Timing and Deferral of Rectal Surgery Following a Continued Response to Pre-operative Chemoradiotherapy

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Acronym: ***'Deferral of surgery'***

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This document is intended to describe a trial protocol which has been adopted by the National Cancer Research Institute (NCRI) lower GI Cancer Group and to provide information about procedures for entering patients. It is not intended that the protocol be used as an aide-memoir or guide for the treatment of other patients. Amendments may be necessary; these will be circulated to known centres in the trial, but centres entering patients for the first time are asked to contact the Royal Marsden GI Clinical Trials Unit to confirm the details of the protocol in their possession.

Clinical problems relating to this study should be referred to the relevant Chief Investigator. If in doubt, contact the RMH GI Clinical Trials Unit (Tel: 0208 661 3365).

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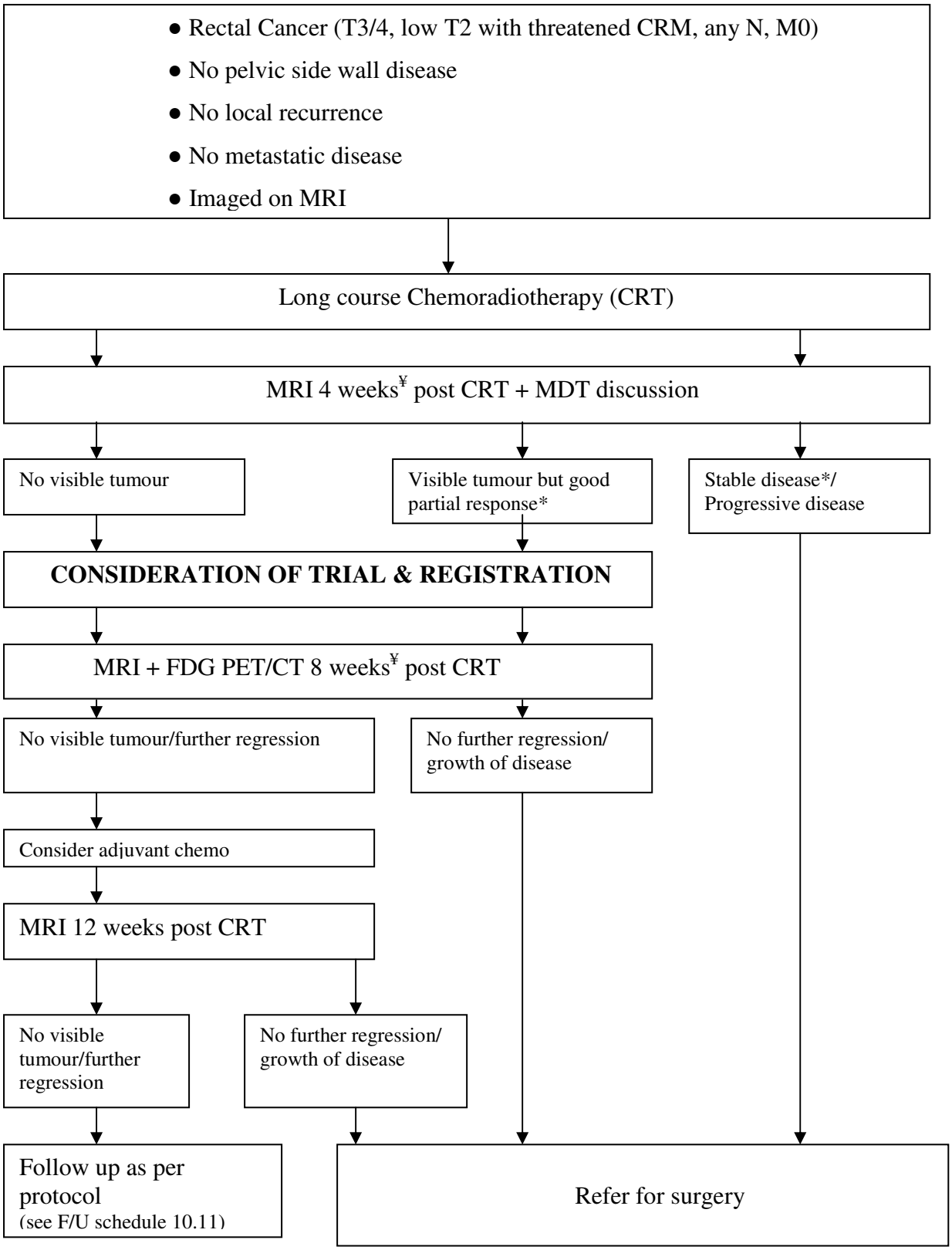
Fig. 1 **'DEFERRAL OF SURGERY' TRIAL OUTLINE**



¥ *Patients who have had am MRI performed more than 4 weeks following completion on CRT can also be included, with the next MRI/18F-FDG PET/CT scheduled 4 weeks afterwards. 18F-FDG PET/CT will be performed at 8 weeks, 16 weeks and 1year following completion of CRT*

** 'partial response' and stable disease' are defined by the RESCIST criteria, appendix 10.5*

2.0 Background

Non-metastatic rectal cancer has been treated with radiotherapy (RT) alone, surgery with adjuvant RT or Chemo-Radiotherapy (CRT), and neo-adjuvant RT or CRT followed by surgery. Reports of RT only for selected patients with early stage resectable rectal cancer yield 5-year survivals of 50-90%, with many deaths from intercurrent illness. RT only for locally advanced disease, usually external beam with a brachytherapy boost, for resectable rectal cancer is reserved for patients refusing surgery or with co-morbidities rendering them medically inoperable. Nevertheless, results are respectable, with 5-year survivals typically greater than 60%[2-5]. Such data establishes RT alone as a curative modality.

For many years, it has been known that adjuvant RT reduces local recurrence in locally advanced rectal cancer[6]. Neo-adjuvant CRT has proven superior to adjuvant CRT in a randomised controlled trial, with reduced acute and long-term toxicity. Two recent randomised trials have demonstrated the efficacy of concomitant chemotherapy, and have established preoperative CRT as the standard of care for locally advanced rectal cancer. The European Organisation for Research and Treatment of Cancer has published preliminary and 5-year results of its EORTC 22921 trial, randomizing over 1000 patients with T3 or resectable T4 into a 2x2 factorial design: preoperative RT alone, preoperative CRT, preoperative RT with 4 cycles of adjuvant chemotherapy, or preoperative CRT with 4 cycles of adjuvant chemotherapy[8]. Chemotherapy was 5-FU (350mg/m^2/day) and Leucovorin (20mg/m^2/day) for all arms, on the first and last week during RT, or as 4 courses every 3 weeks adjuvantly. RT was 45Gy in 25 fractions over 5 weeks in all arms. Patients within the CRT arms had smaller tumours on pathological assessment ($p<0.0001$), and greater downstaging ($p<0.001$). pCR rate was 5.3% and 13.7% in RT and CRT arms respectively. 5-year results reveal a local control advantage (incidence of local recurrence as a first event) for the three chemotherapy arms (7.6-9.6%), compared to RT alone (17.1%, $p=0.002$)[9].

These results are confirmed by a similar French trial, FFCD 9203, with a more straightforward preoperative RT v CRT randomisation, with both arms (n=733) receiving 4 cycles of adjuvant chemotherapy[10]. RT and chemotherapy were delivered using virtually the same regime as EORTC 22921. pCR rates were significantly increased by the addition of concomitant chemotherapy (3.7% vs. 11.7%, $p<0.0001$). Grade 3 and 4 toxicities were increased in the chemotherapy arm (2.7% vs. 14.6%, $p<0.0001$). 5 year overall survival was not improved by the addition of concomitant chemotherapy in either trial.

2.1 Capecitabine

Capecitabine is a fluoropyrimidine carbamate which is rapidly absorbed via the oral route and which offers several advantages over 5FU. Capecitabine and its intermediate metabolites are not cytotoxic. They become effective only after they have been rapidly converted to 5FU which is dependent on the enzyme thymidine phosphorylase (TP). The activity of TP has been found to be significantly higher in a number of different epithelial tumours compared with normal tissue. Thus, the use of capecitabine allows the preferential activation of cytotoxic metabolites in tumour tissue. TP activity is up-regulated by administration of other chemotherapy agents or

by radiotherapy. This process may potentially lead to greater efficacy, synergy with other agents and reduced toxicity compared with 5FU.

The effects of Capecitabine have been compared with bolus 5FU plus Folinic acid (Mayo Clinic regimen) in metastatic colorectal cancer. The use of Capecitabine resulted in superior response rates compared with Mayo Clinic regimen (25.7% vs 16.7%, $p<0.0002$) and led to similar times to disease progression with similar overall survival times. However, the toxicity of Capecitabine was significantly reduced compared with 5FU. Thus, single agent Capecitabine is at least as effective as 5FU with lower toxicity

2.2 Capecitabine as Concomitant Chemotherapy

The combination of 5FU and radiotherapy has been widely used in adjuvant and neo-adjuvant therapy for locally advanced rectal cancer. As RT up-regulates intr-tumoural TP levels, it is anticipated that Capecitabine may be more effective therapy in this context than 5FU.

2.3 EXPERT

For EORTC 22921 and FFCD 9203, concomitant chemotherapy did not demonstrate a significant reduction in the risk of metastatic recurrence. This implies that concomitant chemotherapy, whether by inadequate dose or choice of agent, achieves only a radiosensitising effect within the pelvis, rather than a significant effect on metastatic microscopic disease. Therefore preoperative strategies using newer agents on an induction or concomitant basis have been investigated in an attempt to address this.

Between November 2001 and August 2004, EXPERT (a phase II study of Oxaliplatin Capecitabine and pre-operative RT for patients with locally advanced and inoperable rectal cancer) study has recently completed its accrual of 77 patients at the Royal Marsden hospital[11]. Eligible patients had had MRI-defined poor risk features of tumour extending to within 1mm or beyond of the mesorectal fascia, T3 tumours at or below the Levators, tumour extending 5mm or more into perirectal fat, T4 and N2 tumours. This trial delivered neo-adjuvant chemotherapy with 4 cycles of Oxaliplatin and Capecitabine prior to CRT. A RT boost was delivered to the primary for a total dose of 54 Gy, with concomitant Capecitabine. 67 patients proceeded to appropriate surgery after an interval of 6 weeks with total mesorectal excision. pCR rate was 24% and minimal microscopic disease was found in a further 48%.

2.4 Deferral of Surgery

The optimal interval between completion of CRT and surgery is as yet unknown. Traditionally, surgery takes place 6 weeks after CRT, but maximal tumour downstaging may require a longer period of time depending on individual tumour response. Francois et al evaluated the role of the interval between pre-operative radiotherapy and surgery[12]. The radiotherapy fractionation used was 39Gy in 13# in the absence of chemotherapy. 201 patients were enrolled into the study and randomised the short interval group (surgery within 2 weeks after completion of

radiotherapy) or the long interval group (6-8 weeks after completion of radiotherapy). A long interval between preoperative radiotherapy and surgery was associated with a significantly better clinical tumour response (53.1% in the short interval group vs 71% in the long interval group, p=0.007) and pathologic downstaging (10.3% in the short interval group vs 26% in the long interval group. With a median follow-up of 33 months, there were no differences in morbidity, local relapse and short term survival. Spincter-preserving surgery was performed in 76% of cases in the long interval group versus 68% in the short interval group, although this effect was not statistically significant. Long course chemoradiotherapy, which is more effective than radiotherapy alone, has now superceeded the hypofractionated radiotherapy regimen adopted in this study , but these results illustrate that a longer interval between pre-operative radiotherapy and surgery is beneficial in terms of tumour downstaging.

Habr-Gama et al retrospectively reviewed 250 patients who underwent surgery after CRT. 48.4% had CRT to surgery intervals of 12 weeks or less, with the remainder having surgery more than 12 weeks after CRT[13]. There were no statistical differences in overall survival (86% vs. 81%) or disease free survival rates (56.5% and 58.9%)between patients according to interval (≤12 vs. >12 weeks). Patients with intervals of 12 weeks or less had significantly higher rate of stage III disease (34% vs. 20%, p=0.009). These results indicate that deferral of surgery for the evaluation of tumour response after CRT is safe and does not negatively affect survival.

There has been growing interest in selecting those patients who are likely to achieve pCR. This is of particular importance for patients with low rectal cancers who would otherwise require an Abdomino-perineal resection. Whilst identification of these patients is impossible with a single scan, it is reasonable to adopt a policy of stringent monitoring with serial imaging, clinical examination and CEA, especially in individuals who refuse a stoma and those with significant comorbidities (high risk for surgery) .

The same Brazilian group have reported the long-term results of a non-surgical approach for patients who have achieved a complete clinical and radiological response for chemo-radiotherapy[14]. 265 patients with distal resectable rectal tumours were treated with neo-Adjuvant CRT from 1991 to 2002. RT dose was 50.4 Gy in 1.8 Gy per fraction for 6 consecutive weeks. Patients received concurrent chemotherapy with 5FU (425 mg/m^2) and Leucovorin (20 mg/m^2) on the first and last 3 days of RT. Patients were assessed at 8 weeks following completion of CRT. 71 (26.8%) of patients were judged to have achieved CR on the basis of clinical and radiological grounds ('stage 0'), though MRI was not used. These patients did not have surgery. All other patients proceeded to surgery. 7% of those with incomplete clinical response (residual rectal ulcer) proceeded to surgery and proved to have a pathological complete response (pCR).

The mean follow-up period was 57.3 months (range 18-156 months). 5-year overall and disease-free survival rates were 88% and 83% in the resection group and 100% and 92% in the Observation group respectively. 10-year cancer related overall and disease-free survival rates were 100% and 86% respectively. Of 71 patients considered to be in stage 0 following CRT, 69% were T3, 11% T4, and only 22% radiologically staged as node positive. Apparently 20% of all patients were T2N0.

Of 71 patients who had achieved complete clinical and radiological response, only 2 suffered an endoluminal relapse, both of whom were successfully salvaged. 3 patients developed metastatic disease.

Results from the trials outlined above support the safety of deferral of surgery for the evaluation of maximal tumour response after neo-adjuvant CRT. A non-surgical approach may be reasonable for those who maintain an apparent clinical and radiological response, with the term 'complete responders' reserved for those who achieve this response status with serial imaging and examination for at least 1 year after CRT.

2.5 MRI as a tool assess response to Preoperative Chemo-Radiotherapy

The accuracy of high-resolution MRI in predicting the presence or absence of tumour at the surgical circumferential resection margin of the rectal cancer specimen has been prospectively investigated by the MERCURY group from the Pelican Cancer Foundation[15,16]. 408 consecutive patients from 12 colorectal units in 4 European countries with all stages of rectal cancer underwent MRI prior to TME. Specificity for prediction of a clear circumferential resection margin by magnetic resonance imaging was 92% (327/354, 95% CI: 90-95%).

MRI is also a useful tool for assessing tumour response to CRT for rectal cancer. This has been prospectively evaluated at the Royal Marsden Hospital by the same Consultant Radiologist interpreting serial MRIs in this study[17]. 25 patients with poor-risk adenocarcinoma of the rectum treated with neo-adjuvant chemoradiation underwent MRI imaging before and after chemoradiation treatment and were independently reviewed in consensus by 2 expert radiologists to determine the tumour stage, nodal size, nodal distribution and nodal stage. Total mesorectal excision surgery after chemoradiation allowed MR nodal staging to be compared with histopathology. Before chemoradiation 152 mesorectal nodes were visible and 4 of 52 malignant nodes were in contact with the mesorectal fascia. After CRT, only 29 nodes were visible and none were in contact with the mesorectal fascia. Nodal downstaging was observed: 20/25 N0 and 5/25 N1 ($p<0.01$). The results of this study demonstrates downsizing and downstaging of the primary rectal tumour after CRT with good agreement between MRI and pathologic T and N staging.

The Imaging Principle Investigator has developed a detailed post chemoradiotherapy (CRT) MRI specific tumour response grading (MRI TRG) for rectal cancer generated from the experience gained from the following clinical trials:
- The CORE (Capecitabine, Oxaliplatin, Radiotherapy and Excision) study, a multi-centre European trial, evaluated oxaliplatin, capecitabine and radiotherapy (XELOX-RT) followed by total mesorectal excision (TME), then adjuvant XELOX in patients with MRI-defined locally advanced rectal cancer[18]. Pre- and post CRT MRI was performed for each patient (N=72). High concordance was found when MRI T-staging and tumour regression grading (MRI TRG) was compared with histopathology and overall survival. There was good inter-observer agreement found in this trial. We have provided the analysed data for this trial which is currently awaiting publication (please see pdf attached).

- The results of the MERCURY study assessment in terms of MRI response to neo-adjuvant CRT compared with histology are due to be published (N=80)[19]. Again, we would be pleased to provide the results if requested. This study utilised a detailed proforma (which is identical to that used in the deferral of surgery study), the results of which confirm good inter-observer agreement, with excellent correlation with histology and clinical outcome.
- Barbaro et al utilised this MRI specific TRG to prospectively determine tumour response after CRT in 53 patients with locally advanced non-mucinous rectal cancer, using histopathology as the reference standard[20]. A decrease in signal intensity was considered to represent a morphological response with fibrosis. Response assessment with MR imaging achieved a positive predictive value of 84.2% , with an overall accuracy of 86.8%. MR imaging accuracy for lymph node (N) stage was 86.8%.

This data supports MRI as the modality of choice for preoperative staging prior to surgery or neoadjuvant therapy. However, the ability of MRI to predict pCR accurately following preoperative CRT has not been established. MRI performed 4-6 weeks following the completion of preoperative CRT for locally advanced rectal cancer is rarely normal, even in those patients that will achieve pCR at surgery. Rather, in those patients with an optimal response on MR, a 'scar' replaces the site of disease, represented by a focal area of low-signal intensity on T2-weighted MR. The precise cellular composition of such an area of low signal intensity cannot be known, and a single MRI scan cannot diagnose complete response. However, if surgery is deferred, then the 'scar' may be monitored with serial imaging to exclude any change. By adopting this approach, the time interval to maximal tumour debulking can be established and identification of true 'complete responders' may be made (sustained radiological and clinical complete response).

2.6 18F-FDG PET/CT as a tool to confirm response to Pre-operative Chemo-radiotherapy

Some work has been undertaken to assess the ability of 18F-FDG PET/CT to predict pathological response in rectal cancer. Pathological response is graded by some histopathologists using the Mandard five-point tumour regression grading scale to assess the presence or absence of residual tumour cells[21]. TRG1 represents complete tumour regression, TRG 2 is characterised by the presence of rare residual cancer cells scattered through the fibrosis. In TRG3, fibrosis is still predominant, while TRG4 shows residual cancer outgrowing fibrosis, and TRG5 is characterised by absence of regressive changes. The relationship between this TRG score and 5 year outcomes has been examined by Vecchio et al[22]. The local 5 year local failure rate was 2% for TRG1-2 vs 58% for TRG3-5. The TRG also predicted the incidence of pathological nodal involvement as 91% of patients with TRG1-2 were pN0, versus 63%for TRG3-5.

Capirci et al studied 42 patients with locally advanced rectal cancer who were imaged with FDG PET before and 5-6 weeks after completion of CRT[23]. The pretherapy SUV values were not predictive of pathological response. However, the response index ($SUV_{initial}$ - SUV_{final})/$SUV_{initial}$) showed a good correlation with the Mandard tumour regression grade (TRG). A cut-off of 66% decrease in SUV allowed differentiation of

responders (8 TRG1 + 15 TRG2) from non-responders (9 TRG3 + 13 TRG 4-5) with 80% overall accuracy.

Kalff et al studied the use of PET before and 3-4 weeks after completion of CRT[24]. Response was graded as complete, partial or absent. After a median followup of 3.1 years, all those with complete metabolic response were free of disease. Only 6/10 patients with a partial response were disease free and all 3 patients who had not responded had died.

Cascini et al found that a threshold of 52% decrease in SUV_{mean} resulted in an accuracy of 100% when distinguishing between histological responders (TRG1-2) from non-responders (TRG3-4)[25]. When using SUV_{max} values, a cut off of 42% decrease in SUV_{max} identified responders from non-responders with an overall accuracy of 94%.

These preliminary studies support the use of FDG PET in identifying response to CRT for rectal cancer. It does not hold the same value as MRI in clearly depicting the primary tumour and surrounding nodes, but both imaging modalities used in combination would be complimentary in evaluating continued tumour response after CRT.

3.0 STUDY OBJECTIVES

The primary objective of this study is to establish the time to maximum tumour response following CRT, and to investigate whether surgery can be safely avoided within the tight framework of the trial follow-up protocol in a small group of patients where the cancer becomes undetectable by imaging modalities**.**

It also allows the use of 18F-FDG PET/CT in combination with MRI and clinical examination (tri-modality assessment) to assess for a continued incremental response to CRT. It should be made clear that surgery is not withheld from patients entering this study. Indeed, surgery is an option at each stage of patient follow-up and is a crucial component of a patient's treatment pathway if a point is reached when there is no further regression of disease. However, should the patient refuse surgery or be medically unfit for a rectal surgery, they will continue to be followed up without surgical intervention. If a status of 'no detectable disease' by serial MRI, PET/CT and clinical assessment is achieved and the patient wishes not to have surgery, they will continue to be stringently monitored within the framework of the trial follow-up protocol.

3.1 Primary Endpoints

1) To estimate the percentage of patients who can safely omit surgery, defined as the percentage of patients at two years after end of CRT who have not had surgery and who are in CR (no detectable local disease)

2) The percentage of patients who have local failure at two years, where local failure is defined as surgically unsalvageable disease.

3.2 Secondary endpoints

1) Time to distant disease
2) Time to maximal tumour response after CRT
3) Time to local re-growth
4) Percentages of positive margins, and sphincter-preservation rates in patients who have had surgery.
5) Progression-free and overall survival
6) Quality of Life including long-term bowel, urinary and sexual function

4.0 ELIGIBILITY

Please note that the terms "complete response", "partial response" and "stable disease" are defined by the RECIST criteria, appendix 10.1 [1]. The term "incremental response" is defined as a definite MRI-defined tumour volume reduction which may or may not reach the criteria for a partial response.

Patients suitable for this trial are those with locally invasive high-risk rectal adenocarcinoma with :

● No viable disease seen at MRI performed 4 weeks after long-course CRT, confirmed at 8 week MRI
Or
● **Evidence of a good partial response of rectal tumour to pre-operative long-course CRT, i.e. modified Mandard tumour regression grade (TRG) 2 on MRI, at 4 week MRI OR TRG 3 at 4 weeks and continues to show an incremental response, i.e. TRG 2, at 8 week MRI.**

4.1 Inclusion Criteria

a) Age > 18 years
b) Locally invasive high-risk rectal adenocarcinoma as defined by the local MDT team and on the basis of this underwent chemoradiotherapy
c) The absence of malignant pelvic side-wall disease, local recurrence (either after TME or wide local excision) or metastatic disease
d) Patients having neoadjuvant systemic Chemotherapy are also eligible
e) Completion of pre-operative long-course CRT
f) No viable disease seen at MRI performed 4 weeks after long-course CRT, confirmed at 8 week MRI
g) Evidence of partial response of rectal tumour to pre-operative long-course CRT at 4 week MRI which continues to show an incremental response at 8 week MRI.
h) Histological diagnosis of adenocarcinoma of rectum.
i) WHO performance status 0, 1 or 2.

j) No evidence of metastatic disease as determined by CT scan of chest, abdomen, pelvis or other investigations such as PET scan or biopsy if required.
k) Informed written consent

4.2 Exclusion Criteria

a) Age < 18 years.
b) **Absence of concomitant chemotherapy.**
c) **Stable disease at 4 week MRI.**
d) **Disease that demonstrates a partial response at 4 week MRI but shows no evidence of an incremental response at 8 week MRI.**
Pregnancy or breast feeding
e) **Short course pre-operative radiotherapy**
f) **Previous pelvic radiotherapy**
g) **Medical or psychiatric conditions that compromise the patient's ability to give informed consent**
h) **Any contra-indication to MRI scanning, eg Cardiac Pacemaker or Hip prosthesis.**
i) **Tumours which are mucinous (>50% mucin seen on MRI), as these are more likely to be PET negative**

4.3 Trial Registration

• Before a patient is registered into this trial, written informed consent must be obtained by a doctor who is on the trial log. When obtaining consent from a patient, the deferral of surgery trial and the current version of the deferral of surgery patient information sheet (PIS) should be introduced in full. Written confirmation should be recorded by a qualified, experienced nurse or a clinician according to local practice.
• The completed registration form should be faxed to 020 8661 3610 where eligibility will be checked. Please also fax copies of the pre- and post-treatment MRI and histopathology reports. Written confirmation of the patient's entry into the trial and the trial number will be faxed back. Pre- and post treatment MRI scans on a disc should be sent to the study coordinator for central review.

4.4 Treatment withdrawal criteria

a) Patient decision to withdraw from trial and proceed to surgery
b) Following registration, disease (that has not yet achieved a modified Mandard tumour regression grade 1 or 2; Appendix 10.2) that shows stable disease over 2 consecutive MRI scans, 4 weeks apart.

5.0 TREATMENT PROTOCOL

A schema illustrating the overall treatment/ accrual plan is shown in Figure 1.

5.1 Chemo-Radiotherapy

It is anticipated that patients receiving concomitant chemotherapy will receive oral Capecitabine, though the type of concomitant chemotherapy is not stipulated by the protocol. The absence of concomitant chemotherapy, ie pre-operative RT alone**,** is an exclusion criterion.

Neo-adjuvant chemotherapy, as a single-agent or in combination, prior to neo-adjuvant CRT, is permitted.

Prior chemotherapy for eligible patients presenting with metastatic disease is permitted.

5.2 Pelvic Radiotherapy

Long-course pelvic CRT will have been administrated in all eligible patients. It is emphasized that this protocol does not stipulate the presence or absence of a tumour boost, or planning details. Total dose, however, is stipulated.

5.3 Dose Prescription

All patients must have received a dose of at least 50Gy to the primary rectal tumour, in one or two phases.

At RMH, this is given in two phases:
1. Pelvis: 45 Gy in 25 fractions at 1.8Gy per fraction.
2. Boost: 5.4 - 9 Gy in 3 - 5 fractions at 1.8 Gy per fraction (the smaller dose will be administered if concern about the volume of small bowel included in the boost field).

5.4 18F-FDG PET/CT

18F-FDG PET/CT is incorporated as a part of this trial to assess ongoing tumour response to CRT. Three scans will usually be performed, one at 8 and 16 weeks and then 1 year after completion of CRT.

400MBq is administered for each scan, which equates to an effective dose of 8 mSv (ARSEC Notes for Guidance, 2006). There is an additional dose burden of ***6***mSv for the CT component of each PET/CT scan (scan range mid-skull to mid-thigh) for a standard sized 70kg adult. The total effective dose constraint per subject for these research exposures is ***42*** mSv.

A radiation dose of ***42*** mSv is roughly equivalent to ***19.1*** years natural background radiation. The typical risk of cancer induction in a healthy 40 year subject is 1 patient in 500 per lifetime. The latent period for radiation induced cancer is decades for solid tumours. This level of radiation is unlikely to have an untoward effect on the health of the patient.

All examinations will be completed in compliance with local IR(ME)R Employer's procedures at each site.

PET/CT scans will be assessed (visually and semiquantitatively) for significant glucose uptake and response assessment according to published guidelines and the scoring system detailed in appendix 10.3. All PET/CTs will be reviewed centrally. Where new PET findings may be due to inflammatory or infective pathology a decision on classification of disease status will be made by the PET review panel and the chief investigator/co-investigator, if biopsy of the lesion is not possible or practical. In order to ensure standardisation of PET/CT scans, central approval of QC and QA procedures should be obtained prior to recruitment at participating centres (appendix 10.3). Procedures for transfer of imaging data are also detailed in appendix 10.3.

5.5 Molecular Prognostic and Predictive Markers of Response to Treatment Substudy

5.5.1 Blood specimens for pharmacogenetic studies:

All patients will be asked to consent to an additional blood sample to be collected prior to commencement of treatment. Consent will be obtained as part of consent for study entry as blood collection is minimally invasive, although patients will be able to opt out of this part of the study if they wish. These specimens will be primarily used to correlate germ-line sequence variation with treatment outcomes, inparticular response to treatment and toxicity.

The additional blood sample will consist of two 10ml samples to be collected in EDTA-containing vacutainers (or similar blood specimen tubes), which will be mixed well, spun down and stored at minus 20°C. The samples will then be used for molecular analyses, whereas serum will be removed and stored separately.

5.5.2 Consent to obtain archived paraffin embedded specimens:

All patients will be asked for consent for part of any tissue which has already been collected and which is presently being archived to be donated for future research purposes. The tissue is likely to be specimens already collected to confirm the diagnosis of rectal adenocarcinoma and embedded in paraffin, and surplus to that which is required for diagnostic or other clinical purposes. Patients will not have to undergo any additional procedures or biopsies for this tissue to be obtained. When required, the hospital pathology departments where the specimens are archived will be contacted so that the specimens can be collected centrally and the amount required for research removed, and any surpluss returned to the hospital of origin. One way in which this tissue could be used is to make tissue arrays, however different techniques and technology may be available in the future.

Patients already enrolled in the study will be approached for retrospective consent for this part of the study.

5.5.3 Statement from the Investigators regarding tissue collection:

The Investigators are aware that there are significant and valid concerns relating to the collection of tissue from patients and its potential uses.

Any patient material (including tissue and blood) collected as part of this trial will only be used for the above programme of work which aims to correlate patient characteristics with treatment outcome. All specimens will be anonymized and patient identification by a third party will not be allowed. Results on specific analyses will not correspond with patients or third parties, since results will be of no diagnostic or therapeutic value. All patient data will be held in accordance with the Data Protection Act 1998 and the Freedom of Information Act 2000.

The collected specimens will be considered by the Investigators as a 'gift' from patients. Ownership of specimens (tissue and blood) will exclusively belong to the investigators, who will also be the custodians. Access to specimens by third parties including pharmaceutical companies or commercial researchers will not be allowed without explicit additional consent by patients.

Although patients will not be contacted for further consent, appropriate research ethics approval will be sought before any research is performed on the blood and/or tissue samples collected. This version of the protocol outlines the anticipated general areas of research to be performed on collected tissue, but a full protocol detailing all planned endpoints and analysis methods will be submitted for separate approval before research commences on any tissue or blood collected from patients in this trial.

These points will be made clear to patients at the time consent is obtained. Patients are free to decline to participate in these additional translational studies, and can withdraw consent from the study without affecting participation in the therapeutic part of the study.

5.6 Toxicity

A modified Inflammatory Bowel Disease Questionnaire and the Vaizey Incontinence Questionnaire will be used to assess bowel toxicity after Radiotherapy. These will be assessed at initial assessment then 6 monthly. Late reactions will also be scored at each clinical oncology follow-up visit using the LENT/SOMA system for relevant normal tissues.

5.7 Duration of treatment

Intensive follow-up will continue for a period of 10 years.

5.8 Pre-Registration Evaluation

a) Complete medical history including disease related symptoms, past medical and surgical history, and co-morbidities and their treatment.
b) Physical examination including digital rectal examination (DRE)
c) WHO Performance Status

5.9 Consenting Process

Departmental protocol for all patients upon completion of preoperative CRT is to perform an MRI to assess response of rectal tumour to pre-operative long-course CRT at 4 weeks following completion. The following week each patient is reviewed at a Clinical Oncology clinic for toxicity review and examination, including DRE.

The trial will be discussed with eligible patients at this clinic. Each patient is then reviewed the following day at the GI Unit multi-disciplinary meeting for review of imaging and assessment of suitability for surgery. Results of 4-week MR imaging will be discussed at this time. Suitability for recruitment to the trial will be determined. Subsequent pelvic MRI will be performed 8 weeks after completion of CRT to confirm continued incremental response/sustained status of no visible disease.

Eligible patients will then be contacted, eligibility confirmed, and consent taken. Each patient will have Registration and DRE Pro Formas , and EORTC QOL, Vaizey and Modified Inflammatory Bowel Disease questionnaires completed. Baseline CT and MRI, Post-Chemoradiotherapy CT Reporting and Post-Chemoradiotherapy MRI Reporting Pro Formas will be completed by the same Radiologist, Dr Brown, for all trial imaging

This trial has been opened for multicentre participation. Trial subjects not treated at RMH are recommended to have at least one MRI within 8 weeks of completion of CRT, for comparison with MR imaging prior to neoadjuvant therapy, though this is not stipulated. All MR's will be reviewed for eligibility by Dr Brown and discussed at the Unit MDM. Follow-up is detailed below. All imaging (MR, PET/CT and CT) will be transferred to RMH and undergo central review at RMH. Trial subjects not treated with CRT at RMH will be registered to RMH and subsequent Clinical Oncology follow-up and Imaging will take place at RMH.

5.10 Adjuvant Chemotherapy

Following registration, all patients will be discussed at a Multi-Disciplinary meeting to determine whether adjuvant chemotherapy would be of benefit. All suitable patients will then be referred to Medical Oncology clinics. The inclusion or exclusion of adjuvant chemotherapy does not form part of this protocol.

5.11 Adverse Events

Any serious adverse events will be reported to the Chief Investigator or lead investigators. The Chief Investigator has responsibility to notify CCR/LREC. All SAEs will be reported to the Chief Investigator within 24 hours and the reporting will be in accordance with the RMH/ICR SOP guidance.

5.11.1 Adverse Events not Subject to Reporting

(list of acute toxicity not necessary as trial does not recruit until after acute period, ie during and 30 days after CRT, has elapsed)

Chronic Gastro-Intestinal	LENT-SOMA grades I-III
Chronic Rectal	LENT-SOMA grades I-III
Chronic Genito-Urinary	LENT-SOMA grades I-III
Chronic Cutaneous	LENT-SOMA grades I-III
Chronic Male Sexual	LENT-SOMA all grades
Chronic Female Sexual	LENT-SOMA all grades
Chronic Vaginal	LENT-SOMA grades I-III
Chronic Vulval	LENT-SOMA grades I-III
Chronic Vascular	LENT-SOMA grades I-III
Chronic Bone	LENT-SOMA grades I-III

5.12 End of Trial Definition

The end date will be defined as the date of final follow-up appointment for the last recruited patient.

6.0 ASSESSMENT OF EFFICACY

6.1 Local Recurrence Rate / Tumour Re-growth

Local recurrence rate in patients who have achieved a sustained clinical and radiological complete response will be measured from the end date of CRT to time of documentation of local tumour recurrence/regrowth. It is emphasized that the development, or progression, of metastatic disease does not constitute local failure.

Time to Tumour regrowth / tumour recrudescence in patients who have not achieved a sustained clinical and radiological complete response will be measured from the date of start of CRT to time of documentation of tumour regrowth.

6.2 Overall Survival

This will be measured from date of entry into study to date of death from any cause. Patients remaining alive or lost to follow up will be censored at the date of last follow up.

6.3 Disease free survival

This will be measured from date of start of CRT to time of documentation of local or metastatic tumour progression.

6.4 *Quality of life*

Quality of life will be evaluated at baseline and at each clinical oncology follow-up visit using the EORTC QLQ-C30 questionnaire. Late reactions will also be scored at each clinical oncology follow-up visit using the LENT/SOMA system for relevant normal tissues. A modified Inflammatory Bowel Disease Questionnaire and the Vaizey Incontinence Questionnaire will be used to assess bowel toxicity [23,24]. These will be assessed at initial assessment then 6 monthly.

6.5 *Time to maximum tumour response*

Time to maximum tumour response will be taken from completion of CRT to time when
stable but visible disease is demonstrated on 2 consecutive MRI scans.

6.6 Rectal surgery

The date of rectal surgery will be documented in the event of tumour regrowth. The type of rectal surgery will also be documented (sphincter sparing vs APER). The margin status of the resected specimen will be analysed.

7.0 FOLLOW UP

All patients will be followed up in clinic at regular intervals with CEA estimation at each clinic visit. Patients will be seen at 8-weeks post-CRT for review of 8-week results, DRE and EORTC QLQ-C30 completion (most patients will have been seen at 4-weeks, but for outside referrals, this, or a later appointment, may be a Registration visit). Patients will be followed after completion of all treatment every 3 months for 2 years, every 6 months for 3 years, and then annually until 10 years have elapsed. A follow-up proforma should be completed at each follow-up appointment, Please see Appendix 10.5 for full details of out-patient, MRI, CT, PET and flexible Sigmoidoscopy/colonscopy follow-up. A trial Pro Forma will be completed for all DRE's and Sigmoidoscopies. Colonoscopies are recommended as per NICE guidance[25]. **Radiology proformas will be completed by Dr Brown and Dr Chua at the time of central review. All proformas should be faxed to the RMH GI Clinical Trials unit as soon as possible (Fax: 020 8661 3610).**

A number of patients will be recruited following a surgical 'second opinion' (usually regarding sphincter preservation). It is emphasized that the initial Surgeon (the Surgeon that performed the diagnostic biopsy) will be respectfully requested to perform all surgical follow-up, including sigmoidoscopies as per protocol. A standard letter will be sent after accrual to the initial Surgeon, and to the referring Clinical Oncologist. It is acknowledged that the involvement of the initial Surgeon is essential for the successful running of this trial. It is further acknowledged that there is a possibility that some initial Surgeons may disagree with recruitment into this trial, and thus may not wish to be involved in follow-up. In such situations, unless the Investigator can appoint a suitable alternative Surgeon to take over surgical follow-up and endoscopy (if possible a trial Investigator), the patient will not be eligible for accrual into this trial.

Patients that have not yet achieved a Tumour Regression Grade 1 or 2 on MRI at 8 week following completion of RT / CRT will have identical follow-up until grade 1 or

2 has been achieved (if stable disease is demonstrated for such a patient on 2 consecutive scans during this period, the patient will be referred for immediate surgery). More frequent MRI scanning will be performed at the discretion of the MDM. A modified Mandard Tumour Regression Grade has been used for reporting (please see appendix 10.2).

The timing, indication and interpretation of biopsies is viewed as critically important in the context of this trial. Blind biopsies are discouraged, ie if there is no abnormality on sigmoidoscopy/ colonoscopy, then we do not recommend biopsies directed at the mucosa once occupied by the tumour. Biopsies are discouraged unless: i) an area of residual disease is visualised at (and no earlier than) 3-month Sigmoidoscopy; ii) a clinically suspicious area develops/re-appears at Sigmoidoscopy/colonoscopy; iii) MR changes raise the suspicion of recurrence.

Patients with evidence of clinical or radiological local recurrence will be referred immediately by phone and fax to the surgical team for urgent biopsy. It is anticipated that such concerns will be brought to light by MR imaging, and thus will automatically be discussed at the Unit MDM. If there is a clinical suspicion of recurrence from a source other than MR, then an urgent MRI will be considered depending on date of previous imaging. All such cases will be discussed at the next available MDM. If urgent salvage surgery is recommended, a PET/CT scan will be performed routinely pre-op to outrule occult metastatic disease.

Subjects with metastatic disease detected during follow-up will be treated according to the Unit MDM recommendation.

Patients with evidence of clinical or radiological local recurrence must be treated at least as urgently as a primary rectal cancer by the surgical team.

8.0 STATISTICAL CONSIDERATIONS

Analysis methods

All time-to-event endpoints will be measured from the end date of chemo-radiotherapy, and calculated using Kaplan-Meier methods. The final analysis will be carried out when all patients have had at least 2 years follow-up. An additional overall survival analysis may be carried out after all patients have had at least 10 years follow-up. **Patients who have not yet experienced the event in question will be censored at date of last follow-up**.

Primary endpoints

Since all patients will have at least two years complete follow-up, the percentage of patients in continued response without surgery at two years, and the percentage of patients with local failure at two years, will be calculated as percentages of all patients, with exact 95% binomial confidence intervals.

Secondary endpoints

Time to distant disease will be measured as the time to the first diagnosis of lymph node or other distant disease, confirmed via PET/CT, MRI, CT or pathology.

Time to maximal tumour response will be defined as follows: for patients who achieve CR, it is the time until first recorded MRI scan with tumour grade T0. In patients where this has not happened, it will be the time to the first of two consecutive MRI scans which show the same modified Mandard regression grading (or the first of two consecutive scans in which the second scan shows an increased Mandard regression grade). Patients with a continuing reduction in Mandard grade at the time of analysis will be censored at the date of last scan..Patients who opt for surgery or withdraw for other reasons before recorded maximal response will be censored at date of last scan.

Time to local regrowth will be measured as the time until the first recorded increase in Mandard grade, on MRI. Patients with continued stable disease or complete response will be censored at date of last MRI scan. Patients who opt for surgery or withdraw for other reasons before recorded local regrowth will be censored at date of last scan.

Of all patients who had surgery for progression of local disease, the percentage with positive margins will be calculated, with an exact 95% confidence interval. The percentage who had negative margins and had their sphincters preserved will also be calculated with an exact 95% confidence interval

Progression free survival will be measured as time until the first occurrence of any of the following: increased Mandard grade (in patients who did not achieve CR), any tumour T1 or above (in patients who achieved CR), first diagnosis of nodal or distant disease (diagnosed on MRI, CT, PET or pathology); or death from any cause.

Quality of life will be measured using EORTC QLQ-C30, IBDQ and Vaizey questionnaires. Missing data will not be replaced, but numbers assessed at each time-point will be reported. Change from baseline will be assessed at each time-point and summarised using descriptive statistics. In addition, counts and percentages of LENT-SOMA worst grades at each time-point will be reported.

Sample size

We wish to show that the percentage of patients who can successfully omit surgery is at least 10%, with a true rate expected to be at least 25% (and possibly this may be considerably higher). The two-year failure rate is assumed to be no more than 5%, and a failure rate of 15% or more would be considered to be unacceptable.

Using a single-stage exact phase II design, with one-sided significance level of 0.05, then a total of 59 patients would provide 80% power to prove a 2-year failure rate of less than 15% if the true rate is no more than 5%. The trial would be a success according to this endpoint if no more than 4 patients out of 59 have local failure at 2 years. The same number of patients would provide at least 90% power to show that the proportion of patients safely omitting surgery is more than 10%, if the true rate is

expected to be at least 25%. The trial would be a success according to this endpoint if at least 11 out of 59 patients have safely omitted surgery. To be judged a success overall the trial must pass both of these endpoints (no more than 4 patients with local failure, and at least 11 safely omitted surgery).

We expect to recruit 39 patients from the Royal Marsden and network hospitals and 20 patients from other multi-centre sites. This recruitment is expecting to be completed by 31st December 2012. We believe 60% of eligible patient will wish to participate in the "deferral of surgery". However, only 20% of rectal patients who undergo pre-operative CRT will develop a complete response and meet the inclusion criteria.

Stopping Rule

The trial will be stopped if 5 patients develop disease which is surgically not salvageable or incompletely excised. There will be continuous monitoring of all patients as part of the regular TMG

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