Low Rectal Cancer Study summary

Purpose

Currently there is a great difference in the rate of Circumferential Resection Margin (CRM) positivity between rectal cancers treated with TME anterior resection vs. those treated with abdomino-perineal excision (which is a treatment option for the low rectal cancers <6cm from the anal verge).

It is proposed that accurate MRI staging pre-operatively will allow the correct patients to receive neo-adjuvant chemoradiotherapy (CRT), and also pre-warn the surgeons if the resection margins appear threatened so that the operation can be modified to take this into account.

The primary endpoint is to see if this approach reduces the rate of CRM positivity, as this is an important prognostic factor for local recurrence and survival. It is aimed to reduce this from the current level of around 30% to 15%.

Hypothesis: In low rectal cancer, improved local control and survival can be achieved through a reduction in the involved CRM rates by MRI-planned surgery and selective pre-operative therapy.

Study design

The study is an international multicentre, prospective, observational study, whereby patients with biopsy-proven low-rectal cancer (lower edge of the tumour < 6cms from the anal verge on MRI), will be recruited from participating centres, having given informed, written consent. Data from the radiology, surgical and pathological aspects will be collected and analysed centrally at the Pelican Cancer Foundation. The patient's medical records will be reviewed for five years post surgery, and the patients will also be followed up by quality of life questionnaires.

Research objectives

This project aims to show that in low rectal cancer, improved local control and survival can be achieved through a reduction in the involved CRM rates by MRI-planned surgery and selective pre-operative therapy. It also aims to assess the ability to predict disease recurrence and to provide an assessment of disease-free survival and overall survival.

Full Background

The MERCURY Study demonstrated the accuracy, feasibility and reproducibility of Magnetic Resonance Imaging (MRI) to stage rectal cancer in a prospective, multidisciplinary, multi-centre study (1). However, there were differences in patient outcome, dependent upon the

position of the tumour in the rectum and its height above the anal verge. Whilst the outcome was excellent for patients who underwent an anterior resection (AR), the outcome, based upon margin involvement and quality of the specimen, was poor for patients who underwent an abdomino-perineal excision (APE) for low rectal cancer. Previous observational studies have also reported a less favourable outcome for low rectal cancer, although the variability of outcome may relate to the requirement for a specific surgical procedure, (an APE) and the height of the tumour above the anal verge (2). Other factors such as residual disease and tumour perforation have also been noted as problems with low rectal tumour surgery (3).

The use of pre-operative therapy is also more frequently utilised the low rectal cancer, but there are questions about the additional morbidity and mortality associated with such therapy.

Involvement of the circumferential resection margin (CRM) is an important adverse prognostic factor, as regards local recurrence, and has been well established (4-7). A modification of surgical technique for low rectal cancer (lower edge of the tumour <6cm from the anal verge) has been proposed to improve outcome (8-10), and the morbidity and mortality from such a radical perineal excision needs to be assessed in light of the increased use of pre-operative combined modality therapy.

The use of MRI to identify additional prognostic factors thought to affect outcome in low rectal cancer will be assessed, as will histopathological correlation with MRI and assessment of quality of the specimen. It is particularly important to examine the correlation of MRI to the histopathology in low rectal cancer. Previous studies (11-12) have alluded to the effect of diminished perirectal fat in the lower rectum in decreasing MRI accuracy in predicting CRM status.

The development of this study has followed the protocols of the MERCURY Study of prospective, multi-disciplinary data collection with the addition of quality of life assessment, urogenital function and body image. The end-point of the study will be disease recurrence (local and/or distant).

Other scientific aspects to be addressed:

The collection of data on a large group of patients with rectal cancer allows the potential assessment of other questions relating to the management and outcome of the disease. Patients who consent to the study will be asked to allow their clinical information, radiological images, histopathological data and follow-up data to be used to address a number of other issues of scientific interest. Whilst the primary and secondary aims of the study relate principally to outcome for this group of patients, the outcome is multi-factorial in nature and a number of individual elements are involved. Detailed assessment of the clinical, radiological

and histopathological data would allow a detailed staging system to be developed, with clarification of the staging and clinical assessment of low rectal cancer. The early collection of quality of life and functional data is important to relate to the morbidity of the surgery, in both restorative resections and perineal excision.

Methods

This study is a multidisciplinary, prospective, multi-centre, observational study. Consecutive patients with biopsy-proven low rectal cancer will be asked to participate therefore excluding selection bias towards the better prognostic cases.

In the participating centres, patients with adenocarcinoma within 6cm of the anal verge will be approached to participate in the study, using informed, written consent and they will be able to withdraw at any point. The definition of a low cancer will be based initially upon digital rectal examination and confirmed using MRI criteria. Distance above the anal verge may be assessed in the left lateral position, compared at operation, assessed radiologically and, in those patients undergoing an APE, compared to the dentate line and anal verge histopathologically.

Statistics

Based upon data from The MERCURY Study, of 729 patients registered, a group of 282 had a low (<6cm) rectal cancer. Of these, approximately 100 underwent an APE.

In this study we aim to rule out this lower limit of the positive margin rate of 30% and improve that to around 15%. A single stage Simon design will be employed with a 1-sided alpha of 0.05. We wish to rule out an upper limit of the positive margin rate of 30% (p0 = 1-0.3 = 0.7) with an expected positive margin rate of around 15% (p1 = 1-0.15 = 0.85). This will be achieved if at least 52 out of a total of 65 patients are free from a positive margin, this will be achieved with at least 90% power. (The table below gives the sample sizes for different power assumptions).

P0	P1	Power	N negative	Total
0.7	0.85	80%	40	49
		90%	52	65
		95%	67	85

The proposal is to perform this analysis only on the patient classified as being likely T stage 3 – 4 by MRI, which accounts for around 30% of patients. This errs on the side on an increased positive margin rate as the data suggest that these stage 3 – 4 tumours result in higher positive margin rates. This study will attempt to improve the positive margin rates to around

15% for this group of patients and will therefore require 65 patients in the stage 3 – 4 group. This will require an estimated total sample size of 217 patients with low rectal cancer to be recruited (including an estimated 25% drop-out = 271).

If this study is successful in ruling out the 30% positive margin rate in the stage 3 – 4 tumours then this will also achieve an overall reduction in the positive margin rate for the whole lower rectal cancer cohort.

The sample size will allow accurate, prospective assessment of function, quality of life and outcome. This study will co-exist well with other oncological studies (e.g. EXPERT-C and ARISTOTLE) as individual centres' CRT policies will not be influenced or altered.

Inclusion Criteria

Adults age 18 or over, recently diagnosed with biopsy-proven, primary, low rectal cancer and able to give informed, written consent to participate in the study. No previous therapy for rectal cancer.

Exclusion Criteria

Current pregnancy, including ectopic pregnancy. Previous pelvic/rectal malignancy (excluding carcinoma in-situ). Previous pelvic radiotherapy. Previous pelvic floor surgery for faecal incontinence or prolapse.

MRI Exclusion Criteria

Patients will be excluded from the study if they are unable to undergo MRI in line with current safety guidelines or if they are unable to tolerate the scanning procedure. It is expected that these patients will form less than 5% of the total.

Regulatory & Ethical requirements

Central ethical approval will be applied for through NRES and approval has been given via our sponsor sponsor Hospital (Royal Marsden Foundation NHS Trust, Fulham) Committee for Clinical Research. Each unit will not be responsible for obtaining their local hospital Ethics Committee (EC) approval for the study protocol. After ethical approval has been obtained, the local ethical committees (LREC) will be approached with the trial protocol for their approval.

Experiments or studies proposed including end points

Primary aim: Does MRI planned surgery & selective neoadjuvant therapy produce a reduction of involved CRM from 30% to 15% in rectal cancers <6cm fro the anal verge. The end-point of the study will be disease recurrence (local and/or distant) or death.

Secondary aims: The study will also allow an assessment of prediction of disease recurrence as well as an assessment of disease-free survival and overall survival.