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CoRIPS Research Grant 180

£10,000 awarded

Title: The feasibility of using multi-modality imaging in the radiotherapy treatment planning of locally advanced rectal cancer

Principle Aim

- To assess the feasibility of using MRI-CT registered images in the radiotherapy planning of rectal cancer.

- These results will inform a larger study to assess the role of MRI in predicting response to radiotherapy and adaptive radiotherapy.

Primary research question

1. Is it feasible to acquire repeat MRI images in the radiotherapy treatment position?

    a. This will be deemed feasible if 70% of patients complete MRI_1, MRI_2 and MRI_3 scan acquisitions.

2. Can clinically acceptable plans be produced using planning volumes from CT-MRI?

    a. Is dose to target volume consistent with ICRU guidelines?

    b. Are bladder dose constraints met? V35<50%, V40<40%, V45<15%, V50<0.1%

    c. Are small bowel loop dose constraints met? V35<180cc, V40<100cc, V45<65cc, V50<0.1cc

3. Can anatomical changes in target volume be identified from MRI_1, MRI_2 and MRI_3?

    a. Quantify and compare volumes between MRI_1, MRI_2 and MRI_3.

4. Report differences in volumes using CT and MR volumes.

    a. Quantify difference in MR/CT_1 GTV volume to CT_1 GTV volume and the concordance of these volumes.

    b. Quantify change in volumes between MR_1 GTV MRI_2 GTV.

    c. Report the dice similarity co-efficient (DSC) for repeated volumes.

Secondary research questions

Secondary endpoints and outcome measures

1. Is it feasible to measure ADC change in characteristics on DW MRI using repeat MR i.e MRI_1, MRI_2 and MRI_3?

    a. Measure and record ADC on repeat GTV volumes i.e.MRI_1, MRI_2 and MRI_3.

Outcomes

This study will define if it is feasible to use MRI scan in radiotherapy planning of rectal cancer. It will test if DWMRI can be used to interpret volumes and ADC values. This will confirm if this can be tested in a future study to determine if DWMRI can be used as a predictive imaging biomarker to predict treatment response. This could lead to individualised treatment for this group of patients.

Review of literature and identification of current gap in knowledge

In Europe there are over 704,000 cases of rectal cancer diagnosed every year .1 Locally advanced rectal cancer is managed with pre-operative neo adjuvant chemo-radiotherapy (CRT) treatment to downstage the tumour before surgery. This reduces the margin threatening disease, and enables clear resection margins at surgery.

The addition of pre operative radiotherapy results in a significant overall survival benefit, with a recognised reduced risk of local recurrence. 2-4

Accurate identification of the treatment area, i.e. gross tumour volume (GTV) is essential when planning radiotherapy. This ensures disease is not missed and minimises normal tissue dose. Current standard of care (SOC) is defining the GTV using a planning CT scan, alongside diagnostic imaging and staging information. Definition of the tumour at this stage is crucial otherwise; it could increase the risk of a positive surgical resection margin i.e. cancer cells are still present.5

MRI provides superior soft tissue definition and tumour visualisation compared to CT. By acquiring a planning MRI in treatment position and registering it with CT, it can assist the clinical oncologist with more accurate and precise planning.

Previous work suggests that multi-modality imaging used alongside staging information may improve accurate target delineation.6 Smaller volumes have been reported with CT/MRI registered images, resulting in less normal tissue dose and reduced side effects. This increases the possibility to boost the tumour with higher, more effective doses of radiation.7-8

The use of boost volumes to the target GTV are recommended in rectal cancer, with a known dose response relationship.9-10 Boosting the target GTV increases the likelihood of tumour cell kill.

Currently for this group of patients MRI imaging is the gold standard modality used initially to stage the disease; to stratify treatment; and then post treatment to restage the disease prior to surgery.11-12

Following CRT, patients go on to have surgery, associated with high morbidity and life changing consequences. Increasing evidence shows a small portion of patients (around 16-27%) have a complete pathological response after CRT.13-15 Controversial management strategies include local excision or watch and wait monitoring, instead of full surgical resections. Unfortunately, re staging information prior to surgery is currently limited, and with a lack of validated imaging biomarkers, stratification is not possible. Currently definition of complete pathological response can only be confirmed after the patient has been through the morbidity of surgical resection.

There has been early work investigating diffusion MRI (DW-MRI) sequences.16 These images provide functional information, giving detail on disease characteristics. The movement of water within tissue indicates cellularity, and provides a quantitative measurement called apparent diffusion coefficient (ADC). By repeating DW-MRI at different points e.g. during and after treatment, a change in ADC could quantify tumour response.

This area of research is novel, and if secondary outcomes are achieved from this study results will inform the next phase of research to validate an imaging biomarker to predict response, and stratify complete pathological responders. Colorectal cancer research has identified areas of unmet need, recommending use of innovative technology to improve patient outcomes.17

Methodology

The study design is a single centre prospective feasibility study partly interventional and observational, using quantitative research methodology.

Study Population

Patients with cT3 or greater at staging with operable adenocarcinoma rectal cancer. Patients deemed appropriate for chemo radiotherapy (CRT) as primary treatment at the Beatson WoSCC may be suitable for study participation. Suitable patients will be identified at multi-disciplinary team meetings or from the radiotherapy bookings database and approached by the direct clinical care team as they attend clinic appointments. 10 patients will be recruited to the study following ethically approved patient information and consent process.

Recruitment Strategy

Patients will be identified at the multi-disciplinary meeting prior to initial consultation and approached at point of referral for radiotherapy. Registration to the study will be at standard radiotherapy planning appointments. A random sampling approach will be undertaken and participants identified if they meet the inclusion and exclusion criteria.

The sample size will be 10 participants to define the feasibility. This sample size is consistent with other pilot studies investigating the use of MR in the planning of RT treatment. This data will capture 10 patients and 30 MR scans to be evaluated. The recruitment phase is estimated to last for 12 months.

Study design

This is a single centre study to assess the feasibility of using MRI and CT images in the radiotherapy planning process of rectal cancer.

An MRI planning scan (MRI1) will be acquired the treatment position using the same preparation immediately after CT. The MRI will be registered CT planning scan and used for delineation of the gross tumour volume (GTV). This additional soft tissue information will allow more accurate delineation of the visible tumour. Sequences acquired will include T2 and diffusion weighted (DWMR).

A repeat MRI (MRI2) scan will be acquired on week 3 of radiotherapy treatment, in treatment position using same preparation. This scan will be used for observational purposes and will not alter the patient's treatment course.

A follow up MRI (MRI3) scan will be acquired 10 weeks post radiotherapy treatment. This scan will be a diagnostic scan as per SOC re staging scan prior to surgery. The difference being this will be in the radiotherapy treatment position.

The MRI (MRI1) used to delineate the GTV will provide information to better delineate disease and normal tissue. These volumes will be treated and CO will be responsible for including all disease, as per guidelines. MRI_1 will be obtained prior to radiotherapy commencing. MRI_2 will be carried out during week of radiotherapy treatment. MRI_3 will be obtained 10 weeks post radiotherapy treatment. All scans will be acquired at the Beatson WoSCC diagnostic scanner.

The DW MRI sequences will be used to calculate an ADC map to assess the feasibility of measuring ADC in GTV of rectal cancer patients, and to calculate if change in ADC can be measured between the 3 scans. The MRI_1 and MRI_2 scans will be carried out during routine hospital visits for radiotherapy planning and treatment therefore will involve no extra visits for participants. MRI_3 is a diagnostic scan which participants would require as SOC. All relevant research governance will be in place before commencement of this study.

Inclusion Criteria

1. Histologically confirmed invasive rectal adenocarcinoma
2. Pelvic MRI defined disease (one of the following):
3. Scheduled to undergo radical neo adjuvant chemo radiotherapy prior to surgery.
4. Willing and able to give informed consent
5. Patients willing and able to comply with the protocol for the duration of the study
6. Patients due to have follow up imaging within GGC health board catchment (hence can attend Beatson MRI scanner)

Exclusion Criteria

1. Previous radiotherapy to the pelvis (including brachytherapy)
2. Inflammatory bowel disease
3. Unfit to receive any study treatment or subsequent surgical resection
4. Contra-indications to MRI

Study visits

All study procedures will be carried out during standard visits for participants during radiotherapy planning, treatment and follow up imaging. The additional requirement for the participant is that they attend the Beatson WoSCC for their re staging MRI scan 10 weeks post radiotherapy prior to surgery.

DW MRI scans will be carried out before radiotherapy begins then again during week 3 of radiotherapy treatment and 10 weeks post radiotherapy. Each scan will take approximately 30 minutes.

Data Collection

Data will be collected anonymously on case report forms (CRFs). These will be stored securely in locked NHS offices. A database will collate the anonymous data collected and be stored securely on password protected NHS computers. Scans will be stored securely on password protected NHS computers. Data recorded will be if patients tolerate the MRI scan in radiotherapy position, the planning characteristics recorded from Eclipse planning software, volume measurements and ADC values from Eclipse.

Reliability and validity

The methodology is reproducible but the study would likely produce different results in a different population of patients. It will measure the research question and provide the outcomes for the project. The defined inclusion and exclusion criteria will improve the validity of the data.

Quality assurance (QA) procedures will be carried out and documented by diagnostic physicists to ensure MRI measurements are reliable and valid. Acquiring MR images on same scanner throughout will allow standardisation, and not require normalisation of scans. The scanner will have a robust QA process in place, and this will ensure reliable results from ADC measurements.

Defining GTV will be protocolised, and include consistent and experienced observers. All volumes will be peer reviewed to ensure best practice.

Ethical considerations

Informed Consent- The chief, principal investigator or co-investigator is required to explain the nature and purpose of the trial to the patient prior to trial entry. A detailed patient information sheet and consent form will be given to the patient and written informed consent obtained before trial entry. A period of at least 24 hours will be given for the patient to consider entry to the study prior to obtaining informed consent and all efforts will be made to ensure that patients understand

the commitment required to fulfil the study requirements. Patients will also be made aware that participation is voluntary and that they can leave the study at any time without their standard care being affected.

Potential risks and benefits -No disadvantages or risks to participants' health have been identified by taking part in this study. Planned cancer treatment will not be affected in any way by study participation. DW MRI scans will be carried out during standard radiotherapy planning and treatment and diagnostic scan appointments, therefore no additional visits are required by the participants. Intravenous gadolinium will be used during each MRI scanning sequence to aid characterisation and localisation of target lesions.

Further development of this study will include patient representatives. The research governance process will be followed, with patient and public involvement (PPI), including the design and conduct of the study. Presentation at our Clinical Trials Executive Committee (CTEC) will allow full discussions with expert researchers and PPI.

Statistical analysis

The distribution of baseline demographic and clinical characteristics of patients will be described using proportions for categorical data and means with standard deviations (or medians with inter-quartile ranges) for continuous variables. Analyses will use standard statistical significance level of 0.05. Full statistical support will be provided by the Beatson WoSCC statistician.

Potential impact

The participants in the study may have less normal tissue treated, therefore less side effects.

If deemed feasible to repeatedly measure ADC on DWI images at these time points. It may be possible to predict tumour response to radiotherapy before, during and after radiotherapy.

In the next phase of research if ADC values could be validated as an imaging biomarker it may be possible to predict patients with a complete pathological response prior to surgery.

Dissemination Strategy

The findings of this study will be presented at SOR radiotherapy weekend. The UK imaging and oncology conference and the European Society of Radiation Oncologists. Abstracts will be submitted for oral presentation.

References

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