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APHRODITE - A phase II trial of higher radiotherapy dose in the eradication of early rectal cancer

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Registration date 17/10/2019	**Overall study status** Completed	
Last Edited 17/11/2023	**Condition category** Cancer	

Plain English summary of protocol
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-of-a-higher-dose-of-radiotherapy-for-early-rectal-cancer-aphodite

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 41422

Study information

Scientific Title
A Phase II trial of Higher RadiOtherapy Dose In The Eradication of early rectal cancer

Acronym
APHRODITE

Study objectives
The primary aim is to assess whether radiotherapy dose escalation increases the complete clinical response (cCR) rate, compared with standard dose CRT, with acceptable toxicity, in patients with early rectal cancer who are not suitable for radical surgery.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 15/10/2019, North West - Greater Manchester East Research Ethics Committee (3rd Floor, Barlow House, 4 Minshull Street, Manchester, M1 3DZ, UK; +44 (0)207 104 8009; nrescommittee.northwest-gmeast@nhs.net), REC ref: 19/NW/0565

Study design
Randomized; Interventional; Design type: Treatment, Radiotherapy

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Colorectal cancer

Interventions

APHRODITE is a phase II, multi-centre, open-label, randomised-controlled trial of high dose radiotherapy versus standard dose radiotherapy for early rectal cancer. The primary aim is to assess whether radiotherapy dose escalation increases the clinical complete response (cCR) rate at 6 months from the start of chemoradiotherapy (CRT), compared with standard dose CRT, with acceptable toxicity. A total of 104 eligible patients will be randomised on a 1:2 basis to receive either standard dose CRT or dose escalated CRT. Participants will be recruited to the trial from approximately 10-12 UK radiotherapy sites.

Patients will be enrolled in the trial after referral to a radiotherapy department, but prior to start of radiotherapy. Prior to randomisation the treating clinical oncologist will assess whether patients should receive chemotherapy or not alongside their radiotherapy. After informed consent for trial participation, patients will be randomized to either standard dose or dose escalated radiotherapy, following standard radiotherapy pathways. Treatment-related toxicity will be assessed during and 2 weeks after end of treatment. Patients will then be followed in their standard of care follow-up appointments at 3 months, 6 months (for assessment of primary endpoint), 9 months, 12 months and 24
months after start of treatment, including assessment of treatment response (3 and 6 months) as well as toxicity and patient-reported outcomes (all time points).

Trial design details

The null and any alternative hypotheses:
The null hypothesis for the primary endpoint is that the difference in cCR rates between the intervention and control group is less than 20% at 6 months post start of treatment. The alternative hypothesis is the difference in cCR rates between the intervention and the control group is 20% or higher at 6 months post start of treatment, in favour of the intervention.

The cCR rate of 35% in the control arm is based on published series of CRT trials and adjusted to take account of the early rectal cancer case mix for this study. Previous data suggests that there may be a difference as great as 25%, or even greater, in cCR rate between the two arms (in favour of the experimental arm). Therefore 20% was chosen as a conservative estimate for this difference to ensure that the trial is adequately powered, and will produce an informative result, noting particularly that 20% would be a clinically meaningful difference and one that would warrant further testing of the experimental strategy.

The justification for including a control arm:
The control arm in the APHRODITE trial is standard dose CRT and is the standard of care for the study population. The use of a control arm was essential for the trial as similar previous research into the benefits of dose escalation have been single-arm in design. The parallel design will allow for the comparison of the dose-escalated chemoradiotherapy with a concurrent treatment of standard dose CRT. This design aspect is vital for internal validity of the trial.

Broad timetable for the study

Prior to trial entry:
Patients will be approached for possible recruitment by their clinical oncologist, following the multidisciplinary team (MDT) diagnosis and decision to treat with chemoradiotherapy.

Suitability for inclusion into APHRODITE will be assessed according to the eligibility criteria. A verbal explanation of the trial, Patient Information Sheet (PIS) and Key Fact sheet will be provided to the patient by the attending medical staff (and/or the trial Clinical Research Nurse). This will include detailed information about the rationale, design and personal implications of

the trial. Patients will have as long as they need to consider participation, normally a minimum of 24 hours, and will be given the opportunity to discuss the trial with their family and healthcare professionals before they are asked whether they are willing to take part.

Patients who do decide to enter the trial will then be formally assessed for eligibility and invited to provide informed, written consent. The formal assessment of eligibility and informed consent may only be obtained by the PrincipalInvestigato r (PI) or an appropriate medically qualified healthcare professional. The following procedures are part of the standard assessment for rectal cancer patients and these assessments are usually already obtained as apart of standard care, and will be used to establish eligibility: A diagnostic biopsy (histopathology), performance status (which grades the daily living abilities of patients with cancer), bloods, pregnancy screening, MRI (pelvis), CT (chest, abdo, pelvis), flexible sigmoidoscopy, digital rectal examination and ECG. These will need to have been conducted within a
pre-specified timeframe before trial enrollment.

Pre-treatment:
Following confirmation of written informed consent and eligibility, participants will be randomised for either standard dose CRT or dose escalated CRT on a 1:2 basis, respectively.

A computer-generated minimisation program that incorporates a random element will be used to ensure the treatment groups are well balanced for the following factors:
- Randomising Site
- T-stage (<T3 vs. T3)
- Chemotherapy use (either 100% or 75% dose) vs. no chemotherapy use
Randomisation will be performed centrally using the CTRU automated 24-hour randomisation system

If performance status and Bloods (Full blood count, U&Es, LFTs) were not assessed within 10 days of starting CRT, they will need to be repeated prior to treatment start. Additional pre-treatment assessment will include clinical assessment, baseline symptom scores, and patient reported outcome measures (PROMs) (including health-related quality of life questionnaires).

On treatment:
Dependent upon randomisation, patients will be allocated to either the standard CRT or dose escalated CRT, with or without chemotherapy.
Standard CRT - Radiotherapy using a dose of 50. 4 Gy is applied to the primary tumour and surrounding mesorectum using IMRT, in 28 fractions of 1.8 Gy, one fraction per day, 5 days a week. Daily image guidance is used for treatment delivery.
Dose escalated CRT: Radiotherapy using a dose of 50.4 Gy is applied to surrounding mesorectum and 62 Gy applied to the primary tumour using synchronous integrated boost IMRT, in 28 fractions, one fraction per day, 5 days a week.
Daily image guidance is used for treatment delivery.

The possible concurrent chemotherapy is delivered using one of three regimens, at the discretion of the treating oncologist. The regimen used must be declared prior to randomisation on the pre-randomisation checklist. No crossover between the chemotherapy regimens (capecitabine and 5FU) should occur. If the treating team feel that the patient is not fit enough to receive the full (100%) dose of concurrent capecitabine or 5FU/LV, because of specific comorbidities, or general frailty, then there are the options either to treat with concurrent capecitabine or 5FU/LV chemotherapy at 75% dose, or to omit the chemotherapy altogether and treat with radiotherapy alone. All
chemotherapy regimens are part of standard clinical practice.

Both standard CRT treatment and escalated CRT regimens will commence Monday to Friday for a duration of 5.5 weeks. Other assessments during the treatment period will also be recorded. ECOG Performance status, bloods (full blood count, urea and electrolytes, liver function tests), a clinical assessments and acute toxicity's will be recorded weekly. At 5.5 weeks, another set of PROMs, including health-related quality of life questionnaires, will then be completed.

End of Treatment:
A telephone-based assessment will be carried out two weeks following completion of CRT, i.e. at 7.5 weeks following the start of CRT, to assess toxicity/performance status. This will be done by a trial nurse.

Follow-up assessments:
Follow-up visits will be as follows (from the start of CRT): 3, 6, 9, 12 and 24 months. Data will include (but will not be limited to):
- Performance status will be assessed at 3, 6, 9, 12, 24 months
- High resolution MRI of the pelvis at 3 and 6 months
- Flexible sigmoidoscopy will be assessed at 3, 6 and 12 months
- Digital rectal examination will be assessed at 3, 6, 9, 12 and 24 months
- Clinical assessment will be assessed at 3, 6, 9, 12 and 24 months
- Late toxicity will be assessed at 3, 6, 9, 12 and 24 months
- Health-related quality of life questionnaire will be assessed at 3, 6, 9, 12 and 24 months

Between 6 and 24 months post-CRT start, clinic visits or investigations additional to those defined in the protocol, are eligible and permitted at the discretion of the treating team. In addition, clinical management beyond 24 months is at the discretion of the local treating team.

Use of tissue samples in future research:
The researchers will collect tissue biopsy samples from participants from the outset, to avoid the need to re-consent. The patient information sheet explains that these donations are optional would be considered as a gift to research. The samples collected and centrally reviewed for quality assurance purposes with the plan to assess baseline biological radiosensitivity signatures.

Data analysis
The statistical analysis is the responsibility of the CTRU Statisticians. A separate and fully detailed statistical analysis plan (SAP) will be written before any analyses are undertaken and in accordance with CTRU standard operating procedures.

The primary endpoint analysis will take place once the final participant has reached their primary endpoint, i.e. 6 months post start of treatment, and once all data have been received and cleaned. Analysis of the secondary endpoints will take place once the final participant has been followed-up to 24 months post randomisation.

There will be no formal interim analyses, however, an independent data monitoring and ethics committee will review interim safety and accrual data to monitor the trial progress.

Procedures in place to detect and compensate for any possible "researcher effects" and "researcher bias":
cCR at 6 months post-start of treatment is assessed via a composite of digital examination, high resolution pelvic MRI, and sigmoidoscopy. Such a composite outcome has the risk to be inconsistent between clinicians and sites. A clear definition of cCR is provided in the protocol for clinicians to follow. Additionally, example image packs and detailed clinical descriptions for the

various assessment methods are provided in the supplemental Aphrodite MRI Guidelines. Training has also been provided to sites via attendance of an Imaging Workshop. This will help ensure consistency to the binary primary endpoint response. Further, the baseline, 3 and 6 month post-treatment MRI scans and endoscopic photographs for the first two patient's from each site will be reviewed centrally. Providing clear instructions, training and quality assessments is essential to detect and reduce any possible clinician/researcher bias for the assessment of the patient's outcome

Intervention Type
Other

Primary outcome measure
Clinical complete response at 6 months from start of (chemo-)radiotherapy.
Response to treatment will be assessed via clinical examination, endoscopy and imaging using pelvic MRI in accordance with the Tumour Regression Grading (mrTRG) system. Clinical complete response (cCR) will be defined as:
1. No evidence of either mucosal tumour or submucosal swelling on white light endoscopy. A flat white scar remains, with or without telangiectasia
2. No palpable tumour upon digital rectal examination (DRE)
3. High-resolution pelvic MRI scanning shows either a linear scar only, or dense fibrosis with no obvious tumour signal (mrTRG 1 or 2).
Every effort should be made to ensure that trimodality assessment of response occurs at 3 and 6 months (endoscopy, DRE, MRI). However, in the unusual circumstance when this might not be possible for a specific patient, confirmation of a cCR should always include rectal endoscopy. If one of either DRE or MRI cannot be assessed for a specific patient, then confirmation of cCR may still occur based on the endoscopy plus either DRE (if tumour was originally palpable pre-treatment), or pelvic MRI

Secondary outcome measures
1. Acute toxicity and late toxicity recorded during each visit using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE). These time points will be at baseline, on treatment weeks 1,2,3,4,5,5.5, 7.5 and during follow up at the 3, 6, 9, 12 and 24 month visits.
2. Patient-reported outcome measures (PROMs) including health-related quality of life (HRQoL) will be collected after at baseline, at end of treatment at week 5.5, then during follow up at 3, 6, 9, 12 and 24 months.
3. Other information will be collected during visits, such as stoma rate, treatment compliance and overall survival but these will be collected if and when they occur.

Overall study start date
28/10/2019

Completion date
29/08/2022

Eligibility

Key inclusion criteria
1. Biopsy confirmed adenocarcinoma of the rectum
2. Age 18 or over
3. Able to provide written informed consent
4. MDT deems patient unsuitable for radical TME surgical resection of their tumour either

because they are considered to be at increased surgical risk from TME (for example due to general frailty or due to specific co-morbidities which make anaesthetic or surgery hazardous, such as cardiac disease, pulmonary disease, renal failure, previous anaesthetic problems or previous pelvic surgery), or they have marked anxiety at the prospect of a stoma, or because of anticipated difficulty managing a stoma post-operatively (including physical causes such as arthritis, Dupuytren's contracture and visual problems).
5. Patient is suitable for either pelvic radiotherapy or chemoradiation in the opinion of the treating oncologist
6. ECOG PS 0-2
7. Primary tumour is < = 4 cm in maximum diameter
8. Primary tumour is staged at T1-T3b. (TNM staging as per UICC 8th Edition (Appendix B), with additional T3 subdivisions)
9. Tumour is visible on MRI
10. Superior aspect of tumour is at or below a horizontal line drawn from the anterior aspect of the S2/3 junction on pre-treatment MRI
11. No unequivocally involved lymph nodes, i.e. NX (nodes too small to characterise as to say equivocal nodes) and N0 are both eligible
12. For low rectal tumours superior to the puborectalis sling, patients are eligible if the mesorectal fascia or levator are:
12.1 Clear (> 1 mm from disease to levator ani or mesorectal fascia)
12.2 or threatened (< = 1mm from disease to levator ani or mesorectal fascia)
12.3 or mesorectal fascia is involved but not breached
13. Estimated creatinine clearance > = 50 mls/min (estimated using a validated creatinine clearance calculation e.g. Cockroft and Gault, or Wright formula)
14. Absolute neutrophil count > 1.5 x 109/l; platelets > 100 x 109/l
15. Serum transaminase concentration < 3 x Upper Limit Normal (ULN)
16. Bilirubin concentration < 1.5 x ULN

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 104; UK Sample Size: 104

Key exclusion criteria
1. Nodal involvement identified by nodes showing irregular margins and or heterogeneous signal on the high resolution MRI (i.e. N1-N2)
2. The presence of EMVI discontinuous with the primary tumour
3. Discontinuous tumour deposits (N1c)
4. Dominant mucinous tumour on MRI
5. Signet ring carcinoma or tumours histopathologically containing a neuroendocrine component
6. Tumour has grown through and breached mesorectal fascia

7. Tumour involves or breaches the levator ani (as this would be T4b disease)
8. Involvement of anal intersphincteric plane or external anal sphincter or adjacent organs (If the participant has a low rectal tumour extending inferior to the puborectalis sling, involvement of the internal anal sphincter is permitted)
9. Undergone an attempt at complete local resection of their cancer
10. Previous pelvic radiotherapy
11. Definite distant metastases (equivocal distant metastases on the CT scan are permitted, e.g. indeterminate lung modules, sub-centimetre retroperitoneal nodes or indeterminate liver lesion)
12. Defunctioning colostomy or ileostomy has been fashioned
13. Prior invasive malignancy unless disease free for a minimum of 3 years (excluding basal cell carcinoma of the skin or other in situ carcinomas)
14. Prior systemic chemotherapy for colorectal cancer
15. Women who are pregnant, breastfeeding or a women of child bearing potential who are unwilling to use effective contraceptive methods

Date of first enrolment
04/11/2019

Date of final enrolment
06/11/2023

Locations

Countries of recruitment
England

United Kingdom

Wales

Study participating centre
University Hospitals Bristol NHS Foundation Trust
Trust Headquarters
Marlborough Street
Bristol
United Kingdom
BS1 3NU

Study participating centre
The Christie NHS Foundation Trust
550 Wilmslow Road
Manchester
United Kingdom
M20 4BX

Study participating centre
Clatterbridge Cancer Centre NHS Foundation Trust
Clatterbridge Health Park
Clatterbridge Road
Wirral
United Kingdom
CH63 4JY

Study participating centre
Lancashire Teaching Hospitals Trust
Royal Preston Hospital
Sharoe Green Ln
Fulwood
Preston
United Kingdom
PR2 9HT

Study participating centre
St James's University Hospital
Department of Haematology
Level 3, Bexley Wing
Beckett Street
Leeds
United Kingdom
LS9 7TF

Study participating centre
United Lincolnshire Hospitals NHS Trust
Lincoln
United Kingdom
LN4 4AX

Study participating centre
North Tees and Hartlepool NHS Foundation Trust
Hartlepool
United Kingdom
TS24 9AH

Study participating centre
The Newcastle Upon Tyne Hospitals NHS Foundation Trust
Freeman Hospital

Freeman Road
High Heaton
Newcastle upon Tyne
United Kingdom
NE7 7DN

Study participating centre
Betsi Cadwaladr University LHB
Bangor
United Kingdom
LL57 2PW

Study participating centre
Oxford Health NHS Foundation Trust
Warneford Hospital
Warneford Lane
Oxford
United Kingdom
OX3 7JX

Study participating centre
Sheffield Teaching Hospitals NHS Foundation Trust
Northern General Hospital
Herries road
Sheffield
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S5 7AU

Sponsor information

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Sponsor type
University/education

Website
https://medicinehealth.leeds.ac.uk/

ROR
https://ror.org/024mrxd33

Funder(s)

Funder type
Charity

Funder Name
Yorkshire Cancer Research; Grant Codes: L411

Alternative Name(s)
YCR

Funding Body Type
Government organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal.

Intention to publish date
29/08/2023

Individual participant data (IPD) sharing plan
Current IPD sharing statement as of 04/03/2021:
Individual participant data (with any relevant supporting material, e.g. data dictionary, protocol, statistical analysis plan) for all trial participants (excluding any trial-specific participant opt-outs)

will be made available for secondary research purposes at the end of the trial, i.e. usually when all primary and secondary endpoints have been measured and all key analyses are complete.
Data will be shared according to a controlled-access approach, based on the following principles:
1. The value of the proposal will be considered in terms of the strategic priorities of the CTRU, Chief Investigator and Sponsor, the scientific value of the proposed project, and the resources necessary and available to satisfy any data release request.
2. The researchers encourage a collaborative approach to data sharing, and believe it is best practice for researchers who generated datasets to be involved in subsequent uses of those datasets.
3. The timing and nature of any data release must not adversely interfere with the integrity of the trial or research project objectives, including any associated secondary and exploratory research objectives detailed in the ethically approved original research protocol. On an individual trial or research project basis, a reasonable period of exclusivity will be agreed with the trial or research project team.
4. Any data release must be lawful, in line with participants' rights and must not compromise patient confidentiality. Where the purposes of the project can be achieved by using anonymised or aggregate data this will always be used. The researchers will release individual patient data only in a form adjusted so that recipients of the data cannot identify individual participants by any reasonably likely means. They will also only share data when there is a binding agreement in place stating that data recipients will not attempt to re-identify any individual participants.
5. Any data release must be in line with any contractual obligations to which the CTRU is subject.
6. The research must be carried out by a bone fide researcher with the necessary skills and resources to conduct the research project.
7. The research project must have clear objectives and use appropriate research methods.
8. The research must be carried out on behalf of a reputable organisation that can demonstrate appropriate IT security standards to ensure the data is protected and to minimise the risk of unauthorised disclosure.
Data will only be shared for participants who have given consent to use of their data for secondary research.
Requests to access trial data should be made to CTRU-DataAccess@leeds.ac.uk in the first instance. Requests will be reviewed (based on the above principles) by relevant stakeholders. No data will be released before an appropriate agreement is in place setting out the conditions of release. The agreement will govern data retention requirements, which will usually stipulate that data recipients must delete their copy of the data at the end of the planned project.

Previous IPD sharing statement:
The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication.

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Results article		28/04/2022	17/11/2023	Yes	No