 Gy to 35 %
				Uterus - PTVs	Max DVH	20 Gy to 35 %
				Vagina - PTVs	Max DVH	20 Gy to 35 %
Boost plan objectives	**GTVBoost**	Min Dose	55.0 Gy	**GTVBoost**	Min Dose	61.6 Gy
		Uniform Dose	55.0 Gy		Uniform Dose	61.6 Gy
	PTV	Dose Fall Off	High: 55.0 Gy, Low: 45.0 Gy, Distance: 1.0 cm	**PTV**	Dose Fall Off	High: 61.6 Gy, Low: 53.2 Gy, Distance: 1.0 cm

Table 5-7. Treatment plan initial optimisation parameters for standard and boost plans for anal and rectal cancers.

	Clinical Objectives					
	Rectum			Anus		
	Target volume/OAR	Objective	Goal	Target volume/ OAR	Objective	Goal
Standard plan	PTV	V42.75Gy (95%)	>99.5 %	PTV	D99.5%	≥95 % (50.54 Gy)
		V47.25Gy (105%)	<0.1 %		D50%	≥99 % (52.6 Gy) and ≤101 % (53.7 Gy)
		D50%	≥99 % (44.55 Gy) and ≤101 % (45.45 Gy)		D1%	≤ 105 % (55.9 Gy)
	Bowel Cavity	V20Gy	<400 cc	PTVN - PTV	D99.5%	≥95 % (47.9 Gy)
		V30Gy	<250 cc		D50%	≤ 105 % (55.9 Gy)
	Bladder	V43Gy	<200 cc	PTVE - (PTV+ PTVN)	D99.5%	≥95 % (38.0 Gy)
		V35Gy	<45 %		D50%	≤ 110 % (44.0 Gy)
				Small Bowel	D200cc	≤35 Gy
					D150cc	≤40 Gy
					D20cc	≤50 Gy
		X		Bladder	D5cc	≤55 Gy
					D50%	≤45 Gy
					D35%	≤50 Gy
					D5%	≤55 Gy
				Femoral Heads	D50%	≤45 Gy
					D35%	≤50 Gy
					D5%	≤55 Gy
				Genitalia	D50%	≤35 Gy
					D35%	≤40 Gy
					D5%	≤55 Gy
Boost plan objectives	GTVBoost	V52.25Gy (95%)	>99.5 %	GTVBoost	D99.5%	≥95 % (58.1 Gy)
		V52.25Gy (105%)	<0.1 %		D50%	≥99 % (61.0 Gy) and ≤101 % (62.2 Gy)

Table 5-8. Treatment plan clinical objectives for standard and boost plans for anal and rectal cancers.

		CT (cc)	MR (cc)	Difference (cc)
Rectum	**Bladder**	275 (48-962, 170)	305 (32-746, 167)	30 (-266-458, 169)
	Sigmoid	108 (23-309, 76)	92 (10-310, 77)	-16 (-126-28, 34)
	Small Bowel	264 (0-741, 179)	225 (0-659, 148)	-30 (-406-202, 125)
	Penile Bulb	6 (2-11, 2)	6 (2-11, 2)	0 (0, 0)
	Vagina	18 (9-41, 9)	15 (8-31, 7)	-3 (-10-1, 3)
	Uterus	61 (9-116, 31)	57 (22-108, 28)	-4 (-20-15, 10)
Anus	**Bladder**	318 (95-813, 186)	324 (44-891, 202)	6 (-180-322, 13)
	Sigmoid	156 (36-381, 97)	127 (14-366, 84)	-29 (-99-61, 43)
	Small Bowel	284 (27-818, 212)	212 (50-527, 143)	-72 (-292-136, 109)
	Penile Bulb	5 (2-11, 3)	5 (2-11, 3)	0 (0, 0)
	Vagina	13 (8-25, 6)	12 (5-18, 5)	-2 (-7-2, 3)
	Uterus	34 (13-64, 16)	31 (14-55, 12.5)	-3 (-9-6, 5)
	Genitalia	298 (58-686, 181)	297 (56.8-686, 181)	0 (0, 0)

Table 5-9. Organ volumes on CT and MR for anal and rectal cancer patients including: mean (range, SD).

Chapter 6 Assessing the patient experience of anal and rectal cancer MR simulation for radiotherapy treatment planning

6.1 Abstract

Aim: The patient experience of radiotherapy MR simulation is unknown. This study aims to evaluate the patient experience of MR simulation in comparison to CT simulation, identifying the quality of patient experience and pathway changes which could improve patient experience outcomes.

Materials and Methods: MR simulation was acquired for 46 anal and rectal cancer patients. Patient experience questionnaires were provided directly after MR simulation. Questionnaire responses were assessed after 33 patients (cohort one). Changes to the scanning pathway were identified and implemented. The impact of changes was assessed by cohort two (13 patients).

Results: Response rates were 85 % (cohort one) and 54 % (cohort two). 75 % of cohort one respondents found the MRI experience to be better or similar to their CT experience. Implemented changes included: routine use of blankets, earplugs and headphones, music and feet-first positioning and further MRI protocol optimisation. All cohort two respondents found the MRI experience to be better or similar to the CT experience.

Findings: MR simulation can be a comfortable and positive experience which is comparable to that of standard radiotherapy CT simulation. Special attention is required due to the fundamental differences between CT and MRI scanning.

6.2 Introduction

Computed tomography (CT) scans in the patient radiotherapy treatment position (CT simulation) are routinely acquired within radiotherapy departments as they are used for planning radiotherapy treatments. CT simulation is important as it provides the patients' anatomical data for planning and delivering radiotherapy treatments (1). Radiotherapy staff use their substantial experience of CT to inform scanning protocols which are designed to provide optimal patient experience and data collection.

Many radiotherapy departments within the United Kingdom (UK) do not use dedicated radiotherapy MRI within the pre-treatment pathway, with only 6 % of radiotherapy patient treatments employing MRI guidance in 2018 (2). In most cases within the UK where MRI is utilised, it is in addition to the standard of care CT pathway. The majority of radiotherapy departments rely on scanners in diagnostic MRI departments as only a small number of radiotherapy centres have dedicated radiotherapy MRI equipment (2). However, a rationale for increased use of MRI in radiotherapy is building, through increased evidence of the benefit to patients (3), the development of new techniques such as MR-only planning (4), recommendations from national bodies (5) and the availability of hybrid MR-linacs. Some specialist centres now acquire additional dedicated MRI scans with the patient in the radiotherapy treatment position (MR simulation) and this is likely to become more widespread as new techniques, such as MR-only planning, develop (4). However, as the MRI examination process is substantially different to CT simulation, both in terms of the resultant images and the method of acquisition, it is a challenge to directly relate patient CT and MR simulation experiences. It is vital that the MR simulation process is optimised so that patient experiences are not compromised.

Studies of patient experiences when undergoing diagnostic MRI scanning show that that patients can experience anxiety or claustrophobia prior to or during an MRI scan and that anxious patients are more likely to move resulting in motion artefacts which impairs the quality of the acquired data (6,7). It is therefore hypothesised that in the context of MR simulation, patient anxiety may impact on the image quality, limiting the potential benefit of MRI within radiotherapy, as well as negatively impacting patient treatment experience. However, while we can learn much from diagnostic imaging studies investigating patient experience, radiotherapy imaging differs due to the requirement for specialist immobilisation equipment and specific preparation and scanning

protocols (4,8). These differences have the potential to significantly impact patient experience and as a consequence it is challenging to compare diagnostic MRI to MR simulation. To our knowledge, the only assessment of patient experience in MRI in radiotherapy in the literature assessed the tolerability of MR simulation for patients with lung cancer, and found that one third of patients had adverse anxiety during their scan, recommending that comfort should be a key consideration for optimising these scans (8).

The results presented in this study are part of a wider study looking at MR-only planning for anal and rectal cancers, where dedicated MR simulation scans were acquired. This sub-study aimed to evaluate the patient experience of a MR simulation for ano-rectal cancer patients when compared to their CT simulation, identifying the quality of patient experience, areas where patient experience could be improved and whether changes can be implemented which improve patient experience outcomes.

6.3 Method

This study is part of a wider MR-only radiotherapy study: “Mri-only treAtmeNT planning for Anal and Rectal cAncer radiotherapy” (MANTA-RAY), research ethics committee reference: 18/LO/1298, ISRCTN Registry: ISRCTN82734641. MR simulation scans for guiding radiotherapy treatment planning were acquired between October 2018 and March 2020 at a single centre. Forty six ano-rectal cancer patients (Table 6-1) who were due to undergo radical VMAT (volumetric modulated arc therapy) external beam radiotherapy were consented to have an additional research MRI scan in addition to the standard of care imaging pathway. Exclusion criteria included contra-indications to MRI.

		Cohort 1		Cohort 2	
		Responders	**Non-Responders**	**Responders**	**Non-Responders**
Mean Age (Range) (years)		63 (37-78)	63 (46-76)	62 (50-75)	59 (42-72)
Sex	**Male**	18 (85 %)	3 (14 %)	1 (33 %)	2 (67 %)
	Female	10 (83 %)	2 (17 %)	6 (60 %)	4 (40 %)
Site	**Rectum**	20 (95 %)	1 (5 %)	5 (63 %)	3 (38 %)
	Anus	8 (67 %)	4 (33 %)	2 (40 %)	3 (60 %)
Total patient numbers		**28 (85 %)**	**5 (15 %)**	**7 (54 %)**	**6 (46 %)**

Table 6-1. Demographics of study patients including responders and non-responders.

MRI scans were acquired on a 1.5 T Siemens Aera (Siemens Healthineers, Airlanger, Germany), with radiotherapy radiographers positioning patients on the MRI scanner couch and diagnostic MRI radiographers leading the scanning session. Patients were routinely set up “head first” to match their CT simulation, but were offered a ‘feet first’ scan if they indicated prior to consenting that they found MRI claustrophobic. Patient preparation was also matched between patient’s CT and MR simulation and included a bladder filling protocol and immobilisation indexed to an in-house built radiotherapy flat top couch (knee block and ProStep for rectal cancers, knee block for anal cancers). Buscopan (20 mg) was administered intravenously to patients to reduce muscle motion within the bowels five minutes prior to their MRI. Headphones were placed over the ears of the patients who were given a choice of music or no music to listen to during the examination. MR compatible coil bridges were used to keep the MRI coils from touching and consequently deforming the patient skin position. Axial T2-SPACE (sampling perfection with application optimized contrasts using different flip angle evolution), T2 and DWI (diffusion weighted imaging) MRI scans were acquired.

In order to reduce the inconvenience to the patients, an attempt to schedule the CT and MRI appointments on the same day was made. However, this was not possible for some patients and

in these cases the MRI scan was scheduled for a time when the patient had a clinical appointment prior to or during their first two weeks of treatment. Consequently the mean time between patient CT and MR simulation appointments for all anal and rectal cancer patients recruited at the LCC was 15.1 days (range: 0 to 43 days) where CT simulation was always carried out first.

An audit of MR examination time was carried out by calculating the difference in acquisition time between the first and last acquired sequences from scan data collected from PACS (picture archiving and communication system). No measures of time prior to or after MR sequence acquisition, for example time for patient set up, were acquired as this was outside the scope of this study. Examination time was calculated for all patients, including those who did not respond to the questionnaire to allow a complete assessment of scan duration between cohorts. The number of scanning sessions that were terminated prior to completion were noted and removed from the sample prior to calculation.

The questionnaire was co-designed by the local patient and public involvement group to ensure its suitability for assessing patient experience. We chose to use a locally designed questionnaire, rather than a validated questionnaire from the literature, as it allowed us to concisely ask the specific questions we felt were required to achieve the aims of this study, which were to compare CT and MR simulation. The questionnaire (Table 6-2) consisted of both multiple choice and free-text questions. The content of the questions were designed to assess similarity of the MR simulation compared to the CT simulation and to establish options for further improvement of the patient experience. Multiple choice questions allowed patients to rate aspects of the MRI scan on a Likert scale. Patient experience questionnaires were provided to participants in a paper format directly after their MRI scan, this was provided with a stamped addressed envelope for ease of returning.

Quantitative and qualitative analysis was performed on the responses of the first 33 patients (cohort one). Quantitative analyses were performed on multiple choice questions using a Likert scale and were used to give a general overview of the participants' experiences. Qualitative analyses were performed on the open-ended questions to gain insight into the aspects of the MR simulation that affected patient experiences. Common response themes were identified, and the recurrence of themes was quantified for both positive and negative responses.

	Question	Available responses				
1	Overall how comfortable were you throughout the MRI scan?	Very uncomfortable	Uncomfortable	Neutral	Comfortable	Very comfortable
2	Overall how would you describe your MRI scan experience?	Very negative	Negative	Neutral	Positive	Very positive
3	Did you feel you were provided with sufficient information about what would happen while you were having your MRI scan?	Not enough		Right amount		Too much
4	Is there anything that could have been done to improve your MRI scan experience?	*Open ended text box*				
5	How did the radiotherapy MRI scan experience compare to your previous radiotherapy CT scan experience?	Worse		Similar		Better
	Please describe why in the box.	*Open ended text box*				
6	Any other comments regarding the MRI scan and your experience please write them in the box	*Open ended text box*				

Table 6-2. The questions and available responses in the questionnaire provided.

Potential changes to the MRI scan protocol to improve patient experience, based on the results of cohort one, were discussed with MRI and radiotherapy radiographers to identify feasible changes. Discussions focused on simple practical solutions to the raised experience issues and changes were confirmed where all staff groups had consensus that the solution was achievable and had potential to be beneficial. The identified changes were implemented and 13 patients (cohort two) were asked to complete the experience questionnaire. The questionnaire results from cohort two were analysed with the same method as for cohort one with the aim of assessing whether the implemented changes affected patient experience. No direct comparison between cohorts was undertaken due to the limited number of cohort two questionnaire responses.

6.4 Results

6.4.1 Cohort one

The questionnaire response rate for cohort one participants was 28/33 (85 %). The mean examination time was 29 minutes and 40 seconds (range: 18 minutes 20 seconds to 42 minutes 8 seconds). Two patient MR simulations were deliberately terminated prior to completion due to departmental delays and so were excluded from the examination time analysis.

Figure 6-1 shows the quantitative questionnaire responses (questions 1, 2, 3 and 5). Key findings include; 75 % of respondents found the MRI experience to be similar or better than the CT experience while 25 % of respondents found the MRI experience to be worse than the CT experience; 18 % of respondents described the MRI scan as uncomfortable or very uncomfortable and 11 % of respondents indicated there was not enough information prior to the MRI scan.

Seven themes including; scanner noise, information, music, length of time in scanner, room temperature, staff feedback and claustrophobia, were identified from the qualitative questionnaire responses (questions 4, 5 and 6). Table 6-3 shows the common themes observed from patient responses, the number of responses per theme and examples of patient quotes regarding these themes.

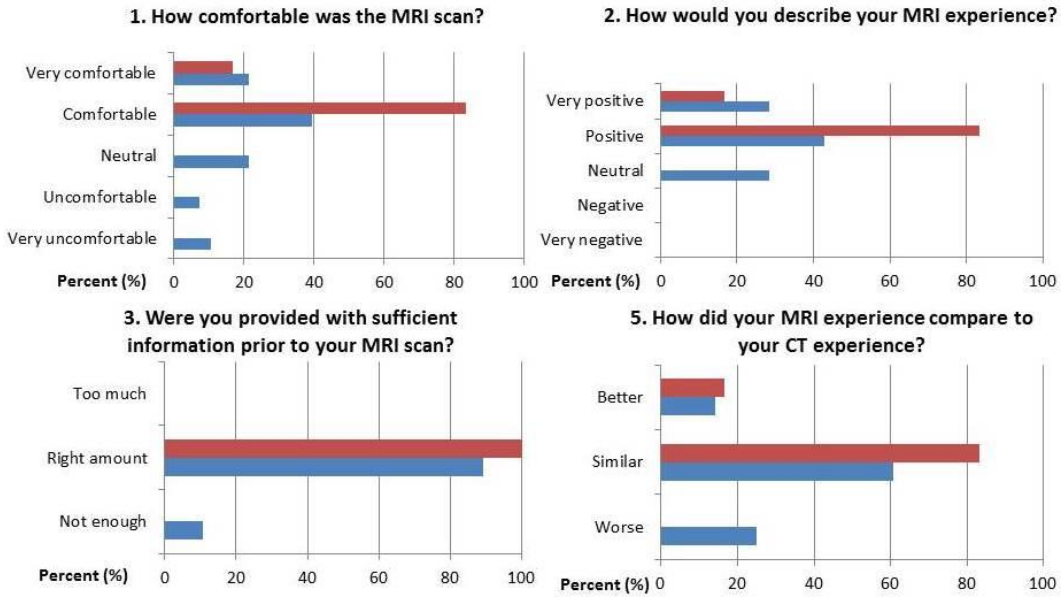

Figure 6-1. Quantitative analysis of the multiple choice responses to the questionnaire from cohort one (blue) and cohort 2 (red), where the percentage is of questionnaire responses.

6.4.2 Changes to MR simulation protocol

The following achievable changes were identified and implemented for cohort two participants:

- Use of both earplugs and headphones for all patients.
- Use of music for all patients as default unless specifically rejected by patients, ensuring that the volume is sufficient.
- Use of blankets below and above coil bridges.
- Patients scanned feet first as standard for MR simulation.
- Reduction of the scanning time by reducing the number of scans - removing the T2 sequence from the scan protocol as other phases of the exploratory research study identified it was no longer required.
- Extra staff focus on ensuring information regarding the MRI scan details, particularly the length of time for the examination, had been explained fully directly prior to MR simulation.

6.4.3 Cohort two

The questionnaire response rate for cohort two participants was 7/13 (54 %). The mean total scan time was 20 minutes and 53 seconds (range: 16 minutes 33 seconds to 28 minutes 8 seconds). No scanning sessions were ended early.

Figure 6-1 shows the quantitative questionnaire responses (questions 1, 2, 3 and 5). Key findings include; all respondents described the MRI scan as comfortable or very comfortable; all respondents indicated they had the appropriate amount of information prior to the MRI scan and all respondents found the MRI experience to be better or similar to the CT experience. The qualitative questionnaire responses were uniformly positive, and no common themes were identified.

Theme	Negative responses		Positive responses	
	Count	Example quotes	Count	Example quotes
Scanner noise and vibrations	8	"*Noisier and more vibrations"* *"The noise on an MRI is off-putting"*	0	N/A
Information provided prior	6	*"Longer scan was needed than known"* *"More explanation* [could improve MRI experience]*"*	3	*"I was well informed of everything that was happening and why"*
Music	5	*"The music on the headphones could have been turned up so that I could hear it and relax"*	1	*"Better - offered music"*
Total scan length	4	*"Too long"* *"Uncomfortable because of position for so long"*	0	N/A
Room temperature	2	*"Turn down the cold blowers"* *"The room was cold - I was provided with a blanket but had to ask"*	0	N/A
Staff feedback	2	*"I was told I could go feet first into the scanner but in the dept. forcefully told that this was not possible."*	6	*"Everyone was helpful"* *"[MRI scan was] More attentive to needs"* *"Very professional team, made feel at ease"*
Claustrophobia (Head first *vs.* feet first*)	2	*"Much more claustrophobic"*	2	*"Much easier going in feet first. I am happier and less anxious if I can at least see the ceiling"*

*Negative comments were from patients who went head first, positive comments were from patient who went feet first

Table 6-3. Thematic structure, number of respondents who address the stated theme, and direct quotes

6.5 Discussion

Here we aimed to assess the patient experience of MR simulation compared to CT simulation, where in both cases patients were positioned using radiotherapy immobilisation devices. Our findings showed that MR simulation for guiding radiotherapy treatment planning can be a comfortable and positive experience that is comparable in experience to standard radiotherapy CT simulation. This is an important finding as it provides confidence that MR simulation can be implemented into widespread use within radiotherapy without the fundamental barrier of unacceptable patient experience.

However, we also found that following a CT simulation protocol without alterations to account for the change in modality led to a significant number of patients (25 %) having experiences that were worse than CT simulation. The analysis of our qualitative responses highlighted a number of areas that affected patient experience, and the challenge was whether it was possible to address these in a practical way that didn't impact the quality of the data collection, which has precise requirements as it is for radiotherapy purposes.

MRI scanning takes place in a noisy, enclosed position for a substantial length of time. These features are necessary consequences of the design and operation of MRI scanners, which use large superconducting magnets in the acquisition of their images - the noise is a bi-product of movement (gradient coils) within the scanner as images are acquired, the enclosed position allows the magnetic field to be uniform within the scanner which is necessary for geometric accuracy and the length of time is required for producing good image quality (9). In addition, MRI scanning rooms are often deliberately cold to help prevent patients from overheating as MRI scans cause patient body temperatures to increase due to radiofrequency energy being deposited in patient tissues as images are acquired (9). However, none of these features are present for CT simulation, and as a consequence it's not surprising that these MRI specific features dominated the experience feedback from patients in cohort one.

The mean examination time for cohort one was 29 minutes and 40 seconds minutes, for cohort two this was reduced to 20 minutes and 53 seconds. This reduction was due to a combination of reducing the number of scans acquired (removing the T2 sequence saved 5 minutes 28 seconds) and improving the efficiency of the scanning session, where staff became more proficient and quicker at managing and acquiring the required sequences as they scanned more patients with

this new protocol. It was fortunate that the T2 sequence could be removed from the protocol, but this was only made possible by findings from a different phase of the wider MANTA-RAY study which meant that the T2 sequence was not required for further patients. The length of scanning time is a fundamental difference between the imaging modalities which accentuates the other differences in the environment. It's easy to attempt to compare MR simulation to diagnostic MRI scans in terms of acquisition time, and consider MR simulation to be similar in length; however an obvious difference is the patient position required for radiotherapy which can be uncomfortable due to the necessary immobilisation. In addition, our assessment only included time spent during image acquisition, in practice patients will be in an uncomfortable position for longer than this due to set up times. Our findings provide evidence that highlights the importance of optimising MR simulation protocols such that the time on the MRI couch is minimised. Particularly this is important for MR-simulation which can often be, as it was in this case, a new intervention and so experience within radiotherapy of MRI protocol optimisation is limited.

The majority of changes to the pathway were simple solutions; the default use of earplugs and headphones with music to reduce noise and provide distraction, blankets to ensure warmth, being scanned feet first rather than head first as standard to prevent patients' heads from entering the scanner bore, and therefore reduce claustrophobia, and minimising time being scanned to limit discomfort. However, the results of the questionnaires suggest that it's these small adjustments that could make a substantial improvement to the patient experience. It is notable that in some MR units interventions such as these for diagnostic MR scans are common practice; however it's important to recognise that when MR simulation is undertaken, even in a diagnostic setting as here, its radiotherapy staff who are responsible for patient set up due to the precise requirements of radiotherapy patient positioning. Therefore these learning points (that these pathway changes are suitable and beneficial for radiotherapy MR simulation) are important as they highlight the challenges of MR simulation to radiotherapy centres and also the benefit of working closely with radiology departments to fully understand our pathway differences.

Our findings from cohort two suggested that our changes were successful in improving patient experience of MR simulation as all cohort two patients found their experience to be as good as their CT simulation, unlike cohort one. However, this finding is only suggestive due to the low cohort two size, which has prevented a more rigorous analysis. Cohort two was originally aiming to recruiting 30 patients rather than 13 until the COVID-19 pandemic caused the study to close

early. Compounding this issue is the lower response rate for cohort two of 54 % vs. 85 % for cohort one which was unexpected. This drop in response rate isn't easily explainable as the only changes to the patient pathway between cohort one and two were those to improve patient experience and the patient demographics (Table 1) of the two cohorts show no clear bias which may impact response.

A small number of patients in cohort one felt not enough information was provided regarding the MRI scan in terms of its how long it would take and there was an isolated misunderstanding regarding patient set up which negatively affected patient experience. Patients were provided with written information sheets explaining what to expect from the MR simulation at the time of entering the study as well as being verbally informed on what to expect by the study recruitment team and radiotherapy and MRI radiographers prior to undertaking the scan. However, our findings suggest that it's challenging to always ensure the correct level of information is provided and it's plausible to suggest this would improve as radiotherapy staff become more experienced at preparing patients for MR simulation. Interestingly, although patients were not asked about staff in the questionnaire, 6 responses in the free text boxes also praised staff and this is a tribute to their professional, kind and positive attitudes. This should not be overlooked as a key factor in positive patient experiences.

Only one other study (8) to our knowledge has assessed the patient experience of MR simulation, in the context of lung radiotherapy treatments. These scans were acquired in a significantly different patient position to the ano-rectal cancer patients in this study, however the environment is comparable. The main findings of claustrophobia and noise being limiting factors were similar to those seen here. Their conclusion that two thirds of patients tolerated additional MRI scans (8) with minimal adverse anxiety levels is similar to our cohort one findings, where 75 % of patients felt the experience was similar to their standard radiotherapy CT scan. It was interesting to note that their implications for clinical practice were that comfort and patient position ought to be considered when introducing MRI into the radiotherapy pathway, as the identification of practical options for improving patient comfort was one of our aims.

6.6 Conclusions

In this study we assessed the patient experience of dedicated radiotherapy MR simulation in the context of pelvic radiotherapy treatments. We found that MR simulation can be comfortable and a positive experience that is comparable to standard radiotherapy CT simulation. Our findings also highlight the importance of taking into account the differences in scanning environment between CT and MRI to ensure comparable experience. Here we described simple changes to the MR simulation pathway that removed or mitigated the causes of worse patient experience including the routine use of blankets, earplugs and headphones, music, feet-first positioning and ensuring an optimised MRI protocol in terms of acquisition time. Our findings also showed the importance of staff to good patient experience.

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Chapter 7 Discussion

7.1 Summary of aims

The MANTA-RAY study was focussed on the development, feasibility and potential benefit of MRI-only radiotherapy treatment planning for anal and rectal cancers with the aim to address the key questions which limit the opportunity for widespread clinical implementation of this new technique. The overall hypothesis was that MRI-only planning for anal and rectal cancers is technically achievable, clinically implementable and improves patient radiotherapy treatments.

At the commencement of this study a further aim was to establish the breadth of research undertaken regarding the clinical implementation of MRI-only treatment planning for pelvic sites through a systematic review of the literature. This aimed to allow the identification of the remaining challenges and barriers to widespread clinical use, as well as highlighting the progress that has been made, to encourage centres to progress further with investigating and implementing MRI-only radiotherapy treatment planning.

MRI-only treatment planning can be considered to be technically achievable when synthetic-CT datasets can be generated with sufficient dosimetric accuracy that they are viable for clinical use in calculating radiotherapy treatment plans. Here the aim was to validate the dosimetric accuracy of a synthetic-CT generation model, showing its generalisability to all anal and rectal cancer patient treatments through its assessment over a large patient cohort and quantifying the impact on dosimetric accuracy of variables such as sex and cancer site on the model.

MRI-only treatment planning can be considered to be clinically implementable when the whole radiotherapy treatment pathway, including patient treatment position verification, can be carried out successfully with only the use of the data generated from the radiotherapy MRI scan. A further requirement is that the radiotherapy MRI scan can replace the planning CT in the treatment pathway without compromising patient experience. Here the aims were to establish the viability of using synthetic-CT or MRI as the reference image for patient treatment position verification and furthermore quantify their impact on the registration accuracy of the verification process and investigate the patient experience of radiotherapy MRI scans in comparison to a routine CT-only pathway including establishing opportunities for improving patient experience.

MRI-only treatment planning has the potential to improve patient treatments in a number of different ways, although investigating its benefit is challenging due to the multiple pathways (CT-only or CT-MRI) which it can be compared to. Here the aim was to establish the impact of MRI-only planning on target volumes and treatment plans compared to a CT-only pathway, with the hypothesis that target volumes would be reduced in size and this would result in treatment plan improvements through reduced doses to OARs when target coverage is maintained, both in standard clinical protocol and GTV dose escalation planning.

7.2 Summary of findings & their implications

7.2.1 A systematic review of the clinical implementation of pelvic magnetic resonance imaging (MR)-only external beam radiation therapy (Chapter 2)

The systematic review of the clinical implementation of pelvic MRI-only radiotherapy treatment planning, discussed in chapter 2, had five key findings including; 1) MRI-only planning has been clinically implemented for prostate cancer treatments; 2) a substantial amount of work remains to translate MRI-only planning into widespread clinical implementation for all pelvic sites; 3) MRI scanner distortions are no longer a barrier to MRI-only planning, but they must be managed appropriately; 4) MRI-only based patient positioning verification shows promise, but limited evidence is reported in the literature and further investigation is required; and 5) a number of MRI-only commissioning processes have been reported, which can aid centres as they undertake local commissioning, but this needs to be formalized in guidance from national bodies. At the time of publication, there was a significant lack of knowledge regarding the scale of the implementation of pelvic MRI-only treatment planning and the barriers to widespread implementation. This systematic review solved this problem through evidence synthesis, including establishing that the clinical implementation of prostate MRI-only treatment planning had been achieved and that the technology barrier of MRI geometric distortions is no longer a limiting factor. These findings had significant implications for the wider clinical implementation of pelvic MRI-only planning however, highlighting that there was no realistic pathway to the widespread clinical implementation of other pelvic MRI-only sites in the short term due to the various challenges and lack of evidence in the literature. The range of issues identified was broad from technical challenges like synthetic-CT

validation and patient positioning verification to whether a sufficient evidence base exists to justify the clinical introduction of MRI-only planning and a lack of formal guidance on how to implement MRI-only planning. It is clear that for centres to consider implementing these techniques, greater confidence across this range of challenges is required. The systematic review informed the phases of this study, which aimed to address many of these issues for anal and rectal cancer treatments, where small investigations had begun elsewhere in the literature for rectal cancers, but no assessments had been undertaken for anal cancers.

On 13th April 2021, the systematic review literature search was updated to include studies from 2019-current. Seventeen additional papers were identified which met the inclusion criteria as defined in chapter 2. Four studies investigated synthetic-CT dosimetric validation (1–4), three studies investigated MRI distortion quantification and phantom development (5–7), three investigated the clinical validation of patient treatment positioning in an MRI-only workflow (1,8,9) and eight investigated MRI-only commissioning processes (10–17). These studies predominantly focussed on prostate cancer MRI-only treatments and enhanced the knowledge of the clinical implementation of pelvic MRI-only planning in the literature. However, these studies did not change the key conclusions of the systematic review.

7.2.2 Multicentre, deep learning, synthetic-CT generation for ano-rectal MR-only radiotherapy treatment planning (Chapter 3)

The synthetic-CT validation phase, discussed in chapter 3, validated a cGAN synthetic-CT generation model for a large cohort of anal and rectal cancer patients, finding excellent dosimetric agreement with CT (PTV D95 % dose difference mean = 0.1 %) and that the model was robust to differences in input data, including patient sex and cancer site. This suggested the model was generalisable across anal and rectal cancer cohorts. Prior to the publication of this work little assessment of synthetic-CT accuracy for rectal cancers, and none for anal cancers, had been undertaken in the literature with these studies reporting promising results but small patient numbers. The lack of validation of synthetic-CT methods in the literature suggested a lack of knowledge regarding whether synthetic-CT generation dosimetric accuracy was sufficient for clinical implementation for anal and rectal cancers. The synthetic-CT validation phase therefore

met this need by providing a comprehensive dosimetric analysis of a synthetic-CT model with excellent dosimetric accuracy results. Particularly that the patient cohort was sufficient to suggest generalisability, including the male and female anatomy represented in both cohorts, was important. Therefore this study suggests insufficient synthetic-CT validation for anal and rectal cohorts is no longer a barrier to clinical implementation.

This work also addressed the use of T2-SPACE MRI sequences and cGAN, deep learning, generation methods. The use of T2-SPACE MRI with excellent dosimetric results, highlighted an alternative method to T1 VIBE Dixon sequences. This is important because the use of the T2-SPACE sequence allowed synthetic-CT generation and target volume and OAR delineation to be undertaken on the same scan, removing the need for an additional delineation scan which can introduce inter-scan registration errors. The use of the cGAN method also highlighted that technological developments have taken place which means that deep learning methods can produce excellent synthetic-CT results. This is pertinent to the wider community as other vendors develop synthetic-CT models and should provide confidence in these methods.

Interestingly, after the publication of this study, an independent study published findings of a multicentre dosimetric analysis of the Philips pelvic MRCAT synthetic-CT generation model, with a large patient cohort (1), similar in patient cohort size to the study presented here. Their findings were similar, but slightly worse than presented in this study, in terms of HU and dosimetric accuracy, where for rectum patients the PTV D95% mean and range for dosimeter differences to CT were approximately 1% and 0 to + 1.7% respectively. In addition the synthetic-CT generation method as detailed above varied considerably to the method presented here.

7.2.3 Patient position verification in magnetic-resonance imaging only radiotherapy of anal and rectal cancers (Chapter 4)

The patient position verification phase, discussed in chapter 4, assessed the differences in CBCT registration when using MRI or synthetic-CT as a reference image compared to CT and the clinical software XVI. Findings were that T2-SPACE MRI or synthetic-CT could successfully be used as reference images for XVI-based CBCT position verification for anal and rectal cancer patients. Systematic differences to CT in all translational and rotational planes were <±1 mm and <±0.5 ° for

both MRI and synthetic-CT but a remaining challenge to widespread implementation is the clinical enabling of MRI as reference images by vendors.

Prior to the publication of this work very little assessment of MRI-only patient treatment position verification for rectal cancers, and none for anal cancers, had been undertaken in the literature, with studies showing promising results but small patient numbers. Similarly to the synthetic CT generation phase, this suggested a lack of confidence regarding how patient treatment positioning would be carried out without a CT reference image and whether it would introduce additional treatment uncertainty. This was a substantial barrier to clinical implementation for these sites as anal and rectal patient positioning relies on soft-tissue CBCT and reference image based registration. Without confidence in MRI-only techniques across the whole treatment pathway, wide-spread implementation is unlikely to occur. The findings here provide evidence and therefore confidence, that the use of either synthetic-CT or MRI would result in minimal systematic differences in patient positioning accuracy. Findings that support the use of either modality, synthetic-CT or MRI, is beneficial to centres as it provides them with image options depending on their individual preferences. The challenge highlighted by these findings is that it is non-trivial to integrate synthetic-CT or MRI into the clinical software and realistically this will prevent at least the widespread use of MRI as a reference image in the immediate future. However, this work demonstrates to vendors that their greater involvement and support is required to enable the use of MRI, but also that its enabling would not be detrimental to patients.

7.2.4 The benefit of MR-only radiotherapy planning for anal and rectal cancers (Chapter 5)

The anal and rectal MRI-only treatment changes study, discussed in chapter 5, assessed the impact on target volumes and treatment plan doses to OARs compared to a CT-only pathway. Findings included that the introduction of MRI-only improved treatments through improved visualisation of target volumes, reducing their volume significantly for both cancer sites (primary PTV volume reduction ~100 cc). Furthermore this translated to reduced doses to OARs when target coverage was maintained for standard clinical protocol and GTV dose escalation treatment plans.

Prior to the publication of this work, for anal and rectal cancers, no evidence detailing the benefit of MRI-only treatment planning to patient treatments had been undertaken in the literature.

While MRI-only planning may be implementable, without evidence showing the benefit of the technique, particularly in evidence based healthcare systems, widespread clinical implementation is unlikely to take place. The challenge of comparing MRI-only treatment planning to current techniques is determining which pathway to compare to, CT-only or CT-MRI. Here the decision was to compare to CT-only as this would further facilitate the widespread implementation of all MRI pathways by highlighting the benefit of MRI soft-tissue contrast compared to CT. The justification for this decision comes down to the lack of MRI provision in many centres internationally. IPEM *(*Institute of Physics and Engineering in Medicine*)* surveys have shown that in the UK less than 10 centres acquire MRI for anal and rectal cancer patients (18) and internationally Denmark was the only surveyed country where over 50% of centres acquired MRI for all anal and rectal cancer patients (19). The study provides evidence that shows a significant change in target volume delineation compared to a CT-only pathway and demonstrates that it leads to reduced doses to OARs if target coverage is maintained. This evidence supports centres by providing a justification of how MRI-only treatment planning would improve treatment planning as well as supporting the development of CT-MRI pathways. When viewed in the context of the potential of MRI-only planning, where there are less uncertainties and costs than associated with CT-MRI pathways, this provides further evidence of the benefit of the clinical implementation of MRI-only treatments compared to CT-only and CT-MRI pathways.

7.2.5 Assessing the patient experience of anal and rectal cancer MR simulation for radiotherapy treatment planning (Chapter 6)

The patient experience study, discussed in chapter 6, evaluated the patient experience of radiotherapy MRI scans in comparison to the planning CT scan, comparing the quality of patient experience and identifying pathway changes which could improve patient experience outcomes. Findings included that radiotherapy MRIs can be comparable to planning CT scans in terms of patient experience, but that attention is required when optimising radiotherapy MRI pathways due to the fundamental differences between CT and MRI scanning environments.

Prior to the publication of this work only a single study in the literature (20) had assessed the patient experience of radiotherapy MRI scans, but for lung cancer patients rather than anal and

rectal cancer patients. This study addressed this lack of knowledge and builds on the understanding of the differences in radiotherapy MRI vs. CT. It aids the development of the clinical implementation of MRI-only for centres with limited MRI experience through highlighting the challenges of radiotherapy MRI scanning and the impact it can have on patient experience. Importantly it provides evidence that the experience of radiotherapy MRI scanning isn't a barrier to treating patients with this new technique.

7.3 Study limitations

Although this study aimed to investigate the key questions and challenges associated with MRI-only radiotherapy treatment planning for anal and rectal cancers, there were a number of limitations to the study and challenges not investigated.

This study aimed to recruit 60 patients, 30 rectal and 30 anal cancer patients respectively. This would have provided a balanced cohort with equal representation between the cancer sites. However, the COVID-19 pandemic ended patient recruitment early due to the ethical consideration that patients would not directly benefit from a research-only radiotherapy MRI scan. Due to the low level of anal cancer incidence this meant it was predominantly the anal cancer cohort that was impacted by this and as a consequence only 17/30 anal cancer patient and 29/30 rectal cancer patients were recruited. The main impact of this was on the treatment changes study (phase 3) where conclusions regarding the doses to some OARs were limited due to the lack of power in the statistical analysis. With greater patient numbers, further OAR differences with statistical significance may have been identified. Likewise for the MRI and synthetic-CT reference images for the CBCT patient position verification study (phase 2) and the patient experience study (phase 4), further patient recruitment would have allowed the further refinement of the findings, allowing a greater certainty with which to make conclusions, specifically regarding the systematic errors associated with changing reference modality and the number of questionnaire responses respectively.

Another limitation associated with patient recruitment was the timing of the research radiotherapy MRI scans due to the LCC having limited radiotherapy MRI provision. This meant patient scans were acquired up to 2 weeks into treatment, when patients were scheduled for a

clinical appointment and an MRI scanning slot was available. While some patients were able to have their planning CT scan and radiotherapy MRI scan on the same day, this also led to some cases where patients had a significant time gap between scans. This was a pragmatic decision to enable sufficient patient recruitment to carry out the aims of this study, however this also introduced greater inter-scan positional differences between the CT and MRI. These were accounted for in the individual phases using various methods including deformable registration (phase 1) and statistical modelling (phases 2 and 3), however compared to a clinical CT-MRI workflow where all planning scans would be acquired within days of each other, this is a difference that would have been preferable to avoid.

The primary limitation of phase 1, synthetic-CT generation accuracy validation, was that the synthetic-CT model generated in-house was a research only model, and not a CE marked commercially available model. This limits the impact of the findings as other centres cannot use these results within their own clinical commissioning, however they do provide a benchmark of the quality of synthetic-CT generation that can be obtained for anal and rectal cancer synthetic-CT generation and can be referred to in commercial product validations.

The primary limitation of phase 3, was that the treatment change comparison only assessed the difference in pathway between CT-only and MRI-only treatment planning. This was a conscious decision to aim to build evidence for centres with limited MRI provision, rather than those who already have already developed CT-MRI pathways. This limits the impact of our findings as they are not applicable to centres that already follow a CT-MRI pathway such as those in Denmark highlighted by the IPEM international survey (19), however it is credible to suggest that these centres will look to other evidence regarding efficiency and inter-scan error propagation to assess whether their patients would benefit from MRI-only planning. Another limitation of the findings of phase 3 was the lack of patient outcome data. While the findings of reduced target volumes and OAR doses suggest that patient outcomes would improve through reduced radiation damage to OARs, it's possible that the difference in dose to the OARs is too minimal to change patient outcomes.

There are a number of potential benefits to MRI-only planning that were not addressed in this study. These include assessing; whether the improved visualisation of MRI reduces inter- or intra-observer delineation variability, the removal of CT-MRI registration errors from the pathway, the health economic impact of moving to an MRI-only pathway and opportunities to use of functional

imaging to further improve the target delineation process. This study aimed to address the core challenges associated with anal and rectal MRI-only planning clinical implementation. However it remains important to continue to build the body of evidence relating to MRI-only treatment planning, to allow centres considering implementation to make a fully informed decision on its benefits and continued challenges.

7.4 Further work

7.4.1 Further work relating to anal and rectal MRI-only planning

This study addressed the key challenges associated with MRI-only treatment planning for anal and rectal cancers. However, further work is required to continue the development of MRI-only treatment planning and support its wider clinical implementation.

For synthetic-CT generation validation within the pelvis, it is becoming clear that the scientific challenge is predominantly solved, particularly when taking this and the recent Philips pelvic MRCAT study into account (1,21). However, further validation of commercially available models is important to ensure a full understanding of the implications of their clinical use. Not all centres have access to Philips scanners and the MRCAT software which is a purchasable additional option. Here we have discussed the potential benefits to employing strategies that do not rely on T1 VIBE Dixon sequences and bulk density assignment strategies. For treatment patient positioning verification, further work is required to integrate the use of MRI and synthetic-CT in clinical registration systems such as XVI (Elekta). This will require industrial collaboration and a focus on streamlining clinical pathways. As discussed previously, there are many potential benefits of MRI-only planning for anal and rectal cancers that were not assessed here. Of these, assessing the impact of removing CT-MRI pathway registration errors when using MRI-only treatment planning is of high priority as it is important to quantify this in the context of broadening the clinical implementation of MRI-only planning to centres that already employ CT-MRI pathways.

Further work investigating the use of anal and rectal MRI-only treatment planning is also required to maximise its benefit to patients. As discussed, the technical challenges of MRI-only planning are now beginning to be resolved and the research questions are correspondingly shifting to how best

to clinically implement MRI-only planning and harness its characteristics to benefit patients. This includes investigating optimal methods for clinical implementation, and developing international guidelines to aid its progression, but also further exploring its patient benefit. For example the quantification of inter-observer variability and MRI-only health economic impacts are questions that would benefit from investigation. An additional avenue of research is the potential inclusion of functional imaging in the treatment planning process. By utilising MRI-only treatment planning, functional imaging becomes considerably easier to combine into the treatment planning process. This could result in an array of scans aimed at assessing, for example, tumour hypoxia, perfusion and diffusion. This could also apply to pre-treatment imaging, through dose painting or improved target definition or it could be incorporated into treatment pathways through adaptive planning to assess tumour response.

7.4.2 Further work related to MRI-only planning

Beyond anal and rectal MRI-only planning much work remains to identify and develop MRI-only planning for all sites that may benefit from it. The challenges assessed in this work also apply to other sites and require further investigation. For example, synthetic-CT generation has been predominantly achieved in the pelvis; however for other areas of the body it faces greater technical challenges such as lung tissue, the complex bony anatomy of the head and neck and the challenge of breathing motion. While similar challenges will require further assessment for patient treatment position verification, and for each individual site, the question of whether MRI-only benefits patients sufficiently needs to be assessed.

The development of new technology and its integration with the development of MRI-only planning is also an important topic of investigation for the future. With the introduction of the MR-linac (22), establishing how these two distinct MRI related radiotherapy machines, the MR-linac and MR sim, can and should work together in a complimentary manner is a complex but important issue. Similarly the greater adoption of artificial intelligence (AI) in radiotherapy (23) has the potential to greatly increase the efficiency and scope of MRI-only planning through for example auto-contouring, synthetic-CT generation and radiomic target assessment. Greater focus on assessing how the use of AI would complement MRI-only planning would be beneficial (24,25).

7.5 Conclusion

MRI-only radiotherapy treatment planning synthetic-CT solutions are now commercially available in the pelvis, but the clinical implementation of pelvic MRI-only treatment planning has been limited. The aim of this study was to address the key challenges facing the clinical introduction of MRI-only treatment planning for anal and rectal cancers with the intention of providing evidence which would facilitate its widespread clinical implementation. These challenges can be described as assessing whether MRI-only planning is technically achievable, clinically implementable and improves patient radiotherapy treatments.

To be technically achievable, synthetic-CT generation for anal and rectal cancer sites needs to be sufficiently dosimetrically accurate for clinical use. The clinical implementation of MRI-only planning requires that a radiotherapy MRI or synthetic-CT scan can replace CT as the reference image for patient treatment position verification and the patient experience of radiotherapy MRI scans needs to be acceptable. To support the widespread clinical implementation of MRI-only planning, the benefit to patient treatments needs to be quantified.

Here, a systematic review of the clinical implementation of pelvic MRI-only treatment planning was carried out to assess the progress of development for MRI-only treatments within the pelvis (26). The remaining challenges identified included synthetic-CT validation, patient positioning verification using MRI and synthetic-CT as a reference image and the challenge of providing evidence of benefit for MRI-only planning. This study assessed synthetic-CT dosimetric accuracy validation in phase 1, and the following publication “Multicentre, deep learning, synthetic-CT generation for ano-rectal MR-only radiotherapy treatment planning” (21)**,** demonstrated that the generation of synthetic-CTs with excellent dosimetric accuracy can be achieved using a cGAN deep learning model and that this finding is generalisable to all anal and rectal cancer treatments. The challenge of patient position verification using MRI or synthetic-CT was assessed in phase 2, and the following publication “Patient position verification in magnetic-resonance imaging only radiotherapy of anal and rectal cancers” (27) demonstrated the achievability of using MRI or synthetic-CT as a replacement reference image for CT with minimal systematic registration errors. The benefit of MRI-only planning for anal and rectal cancers was assessed in phase 3, and the following publication “The benefit of MR-only radiotherapy planning for anal and rectal cancers” (28) demonstrated that MRI-only planning reduces treatment target volumes and as a

consequence reduces the doses to OARs when target coverage is maintained. The patient experience of radiotherapy MRI scans was assessed in phase 4, and the following publication "Assessing the patient experience of anal and rectal cancer MR simulation for radiotherapy treatment planning" (29) demonstrated that radiotherapy MRI scans can be acquired with comparable patient experience to planning CT scans if the differences in scanning environment are taken into account.

The research included within this thesis addresses the key questions facing MRI-only treatment planning for anal and rectal cancers. It shows that MRI-only planning can be safely delivered with accurate treatment plan dosimetric calculation and without introducing clinically significant registration errors into the radiotherapy patient positioning treatment pathway or affecting the patient experience of radiotherapy simulations. This study also provided evidence that MRI-only treatment planning improves patient treatments compared to CT-only pathways. As a result, the work presented here provides evidence to support and facilitate the widespread clinical implementation of MRI-only planning for anal and rectal cancers.

7.6 References

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