Mark Warren

College of Radiographers Doctoral Fellowship 012

£24,468 awarded

Title: Real-time MRI guidance for Stage III Non-Small Cell Lung Cancer.

Aims & Objectives:

The aim of this research is to assess the use of real-time MR imaging to guide radiotherapy for locally advanced non-small cell lung cancer (LANSCLC). The hypothesis is that real-time tumour tracking with MRI can provide accurate localisation of the tumour, as well as improved probability of tumour control through isotoxic dose escalation using a combined track and gate delivery.

The research will answer the following:

1) Will an MRI only-workflow reduce inter and intra-observer variability in GTV and organs at risk identification compared to a CT-only workflow?
2) Is tumour centroid motion and volume deformation different on MRI to 4DCT, and what is the cycle-to-cycle variability on MR?
3) Is there a therapeutic gain to using MRI over 4DCT to plan and verify isotoxic radiotherapy with combined tracking and gating strategies?

Expected Outcomes:

We hope to understand how MRI can be used to plan and deliver our radiotherapy. We will have data on image quality, and on how the disease moves. This is important as we have not been able to collect this data before.

A technique for treating this disease with MRI guidance will be developed, and we will have important data on its likely benefit to patients. This will allow us to set clinical guidelines, and start to devise clinical trials. The trials would look to improve the chance of cure, but keep side effects (such as shortness of breath, and pain when swallowing) low.

Background to the Project:

For patients with Locally Advanced Non-Small Cell Lung Cancer (LANSCLC), standard chemoradiotherapy regimens still result in poor local control (1). Radiation dose is thought to be contributing (2,3), and modelling studies suggest that a 30% increase in 2 year local disease-free survival might be achieved by raising prescribed doses from 60 to 75Gy (4). However, tumour volume is often large and centrally located, resulting in unacceptable dosage to organs at risk (OAR) in the mediastinum. As a result, a major avenue for radiotherapy research is isotoxic radiotherapy, whereby prescription dose for individuals is limited only by acceptable toxicity to healthy tissue (5). This results in a personalised prescription dose based upon tumour size and location, but a standardised toxicity rate.

Delivery of isotoxic radiotherapy for LANSCLC is complex. The tumour itself is subject to respiratory and cardiac motion, giving rise to significant intra-fraction changes in position during the breathing cycle. The position of nodal disease is also subject to intra-fractional motion, and its relationship to critical organs is independent of the primary. CT Imaging is used to quantify these uncertainties at the radiotherapy planning stage and at treatment delivery. A safety margin (0.5-1.5cm) around the tumour needs to added (the Planning Target Volume or PTV) to treatments to compensate (6). Further improvements in prescription dose require additional reduction in this margin.

Reducing the PTV margin may be possible with gated radiotherapy (where the treatment beam is switched off for part of the breathing cycle) and tumour tracking (where the radiation beams move with the tumour), but they require motion data in real-time (7). The need to keep radiation dose low places limitations on the use of 4D Cone Beam CT (4DCBCT), the common volumetric imaging system within treatment rooms. Furthermore, CBCT is subject to low noise to contrast ratio. Resultantly, surrogates for tumour position have been explored and have been shown to reduce radiation field size for early stage NSCLC (8). .

MRI LINACs now exist that perform imaging continuously throughout treatment. MRI sequences capture motion within the thorax over each breathing cycle, with 4DCT, only a composite image over several cycles is produced. MRI therefore allows us to observe the breathing cycle over extended periods of time, and quantify the effect breathing changes have on dose delivery. It also promises improved image quality, as well as additional data on tumour shape and volume during the breathing cycle (9).

A major avenue for exploration with MRI is the processing of images in real time. Acquisition sequences such as HASTE are able to sample the movement of tumour and OAR at the recommended temporal sampling interval of 0.5s for real-time monitoring (7), however only 2-4 2D slices are able to be captured at this speed. A full 3D picture can be produced by mapping these 2D images onto baseline TWIST images captured at the radiotherapy planning stages (12). The radiation beam can therefore be synchronised with tumour motion during breathing cycle, and be switched off when dose to OARs is likely to be high (13,14).

Preliminary data:

This proposal is part of a larger research collaboration with The University of Liverpool, The University of Oxford and Clatterbridge Cancer Centre. Multislice 4D-MR and single-slice real-time images of healthy volunteers have been collected using fast TWIST (3D-spoiled gradient-echo) and HASTE (planar-echo) sequences. Voxel-size, field-of-view and TR sequence parameters have been optimised to obtain the best trade-offs between image signal, noise, and spatial and temporal resolution.

The applicant has conducted a qualitative study of image quality for this healthy volunteer cohort. The aim of this study was to establish if OAR visualisation which OARs are likely to be well visualised on TWIST MRI. OAR were outlined according to UK SABR consortium guidelines on coronal and axial TWIST images, as well as on helical CT and CBCT. The visualisation of OAR was then assessed using a 5 point scale adapted from (15,16). Preliminary results suggest that visualisation of vessels, heart and anterior mediastinal structures is similar between CT and TWIST MRI, with CT showing some advantage in visualising the bronchus and airways. TWIST MRI showed improved visualisation compared to CBCT on 14/17 structures. This method will be used to refine sequences for further volunteer studies before clinical studies begin.

Detailed plan of investigation:

An initial systematic review of the literature of real-time tumour tracking for LANSCLC will be performed and registered with PROSPERO (http://www.crd.york.ac.uk/prospero). Current systematic reviews exist that address the role of MRI in precision radiotherapy for lung cancer, target motion in lung cancer, breathing guidance in radiotherapy, and have informed this proposal. We propose to update and extend current reviews to consider the dosimetric effects of tracking and gating with particular emphasis on LANSLC and MRI guidance.

The clinical phase of the project will involve recruiting stage III NSCLC patients for MRI imaging. The first 3 stage III NSCLC patients receiving radiotherapy will be imaged, each for a single MRI session using TWIST and HASTE sequences. Initial sequence parameters will be those determined during the preceding technical development, but these will be fine-tuned to maximize tumour visualisation using the methods developed for the healthy volunteer study described above.

A further 12 patients will then be imaged, each for two MRI sessions taking place during the radiotherapy schedule and separated by at least a week. TWIST and HASTE images will be collected during each session, and radiotherapy planning CT and CBCT that coincide with MRI image capture will be collected. Analyses will be carried out to answer the three questions above.

Question 1 will be addressed by an outlining study to compare an all-CT IGRT workflow vs an all-MRI workflow.

The OAR and Gross Tumour Volumes (GTVs) will be outlined by 2 radiologists and 2 oncologists on TWIST and HASTE MRI, 4DCT and 4DCBCT in Aria Treatment Planning Software. A time-resolved average image (as in (20)) will be created from the TWIST MRI and 4DCT images and used for outlining.

The GTV for each patient will be determined using staging information on size, location and involved nodal stations gathered from the patient's case notes. Both organ at risk and GTV delineation will follow the protocol set out in the (isotoxic) IDEAL RT Trial Protocol (5). To determine intra-observer error, one observer will re-outline all images for one case after a significant time period has lapsed.

Observer variability in radiotherapy planning

GTV

All observer outlines will be transferred to MATLAB for analysis. A STAPLE outline will be produced and used as the ground truth for investigating contouring variability (21). The bilateral local distance (22) from each point on the STAPLE outline to each observer's contour will be determined and mean and local standard deviation calculated. Root Mean Squared standard deviations of all points on the contour from the STAPLE outline will then be calculated to give a measure of contouring variation (Σdelineation uncertainty) as in (23). This systematic component of delineation error can be used to calculate the systematic contribution of delineation uncertainty to planning margin using Margindelineation = 2.8 Σdelineation uncertainty (23). An effect size for margin reduction will be calculated. Reduced planning margins in MRI-guided isotoxic radiotherapy are thought to bring a relative improvement in survival by 4% for every 1Gy BED dose increase based upon 2 and 5 year survival data. Based upon (24), this would equate to a margin reduction of 1.2 mm to see a 1Gy increase in BED.

Organs at risk

No previous studies of OAR outlining on MRI have been undertaken. STAPLE outlines will allow max, min and mean distance to agreement to be calculated for each observer. A student t-test can be used to compare variability of mean distance to agreement between each imaging modality for each organ at risk. Baseline measurements of metrics such as bilateral local distances, volume changes, Dice coefficient and Haussdorf distance will be made.

Observer variability during image guided treatment delivery

For real time tumour matching, time-resolved HASTE images of 2-4 slices of the target and OAR will be used to sample the motion. This sample will be used to create a real-time motion field (12) and produce real-time 3D maps of tumour motion. The GTV and OAR outline from 2D motion samples will be transformed onto 3D images through deformable registration techniques. Delineation variability will be determined and compared to TWIST MRI and 4DBCT.

Question 2: The GTV will be outlined on each of phase of the 4DCT, TWIST and HASTE MRI for all patients. For MRI images, intra-sessional and intersessional differences in phase length, amplitude and baseline variation will be calculated against time-weighted average positions. Means will be compared to 4DCT (26).

For a measurement of tumour deformation, a 3D object representing the tumour for each phase of the breathing cycle will be created in Matlab. The spatial extent of the tumour in the superior-inferior directions, and the extent of change during the breathing cycle with respect to the centroid will be determined.

Question 3 will be investigated using an in-silico planning study. Isotoxic plans will be produced for this cohort of patients in line with the IDEAL CRT trial protocol (5). Conventional target volume concepts such as the MiDV and ITV will be used for comparison against real-time MRI moving target volumes (MTV).

Contouring, deformation and positional uncertainty data collated in Questions 1 and Questions 2 will be used in combination with data on tracking latency data for MLCs (13,14,27,28). This will make for accurate tracking and gating PTVs using margin recipes given in (25). Isotoxic plans will be produced with dose correction. Planned dose escalation will then be compared between the 4 techniques using TCP analysis as in (29).

To understand the effects of motion and deformation during delivery, a 4D dose calculation will be undertaken. The IMRT treatment plan will be split into segments to coincide with the real-time phase data gathered from the HASTE images (30). Treatment isocentre will be shifted to coincide with the centroid of the tumour for the corresponding image phase. 4D dose accumulation for tumour and organs at risk will then be performed with Eclipse and MIRADA software.

Potential problems and contingency plans:

This study is being carried out right at the start of our lung MRI programme, and will be followed by more extensive studies designed to further test the accuracy and reproducibility of 4D and real-time MR imaging of tumours and normal tissues during radiotherapy.

We propose to image 3 patients during sequence fine-tuning, allowing two rounds of sequence modification from the baseline sequences already fine-tuned on volunteers. We will follow this by imaging a further 12 patients using these fine-

tuned sequences, this number being chosen so that even with some patient drop-out we are likely to collect data for at least 10 patients during this part of the study.

User Involvement plans:

An ethics application has been submitted to conduct this research and is in its final stages. Recruitment of 15 patients is planned over 6 months from June 2018. The CCC Patient Advice and Liaison Service have provided advice on patient information sheets for the study. Additional MRI imaging is to be scheduled with the patient in mind: appointments for MRI scans will coincide with radiotherapy planning CT and treatment appointments on the same hospital site. Although this may require a small wait in between appointments, the inconvenience and cost of travelling will be kept to a minimum.

Additionally, The Roy Castle Foundation is providing the applicant the opportunity to meet and discuss the specifics of the research with services users. A service user has been identified to help steer the research from a service user's perspective.

Dissemination Plans:

Within the duration of the award, findings of a systematic review of the literature of real-time tumour tracking for LANSCLC will submitted for peer-review publication in Radiography. This will be used to inform UK Guidelines into IGRT through the applicant's membership of the UK working group to update IGRT Guidance led by the Royal College of Radiologists. Initial findings and details of the project will be submitted for consideration at the 2019 CoR Annual Radiotherapy Conference.

Results of the clinical phase will be submitted for peer-review publication in journals such as Radiotherapy and Oncology and the International Journal of Radiation Oncology Biology Physics and as well as national and international conferences. Funds for conference attendance will be found by my employer where appropriate.

Integration of this project into the ongoing work of the group/department and into patient care:

The PhD supervisory group of Prof Brada and Dr Fenwick are clinical academics in radiotherapy research at The University of Liverpool and Clatterbridge Cancer Centre (CCC). The project is supported by the Therapy Radiography Research Expert Practitioner at CCC. This proposal is part of a larger research collaboration with The University of Liverpool (UoL) and CCC.

The output of research is expected to feed into the MRI-LINAC project at CCC: MRI-guided delivery of isotoxic radiotherapy is expected to be an outcome of this project in the context of phase 1 clinical trials within 5 years. The major benefit for patients is increased local control and better monitoring of potential radiation damage to OAR.

This research also investigates established motion management strategies and IGRT. It is expected that conventional IGRT practice with CBCT and 4DCT will be influenced by new data and this will feed into national IGRT guidance. For patients, there are currently a number of methods to manage breathing such as breath hold, and respiratory coaching. Some of these are not well tolerated or have poor patient compliance. The development of real-time guidance will eliminate the need for these techniques. It is hoped that this research will inform the clinician and patient discussion regarding motion management interventions by providing clearer evidence.

Potential impact of the project:

Academic: New methods and data on tumour motion and observer identification for LANSCLC. New methods for dose escalation will be tested and validated ahead of clinical phase 1 trials.

Clinical: Output will feed into IGRT clinical guidelines through the systematic review, clinical findings will allow evidence-based selection of MRI in pre-treatment and treatment. New techniques will feed into clinical dose escalation trials and quality assurance, and then into clinical management guidelines.

Economic: Evidence to support (or not) NHS investment into MRI-guided radiotherapy.

Patient: Survival and toxicity benefits from improved radiotherapy technique. Clear advice on motion management and patient-specific intervention.

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