Multiparametric MRI as an Outcome Predictor for Anal Canal Cancer Managed with Chemoradiotherapy

Funding Sponsor: Hunter Translational Cancer Research Unit (HTCRU)
Priority Research Centre for Cancer (PRC Cancer)
C/O Calvary Mater Newcastle Hospital
Mayfield NSW 2304

Protocol Number: **CMNDRO-1201**

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This document is a protocol for a clinical research study. The study will be conducted in compliance with all stipulations of this protocol, the conditions of the ethics committee approval, the NHMRC National Statement on Ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).

TRIAL MANAGEMENT COMMITTEE

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1 STUDY SUMMARY

Title	Multiparametric MRI as an outcome predictor for anal canal cancer managed with chemoradiotherapy
Short Title	MPM MRI Anal SCC
Protocol Number	CMNDRO-1201
Phase	Phase II
Methodology	Prospective non-interventional clinical trial
Study Duration	36 months
Study Centre	Calvary Mater Newcastle Royal Prince Alfred Hospital/Chris O'Brien Lifehouse Liverpool Hospital
Objectives	We aim to explore if the use of DWI-MRI and dCE-MRI during chemoradiotherapy for anal cancer can supply the clinician with an early, and accurate, indication of the eventual response of the tumour to therapy
Number of Subjects	20
Diagnosis and Main Inclusion Criteria	Consenting patients with histologically confirmed primary invasive squamous cell carcinoma of the anal canal treated with radical chemoradiotherapy
Statistical Methodology	Our radiologist will review all images and provide data for the following primary outcome measures to enable comparison between images • Primary and nodal tumour dimensions • Primary and nodal tumour apparent diffusion coefficient (ADC) values • Primary and nodal tumour perfusion coefficients (K^{trans} and K_{ep}) Statistical analysis of primary endpoint • The change in ADC, K^{trans} and K_{ep} values between baseline and subsequent scans will be measured and stratified according to later tumour complete response. The Mann-Whitney test will be used to compare the change in ADC, K^{trans} and K_{ep} for responders verses non-responders at a significance level of 0.1.

2 INTRODUCTION

This document is a clinical research protocol. Study design and implementation will comply with this protocol and the conditions of the ethics committee approval.

2.1 Investigators and Facilities

Study Location

Primary Site:

Calvary Mater Newcastle
Corner Edith & Platt Streets
Waratah, Newcastle
New South Wales 2298
Australia

Recruiting sites:

Royal Prince Alfred Hospital/Chris O'Brien Lifehouse
119-143 Missenden Road
Camperdown
New South Wales 2050
Australia

Liverpool Hospital
Corner of Elizabeth and Goulburn Streets
Liverpool
New South Wales 2170
Australia

Study Management

The principal investigator and trial coordinator will be primarily responsible for the coordination and implementation of this study. Michael Jones is the Principal Investigator and this study is funded through a competitive grant from the Hunter Translational Cancer Research Unit (HTCRU).

2.2 Background

2.2.1 Background for Anal Cancer

Prevalence and risk factors

Anal cancer is an uncommon malignancy. It represents 2.2% of all gastrointestinal cancers. However, the rate of anal cancer is increasing[1]. This is likely due to the rising prevalence of its strongest risk factors – sexual promiscuity, HPV and HIV[2-5]. It appears the majority of anal squamous cell carcinomas are associated with HPV infection and, in particular, the HPV-16 subtype[3,6]. HIV mediated immunosuppression is likely to facilitate HPV persistence[7].

Treatment

In 1974, Nigro et al. found that combined chemoradiotherapy could achieve a complete response in anal cancer[8]. Radical chemoradiotherapy has since become the recommended standard of care for non-metastatic anal cancer[9]. The long-standing combination of radiotherapy, 5-Fluorouracil (5-FU) and Mitomycin-C (MMC) has been validated in a number of large prospective randomised controlled trials[10-14].

2.2.2 Background for Multiparametric MRI

Diffusion Weighted MRI (DW-MRI)

DW-MRI is a functional MRI technique that measures molecular diffusion resulting from normal Brownian motion of water protons within biological tissues[15]. Due to architectural differences, biological tissues are variably restrictive of diffusion. In particular, the densely cellular and disorganised architecture characteristic of cancer results in low molecular diffusion and therefore low signal response. Diffusion is measured quantitatively by the computerised calculation of the apparent diffusion coefficient (ADC).

Dynamic Contrast Enhanced MRI (dCE-MRI)

DCE-MRI is performed by obtaining sequential MRI images acquired before, during and after IV injection of paramagnetic contrast[16]. DCE-MRI measures the rate of contrast movement between the intravascular and extra-cellular extravascular space. This rate reflects tissue microvasculature permeability and perfusion. Cancer, with its abnormal microvasculature, tends to show a greater increase in the signal intensity than normal tissues[17].

2.2.3 Rationale for the Proposed Study

Multiparametric MRI as a biomarker in Anal Cancer

Presently, chemoradiotherapy results in local failure rates of 14 to 37%, even in patients with early stage disease[18-20]. Although it is feasible to intensify the radiotherapy dose, this increases toxicity, and a recent randomized trial has shown that this dose escalation strategy is not beneficial for an unselected patient population[11].

Nigro et al. reported local control in 23 of 28 patients who received an intermediate radiation dose of 30 Gy in 15 fractions combined with 1000mg/m^2 of 5-FU delivered on days 1-5 and 29-33, and 15mg/m^2 of Mitomycin-C on day 1 only[21].

This suggests there are some anal cancers that require less than the current regimen of approximately 50-55 Gy, and others that require more. Adaptive radiotherapy using a biomarker would allow clinicians to tailor the treatment dose to an individual patient's tumour response. Such a strategy could see decreased unnecessary toxicities and improved local control rates.

Diffusion-weighted MRI (DW-MRI) and dynamic contrast enhanced MRI (dCE-MRI) performed during chemo-radiotherapy have early data suggesting it to be an effective tool in predicting later tumour response for both rectal and head & neck cancer[22,23]. Application of this modality to anal cancer may allow adaptation to radiotherapy dosing to compensate for unfavourable biology.

3 STUDY OBJECTIVES

3.1 Primary Hypothesis

DW-MRI and dCE-MRI performed during chemo-radiotherapy for anal cancer is reflective of later tumour response to treatment and is predictive of treatment outcome.

4 STUDY DESIGN

4.1 General Design

A Phase 2 clinical trial investigating the use of multiparametric MRI as a biomarker for tumour response during chemoradiotherapy (CRT) for anal squamous cell carcinoma

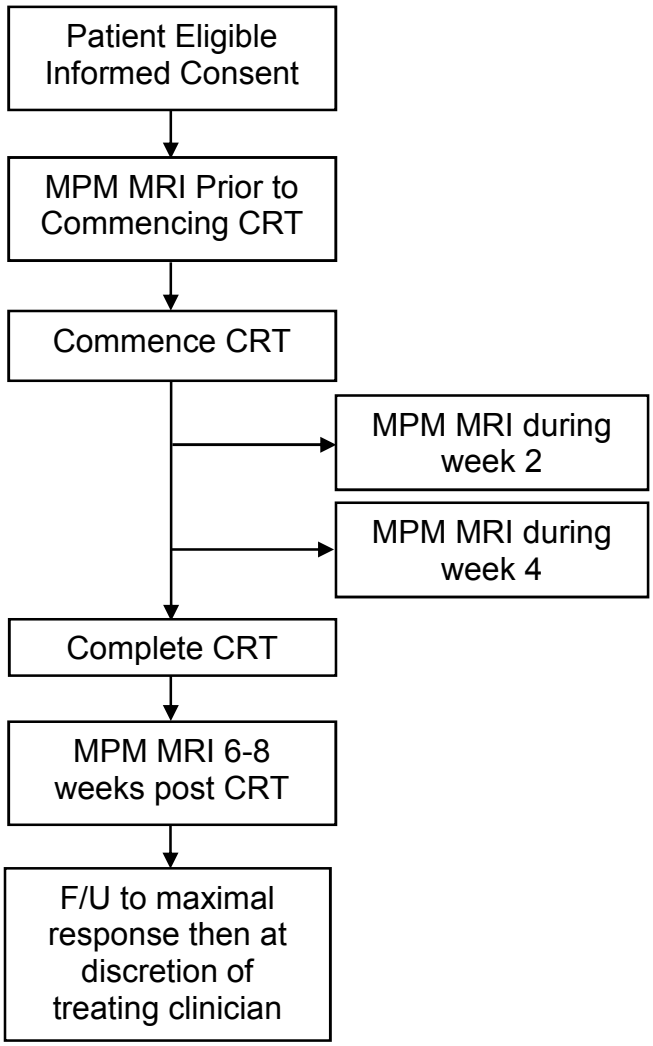
4.2 Primary Study Endpoints

1. Correlation of Standard Morphological MRI (SM-MRI) with tumour response
2. Correlation of DW-MRI with tumour response
3. Correlation of dCE-MRI with tumour response

4.3 Secondary Study Endpoints

1. Determine the feasibility of performing Multiparametric MRI during chemoradiotherapy for anal cancer

4.4 Study schematic



5 SUBJECT SELECTION AND WITHDRAWAL

5.1 Inclusion Criteria

1. Patient capable of providing informed consent
2. Patient deemed suitable for protocol treatment as assessed by Radiation and Medical Oncologists
3. Histological diagnosis of invasive primary squamous cell carcinoma of the anal canal
4. TNM Stage: T2-4, N0-3 (Appendix 1) based on the following diagnostic work-up
    a. History & physical examination
    b. Digital Rectal Exam (DRE) stating primary size and distance from anal verge
    c. Groin examination with documentation of any lymphadenopathy (location: right vs. left; medial vs. lateral; mobile vs. fixed; and size)
    d. Clinically positive nodes
        i. Small inguinal nodes < 1cm in size felt to be clinically positive must be confirmed via biopsy
        ii. A biopsy is not needed for enlarged inguinal, perirectal or pelvic nodes on examination or imaging if >1cm and considered to be clinically positive
    e. Anal biopsy
    f. CT abdomen and pelvis
    g. PET/CT
5. Age ≥18

5.2 Exclusion Criteria

1. ECOG performance status >2 (Appendix 2)
2. Significant comorbidities that would interfere with the completion of treatment
3. Renal insufficiency (Creatinine > 150)
4. Prior radiotherapy to the pelvis that would overlap in the treatment fields
5. Prior surgery for cancer of the anus that removed all macroscopic cancer
6. Prior systemic chemotherapy for anal cancer
7. Evidence of distant metastases (M1) if this precludes radical pelvic treatment
8. Women who are pregnant or lactating
9. Inability to have a MRI due to:
    a. Implanted magnetic metal e.g. intraocular metal
    b. Pacemaker / Implantable defibrillator
    c. Extreme claustrophobia

5.3 Subject Recruitment and Screening

Patients from outpatient Radiation Oncology clinics at the recruitment sites, who meet the inclusion criteria, will be offered enrolment by the relevant Radiation Oncologist. The study procedures will be discussed and the patient presented with an information leaflet detailing in clear language the study aims, methods and all requirements of the patient. It will be explained to the patient that enrolment in this study does not, in any way, alter, delay or extend their intended treatment. Patients will be free to join this study and failure to do so will not impact on their treatment. The trial coordinator will contact the patient to discuss and take questions from the

patient approximately 48 hours after information is given. Final consent will be acquired by a Radiation Oncologist or Radiation Oncology Registrar. The trial coordinator will be present at the consent appointment.

5.4 Early Withdrawal of Subjects

The investigator may withdraw a patient from the study treatment and follow-up procedures if the patient:

- Is in violation of the protocol;
- Experiences a serious or intolerable adverse event
- Develops, during the course of the study, symptoms or conditions listed in the exclusion criteria
- Requests or requires early discontinuation for any reason
- Metastatic disease confirmed prior to commencing pelvic radiotherapy. For such patients, the pelvic radiotherapy component of the study will be suspended.

The investigator will also withdraw all subjects from the study if the study is terminated. Subjects are free to withdraw from the study at any time upon their request or the request of their legally acceptable representative.

5.4.1 Data Collection and Follow-up for Withdrawn Subjects

When a patient withdraws from the study, the reasons, if disclosed by the patient, shall be recorded by the investigator on the relevant page of the CRF to ensure there are no systematic issues with the study which may put other participants at risk. Subjects who withdraw from the study prematurely will have ongoing follow-up at the discretion of the treating clinician.

Subjects who fail to return for study assessments will be contacted by the research team in an attempt to have them comply with the protocol via two documented phone calls and one registered letter.

6 STUDY PROCEDURES

6.1 Radiation Therapy

The radiation technique must be one of either:

- Intensity Modulated Radiation Therapy (IMRT)
- Volumetric Modulated Arc Therapy (VMAT)
- Tomotherapy

The treatment plan is at the discretion of the treating Radiation Oncologist and should be determined by analysis of the volumetric dose, the Dose Volume Histograms, PTV and critical normal structures. An “inverse” planning method shall be used with the aim of delivering treatment dose to the PTV while maximally sparing the normal tissues.

6.1.1 Target Prescription Dose

Dose and fractionation for radical treatment is guided by the AGITG guidelines[24]. The target prescription dose shall be determined as follows:

<u>For T2N0 disease</u>

- The primary tumour PTV will receive 50.4 Gy in 28 fractions at 1.8 Gy per fraction
- The uninvolved nodal PTVs will receive 42 Gy in 28 fractions at 1.5 Gy per fraction

For T3-4N0 disease

- The primary tumour PTV will receive 54 Gy in 30 fractions at 1.8 Gy per fraction.
- The uninvolved nodal PTVs will receive 45 Gy in 30 fractions at 1.5 Gy per fraction.

For N+ disease:

- The primary tumour PTV will receive 54 Gy in 30 fractions at 1.8 Gy per fraction.
- For involved nodes ≤ 3 cm in maximum dimension, the involved nodal PTV will receive 50.4 Gy in 30 fractions at 1.68 Gy per fraction.
- For involved nodes > 3 cm in maximum dimension, the involved nodal PTV will receive 54 Gy in 30 fractions at 1.80 Gy per fraction.

6.1.2 Dose Specifications

The following dose specifications are recommended:

- No more than 2% of the PTV should receive < 95% of the prescription dose
- No more than 2% of the PTV should receive > 107% of the prescription dose

6.1.3 Treatment Schedule

Treatment will be delivered once daily on weekdays, 5 days per week except on public holidays. Missed fractions will be made up for at the end of treatment at the discretion of the treating clinician. All targets will be treated simultaneously. Treatment breaks will be avoided, if possible, or minimised.

6.1.4 Treatment Planning

Target volume definitions are as per ICRU Reports 50, 62 and 83. Treatment planning is as per the Australasian Gastrointestinal Trials Group (AGITG) Contouring Atlas and Planning Guidelines for Intensity-Modulated Radiotherapy in Anal Cancer[24].

Elective Nodal Irradiation

All nodal volumes listed below should be covered for all disease stages as described by the AGITG guidelines.

- Mesorectum
- Pre-sacral space
- Internal Iliac lymph nodes
- Ischiorectal fossa
- Obturator nodes
- External iliac lymph nodes
- Inguinal lymph nodes

Gross Tumour Volumes (GTV)

The gross disease is determined by physical examination, CT, PET and/or MRI.

Clinical Target Volume (CTV)
The primary CTV must encompass:

1. GTV
2. Entire anal canal from the ano-rectal junction to the anal verge
3. Internal and external anal sphincters

A further 10-20mm isotropic margin should be added to items (1), (2), and (3) above, to account for microscopic disease, while respecting anatomical boundaries.

For the involved nodes or nodal regions, a 10-20mm margin should be used, respecting anatomical boundaries.

Planning Target Volume (PTV)
An isotropic 10mm expansion is recommended on CTVs to generate PTVs. Daily image guidance is recommended, especially for prone patients, which may allow CTV-PTV margin reduction to 5-7mm.

6.1.5 Organs at Risk

Femoral head and neck
The entire femoral head and neck should be contoured. The inferior extent is the cranial edge of the lesser trochanter.

Urinary bladder
The entire external outline of the bladder wall should be contoured.

Bowel
In the anterior-posterior direction, the bowel will be contoured from the anterior abdominal wall to the most posterior extent of bowel. In the lateral direction, the borders are bowel edge to bowel edge.

External genitalia and perineum
In males, this volume will include the penis, scrotum, and area including skin and fat anterior to the pubic symphysis. In females, this volume will include the clitoris, labia majora and minora, and area including skin and fat anterior to pubic symphysis. The cranial extent of this volume is the caudal edge of the pubic symphysis.

Bone marrow
Both iliac crests will be used to define “bone marrow.” Delineation will extend cranially from the top of the iliac crests to the superior part of the acetabulum caudally. The left and right iliac crests are combined into one volume.

6.1.6 Dose constraints

The following dose constraints are recommended. Where available, values are taken from the QUANTEC papers. Where not available for that organ, dose constraints are listed as per the RTOG 0529 closed study protocol.

Small bowel

- No more than 195 cc above 45 Gy
- No more than 1% of small bowel > 52 Gy

Femoral heads

- No more than 50% above 30 Gy
- No more than 35% above 40 Gy
- No more than 5% above 44 Gy

Iliac crests

- No more than 50% above 30 Gy
- No more than 35% above 40 Gy
- No more than 5% above 50 Gy

External genitalia

- No more than 50% above 20 Gy
- No more than 35% above 30 Gy
- No more than 5% above 40 Gy

Bladder

- No more than 50% above 55 Gy

Large bowel

- No more than 50% above 50 Gy

6.2 Chemotherapy[4,10]

Concurrent chemotherapy will start on the first day of radiotherapy. The second course of chemotherapy will commence on calendar day 29.

The insertion of a power injectable PICC line should be considered for patients with difficult venous access to allow for contrast injection.

6.2.1 5-Fluorouracil (5-FU)

5-FU shall be delivered at a dose of 800-1000 mg/m^2/day via the IV route in 5% dextrose or 9% Normal Saline (NS) daily for 96 hours continuously starting on day 1 and repeated on day 29.

In the instance of an unplanned treatment break, the second cycle of 5-FU shall be delivered on the 29th day of radiotherapy treatment.

6.2.2 Mitomycin-C

Mitomycin-C shall be delivered at a dose of 10mg/m^2 (without exceeding a maximal single dose of 20mg) via the IV route on day 1 +/- day 29, depending on local practice.

6.3 Pathology

All biopsy tissues will be formalin fixed, paraffin embedded and routine H&E stained. Immunohistochemical p16 staining is to be performed for all tumours.

6.4 Follow-Up and Surgery

At 6-8 weeks post chemoradiotherapy, the patient will have a Multiparametric MRI performed.

The follow-up schedule is at the discretion of the treating clinician. However, the following suggestions apply:

Progressive disease

- Biopsy

- If negative, reassess in 4 weeks
- If positive and no evidence of distant disease, an abdominopelvic resection (APR) is recommended

Persistent disease

- No biopsy, reassess in 4 weeks
- Patients with clinical suspicion of persistent disease at 26 weeks should undergo a biopsy and APR, if positive.

Complete clinical response

- No biopsy
- Continue to follow-up at the discretion of treating clinician

6.5 Imaging

6.5.1 Imaging schedule

Multiparametric MRI consists of standard morphological MRI, Diffusion Weighted MRI and Dynamic Contrast Enhanced MRI. Patients will undergo multiparametric MRI at the following four time points:

- Prior to chemoradiotherapy
- During the second week of treatment (fraction days 6-10)
- During the fourth week of treatment (fraction days 16-20)
- At 6-8 weeks post treatment

6.5.2 Imaging Process

MRI's are performed on a 3 Tesla Skyra by Siemens machine. Patients are scanned in the supine position. No rectal coil is used. All patients should have a single IV bolus of Buscopan (20mg/1ml) immediately prior to the first sequence.

Diffusion Weighted Imaging

- Performed at 4 b-values
  - 0, 400, 800 and 1200

Dynamic Contrast Enhanced Imaging

- Contrast injection:
  - Magnevist 0.2ml/kg
  - Power Injector (2.5ml/s)
  - 20ml saline chase at same rate as injection

Note: A power injector is essential to achieve this consistency across all patients.

The eGFR must be checked prior to the appointment to ensure eligibility for full contrast injection. Half doses are not permitted.

6.5.3 Imaging analysis

Standard Morphological MRI (SM-MRI)

- All images will be assessed independently by two radiologists to determine primary and nodal tumour dimensions. Where there is disagreement, a third will be asked to mediate.

Diffusion Weighted MRI (DW-MRI)

- A Region Of Interest (ROI) will be placed over the entire primary lesion while avoiding areas of obvious necrosis to calculate mean and median ADC values
- A ROI will be placed over each pathological node while avoiding areas of obvious necrosis to calculate mean and median ADC values

Dynamic Contrast Enhanced MRI (dCE-MRI)

- A ROI will be placed over the entire primary lesion while avoiding areas of obvious necrosis to calculate mean and median K^{trans} and K_{ep} values and Relative Signal Intensity (RSI)
- A ROI will be placed over each pathological node while avoiding areas of obvious necrosis to calculate mean and median K^{trans} and K_{ep} values

6.5.4 Criteria for image evaluation

All images will be assessed independently by two radiologists.

Standard Morphological MRI (SM-MRI)

- Primary tumour maximal dimensions
- Nodal tumour maximal dimensions

Diffusion Weighted MRI (DW-MRI)

- Primary tumour apparent diffusion coefficient (ADC) values
- Nodal tumour apparent diffusion coefficient (ADC) values

Dynamic Contrast Enhanced MRI (dCE-MRI)

- Primary tumour perfusion coefficients (K^{trans} and K_{ep})
- Nodal tumour perfusion coefficients (K^{trans} and K_{ep})

7 STATISTICAL PLAN

7.1 Sample Size Determination

Assuming that 70% of patients are positive responders, then sample sizes of 14 responders and 6 non-responders will achieve between 70% and 80% power to show a difference in mean change (initial to final) in SM-MRI of between 1.2 and 1.4 standard deviations at the 0.05 significance level (alpha) using a two-sided Mann-Whitney-Wilcoxon Test. Previous studies in other body locations have shown a positive result with similar patient numbers. We anticipate recruitment to be achieved within 24 months.

7.2 Definition of complete response

- No evidence of residual tumour at 26 weeks post CRT
- No progression requiring APR prior to 26 weeks

7.3 Statistical analysis of primary endpoint

The Mann-Whitney U test will be utilised to determine the following correlations. A significance level of 0.1 will be used.

Standard Morphological MRI (SM-MRI)

- Correlation of responders verses non-responders with:
    - Initial dimensions

- Dimensions at 2 weeks
- Dimensions at 4 weeks
- Dimensions post CRT
- Mean change in initial to 2 week dimensions
- Mean change in initial to 4 week dimensions
- Mean change in initial to post CRT dimensions

Diffusion Weighted MRI (DW-MRI)

- Correlation of responders verses non-responders with:
  - Median initial ADC value
  - Median 2 week ADC value
  - Median 4 week ADC value
  - Median post CRT ADC value
  - Mean change in ADC from initial to 2 week ADC value
  - Mean change in ADC from initial to 4 week ADC value
  - Mean change in ADC from initial to post CRT ADC value
  - Initial Relative Signal Intensity (RSI)

Dynamic Contrast Enhanced MRI (dCE-MRI)

- Correlation of responders verses non-responders with:
  - Median initial K^{trans} and K_{ep} values
  - Median 2 week K^{trans} and K_{ep} values
  - Median 4 week K^{trans} and K_{ep} values
  - Median post-CRT K^{trans} and K_{ep} values
  - Mean change in K^{trans} and K_{ep} from initial to week 2
  - Mean change in K^{trans} and K_{ep} values from initial to week 4
  - Mean change in K^{trans} and K_{ep} values from initial to post CRT

8 SAFETY AND ADVERSE EVENTS

8.1 Radiation Therapy

Interruption to the radiotherapy course during treatment is discouraged. A rest period of ≤ 7 days is suggested for excess skin toxicity.

Following is a list of indications for the interruption of radiotherapy

- Grade 3 diarrhoea
- Grade 4 dermatitis
- Grade 3 vomiting
- Localised or generalised infection

8.2 Chemotherapy

Following is a list of indications for the interruption of chemotherapy

- If grade 4 toxicity occurs during the 96 hour infusion of 5-FU, it must be stopped immediately and permanently for that cycle.
- The second cycle of chemotherapy shall not be administrated until all toxicities have resolved to ≤ grade 2 with appropriate dose reductions as per departmental guidelines

9 DATA HANDLING AND RECORD KEEPING

9.1 Confidentiality

Subject confidentiality is strictly held in trust by the participating investigators, research staff, and the sponsoring institution and their agents. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participating subjects. The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party, without prior written approval of the principal investigator. All laboratory specimens, evaluation forms, reports and other records that leave the site will be identified only by the Subject Identification Number (SIA) to maintain subject confidentiality. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by HREC or regulatory agencies.

9.2 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 15 years after the completion of this clinical trial. All information will be stored in the Radiation Oncology research office of the Calvary Mater Newcastle, either on a password protected computer or in files kept in a locked room. Access to this information will be limited to the principal investigator, research assistants and statistician as authorized by the delegation log.

10 ETHICAL CONSIDERATIONS

This protocol along with the informed consent document will be submitted for approval by the Human Research Ethics Committee (HREC) prior to study commencement.

All alterations to this protocol will be documented and submitted to the HREC for approval prior to incorporation into study procedures.

11 STUDY FINANCES

This study has been funded by the Hunter Translational Cancer Research Unit (HTCRU) with a $20,000 competitive research grant. The HTCRU have not been involved in the construction of this protocol or the design of the study. All funding sources will be acknowledged in any publication.

12 PUBLICATION PLAN

Publication is the sole responsibility of the principal investigator. Data from this study cannot be accessed or utilized by any unauthorised third party without the consent of the principle investigator.

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14 APPENDICES

14.1 Appendix 1: TNM Staging for Anal Cancer (AJCC, 7th ed. 2010)

Primary Tumour (T)

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ (Bowen's disease, high-grade squamous intraepithelial lesion (HSIL), anal intraepithelial neoplasia II-III (AIN II-III))
T1	Tumour 2 cm or less in greatest dimension
T2	Tumour more than 2 cm but not more than 5 cm in greatest dimension
T3	Tumour more than 5 cm in greatest dimension
T4	Tumour of any size invades adjacent organ(s), e.g. vagina, urethra, bladder*

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in perirectal lymph node(s)
N2	Metastasis in unilateral internal iliac and/or inguinal lymph node(s)
N3	Metastasis in perirectal and inguinal lymph nodes and/or bilateral internal iliac and/or inguinal lymph nodes

Distant Metastasis (M)

M0	No distant metastases
MI	Distant metastases

14.2 Appendix 2: ECOG Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disable. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

14.3 Appendix 3: Patient Information Sheet

You are being invited to take part in a clinical research study for individuals with anal cancer. The doctors at this hospital are trying to develop better methods of treatment for this disease. This is called clinical research. In order for you to decide whether you should agree to be part of this study, you should understand enough about its aims, risks and benefits to make an informed decision. This process is known as informed consent.

This Participant Information Sheet contains information about the research trial. Its purpose is to explain to you as openly and clearly as possible all the procedures involved in this project before you decide whether or not to take part in it.

Please read this Participant Information Sheet carefully. Feel free to ask questions about any of material in the Information Sheet. Before deciding whether or not to take part, you may wish to discuss the trial with friends or relatives or your local health worker.

Should you decide not to participate in this trial, your doctor will discuss details of your treatment options with you. Your decision not to participate will not affect any other aspect your treatment.

'What is the main purpose of this trial?'

Your doctor has explained that you require both chemotherapy and radiotherapy for your anal cancer. These treatments will be delivered at the same time over 5-6 weeks. Although scans are performed to determine the extent of disease and to plan the radiotherapy before it starts, they are not routinely performed during or after your treatment. This makes it difficult to determine how well the chemotherapy and radiotherapy is working.

New Magnetic Resonance Imaging (MRI) techniques called Diffusion Weighted MRI and Dynamic Contrast Enhanced MRI have been shown in some studies to be effective for imaging cancer of other body parts.

The main purpose of this study is to see whether using these new MRI techniques before, during and after your treatment provides the doctors with accurate information which predicts the later response of your tumour to the treatment.

'Does the trial have any other purposes?'

Yes. We will also be performing a number of laboratory tests on your tumour biopsy sample to determine the cause of your cancer. Presently, only one laboratory test is performed. In this study, three different laboratory tests will be performed as it has not yet been determined which is the best test or if one test alone is adequate.

These tests can all be performed on your single biopsy sample. You will not be asked to undergo any further biopsies to allow these tests to be performed.

'What if I don't want to take part in this trial or withdraw later?'

Participation in this trial is voluntary. It is completely up to you whether you participate. If you decide not to participate, it will not affect the treatment you receive now or in the future. Whatever your decision, it will not affect your relationship with the staff caring for you. Your doctor will discuss other treatment options that may be available if you do not wish to take part in the trial. Discuss all these options with your doctor before deciding whether to take part in this research trial.

New information about the treatment being studied may become available during the course of the trial. You will be kept informed of any significant new findings that may affect your willingness to continue in the trial.

If you wish to withdraw from the trial once you have started, you can do so at any time without having to give a reason. However, data or samples which have been made anonymous may not be withdrawn. If you join the trial and then decide to withdraw your consent, please notify a member of the research team immediately. This is important so that you can be informed if there are any health risks or special requirements that you need to know.

Your doctor may decide you should stop treatments if they consider it in your best interest, but this does not mean that you have to withdraw from the trial. Your doctor will advise you if alternative treatment is available or appropriate if you stop the trial treatment or withdraw from the trial.

'What does this trial involve - What will happen if I take part?'

If you agree to participate in this trial, you will be asked to sign this Participant Consent Form. The timing of the start of your treatment is usually between 2 to 4 weeks following your first meeting with the radiation oncologist.

Routine Procedures:

There are some routine assessments that will be done before you start any treatment that would have been completed whether you decide to participate in this study or not. These assessments will be performed to evaluate the extent of your disease. Some of these assessments include blood tests and scans.

Standard Treatment:

Your radiotherapy and chemotherapy treatments will be the same as for all anal cancer patients treated at Calvary Mater Newcastle whether on the trial or not.

Radiotherapy

During this study, the radiation treatment will go for a period of 5-6 weeks, with 28-30 days of treatment. Treatments will be given daily, Monday to Friday. The area treated will include not only the anal cancer, but also areas surrounding the tumour such as the lymph nodes in your pelvis.

Treatment takes approximately 10-15 minutes each day. The actual areas treated will depend on the type of anal cancer you have, and your doctor will be able to discuss this with you prior to you starting the radiotherapy.

Chemotherapy

You will receive two types of chemotherapy while you are having radiotherapy. The first, called 5-Fluorouracil (5-FU) is delivered by a continuous infusion pump into your veins over 4 days. The pump is only small and you can carry it around with you. You will receive this chemotherapy twice – it will be commenced on Day 1 and Day 29 of your treatment.

The second chemotherapy agent you will receive is called Mitomycin-C. It is also delivered via your veins but only takes 15 minutes. But you only require this chemotherapy once or twice on the first day of radiotherapy, and possibly a second time after 4 weeks.

Post-Treatment Follow-up:

Following the completion of your treatment you will have regular follow-up visits by your doctors, occurring at least every 6 months for a total of 5 years. You will have complete clinical examinations and will be monitored for the effect of the treatment.

Other Tests:

Your doctor may need to do other tests not already listed. These tests, as well as determining the extent of your cancer, will assess how well your various organs are working.

Trial Specific Assessments:

The following assessments will only be performed if you agree to participate in the trial:

MRI Scans

In total, four MRI's will be performed; one before treatment, one in the second week of treatment, one in the fourth week of treatment and one 6-8 weeks after treatment has finished.

It is important you tell your doctor if you have a pacemaker, defibrillator, or have ever had metal in your eye as this may prevent you from having an MRI. An MRI tunnel is similar to a CT, except more narrow. Tell your doctor if you have claustrophobia. The total time for the scan is around 45 minutes. You will need an injection of contrast (dye) to improve the quality of the scans. There is a possibility of an allergic reaction (anaphylaxis) to the contrast used in scans which can be life threatening, however a severe (anaphylactic) reaction to contrast is rare.

'Are there risks to me taking part in the trial?'

The standard risks of treatment have already been discussed with you by your doctor. Risks from participating in this study include only those that relate to having an MRI scan. Although there are no known short or long term side effects of an MRI scan, the use of contrast with the MRI does carry a small risk of an allergic reaction (anaphylaxis) which, although rare, can be severe.

'Are there benefits to me taking part in the trial?'

This trial aims to further medical knowledge and may improve future treatment of anal cancer; however it may not directly benefit you. Your doctor will discuss with you the benefits for your personal circumstances of the standard treatments recommended.

It is not possible to predict if participating in this study will have any personal benefit for you. By performing MRI scans during your treatment, it is hoped that it will improve our understanding of the usefulness of MRI to monitor tumour response to treatment in anal cancer. If we are able to answer this question, further research will be needed to confirm the results. Your personal benefit cannot be guaranteed, however other patients may benefit in the future from knowledge gained in this trial.

'What happens if I suffer injury or complications as a result of the trial?'

If you suffer any injuries or complications that may be as a result of your participation in this cancer research trial, you should immediately contact your radiation oncologist, general practitioner or local hospital emergency department, who will assist you in arranging appropriate medical treatment.

'Will taking part in this trial cost me anything, and will I be paid?'

Participation in this trial will not cost you anything more than your usual treatment costs. You will not receive payment for taking part in this research trial.

'How will my confidentiality be protected and what happens with the results?'

All records including medical history, radiological imaging, laboratory tests and radiotherapy treatment records will be considered "source data" and will be kept for at least 15 years after the completion of the study. The information will be kept in the Calvary Mater Newcastle Research Unit under lock and key and computer password protection. Your medical records may be released in confidence to the regulatory authorities and Human Research Ethics Committee with the understanding that these records will be used only in connection with carrying out our obligations relating to this study. Your information will be accessed, used, managed and stored in accordance with the NSW Health Records and Information Privacy Act 2002.

If you withdraw from the study, the study data collected prior to your withdrawal may still be processed along with other data collected as part of the clinical trial. Should you allow it, your medical information regarding your progress would still be collected.

When the results of the trial are presented at scientific meetings or published in a medical journal no individual participant will be recognisable from the data presented. In any publication, information will be provided in such a way so you cannot be identified. By signing the attached Consent Form, you authorise release of, or access to, this confidential information to the relevant trial personnel and regulatory authorities.

It is desirable that your family doctor be advised of your decision to participate in this research trial. By signing the Consent Form, you agree to your family doctor being notified of your decision to participate in this research trial.

At all times, you have the right to access and to request correction of information held about you by the Calvary Mater Newcastle Research Centre. If you do not consent to the access to your information described above and how it will be used, you will not be able to join the research trial.

'What should I do if I want to discuss this trial further before I decide?'

When you have read this information, your doctor will discuss it with you and any queries you may have. If you would like to know more at any stage, please do not hesitate to contact your doctor on 02 4014 3632 or the Clinical Trial Coordinator, Sarah Gallagher, on 02 4014 3947.

'Who should I contact if I have concerns about the conduct of this trial?'

This research has been approved by the Hunter New England Human Research Ethics Committee of the Hunter New England Local Health District, Reference 12/11/21/3.06.

Should you have concerns about your rights as a participant in this research, or you have a complaint about the manner in which the research is conducted, it may be given to the researcher, or, if an independent person is preferred, to Dr Nicole Gerrand, Manager, Research Ethics and Governance Unit, Hunter New England Human Research Ethics Committee, Hunter New England Local Health District, Locked Bag 1, New Lambton NSW 2305, Telephone (02) 49214950, email hnehrec@hnehealth.nsw.gov.au

'What are my rights?'

a) You may ask questions regarding this trial and can expect clear and understandable answers in return.
b) Participation in this trial is voluntary and you are not obligated to participate if you do not wish to. You may withdraw from this trial at any time you wish without jeopardising further treatment at this hospital. Your doctor may withdraw you from the trial if it is felt that continuing would involve a risk to you.
c) Your medical records will be released in confidence to the trial coordinators, to the regulatory authorities and the Human Research Ethics Committee with the understanding that these records will be used only in connection with

carrying out our obligations relating to this trial. You will not be identified as an individual in any of these reports or subsequent publications.

d) If any complications of this disease or of the treatment occur, the oncology centre will provide appropriate treatment for these problems.
e) If any new information becomes available that may influence your decision to continue in this trial, such information will be given to you.
f) Your participation in this trial will not involve any additional costs.

This study has been reviewed and approved by the Human Research Ethics Committee for the Calvary Mater Newcastle. Should you wish to discuss the study with someone not directly involved, in particular in relation to matters concerning policies, information about the conduct of the study or your rights as a participant, or should you wish to make an independent complaint, you can contact the coordinator of the Research Ethics Committee of the Calvary Mater Newcastle on 02 4921 4950.

'Who do I ask if I have a question?'

Clinical Trial:

The doctor you should contact is Dr Michael Jones on 02 4014 3632.

Urgent Medical Assistance:

If at any time during your treatment you require urgent medical assistance after-hours, contact your nearest general practitioner or hospital emergency department. You should tell the medical staff if you are participating in this clinical research study.

14.4 Appendix 4: Consent Form

Multiparametric MRI as an Outcome Predictor for Anal Canal Cancer Managed with Chemoradiotherapy

Dr _____ has discussed this trial with me.

I have:

- Read, understood and kept a copy of the Patient Information Sheet;
- Had the opportunity to ask questions about this trial and have had any questions or queries answered to my satisfaction;
- Been informed of the possible risks or side effects of the tests or procedures being conducted;
- Understood that the project is for the purpose of research and not for treatment;
- Been informed that the confidentiality of the information will be maintained and safeguarded;
- Given permission for access to my medical records, for the purpose of this research;
- Given permission for medical practitioners, other health professionals, hospitals or laboratories outside this hospital, to release information concerning my disease and treatment, which is needed for this study and understand that such information will remain confidential.
- Given permission for my pathology samples to be reviewed and further non genetic tests to be performed on this material to confirm diagnosis.
- Given consent to the publishing of results from the study provided my identity is not revealed.
- Been assured that I am free to withdraw at any time without comment or penalty; and
- Agreed to participate in the study.

PATIENT'S NAME: _____

PATIENT'S SIGNATURE: _____ DATE: _____

I, the supervising physician, confirm that I have fully explained the nature, purpose and reasonably foreseeable risks to the patient taking part in the study. I confirm that he/she has read and kept a copy of the Patient Information Sheet and that he/she freely agrees to participate in the study.

PHYSICIAN'S NAME: _____

PHYSICIAN'S SIGNATURE: _____ DATE: _____

14.5 Appendix 5: Revocation of Consent Form

Multiparametric MRI as an Outcome Predictor for Anal Canal Cancer Managed with Chemoradiotherapy

I hereby wish to;
(Please circle one)

1. Partially withdraw from the study above.
   a. I do not wish to receive any further treatment prescribed by the study named above however I consent for my information to continue to be collected for the purposes of this study.
2. Totally withdraw my consent to participate in the study named above.
   a. I do not wish to receive any further treatment or attend study related follow up assessments. I understand that such withdrawal WILL NOT jeopardise the treatment that I receive now or in the future or my relationship with the staff caring for me.

PATIENT'S NAME: _____

PATIENT'S SIGNATURE: _____ DATE: _____

14.6 Appendix 6: Causality and assessment of severity – Adverse Events

The severity of an Adverse Event will be assessed as follows:

Mild: Events that require minimal or no treatment and do not interfere with the patient's daily activities

Moderate: Events that cause sufficient discomfort to interfere with daily activity and/or require a simple dose of medication

Severe: Events that prevent usual daily activity or require complex treatment

The relationship of the event to the study drug will be assessed as follows:

Unrelated: There is no association between the exposure and the reported event. AEs in this category do not have a reasonable temporal relationship to exposure, or can be explained by a commonly occurring alternative aetiology.

Possible: The event could have cause or contributed to the AE. AEs in this category follow a reasonable temporal sequence from the time of exposure and/or follow a known response pattern to the test article, but could also have been produced by other factors.

Probable: The association of the event with the exposure seems likely. AEs in this category follow a reasonable temporal sequence from the time of exposure and are consistent with the known action of the exposure, known or previously reported adverse reactions to the exposure, or judgment based on the investigators clinical experience.

Definite: The AE is a consequence of exposure. AEs in the category cannot be explained by concurrent illness, progression of disease state or concurrent medication reaction. Such events may be widely documented as having an association with the exposure or that they occur after re-challenge.