



ARISTOTLE

A phase III trial comparing standard versus novel CRT as pre-operative treatment for MRI defined locally advanced rectal cancer



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authorised by:**

Signature

Date



Please note: This trial protocol must not be applied to patients treated outside the ARISTOTLE trial. UCL CTC can only ensure that approved trial investigators are provided with amendments to the protocol.

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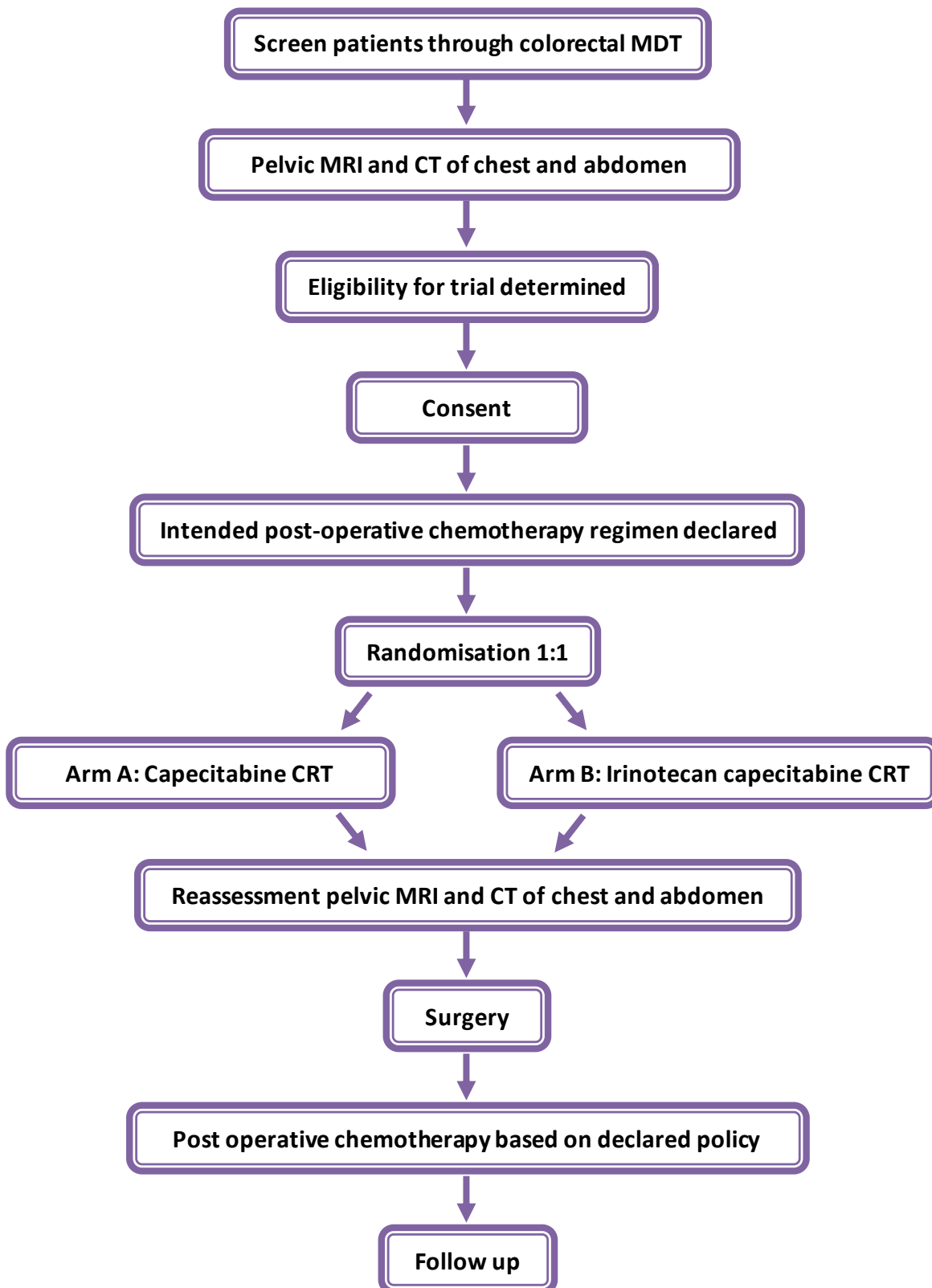
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1. Protocol Summary

1.1 Summary of Trial Design

| | |
|---|--|
| Title: | A phase III trial comparing standard versus novel chemoradiotherapy as pre-operative treatment for MRI defined locally advanced rectal cancer |
| Short title | ARISTOTLE |
| EUDRACT no: | 2008-005782-59 |
| Sponsor name & no: | University College London- UCL/08/136 |
| Funder name & no.: | Cancer Research UK- C19942/A10016 |
| ISRCTN no: | ISRCTN09351447 |
| Design: | Randomised, multi-centre, phase III trial (two arm study) |
| Aims: | To determine whether the addition of a second drug (irinotecan) to the standard treatment of oral chemotherapy using capecitabine and radiotherapy improves outcome. |
| Primary endpoint: | <ul style="list-style-type: none"> ▪ Disease-free survival (DFS) |
| Secondary endpoints: | <ul style="list-style-type: none"> ▪ Disease-specific survival ▪ Loco-regional failure ▪ Overall survival ▪ Histopathologically confirmed CRM-ve resection rate ▪ Histopathological complete response (pCR) rate ▪ Histopathologically quantitated tumour cell density ▪ Surgical morbidity ▪ Health related Quality of Life and functional outcome |
| Subjects: | 600 patients with MRI defined locally advanced, non-metastatic rectal cancer. |
| Planned number of sites: | ~100 |
| Target countries: | United Kingdom |
| Treatment Summary: | <p>Patients will be randomised to one of two pre-operative CRT regimens:</p> <ul style="list-style-type: none"> ▪ Arm A – Capecitabine 900 mg/m² orally twice daily, Mon – Fri for five weeks with radiotherapy 45 Gy in 25 fractions ▪ Arm B – Irinotecan 60 mg/m² once weekly (weeks 1 – 4) and capecitabine 650 mg/m² orally twice daily, Mon – Fri for five weeks with radiotherapy 45 Gy in 25 fractions <p>Surgery is strongly recommended to take place 8 – 10 weeks after completion of CRT. Post-operative adjuvant chemotherapy policy will be declared prior to randomisation and should reflect standard unit practice.</p> |
| Anticipated duration of recruitment: | 6 years |
| Duration of patient follow-up: | Up to 5 years after randomisation |
| Definition of end of trial: | 5 years after the last patient has been randomised, or once all patients have progressed or died, whichever happens first. |
| Statistical summary: | The trial is powered to detect a 9% absolute improvement in 3 year DFS from 65% to 74%. This equates to a hazard ratio of 0.70 with power of 80% using a two-sided alpha of 0.05. This will require 247 DFS events which we expect to observe after recruiting 600 patients with a minimum of 3 years of follow-up. |
| Ancillary studies: | Blood samples and archival tumour tissue will be collected from consenting patients for future research. |

1.2 Trial Schema



ARISTOTLE Schema 2012JUL17

2. Introduction

2.1 Background

Rectal cancer affects 10,000 new patients per year and causes 4,700 deaths each year in England and Wales. Radiotherapy has a major role in reducing the risk of local failure and shrinking locally advanced cancers to facilitate a curative resection. The use of pre-operative MRI can identify patients who have locally advanced rectal cancer who would benefit from pre-operative chemo-radiotherapy (CRT). The proposed randomised controlled trial will investigate whether the addition of a second chemotherapy drug will further improve disease free survival and loco-regional control.

There is a clear established role for the use of neoadjuvant radiotherapy in resectable rectal cancer. Two meta-analyses (1, 2) have demonstrated a significant reduction in local recurrence and improvement in cancer specific survival. This evidence base consists of 8,500 patients in 28 randomised trials. Recent trials have established that pre-operative fluoropyrimidine and concurrent CRT is superior to long course radiotherapy alone (3) and that pre-operative CRT is superior to post-operative CRT (4).

In the UK, pelvic MRI has become the standard method of staging rectal cancer pre-operatively and is routinely used to select patients for pre-operative CRT and to assess the response to this approach after CRT. The accuracy of pelvic MRI has been demonstrated in a large multi-centre, UK led, international, prospective study (MERCURY) (5, 6). The impact of this and preceding smaller studies has changed UK practice and provides a unique opportunity for the UK to lead on the use of pelvic MRI within future phase III rectal cancer trials.

Another key advantage in the UK is the use of high quality histopathological examination of resected rectal cancer specimens and the use of the circumferential resection margin status in predicting the risk of both local recurrence and survival. The work by Quirke and colleagues in Leeds demonstrates that the circumferential resection margin (CRM) is the most important histopathological factor that predicts outcome. A clear CRM (> 1 mm microscopic clearance from tumour to the CRM) is associated with a lower risk of local recurrence and improved survival. These findings have been confirmed in a large national population based audit (7), within three phase III trials (CLASSIC (8), MRC CR07 (9), the Dutch rectal cancer trial (10, 11)) and a meta-analysis (12). Recent UK data also confirms that CRM status is also reliable in predicting outcome when assessed after pre-operative CRT (12, 13). In addition, the MRC CR07 trial (14) showed that the (prospective) grading of the surgical resection specimen correlates strongly with the risk of local recurrence.

This study provides the opportunity to evaluate the extent of tumour regression induced by the pre-operative CRT in the resected specimen by the use of the Dworak grading system and the recently reported quantitative approach measuring tumour cell density (15).

The recent results from the MRC CR07 trial demonstrate that high quality surgery can be achieved in resectable rectal cancer (14). Despite such surgical skill, locally advanced rectal cancer that threatens or involves the margins of resection requires improved pre-operative non surgical treatment to improve outcome. In low rectal cancer the extralevator approach has been shown to be superior to standard abdominoperineal excision (APE) and this is slowly being introduced into practice (16).

Current approach using a fluoropyrimidine combined with radiotherapy

In the UK, a combination of clinical examination and cross sectional imaging (CT scan to exclude metastases and pelvic MRI to determine the loco-regional disease extent) will identify patients in whom pre-operative CRT is required to induce macroscopic tumour regression, and to increase the chances of complete macroscopic tumour resection with clear resection margins. This study will use clearly defined MRI eligibility criteria to determine appropriate patient selection for this study. To our knowledge this will be the first phase III rectal cancer trial that includes this important quality measure.

It is clear that for patients in whom a resection is performed and the CRM is involved, there is a substantial risk of local recurrence and poor survival. Retrospective data on 677 patients, treated in 6 UK centres with pre-operative 5FU CRT, demonstrates a 43% 3 year disease free survival (DFS) (13). 13% of patients had complete sterilisation of the resected specimen (pCR). 30% of patients had CRM involvement with a 44% risk of local failure at 3 years. The 70% of patients who had an uninvolved CRM (were CRM-ve) had a 12% risk of local failure at 3 years. Mawdsley and colleagues (17) have reported their experience of 150 patients where 12% attained pCR and 65% of patients attained CRM-ve resections based on an intention to treat analysis. A total of 27% of patients had local failure. The overall median and 5 year DFS was 28 months and 31% respectively.

The causes of local failure include unresectable local disease, incomplete resection of tumour and complete tumour resection followed by confirmed loco-regional recurrence. All these outcomes constitute a disease-related event within a disease-free survival analysis

Choice of the reference treatment regimen for this trial - oral capecitabine CRT

The EORTC 22921 and FFCD 9203 trials (18) both demonstrated a reduction in loco-regional failure when concurrent 5 fluorouracil (5FU) and leucovorin (LV) was added on days 1 – 5 and 29 – 33 to 45 Gy of pelvic radiation, given in 25 fractions over 5 weeks. The German rectal cancer group study (4), that demonstrated the superiority of pre-operative CRT over post-operative CRT, used a 96 hour infusion of intravenous 5FU given on days 1 – 4 and 29 – 32.

However, following these studies, two large phase III trials (19) have demonstrated equivalent time to progression and survival, when oral capecitabine was compared with intravenous 5FU/LV regimens, as first line treatment of advanced or metastatic colorectal cancer. In the adjuvant setting, a large phase III trial has demonstrated non-inferiority of oral capecitabine compared with intravenous 5FU/LV (20).

Concurrent fluoropyrimidine CRT in clinical trials has used bolus 5FU, 5FU/LV, continuous infusion 5FU and oral agents including capecitabine and tegafur-uracil (UFT)/LV. There is no evidence to demonstrate superiority of any one of these approaches.

Two dose finding studies have been performed of oral capecitabine CRT, using a 5 day per week and a 7 day per week chemotherapy regimen (21, 22). Phase II studies have confirmed similar toxicity and histopathological response parameters for capecitabine CRT compared with previous 5FU CRT studies (23). All of these studies have led to an increasing use of oral capecitabine CRT in routine clinical practice. A survey of potential ARISTOTLE collaborators and interactive voting at the annual National Cancer Research Institute (NCRI) colorectal meeting strongly supported the choice of capecitabine CRT as the reference arm for this study. The study design for this trial was to use a

5 day per week capecitabine regimen. A recent publication from Leeds (24) supports the choice of the chosen regimen of 900 mg/m² orally twice daily Monday to Friday for the five weeks of radiotherapy.

Choice of the novel treatment regimen for this trial - irinotecan capecitabine CRT

Numerous dose finding and phase II studies have been performed with the addition of a second chemotherapy drug to a five week course of fluoropyrimidine CRT. Most studies have evaluated either oxaliplatin or irinotecan with a reduced dose of either 5FU or oral capecitabine

A recent meta-analysis identified 52 phase II/III trials of pre-operative CRT with a total of 3157 patients. The overall pCR rate was 10% for fluoropyrimidine CRT (n = 2524) and 19% for CRT using two drugs (n = 633). Two UK phase I/II studies reported acceptable toxicity with the addition of irinotecan (25) and oxaliplatin (26) to 5FU/LV CRT. Three further large phase II studies either led by UK investigators or performed in the UK have evaluated the addition of oxaliplatin (SOCRATES (27) and CORE) and irinotecan (RICE) (28) to capecitabine CRT. The key toxicity and early pathological outcome measures are very similar and are summarised in the table below. The addition of a second concomitant chemotherapy drug is associated with an increase in acute grade 3/4 toxicity (most commonly diarrhoea) but without any significant impact on radiotherapy compliance.

| | RICE Phase II | SOCRATES Phase II | CORE Phase II |
|--|--|---|---|
| Number | 96 commenced CRT, 94 resected | 83 77 resected | 87 |
| Regimen: • Capecitabine • Second drug | 650 mg/m ² bd 7/7 Ir 60 mg/m ² x 4 | 650 mg/m ² bd 7/7 Ox 130 mg/m ² x2 | 825 mg/m ² bd 5/7 Ox 50 mg/m ² x 5 |
| Radiotherapy compliance | 94% of patients received 100% dose (45 Gy). Mean RT dose = 98.5% | 82/83 99% | ➤ 90% |
| Grade 3/4 diarrhoea | 22% gr3 (no gr4) | 7% | 17% |
| pCR (resected pts) | 18/94 = 19% T0N0 plus a further patient T0N1 and one T0N2 | 13/83 = 16% T0N0 | 12% |
| CRM -ve (resected pts) | 86/94 = 91% | 68/83 = 82% | 67% |

Capecitabine dosing 7/7 = continuous; 5/7 = weekdays only Ox – oxaliplatin; Ir – irinotecan

At least eight studies have evaluated pre-operative irinotecan fluoropyrimidine CRT and are summarised in the table below. The largest study is that of Gollins performed by the North West Clinical Oncology Group in the UK.

The TMG considered that 5 day per week dosing of capecitabine should be used in both arms and so the RICE regimen has undergone the modification from seven days per week to five days per week capecitabine.

| | Drug regimen (mg/m²) | No patients | RT dose | pCR | Grade 3/4 toxicity |
|----------------------------------|---|--------------------|----------------|--------------|--|
| Mehta 2003(29) | Ir 50 x 4 PVI 5FU 200 continuous | 32 | 50.4 | 37% | 28% |
| Mohiuddin 2006 (30) | Ir 50 mg/m ² x 4 PVI 5FU 225 mg/m ² continuous | 53 | 50.4 – 54 | 28% | 19% Grade 3/4 GI toxicity |
| Navarro 2006 (31) | Ir 50 x 5 PVI 5FU 225 continuous | 74 | 45 | 14% | 14% grade 3 diarrhoea |
| Iles 2008 (32) | Ir 60 x4 PVI 5FU 200 continuous | 31 | 45 | 19% | 13% grade 3 diarrhoea |
| Glynn-Jones 2007 (25) | Ir 6 – 20 mg/m ² D1 – 5, 29 – 33 5FU 350 mg/m ² LV 20 mg/m ² D1 – 5, 29 – 33 | 57 | 45 | 24% | Dose limiting Grade 3/4 toxicity in 7/57 patients |
| Klautke 2005 (33) | Ir 40 x 6 PVI 5FU 250 continuous | 37 | 50.4 | 22% | 27% grade 3 diarrhoea 5% grade 4 diarrhoea |
| Hofheinz 2005 (34) | Ir 50 x 5 Cape 500/625 bd continuous | 19 | 50.4 | 4/19 | 8% at 500 bd dose level |
| Klautke 2006 (35) | Ir 40 x 6 Cape 500/650/825/750 bd continuous | 28 | 55.8 | 16% | 38% Gd 3 diarrhoea at 750 mg/m ² No grade 4 diarrhoea |
| Willeke 2007 (36) | Ir 50 x 5 Cape 500 bd continuous | 36 | 50.4 | 15% | 4/36 (11%) grade 3 diarrhoea 2/36 grade 3 N+V 1/36 grade 3 fatigue 7/36 grade 3 leucopenia 2/36 grade 4 leucopenia |
| Klautke 2007 (37) | Ir 60 x 4 Cape 750/m ² D1 – 14, 22 – 35 | 20 | 55.8 | 35% | 15% grade 3/4 diarrhoea |
| Gollins 2009 (28) | Ir 50x5/60x5/ 60x4/70x4 Cape 500/650/825/825 continuous | 46 | 45 | 27% | 21% grade 3 diarrhoea at Ir 50x4 Cape 650 bd |
| Gollins Ph II cohort (38) | Ir 60 x 4 Cape 650 bd continuous | 96 | 45 | 18/94 19% | 22% grade 3 diarrhoea No grade 4 diarrhoea |

Phase III trials are required to determine whether there is a benefit from the addition of a second chemotherapy agent to capecitabine CRT, and are major opportunities for translational studies of predictive markers of toxicity and efficacy concerning the addition of an additional chemotherapy drug. The above trials provide a clear rationale for testing the addition of either irinotecan or oxaliplatin to capecitabine CRT.

The proposed novel arm in ARISTOTLE is irinotecan capecitabine CRT. A questionnaire to UK investigators has indicated strong support for ARISTOTLE from 40 UK centres. This is based on the RICE regimen reported by Gollins et al (27, 38) with irinotecan given once weekly during weeks 1 – 4. A modification has been made to the capecitabine regimen (from continuous to 5 days per week for 5 weeks) taking into account the observed toxicities within the studies in the above table and the use of a 5 day per week schedule in the reference (capecitabine CRT) schedule. This is the first phase III trial to our knowledge to test the addition of irinotecan to fluoropyrimidine CRT schedule. A number of trial groups have elected to study the addition of oxaliplatin (STARR trial in Italy, NSABP R04 in the United States, FFCD in France and PETTAC 6 in Europe). Two of these trials (STARR and

the FFCD trials) have recently reported preliminary pathological and toxicity data by treatment arm (39, 40). No long term data has been presented. ARISTOTLE is the only phase III trial to our knowledge that is addressing the benefit of intensification of chemoradiation in a MRI defined group of patients who have a substantial risk of loco-regional failure.

Standardisation of the trial structure

This trial uses MRI eligibility criteria that define patients in whom there is a high probability of involvement of the CRM with initial surgery. The MERCURY trial has established pelvic MRI as the definitive staging and selection tool for neoadjuvant radiotherapy and this is accepted as a routine staging investigation in UK practice and UK guidelines, whereas in other European countries and North America there remain problems with both access and reimbursement for staging pelvic MRI.

The multicentre phase II CORE trial defined the methodology to examine the resected rectal cancer specimen and the detail of the process used to determine histopathological complete response (pCR), an important secondary endpoint. This has subsequently been supported by a recent rectal cancer consensus document (41).

The MRC CR07 phase III rectal cancer trial (14) demonstrated that a simple three point grading system to assess the quality of the resected rectal cancer specimen correlated with loco-regional failure and will be used as part of the histopathological assessment in this study as will an assessment of the sphincters as to whether an extralevator approach has been undertaken.

A detailed radiotherapy protocol has been developed by the Trial Management Group (TMG) where the gross tumour (GTV), clinical target (CTV) and planning target volumes (PTV) are defined (see Appendix 5). This approach will improve the coverage of the CTV and reduce the volume to normal tissue compared with the historical approach of a pelvic target volume based on bony anatomy.

Timing of planned surgery

There is no definitive evidence to define the optimal timing of surgery after pre-operative CRT. In the trial setting it is important to determine the timing of surgery to allow unbiased comparisons of the secondary endpoints of the trial between the two treatment arms. A large majority of potential ARISTOTLE investigators supported surgery taking place at 8 – 10 weeks from completion of CRT.

It should be noted that whilst there is interest in a “watch and wait” or deferral of surgery in patients with complete response, this approach is NOT part of the ARISTOTLE trial design. Patients and investigators participating in this study are evaluating the role of pre-operative CRT with the plan for surgical resection (unless, for example, disease progression precludes this). In the defined ARISTOTLE study group there is no evidence of long term outcome to support the safety of a deferral of surgery approach.

Post-operative adjuvant chemotherapy

There is considerable debate concerning the role of post-operative adjuvant chemotherapy after pre-operative CRT. Two phase III trials have tested the role of post-operative adjuvant 5FU/LV compared with no further treatment in this setting. Both studies, one in abstract form and the other published (18) failed to demonstrate a benefit for 5FU/LV. A retrospective subset analysis (42) that suggested a benefit for patients whose primary was down-staged has not been validated in any phase III trials. The NCR1 CHRONICLE trial (43) that tested the role of post-operative capecitabine and oxaliplatin against no treatment closed early due to poor recruitment (personal communication

Rob Glynn-Jones). In colon cancer there is clear evidence that adjuvant post-operative chemotherapy using 5FU/LV and oxaliplatin 5FU/LV improves outcome (44, 45). A recent consensus document states “There is insufficient evidence on the benefit of adjuvant post-operative chemotherapy after pre-operative chemoradiation to come to a consensus about its use” (41). This view is confirmed by a recent systematic analysis.

There are widely differing clinical views regarding the use of post-operative chemotherapy in this patient group and considerable facilitated debate and discussion has taken place within the TMG and the potential ARISTOTLE investigators. The majority of clinicians make their decision regarding post-operative chemotherapy based on the disease extent at presentation. It is also agreed that there is no convincing evidence that allows such decisions to be made based on a “downstaging” effect (e.g. the post CRT stage). It is a requirement of the trial that patients eligible for ARISTOTLE are discussed by the team prior to randomisation and the proposed post-operative chemotherapy approach (no chemotherapy, single agent fluoropyrimidine or combination chemotherapy (oxaliplatin + fluoropyrimidine)) is declared *prior to* randomisation. This should avoid any imbalance in the use of post-operative adjuvant chemotherapy between treatment arms in ARISTOTLE. This will be carefully monitored by the TMG.

2.2 Proposed Trial

ARISTOTLE is a randomised multi-centre phase III trial with a target accrual of 600 patients with MRI defined locally advanced non metastatic rectal cancer. Patients will be allocated, using minimisation, in a 1:1 ratio to two treatment arms:

- **Arm A (Standard arm)**
 - Capecitabine 900 mg/m² orally twice daily on days of radiotherapy only (normally Mon – Fri) for five weeks
 - Radiotherapy 45 Gy in 25 fractions
- **Arm B (Experimental arm)**
 - Irinotecan 60 mg/m² iv once weekly weeks 1 – 4 only
 - Capecitabine 650 mg/m² orally twice daily on days of radiotherapy only (normally Mon – Fri) for five weeks
 - Radiotherapy 45 Gy in 25 fractions

The intended post-operative chemotherapy policy will be declared prior to randomisation.

2.2.1 Primary end point

- Disease-free survival

2.2.2 Secondary end points

- Disease-specific survival
- Loco-regional failure
- Overall survival
- Histopathologically confirmed CRM-ve resection rate
- Histopathological complete response (pCR) rate

- Histopathologically quantitated tumour cell density
- Surgical morbidity
- Health-related Quality of Life (QoL) and functional outcome

2.3 Trial activation

UCL CTC will ensure that all trial documentation has been reviewed and approved by all relevant bodies and that the following have been obtained prior to activating the trial:

- Research Ethics Committee (REC) approval
- Clinical Trial Authorisation (CTA) from the Medicines and Healthcare products Regulatory Agency (MHRA)
- 'Adoption' into NIHR portfolio
- NHS permission
- Adequate funding for central coordination
- Confirmation of sponsorship
- Adequate insurance provision

3. Selection of Sites/Site Investigators

3.1 Site selection

In this protocol, trial “**site**” refers to a hospital, organisation, or site where trial-related activities are actually conducted.

Each site must be able to comply with the following, as applicable to the trial activities taking place at the site:

- Trial treatments, imaging, clinical care, follow-up schedules and all requirements of the trial protocol
- Requirements of the Research Governance Framework and the Medicines for Human Use (clinical trials) Act (SI 2004/1031 and all amendments)
- Data collection requirements, including adherence to CRF submission timelines as per section 11.4; Submission Timelines
- Collection, preparation and shipment of biological samples as per section 9; Collection of Tissue and Blood for Exploratory Biological Research
- Monitoring requirements as outlined in section 14; Trial Monitoring and Oversight and trial monitoring place

This study will be conducted in over a 100 sites in the UK. Participating sites will be required to complete the requested registration forms to confirm that they have adequate resources and experience to conduct the study. Patients requiring admission for treatment related toxicity should be admitted to the radiotherapy centre in-patient facility, or if possible transferred there if admitted elsewhere.

3.1.1 Selection of Principal Investigator and other Investigators at Sites

Sites must have an appropriate Principal Investigator (PI) i.e. a health care professional authorised by the site, ethics committee and regulatory authority to lead and coordinate the work of the trial on behalf of the site. Other investigators at site wishing to participate in the trial must be trained and approved by the PI. Investigators involved in the treatment and care of patients must be medical doctors and have experience of treating rectal cancer. PIs at pathology only sites (i.e. sites in which trial-specific pathology is performed only), who are not involved in the treatment or care of patients, may be surgeons or pathologists.

3.1.2 Training Requirements for Site Staff

All site staff must be appropriately qualified by education, training and experience to perform the trial related duties allocated to them, which must be recorded on the site delegation log.

CVs for all staff must be kept up-to-date, signed and dated and copies held in the Investigator Site File (ISF). An up-to-date, signed copy of the CV for the PI must be forwarded to UCL CTC prior to site activation and upon request.

GCP training is required for all staff responsible for trial activities. The frequency of repeat training may be dictated by the requirements of their employing institution, or 2 yearly where the institution has no policy, and more frequently when there have been updates to the legal or regulatory

requirements for the conduct of clinical trials. Evidence of current GCP training for the PI must be forwarded to UCL CTC upon request.

3.2 Site initiation and activation

3.2.1 Site initiation

Before a site is activated, the UCL CTC trial team will arrange a site initiation with the site which, as a minimum, the PI, the pharmacy lead and site research team must attend. The site will be trained in the day-to-day management of the trial and essential documentation required for the trial will be checked. Site initiation will normally be performed for each site by teleconference. On-site visits will be conducted if deemed appropriate.

3.2.2 Required documentation

The following documentation must be submitted by the site to UCL CTC prior to a site being activated by the UCL CTC trial team:

- Trial specific Site Registration Form (identifying relevant local staff) and Site Summary Form
- All relevant institutional approvals (e.g. local NHS permission)
- A completed Site Delegation Log that is initialled and dated by the PI (with all tasks and responsibilities delegated appropriately)
- Completed Site Contacts Form (with contact information for the PI, co-investigators, research/trial, pharmacy, radiography and pathology staff)
- A copy of the PI's current CV that is signed and dated (with documented up to date GCP training, or copy of GCP training certificate)
- ARSAC approval (where required)
- Radiotherapy Quality Assurance approval (for radiotherapy centres)
- Template prescriptions (required) and sample IMP labels for capecitabine (as required according to the trial activities taking place at the site)

In addition, the following agreement must be in place:

- A signed Clinical Trial Site Agreement (CTSA) between the Sponsor and the relevant institution (usually a NHS Trust/Health Board)

Sites must inform UCL CTC of any additional sites involved in the patient pathway. Recruiting sites which will be referring patients to a different site, for all or some of the trial activities, will not be activated until the relevant site involved is ready to be activated.

3.2.3 Site activation

Once the UCL CTC trial team has received all required documentation and the site has been initiated, a site activation letter will be issued to the PI. Sites must not approach any potential patients until they have received an activation letter from UCL CTC.

Following site activation, the PI is responsible for ensuring:

- Adherence to the most recent version of the protocol
- All relevant site staff are trained in the protocol requirements

- Appropriate recruitment and medical care of patients in the trial
- Timely completion and return of Case Report Forms (CRFs) (including assessment of all adverse events)
- Prompt notification and assessment of all serious adverse events
- That the site has facilities to provide **24 hour medical advice** for trial patients

4. Informed Consent

Sites are responsible for assessing a patient's capability to give informed consent.

Sites must ensure that all patients have been given the current approved version of the Patient Information Sheet (PIS), are fully informed about the trial and have confirmed their willingness to take part in the trial by signing the current approved Consent Form.

Sites must assess a patient's ability to understand verbal and written information in English and whether or not an interpreter would be required to ensure fully informed consent. If a patient requires an interpreter and none is available, the patient should not be considered for the trial.

The PI, or, where delegated by the PI, other appropriately trained site staff, are required to provide a full explanation of the trial and all relevant treatment options to each patient prior to trial entry. During these discussions the current approved PIS for the trial should be discussed with the patient. A minimum of 24 hours must be allowed for the patient to consider and discuss participation in the trial. Written informed consent on the current approved version of the Consent Form for the trial must be obtained before any trial-specific procedures are conducted. The discussion and consent process must be documented in the patient notes.

Site staff are responsible for:

- Checking that the correct (current approved) versions of the PIS and Consent Form are used
- Checking that information on the Consent Form is complete and legible
- Checking that the patient has completed/initialled all relevant sections and signed and dated the form
- Checking that an appropriate member of staff has countersigned and dated the Consent Form to confirm that they provided information to the patient
- Checking that an appropriate member of staff has made dated entries in the patient's medical notes relating to the informed consent process (i.e. information given, consent signed, etc.)
- Following randomisation:
 - Adding the patient trial number to all copies of the Consent Form, which should be filed in the patient's medical notes and Investigator Site File (ISF)
 - Giving the patient a copy of their signed Consent Form, PIS, patient diary and patient contact card

The right of the patient to refuse to participate in the trial without giving reasons must be respected. All patients are free to withdraw at any time. Also refer to section 15; Withdrawal of Patients.

5. Selection of Patients

5.1 Pre-randomisation Evaluation

Potential trial participants will normally be identified in the weekly colorectal MDT meeting. Histological confirmation of invasive adenocarcinoma is an absolute trial requirement. It is recognised that CT scanning of the thorax and abdomen may reveal “equivocal” findings concerning metastatic disease. Patients with equivocal findings are considered eligible (consensus view of MDT). However, patients with unequivocal evidence of metastatic disease are not eligible.

The assessments and procedures outlined in section 8.1; Pre-randomisation Evaluation, are required to confirm the eligibility of patients for the trial.

5.2 Screening Log

A screening log should be maintained by the site and kept in the ISF. This should record each patient screened for the trial (i.e. any patients identified with locally advanced rectal cancer who are considered for CRT) and the reasons why they were not randomised if this is the case. The log should be sent to UCL CTC when requested, with patient identifiers removed prior to sending.

5.3 Patient Eligibility

There will be no exception to the eligibility requirements at the time of randomisation. Ensuring patient eligibility is the responsibility of the PI or other delegated Investigator(s). Queries in relation to the eligibility criteria must be addressed prior to randomisation. Patients are eligible for the trial if all the inclusion criteria are met and none of the exclusion criteria applies.

5.3.1 Patient Inclusion Criteria

- Diagnosis of primary rectal cancer
- Histologically confirmed invasive adenocarcinoma
- Pelvic MRI defined disease (one of the following):
 - Mesorectal fascia involved or breached
 - includes involvement of adjacent organ
 - Mesorectal fascia threatened (tumour \leq 1 mm from mesorectal fascia) includes:
 - primary tumour \leq 1 mm from mesorectal fascia or
 - extra-mural vascular invasion \leq 1 mm from mesorectal fascia or
 - tumour deposit with irregular border and mixed signal intensity \leq 1 mm from mesorectal fascia
 - Low tumours at/below level of levators where:
 - tumour \leq 1 mm from levator on two imaging planes or
 - tumour through full thickness of muscularis propria or beyond at level of puborectalis sling or below or
 - tumour involving the intersphincteric plane or
 - tumour involving the external anal sphincter

- Patients with enlarged pelvic side wall nodes are eligible only if they also meet at least one of the above criteria.
- Superior extent of macroscopic tumour no higher than S1/2 junction on sagittal MRI
- ECOG performance status 0 or 1 (see Appendix 2)
- Considered fit to receive all trial treatments
- Bowel function controlled with ≤ 6 mg loperamide per day
- Absolute neutrophil count $\geq 1.5 \times 10^9/L$; platelets $\geq 100 \times 10^9/L$
- Serum transaminase $< 3 \times$ ULN
- Adequate renal function (Cockcroft-Gault estimation ≥ 50 mL/min) (see appendix 3)
- Bilirubin $< 1.5 \times$ ULN
- Able to swallow oral medication
- Willing and able to give informed consent and comply with treatment and follow-up schedule
- Aged 18 or over

5.3.2 Patient Exclusion Criteria

- Previous radiotherapy to the pelvis (including brachytherapy)
- Uncontrolled cardiorespiratory comorbidity (includes patients with inadequately controlled angina or myocardial infarction within 6 months prior to randomisation)
- Unequivocal evidence of metastatic disease (includes resectable metastases)
 - Patients with equivocal lesions (determined at MDT) are eligible
- Major disturbance of bowel function (e.g. gross faecal incontinence or requiring > 6 mg loperamide each day)
- History of another malignancy within the last 5 years except successfully treated non-melanoma cancer of skin or carcinoma in situ of uterine cervix.
- Known dihydropyrimidine dehydrogenase (DPYD) deficiency
- Known Gilberts disease (hyperbilirubinaemia)
- Taking warfarin that cannot be discontinued at least 7 days prior to starting treatment
- Taking phenytoin or sorivudine or its chemically related analogues, such as brivudine (see section 7.9; Concomitant Medication, for further details)
- Gastrointestinal disorder which would interfere with oral therapy and its bioavailability
- Pregnant, lactating, or pre menopausal women not using adequate contraception
- Oral St John's Wort therapy that cannot be discontinued at least 14 days prior to starting treatment
- Unfit to receive any study treatment or subsequent surgical resection

5.3.3 Pregnancy and Birth Control

Female patients of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with capecitabine and irinotecan.

The risks to the human embryo or foetus from exposure to capecitabine and irinotecan are currently unknown and it should be assumed that capecitabine or irinotecan may cause foetal harm if administered to pregnant women.

If a patient or the partner of a male trial patient becomes pregnant during the trial UCL CTC must be informed immediately (See section 12; Pharmacovigilance, for details on the reporting procedure).

Pregnancy Testing

All women of childbearing potential who are at risk of becoming pregnant must undergo a pregnancy test prior to randomisation.

A woman of childbearing potential is a sexually mature woman (i.e. any female who has experienced menstrual bleeding) who has not:

- undergone a hysterectomy or bilateral oophorectomy/salpingectomy
- been postmenopausal for 24 consecutive months (i.e. who has had menses at any time in the preceding 24 consecutive months without an alternative medical cause)

Contraceptive Advice

Due to insufficient data for the effects of capecitabine, irinotecan and radiotherapy during pregnancy and lactation, patients must consent to use one method of contraception until 3 months post CRT.

Acceptable methods of effective contraception for this trial are:

- Established use of oral, injected or implanted hormonal methods of contraception.
- Placement of an intrauterine device (IUD) or intrauterine system (IUS).
- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository). The use of barrier contraceptives should always be supplemented with the use of a spermicide. The following should be noted:
 - Failure rates indicate that, when used alone, the diaphragm or condom are **not** highly effective forms of contraception. Therefore the use of additional spermicides does confer additional theoretical contraceptive protection.
 - However, spermicides alone are inefficient at preventing pregnancy when the whole ejaculate is spilled. Therefore, spermicides are not a barrier method of contraception and must not be used alone.
- Male sterilisation (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female patients, the vasectomised male partners must be the sole partner for that patient. Please note that sterilisation is not usually regarded as completely reliable enough on its own to ensure that pregnancy can never occur.
- Absolute and continuous abstinence: When this is in line with the preferred and usual lifestyle of the patient. Please note that periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

It is routine practice to offer sperm banking to male patients prior to pelvic CRT.

6. Randomisation procedures

Patient randomisation will be undertaken centrally at UCL CTC and this must be performed prior to commencement of any trial treatment.

In order to account for the potential confounding effects of post-operative adjuvant chemotherapy, randomisation will be stratified by:

- Radiotherapy centre
- Whether the tumour has breached the fascia or not (determined by MRI)
- Whether the patient has no metastases confirmed or whether the presence of metastases is equivocal.

Post-operative adjuvant chemotherapy decisions will be recorded on the Eligibility Checklist to avoid post-randomisation bias.

6.1 Randomisation

Following pre-randomisation evaluation (as detailed in section 8.1; Pre-randomisation Evaluation) and confirmation of eligibility and consent of a patient at a site, the Eligibility Checklist and Pre-randomisation Forms must be fully completed and faxed to UCL CTC. The faxed forms will be used to confirm patient eligibility by UCL CTC. If further information is required, UCL CTC will contact the person requesting randomisation to discuss the patient and request updated forms to be faxed (if required).

It is important that the randomising site is aware of all sites where trial activities are due to take place and that all such sites are open and recruiting within the ARISTOTLE trial. This information will be required during the randomisation process.

Once randomised, UCL CTC will assign a trial number and treatment allocation for the patient. UCL CTC will fax or email confirmation of the patient's inclusion in the trial, their trial number and treatment allocation to the main contact and pharmacy.

Please contact UCL CTC if the randomisation confirmation or request for further information has not been received within 2 hours after faxing the forms. If forms are received at UCL CTC after 3pm, the randomisation may not be processed until the next working day.

| Randomisation contacts numbers | |
|----------------------------------|---|
| Randomisation fax number: | 020 7679 9871 |
| General queries | 020 7679 9608 020 7679 9688 |
| Office hours: | 9am to 5pm Monday to Friday, excluding Bank Holidays |

Once a patient has been randomised onto the trial they must be provided with the following:

- A copy of their **signed Consent Form and PIS**
- **A patient diary.** Patients should be asked to use this to record the date, time and number of capecitabine tablets taken and also to record any adverse events. They must be reminded to bring this with them every time they visit the hospital

- **A patient contact card.** Site on-call contact details for out-of-hours medical care must be added to this card and patients informed to carry this with them at all times while on the trial

7. Trial Treatment

7.1 Treatment Summary

For the purpose of this protocol the Investigational Medicinal Products (IMPs) are:

- Capecitabine
- Irinotecan

Patients will be randomised to one of two CRT regimens:

- **Arm A**
 - Capecitabine 900 mg/m² orally twice daily on days of radiotherapy only (normally Mon – Fri) for five weeks
 - Radiotherapy 45 Gy in 25 fractions
- **Arm B**
 - Irinotecan 60 mg/m² iv once weekly; weeks 1 – 4 only
 - Capecitabine 650 mg/m² orally twice daily on days of radiotherapy only (normally Mon – Fri) for five weeks
 - Radiotherapy 45 Gy in 25 fractions

PLEASE NOTE THAT THE CAPECITABINE DOSES ARE DIFFERENT IN ARM A AND ARM B

7.2 Summary Treatment Schedule

Arm A – Capecitabine CRT

| Week | 1 | 2 | 3 | 4 | 5 |
|---|---------|----------|-----------|-----------|-----------|
| Days | D 1 – 5 | D 8 – 12 | D 15 – 19 | D 22 – 26 | D 29 – 33 |
| Radiotherapy: 45 Gy/25# | ••••• | ••••• | ••••• | ••••• | ••••• |
| Oral capecitabine* 900 mg/m² orally bd Mon – Fri x 5 weeks | ••••• | ••••• | ••••• | ••••• | ••••• |

Arm B – Irinotecan capecitabine CRT

| Week | 1 | 2 | 3 | 4 | 5 |
|---|---------|----------|-----------|-----------|-----------------|
| Days | D 1 – 5 | D 8 – 12 | D 15 – 19 | D 22 – 26 | D 29 – 33 |
| Radiotherapy: 45 Gy/25# | ••••• | ••••• | ••••• | ••••• | ••••• |
| Irinotecan 60 mg/m ² once weekly; weeks 1 – 4** | • | • | • | • | Not given*** |
| Oral capecitabine* 650 mg/m² orally bd Mon – Fri x 5 weeks | ••••• | ••••• | ••~•• | ••~•• | ••~•• |

* Capecitabine should be taken on the days of radiotherapy only (normally Monday – Friday). If radiotherapy is not given due to bank holiday or machine breakdown then capecitabine should not be taken. If the morning dose of capecitabine is taken and the radiotherapy is not given that day, omit the evening dose and restart capecitabine the morning of the next radiotherapy fraction.

** Irinotecan should be administered on the same day each week (+/- one day) and before radiotherapy is given that day. In order to avoid problems with bank holidays it is recommended that irinotecan be administered on a Tues, Weds or Thurs.

*** Irinotecan should not be given in week 5 without prior approval of the TMG. Please contact the ARISTOTLE trial coordinator to discuss.

7.3 Trial Treatment Details - Chemotherapy

7.3.1 Capecitabine

Capecitabine is licensed for use in rectal cancer.

PLEASE NOTE that the capecitabine doses are different in each Arm

- Arm A – **900 mg/m²** orally twice daily on days of radiotherapy only (normally Mon – Fri) for five weeks
- Arm B – **650 mg/m²** orally twice daily on days of radiotherapy only (normally Mon – Fri) for five weeks

Administration

Capecitabine is taken orally twice a day in equal doses for 5 days per week (normally Monday – Friday), on the days of radiotherapy administration only, throughout the 5 week course of radiotherapy. If radiotherapy is not given (e.g. due to machine maintenance or bank holiday), then capecitabine should not be given that day either (see section 7.6; Unplanned Breaks in Treatment). Capecitabine treatment can begin on any day of the week; however **there is normally no capecitabine treatment on Saturday or Sunday**, unless radiotherapy is given on one of these days. Patients are asked to take capecitabine with a glass of water each day within 30 minutes after the ingestion of food (ideally after breakfast and evening meals), commencing the morning of the first dose of radiotherapy treatment. If patients have difficulty swallowing tablets, it is possible to dissolve the tablets in approximately 200 mL of lukewarm water. There is no stability data for any form of capecitabine suspension, so this should be done immediately prior to use and the solution swallowed immediately, rinsing to ensure all of the suspension has been ingested. As the solution has a bitter taste, flavouring with a fruit juice or squash (except grapefruit juice) is allowed.

Dose banding

Dose banding is recommended for oral capecitabine in both trial arms. See tables below for dose banding for capecitabine 900 mg/m² and 650 mg/m². **Sites may use different dose banding as long as this has been approved by UCL CTC.**

Tables for dose banding following a dose modification are in Appendix 4.

Body surface area (BSA) should be calculated as per local practice. BSA should be re-calculated weekly and capecitabine prescribed according to the corresponding dose band.

| Capecitabine dose = <u>900 mg/m² bd</u> | | Number of tablets to be taken at each dose (morning and evening) Mon – Fri | |
|---|------------------------------|---|---------------|
| BSA (m²) | Twice daily dose (mg) | 150 mg | 500 mg |
| ≤ 1.46 | 1250 | 5 | 1 |
| 1.47 – 1.66 | 1400 | 6 | 1 |
| 1.67 – 1.89 | 1650 | 1 | 3 |
| 1.90 – 2.12 | 1800 | 2 | 3 |
| ≥ 2.13 | 2000 | 0 | 4 |

| Capecitabine dose = 650 mg/m² bd | | Number of tablets to be taken at each dose (morning and evening) Mon – Fri | |
|--|--------------------------|---|--------|
| BSA (m ²) | Twice daily dose (mg) | 150 mg | 500 mg |
| ≤ 1.46 | 900 | 6 | - |
| 1.47 – 1.66 | 1000 | - | 2 |
| 1.67 – 1.89 | 1150 | 1 | 2 |
| 1.90 – 2.12 | 1300 | 2 | 2 |
| ≥ 2.13 | 1450 | 3 | 2 |

7.3.2 Irinotecan

Irinotecan is a licensed drug but not currently licensed for use in rectal cancer.

Administration

Irinotecan is given as a 30 – 60 minute (or as per local policy) intravenous infusion during weeks 1, 2, 3 and 4 of radiotherapy (with equal, weekly spacing between infusions). Irinotecan should be administered prior to radiotherapy on the same day of the week for each of the four weeks (+/- one day; see also section 7.6; Unplanned Breaks in Treatment). Irinotecan should not be given in week 5 without prior approval of the TMG; please contact the ARISTOTLE trial coordinator to discuss. There is no limit on the time interval between irinotecan administration and radiotherapy. In order to avoid problems with bank holidays the preferential use of Tuesday, Wednesday or Thursday for the irinotecan infusion is recommended. Irinotecan should be reconstituted in 0.9% (w/v) sodium chloride solution or 5% (w/v) glucose solution according to local practice and the summary of product characteristics (SPC). Any planned deviation from the SPC must be approved by UCL CTC.

Dose banding

Irinotecan can be dose banded according to local policy.

Precautions

Irinotecan and its metabolites are cleared by biliary excretion and patients with cholestasis have delayed clearance. If hepatobiliary function deteriorates below eligibility criteria limits during treatment, modification of irinotecan administration may be applied as described in section 7.5; Management of Acute Toxicity.

7.3.3 Pharmacy Responsibilities

All pharmacy aspects of the trial at participating sites are the responsibility of the PI, who may delegate this responsibility to the local pharmacist or other appropriately qualified personnel, who will be the Pharmacy Lead. The delegation of duties must be recorded on the site staff delegation log.

Drug accountability

The Pharmacy Lead must ensure that appropriate records are maintained.

These records must include accountability for each drug including, dispensing, returned medication and destruction of returned medication. Template accountability forms will be supplied, however, sites may be permitted to use their own drug accountability records providing the same information is captured, as a minimum. Such in-house records must be submitted to UCL CTC for review and authorisation for use prior to site activation.

Copies of completed drug accountability logs must be submitted to UCL CTC for all trial patients following the end of a patient's treatment, or upon request. Also refer to section 14.1; Central Monitoring.

For detailed information on the supply, labelling and accountability of capecitabine and irinotecan, please refer to the Summary of Trial Drug Arrangements document in the ARISTOTLE Pharmacy Site File.

Capecitabine

Capecitabine will be available through routine hospital supplies. Chemotherapy prescriptions should conform to local best practice including electronic prescribing systems where available. The full 5 week course of capecitabine can be dispensed at the start of treatment. Patients will be asked to keep a diary of the number of capecitabine tablets taken and should be checked on a weekly basis.

An exemption from IMP labelling of capecitabine was granted from the MHRA. However, some sites may pack-down the capecitabine in order to dispense as close to the exact quantity of capecitabine as they do in routine clinical practice. Sites must label the capecitabine according to the Summary of Drug Arrangements (SoDA) document in the ARISTOTLE Pharmacy Site File.

Irinotecan

Irinotecan will be available through routine hospital supplies. Chemotherapy prescriptions should conform to local best practice including electronic prescribing systems where available.

Irinotecan has an exemption from clinical trial labelling granted by the MHRA.

Any dispensed and subsequently unused irinotecan should be processed according to local policy and a record maintained.

7.4 Trial Treatment Details - Radiotherapy

A detailed description of radiotherapy target volume definition, verification and quality assurance is provided in Appendix 5 and should always be used during the radiotherapy planning and treatment process. A brief summary is provided here in the main section of the protocol.

Patients should be planned using the details provided in Appendix 5.

7.4.1 Radiotherapy planning

The use of a planning CT scan with target volumes delineated on each slice and pixel based inhomogeneity correction is considered standard practice and is a mandatory requirement.

Patient set-up: We recommend that appropriate immobilisation and a scan/treatment position is used which the site is familiar with. A radio-opaque marker must be placed at the anal verge prior to the CT planning scan.

Contrast: Intravenous contrast is strongly encouraged but not mandated. Intravenous contrast allows easy identification of the internal iliac arteries - the alternative approach of using the diagnostic imaging to identify the arteries and then identify them on a non-contrast planning scan is more time consuming and less accurate. Oral contrast is recommended but not mandated.

Patient data acquisition: The scan limits are the superior aspect of L5 superiorly to 4 cm below a radio-opaque marker indicating the anal verge or the inferior extent of tumour, whichever is more inferior. The recommended slice thickness is 3 mm (a maximum of 5 mm is acceptable).

Definition of target volumes

- **Gross target volume (GTV):** All macroscopic tumour (primary, nodal, extramural vascular invasion) are outlined on each CT slice and any intervening normal rectal wall.
- **Clinical target volume (CTV):** This is defined in two parts CTVA and CTVB and then combined to form the Final CTV (CTVF).
- **CTVA:** This consists of the GTV with a 1 cm margin applied in the superior, inferior, lateral, anterior and posterior direction.
- **CTVB:** This includes the mesorectum (and therefore the mesorectal nodes), the presacral and internal iliac nodal structures.
- **Superior limit:** This is the S2/3 interspace (determined on the sagittal or scout view on the planning system) providing there is a 2 cm margin above the most superior limit of GTV. The CTVB superior border should extend above the S2/3 interspace if necessary to achieve a minimum 2 cm margin above the most superior aspect of GTV.
- **Inferior limit:** The inferior limit of CTVB is either 1 cm inferior to CTVA or at the superior limit of puborectalis (seen on CT scans where the mesorectum stops) whichever is the more inferior.
- **Lateral limit:** This is the medial aspect of obturator internus in the absence of internal iliac nodal enlargement. In the presence of involved pelvic side wall nodes, the limit is the bony pelvic side wall.
- **Anterior limit:** This is defined superiorly as 7 mm anterior to internal iliac arteries. Lower down in the pelvis it is either 1 cm anterior to the mesorectal wall or 1 cm anterior to the lateral (internal iliac) pelvic lymph node "compartment" whichever is more anterior. Further guidance on the definition of this border is provided in the Appendix.
- **Posterior limit:** This is the anterior margin of the sacrum or coccyx (see appendix 5 for further detail)
- **Final CTV (CTVF):** This is derived by combining CTVA and CTVB
- **Planning target volume (PTV):** This is derived by adding a 1 cm margin anteriorly, posteriorly, laterally, superiorly and inferiorly to CTVF.

7.4.2 Treatment

Radiation therapy should be delivered with photon energies ≥ 6 MV using a linear accelerator. Equipment capable of 10 MV or higher is recommended, as is the use of 3D conformal radiotherapy. The field arrangements require a minimum of three fields. Mixed energy beams are allowed with higher photon energy for the lateral beams compared to the posterior beam. The use of 3D conformal treatment with multileaf collimators is strongly recommended. VMAT or IMRT may also be used (for more detail, see section 10.1; Radiotherapy QA).

Total Dose

A total dose of 45 Gy in 25 daily fractions over a total time of 5 weeks should be delivered, treating 5 days per week, **1 fraction per day**, using 1.8 Gy per fraction (see also section 7.6; Unplanned Breaks in Treatment). All fields must be treated during one treatment session. The isocentric treatment plan is usually specified to receive 100% with the 95% isodose line encompassing the PTV and it is recommended that -5% and +7% inhomogeneity is achieved within the target volume.

Detailed definition of dose constraints and discussion of the organs at risk are included in Appendix 5.

Verification and correction procedures

On treatment set-up verification - consideration should be given to imaging the initial 3 fractions so that a correction for the systematic error can be applied and then continue with imaging weekly. The best available positional verification methods should be used which may include electronic portal images compared to digitally reconstructed radiographs (DRRs), or cone beam CT matched using the planning scan. Imaging can monitor set-up displacement on a daily basis in the initial phase of treatment and the isocentre should be moved if disagreement is seen in excess of agreed tolerance levels which would preferable be based on local study – usually 5 mm.

7.4.3 Quality assurance for radiotherapy

Each radiotherapy site will be required to complete a Quality Assurance exercise prior to activation. Thereafter, ongoing QA review will be carried out for the first patient and then 10% of all patients randomised who would receive radiotherapy at that site. The 10% of patients will be selected at random and sites will be notified by email at the time of randomisation. This latter review will be carried out retrospectively.

For details of the initial and ongoing QA processes, please refer to section 10; Quality Assurance.

7.5 Management of Acute Toxicity

Patients should be reviewed at least weekly during CRT when acute toxicity assessments are performed. **However, the local team should have a structure in place that ensures that patients experiencing side effects can be seen on any day and that patients can undergo daily review if required to monitor the severity of side effects and respective treatment.**

The following guidance should be followed for the management of acute toxicity and dose modifications:

- AEs should be graded according to the NCI Common Terminology Criteria for Adverse Events version 4.02 (CTCAE v4.02)
- For non-haematological AEs (excluding diarrhoea) which are considered by the Investigator unlikely to develop into serious or life-threatening events (e.g. alopecia, altered taste etc.), treatment may be continued at the same dose without interruption.
- No dose reductions or interruptions are required for anaemia (non-haemolytic) if it can be satisfactorily managed by transfusions or erythropoietin.
- In the event of overlapping toxicities, dose modification should be based on the worst toxicity grade observed.
- All dose modifications should be documented with clear reasoning and documentation of the approach taken in the case report and in the medical notes.
- If a patient experiences a toxicity, then dose modifications should be applied as per protocol, even if the toxicity has resolved by the time the patient is next seen.

See Appendix 4 for dose banding tables to 75% capecitabine dose reduction.

7.5.1 Diarrhoea

It is particularly important to assess and monitor patients who experience diarrhoea during CRT.

If admission is required, it is recommended that this is to the radiotherapy centre. If circumstances prevent this, then this guidance must be rapidly shared with the local treating team and regular contact maintained. The option of subsequent transfer to the centre should be discussed.

The site team should document a baseline assessment of stool frequency/stoma output and this should be repeated once weekly at the same time as toxicity assessment (distinguishing from tenesmus/mucous discharge/wet wind).

The following guidance is recommended for patients who experience diarrhoea during concurrent chemo-radiotherapy:

Onset of grade 1 diarrhoea:

- Continue CRT if the patient is considered fit for treatment and loperamide usage is ≤ 6 mg per day

Onset of grade 2 diarrhoea:

- Suspend all chemotherapy
- Send stool for culture and *C. difficile* toxin
- Commence loperamide
- Ensure adequate oral rehydration
- Continue with RT if patient considered fit for treatment
- Daily review (including weekends)

If bowel frequency returns to \leq grade 1 and loperamide usage is ≤ 6 mg per day, chemotherapy (and radiotherapy if suspended) can recommence.

If bowel frequency does not return to \leq grade 1 and loperamide usage is > 6 mg per day, then admit the patient and manage as below.

Onset of grade 3 diarrhoea or ongoing grade 2 diarrhoea despite above measures:

- Admit the patient
- Commence loperamide
- Send stool for culture and *C. difficile* toxin
- Commence iv fluids with regular appropriate volumetric assessment
- Suspend all trial treatment (radiotherapy **and** chemotherapy)
- If neutropenic, commence iv antibiotics and consider G-CSF

If grade 3 diarrhoea is not controlled to \leq grade 1 by regular loperamide within 24 hours and patient not neutropenic:

- Commence iv broad spectrum antibiotics (including patients who are not pyrexial). The regimen used should be determined locally (an example option includes an intravenous second or third generation cephalosporin and metronidazole). The regimen used should cover likely enteric pathogens.

If grade 3 diarrhoea not controlled \leq grade 1 by iv antibiotics and iv fluids and regular loperamide within 48 hours:

- Commence s/c octreotide – the recommended starting dose is 300 μ g per 24 hours by either s/c continuous infusion or s/c tds injections. The dose can be increased in accordance with BNF guidance and should be reviewed daily
- Closely monitor serum CRP, renal function and albumin. The role of total parenteral nutrition should be discussed with the multi-disciplinary team who are responsible for this therapy and may play an important role for patients not responding well to the supportive treatments described above

If Grade 4 diarrhoea

- By definition grade 4 diarrhoea is life-threatening. Patients developing grade 4 diarrhoea at any stage must be admitted urgently and treated with full supportive measures including fluid replacement, iv antibiotics and iv octreotide in addition to any other immediate resuscitative measures that might be deemed necessary.

[Loperamide is recommended as the initial anti-diarrhoeal medication. Codeine phosphate up to 30 mg four times a day can be added if diarrhoea is not controlled with 16 mg loperamide per day. Please note the criteria for admission stated above]

CRT should only be recommended when the following criteria are met:

- Bowel function has returned to grade 0/1
- Loperamide usage is \leq 6 mg per 24 hours
- The patient is considered fit to resume therapy by a trial Investigator
- Dose reductions are applied according to the table below

This guidance is designed to enhance existing guidance for the management of treatment related diarrhoea. The TMG consider the described intensity of supportive care and treatment to be required for patients receiving CRT within this trial.

| CTCAE Grade | Description | Dose Modifications | | |
|-------------|--|--|--|--|
| | | Radiotherapy | Capecitabine | Irinotecan |
| 1 | Increase of < 4 stools per day over baseline ; mild increase in ostomy output compared to baseline | Continue if ≤ 6 mg loperamide per 24 hours required. | Continue if ≤ 6 mg loperamide per 24 hours required | Continue if ≤ 6 mg loperamide per 24 hours required. |
| 2 | Increase of 4 – 6 stools per day over baseline ; moderate increase in ostomy output compared to baseline; Moderate cramping | Continue as long as patient considered fit for treatment. | Interrupt until grade 0 – 1 and ≤ 6 mg loperamide per 24 hours required; then recommence at 75% of starting dose | Interrupt until grade 0 – 1 and ≤ 6 mg loperamide per 24 hours required; then recommence at 75% of starting dose |
| 3 | Increase of > 7 stools per day over baseline ; severe increase in ostomy output compared to baseline; limiting self care ADL; Severe cramping or peritonism (localised guarding on abdominal examination) | Interrupt until grade 0 – 1, ≤ 6 mg loperamide per 24 hours required, and patient considered fit. | Interrupt until grade 0 – 1 and ≤ 6 mg loperamide per 24 hours required; then recommence at 75% of starting dose. If patient is neutropenic and has sepsis stop permanently. | Interrupt until grade 0 – 1 and ≤ 6 mg loperamide per 24 hours required; then recommence at 75% of starting dose. If patient is neutropenic and has sepsis stop permanently. |
| 4 | Life threatening consequences; urgent intervention indicated | Interupt until grade 0 – 1, ≤ 6 mg loperamide per 24 hours required, and patient considered fit. | Discontinue treatment permanently | |

In the event of a **second episode of grade 2 diarrhoea** the patient's management should be discussed with a TMG member by contacting the ARISTOTLE trial coordinator.

In the event of a **second episode of grade 3 diarrhoea** stop all chemotherapy permanently.

Radiotherapy may be continued if the diarrhoea has resolved to grade 0/1, ≤ 6 mg loperamide per 24 hours is required and patient is considered fit.

The TMG are available to discuss the management of grade 3/4 toxicity. If you would like to contact the TMG, please contact the ARISTOTLE trial coordinator.

7.5.2 Palmar-plantar syndrome

The table below describes dose modifications in case of palmar-plantar syndrome.

| CTCAE Grade | Description | Capecitabine |
|-------------|--|---|
| 1 | Minimal skin changes or dermatitis (e.g., erythema, oedema, or hyperkeratosis) without pain | Continue |
| 2 | Skin changes (e.g., peeling, blisters, bleeding, oedema, or hyperkeratosis) with pain; limiting instrumental ADL | Interrupt until grade 0 – 1 then resume at 75% of starting dose |
| 3 | Severe skin changes (e.g., peeling, blisters, bleeding, oedema, or hyperkeratosis) with pain; limiting self care ADL | Interrupt until grade 0 – 1 then resume at 75% of starting dose |

In the event of a second grade 3 episode of the same toxicity, stop capecitabine permanently.

7.5.3 Deranged renal function

The calculated creatinine clearance (using Cockcroft Gault formula) should be used to estimate GFR each week. If less than 50 mL/min then the capecitabine dose should be reduced or stopped according to the table below and an isotope clearance or a formal 24 hour urine collection requested. When this result is available, the capecitabine dose should then be re-adjusted using the table below. If the isotope clearance or formal 24 hour urine collection GFR estimation is higher than the calculated creatinine clearance, then the former be used and if this result is ≥ 50 mL/min, the patient can be re-escalated to 100% starting dose. The isotope clearance or formal 24 hour urine collection can guide capecitabine dosing in subsequent weeks providing the serum creatinine does not rise by $> 10\%$.

| GFR (see above) | Capecitabine |
|------------------|--------------------------------|
| ≥ 50 mL/min | Continue |
| 30 – 49 mL/min | Resume at 75% of starting dose |
| < 30 mL/min | Stop permanently |

7.5.4 Deranged hepatic function

The table below describes dose modifications in case of deranged hepatic function which are considered to be related to treatment.

| CTCAE Grade | Toxicity | Radiotherapy | Capecitabine | Irinotecan |
|-------------|---|--------------|--|------------|
| 2 | Elevated bilirubin $> 1.5 - 3.0 \times$ ULN Perform blood tests x2 per week | Continue | 75% | 50% |
| 3 | Elevated bilirubin $> 3.0 - 10 \times$ ULN | Continue | Stop permanently | |
| ≥ 2 | ALT or AST $> 3 \times$ ULN Perform blood tests x2 per week | Continue | Interrupt until grade 0 – 1, then recommence at 75% of starting dose | |

7.5.5 Fatigue (grade 3)

The table below describes dose modifications in case of grade 3 fatigue, **which is considered to be related to treatment.**

| CTCAE Grade | Description | Radiotherapy | Capecitabine | Irinotecan |
|-------------|--|-----------------------------|--|--|
| 3 | Fatigue not relieved by rest, limiting self care ADL | Interrupt until grade 0 – 1 | Interrupt until grade 0 – 1, then resume at 75% of starting dose | Interrupt until grade 0 – 1, then resume at 75% of starting dose |

7.5.6 Vomiting (grade 3 and 4)

The table below describes dose modifications in case of grade 3 and 4 vomiting which is considered to be related to treatment.

| CTCAE Grade | Description | Radiotherapy | Capecitabine | Irinotecan |
|-------------|---|--|--|--|
| 3 | ≥ 6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalisation indicated | Interrupt until grade 0 – 1 | Interrupt until grade 0 – 1, then resume at 75% of starting dose | Interrupt until grade 0 – 1, then resume at 75% of starting dose |
| 4 | Life-threatening consequences; urgent intervention indicated | Interrupt all treatment and contact the ARISTOTLE trial coordinator to discuss the patient's management. | | |

7.5.7 Mucositis

The table below describes dose modifications in case of mucositis.

| CTCAE Grade | Radiotherapy | Capecitabine | Irinotecan |
|-------------|--|--|--|
| 1 | Continue | 100% | 100% |
| 2 | Continue | Interrupt until grade 0 – 1, then resume at 75% of starting dose | Interrupt until grade 0 – 1, then resume at 75% of starting dose |
| 3 | Continue but treat with appropriate supportive therapy | Interrupt until grade 0 – 1, then resume at 75% of starting dose | Interrupt until grade 0 – 1, then resume at 75% of starting dose |
| 4 | Continue but treat with appropriate supportive therapy | Stop permanently | |

In the event of a second grade 3 episode of the same toxicity, stop all chemotherapy permanently

7.5.8 Other non haematological toxicity

The table below describes dose modifications in case of other non haematological toxicities which are considered to be related to the treatment. Dose modifications should be made to the treatment most likely responsible for the toxicity necessitating the dose reduction.

| CTCAE Grade | Radiotherapy | Capecitabine | Irinotecan |
|-------------|---|--|--|
| 1 | Continue | 100% | 100% |
| 2 | Continue | Interrupt until grade 0 – 1, then resume at 75% of starting dose | Interrupt until grade 0 – 1, then resume at 75% of starting dose |
| 3 | Continue but treat with appropriate supportive therapy | Interrupt until grade 0 – 1, then resume at 75% of starting dose | Interrupt until grade 0 – 1, then resume at 75% of starting dose |
| 4 | Interrupt until grade 0 – 1 and patient considered fit. | Stop permanently | |

In the event of a second grade 3 episode of the non-haematological toxicity the patient's management should be discussed with a TMG member by contacting the ARISTOTLE trial coordinator.

7.5.9 Haematological toxicity

Blood tests should be done routinely once weekly during CRT for both arms. Blood tests to assess the need for dose modification for irinotecan must be performed within 72 hours prior to the next irinotecan administration.

The recommendations in the table below for alteration in radiotherapy, capecitabine and irinotecan doses are based on the weekly blood count. Dose alterations should follow the most conservative option in cases where there is a conflict.

| CTCAE Grade | Toxicity | Radiotherapy | Capecitabine | Irinotecan |
|--|---|---|--|--|
| 1 | Neutrophils < LLN – 1.5 x 10 ⁹ /L | Continue | 100% | 100% |
| | Platelets < LLN – 75 x 10 ⁹ /L | | | |
| 2 | Neutrophils < 1.5 – 1.0 x 10 ⁹ /L perform FBC x 2 per week | Continue | 100% | 100% |
| | Platelets < 75 – 50 x 10 ⁹ /L perform FBC x 2 per week | Interrupt until grade 0 – 1 | Interrupt until grade 0 – 1, then resume at 100% dose | Interrupt until grade 0 – 1, then resume at 100% dose |
| 3 | Neutrophils < 1.0 – 0.5 x 10 ⁹ /L perform FBC daily | Continue | Interrupt until grade 0 – 1 then resume at 75% of starting dose | Interrupt until grade 0 – 1, then resume at 75% of starting dose |
| | Platelets < 50 – 25 x 10 ⁹ /L perform FBC daily | Interrupt until grade 0 – 1 and patient considered fit. | Interrupt until grade 0 – 1, then resume at 75% of starting dose | Interrupt until grade 0 – 1, then resume at 75% of starting dose |
| If patient is neutropenic and has sepsis, combined with grade 3 or 4 diarrhoea | | Interupt until grade 0-1 and ≤ 6 mg loperamide per 24 hours required and patient considered fit | Stop permanently | |
| 4 | Neutrophils < 0.5 x 10 ⁹ /L perform FBC daily | Interupt until grade 0 – 1 and patient considered fit. | Stop permanently | |
| | Platelets < 25 x 10 ⁹ /L perform FBC daily | Interupt until grade 0 – 1 and patient considered fit. | Stop permanently | |

In the event of a second grade 3 episode of the same toxicity, stop all chemotherapy permanently.

7.6 Unplanned Breaks in Treatment

When an unplanned break in radiotherapy occurs (bank holiday, machine breakdown), capecitabine should be interrupted for that day and then resumed on the next planned day of radiotherapy. If irinotecan was scheduled to be given that day, it may be given either the day before or the day after the break, provided this is not more than one day from the date originally scheduled. Otherwise, it should be omitted that week.

In the above circumstances the radiotherapy prescription remains unchanged i.e. the dose prescription remains 45 Gy in 25 fractions even if this is delivered over a longer treatment time – **additional fractions should NOT be given on the same day.**

If a break in treatment has occurred due to toxicity then treatment can be extended into week 6 and beyond, provided that the patient is considered fit for treatment and dose modifications have been applied as per protocol.

7.7 Capecitabine and Irinotecan Dose Modification and Omission

When a dose reduction is made for the development of Grade 2 or Grade 3 toxicity – this modification remains in place for the remainder of the planned treatment course.

If a patient experiences a toxicity, then dose modifications should be applied as per protocol, even if the toxicity has resolved by the time the patient is next seen.

If a dose of capecitabine is omitted in error, no attempt should be made to account for this.

7.8 Support Medication

7.8.1 Irinotecan

Irinotecan may cause a cholinergic syndrome which may include 'early' diarrhoea, abdominal cramps, profuse perspiration, salivation, lacrimation, nausea and vomiting. Recommended treatment is subcutaneous atropine 300 µg which may also be prescribed prophylactically and given prior to all subsequent irinotecan infusions. Individual sites are allowed (but not required) to use prophylactic atropine as part of their local policy for all irinotecan infusions

7.8.2 Anti-emetic recommendations

Arm A - Capecitabine CRT

- Oral anti-emetics according to local policy as required

Arm B - Irinotecan capecitabine CRT

- Oral and iv anti-emetics according to local policy as required

7.8.3 Anti-diarrhoeals

It is strongly recommended that all patients have loperamide prescribed prior to commencement of treatment in case of the development of diarrhoea.

It is strongly recommended that patients are instructed to contact the radiotherapy centre urgently if diarrhoea is not controlled after 12 hours of loperamide therapy.

7.9 Concomitant Medication

7.9.1 Capecitabine

Precautions: The effects of capecitabine are potentiated when co-administration occurs with warfarin, phenytoin and sorivudine (an antiviral). **Please note that patients who are receiving any of these three drugs are not eligible for this study:**

- Concurrent phenytoin – patients are not eligible for this study
- Concurrent sorivudine or its chemically related analogues, such as brivudine – patients are not eligible for this study
- Anticoagulants – patients receiving oral warfarin are eligible for this study with one of the two options listed below according to clinical judgement that is used in routine clinical practice:
 1. Discontinuation of warfarin at least 7 days prior to commencement of treatment and for the duration of CRT (this may be reasonable when given as prophylaxis for patients with atrial fibrillation – this is a local clinician decision)
 2. Conversion from oral warfarin to low molecular weight heparin where local clinical opinion considers this an acceptable option – the change to low molecular weight heparin

with discontinuation of warfarin should be made at least 7 days prior to the commencement of treatment.

Warfarin must not be commenced during CRT. In the unlikely event that this does occur (commenced without consultation with the oncology team), the warfarin must be immediately discontinued, low molecular weight heparin commenced and an INR performed. The patient management should be discussed with a TMG member by contacting the ARISTOTLE trial coordinator.

7.9.2 Irinotecan

Patients should not take St. Johns Wort whilst receiving irinotecan therapy.

7.9.3 Out-of-hours medical care

Medical care, including out-of-hours medical care is the responsibility of the site.

Patients should carry an ARISTOTLE patient card with emergency and routine contact telephone numbers for the trial team at the radiotherapy centre.

It is recommended that patients with treatment-related toxicity are admitted to the radiotherapy centre. If this does not happen the trial team must have daily contact with the treatment hospital and consider transfer to the radiotherapy centre.

7.10 Other Precautions

7.10.1 DPD deficiency

Dihydropyrimidine dehydrogenase (DPD) plays an important role in the metabolism of fluorouracil. Since capecitabine is a prodrug, that is enzymatically converted to 5-fluorouracil (5FU) in the body, patients with DPD deficiency may experience increased toxicity when administered capecitabine, and in some cases these events can be fatal. There is no routine screening test for DPD deficiency, therefore severe adverse events considered related to capecitabine should be treated promptly and with maximum supportive care.

7.11 Management after Treatment Withdrawal

If patients withdraw consent or stop treatment due to toxicity, subsequent treatment will be at the discretion of the treating Investigator.

8. Assessments

For summary of scheduled assessments, please see Schedule of Assessments (appendix 8).

8.1 Pre-randomisation Evaluation

The following assessments or procedures are required to evaluate the suitability of patients for the trial:

- Histological confirmation of disease
- Within 42 days prior to randomisation:
 - CT chest and abdomen
 - MRI pelvis
- Within 14 days prior to randomisation:
 - Physical examination including height and weight
 - Medical history, including Assessment of AEs
 - Concomitant medications
 - ECOG performance status
 - Assessment of fitness for all trial treatments
 - Full blood count including a differential with neutrophil and lymphocyte count
 - Biochemistry: sodium, potassium, urea, creatinine, AST or ALT, alkaline phosphatase, bilirubin, albumin, GGT
 - Calculated creatinine clearance (using Cockcroft-Gault formula) to estimate glomerular filtration rate (GFR) (Appendix 3)
If the calculated creatinine clearance is < 50 mL/min, a formal 24 hour urine collection or isotope clearance must be carried out demonstrating GFR ≥ 50 mL/min.
 - ECG
 - Pregnancy test (if applicable)
- Declared post-operative chemotherapy

The following assessments or procedures are required prior to commencing treatment and may, if desired, be carried out prior to randomisation (note that some may need to be repeated if trial treatment does not commence within 10 days of the assessment being carried out):

- Serum CEA
- CRP
- Pelvic functional questionnaire
- (**N.B.** patients must give written informed consent to take part in the trial **before** any trial specific assessments/procedures are carried out)

8.2 Pre-treatment Investigations

The following tests and investigations should be carried out **within 10 days prior to day 1 of week 1 of treatment**:

- Physical examination including weight
- ECOG performance status
- Acute toxicity assessment (assessment of AEs)
- Full blood count and differential with neutrophil and lymphocyte count
- Biochemistry: sodium, potassium, urea, creatinine, AST or ALT, alkaline phosphatase, bilirubin, albumin, GGT
- Calculated creatinine clearance (using Cockcroft-Gault formula; see Appendix 3) to estimate GFR (Appendix 3)

If the calculated creatinine clearance is < 50 mL/min, a formal 24 hour urine collection or isotope clearance must be carried out demonstrating GFR ≥ 50 mL/min.

For patients who required a 24 hour urine or isotope clearance prior to randomisation to confirm GFR ≥ 50 mL/min, these tests do not need to be repeated unless the creatinine rises by > 10%.

- Serum CEA
- CRP
- Pelvic functional questionnaire (does not need to be repeated if completed prior to randomisation)

The tests above do not need to be repeated if they were performed for pre-randomisation evaluation, and were done within 10 days prior to start of trial treatment.

The following samples should be collected within **14 days prior to starting treatment** from consenting patients:

- **Whole blood sample for circulating tumour (ct)DNA (collected in Streck tube)** for future research (see section 9.3; Blood Samples, for more information)
- **Whole blood sample for germline DNA (collected in EDTA tube)** for future research (see section 9.3; Blood Samples, for more information). It is recommended that this sample is collected at baseline, although it is acceptable for the sample to be taken at any point during the trial.

8.3 Assessments during Treatment

The following assessments should be performed once a week during treatment (weeks 1 – 6). If treatment continues after week 5, the following assessments should be performed each treatment week thereafter and on the week following the completion of treatment.

- Weight
- Acute toxicity assessment (Assessment of AEs)
- ECOG performance status
- Full blood count including a differential with neutrophil and lymphocyte count

- Biochemistry: sodium, potassium, urea, creatinine, AST or ALT, Alkaline phosphatase, bilirubin, albumin, GGT

(Patients who are on Arm B must have bloods done within 72 hours prior to irinotecan administration)

- Calculated creatinine clearance (using Cockcroft-Gault formula; see Appendix 3) to estimate GFR (Appendix 3)

If the calculated creatinine clearance is < 50 mL/min, a formal 24 hour urine collection or isotope clearance must be carried out demonstrating GFR ≥ 50 mL/min.

For patients who required a 24 hour urine or isotope clearance to before starting treatment to confirm GFR ≥ 50 mL/min, these tests do not need to be repeated unless the creatinine rises by > 10%.

- Capecitabine compliance check
- Patients must be reminded to bring their diary with them to every hospital visit. The diary should be reviewed with the patient and adverse events recorded in the patient's notes and trial CRFs. The diary should also be used to assess patient compliance with capecitabine
- Diaries must be reconciled with returned medication to ensure consistency
- **Week 1 & 5:** Whole blood sample for ctDNA (collected in Streck tube) for future research (for consenting patients; see section 9.3; Blood Samples, for more information)

8.4 Assessments on Completion of Treatment

8.4.1 Assessments at week 10 (from start of CRT)

The following assessments should be performed **10 weeks after the start of CRT:**

- Weight
- Acute toxicity assessment (Assessment of AEs)
- ECOG performance status
- Full blood count including a differential with neutrophil and lymphocyte count
- Biochemistry: sodium, potassium, urea, creatinine, AST or ALT, Alkaline phosphatase, bilirubin, albumin, GGT
- CEA
- **Week 10:** Whole blood sample for ctDNA (collected in Streck tube) for future research (for consenting patients; see section 9.3; Blood Samples for more information)

8.4.2 Assessments at weeks 6 – 8 weeks after completion of CRT

The following investigations should be performed **6 – 8 weeks after completion of CRT** (12 – 14 weeks after start of CRT):

- CT chest and abdomen
- MRI pelvis

8.5 Surgery

Surgery is strongly recommended to take place **8 – 10 weeks after completing CRT.**

The decision to proceed to surgical resection, in keeping with standard practice, is based on MDT review of the cross-sectional imaging before and after CRT and clinical assessment.

The decisions concerning the planned surgical procedure should be made in keeping with standard practice. The Surgery CRFs will record the details of the type of surgical resection, the method used, the plane of surgical excision and whether a curative resection was achieved. Any macroscopic residual tumour or equivocal areas should be both biopsied and recorded.

Post-operative morbidity will be assessed at the time points noted below.

8.6 Histopathology

Appendix 6 describes the method of the examination of the resected specimen and any additional biopsy material. The Pathology CRF must be completed. Ancillary studies using histopathological material are described in section 9.2; Tissue Blocks.

8.7 Assessments during Follow-up

8.7.1 Assessments after surgery

Patients should then be seen at 4, 6, 12, 24, 36, 48 and 60 months after completing CRT.

Assessments should be carried out as follows:

| Months post-CRT | 4 | 6 | 12 | 24 | 36 | 48 | 60 |
|---|---|---|----|----|----|----|----|
| Physical examination | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| ECOG | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Post-operative toxicity assessment | ✓ | | | | | | |
| Details of post-op chemotherapy planned | ✓ | | | | | | |
| Details of post-op chemotherapy given | | | ✓ | | | | |
| CT chest, abdomen, pelvis | | | ✓ | ✓ | ✓ | | |
| Pelvis questionnaire | | | ✓ | ✓ | ✓ | | |

Routine investigations including the frequency of serum CEA, surveillance colonoscopy and imaging beyond 3 years may be performed according to site policy.

Patients will be followed up for 5 years. All efforts should be made by the site to contact the patient's GP to assess their condition if a patient fails to attend a clinic or cannot be followed up at site.

8.8 Assessments of Primary Endpoint

8.8.1 Confirmation of residual disease and recurrence

Residual disease is defined as evidence of persisting disease (that has failed to adequately respond to pre-operative CRT). Disease recurrence is defined as the diagnosis of either loco-regional recurrence or established metastatic disease.

When disease recurrence is reported, the supporting evidence will either constitute "suspected" or "confirmed" depending on whether the investigations meet the pre-defined criteria listed below.

Confirmed Evidence of Loco-regional Failure

This is defined as any confirmed evidence of disease below the L5/S1 junction:

A Confirmed evidence of PERSISTING DISEASE following pre-operative CRT

- MDT decision that the local extent of disease on the post CRT pelvic MRI is not resectable
- Decision that at laparotomy after pre-operative CRT the local extent of disease is not resectable
- Incomplete resection of tumour at laparotomy after pre-operative CRT with biopsy proof of residual disease. (Lack of biopsy proof in this situation would constitute "suspected" persisting disease)

B Confirmed evidence of loco-regional recurrence

- Clinical recurrence with biopsy proof of recurrence
- CEA elevation and enlarging or new mass (includes pelvic, nodal and peritoneal disease). Biopsy confirmation is contraindicated or not feasible
- CEA non-secretors: enlarging or new mass (includes pelvic, nodal and peritoneal disease). Biopsy confirmation is contraindicated or not feasible (with or without PET/CT confirmation):
 - Initial report to UCL CTC should define this as SUSPECTED
 - Further report 6 months later should define this as CONFIRMED if supported by MDT review

Confirmed Evidence of Distant Metastases

This is defined as any confirmed evidence of disease above the L5/S1 junction

- Clinical recurrence with biopsy proof of recurrence
- CEA elevation and evidence of distant metastases. Biopsy confirmation is contraindicated or not feasible
- CEA non-secretors: evidence of distant metastases. Biopsy confirmation is contraindicated or not feasible (with or without PET/CT confirmation)
 - Initial report to UCL CTC should define this as SUSPECTED
 - Further report 6 months later should define this as CONFIRMED if supported by MDT review

Suspected Recurrence

It is recognised that there are various clinical scenarios where there is a significant suspicion of recurrent disease but the evidence is not definitive. This includes:

- Elevated CEA but without definitive evidence of loco-regional or metastatic disease
- Appearance of equivocal findings on CT or pelvic MRI scanning

Whilst PET/CT is helpful in some of these situations it is recognised that both false positive and false negative findings may occur.

Once a suspected recurrence is reported then the case must be reviewed by the MDT 6 months later and a further report submitted to UCL CTC. A CONFIRMED local recurrence is defined at this point if supported by the MDT.

9. Collection of Tissue and Blood for Exploratory Biological Research

9.1 Collection of Tissue and Blood Samples

At the time of trial entry, consent will be sought for the collection and storage of blood samples and archival tissue blocks for future research

Consent for future research on blood and tissue samples is optional for patients and refusal will not preclude trial entry.

For patients who are already randomised on the trial consent may be sought for an additional blood sample for germline DNA (see section 9.3.2; Whole blood sample for Germline DNA). Refusal will not affect their standard of care on the trial.

Refer to the ARISTOTLE lab manual in the Investigator Site File for more details on sample collection, processing, storage and shipping.

9.2 Tissue Blocks

9.2.1 Samples to collect

Sites are asked to provide the following **for patients who have consented to collection of tissue**:

- Formalin-fixed paraffin-embedded Tissue Blocks from:
 - Pre-treatment diagnostic biopsy (tumour and normal mucosa)
 - Post-treatment resection (one or more blocks from tumour and one block from normal mucosa)

The tissue blocks from the resection will be used in further molecular studies of the response to radiotherapy/chemotherapy. This should preferably be material that is not required for diagnosis locally i.e. additional blocks should be taken at the time of specimen dissection. In cases with no residual tumour a block of normal mucosa only is required. Tissue will be kept in wax blocks and stored separately for future studies. Use of this tissue will be addressed in separate study applications for funding and to the TMG but will include the assessment of regression by morphometry together with immunohistochemical and molecular markers predicting response.

9.2.2 Shipment of samples

All blocks should be **carefully** packaged to avoid breakage and sent to the address below. Blocks should be wrapped in a protective layer e.g. bubble wrap. Any queries should be sent to either Dr Nick West (n.p.west@leeds.ac.uk) or Professor Phil Quirke (p.quirke@leeds.ac.uk). If any of the held material is required for clinical purposes prior to its standard return then it will be returned temporarily as soon as possible.

Tissue blocks may be shipped together with material requested for Quality Assurance (see section 10; Quality Assurance).

Ship blocks (and material for QA if applicable) to:

Dr Nick West
Pathology and Tumour Biology, Level 4
Wellcome Trust Brenner Building
St. James's University Hospital
Beckett Street
Leeds LS9 7TF

9.3 Blood Samples

9.3.1 Whole blood sample for ctDNA

Timing of collection

Whole blood for ctDNA should be collected from patients at each of the following time points during the trial:

- Baseline (within 14 days prior to starting treatment)
- During week 1 of treatment
- During week 5 of treatment
- During week 10 after starting treatment

Preparation of samples

Blood should be collected into a 10 mL Streck tube. Samples must not be frozen or put in the fridge. They must be shipped on the same day as collection.

9.3.2 Whole blood sample for Germline DNA

Timing of collection

Whole blood sample for germline DNA should be collected from each patient at baseline, although it is acceptable for the sample to be taken at any point during the trial.

Preparation of samples

Blood should be collected into a 10 mL EDTA tube. Samples must not be frozen, but may be put into the fridge. Samples must be shipped on the same day as collection.

9.3.3 Shipment of samples

All blood samples must be shipped the same day they are taken (it is acceptable to ship samples on a Friday or the day before bank holidays), in Royal Mail Safe Boxes to the Institute of Medical Genetics at the address below.

Rana Hussein
All Wales Genetics Laboratory
Institute of Medical Genetics
University Hospital of Wales
Heath Park
Cardiff CF14 4XW

Detailed information on sample handling, labelling, storage and shipping are provided in the Laboratory Manual in the Investigator Site File.

10. Quality Assurance

Quality Assurance will be carried out for radiotherapy, and for surgery and histopathology.

10.1 Radiotherapy QA

We have taken the advice from the NCRI CTRad Quality Assurance workstream which has recommended the following package of QA checks. **For full details of QA processes, access to exercises and forms, and contact details of the QA team, please refer to the RT Trials QA website (<http://www.rtrialsqa.org.uk>).**

For centres who wish to use IMRT or VMAT, please refer to Appendix 5; Radiotherapy Treatment Planning and Quality Assurance Protocol.

Pre-trial quality assurance

- Completion of the following questionnaires:
 - National radiotherapy trials QA baseline questionnaire
 - National radiotherapy trials QA staff questionnaire
 - Trial specific questionnaire
- Production of a Radiotherapy Process Document – in line with which all trial patients will be scanned, planned and treated
- Completion of an outlining exercise
 - At least one patient case (from PI) per radiotherapy site. PI then responsible for approving contour delineation at that site for each patient
- Completion of a planning exercise
 - One pre outlined patient per radiotherapy site
 - Plan Assessment Form (PAF)

IMRT/VMAT

Sites wishing to use IMRT or VMAT techniques must first discuss this with the UCL CTC and RTTQA team, by contacting the ARISTOTLE trial coordinator.

If new sites wish to use IMRT/VMAT, they will be required to submit all pre-trial QA documents (as above) including the pre-trial planning case and a process document for IMRT/VMAT. New sites must have successfully undertaken the relevant dosimetry audit to allow for credentialing.

If existing sites wish to use IMRT/VMAT, they will be required to re-submit the pre-trial planning case and an updated process document for QA, and must have successfully undertaken the relevant dosimetry audit to allow for credentialing.

For both new and existing sites, the first trial case should be submitted for real-time QA of plan and dose distribution. The outlining protocol should be adhered to. Where adaptations are considered to reduce small bowel volume irradiated these should be reviewed in real-time by the RTTQA team.

In case of change of PI

In the event that there is a change of PI at site, the new PI must submit an outlining exercise which must be approved by the RTTQA team outlining before the site can treat any new patients.

Ongoing QA requirements

- Real time review of first patient recruited from each radiotherapy site before radiotherapy is carried out (outline, plan and PAF)
- Retrospective review of 10% patients randomised per radiotherapy site
- Plan and PAF export for all trial patients
- The PAF for all patients should be submitted prior to the patient starting treatment

10.2 Surgery and Histopathology QA

Sites are asked to provide the following material for central review:

- **Copies of H&E stained glass slides** (or originals which will be returned to site after scanning) of:
 - Pre-treatment diagnostic biopsy tissue
 - Post-treatment resection tissue
- **Pathology CRF** (submit original to UCL CTC and include a copy with the shipment of slides to Pathology & Tumour Biology, University of Leeds)
- **Anonymised Histopathology Report** identifiable by trial number
- **Digital photographs** of the resection specimens (sites are strongly recommended to take and submit photographs as described in the Histopathology Guidance Appendix, however it is not mandatory)

Please also refer to Appendix 6; Histopathology Guidance.

10.2.1 Shipping

Slides should be **carefully** packaged to avoid breakage and sent to the address below. Slides should be packed in dedicated slide boxes which should be securely sealed. Any queries should be sent to either Dr Nick West (n.p.west@leeds.ac.uk) or Professor Phil Quirke (p.quirke@leeds.ac.uk). If any of the held material is required for clinical purposes prior to its standard return then it will be returned temporarily as soon as possible.

The above material for central review may be shipped together with the tissue blocks requested for future research (see section 9; Collection of Tissue and Blood for Exploratory Biological Research).

Ship slides, pathology CRF, histopathology report and photographs (and tissue blocks for future research if applicable) to:

Dr Nick West
Pathology and Tumour Biology, Level 4
Wellcome Trust Brenner Building
St. James's University Hospital
Beckett Street
Leeds LS9 7TF

11. Data Management Guidelines

Data will be collected from sites on version controlled CRFs designed for the trial and supplied by UCL CTC.

Data must be accurately transcribed onto CRFs and must reflect source documents at site. Examples of source documents include patient notes, laboratory results and other clinical reports etc.

Where supporting documentation (e.g. autopsy reports, pathology reports, CT scan images etc.) is being submitted to UCL CTC, the patient's trial number must be clearly indicated on all material and any patient identifies removed/blacked out prior to sending to maintain confidentiality.

Some data may be recorded directly on the CRFs (i.e. no prior written or electronic record of data) and it will be considered to be the source document. Such CRFs include the MRI Pelvis CRF at baseline and post-treatment, and the Pathology CRF. If preferred, we can provide sites with MRI and Pathology Worksheets for the Radiologist/Pathologist to complete. The data can then be transcribed onto the MRI and/or Pathology CRF by a member of staff listed on the site staff delegation log. In this instance, the Worksheets would be considered as source documents.

11.1 Completing Forms

All CRFs must be completed and signed by staff who are listed on the site staff delegation log and authorised by the PI to perform this duty. The PI is responsible for the accuracy of all data reported on the CRF.

All entries must be clear, legible and written in ball point pen. Any corrections made to a CRF at site must be made by drawing a single line through the incorrect item ensuring that the previous entry is not obscured. Each correction must be dated and initialled. Correction fluid must not be used.

The use of abbreviations and acronyms must be avoided.

Once completed the original CRFs must be sent to UCL CTC and a copy kept at site.

11.2 Missing Data

To avoid the need for unnecessary data queries CRFs must be checked at site to ensure there are no blank fields before sending to UCL CTC. When data is unavailable because a measure has not been taken or test not performed, enter "ND" for not done. If an item was not required at the particular time the form relates to, enter "NA" for 'not applicable'. When data are unknown, enter the value "NK" (only use if every effort has been made to obtain the data).

11.3 Data Queries

Data arriving at UCL CTC will be checked for completeness, accuracy and consistency including checks for legibility, missing or unusual values. Query Reports will be sent to the data contact at site. Further guidance on how data contacts should respond to Data Queries can be found on the Query Reports.

11.4 Submission Timelines

CRFs must be completed at site and returned to UCL CTC as soon as possible after patient visit and within one month of the patient being seen.

Sites who persistently do not return data within the required timelines may be suspended from recruiting further patients into the trial by UCL CTC and be subjected to a 'for cause' monitoring visit (see section 14.2; 'For Cause' On-Site Monitoring) for details.

12. Pharmacovigilance

12.1 Definitions of Adverse Events

The following definitions have been adapted from Directive 2001/20/EC, ICH E2A "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting" and ICH GCP E6:

12.1.1 Adverse Event (AE)

Any untoward medical occurrence in a patient treated on a trial protocol, which does not necessarily have a causal relationship with a trial treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a trial treatment, whether or not related to that trial treatment.

12.1.2 Adverse Reaction

All untoward and unintended responses to a trial treatment related to any dose administered. A causal relationship between a trial treatment and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

12.1.3 Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

An adverse event or adverse reaction that at any dose:

- Results in death
- Is life threatening (The term "life-threatening" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires in-patient hospitalisation or prolongs existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is otherwise medically significant (e.g. important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent of the other outcomes listed above)

12.1.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction, the nature or severity of which **is not consistent** with the reference safety information (RSI).

12.2 Reporting Procedures

12.2.1 All Adverse Events (AEs)

All adverse events that occur between informed consent and 30 days post last trial treatment administration must be recorded in the patient notes and the trial CRFs. Those meeting the definition of a Serious Adverse Event (SAE) must also be reported to UCL CTC using the trial specific SAE Report.

Also refer to section 12.2.6; Serious Adverse Events (SAEs).

Post-operative AEs must be recorded in the patient notes at 4 months post CRT and on the 4 month Follow-up CRF. Late AEs must be recorded in the patient notes at 12, 24 and 36 months post CRT. (Also refer to section 8.7; Assessments during Follow-up).

Pre-existing conditions do not qualify as adverse events unless they worsen.

12.2.2 Overdoses

All accidental or intentional overdoses, whether or not they result in adverse events, must be recorded in the patient notes and CRFs. Overdoses resulting in an adverse event are classified as SAEs and must be reported to UCL CTC according to SAE reporting procedures. The fact that an overdose has occurred must be clearly stated on the SAE Report. Also refer to section 12.2.6; Serious Adverse Events (SAEs).

Sites must inform UCL CTC immediately when an overdose has been identified. Also refer to section 13; Incident Reporting and Serious Breaches.

12.2.3 Adverse Event Term

An adverse event term must be provided for each adverse event, wherever possible using the term listed in the Common Terminology Criteria for Adverse Events (CTCAE) v4.02, available online at:

www.acrin.org/Portals/0/Administration/Regulatory/CTCAE_4.02_2009-09-15_QuickReference_5x7.pdf

12.2.4 Severity

Severity of each adverse event must be determined by using the Common Terminology Criteria for Adverse Events (CTCAE) v4.02 as a guideline, wherever possible. The criteria are available online at:

www.acrin.org/Portals/0/Administration/Regulatory/CTCAE_4.02_2009-09-15_QuickReference_5x7.pdf

In those cases where the CTCAE criteria do not apply, severity should be coded according to the following criteria:

- 1 = Mild (awareness of sign or symptom, but easily tolerated)
- 2 = Moderate (discomfort enough to cause interference with normal daily activities)
- 3 = Severe (inability to perform normal daily activities)
- 4 = Life threatening (immediate risk of death from the reaction as it occurred)
- 5 = Fatal (the event resulted in death)

12.2.5 Causality

The PI, or other delegated site investigator, must perform an evaluation of causality for each adverse event. Causal relationship to each trial treatment must be determined as follows:

- **None**

There is no evidence of any causal relationship.

- **Unlikely**

There is little evidence to suggest a causal relationship (e.g. because the event did not occur within a reasonable time after administration of a trial treatment). There is another reasonable explanation of the event (e.g. the patient's clinical condition, other concomitant treatments).

- **Possibly**

There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of a trial treatment). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).

- **Probably**

There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

- **Definitely**

There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

UCL CTC will consider events that are evaluated as possibly, probably or definitely related to a trial treatment to be adverse reactions.

12.2.6 Serious Adverse Events (SAEs)

All SAEs that occur between the signing of informed consent and 30 days post the last trial treatment administration (or after this date if the site investigator feels the event is related to the trial treatment) must be submitted to UCL CTC by fax within **24 hours** of observing or learning of the event, using the trial specific SAE Report. All sections on the SAE Report must be completed. If the event is **not being reported within 24 hours** to UCL CTC, the circumstances that led to this must be detailed in the SAE Report to avoid unnecessary queries.

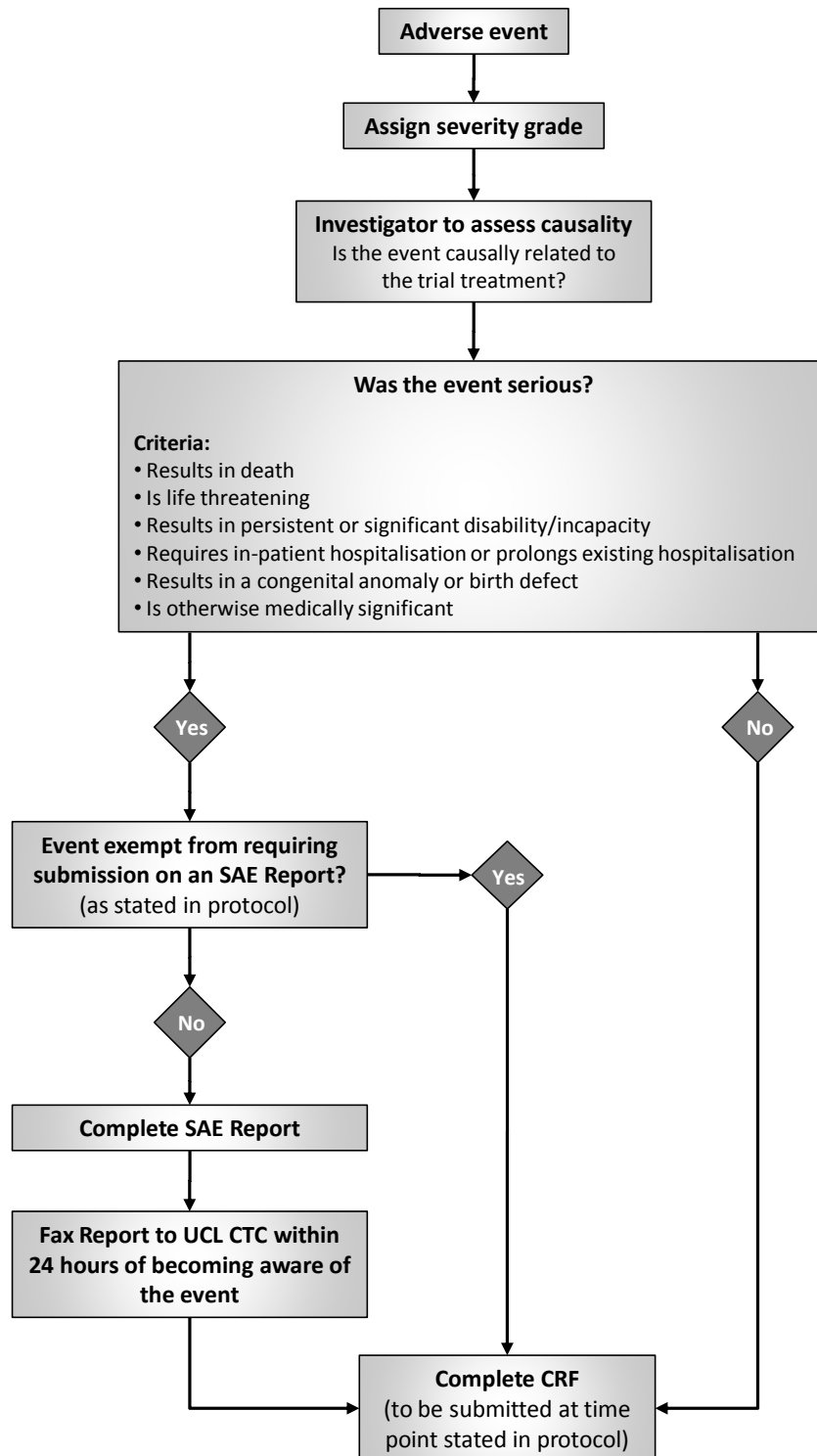
Exemptions from SAE Report Submission

For this trial, the following events are exempt from requiring submission on an SAE Report, but must be recorded in the relevant section(s) of the CRF:

- Events that occur after 30 days post last trial treatment administration that are not considered to be side-effects of the trial treatment
- Disease progression (including disease related deaths)

Please note that hospitalisation for elective treatment or palliative care does not qualify as an SAE.

**Completed SAE Reports must be faxed within 24 hours of becoming
aware of the event to UCL CTC
Fax: 020 7679 9871**

Adverse Event Reporting Flowchart

SAE Follow-Up Reports

All SAEs must be followed-up until resolution and until there are no further queries. The PI, or other delegated site investigator, must provide follow-up SAE Reports if the SAE had not resolved at the time the initial report was submitted. If possible, the original SAE report should be amended with follow-up information and faxed to UCL CTC as appropriate.

12.2.7 SAE Processing at UCL CTC

On receipt of the SAE Report, UCL CTC will check for legibility, completeness, accuracy and consistency. Expectedness will be evaluated, to determine whether or not the case qualifies for expedited reporting, using the RSI (the list of expected adverse events in protocol appendix 7 for radiotherapy and the approved SPCs for capecitabine and irinotecan).

The CI, or their delegate (e.g. a clinical member of the TMG), will be contacted to review the SAE and to perform an evaluation of causality on behalf of UCL CTC. If UCL CTC has considered expectedness difficult to determine, the CI, or their delegate, will be consulted for their opinion at this time.

12.3 SUSARs

If the event is evaluated as a Suspected Unexpected Serious Adverse Reaction (SUSAR), i.e. unexpected events that are evaluated as related to a trial treatment, UCL CTC will submit a report to the MHRA and the REC within 7 calendar days for fatal/life threatening events, (with a follow-up report within a further 8 calendar days) and 15 calendar days for all other events. Where there are conflicting evaluations of causal relationship by the site and UCL CTC/CI, both opinions will be reported.

12.3.1 Informing sites of SUSARs

UCL CTC will inform all PIs of any SUSARs that occur on the trial. PIs will receive a quarterly line listing which must be processed according to local requirements.

12.4 Safety Monitoring

UCL CTC will provide safety information to the TMG and the IDMC on a periodic basis for review.

Trial safety data will be monitored to identify:

- New adverse reactions to the trial treatment regimen or individual trial treatments
- Trial related events that are not considered related to the trial treatment regimen

Should UCL CTC identify or suspect any issues concerning patient safety at any point throughout the trial, the CI or TMG will be consulted for their opinion.

12.5 Pregnancy

If a patient or the partner of a male patient becomes pregnant from consent up to three months after stopping trial treatment, a completed trial specific Pregnancy Report must be submitted to UCL CTC by fax within **24 hours** of learning of its occurrence. Consent to report information regarding the pregnancy must be obtained from the pregnant patient/partner. The trial-specific pregnancy

monitoring information sheets and informed Consent Forms for trial patients and the partners of trial patients must be used for this purpose.

**All pregnancies must be reported by faxing a completed Pregnancy Report within 24 hours of becoming aware of the pregnancy to UCL CTC
Fax: 020 7679 9871**

12.5.1 Pregnancy Follow-Up Reports

For pregnant patients or partners who consent, their pregnancies must be followed-up until an outcome is determined. Follow-up Pregnancy Reports must be submitted to UCL CTC by fax within **24 hours** of learning of the outcome. Reports must include an evaluation of the possible relationship of each trial treatment to the pregnancy outcome.

12.5.2 SAEs During Pregnancy

Any SAE occurring in a pregnant patient must be reported using the trial specific SAE Report, according to SAE reporting procedures. Refer to section 12.2.6; Serious Adverse Events (SAEs), for details.

12.5.3 Pregnancy Report Processing at the UCL CTC

UCL CTC will submit a report to the MHRA and the REC should the pregnancy outcome meet the definition of a SUSAR. Refer to section 12.3; SUSARs, for details.

12.6 Development Safety Update Reports (DSURs)

Safety data obtained from the trial will be included in DSURs that UCL CTC will submit to the MHRA and the REC.

13. Incident Reporting and Serious Breaches

13.1.1 Incident Reporting

Organisations must notify UCL CTC of all deviations from the protocol or GCP immediately. UCL CTC may require a report on the incident(s) and a form will be provided if the organisation does not have an appropriate document (e.g. Trust Incident Form).

If site staff are unsure whether a certain occurrence constitutes a deviation from the protocol or GCP, the UCL CTC trial team will be contacted immediately to discuss.

UCL CTC will assess all incidents to see if they meet the definition of a serious breach.

UCL CTC will use an organisation's history of non-compliance to make decisions on future collaborations.

13.1.2 Serious Breaches

Systematic or persistent non-compliance by a site with GCP and/or the protocol, including failure to report SAEs occurring on trial within the specified timeframe, may be deemed a serious breach.

In cases where a serious breach has been identified, UCL CTC will inform the MHRA within 7 calendar days of becoming aware of the breach.

Sites must have written procedures for notifying the sponsor of serious breaches (MHRA Guidance on the Notification of Serious Breaches, 2009).

UCL CTC will use an organisation's history of non-compliance to make decisions on future collaborations.

14. Trial Monitoring and Oversight

Participating sites and PIs must agree to allow trial-related on-site monitoring, Sponsor audits and regulatory inspections by providing direct access to source data/documents as required. Patients are informed of this in the patient information sheet and are asked to consent to their medical notes being reviewed by appropriate individuals on the Consent Form.

UCL CTC will determine the appropriate level and nature of monitoring required for the trial. Risk will be assessed on an ongoing basis and adjustments made accordingly.

14.1 Central Monitoring

Sites will be requested to submit screening logs, staff delegation logs, accountability logs and PI CVs to UCL CTC on request and these will be checked for consistency and completeness. Also refer to sections 3.2.2; Required Documentation, and 5.2; Screening Logs.

Eligibility of all patients entered in the trial is assessed by the PI, or, if delegated by the PI, other appropriately trained site staff. Checks of the criteria listed on the Eligibility Checklist and Pre-randomisation Forms will be undertaken by an appropriately trained UCL CTC staff member prior to randomisation. Also refer to section 6.1; Randomisation.

Details relating to the informed consent process will be collected on the Randomisation Form and are subject to review by UCL CTC as part of patient eligibility.

Copies of completed drug accountability logs will be collected at UCL CTC for all trial patients. Sites will be required to submit logs following completion of a patient's treatment or on request. A proportion of these will be monitored centrally to ensure completeness and correlation with data captured in the CRF. Also refer to section 7.3.3; Pharmacy Responsibilities.

Sites will be requested to conduct quality control checks of documentation held within the Investigator Site File and Pharmacy Site File at the frequency detailed in the trial monitoring plan. Checklists detailing the current version/date of version controlled documents will be provided for this purpose.

Data received at UCL CTC will be subject to review in accordance with section 11.3; Data Queries.

Where central monitoring of data and/or documentation submitted by sites indicates that a patient may have been placed at risk (e.g. dose modifications not being observed following an adverse reaction, etc.), the matter will be raised urgently with site staff and escalated as appropriate (refer to section 13; Incident Reporting and Serious Breaches and 14.2; 'For Cause' On-site Monitoring, for further details).

14.2 'For Cause' On-Site Monitoring

On-site monitoring visits may be scheduled where there is evidence or suspicion of non-compliance at a site with important aspect(s) of the trial protocol/GCP requirements. Sites will be sent a letter in advance outlining the reason(s) for the visit. The letter will include a list of the documents that are to be reviewed, interviews that will be conducted, planned inspections of the facilities, who will be performing the visit and when the visit is likely to occur.

Following a monitoring visit, the Trial Monitor/Trial Coordinator will provide a report to the site, which will summarise the documents reviewed and a statement of findings, deviations, deficiencies, conclusions, actions taken and actions required. The PI at each site will be responsible for ensuring that monitoring findings are addressed (this may be delegated to an appropriate member of staff).

UCL CTC will assess whether it is appropriate for the site to continue participation in the trial and whether the incident(s) constitute a serious breach. Refer to section 13; Incident Reporting and Serious Breaches, for details.

14.3 Oversight Committees

14.3.1 Trial Management Group (TMG)

The TMG will include the Chief Investigator, clinicians and experts from relevant specialities and ARISTOTLE trial staff from UCL CTC. The TMG will be responsible for overseeing the trial. The group will meet regularly (at least 4 times per year during the recruitment phase – with greater frequency at the start of the study) and will send updates to PIs (via newsletters or at Investigator Meetings) and to the NCRI Colorectal Clinical Studies Group.

The TMG will review substantial amendments to the protocol prior to submission to the REC and MHRA. All PIs will be kept informed of substantial amendments through their nominated responsible individuals.

14.3.2 Trial Steering Committee (TSC)

The role of the TSC is to provide overall supervision of the trial. The TSC will review the recommendations of the Independent Data Monitoring Committee and, on consideration of this information, recommend any appropriate amendments/actions for the trial as necessary. The TSC acts on behalf of the funder and Sponsor.

14.3.3 Independent Data Monitoring Committee (IDMC)

The role of the IDMC is to provide independent advice on data and safety aspects of the trial. Meetings of the Committee will be held periodically to review interim analyses, or as necessary to address any issues. The IDMC is advisory to the TSC and can recommend premature closure of the trial to the TSC.

14.3.4 Role of UCL CTC

UCL CTC will be responsible for the day to day coordination and management of the trial and will act as custodian of the data generated in the trial (on behalf of UCL). UCL CTC is responsible for all duties relating to pharmacovigilance which are conducted in accordance with section 12; Pharmacovigilance.

15. Withdrawal of Patients

In consenting to the trial, patients are consenting to trial treatment, assessments, follow-up and data collection.

15.1 Discontinuation of Trial Treatment

A patient may be withdrawn from trial treatment whenever continued treatment is no longer in the patient's best interests, but the reasons for doing so must be recorded. Reasons for discontinuing treatment may include:

- Disease progression whilst on therapy
- Unacceptable toxicity
- Intercurrent illness which prevents further treatment
- The patient withdraws consent to further treatment
- Any alterations in the patient's condition which justifies the discontinuation of treatment in the site investigator's opinion

In these cases patients remain within the trial for the purposes of follow-up and data analysis according to the treatment option to which they have been allocated.

15.2 Patient Withdrawal from Trial Treatment

If a patient expresses their wish to withdraw from trial treatment, sites should explain the importance of remaining on trial follow-up, or failing this of allowing routine follow-up data to be used for trial purposes and for allowing existing collected data to be used. If a patient gives a reason for their withdrawal, this should be recorded.

15.3 Withdrawal of Consent to Data Collection

If a patient explicitly states they do not wish to contribute further data to the trial their decision must be respected and recorded on the relevant CRF. In this event, details should be recorded in the patient's hospital records, no further CRFs must be completed and no further data sent to UCL CTC.

15.4 Losses to Follow-up

If a patient moves from the area, sites should make every effort to ensure the patient is followed up at another participating trial site and for this new site to take over the responsibility for the patient, or to obtain follow-up information from the patient's GP. Details of participating trial sites can be obtained from the UCL CTC trial team who must be informed of the transfer of care and follow-up arrangements.

Patients should be considered to be lost to follow-up only once documented efforts on the part of the site have failed to produce any response or information from the patient or GP over the course of one year.

16. Trial Closure

16.1 End of Trial

For regulatory purposes the end of the trial will be 5 years after the last patient has been randomised, or once all patients have progressed or died, whichever happens first. At this point the 'Declaration of End of Trial' Form will be submitted to the participating Regulatory Authority and Ethics Committee, as required.

Following this, UCL CTC will advise sites on the procedure for closing the trial at the site.

16.2 Archiving of Trial Documentation

At the end of the trial, UCL CTC will archive securely all centrally held trial related documentation for a minimum of 5 years. Arrangements for confidential destruction will then be made. It is the responsibility of PIs to ensure data and all essential documents relating to the trial held at site are retained for a minimum of 5 years after the end of the trial, in accordance with national legislation.

Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with the principles of GCP and all applicable regulatory requirements.

UCL CTC will notify sites when trial documentation held at sites may be archived. All archived documents must continue to be available for inspection by appropriate authorities upon request.

16.3 Early Discontinuation of Trial

The trial may be stopped before completion as an Urgent Safety Measure or on the recommendation of the TSC or IDMC (see section 14.3.2; Trial Steering Committee (TSC) and 14.3.3; Independent Data Monitoring Committee (IDMC)). Sites will be informed in writing by UCL CTC of reasons for early closure and the actions to be taken with regards the treatment and follow-up of patients.

16.4 Withdrawal from Trial Participation by Sites

Should a site choose to close to recruitment, the PI must inform UCL CTC in writing. Follow-up as per protocol must continue for all patients recruited into the trial at that site and other responsibilities continue as per CTSA.

17. Statistics

17.1 Sample Size Calculation

The primary outcome measure is disease free survival (DFS). The main comparison is irinotecan vs. no irinotecan.

The original statistical plan required a sample size of 916 patients. The primary end point was disease free survival (DFS). An improvement in 20 month DFS rate from 60% to 70% equated to a Hazard Ratio of 0.70. A multistep analysis plan for futility was used based on estimates of recruitment and the timing of disease related events. Since the ARISTOTLE trial started, five phase III trials have addressed the addition of oxaliplatin to fluoropyrimidine CRT, only two trials have published long term outcome data (46-50). These trials have used 3 year DFS as a primary or secondary end point and have been used to assist in our estimates for the revision of the sample size. The case mix of the trial entry criteria and the limited use of pelvic MRI have also been taken into account. In addition, the multistep analysis plan has been removed which reduces the sample size allowing the trial to address the scientific questions within a reasonable period of time. These changes have been supported by the trial funder.

The trial now targets an absolute improvement in DFS of 9% from 65% to 74% at 3 years. This absolute difference of 9% equates to a HR of 0.70. A difference of this size would be both clinically worthwhile and realistic.

In order to calculate the number of patients and the number of events required, the following assumptions have been made:

1. 3 year DFS rate in the control arm is 65%.
2. 3 year DFS rate in the experimental arm is 74%.
3. 2-sided alpha of 0.05.
4. The HR under the alternative hypothesis is 0.70
5. Power is 80%.
6. Recruitment of 6 years and a minimum of 3 years of follow-up
7. Allocation ratio of 1:1

Using these assumptions, the sample size calculation calls for 247 DFS events from 496 patients (nQuery Advisor 7.0) (51). However, the number of patients required is likely to be underestimated since the software assumes a constant event rate over time. In order to account for the possibility that the event rate declines after 3 years follow-up, the target recruitment has been increased to 600 patients.

If, however, accrual improves and/or event rates are sufficiently high, the TMG may decide to continue recruitment to achieve an HR of 0.73, which would require 304 events.

17.2 Populations for Analysis

The primary analysis of the trial will be carried out on an intention to treat basis, which will include all patients randomised to the trial.

A secondary analysis will also be carried out on a per-protocol population. The per-protocol population will consist of patients who received 90% or greater of their planned radiotherapy dose.

17.3 Analysis of the Primary Endpoint

DFS will be estimated using the Kaplan-Meier method, and the two arms of the trial compared using a log-rank test. The hazard ratio and 95% CI will be estimated using a Cox proportional hazards model.

17.4 Analysis of Secondary Endpoints

17.4.1 Efficacy (secondary)

Overall survival, disease-specific survival and time to loco-regional failure will all be estimated using the Kaplan-Meier method with the log-rank test used to compare the two arms of the trial. A Cox proportional hazards model will be used to estimate the hazard ratio for each outcome.

Disease-specific survival is defined as the time from randomisation until death from rectal cancer. Patients dying of other causes will be censored at this point, but will not be counted as an event for this outcome.

The chi-square test will be used to compare surgical morbidity, functional outcome, the CRM negative resection rates and pCR rates of the two arms in the trial.

A CRM negative resection will be defined as having a complete macroscopic resection with microscopic tumour > 1 mm from the radial. The CRM negative rate will be calculated as the total number of CRM negative patients, divided by the total number of patients randomised to the trial.

A pCR will be defined as having no residual cancer cells in the resected specimen. The pCR rate will be calculated as the number of patients with a pCR, divided by those who undergo a surgical procedure to resect the primary tumour (even if this is not successful).

The two arms of the trial will be compared for all outcomes for predefined subgroups. Patients will be split into subgroups based on their tumour regression grade (TRG) classification.

17.4.2 Safety

Toxicity rates in the two arms will be analysed using a chi-square test.

17.4.3 Economic Evaluation

No economic evaluation is planned for this trial.

17.4.4 Health Related Quality of Life and Functional Assessment

Specific questions regarding bowel urinary and sexual quality of life and function will be assessed at baseline and annually to year three using a trial CRF. These will be analysed using a chi-square test.

17.5 Interim Analysis

It has always been expected that toxicity in the irinotecan arm would be greater than in the control arm, but the degree to which the frequency and severity of AEs, especially diarrhoea, would increase was not known. An interim analysis of safety and compliance data will be performed using data from approximately 200 patients in order to understand the impact of adding irinotecan to capecitabine

CRT. The results of this analysis will be reviewed by the relevant trial committees, as appropriate and will also be disseminated to ARISTOTLE Investigators. The aim will be to reassure investigators of the safety and tolerability of the irinotecan arm, or to enable informed discussions regarding potential amendments to the trial.

The IDMC will review efficacy, safety and compliance data annually and will make recommendations to the TSC and TMG. A futility analysis will be done once 50 DFS events have been reported for review by the IDMC.

18. Ethical and Regulatory Approvals

In conducting the trial, the Sponsor, UCL CTC and sites shall comply with all laws and statutes, as amended from time to time, applicable to the performance of clinical trials including, but not limited to:

- Principles of ICH Harmonised Tripartite Guideline for Good Clinical Practice as set out in Schedule 1 (Conditions and Principles of Good Clinical Practice and for the Protection of Clinical Trial Subjects) of the Medicines for Human Use (Clinical Trials) Regulations 2004 and the GCP Directive 2005/28/EC, as set out in SI 2006/1928
- Human Rights Act 1998
- Data Protection Act 1998
- Freedom of Information Act 2000
- Human Tissue Act 2004
- Medicines Act 1968
- Medicines for Human Use (Clinical Trials) UK Regulations SI 2004/1031, and subsequent amendments
- Good Manufacturing Practice
- Research Governance Framework for Health and Social Care, issued by the UK Department of Health (Second Edition 2005) or the Scottish Health Department Research Governance Framework for Health and Community Care (Second Edition 2006)

18.1 Ethical Approval

The trial will be conducted in accordance with the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Subjects' (1996 version) and in accordance with the terms and conditions of the ethical approval given to the trial.

The trial has received a favourable opinion from NRES Committee London - Riverside.

UCL CTC will submit Annual Progress Reports to the REC, which will commence one year from the date of ethical approval for the trial.

18.2 Regulatory Approval

A Clinical Trial Authorisation (CTA) has been granted for the trial.

The trial will be conducted at approved trial sites in accordance with the trial protocol and the terms of the CTA granted by the MHRA.

18.3 Site Approvals

Evidence of approval from the Trust R&D for a site must be provided to UCL CTC prior to site activation. Sites will only be activated when all necessary local approvals for the trial have been obtained.

18.4 Protocol Amendments

UCL CTC will be responsible for gaining ethical and regulatory approvals, as appropriate, for amendments made to the protocol and other trial-related documents. Once approved, UCL CTC will ensure that all amended documents are distributed to sites as appropriate.

Site staff will be responsible for acknowledging receipt of documents and for implementing all amendments.

18.5 Patient Confidentiality & Data Protection

Patient identifiable data, including initials, date of birth and NHS number will be required for the randomisation process and will be provided to UCL CTC. UCL CTC will preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified. Data will be stored in a secure manner and UCL CTC trials are registered in accordance with the Data Protection Act 1998 with the Data Protection Officer at UCL.

19. Sponsorship and Indemnity

19.1 Sponsor Details:

Sponsor Name: University College London

Address: Joint Research Office
Gower Street
London
WC1E 6BT

Sponsor Contact: Director of Research Support
Tel: 020 3447 9995/2178 (unit admin)
Fax: 020 3447 9937

19.2 Indemnity

University College London holds insurance to cover participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or not. This does not affect the participant's right to seek compensation via the non-negligence route.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London, upon request.

20. Funding

Cancer Research UK is supporting the central coordination of the trial through UCL CTC.

21. Publication Policy

All publications and presentations relating to the trial will be authorised by the TMG. Publication of the trial results will include named members of the TMG, meeting the three criteria of i) scholarship (contribution to the design execution and/or analysis and interpretation of the data, ii) authorship (participation in the drafting, reviewing and revising of the manuscript and iii) approval (approve the manuscript to be published). It is anticipated that this will include the Chief Investigator, Trial Coordinator, and Statistician involved in the trial. The TMG will form the basis of the writing committee and advise on the nature of publications. Data from all sites will be analysed together and published as soon as possible. Participating centres may not publish trial results prior to the first publication by the TMG or without prior written consent from the TMG. The trial data is owned by the TMG. If individual centres demonstrate high recruitment rates, the principal investigator may be invited to become a member of the TMG. The ISRCTN number (ISRCTN09351447) allocated to this trial will be quoted in any publications resulting from this trial.

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Appendix 1: Abbreviations

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|------------------|--|
| 5FU | 5 Fluorouracil |
| ADL | Activities of Daily Living |
| AE | Adverse Event |
| ALT | Alanine transaminase |
| APE | Abdominoperineal Excision |
| AR | Adverse Reaction |
| ARSAC | Administration of Radioactive Substances Advisory Committee |
| ASR | Annual Safety Report |
| AST | Aspartate aminotransferase |
| BSA | Body Surface Area |
| CEA | Carcinoembryonic Antigen |
| CI | Chief Investigator |
| CLRN | Comprehensive Local Research Network |
| CRF | Case Report Form |
| CRM | Circumferential Resection Margin |
| CRM-ve | Clear CRM |
| CRT | Chemoradiotherapy |
| CT | Computerised Tomography |
| CTA | Clinical Trial Authorisation |
| CTAAC | Clinical Trials Advisory & Awards Committee |
| CTCAE | see NCI CTCAE |
| ctDNA | Circulating tumour DNA |
| CTSA | Clinical Trial Site Agreement |
| CTV | Clinical Target Volume |
| CTVF | Final CTV |
| DFS | Disease Free Survival |
| DPA | Data Protection Act |
| DFS | Disease Free Survival |
| DSUR | Development Safety Update Report |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| EudraCT | European Clinical Trials Database |
| FBC | Full Blood Count |
| GCSF | Granulocyte Colony Stimulating Factor |
| GFR | Glomerular Filtration Rate |
| GTV | Gross Tumour Volume |
| HR | Hazard Ratio |
| ICH GCP | International Conference of Harmonisation-Good Clinical Practice |
| IDMC | Independent Data Monitoring Committee |
| IMP | Investigational Medicinal Product |
| ISF | Investigator Site File |
| ISRCTN | International Standard Randomised Controlled Trial Number |
| IV | Intravenous |
| LFT | Liver Function Tests |
| LLN | Lower Limit of Normal |
| LV | Leucovorin |
| MDT | Multidisciplinary Team |
| MRC | Medical Research Council |
| MRI | Magnetic Resonance Image |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| NCI CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |

| | |
|----------------|---|
| NCRI | National Cancer Research Institute |
| NCRN | National Cancer Research Network |
| pCR | Histopathological Complete Response |
| PI | Principal Investigator |
| PIS | Patient Information Sheet |
| PTV | Planning Target Volume |
| QoL | Quality of Life |
| RSI | Reference Safety Information |
| SAE | Serious Adverse Event |
| SAR | Serious Adverse Reaction |
| SPC | Summary of Product Characteristics |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TMG | Trial Management Group |
| TSC | Trial Steering Committee |
| UCL | University College London |
| UCL CTC | CR UK and UCL Cancer Trials Centre |
| U&E | Urea and Electrolytes |
| UFT | Tegafur-Uracil |
| ULN | Upper Limit of Normal |

Appendix 2: ECOG Performance Status Scale

| Status | Description |
|--------|---|
| 0 | Fully active, able to carry out 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 self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours |
| 3 | Capable of only limited self-care, confined to bed or chair more than 50% of waking hours |
| 4 | Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair |
| 5 | Dead |

Appendix 3: Cockcroft-Gault Formula

The estimated GFR is given by:

Males:
$$\frac{1.25 \times (140 - \text{age}) \times \text{weight (kg)}}{\text{Serum creatinine } (\mu\text{mol/L})}$$

Females:
$$\frac{1.05 \times (140 - \text{age}) \times \text{weight (kg)}}{\text{Serum creatinine } (\mu\text{mol/L})}$$

Appendix 4: Capecitabine Dose Reductions

| ARM A – 75% DOSE | | | |
|--|-----------------------|--|--------|
| Capecitabine dose = 675 mg/m ² bd | | Number of tablets to be taken at each dose (morning and evening) Mon – Fri | |
| BSA (m ²) | Twice daily dose (mg) | 150 mg | 500 mg |
| ≤ 1.46 | 900 | 6 | - |
| 1.47 – 1.66 | 1000 | - | 2 |
| 1.67 – 1.89 | 1150 | 1 | 2 |
| 1.90 – 2.12 | 1300 | 2 | 2 |
| ≥ 2.13 | 1500 | 0 | 3 |

| ARM B – 75% DOSE | | | |
|--|-----------------------|--|--------|
| Capecitabine dose = 500 mg/m ² bd | | Number of tablets to be taken at each dose (morning and evening) Mon – Fri | |
| BSA (m ²) | Twice daily dose (mg) | 150 mg | 500 mg |
| ≤ 1.46 | 650 | 1 | 1 |
| 1.47 – 1.66 | 750 | 5 | - |
| 1.67 – 1.89 | 900 | 6 | - |
| 1.90 – 2.12 | 1000 | - | 2 |
| ≥ 2.13 | 1150 | 1 | 2 |

Appendix 5: Radiotherapy Treatment Planning and Quality Assurance Protocol

We wish to acknowledge the contribution of the following people who assisted in the development of the following guidance: Dr Rob Hughes, Dr Vinod Mullassery, Dr Suzie Mawdsley, Liz Miles (Mount Vernon); Dr Rob Glynn-Jones and Dr Mark Harrison (Mount Vernon and Aristotle TMG members); Prof David Sebag-Montefiore, Dr Simon Gollins, Dr Sun Myint, Dr Richard Adams, Dr Robert Harte, Dr Les Samuel (Aristotle TMG members); Dr John Staffurth, Lisette Nixon, Rhydian Maggs (Cardiff). Professor David Sebag-Montefiore created the CT scan and diagram examples.

Introduction

This document describes the process for radiotherapy treatment planning of rectal cancer and has been developed for the purpose of the ARISTOTLE trial. The aim is to facilitate the delivery of a protocol-defined radiotherapy technique and to allow quality assurance (QA) procedures to be applied to demonstrate that this is achieved.

There is considerable debate about target volume definition in rectal cancer. Reasons for this include the limited number of studies of patterns of failure, the lack of QA in the delivery of radiation therapy and a paucity of data from surgical lymphadenectomy series. An additional factor is widespread differences in views amongst radiation oncologists regarding their preferred volume of elective nodal irradiation. To our knowledge, a direct comparison of differing target volumes within the context of clinical trials has never been performed.

The ARISTOTLE TMG has spent considerable time discussing this issue and here define the radiotherapy target volume definition guidelines for use in this study. We have considered the target volume definition guidelines used in our own phase II studies (25-28, 52), the recommendations of a Belgian group (53) and the recent RTOG contouring guidelines (54). Important recent publications include data from the Dutch TME trial (55), a Swedish group (56), a review of lateral pelvic lymph node dissection (57) and studies from the Netherlands in alteration in target volume shape (58, 59).

It is important to recognise that the TMG consider that the target volumes used in our large phase II studies are associated with good outcomes when used in studies of novel chemoradiation. We are also concerned that the routine application of the same volume that extends superiorly to the sacral promontory and the routine elective irradiation of external iliac nodal structures is likely to be associated with an increased risk of late toxicity with fluoropyrimidine chemoradiation and an even greater risk with doublet CRT. It is somewhat surprising that there is relatively limited published late toxicity or quality of life data from the two phase III trials that demonstrated the superiority of pre-operative fluoropyrimidine CRT over radiotherapy alone (60).

As ARISTOTLE is testing the intensification of pre-operative CRT by the addition of a second drug, the TMG have elected to use the tailored delineation of the clinical target volume (CTV) according to tumour position that was used in the preceding large phase II trials.

It is recognised that during the conduct of ARISTOTLE, it may be necessary to modify the defined protocol either because of the publication of convincing new data regarding target volume definition or consensus views derived from the radiotherapy planning workshops (see below). A formal protocol amendment will be made should the TMG decide that a significant change in the described protocol is required.

Radiotherapy Treatment Planning

CT planning and delineation of defined target volumes on individual planning CT scans is mandatory. This approach is superior to the determination of the CTV according to bony landmarks approach (Corner et al).

Patient set-up:

It is recommended that appropriate immobilisation is used and that a scan/treatment position is used which the centre is familiar with. It is recognised that the supine position may be used by some centres and for some patients particularly after creation of a defunctioning stoma. A belly board may be used but it is not a requirement.

A radio-opaque marker must be placed at the anal verge prior to the CT planning scan.

Patient data acquisition

The scan limits are the superior aspect of L5 superiorly to 4 cm below a radio-opaque marker indicating the anal verge or the inferior extent of tumour, whichever is more inferior. The recommended slice thickness is 3 mm (a maximum of 5 mm is acceptable).

Use of contrast

Intravenous (iv) – the use of iv contrast is strongly recommended and encouraged but not mandated. The major advantage of using intravenous contrast is the ability to identify the internal iliac arteries in the planning scan in the superior aspect of the pelvis (and to distinguish them from nodal structures) and assist in the delineation of the anterior CTV. The alternative approach of using the diagnostic imaging to identify the arteries and then identify them on a non-contrast planning scan is more time consuming and less accurate.

An outline template for iv contrast is described at the end of this document to assist departments who currently do not have such a protocol. All participating centres are encouraged to develop their own local protocol in keeping with Royal College of Radiologists (RCR) guidelines

Where contrast-enhanced CT planning scans are to be used, for the dose calculation there may be an effect on the monitor unit calculation which will not be representative of the treatment situation. The magnitude of this effect will vary between individual patients, scanning protocols and centres. There are two acceptable approaches to accounting for this if required:

1. Use of both contrasted-enhanced and non-contrast CT scans. The contrast-enhanced scan is used for target volume definition and fused with the non-contrast scan which is used for dose calculation.
2. Use of single contrast-enhanced scan and assignation of unit density to heavily contrasted areas.

Definition of Treatment Volumes

The target volume definition process requires the delineation of gross, clinical and planning target volumes. A colour scheme is useful to define the different volumes. An optional colour scheme is provided below.

These are defined as follows. It is recommended that this nomenclature is adhered to in order to aid Plan Assessment Form completion and dose reporting:

Gross tumour volume (GTV) (Contour = red) - all gross sites of disease (primary, nodal and extramural vascular invasion). This information is derived from the diagnostic imaging (pelvic MRI and supplemented by pelvic CT if also available). The determination of macroscopic disease is based on a combination of clinical and radiological information.

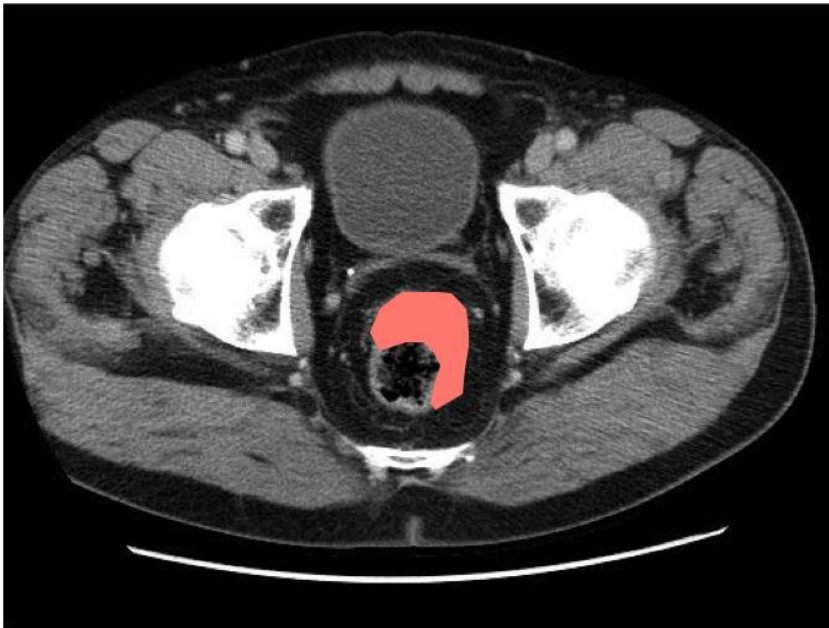
Clinical target volume (CTV) will encompass areas of microscopic spread beyond the defined GTV. The system used describes two distinct volumes - CTVA and CTVB which are then combined to form the Final CTV (CTVF).

- **CTVA** (contour = light blue) includes GTV + 1 cm. This defines the surrounding safety margin of potential subclinical involvement (superior, inferior, lateral, anterior and posterior).
- **CTVB** (contour = dark/royal blue) includes the mesorectum and the loco-regional nodes considered at risk of involvement
 - This include the nodes within the mesorectum, presacral space and the internal iliac nodes
 - In patients with invasion of the levator muscle or sphincter complex a 1 cm lateral and posterior margin is applied to the CTVA (see later diagrams)
 - Uninvolved external iliac nodes are not included in CTVB
- **Final CTV (CTVF)** (contour = purple) is produce by combining CTVA and CTVB. Discuss with treatment planning the best way of combining these two volumes.

Planning Target Volume (PTV) (contour = green) is defined as CTVF+ 1 cm (superiorly, inferiorly, anteriorly, posteriorly and laterally). This volume ensures coverage of the CTV taking into account the systematic and random set-up errors, changes over time in the patient geometry and internal organ movement that may occur when delivering a radical course of radiation. The most important factor is inter-fraction organ motion. (ICRU Report 50, ICR 1993 (61)).

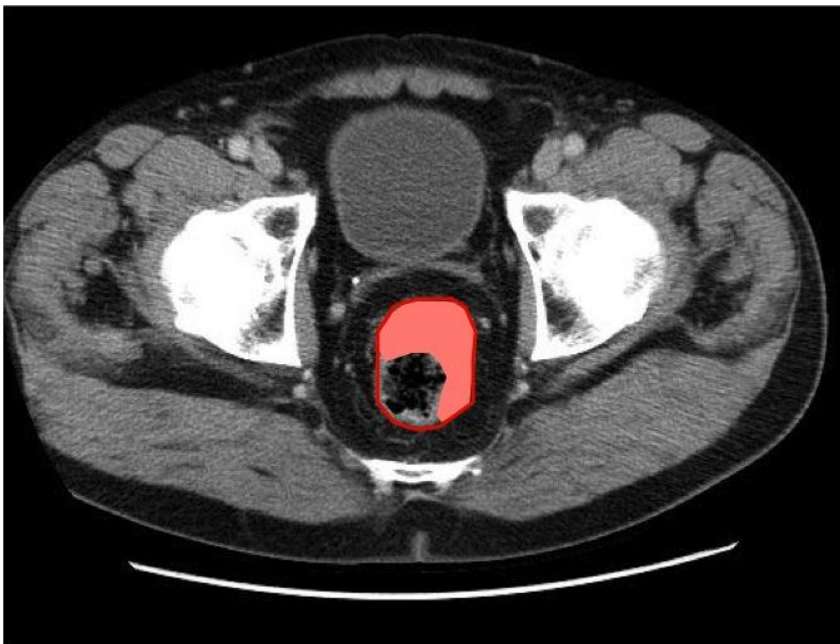
Further detail is now provided to assist as the guide of the creation of the various volumes:

GTV delineation (contour = red) – all macroscopic disease should be outlined (includes the primary tumour, involved macroscopic disease separate from the primary tumour including extramural vascular invasion. It is recognised that the interface between gross tumour and the normal rectum may be difficult to define and that the rectal lumen may change in shape and size. It is recommended that on each slice all normal rectal wall between areas of macroscopic disease should be included as part of the GTV (see below).



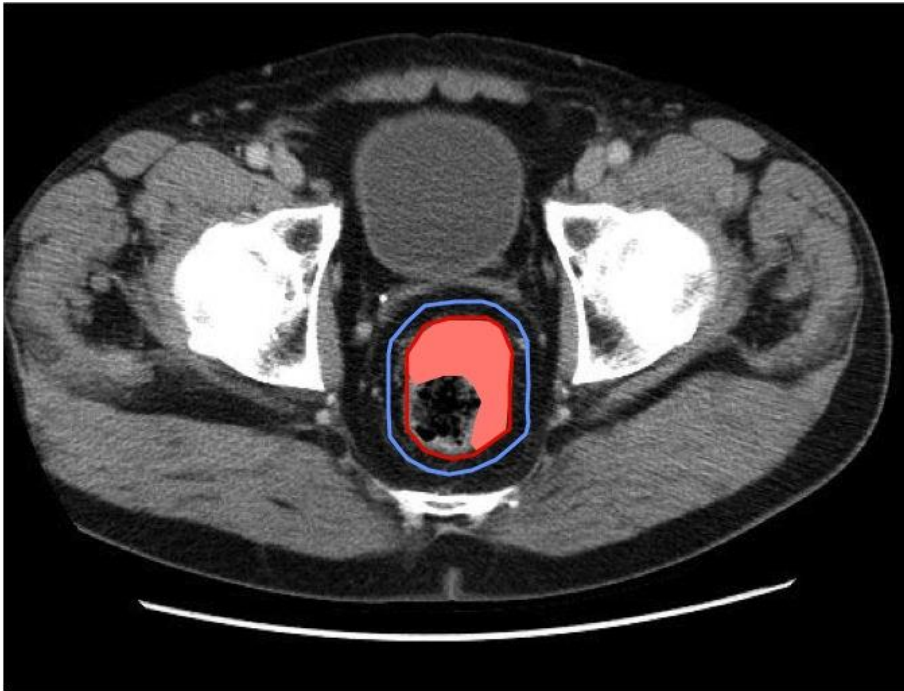
The obvious macroscopic tumour is shown in highlighted in pink – however the remainder of the rectal wall is thickened in places and internal size of the bowel lumen may change.

Recommended delineation of the GTV:



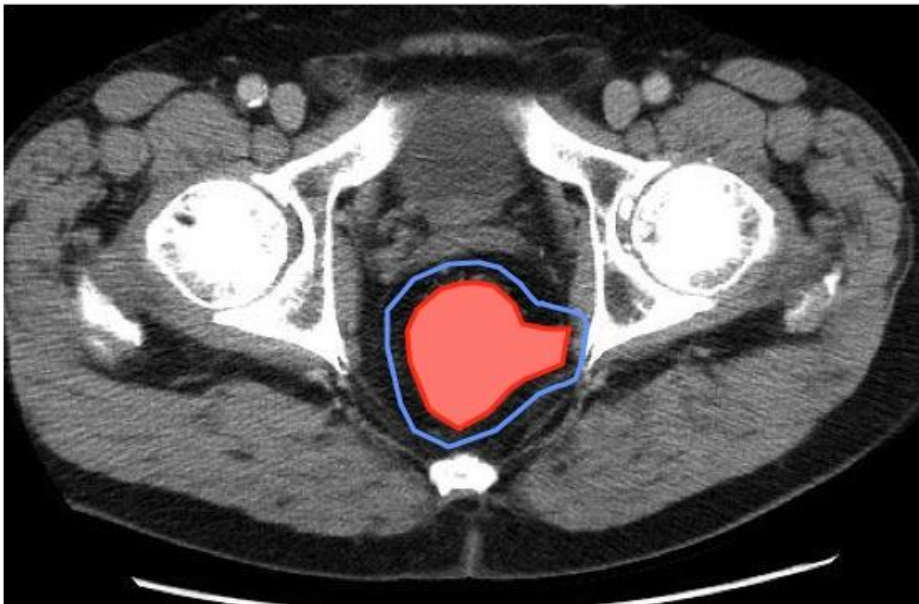
The outlined GTV is shown in red – this encompasses all macroscopic extent of tumour and also the uninvolved rectal wall.

CTV A (contour = light blue) is derived by applying a 1 cm margin to the GTV in all directions (anterior, posterior, superior, inferior and lateral). This is shown schematically below:

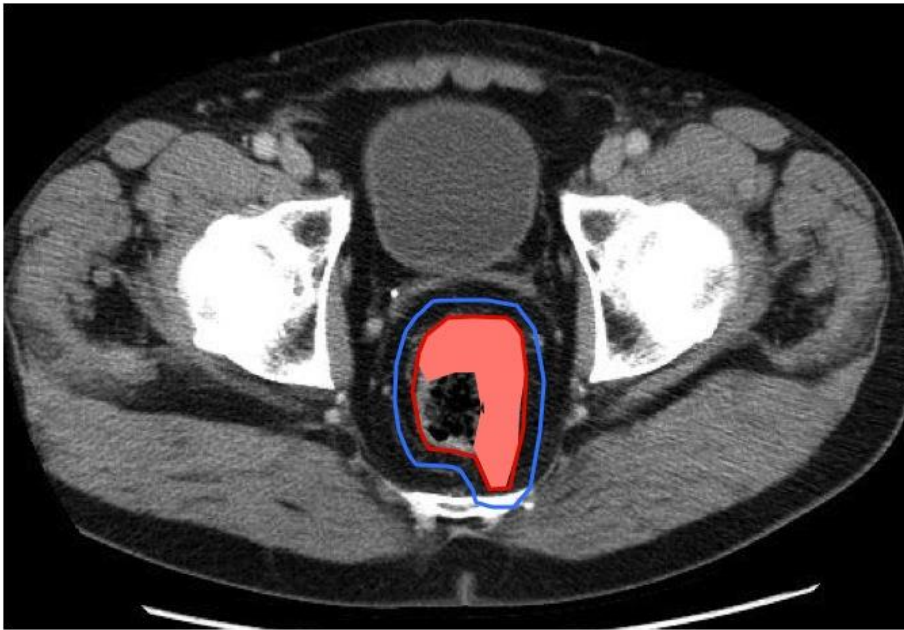


The GTV is shown in red and the CTVA is shown in light blue.

If the CTVA extends beyond the limit of a lateral bony structure (pelvic side wall), the CTVA can be modified (trimmed) so that the CTVA lies on the soft tissue/bony interface. In the example below the lateral CTVA is at this interface.

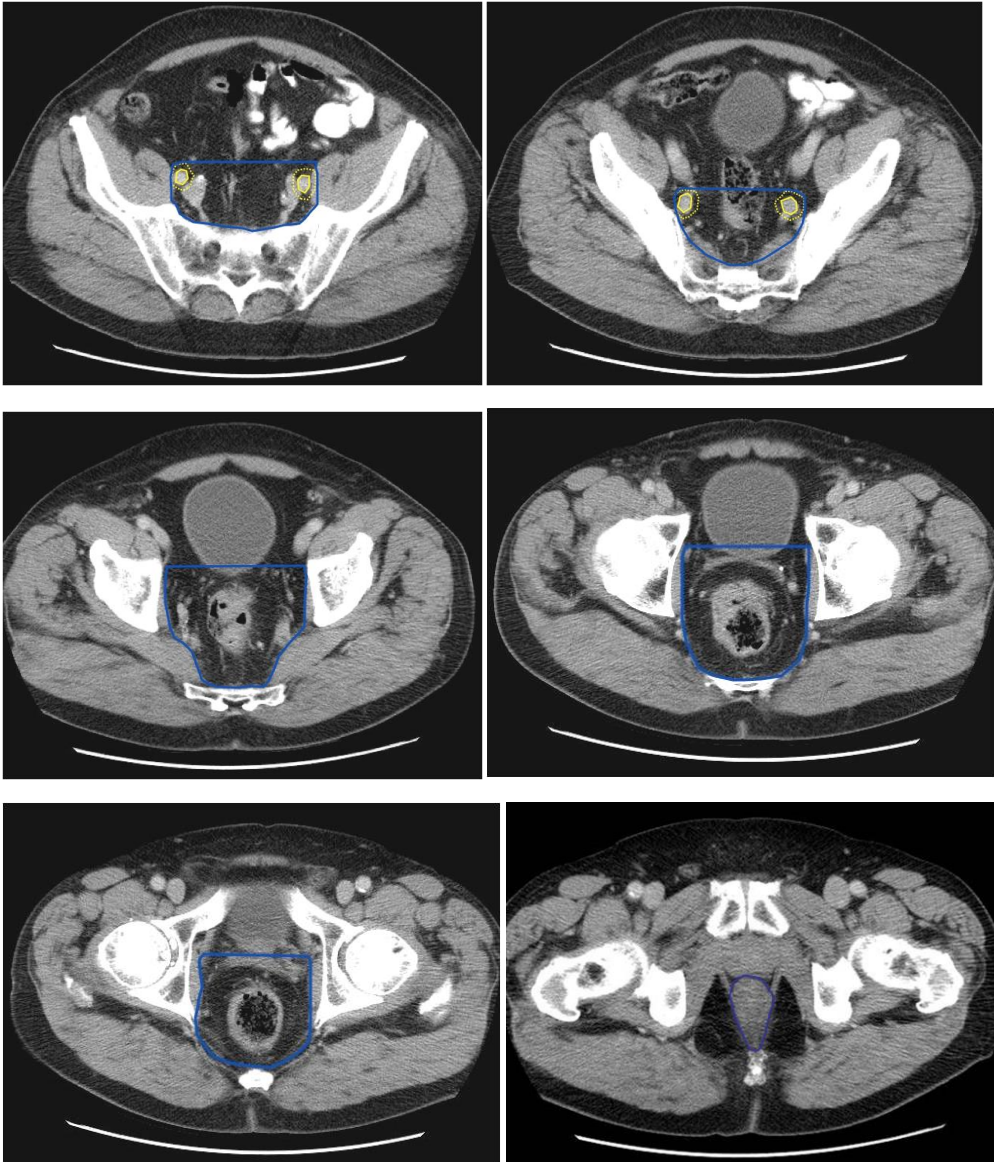


Clinicians should avoid such an approach of “trimming” where the CTVA extends posteriorly into the sacrum or coccyx.



Here the CTVA extends into the sacrum and should NOT be trimmed.

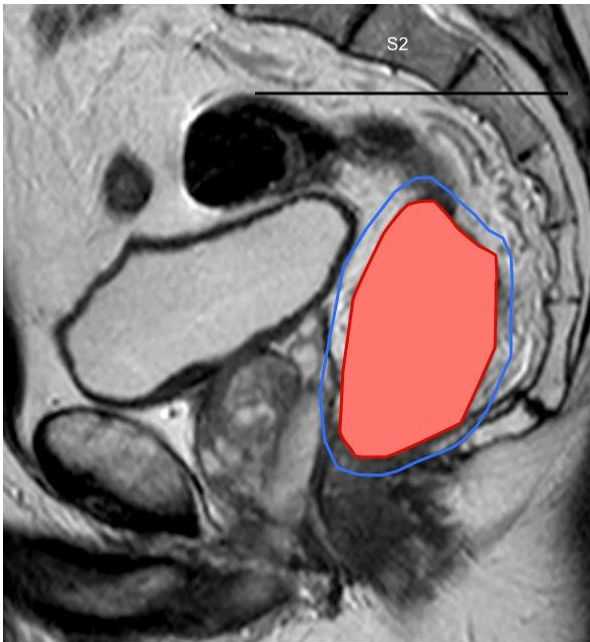
CTV B (contour = **dark/royal blue contour**) – includes the mesorectum, presacral and internal iliac nodes. The external iliac nodes are NOT electively included when there is no evidence of external iliac lymph node enlargement. An example of CTVB contouring is shown below:



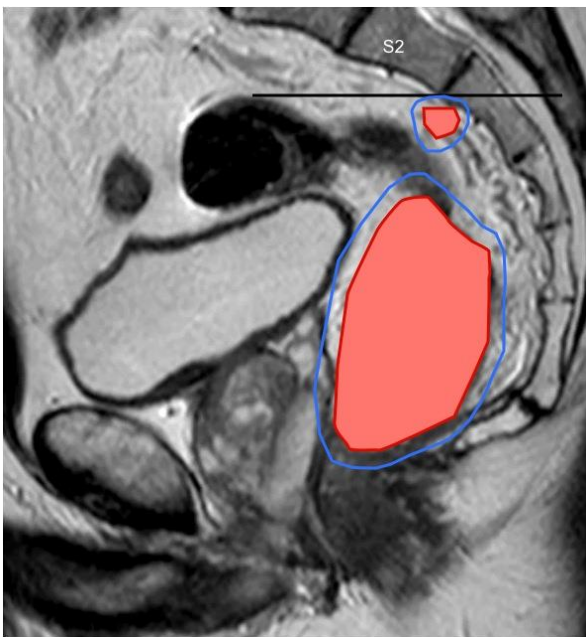
In this example the internal iliac arteries are outlined by a yellow contour and the 7 mm margin by a dotted yellow contour. This patient has a generous mesorectum. The anterior border is 1 cm anterior to the anterior mesorectal fascia. The internal iliac arteries are shown in yellow with a 7 mm margin shown with a yellow dotted line. In the most inferior slice the contour are shown (the is used in the absence of levator/sphincter complex involvement (see below).

Examples are used below to illustrate further detail for each of the borders of the CTVB.

Superior limit is at the level of the S2/3 interspace (determined on the sagittal or scout view on the planning system) **providing** there is a 2 cm margin above the most superior limit of GTV. The CTVB superior border should be extended above the S2/3 interspace if necessary to achieve a minimum 2 cm margin above the most superior aspect of GTV.

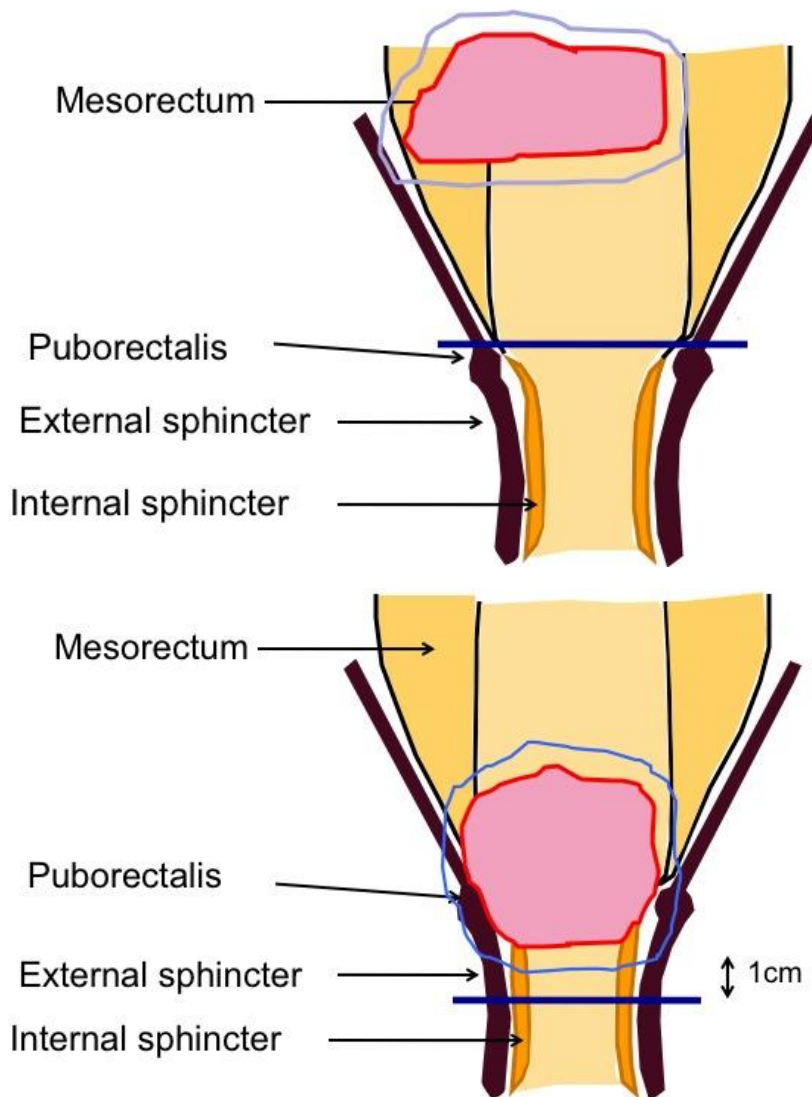


In this example the CTVB superior border will be the S2/3 junction (shown on a sagittal MRI for ease of illustration) but seen on the sagittal reconstructed view using the CT planning scan.



In this example there is an involved nodal mass in front of S3 – in this example the CTVB superior border will be 1 cm superior to the S2/3 junction (a 1 cm margin above the most superior aspect of the CTVA) ensuring a 2 cm margin above the most superior aspect of GTV.

Inferior limit - is at the superior limit of puborectalis or 1 cm inferior to CTVA **whichever is the more inferior**. The superior limit of puborectalis is best identified on the CT planning scan as the slice where the mesorectal fat is no longer seen (tapers to nothing).



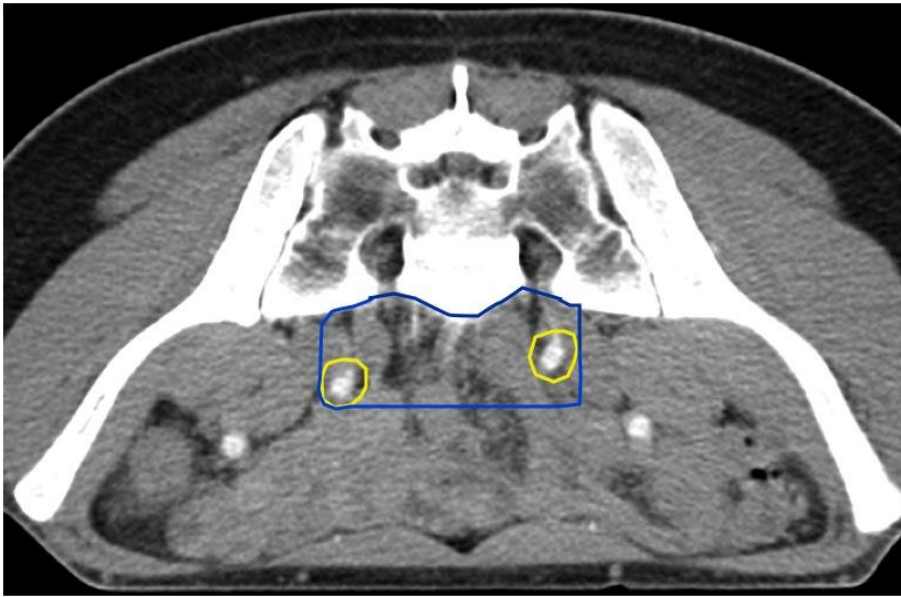
In this example the inferior border of the CTVB is at the point where the mesorectum stops inferiorly.

In this example the inferior border of the CTVB is 1 cm inferior to CTVA.

Above diagram redrawn from Shihab *et al* (62).

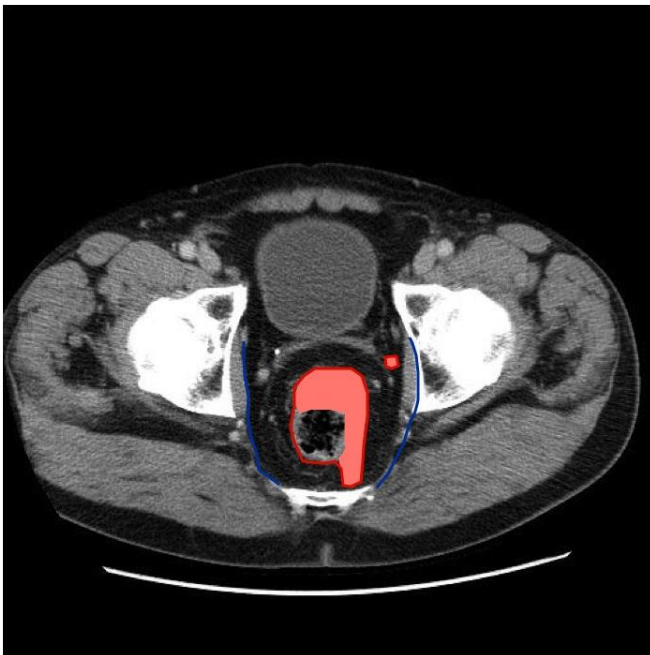
Lateral limit – is defined at different levels in the pelvis.

Upper pelvis – is determined by the 7 mm margin lateral to the internal iliac arteries.

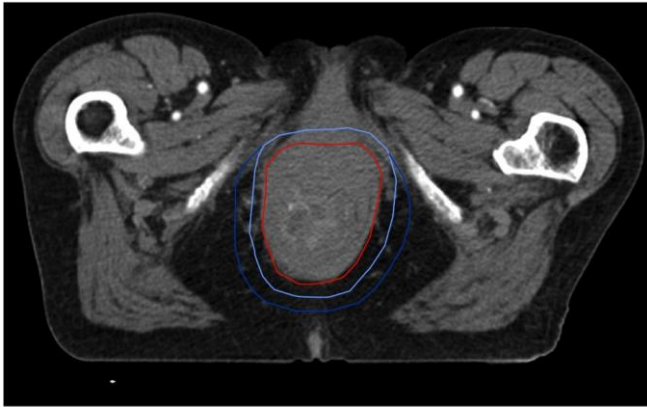


In this diagram contrast is seen in the internal iliac vessels and the yellow contour is a 7 mm margin around each vessel (the anterior and posterior borders are discussed below). The lateral contour is placed on the lateral aspect of the 7 mm margin and extends "vertically" back to the sacrum as shown above.

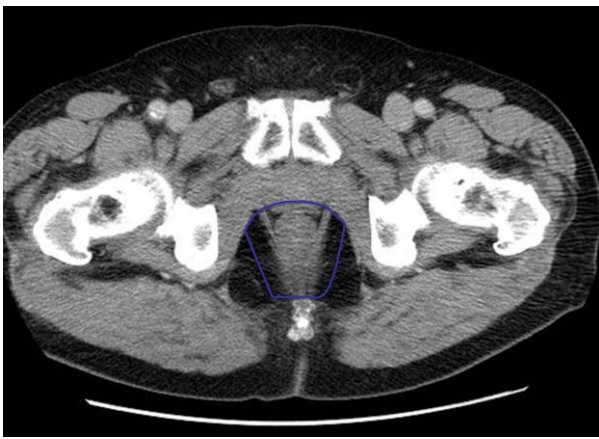
Mid pelvis - is the medial aspect of obturator internus in the **absence** of internal iliac nodal enlargement. In the **presence** of involved lateral side wall nodes, the limit is the bony pelvic side wall.



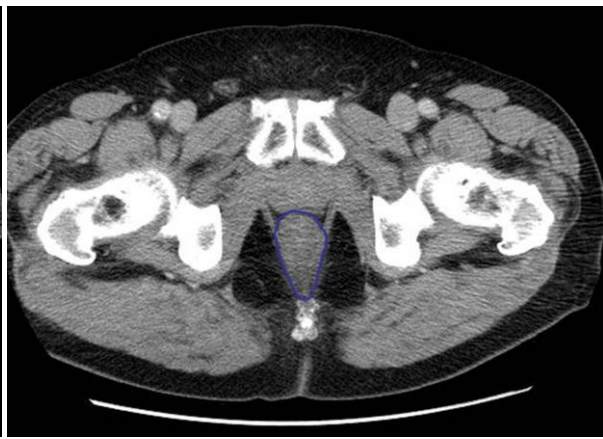
Low pelvis – is determined by the extent of the GTV. In the presence of levator or sphincter involvement the lateral border is 1 cm lateral to the CTVA (when present). In the absence of levator or sphincter involvement it is the outer border of the anorectal sphincter complex.



In this example with sphincter involvement, at the level of the tumour the CTVB is 1 cm lateral and posterior to the CTVA (not the whole of the ischiorectal fossa).



CTVB where there IS sphincter involvement below CTVA – 1 cm margin lateral to the sphincter complex.



CTVB if there is NO sphincter involvement below CTVA – contour lateral aspect of sphincter complex.

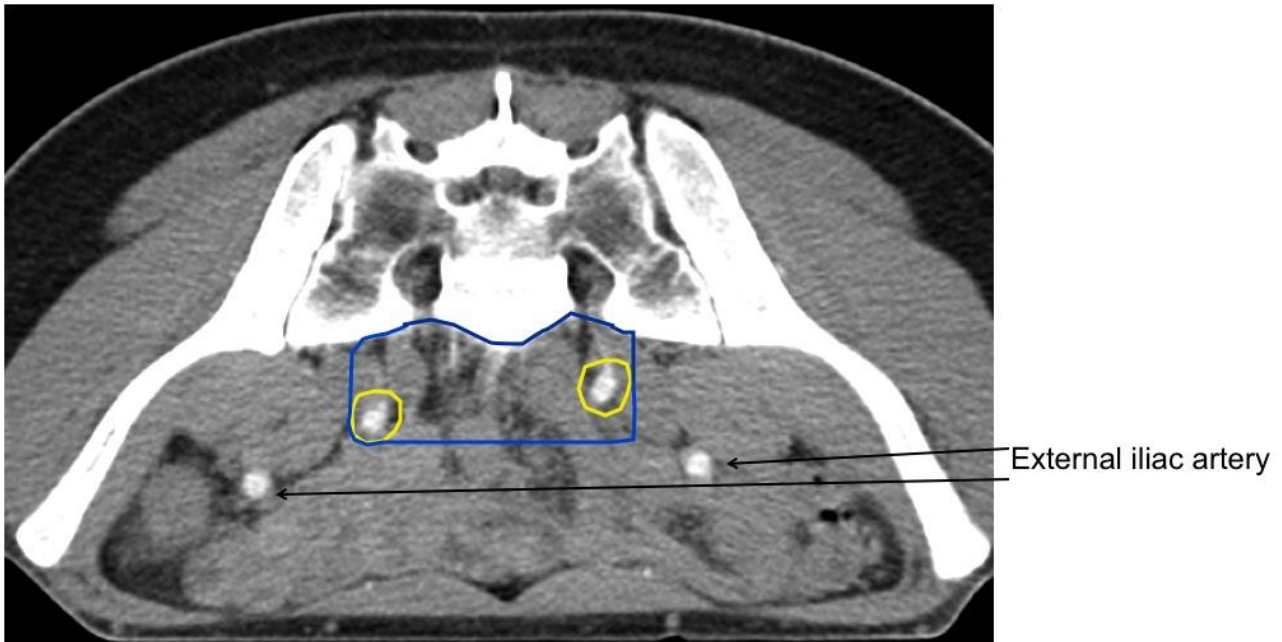


CTVB where there is NO involvement of the levator or sphincter complex.

After careful consideration the TMG decided that there was no supporting evidence to justify the inclusion of the entire ischiorectal fossa in cases of levator or sphincter complex involvement.

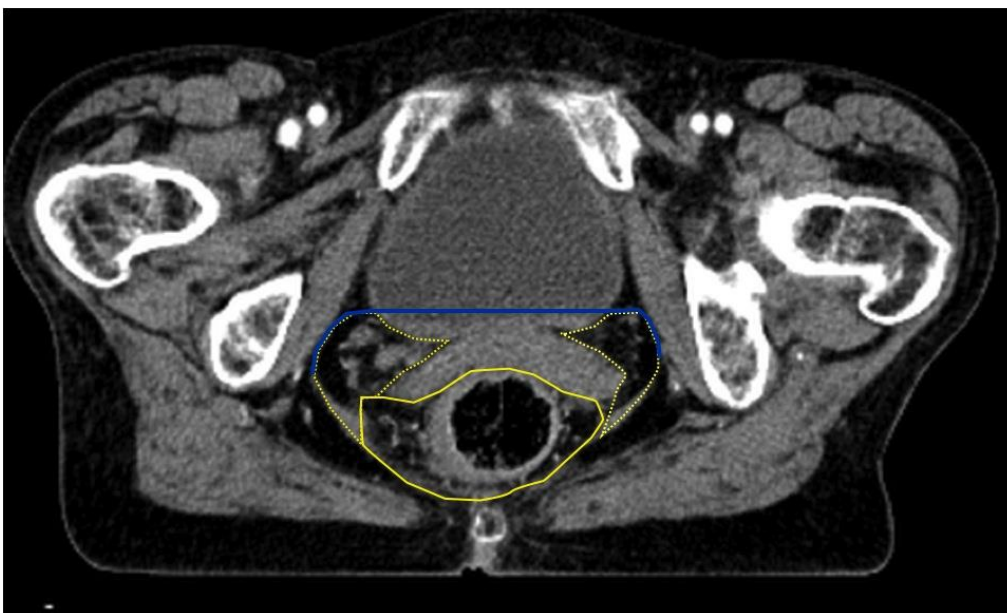
Anterior limit – is determined at different levels described below.

Upper pelvis – is determined by the position of the internal iliac arteries. The internal iliac arteries (or the most anterior branch if more than one artery is seen) should be identified. The anterior limit is 7 mm anterior to these vessels. It is common for the artery to be more anterior on one side compared with the other. The CTVB is defined by the more anterior of the two and the border is drawn parallel to the couch (see diagram below).

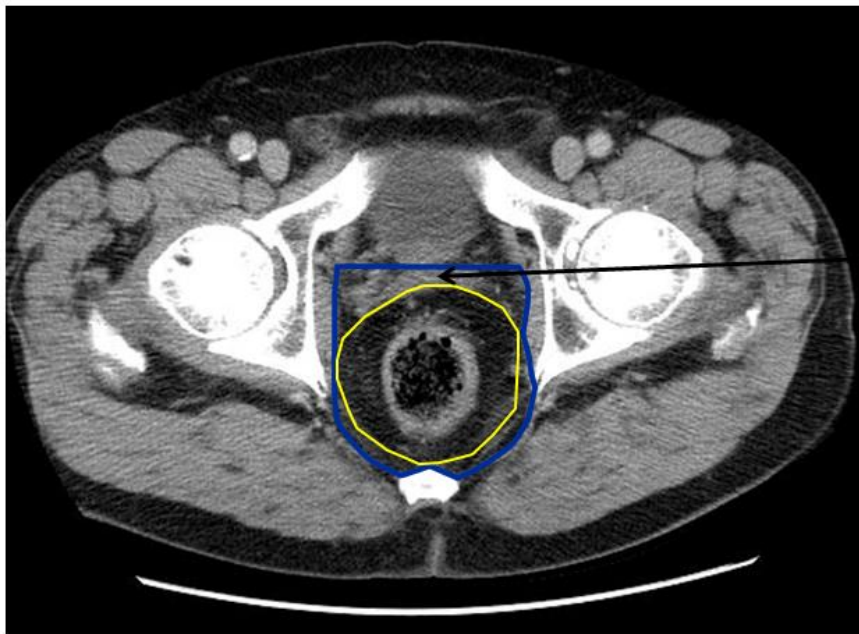


A 7 mm contour is shown around the internal iliac arteries and the contour is defined by the more anterior of the two with a contour parallel with the couch.

Mid pelvis – the anterior border is 1 cm anterior to the anterior mesorectal fascia or the anterior limit of the lateral (internal iliac) pelvic lymph node "compartment" whichever is the more anterior. (The shape and volume of the mesorectum varies considerably between patients).



In this example there is a small mesorectum and the anterior border is determined by the lateral pelvic node "compartment".



CTVB 1cm anterior to the anterior mesorectal fascia

In this case the anterior border is 1 cm anterior to the anterior mesorectal fascia.

It is recognised that the anterior border is more difficult to define between the two regions described above (i.e. moving from superior to inferior, where the internal iliac arteries are no longer seen and before the anterior mesorectal fascia is well seen). This difficult area varies in length between patients. The following may be helpful:

- define CTVB starting at the cranial end using the internal iliac arteries as far as they are visible
- define the CTVB from the mid pelvis level upwards as far as the anterior mesorectum and lateral pelvic nodal compartment are easily seen
- aim for a smooth transition between these two (viewed on the sagittal CT planning view)

This difficult area is addressed in the radiotherapy workshops.

Low pelvis

The anterior border is determined by the absence or presence of gross tumour involvement of levator or the sphincter complex.

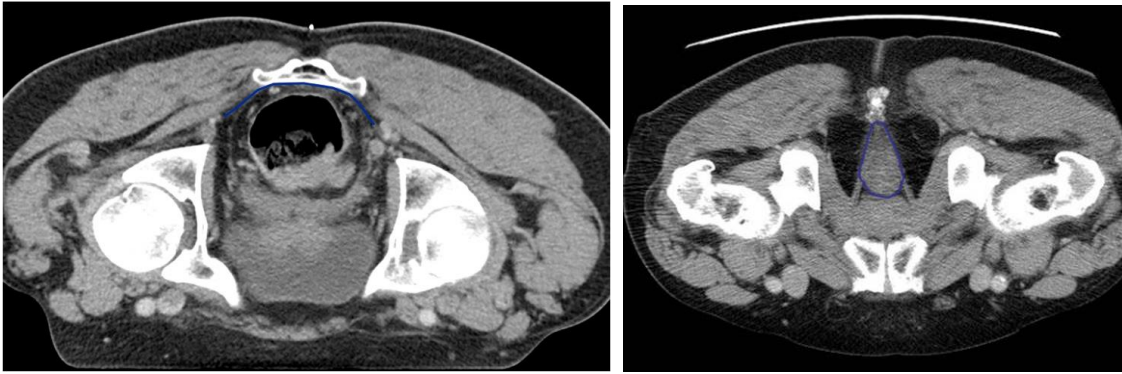


Levator or sphincter involvement absent.



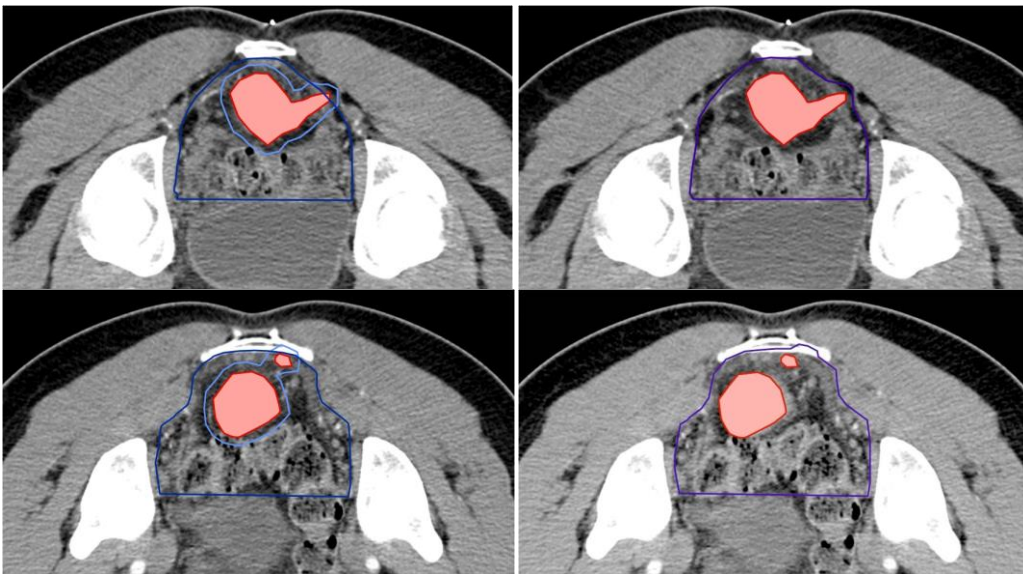
Levator or sphincter involvement present (1cm margin around the of the sphincter complex shown here in yellow).

Posterior margin - sacrum - throughout most of the pelvis the posterior border is the anterior surface of the sacrum. This also applies at the level of the coccyx.



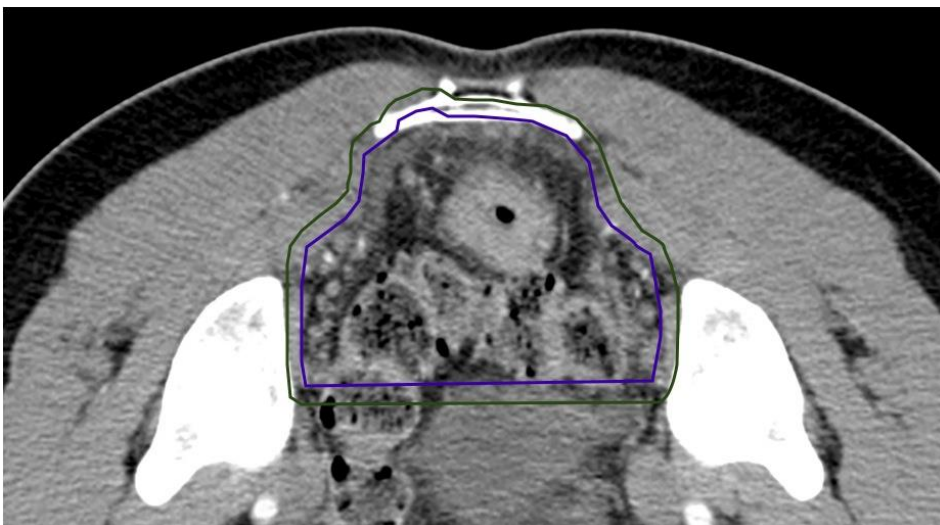
In the presence of symptoms of nerve infiltration but in the absence of macroscopic tumour the CTVB may be placed 0.5 cm posterior to the anterior border of the sacrum.

The CTVF (purple contour) – is created by combining the CTVA and CTVB.



Two scenarios are shown where the left hand panel shows the GTV CTVA and CTVB and the right hand panel the CTVF.

PTV (green contour) – this is defined as the addition of a 1 cm margin (anteriorly, posteriorly, laterally, superiorly and inferiorly) to the CTVF.



Trial Management Group assessment of CTV definition

The TMG recognise the challenge to deliver a consistent approach to delineation of the CTV in rectal cancer and the relative lack of training for clinical oncologists in normal radiological pelvic anatomy. The TMG have used this protocol to contour test cases and the results from this experience have lead to modifications to this planning Appendix.

Radiotherapy treatment planning workshops

The majority of centres participated in radiotherapy planning workshops led by members of the TMG. The workshops were held on a regional basis and facilitated an interactive environment to enhance skills in target volume definition, to allow sharing of outlining techniques and identify areas of uncertainty.

Organs at

There are unresolved difficulties posed in the planning of adjuvant radiotherapy rectal cancer when considering the production of a treatment plan and the organs at risk. When delivering 45 Gy in 25 fractions to a planned pelvic volume the priority is the achievement of homogenous coverage of the PTV usually achieved with the use of 3 or 4 fields (posterior, two wedged lateral and sometimes an anterior field). This results in limited options to alter the dose to the organs at risk.

The femoral neck, bladder and small intestine are considered organs at risk and it is recommended these are outlined.

When outlining the small bowel, the superior limit should be drawn 2 cm above the upper limit of PTV. It is not usually possible to influence the dose to the posterior bladder that is delivered. It is accepted that limiting the dose delivered to the femoral neck is an important aim but there is a lack of data to define a dose volume constraint in the context of rectal cancer planning. There is no consensus concerning dose volume constraints for the small intestine. There is no consensus regarding a possible correlation between the volume of small bowel within the PTV and the risk of late small bowel complications. This view is supported by two key papers describing target volume definition approaches (53, 54) that do not recommend any dose volume constraints but recognise the need to try and reduce dose to the femoral neck.

Historical data and case series have indicated that certain well described toxicities during and after pelvic radiotherapy are related to the dose of radiotherapy delivered to a given volume of "normal tissue" (organ at risk). However, there is no consensus regarding possible correlations between the volume of small bowel being irradiated or the dose delivered and the risk of early or late small bowel complications. This view is supported by two key papers describing target volume definition approaches (53, 54) that do not recommend any specific dose volume constraints but recognise the need to try and reduce dose to the femoral neck. Given the standardisation of radiotherapy with associated quality assurance in the ARISTOTLE trial, there is a unique opportunity to explore the relationships between organs at risk and associated toxicities. Data collected as a part of the quality assurance exercise within the trial will be used to inform a sub-study which will explore the relationships between irradiated organs at risk, acute and late toxicities. Specifically we will define the volume of small bowel or peritoneal cavity receiving radiotherapy in a large number of patients and assess if specific thresholds identify patients at high risk of treatment interruptions, diarrhoea, fatigue, nausea, abdominal pain, post-operative complications such as ileus or late adhesions. We will analyse data both in terms of lower dose radiotherapy to a larger volume as well as higher dose

radiotherapy to smaller volumes. This data will be explored during the trial to inform adaptations to assist in the safe delivery of therapy. Similarly we will aim to identify whether different thresholds exist for patients in the two arms of the trial.

Dose and dose volume guidelines

All doses are prescribed as target absorbed doses according to International Commission on Radiation Units (ICRU) guidelines. A total dose of 45 Gy in 25 daily fractions over a total time of 5 weeks should be delivered treating 5 days per week, 1 fraction per day, using 1.8 Gy per fraction. All fields must be treated during one treatment session. It is conventional to report the dose to the ICRU reference point, the maximum dose to the PTV and the minimum dose to the PTV. The isocentric treatment plan is usually specified to receive 100% with the 95% isodose line encompassing the PTV and no more than +7% and -5% inhomogeneity within the target volume.

It is also advised to examine the dose distribution in both coronal and sagittal views to ensure the optimal anatomical arrangement of isodoses around the target volume.

The following dose volume requirements are provided for the PTV and external patient outline.

| ROI objective | Defined as |
|------------------------------|---|
| PTV min | D99% \geq 95% (42.75 Gy) |
| PTV max | D5% < 105% (47.25 Gy) D2% < 110% (49.5 Gy) |
| Patient Outline absolute max | D1.8cc < 110% (49.5 Gy) Lateral patient dose distant from PTV < 80% to 85% |

Treatment Planning

Dose calculation should be performed on a 3D scan using either Type A or Type B algorithm and pixel-based inhomogeneity correction is considered standard practice and is a mandatory requirement. A minimum dose calculation matrix of 5 mm is mandated.

In instances where the PTV, due to margin creation, extends up to or beyond the patient external outline it is recommended that the original, unaltered PTV is used for planning but that a further modified PTV (labelled appropriately as 'PTV_mod') may be generated which avoids encroaching outside but approaches the external patient outline to within at least 5 mm and includes CTVF, and is used for dose reporting purposes only – i.e. shielding is defined in beams-eye-view based on original PTV but min dose might be low as < 99% of PTV lies within patient volume, so in this instance minimum dose may be considered to 'PTV_mod' which has been modified to no more than 5 mm within the patient external outline.

Radiation therapy should be delivered with photon energies \geq 6 MV using a linear accelerator. Equipment of 10 MV or higher is recommended, as is the use of 3D conformal radiotherapy. Typically a three field arrangement will be used, though it is recognised that an additional anterior field may be required in exceptional circumstances where the lateral patient dose distant from the target volumes exceeds 80 – 85% of the reference dose. Mixed energy beams are allowed with higher photon energy for the lateral beams compared to the posterior beam (which may be of lower energy to improve superficial coverage where the target approaches the patient surface). The use of multileaf collimators is strongly recommended.

IMRT/VMAT are acceptable alternatives within the ARISTOTLE trial, although the reproducibility of treatment delivery is an important consideration. In the instance where a significantly different

approach to treatment from that used for the pre-trial test case is to be used, the centre must discuss this with the UCL CTC and RTTQA team by contacting the ARISTOTLE trial coordinator (see section 10.1; Radiotherapy QA, for details). If new or existing sites wish to use IMRT/VMAT, they will be required to (re)submit the pre-trial planning case and an updated process document for QA, and must have successfully undertaken relevant dosimetry audit to allow for credentialing. In addition the first trial case should be submitted for real-time QA of plan and dose distribution. The outlining protocol should be adhered to. Any adaptation for small bowel outside of protocol will also require real-time review by the RTTQA team.

Verification and correction procedures

The rectum does move during a course of radiotherapy (63, 64). Recent data suggests that this is most marked in the upper rectum in patients with resectable disease (58). However the patient group included in the ARISTOTLE trial will mainly consist of low and mid rectal cancer. In addition the locally advanced nature of these tumours threaten or involve the mesorectal fascia with a high proportion having lateral extramural tumour extension suggesting that less rectal movement may occur. Also if a defunctioning stoma is performed, there will be less distortion of the rectal lumen by gas and faecal material. At present there is insufficient evidence to guide modification of the treatment planning margins to account for this.

On treatment verification

It is recommended that the best available positional verification methods should be used to ensure correct delivery – which may include electronic portal imaging compared to treatment planning DRRs, or cone beam CT imaging matched to planning CT scan.

Consideration should be given to imaging the initial three fractions so that a correction for systematic error can be applied and then continue with weekly imaging. Electronic portal imaging (EPI) can monitor set-up displacement on a daily basis in the phase of treatment (65). Isocentre should be moved if disagreement is seen in excess of agreed tolerance levels preferably based on local study – usually 5 mm. This process also allows radiographers to evaluate the whole set-up and thus to assess and correct systematic errors. These images should be audited on a weekly basis. Using EPI the MLC configuration can also be verified for consistency and reproducibility.

Intravenous contrast template

This policy should be in broad agreement with RCR Recommendations.

Where contrast-enhanced CT planning scans are to be used for the dose calculation there may be an effect on the monitor unit calculation, which will not be representative of the treatment situation. The magnitude of this effect will vary between individual patients, scanning protocols and centres. There are three acceptable solutions:

- use of single contrast-enhanced scan only. If the centre is satisfied that there are no dosimetric implications of using contrast.
- use of single contrast-enhanced scan and assignation of unit density to heavily contrasted areas.
- use of both contrasted-enhanced and non-contrast CT scans. The contrast-enhanced scan is used for target volume definition and fused with the non-contrast scan which is used for dose calculation.

It is anticipated that the first or second option will be used in most if not all centres.

Additional issues to consider with the use of iv contrast enhanced radiotherapy planning scans.

Safety

- It is strongly recommended that each centre develop its own working instructions for the delivery of iv contrast for radiotherapy planning scans.
- It is also recommended that the RCR document 'Standards for Iodinated Intravascular Contrast Agent Administration to Adult Patients' is read and followed.
- The following should be considered:

Patient identification

- Ensure the correct patient is scanned following the correct protocol.
- Ensure Consent Form is completed.

Awareness of features associated with increased risk of reaction

- History of allergy or asthma.
- Ask if patient has had previous contrast-enhanced imaging

Awareness of medical support

A member of the radiotherapy team should be contactable through-out the duration of the scan and the emergency drugs trolley should be brought round to the scanner or be easily accessible.

Effects of intravenous contrast in renal insufficiency

- Ensure recent creatinine is available and that patient is not clinically dehydrated. Risks are increased in elderly patients, patients with cardiac failure, and diabetics (especially if taking oral metformin).
- The trial protocol require patients to have a calculated creatinine clearance ≥ 50 mL/min – iv contrast should not be administered to patients whose serum creatinine is greater than 150 μ mol/L if there is doubt concerning the patients suitability for iv contrast it should not be administered as this is not a protocol requirement.

Practical issues

- Insert cannula
- Position patient in radiotherapy position
- Select correct imaging protocol; consider requirement for pre and post- contrast image acquisition
- Optimise image quality with iv contrast: These are recommendations based on experience from three centres, who have kindly allowed us to review their clinical protocols: Mount Vernon Hospital, Royal Marsden NHS Trust, and Velindre NHS Trust. Centres need to be aware that these recommendations are from clinical experience with their own hardware and software, and that some degree of local development may be required.
 - Type: Omnipaque or Visipaque
 - Temperature: ensure contrast is brought to room temperature
 - Volume: 100 mL

- Infusion rate: 2.5 – 3 mL per sec
- Time between injection and CT: 35 – 40 sec

Remove cannula at completion of scan.

Appendix 6: Histopathology Guidance

Introduction

The guidance below is provided to assist the key role of the histopathologist in the assessment of the excised rectal cancer specimen. This section should be used in conjunction with the ARISTOTLE Pathology CRF.

Histopathologists at participating sites will be requested to collaborate in this trial in the following ways:

- By following the guidance in this appendix
- By submitting and/or facilitating submission information and specimens for central review (see section 10; Quality Assurance, for details)
- By submitting and/or facilitating submission of archival tissue blocks for future tissue-based cancer research (see section 9; Collection of Tissue and Blood for Exploratory Biological Research for details)

Pathology dissection

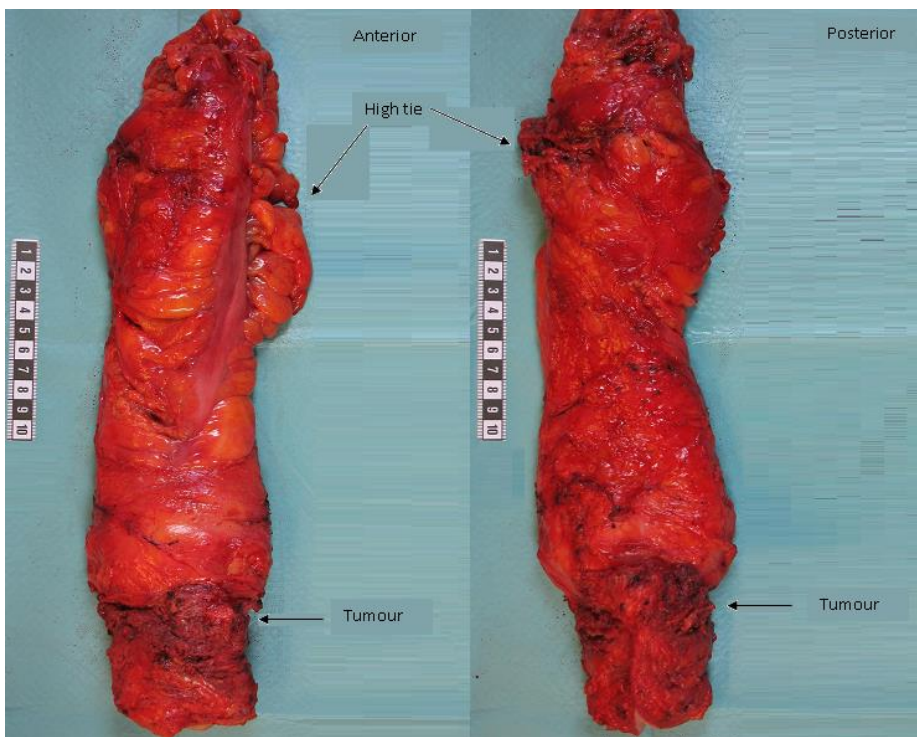
High quality histopathology is a key component of this trial. The pathologist has a key role to play in assessing the circumferential resection margin (CRM), identifying and describing perforations and evaluating the planes of surgery of the mesorectum and the levator/anal sphincter. It is important that the pathologist determines the degree of response to therapy (tumour regression), retrieves substantial numbers of lymph nodes (in cases with strong chemotherapy and radiotherapy), and confidently identifies extramural venous invasion (EMVI) and peritoneal involvement to the highest standards. For the TNM staging in this trial, we are using TNM5, not TNM6 or TNM7. This is in line with current RCPATH reporting recommendations. This is because of the poor reproducibility associated with the TNM6 definitions of EMVI and lymph nodes, and the introduction of tumour deposits (pN1c) in TNM7, which was based on little evidence with no assessment of interobserver variability. Thus in this trial, any tumour deposits that are 3 mm or larger in size are classed as fully replaced lymph nodes (the so called '3 mm rule'). Any deposit less than 3 mm in size is counted as discontinuous tumour spread. This allows this trial to be consistent with other trials such as the Dutch TME trial and MRC CR07 trials. In order to collect further prospective data on the importance of tumour satellite nodules, we will ask you to separately list within the Pathology CRF the number of true lymph nodes identified, the number of true lymph nodes involved by tumour, the number of tumour deposits that are 3 mm or greater in size (and therefore would be counted in the final lymph node count in TNM5) and whether or not additional tumour deposits less than 3 mm in size are present.

Thank you for your efforts and for participating. The key issues are specimen photography, consistent high quality specimen dissection and providing the slides for scanning to create a permanent record of the pathology.

Preparation of the specimen

The surgeon will be asked to provide information regarding the height of the tumour and its location within the bowel wall on the histopathology request form. This will help the pathologist to identify the tumour and is particularly important in cases showing an excellent response to pre-operative therapy.

The intact specimen should be photographed whole prior to opening the bowel and further dissection. It is preferable for the specimen to be submitted fresh from the operating room to the pathology department as soon as possible after resection. Upon receipt in the pathology department, digital colour photographs should be taken of the anterior and posterior surface of the whole specimen, preferably prior to formalin fixation (see example below). It may be advisable to ask the surgeon to take photographs of the fresh specimen following resection if this opportunity is likely to be missed in the pathology laboratory. All photographs **must** include a metric ruler (for calibration) and the site of the tumour and the high vascular ties should be marked (e.g. with forceps or pre-printed labels). If the tumour location cannot be ascertained by palpation, this should be indicated on the photograph with an additional label. Additional images of the lateral views (left and right side), close ups of the anterior and posterior surfaces of the levator/sphincters (in abdominoperineal excision specimens), close ups of any perforation site or other defects, and any other unusual findings should also be taken.



The plane of surgery should be assessed by the local pathologist on the intact specimen (prior to opening) for both the mesorectum and the levator/sphincters (as appropriate). This is preferably done on the fresh specimen prior to fixation. If the specimen is received already fixed in formalin, grading and photography can be done at this stage prior to opening the specimen. Surgeons should be asked not to open specimens prior to receipt in the pathology department as this can affect the assessment of the surgical planes and the status of the CRM. The grading systems for the planes of surgery are given below.


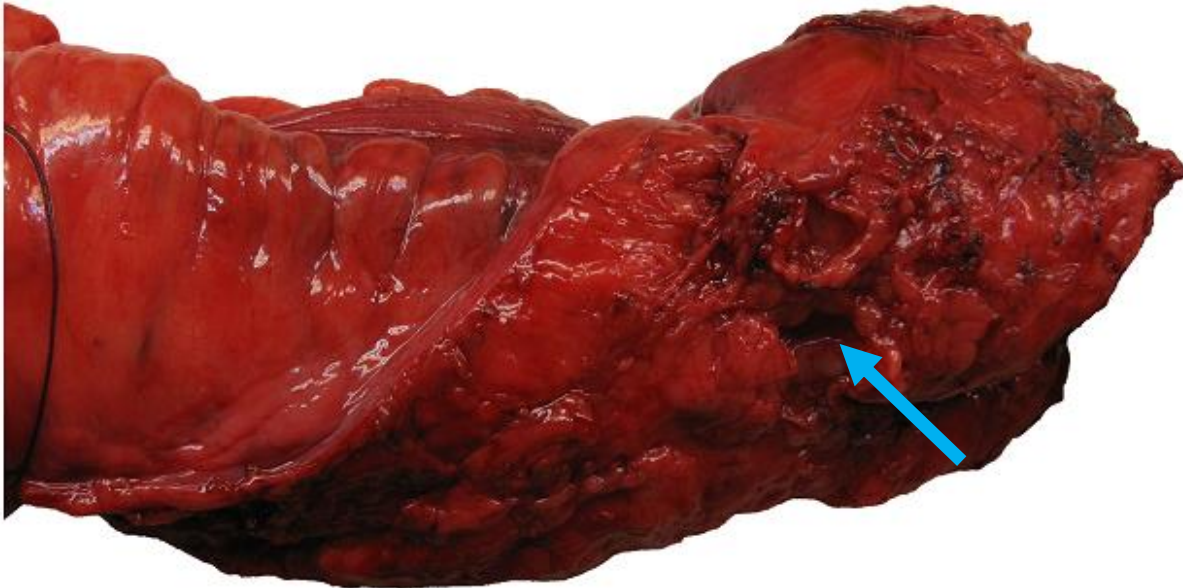
After photography and grading of the surgical planes, the specimen can be opened along the anterior peritonealised surface from the proximal margin down to a point approximately 20 to 50 mm above level of the tumour or down to the level of the anterior peritoneal reflection if the tumour is lower down in the rectum. The mesorectum and bowel wall distal to the tumour should ideally be kept intact, although the distal resection margin can be opened if desired to aid fixation or obtain fresh tissue for local tissue banking. THE AREA OF THE TUMOUR MUST NEVER BE OPENED AS THIS DESTROYS THE ANTERIOR CRM AND/OR PERITONEUM. A piece of foam/paper soaked in formalin can be inserted through the tumour if felt appropriate to aid fixation. The specimen should then be pinned out onto a cork board and placed in formalin fixative for approximately 48 hours prior to further dissection. It is acceptable to inflate the specimen with formalin after receipt, leave it to fix and then take photographs, but this should always be done prior to opening the specimen and undertaking any dissection.


Assessment of the plane of surgery

The planes of surgery in the area of the mesorectum and the levator/sphincters should both be graded separately (as appropriate). Thus for anterior resection specimens there will only be one grade - the grade for the mesorectum. For abdominoperineal excision specimens there will be a grade for the mesorectum and a separate grade for the levator/sphincters. The final specimen grade(s) should always be based on the area of the 'worst' plane of excision.

Quality of resection of the mesorectum (all specimens)

The quality of the mesorectal dissection can be determined from the intact specimen and confirmed from the cross-sectional slices. The three point grading system described below has been used in the MRC CR07 trial (9), MRC CLASICC trial (8) and the Dutch TME/RT (10, 11) study, where poorer planes have been shown to predict a higher risk of local recurrence and poorer survival.

| Plane | Description |
|--|--|
| Mesorectal (good plane of surgery) | The mesorectum should be smooth with no violation of the fascial covering. There should be a good bulk to the mesorectum both anteriorly and posteriorly, and the distal margin should appear adequate with no coning near the tumour. Any defect should not be more than 5 mm deep. |
|  <p data-bbox="261 909 1410 945" style="text-align: center;">Mesorectal plane showing shiny fascial covering over the CRM and no defects</p> | |
| Intramesorectal (moderate plane of surgery) | There should be a moderate bulk to the mesorectum with minor irregularity of the mesorectal surface. A moderate degree of coning of the specimen may be seen towards the distal margin. Importantly, the muscularis propria should not be visible, except at the area of insertion of levator muscles at the very distal aspect. There will be moderate irregularity of the CRM. |
|  <p data-bbox="165 1868 1430 1935">Intramesorectal plane with significant defects into the mesorectum without the muscularis propria being visible (blue arrow)</p> | |
| Muscularis propria | There will be substantial areas where mesorectal tissue is missing with deep cuts and tears down onto the muscularis propria. On cross-sectional slicing, the CRM will be very irregular and formed by the muscularis propria in places. |

| Plane | Description |
|--|---|
|  | <p data-bbox="328 880 1362 947">Muscularis propria plane with significant mesorectal defects exposing extensive areas of muscularis propria (blue arrow)</p> |

Quality of resection of the levators/sphincters (APE specimens only)

The quality of surgical dissection in the levator/sphincter area around the anal canal and below the mesorectum needs to be assessed separately in APE specimens.

| PLANE | Description |
|---|---|
| Levator | The surgical plane lies external to the levator ani muscle, which are removed <i>en bloc</i> with the mesorectum and anal canal. This creates a more cylindrical-shaped specimen with the levators forming an extra protective layer above the sphincters. There should be no significant defects into the sphincter muscles or levators. |
| Sphincteric | Either there are no levator muscles attached to the specimen or only a very small cuff, and the CRM is formed by the surface of the sphincter muscles. There should be no deviations into the sphincter muscle themselves. The specimen shows coning at the level of the puborectalis muscle resulting in the classical surgical waist. |
| Intra-sphincteric / submucosal/Perforation | The surgeon has inadvertently entered the sphincter muscle or even deeper into the submucosa. Perforations of the specimen at any point below the peritoneal reflection should also be classified into this group. |

Macroscopic specimen dissection

Once the whole specimen photographs have been taken and the planes of surgery graded (preferably on the fresh specimen but if not on the unopened formalin-fixed specimen), the specimen is ready to be dissected.

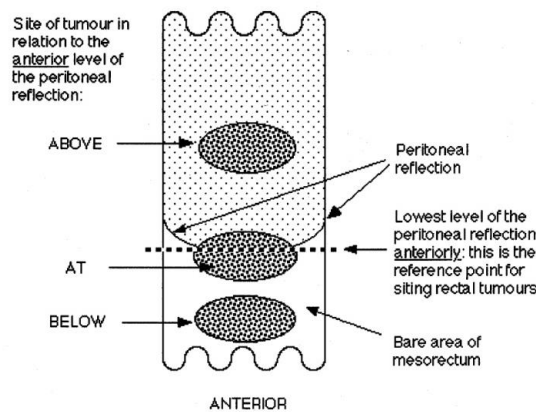
Assessing for the presence of intra-operative perforations

The specimen should firstly be described in detail, in particular, the pathologist should search for the presence of intra-operative perforations irrespective of whether these are located at the tumour site (tumour perforation) or in the rest of the bowel away from the tumour (bowel perforation). For perforations that involve the tumour site, it should be stated whether the perforation is in an area covered by peritoneum (TNM stage pT4) or in an area of a surgically created margin e.g. below the peritoneal reflection (RCPATH guidelines also recommend staging these cases as pT4 and you should look very carefully for the presence of CRM involvement in the area of perforation). Additionally it is useful to document whether the perforation is above or at the height of the sphincters in APE specimens.

Relationship of the tumour to the anterior peritoneal reflection

The crucial landmark for recording the height of rectal cancers is the anterior peritoneal reflection. This is identified from the exterior surface of the anterior aspect of the specimen. Rectal cancers are classified according to whether they are (see diagram below):

1. Entirely ABOVE the level of the anterior peritoneal reflection
2. Astride (or AT) the level of the anterior peritoneal reflection
3. Entirely BELOW the level of the anterior peritoneal reflection

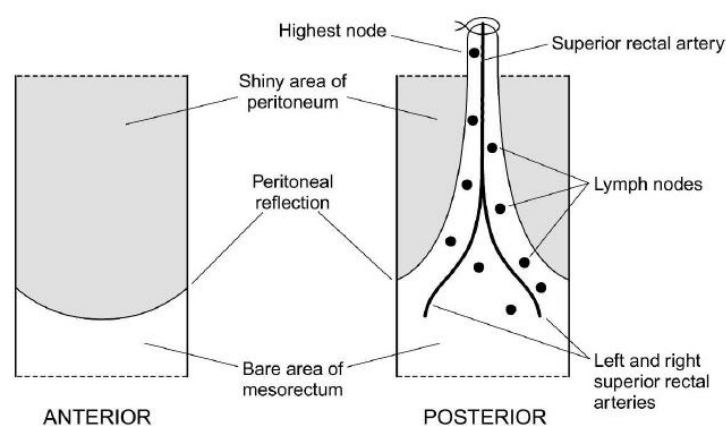


Distance from the tumour to the distal and proximal resection margins

This is measured from the longitudinal cut-ends of the specimen (distal and proximal). It is only necessary to examine the longitudinal margins histologically if tumour extends macroscopically to within 30 mm of one of these. For tumours located further away, it can be assumed that the cut ends are not involved. Exceptions to this recommendation are adenocarcinomas that are found on subsequent histology to have an exceptionally infiltrative growth pattern, show extensive vascular or lymphatic permeation or are undifferentiated carcinomas.

Inking the specimen

It is recommended that the whole of the CRM (i.e. the non-peritonealised mesorectum and levator/sphincters) is painted with ink (e.g. India ink or silver nitrate) before dissecting the specimen to facilitate the assessment of the CRM. Inking can be done before or after fixation according to local practice. It should be remembered that the CRM only applies to the surgically incised tissue planes and not the peritonealised surfaces. Anteriorly, the upper rectum is covered by peritoneum. Only the area below the peritoneal reflection is at risk of CRM involvement. The mesorectal surface of the CRM is larger posteriorly and extends up to a higher level than it does anteriorly (see diagram below).



Cross-sectional slicing and photography

The specimen should then be cross-sectioned into slices as thinly as possible (3 to 4 mm thickness is recommended) starting from the distal resection margin to at least the anterior peritoneal reflection or 20 to 50 mm above the tumour if this is higher. These slices should be laid out in order on a board

and the cut surface presented should be consistent in all of the slices (preferably the distal aspect to correlate with the MRI scans). The slices should then be photographed, either as a whole (with additional close ups of individual slices containing the tumour), or alternatively individual photographs of each slice can be taken. It is important that it is made clear on the photographs which slice is the most distal and the most proximal one by using appropriate labels. All photographs **must** always include a metric ruler scale for calibration. An example of cross-sectional slicing and photography is given below.



Assessment of the CRM and maximal extent of tumour spread

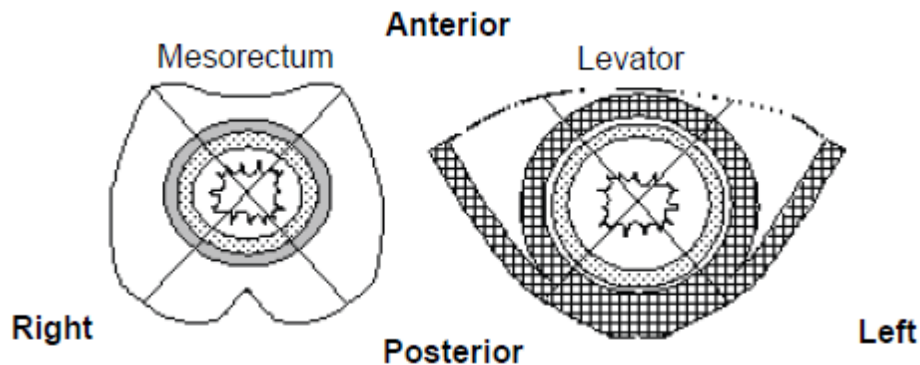
The cross-sectional slices should be carefully assessed after photography and the minimum distance of the macroscopic tumour to the inked CRM as well as the maximum depth of tumour invasion beyond the outer muscle coat of the muscularis propria should be recorded. In APE specimens, both the maximal extent of tumour spread beyond the muscularis propria at the level of the mesorectum and additionally the maximal extent of tumour spread beyond the internal sphincters at the level of the levator/sphincters should be recorded.

These macroscopic measurements should be confirmed histologically, preferably on whole mount sections e.g. using the Vernier scale. The minimum distance from the tumour to the CRM should be reported to the nearest millimetre apart from CRM positive tumours (1 mm or less from the inked CRM), which should be reported to the nearest 0.1 mm. If the position of the muscularis propria and/or internal sphincter is obscured by tumour or fibrosis, the position of these structures should be estimated by comparison to subsequent slices.

Position of the tumour

The position of the tumour should be noted on the ARISTOTLE Pathology CRF. This involves documentation of the quadrant of involvement from the cross-sectional slices – i.e. anterior quadrant, posterior quadrant, lateral quadrant or combinations of these. Also it would be helpful to trace the

position of the tumour at the point of maximum extension both above the sphincters in the region of the mesorectum and below the levator/sphincters on the diagrams provided in the CRF (see below for a copy of the CRF diagram).



To correlate the position of the tumour with the MRI report, the location of the tumour should be described using a clock-face with the anterior peritoneal reflection being 12 o'clock and looking at the specimen slice from the distal aspect.

Sampling the specimen

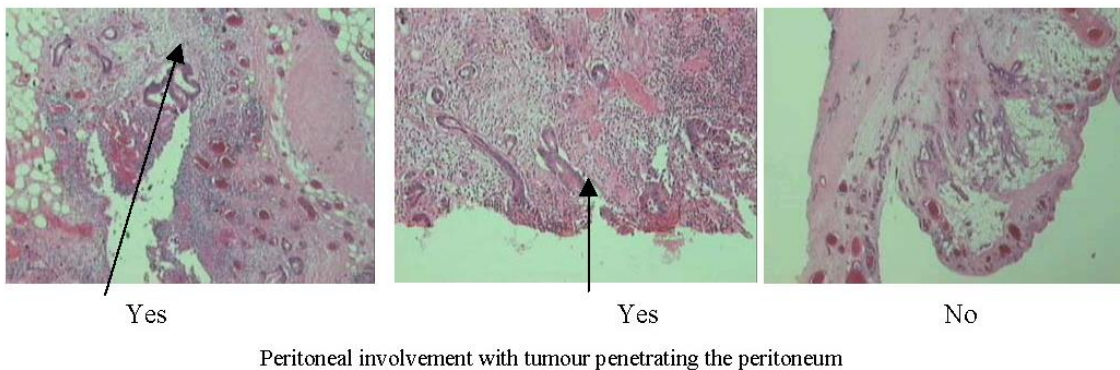
If possible, each tumour bearing slice should be processed into a 'large' (mega) block to produce whole mount sections. However, it is recognised that this is not possible in all laboratories, and therefore a minimum of 5 tumour blocks should be taken (either in standard or large cassettes or a combination of both). Tumour blocks should be taken to demonstrate the point of deepest tumour invasion, areas suspicious for CRM and/or peritoneal involvement, and areas with possible extramural vascular invasion. Please see below for the sampling protocol in cases where tumour cells are difficult to find after pre-operative therapy.

All of the lymph nodes within the specimen should be identified, retrieved and assessed, regardless of their site and size. A running mean of at least fifteen is to be expected. The number of positive lymph nodes must be equal to or less than the number of lymph nodes sampled. The apical node (the lymph node closest to the high vascular tie) should be identified and embedded separately to allow staging according to Dukes' classification. If lymph nodes lie close to or against the CRM then these should be blocked out in such a way that the minimum distance from any tumour to the CRM can be assessed.

Microscopic reporting

Peritoneal involvement and extramural vascular invasion

Involvement of the peritoneum by tumour should be carefully looked for and is defined as per the definition of Shepherd et al (66) (see figure below). Tumour cells must actually perforate through the serosa and lie on the surface of the specimen. It is expected that on average peritoneal involvement will be present in 10% of rectal cancer specimens.

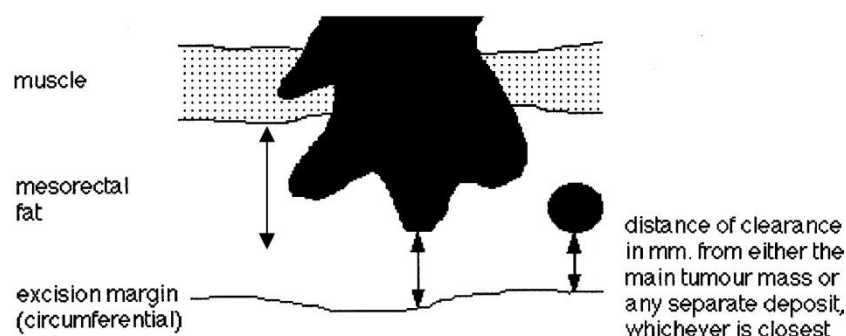


Extramural vascular invasion is defined as involvement of a vascular structure which has smooth muscle in the wall and can frequently be seen macroscopically as finger-like protrusions extending beyond the muscularis propria. If tumour is present close to an artery and the accompanying vein is not visible, then there should be a high level of suspicion for vascular invasion. This should be looked for closely as it is often missed. On average, it is expected to see extramural vascular invasion in greater than 25% of rectal cancer specimens.

CRM involvement

Involvement of the CRM by tumour is defined as viable tumour cells being present at or within 1 mm of the inked CRM. The CRM is at risk not only from direct tumour spread but also metastatic deposits in lymph nodes that lie close to or against the CRM, and through extension along lymphatics, blood vessels and nerves. If the CRM is involved by tumour then the mode of involvement should be stated (e.g. primary spread, lymph node deposit, isolated tumour deposit, vascular, lymphatic, perineural etc.), as well as the minimum distance between the closest tumour and the CRM. The maximum length of CRM involvement in millimetres should also be estimated in the slice showing the greatest extent of CRM involvement.

If the CRM is free of tumour it should be noted whether there is normal tissue at the margin or whether the margin contains abnormal fibrotic tissue suggestive of tumour regression.



pT staging of low rectal cancers

The pT-staging of cancers above the sphincters is straightforward; however, many low rectal cancers are partly located within the region of the sphincters. The anatomy of the levator/sphincters area is very complex and shows considerable variation between individuals. pT staging of adenocarcinoma in the area of the sphincters is currently controversial. Both TNM6 and TNM7 state that such tumours should be staged as anal cancers according to tumour size. However, in the absence of a robust

evidence-based staging system, the only solution is to separately describe the anatomical extent of tumour spread both above the sphincters (in the area of the mesorectum) and at the height of the levator/sphincters to allow subsequent analysis.

Tumour differentiation

The grade of differentiation of the tumour should be defined by the predominant area of tumour and not on the area of the worst grade. Other types of differentiation, i.e. mucinous adenocarcinomas, signet ring adenocarcinomas and undifferentiated tumours should be documented.

Lymph node assessment and tumour deposits

As stated in TNM5, extramural tumour deposits measuring ≥ 3 mm in maximum size are counted as involved lymph nodes even if no residual lymph node structure can be identified. Smaller deposits are regarded as apparent discontinuous extensions of the main tumour. The number of ≥ 3 mm tumour deposits classified as lymph nodes should be indicated in the report separately to the number of true lymph nodes. Mucin or fibrosis only within a node should be commented upon in the report as a sign of tumour regression but should not be classed as lymph node metastases. In the TNM staging system, pN1 corresponds to involvement of 1 – 3 nodes and pN2 to involvement of 4 or more nodes.

Preoperative chemoradiotherapy regression scoring

The Dworak method is recommended and is summarised below (67). However, it is preferable to use descriptive text rather than a numeric grading system to avoid confusion with other tumour regression grading systems. The final grading should be based on the overall assessment of all tumour blocks (there should be a minimum of five) but should not include the assessment of lymph nodes.

- **No regression detectable.**
- **Minimal regression:** dominant tumour mass with obvious fibrosis and/or vasculopathy.
- **Moderate regression:** dominantly fibrotic changes with few tumour cells or groups (easy to find).
- **Good regression:** very few (difficult to find microscopically) tumour cells in fibrotic tissue with or without mucin.
- **Total regression:** no tumour cells, only fibrotic mass or mucin.

Assessment of specimens where tumour cells are difficult to find

Where tumour cells cannot be found on the first assessment of at least five blocks of tumour, the whole area of the fibrotic scar should be embedded and examined. If no tumour cells can be seen following assessment of these extra blocks, then three deeper levels should be taken and examined from each fibrotic scar block. If after these assessments still no tumour cells are identified then the tumour should be considered to have undergone a complete pathological response (TNM stage ypT0 ypN0). Additional levels beyond the above should not be taken, as it is important to standardise the degree of effort made to find residual tumour cells.

Collection of photographs, tissue, and Case Report Form

Photographs

- Photographs of the resection specimen should be taken with a digital colour camera and include:
 - The whole intact resection specimen from both the anterior and posterior aspects. Additional lateral views and close ups of the sphincters (if present), any defects or perforations will be helpful. Photographs of the fresh unopened specimen are preferable although fixed specimens are acceptable. The site of the tumour (if palpable) and the closest high vascular tie should be marked (e.g. with pre-printed labels or forceps).
 - All of the serial cross-sectional slides in order (3 to 4 mm slices from the distal margin of excision to a level above the tumour). Please mark the proximal and distal slices with labels and indicate the direction if not clear. These can be either taken as one whole image (containing all slices) or sequential images of individual slices.
- All photographs **must** include a metric scale to allow calibration.
- The whole specimen (or slices) should be visible in the image. A white background is ideal although any plain colour is acceptable. Photographs should be taken directly above the specimen and not at an angle to reduce any distortion artefact.
- Images should **not** contain any direct patient identifiers (e.g. name, NHS number) but should be identifiable by trial name (ARISTOTLE), laboratory number, and patient's initials, date of birth, and trial number.
- All images should be copied to CD-ROM and sent to:

Dr Nick West
Pathology & Tumour Biology, Level 4
Wellcome Trust Brenner Building
St. James's University Hospital
Beckett Street
Leeds LS9 7TF
- If images cannot be copied to a CD-ROM, please contact Dr. Nick West (n.p.west@leeds.ac.uk) to discuss possible alternative arrangements.

Tissue and reports

All of the H&E stained glass slides from both the original diagnostic biopsy and the surgical resection specimens should be sent to Leeds for scanning along with a copy of the anonymised histopathology reports. Copies of the slides can be sent if the local site does not want to release the originals. Alternatively high resolution digital slides can be sent if slide scanning facilities are available locally. The glass slides will be returned as soon as possible after scanning – this is likely to take around 4-6 weeks. Please send slides to:

Dr Nick West
Pathology & Tumour Biology, Level 4
Wellcome Trust Brenner Building
St. James's University Hospital
Beckett Street,
Leeds LS9 7TF

Slides (originals or copies) and reports should be identifiable by trial name (ARISTOTLE), laboratory number and patient's initials, date of birth, and trial number. Any direct identifiers, e.g. patient name and NHS number, should be blanked out on the slides.

All patients, as part of the consent process, will be asked to donate paraffin embedded blocks of tissue for future research:

1. Pre-treatment diagnostic biopsy tissue including one or more blocks of tumour and one block of normal mucosa. In practice, most biopsy samples will have been embedded in one block.
2. Surgical resection material including one or more blocks of primary tumour (or tumour in lymph nodes if there is insufficient primary tumour) and one block of normal mucosa. It may be preferable to take extra blocks for this purpose at the time of specimen dissection if sufficient tumour is available. If no tumour is available e.g. ypT0 ypN0, then one or two blocks from the area showing complete tumour regression should be sent in addition to a block of normal mucosa.

The Research Nurse will collect these tissue blocks from histopathology and send them to Leeds. We are happy for the local pathologists to select the best blocks to send. Alternatively, all of the blocks can be sent with the slides and we will select the best blocks and return the others, or we can select the best blocks from the slides received and request these blocks from the research nurse.

Case Report Form

Please complete ARISTOTLE Pathology CRFs using guidance in the protocol. Once completed, please submit the original to UCL CTC and include a copy with the shipment of slides to Pathology & Tumour Biology, University of Leeds (full address above).

Contacts

If you have any queries about anything in this document then please direct them to either:

Dr Nick West

Email: n.p.west@leeds.ac.uk

Tel: 0113 3438509

or

Professor Phil Quirke

Email: p.quirke@leeds.ac.uk

Tel: 0113 3438408

Appendix 7: Expected Adverse Events

The following AEs are commonly associated with radiotherapy (68, 69) and will be considered expected for this treatment:

- Nausea
- Abdominal pain
- Diarrhoea
- Proctitis
- Dermatitis
- Cystitis
- Fatigue
- Skin reaction
- Vomiting
- Dehydration

Appendix 8: Schedule of Assessments

| Assessment | Pre-rand | Pre-treat | Treatment | | | | | | | End of treatment | | Post completion of CRT | | | | | | |
|--------------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|--|---|------------------------|----------------|----------------|----------------|--------|--------|--------|
| | | | Wk 1 | Wk 2 | Wk 3 | Wk 4 | Wk 5 | Wk 6 | Wk 10 | Wks 12 – 14 (6 – 8 wks after completion of CRT) | Wks 14 – 16 (8 – 10 wks after completion of CRT) | Mth 4 | Mth 6 | Mth 12 | Mth 24 | Mth 36 | Mth 48 | Mth 60 |
| Informed consent | X | | | | | | | | | | | | | | | | | |
| Histological confirmation of disease | X | | | | | | | | | | | | | | | | | |
| CT chest & abdomen | X ^a | | | | | | | | | X | | | | | | | | |
| CT chest, abdomen & pelvis | | | | | | | | | | | | X | X | X | | | | |
| MRI pelvis | X ^a | | | | | | | | | X | | | | | | | | |
| Medical history | X ^b | | | | | | | | | | | | | | | | | |
| Concomitant medication | X | | | | | | | | | | | | | | | | | |
| Physical exam | X ^b | X ^f | | | | | | | | | | X | X | X | X | X | X | X |
| Pregnancy test (if applicable) | X ^b | | | | | | | | | | | | | | | | | |
| Height | X ^b | | | | | | | | | | | | | | | | | |
| Weight | X ^b | X ^f | X | X | X | X | X | X | X | | | | | | | | | |
| ECOG PS | X ^b | X ^f | X | X | X | X | X | X | X | | | X | X | X | X | X | X | X |
| FBC ^c | X ^b | X ^f | X ^g | X ^g | X ^g | X ^g | X ^g | X ^g | X ^g | X | | | | | | | | |
| Biochemistry ^d | X ^b | X ^f | X ^g | X ^g | X ^g | X ^g | X ^g | X ^g | X ^g | X | | | | | | | | |
| Renal Function ^e | X ^b | X ^f | X | X | X | X | X | X | X | | | | | | | | | |
| ECG | X ^b | | | | | | | | | | | | | | | | | |
| Declared post-op chemo | X ^b | | | | | | | | | | | | | | | | | |
| Serum CEA | | X ^f | | | | | | | X | | | | | | | | | |
| CRP | | X ^f | | | | | | | | | | | | | | | | |
| Pelvic functional questionnaire | | X ^f | | | | | | | | | | | X | X | X | | | |
| Capecitabine compliance check | | | X | X | X | X | X | X | X | | | | | | | | | |
| Blood sample in Streck tube | | X ^h | X | | | | | X | | X | | | | | | | | |
| Blood sample in EDTA tube | | X ⁱ | | | | | | | | | | | | | | | | |
| Acute Toxicity Assessment | X ^b | X ^f | X | X | X | X | X | X | X | | | | | | | | | |
| Surgery | | | | | | | | | | | X | | | | | | | |
| Post-operative toxicity assessment | | | | | | | | | | | | X | | | | | | |
| Late toxicity assessment | | | | | | | | | | | | | X ^j | X ^j | X ^j | | | |
| Post-operative chemotherapy planned | | | | | | | | | | | | X | | | | | | |
| Post-operative chemotherapy given | | | | | | | | | | | | | X | | | | | |

a Within 42 days of randomisation

b Within 14 days of randomisation

c Including a differential with neutrophil and lymphocyte count

d Sodium, potassium, urea, creatinine, AST or ALT, alkaline phosphatase, bilirubin, albumin, GGT

e Calculated creatinine clearance (using Cockcroft-Gault formula) to estimate renal function (Appendix 3)

f Tests do not need to be repeated if they were performed for pre-randomisation evaluation and within 10 days prior to start of treatment

g ARM B patients must have bloods taken within 72 hours of irinotecan administration

h Within 14 days prior to starting treatment

i If this sample is missed at pre-treatment, it may be taken at any time during the trial

j Late toxicities captured on the Male/Female Pelvis Questionnaire

Appendix 9: Protocol Version History

| Version no. | Date | Section (no./title) | Summary of main changes from previous version. |
|-------------|------------|---|---|
| v1.0 | 14/08/2010 | | N/A |
| v1.1 | 18/02/2011 | 1.1. 5.3.1. 7.3.1. 7.3.3. 7.4. 7.5. 8.1. 8.3. 8.4. 10.2.1. 10.5. 16.5. 20. Appendix 5. | Ancillary studies updated Eligibility criteria order changed and wording of second criterion changed Correction to Dose Banding of Oral Capecitabine table IMP dispensing details clarified Radiotherapy planning section updated EDTA replaced by isotope Dose modifications for renal function updated Serum EDTA replaced by isotope in pre-treatment assessments Correction to frequency of post-operative morbidity assessment QoL added to table of assessments during follow-up Detail added to the period of time when adverse events should be recorded and correction to the version of CTCAE to be used Additional safety monitoring details added Hospital number replaced by NHS number Clarification that blood sample will be used for future research Additional details added to Radiotherapy Planning and QA protocol Other minor formatting and corrections Change of statistician |
| v2.0 | 27/10/2011 | 1.2. 2.3. 3.1. 3.1.1. 3.1.2. 3.2.1. 3.2.2. 3.2.3. 4.0. 5.1. 5.3. 6.1. 7.3.1. 7.3.2. | Addition of Mark Harrison and Rhydian Maggs to TMG Senior Trial Coordinator changed from Wendy Wood to Marian Duggan Arm names added to trial schema 'NHS permission' added to pre-activation requirements 'Feasibility questionnaire' corrected to 'site registration form' Investigator requirements changed so they no longer have to have consultant status or routinely present to a MDT Section added: 'Training requirements for site staff' Detail added to site initiation All site initiations will be via teleconference Detail added for documentation requirements for site activation Detail added to 'Site activation' Minor details added to 'Informed consent' Additional responsibilities for site staff added 'Baseline quality of life/functional assessment' corrected to 'Pelvic functional assessment' Detail added to 'Patient Eligibility' Diary cards added to documentation patients must be provided with once they have been randomised Addition of sites being able to use different dose banding for capecitabine Deletion of 'in 250 mL of sodium chloride 0.9%' Addition of irinotecan should be reconstituted in 0.9% (w/v) sodium chloride solution or 5% (w/v) glucose |

| Version no. | Date | Section (no./title) | Summary of main changes from previous version. |
|-------------|------------|---|---|
| | | 7.6. 8.1. 8.2. 8.4. 9. 10.2.1. 10.2.2. 10.4. 10.6. 11. 12. 12.1. 13. 14.1. 16.1. 17.1. 21. Appendix 5. Appendix 7. Appendix 8. | <p>solution according to local practice and the summary of product characteristics (SmPC). Any planned deviation from the SmPC must be approved by UCL CTC.'</p> <p>Changes to text to make support medication less prescriptive</p> <p>'Baseline quality of life/functional assessment' corrected to 'Pelvic functional assessment'</p> <p>Wording changed so pre-treatment radiology must be 35 days before randomisation rather than before treatment starts</p> <p>Detail added to 'Assessments during treatment'</p> <p>QoL corrected to 'Pelvic functional assessment'</p> <p>Detail added regarding confidentiality when sending supporting documentation</p> <p>Correction to wording for reporting procedures for AEs</p> <p>Overdoses are not classed as 'Other medically significant event' on SAE Report</p> <p>SAEs must be reported within 24hours of being aware of the event rather than 1 business day</p> <p>Reference to Appendix 7 for expected toxicities for radiotherapy added</p> <p>Renamed as 'Safety Monitoring' and detail added</p> <p>Renamed as 'Development Safety Update Reports' and detail added</p> <p>Detail added to 'incident reporting'</p> <p>Detail added to 'Trial Monitoring and Oversight'</p> <p>Section updated to reflect changes to monitoring plan and section on 'Self-assessment Monitoring' removed</p> <p>Detail added to 'Patient Withdrawal from Trial Treatment'</p> <p>Detail added to 'End of Trial'</p> <p>REC name updated</p> <p>Sponsor details updated</p> <p>Reference added</p> <p>Correction to table on page 90</p> <p>Minor clarifications added</p> <p>Expected Adverse Events for radiotherapy added</p> <p>Protocol Version History is now Appendix 8</p> <p>Other minor formatting, corrections & clarifications</p> |
| v3.0 | 27/07/2012 | 5.1. 5.3.1. 7.5. 7.7. 7.8. | <p>Pre randomisation evaluations updated</p> <p>Patient inclusion criteria updated</p> <p>Management of acute toxicities updated</p> <p>Capecitabine dose modifications and omissions updated</p> <p>Support medication updated</p> |
| v3.1 | 01/08/2012 | 7.5.1. | Minor clarifications and corrections |
| v4.0 | 17/07/2013 | 1.1. 1.2. 2.2. 3.1. | <p>ARISTOTLE mailbox email added. Prof Matt Seymour removed from TMG. Dr Nick West and Richard Haslop added to the TMG.</p> <p>Changes to secondary endpoints, number of subjects changed from 920-916, number of centres increased to 120, minor change to wording of treatment summary, minor change to wording of definition of end of trial</p> <p>'Pelvic MRI and CT of chest and abdomen' added to trial schema</p> <p>Clarification of wording and addition of 'radiotherapy (normally Mon – Fri) for five weeks</p> <p>'Clinical care' added to trial activities</p> |

| Version no. | Date | Section (no./title) | Summary of main changes from previous version. |
|-------------|------|---------------------|---|
| | | 3.2.1. | 'Recruiting sites which will be referring patients to a different site, for all or some of the trial activities, will not be activated until the relevant site involved is ready to be activated' has been added |
| | | 3.2.3. | 'Sites must not approach any potential patients until they have received an activation letter from UCL CTC' has been added |
| | | 4. | Wording amended to ensure that sites assess the patient's ability to understand verbal and written consent in English, and if necessary provide an interpreter |
| | | 5.1. | Both CT of chest and abdomen and MRI of pelvis must take place within 35 days prior to randomisation. Protocol now clarifies that biochemistry tests as follows are required: sodium, potassium, urea, creatinine, AST or ALT, alkaline phosphatase, bilirubin, albumin, GGT |
| | | 5.2. | 'Any patients identified with locally advanced rectal cancer who are considered for CRT' added as an example of patients to screen |
| | | 5.3.1. | The following additions made to the inclusion criteria – 'diagnosis of primary rectal cancer' and 'patients with enlarged pelvic sidewall nodes are eligible only if they meet the above criteria' |
| | | 5.3.2. | The following amendments made to the exclusion criteria – 'Patients with equivocal lesions (determined at MDT) are eligible' has been added, 'major impairment of bowel function has been altered to 'Major disturbance of bowel function (e.g. gross faecal incontinence or requiring > 6 mg loperamide each day)', a washout period has been added for use of warfarin, 'taking phenytoin or sorivudine' has been altered to 'Taking phenytoin or sorivudine or its chemically related analogues, such as brivudine (see section 7.9 for further details)' and a washout period of 14 days has been added for oral St John's wort |
| | | 5.3.3. | Mandatory pregnancy testing prior to randomisation has been added. Contraceptive advice has been amended and clarified |
| | | 6. | Patients will now be stratified by radiotherapy centre as opposed to treating clinician. Randomisation will now take place by fax |
| | | 7.1. | Treatment summary has been clarified to include that capecitabine must be taken on days of radiotherapy only |
| | | 7.3.2. | Irinotecan should be administered prior to radiotherapy on the same day of the week |
| | | 7.3.3. | Further information on drug accountability has been added |
| | | 7.5. | 'In the event of overlapping haematological and non-haematological toxicities, dose modification should be based on the worst toxicity grade observed.' has been added |
| | | 7.5.1. | Several clarifications and alterations have been made to the management of diarrhoea including – 'In the event of a second episode of grade 2 diarrhoea the patient's management should be discussed with a TMG member by contacting the ARISTOTLE trial coordinator' and also 'In the event of a second episode of grade 3 diarrhoea |

| Version no. | Date | Section (no./title) | Summary of main changes from previous version. |
|-------------|------|---------------------|--|
| | | | stop all chemotherapy permanently. Radiotherapy may be continued if the diarrhoea has resolved to grade 0/1, ≤ 6 mg loperamide per 24 hours is required and patient is considered fit' |
| | | 7.5.2. | 'In the event of a second grade 3 episode of the same toxicity, treatment should discontinue permanently' has been changed to 'In the event of a second grade 3 episode of the same toxicity, stop capecitabine treatment permanently' |
| | | 7.5.3. | Formal 24 hour urine collection can now be used as well as isotope clearance |
| | | 7.5.4. | For grade 3 deranged hepatic function capecitabine and irinotecan must be interrupted until grade 0-1 then recommenced at 75% starting dose |
| | | 7.5.5. | Grade 3 fatigue and vomiting table has been separated and some elements clarified |
| | | 7.5.6. | Mucositis table has been separated and some elements clarified |
| | | 7.5.7. | 'In the event of a second grade 3 episode of the non-haematological toxicity the patient's management should be discussed with a TMG member by contacting the ARISTOTLE trial coordinator' has been added |
| | | 7.5.8. | Blood tests to assess the need for dose modification for irinotecan must now be performed within 72 hours prior to the next irinotecan administration. Amendments have been made to the haematological toxicity table including instruction regarding a combination of grade 3 or 4 diarrhoea and grade $\frac{3}{4}$ neutropaenia/platelets |
| | | 7.6. | 'If irinotecan was scheduled to be given that day, it may be given either the day before or the day after the break, provided this is not more than one day from the date originally scheduled. Otherwise, it should be omitted that week' added |
| | | 7.9.1. | 'Warfarin must not be commenced during CRT. In the unlikely event that this does occur (commenced without consultation with the oncology team), the warfarin must be immediately discontinued, low molecular weight heparin commenced and an INR performed. The patient management should be discussed with a TMG member by contacting the ARISTOTLE trial coordinator' has been added |
| | | 8.1. | A section has been added on pre-randomisation evaluation |
| | | 8.2. | Pre-treatment investigations section has been elaborated and clarified |
| | | 8.3. | Assessment during treatment section has been clarified and 'Patients who are on Arm B must have bloods done within 72 hours prior to irinotecan administration' has been added along with 'diary should also be used to assess patient compliance with capecitabine' |
| | | 8.4.1. | Section has been altered to refer to assessments carried out 10 weeks after the start of CRT |
| | | 8.4.2. | Section has been altered to refer to assessments carried out 6-8 weeks following the end of CRT |
| | | 8.7.1. | Assessments after surgery now take place as follows: 'Patients should then be seen at 4, 6, 12, 24, 36, 48 and 60 months after completing CRT' |

| Version no. | Date | Section (no./title) | Summary of main changes from previous version. |
|-------------|------------|---------------------|--|
| | | 9. | This section has been added to the protocol in order to clarify the procedures regarding the collection of tissue and blood for exploratory research. This aspect of the trial is optional for patients |
| | | 10. | This section has been added to the protocol in order to clarify the procedures regarding both the radiotherapy quality assurance and surgery/histopathology quality assurance taking place in the trial |
| | | 11. | The following instructions have been added to the data management section: 'Data must be accurately transcribed onto CRFs and must reflect source documents at site. Examples of source documents include patient's notes, laboratory and other clinical reports etc'. 'Some data will be recorded directly on the CRFs (i.e. no prior written or electronic record of data) and it will be considered to be the source document. Such CRFs would include MRI pelvis form (baseline and post-treatment) and pathology form' |
| | | 11.1. | 'Use of abbreviations and acronyms' has been added to the completing forms section |
| | | 11.4. | Sites may now be subjected to a 'for cause' on site monitoring visit |
| | | 12.2.1. | 'Post-operative AEs must be recorded in the patient's notes and trial CRFs 4, 6 and 12 months post CRT. Late AEs must be recorded in the patient's notes and trial CRFs at months 12, 24 and 36 months post CRT. (Also refer to section 8.5 Assessments during Follow-up)' has been added to the All Adverse Events section |
| | | 17.3. | The total number of patients has been altered to 916. Disease free survival has also been defined as 'time from randomisation until disease recurrence (local or distant) or death. Those patients having neither event will be censored at date last seen alive' |
| | | Appendix 1. | Final CTV and Intravenous have been added to the abbreviations list |
| | | Appendix 2. | 'Oral - small bowel contrast is recommended. Gastrograffin 20 mL in 1 litres of water is taken 45-60 minutes prior to the planning scan is in routine use. Alternatively, dilute contrast agents in routine diagnostic use are allowed' has been added, along with further explanations of planning scans and example diagrams |
| | | Appendix 6. | Histopathology guidance has been largely re-written to include more detail and examples |
| | | Appendix 8. | A schedule of assessments for the trial has been added Further minor clarifications or alterations to the text have also taken place. |
| v5.0 | 31/07/2015 | Throughout | Minor clarifications and corrections throughout. ARISTOTLE telephone and fax number updated. TMG membership updated. |
| | | 1.1 | Reduction of target sample size to 600 patients and rewording of statistics summary. |
| | | 5.1. and 8.1. | The timeframe for CT and MRI has been increased to within 42 days of randomization. |
| | | 7.3.1. | Under 'Dose banding', instructions have been added to state that BSA should be recalculated weekly. |

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|-------------|------|---------------------|--|
| | | 7.4.2. | Addition of wording to state that VMAT/IMRT are acceptable treatment options on trial. |
| | | 7.5 | Addition of wording to clarify that dose modifications should be applied for toxicities that have occurred and resolved over a weekend. |
| | | 7.5.1. | Guidance added on how to manage grade 1 diarrhoea. |
| | | 7.5.5. | Removed the management of vomiting (grade 3) from this section so it only provides instructions for the management of fatigue (grade 3). |
| | | 7.5.6. | Added separate section for the management of vomiting (grade 3). |
| | | 7.6 | Change of section heading to 'Unplanned Breaks in Treatment'. Addition of wording to clarify making up for missed treatment by adding on additional week(s) of treatment to the end of the treatment schedule. |
| | | 7.7 | Change of section heading to include irinotecan. Addition of wording to clarify that dose modifications should be applied for toxicities that have occurred and resolved over a weekend. |
| | | 7.10. | Section 7.10 added to highlight precaution to DPD deficiency. |
| | | 8.2. | Wording added to state that height and weight should be "(used to calculate BSA)". Addition of baseline whole blood sample to the list of investigations. |
| | | 8.3. | Wording added to state that weight should be "(used to recalculate BSA)". |
| | | 8.4.1. | Addition of baseline whole blood sample to the list of investigations. |
| | | 9.3.1. | Addition of information regarding the collection of plasma samples. |
| | | 9.3.2. | 'Preparation of samples' wording has been entirely changed as plasma samples will now be collected in Streck tubes, which will then be sent to the laboratory immediately rather than being centrifuges and stored at -80°C at site. |
| | | 9.3.3. | 'Storage and shipping' section has been renamed 'Shipment of samples' as blood samples will now be sent immediately to the laboratory and will not be stored at site. All wording has been entirely changed to reflect the samples being shipped immediately and new instructions for the shipment. |
| | | 9.4. | A new section has been added specifically for whole blood samples which will now be collected in addition to the plasma samples. This section is divided into three sections as was done for the plasma samples (section 9.3). |
| | | 10.1.1.1. | Addition of wording to state that if a PI is changed, the outlining RTQA exercise will need to be re-submitted. |
| | | 11. | Addition of wording to notify sites of the availability of MRI/Pathology Worksheets. |
| | | 12.2.2.1 | Clarification to wording on when and how post-operative and late AEs should be captured. |
| | | 12.5 | Wording changed for the reporting period for pregnancies. |

| Version no. | Date | Section (no./title) | Summary of main changes from previous version. |
|--------------------|-------------|--|--|
| | | 17. Appendix 5. Appendix 7. Appendix 8. | Rewording throughout the statistics in order to remove the multistage futility analyses and decrease the target recruitment to 600 patients in order to achieve the required 247 DFS events at 3 years. Addition of wording to state that VMAT/IMRT are acceptable treatment options on trial. Addition of wording to provide details of the small bowel sub-study. Addition of Dehydration, Fatigue, Skin Reaction and Vomiting. Addition of whole blood sample to the schedule of assessments. |