Protocol for

Low Rectal Cancer

Study

MERCURY 2 Study

Research Group

CONTENTS

1. STUDY MANAGEMENT GROUP 4
2. PARTICIPATING CENTRES 5
3. GLOSSARY OF TERMS 6
4. INTRODUCTION 7
4.1 Background & overview of the Study 7
4.2 Hypothesis 10
5.0 AIMS 10
5.1 Primary Aims 10
5.2 Secondary Aims 10
6. OUTLINE OF THE STUDY 12
7.1 Sample size 14
7.2 Analysis methods 16
7.2.1 Primary endpoints 16
7.2.2 Secondary endpoints 18
7.3 Timing of analysis 25
8. STUDY METHODOLOGY 27
8.1 Design Overview 27
8.2 Key Definitions 27
8.3 Study Registration 27
8.4 Data Collection 27
8.5 Study Coordination 28
9. CLINICAL PRACTICE 29
9.1 Patient monitoring 29
9.2 Clinical Laboratory Tests 29
9.3 Participating Centres and Duration of Study 29
9.4 Patient Registration 29
9.5 Inclusion Criteria 29
9.6 Exclusion Criteria 30
9.7 MRI Exclusion Criteria 30
9.8 Withdrawal from the study 30
9.9 Data Storage and Analysis 31
10. SURGICAL FACTORS 32
11. RADIOLOGICAL FACTORS 33
11.1 Magnetic Resonance Imaging (MRI) 33
12. HISTOPATHOLOGICAL FACTORS 35
13. ONCOLOGICAL FACTORS 36
13.1 Locally Advanced Rectal Cancer 36
13.2 Early Operable Cancers 37
13.3 Adjuvant Chemotherapy 37
13.4 MDT Documentation 37
14. FOLLOW-UP 38
15. QUALITY OF LIFE AND FUNCTION 39
16. DATA MANAGEMENT 40
16.1 Data Collection Forms 40
16.2 Data Handling 40

16.3 Database System 40
16.4 Data Interpretation/Analysis 40
17. REGULATORY AND ETHICAL REQUIREMENTS 41
17.1 Ethics Committee Submissions and Approval 41
17.2 Informed written Consent 41
17.3 Patient Confidentiality 41
17.4 Protocol Amendments 42
17.5 Study Monitoring 42
17.6 Data Ownership, Publication and Reporting. 42
17.7 Personal Responsibilities 43
17.8 Early Termination 43
18. REFERENCES 45
19. APPENDICES 47
Appendix 1: Steps of Data Collection - p. 49 47
Appendix 2: MRI Methods - pp 50-59 47
Appendix 3: Pathology Protocol - pp 60-78 47
Appendix 1: Steps of Data Collection 48
Appendix 2: MRI Methods 49
Appendix 3: Pathology Protocol 59
Appendix 4: Radiotherapy Planning Details 78
Appendix 5: Suggested Follow-Up Policy 80
Appendix 6: Case Report Forms 81

Deleted: 808

1. STUDY MANAGEMENT GROUP

Principal Investigators

Mr Brendan Moran	Surgeon	North Hampshire Hospital
Dr Gina Brown	Radiologist	Royal Marsden Hospital, Surrey

Co-Investigators

Mr Graham Branagan	Surgeon	Salisbury District Hospital
Ms Helen Chave	Nurse	Salisbury District Hospital
Professor Bill Heald	Surgeon	Pelican Cancer Foundation
Prof Phil Quirke	Pathologist	St James University Hospital
Dr Nick West	Pathologist	St James University Hospital
Mr Peter How	Research Fellow	Pelican Cancer Foundation
Mr Sigmar Stelzner	Surgeon	Dresden-Friedrichstadt General Hospital
Mr Joachim Strassburg	Surgeon	Dresden-Friedrichstadt General Hospital
Dr Bodil Ginnerup	Radiologist	Aarhus University Hospital
Mr Soeren Laurberg	Surgeon	Aarhus University Hospital

Statistician

Karen Thomas	Royal Marsden Hospital, Surrey

2. PARTICIPATING CENTRES

UK

Ashford St Peters NHS Trust

East Surrey Hospital

Epsom and St Helier NHS Trust

Frimley Park Hospital

Kingston Hospital

Llandough Hospital, Cardiff

Mayday University Hospital

North Hampshire Hospital, Basingstoke

Royal Marsden Hospital

Salisbury District Hospital

Ulster Hospital

European

Aarhus Hospital, Denmark

Clinical Centre of Serbia, Belgrade

Dresden-Friedrichstadt General Hospital

Krankenhaus im Friedrichshain, Berlin

3. GLOSSARY OF TERMS

MERCURY	The Magnetic Resonance Imaging and Rectal Cancer European Equivalence Study
MRI	Magnetic Resonance Imaging
AR	Abdominoperineal Excision
LAR	Anterior Resection
APE	Low Anterior Resection
CRM	Circumferential Resection Margin
CRT	Chemoradiotherapy
Low Rectal Cancer	Lower edge of the tumour < 6cm from the anal verge
SMG	Study Management Group
DOSE	Difficulty Of Surgical Excision
QoL	Quality of Life
REC	Research Ethics Committee
COREC	Central Office for Research Ethics Committees

4. INTRODUCTION

4.1 Background & overview of the Study

The MERCURY Study demonstrated the accuracy, feasibility and reproducibility of Magnetic Resonance Imaging (MRI) in staging 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 in the treatment of 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 the surgical technique for abdomino-perineal excision 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 requires 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. Histopathological correlation with MRI and assessment of quality of the specimen will also be assessed. 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.

4.2 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 to determine the optimum plane of surgery. The plane of surgery and the use of pre-operative therapy have an impact on the quality of life.

5.0 AIMS

5.1 Primary Aims

To assess the rate of CRM positivity rate in low rectal cancer.

To assess the difference in global quality of life at two years post surgery in patients according to plane of surgery with or without sphincter preservation.

5.2 Secondary Aims

1. To assess the difference in other patient reported outcomes in patients according to plane of surgery with or without sphincter preservation. Sexual, urogenital and bowel function assessment is part of continued follow-up through questionnaire and medical note review.

2. Analysis of the clinical and radiological factors influencing the decision by surgeons to carry out Anterior Resections, APE or extralevator APE. Factors include: clinical

and radiological tumour distance from anal verge, MRI predicted safety of the planes of surgery, initial stage of the tumour and the quadrants involved.

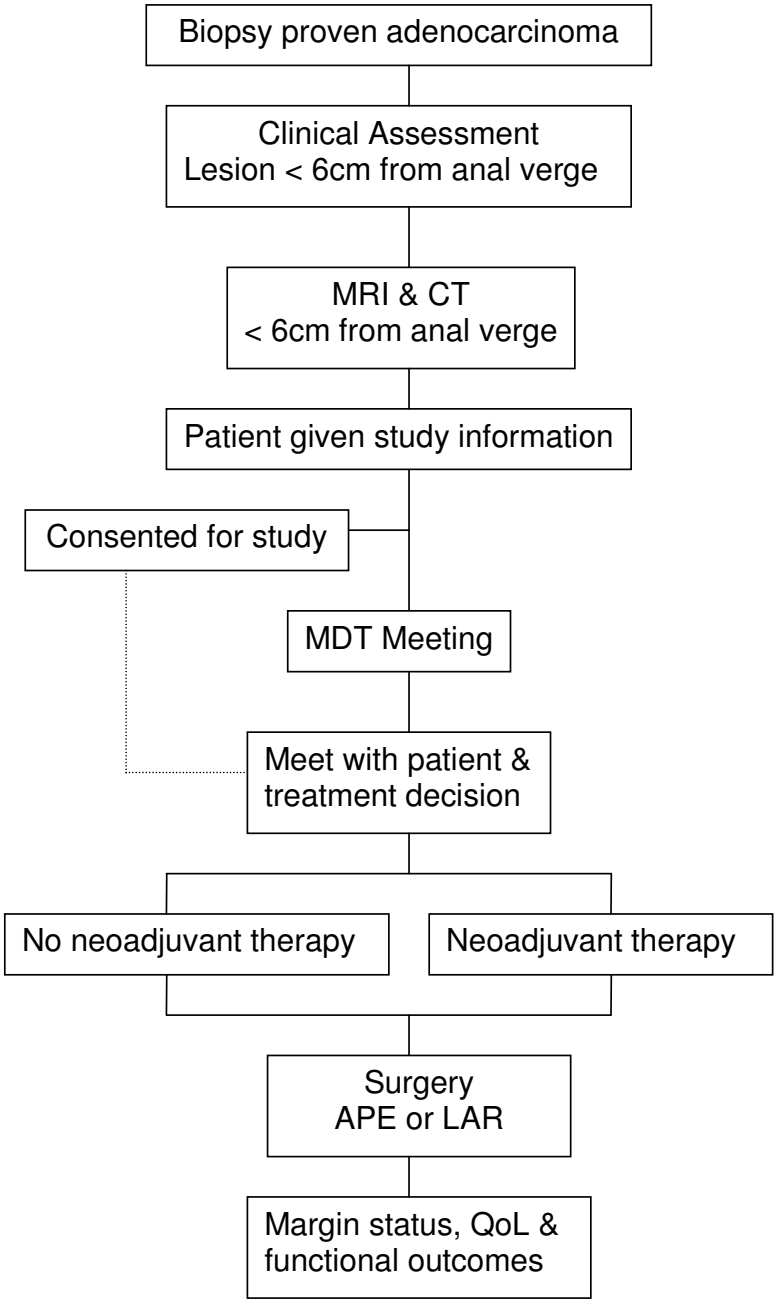
3. Assessment of time to local recurrence, disease-free and overall survival.

4. Comparison of imaging and pathology staging assessment, patient characteristics and complication rates, between different types of surgery and surgical approaches.

5. Investigation of potential associations between imaging and pathology assessment of radial and distal margins, neo-adjuvant chemoradiotherapy, perineal complications and sphincter preservation rates.

6. Investigation of potential association between length of operation with number of complications and length of post-operative ITU/HDU stay.

6. OUTLINE OF THE STUDY



In the participating centres, patients with biopsy-proven adenocarcinoma, with the lower edge <6cm of the anal verge will be approached to participate in the study. The definition of a low cancer will be based initially upon digital rectal examination and confirmed using MRI criteria. However, MRI assessment of a low rectal cancer will also allow inclusion for later assessment of distance. Distance above the anal verge may be assessed in the left lateral position, compared to measurement at operation, assessed radiologically and, in those patients undergoing an APE, measured to the dentate line and anal verge histopathologically.

7. STATISTICS

7.1 Sample size

Based upon data from The MERCURY Study, approximately 100 patients had low rectal cancer defined as tumours <6cm from the anal verge. The aim of this study is to reduce the positive margin rates in low rectal cancer patients of 30% 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 with at least 90% power if at least 52 out of a total of 65 patients have a clear margin. (The table below gives the sample sizes for different power assumptions).

P0	P1	Power	Number with negative margins	total
0.7	0.85	80%	40	49
		90%	52	65
		95%	67	85

The original protocol specified the primary analysis was to be performed only in patients classified as stage 3-4 on MRI (expected to be 30%), and allowed for a 25% drop-out rate. Hence the total sample size was set as 271, in order to achieve 217 evaluable patients and 65 with MRI stage 3-4.

However we now plan to analyse the primary endpoint in all patients, and to prove that the positive margin rate is less than 30% regardless of MRI stage. Any patient who has

had surgery intended to be curative followed by a pathology report will be included in the primary analysis

We wish to extend the power of the study to meet an additional co-primary endpoint (previously defined as a secondary endpoint) of assessing difference in quality of life in patients undergoing APE vs. Anterior resection. Based on data collected so far, we expect approximately 50% of patients to undergo an APE, and 40% to undergo anterior resection (with 10% of patient having other or no surgery). We wish to estimate the mean difference, with 95% confidence interval, of quality of life at 2 years post-operatively as measured by the global QoL scale taken from the QLQ-C30, in patients undergoing APE vs. LAR. Only patients who survive (with or without recurrence) at two years will be included in this analysis (expected to be 85%). Measurements taken within +/-6 months of the target date will be accepted.

The EORTC reference manual suggests a difference of 16 points in global QOL between groups could be interpreted as a ‘large’ difference, and 5 or less is a ‘small’ difference. Hence we wish the 95% confidence interval for the difference in quality of life between groups to be no more than +/-5.

Based on preliminary data for 24 patients, the standard deviation of 2 year global quality of life was 23 for both LAR (n=13) and APE (n=11) patients. There was an observed difference of 11 points between the groups.

With a total sample size of 330 patients evaluable at 2 years (147 LAR and 183 APE) and a common standard deviation of no more than 23, the 95% confidence interval for the difference in means should be no more than +/-5 from the observed difference. With an expected 2 year survival rate of 85%, the total sample size required is therefore 389. In order to allow for a 20% non-completion rate for surviving patients, we will aim to recruit a total of 485 patients.

At the time of writing a total of 323 have been recruited, but not all centres have participated in the quality of life data collection. From participating centres, a total of 222 patients have been recruited. Therefore a further 263 are required, from participating centres only.

7.2 Analysis methods

Baseline characteristics will be reported for all patients using descriptive statistics. These will include age at surgery, sex, ASA score, neoadjuvant therapy (yes or no), pathological T-stage, tumour height on pre-operative MRI, and type of operation. Numbers and type of operations performed will be reported for all patients and by centre.

7.2.1 Primary endpoints

The first primary endpoint will be calculated as the percentage of patients with CRM recorded as involved on the pathology report. All patients who have undergone surgery

will be included in the denominator. Patients with a missing pathology report will be included as having an involved margin. An exact one-sided binomial test will be used to test the null hypothesis that the percentage of involved margins is 30% or more. A p-value of < 0.05 will be considered as statistically significant.

Global quality of life will be measured using the EORCT QLQ-C30 questionnaire, at baseline (pre-operatively), then at 1, 2, 3, and 4 years post-operatively. Quality of life forms will be reported for the closest scheduled time-point as defined in section 15. Hence forms completed between 18 and 30 months will be used for reporting quality of life at 2 years post-operatively. Where patients have completed more than one form within this assessment window, the one closest to the scheduled assessment time-point of 2 years will be used for reporting.

Global quality of life scores at 2 years will be reported, using standard summary descriptive statistics. Only patients with at least one completed form within the assessment window will be included. The number of completed and missing forms will be reported at each time-point.

The mean and 95% confidence intervals for the difference in 2 year global scores from the QLQ-C30, by type of operation performed (APE vs. LAR only) will be calculated. Univariate analysis will be used to test for significant differences between operation types. The data will first be assessed for normality and either a two-sided t-test or Mann-Whitney test will be used as appropriate.

If the two year score shows significant difference on univariate analysis, a multivariate linear regression model will be constructed. The effect of operation type (APE vs. LAR) on score after adjusting for age at operation, sex, neoadjuvant therapy (yes/no), ASA (1, 2 or 3), tumour height from anal verge (0-2, 3-4, or 5-6 cm) and pre-operative MRI stage (T1/2 vs. T3/4) will be reported with a 95% confidence interval. If the scores are markedly non-normal in distribution (and no appropriate transformation can be made), then scores will be dichotomised about the median (or other clinically significant cut off if known) and binary logistic regression will be used instead.

7.2.2 Secondary endpoints

1) Other patient reported outcome scores will be measured using the EORCT QLQ-C30 and QLQ-CR38, and St Marks bowel function or coloplast stoma QoL questionnaire, at baseline (pre-operatively), then at 1, 2, 3, and 4 years post-operatively. Similar methods to those described above will be used to analyse these scores. Quality of life forms completed at any time will be included, and reported for the closest scheduled time-point as defined in section 15. Hence a form completed at 15 months post-operatively will be reported as 1 year, and forms completed at 20 months post-operatively will be reported as 2 years, etc. Where patients have completed more than one form within a single assessment window, the one closest to the scheduled assessment time-point will be used for reporting.

Standard scoring methods will be used for each questionnaire. Scores will be reported at each timepoint, for the whole group of patients, using standard summary descriptive

statistics. Only patients with completed forms will be included at each time-point. The number of completed and missing forms will be reported at each time-point.

The mean and 95% confidence intervals for the difference in global and subscores from the QLQ-C30 and QLQ-CR38 questionnaires, by type of operation performed (APE vs. LAR only) will be calculated, for scores at 1 and 2 years post-operatively. Univariate analysis will be used to test for significant differences between operation types, for each subscore at 1 and at 2 years. The data will first be assessed for normality and either a two-sided t-test or Mann-Whitney test will be used as appropriate. At each of the two time-points, the overall false discovery rate will be set at 5% and p-values adjusted using a Benjamini-Hochberg correction.

For scores with a significant difference on univariate analysis, a multivariate linear regression model will be constructed. The effect of operation type (APE vs. LAR) on score after adjusting for age at operation, sex, neoadjuvant therapy (yes/no), ASA (1, 2 or 3), tumour height from anal verge (0-2, 3-4, or 5-6 cm) and pre-operative MRI stage (T1/2 vs. T3/4) will be reported with a 95% confidence interval. If the scores are markedly non-normal in distribution (and no appropriate transformation can be made), then scores will be dichotomised about the median (or other clinically significant cut off if known) and binary logistic regression will be used instead.

2) The following clinical and radiological characteristics will be reported using summary statistics (percentages, mean, median, standard deviations) in all patients and by type of operation performed

- Clinical tumour distance from anal verge
- Radiological tumour distance from anal verge (on diagnostic MRI and last pre-operative MRI)
- Safety of the planes on the diagnostic MRI – predicted surgical plane defined as:

  TME Plane

    Low Anterior Resection

    APE:

      Standard

      Intersphincteric

  Extralevator

    Enhanced APE:

      Left Lateral

      Right Lateral

      Posterior

    Anteriorly enhanced APE

    Extenteration

- Initial stage of the tumour on diagnostic MRI
- T stage, EMVI Status, nodes, pelvis sidewall nodes, tumour regression grade (if the patient receive pre-operative chemoradiotherapy) from last pre-operative MRI
- Quadrants involved (from pathology report)

For the purpose of this endpoint, type of surgery will be classified into the following three groups:

Anterior resection is defined as all operations reported by surgeon as Anterior Resection

Extralevator APE is defined as operations where the following three conditions are all met:

- APE with distal TME dissection ended at levator insertion or at coccyx/recto-sacral fascia (as reported by surgeon)
- intended margins of excision are anterior either outer limit of EAS or posterior wall of vagina or other, and lateral inner aspect of ischial tuberosities, and posterior excision of coccyx (as reported by surgeon)
- surgical APE plane equals levators (as reported by pathologist).

Standard APE is defined as all other operations reported by surgeon as APE

3) Overall survival will be measured from date of diagnosis (i.e. the date of the initial MRI staging scan), for all patients. Surviving patients will be censored at date of last follow-up. Disease-free survival will be measured from date of surgery, in all patients undergoing curative surgery, to date of local or distant recurrence, or death from any cause. Surviving patients without disease will be censored at date of last follow-up. Time to local recurrence will be measured from date of surgery, in all patients undergoing curative surgery, to date of local recurrence. Surviving patients without local disease will be censored at date of last follow-up. Death from distant metastases or other causes will be treated as a censored event. All endpoints will be described using Kaplan-Meier methods, median survival with 95% confidence intervals will be reported.

4) Patients will be grouped according to the type of operation done, defined as follows:

- ELAPE defined as for endpoint 6 above
- Intersphincteric APE: APE with intended margin of excision anterior, lateral or posterior intersphincteric
- Standard APE (SAPE): defined as all other APEs not meeting the above criteria (as reported by surgeon)
- LAR: all LAR as reported by surgeons

The following variables will be compared between types of operation (LAR, SAPE or ELAPE):

Age (Kruskal-Wallis test)

Sex (Chi-squared test)

ASA grade (Kruskal-Wallis)

Neoadjvant therapy (yes/no) (Chi squared)

Tumour height as reported by last pre-operative MRI (Kruskal-Wallis)

Pathologic T-stage (Chi-squared or Fisher's exact test)

The following variables will be compared between ELAPE vs. SAPE:

CRM positivity (Chi-squared test)

Specimen perforation (Chi-squared test)

Tumour perforation (Chi-squared test)

Length of operation (Mann-Whitney)

Intra-operative rectal injury (Chi-squared)

Peri-operative blood loss (Mann-Whitney test)

Worst grade of post-operative complications (Mann-Whitney)

Number of perineal complications (infection or breakdown) (Chi squared)

Length of post-operative ICU/HDU stay (Mann-Whitney)

All tests will be two-sided with alpha=0.05. Specimen perforation is defined by pathology reporting of APE plane of resection equal to Perf/sub mucosal/in sphincter. Post-operative complications are graded according to the Clavier-Dindo system as follows:

Grade 1: Atelectasis

Pulmonary Oedema

Paraytic Ileus

Diarrhoea

post-opertive perineal wound breakdown, managed conservatively

Grade 2: Pneumonia

Pulmonary embolus

Gastrointestinal obstruction

Deep vein thrombosis

AF/other arrhythmia

Any post-operative surgical complication, excepting perineal wound breakdown, managed conservatively

Grade 3: Any post-operative surgical complication requiring return to theatre

Grade 4: Any post-operative surgical complication requiring return to ITU

ARDS

Myocardial infarct

Heart failure

Renal failure

Stroke

Grade 5: Death related to post-operative complication

All other complications will be graded individually by a clinician.

5) Craniocaudal regression from the anal verge will be measured by calculating the difference in tumour height from anal verge between the last available pre-CRT MRI and the last available pre-operative MRI. This will be described using summary statistics in patients who have undergone APE vs. patients who have undergone any other surgery, and between patients with and without perineal wound complications.

Patients will be classified according to their predicted operation types (grouped as low anterior resection vs. any other) on pre-CRT MRI and on last post-operative MRi (resulting in four possible distinct groups overall). Within these groups, the count and percentage of patients undergoing APE, and the count and percentage of patients with perineal wound complications will be presented.

The difference between tumour height on anal verge on the last pre-operative MRI, and distance to distal margin on pathology will be described using summary statistics, in patients who have undergone APE only. As a consistent (but unknown) shrinkage

factor is expected between MRI and pathology, summary statistics presented will include standard deviations, and lower and upper quartiles.

In a subset of patients where possible operation is anything other than low anterior resection on last pre-CRT MRI AND possible operation equal to low anterior resection and tumour regression grade <=3 on last pre-operative MRI, the number and percentage with pathology reported tumour at the sphincter extending to submucosal/internal only, or tumour above sphincter only, will be reported.

6. Possible association between length of operation and total number of complications will be assessed using a non-parametric correlation coefficient. Association between length of operation and length of post-operative admission to ITU/HDU will be assessed in the same way. All operations will be included in these analyses.

7.3 Timing of analysis

Data will be analysed in two stages. The first stage will include patients recruited up to and including 1st December 2011 (n=322). In this stage the primary endpoint will be assessed, and all secondary endpoints excepting quality of life will be analysed.

The final analysis will be performed after all patients have been recruited to the study (n=485) and will occur no earlier than 2 years following the last operation in the study. At

this stage quality of life will be analysed (secondary endpoint 1), and all other secondary endpoints will again be reported. The primary endpoint analysis will not be repeated at this stage.

8. STUDY METHODOLOGY

8.1 Design Overview

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.

8.2 Key Definitions

- Rectal Cancer - Histologically proven adenocarcinoma of the rectum.
- Low Rectal Cancer - This includes all patients with a tumour whose lower border is less than 6cm from the anal verge on digital rectal examination (DRE) or rigid sigmoidoscopy, or within 6cm on MRI assessment.

8.3 Study Registration

All patients diagnosed with primary low rectal cancer will be approached to participate in the study in each centre.

8.4 Data Collection

Individual patients will not be visited by the study coordinating team. Quality of life questionnaires and follow-up questionnaires will be sent to patients by post.

Patients' medical records will be accessed and reviewed for a period of seven years following surgery. Local investigators will be responsible for data collection and have access to the study coordinators. Data collection will be prospective, using specialised

proformas, or directly using web-based data collection. All centres will be asked to send dedicated CDs containing DICOM images of all MRIs and specimen photographs (by e-mail).

8.5 Study Coordination

The study will be coordinated by the study management group (SMG), based at The Pelican Cancer Foundation.

Any major change in study direction will be proposed to and agreed by all members of the SMG. The SMG will meet at six monthly intervals. The entire Study Group will be invited to meet prior to study launch and, on study Informed, written consent will be obtained from each patient with copies retained in their hospital records and workshops have been held for training and quality control.

9. CLINICAL PRACTICE

9.1 Patient monitoring

Each centre's colorectal MDT will be responsible for the management and care of registered patients.

9.2 Clinical Laboratory Tests

No additional laboratory tests will be required for the study, other than those performed as part of routine clinical practice.

9.3 Participating Centres and Duration of Study

Participating centres will be required to agree to follow the study protocol, register consecutive patients with low rectal cancer and submit completed data proformas.

Patient recruitment is estimated to take 24 months (from May 2012), completed data capture will be around 30 months. Patients will be followed up for 5 years from surgery.

9.4 Patient Registration

Patients with biopsy-proven, primary low rectal cancer will be approached for consent for the study.

9.5 Inclusion Criteria

- Ability to give informed, written consent.
- Adults age 18 or over - male or female

- Recently diagnosed with biopsy-proven, primary, low rectal cancer
- No previous therapy for rectal cancer

9.6 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.

9.7 MRI Exclusion Criteria

Patients will be ineligible for the study if they are unable to undergo MRI in line with current safety guidelines. These include:

- Evidence of metal fragments within the eyes
- Pregnancy
- Implanted metal devices
- Pacemakers
- Artificial heart valves
- Previous surgery to the brain
- Cochlear implants

Some patients may find an MRI scan a distressing experience due to claustrophobia or cardio-respiratory compromise and are unable to tolerate an MRI. It is expected that these patients will form less than 5% of the total.

9.8 Withdrawal from the study

A patient may withdraw from the study at any time. Reason for and date of withdrawal should be documented when possible and returned to the study coordinators.

9.9 Data Storage and Analysis

Data will be collected locally then collated and stored centrally in the Radiology Department at the Royal Marsden Hospital, Surrey. Data will be managed and analysed using the Royal Marsden Hospital Data System. The local lead investigator at each centre will be responsible for the collection and submission of data.

10. SURGICAL FACTORS

The following proformas need to be completed by participating surgeons:

- On initial assessment in the outpatient clinic the tumour site and local tumour factors should be documented by the surgeon.
- Operative procedure data should be completed immediately following surgery.
- The 30-day morbidity and mortality should be documented.

11. RADIOLOGICAL FACTORS

All patients will be assessed with a CT scan of chest/abdomen and pelvis for pre-operative assessment of metastatic disease.

11.1 Magnetic Resonance Imaging (MRI)

MRI is used as routine clinical practice in each of the participating centres. A training workshop will be held for radiologists and radiographers prior to the study to ensure standardisation of technique and reporting. The MRI protocol will be standardised for the study.

The definition of a technically valid MRI examination must include the following:

- Demonstration of the tumour in the correct plane.
- High resolution images
- Satisfactory image quality demonstrating the tumour, the mesorectal fascia, the outer muscle coat, tumour spread and deposits, the pelvic floor and its relationship to the tumour. (Appendix 2. MRI scanning technique.)

Incomplete or poor quality images, due to patient non-compliance or technical failure, will be included as part of the assessment of the feasibility and reproducibility of the staging technique for low rectal cancer.

The Radiologist will send an MRI data form and tumour features checklist to the Pathologist to facilitate MRI/histological correlation.

All MRI scans performed will be stored on CD or optic disc and sent to The Pelican Centre. Image format will be DICOM.

A sub-set of specimens will undergo MRI following fixation and prior to histological assessment to assess surgical resection planes and excised tissue.

Should surgery be delayed by more than 6 weeks after radiotherapy there should be another MRI scan done and MRI datasheet submitted. This scan should be within 4 weeks of the surgery date.

12. HISTOPATHOLOGICAL FACTORS

The pathological assessment is critical for this study as the primary endpoint is CRM positivity. A further important role is to identify perforation and the planes of surgery of the mesorectum and the levator/anal sphincter. Also the response to therapy, numbers of lymph nodes, extramural venous invasion and peritoneal involvement will be identified.

To this end pathology workshops will be undertaken in order to standardise reporting and technique. (Appendix 3: Pathology Protocol.)

In the second part of a two-part consent form, patients will be asked for consent to obtain their redundant tumour samples from the pathology laboratories in order to subject them to tissue microarray analysis. Research staff from St. James' University Hospital will request the fixed tumour block from the relevant pathologist. On receipt, the sample will be anonymised and securely stored in a Human Tissue Authority (HTA)-licensed facility.

13. ONCOLOGICAL FACTORS

The management, including neoadjuvant therapy and surgical technique, will be decided by the local MDT.

- There is no consensus on the use of radiotherapy in operable tumours and this protocol reflects this although a recommendation is given for each MRI-predicted TNM stage.
- Where considered clinically safe, radiotherapy volumes have been reduced in order to try to minimise late treatment effects.
- Functional outcome is being monitored and will be correlated with radiotherapy dose and volumes.

Suggestions for neoadjuvant therapy, based on predicted MRI staging, include:

13.1 Locally Advanced Rectal Cancer

- See Appendix 10 for planning details

In patients with either a threatened circumferential margin or poor prognostic factors, pre-operative long course chemoradiation will be considered. Patients who are already enrolled in a neoadjuvant strategy trial can be included in this study and will continue with the treatment as allocated in the neoadjuvant trial. Other patients will be treated with concomitant Flouroparmidine, either Capecitabine or 5-FU (Bolus or infusional).

Patients will be treated prone where possible, with a full bladder and be CT planned.
The aim will be to deliver a minimum of 45Gy in 1.8 Gy daily fractions to the tumour and up to a maximum of 55Gy in 1.8 Gy daily fractions. The nodes will receive 45GY.

13.2 Early Operable Cancers

Patients will either receive no pre-operative radiotherapy or be treated with short course radiotherapy.

Predicted T1 T2, N0 - Radiotherapy may be omitted for these good prognostic tumours as staged on MR.

- Short course radiotherapy may be employed.
- Predicted T1 T2, N1 - Short course radiotherapy may be of benefit in this group (CR-07), and may be considered.
- Centres may prefer not to treat with radiotherapy.

Predicted T3, N0, CM negative - Short Course radiotherapy may be considered.

Predicted T3, N1, CM negative - Short Course radiotherapy may be considered.

13.3 Adjuvant Chemotherapy

Adjuvant chemotherapy will be given according to local policy.

13.4 MDT Documentation

The MDT discussion, decision-making process and treatment plan should be documented. Documentation of initial MDT discussion and final surgical procedure will allow an assessment of the impact of imaging and CRT on sphincter preservation or change of treatment policy.

14. FOLLOW-UP

Patients will be followed up for a period of 5 years after surgery. Follow up data will be collected from individual patient medical records. The follow up policy will be standardised for the study (Appendix 5 Suggested Follow-Up Policy).

15. QUALITY OF LIFE AND FUNCTION

Quality of life will be assessed using the EORTC-C30 quality of life questionnaire combined with EORTC-C38 (colorectal module) questionnaires and either the St. Mark's Bowel function questionnaire or the coloplast stoma QoL questionnaire. These have been validated and used in trials assessing patients with rectal cancer. The EORTC QLQ-38 comprises 38 questions that include a total of 4 functional scales/ items:

- Body image
- Sexual function
- Sexual enjoyment
- Future perspective

The questionnaire includes a variety of symptoms often encountered in patients with colorectal cancer:

- Radiotherapy effects on micturition
- Chemotherapy side effects
- Gastro-intestinal symptoms
- Sexual dysfunction in males and females
- Defaecation problems
- Stoma related problems
- Weight loss

The questionnaires will be given to patients pre-operatively, following CRT and at 3, 6, 9 12, 18 and 24 months post-operatively. Further questionnaires will be sent at yearly intervals for the remainder of the study.

16. DATA MANAGEMENT

16.1 Data Collection Forms

Data will be collected locally by the members of each MDT. All data will be submitted to the Royal Marsden Hospital, Radiology Department. Each patient will be assigned an individual study number. Copies of each patients consent form will be kept in both the patients' hospital notes and at the Royal Marsden Hospital. All data collection forms will be designed and standardised for each individual discipline.

16.2 Data Handling

Hard copy data will be collated and stored in a secure research office at the Royal Marsden Hospital. Data will be transferred from hard copy, to the Royal Marsden Data Management System, by the Trial Coordinator, Radiology Department, at the Royal Marsden Hospital. Hard copy data will be archived and stored for a period of 5 years after study completion.

16.3 Database System

The data storage tool will be the Royal Marsden Data Management System. This system has been used and modified over the last 15 years and has a proven 'track record'. It can only be accessed via the NHS Intranet and data can be exported securely as an Excel file to other sites within the intranet.

16.4 Data Interpretation/Analysis

Analysis will be performed using SPSS for windows. Data analysis will be performed by the Study Statistician, who is based at the Royal Marsden Hospital.

17. REGULATORY AND ETHICAL REQUIREMENTS

17.1 Ethics Committee Submissions and Approval

Central ethical approval will be applied for through COREC. 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.

(For European centres, local approval must be sought and local ethical approval will need to be clarified.)

17.2 Informed written Consent

The study, and its risks and benefits, will be explained to the patient in understandable, non-medical language by the patient's medical team (usually the consultant or nurse specialist). The patient will be given time to read the Patient Informed Consent Form, all questions raised by the patient will be answered if possible. The patient and person taking consent (a member of the patient's medical team- usually the consultant or nurse specialist) will sign the informed consent form, a copy of this will be placed in both the patient's medical notes and at the Royal Marsden Hospital. At the Royal Marsden Hospital the form will be verified and signed by the researcher. The original form will be kept with the patient's medical notes.

17.3 Patient Confidentiality

All study personnel and the Regulatory Authority representatives will maintain patient confidentiality at all times.

17.4 Protocol Amendments

Any change in study design/protocol amendment must be agreed by all members of the Steering Committee. Major protocol amendments (those altering the nature of the study) must be agreed by all collaborators. Any amendments must be submitted to the Steering Committee by the investigator and, where appropriate, the amended patient informed consent form will accompany this submission.

The Study Management Group reserves the right to invite additional centres to participate in the study. They also reserve the right to exclude centres from the study in the event of major protocol violations.

Any major changes to the protocol will be submitted to COREC

17.5 Study Monitoring

- The steering group will monitor the progress of study throughout its course
- Trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/ document will also be permitted at any stage.

17.6 Data Ownership, Publication and Reporting.

All publications from the study data must be approved, prior to submission, by the Steering Committee. All publications will be presented by named authors on behalf of The MERCURY Study Group. Subset analysis may be presented by individual clinicians or specialities from within the Study Group but recognition of the MERCURY Study Group must be in the title/authors.

All results must be treated as strictly confidential until they are published.

17.7 Personal Responsibilities

The investigators, members of the study group and sponsors undertake to conduct the study in conformity with the Declaration of Helsinki, the ICH European Good Clinical Practice recommendations and the law in force in the country concerned.

All members of the study group will:

- Adhere to the conduct of the study as described in this protocol.
- Ensure the accuracy and legibility of the data collection forms.
- Immediately report any serious adverse breaches in the study to the steering group.
- Ensure appropriate data storage.
- Maintain an accurate data accountability log.
- Provide access at monitoring visits to the source documents, together with any other relevant medical information on the patients participating in the study.

17.8 Early Termination

It is the intention that this study will be undertaken until its planned conclusion. The study will be discontinued in the event of:

- Substantial breach of the terms either of the agreement or the conduct of the protocol
- Irregularities in the methodology by which the study is carried out and, although capable of being rectified, are not rectified within 30 days of notice of this.

In the event of early termination, use of investigational materials will cease as soon as possible. All case record forms outstanding must be completed and returned to the Research Fellow with a completed investigational materials inventory and records.

18. REFERENCES

1. MERCURY study group. Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study. *British Medical Journal* 2006;333:779-782

2. Holm T, Rutqvist LE, Johansson H, Cedermark B. Abdominoperineal resection and anterior resection in the treatment of rectal cancer: results in relation to adjuvant preoperative radiotherapy. Br J Surg 995;82(9):1213-6.

3. Wibe A, Syse A, Andersen E, Tretli S, Myrvold HE, Soreide O. Oncological outcomes after total mesorectal excision for cure for cancer of the lower rectum: anterior vs. abdominoperineal resection. Dis Colon Rectum 2004;47(1):48-58

4. Adam IJ, Mohamdee MO, Martin IG, et al. Role of circumferential margin involvement in the local recurrence of rectal cancer. *Lancet*. 1994;344:707-711.

5. de Haas-Koch DF, Baeten CGMI, Jager JJ, et al. Prognostic significance of radial margins of clearance in rectal carcinoma. Br J Surg. 1996;83:781-785.

6. Wibe A, Rendedal PR, Svensson E, et al. Prognostic significance of the circumferential resection margin following total mesorectal excision for rectal cancer. Br J Surg. 2002;89:327-334.

7. Quirke P, Durdey P, Dixon MF, Williams NS. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision. *Lancet* 1986;2:996-999.

8. Nagtegaal ID, van de Velde CJ, Marijnen CA, van Krieken JH, Quirke P. Low rectal Cancer: A Call for a Change in Approach in Abdominoperineal Resection. J Clin Oncol. 2005; 20;23(36):9257-64.

9. Marr R, Birbeck K, Garvican J, et al. The modern abdominoperineal excision: the next challenge after total mesorectal excision. Ann Surg. 2005;242:74-2.

10. Holm T, Ljung A, H„ggmark T, et al. Extended abdominoperineal resection with gluteus maximus flap reconstruction of the pelvic floor for rectal cancer. British Journal of Surgery. 2007; 94(2): 232-238.

11. Peschaud F, Cuenod CA, Benoist S et al. Accuracy of magnetic resonance imaging in rectal cancer depends on location of the tumor. Dis Colon Rectum 2005; 48: 1603-9.

12. Torkzad M, Hansson K, Lindholm J, Martling A, Blomqvist L. Significance of mesorectal volume in staging of rectal cancer with magnetic resonance imaging and the assessment of involvement of the mesorectal fascia. European Radiology Dec 2006 online, http://www.springerlink.com/content/62v011k718756020.

19. APPENDICES

Appendix 1: Steps of Data Collection - p. 49

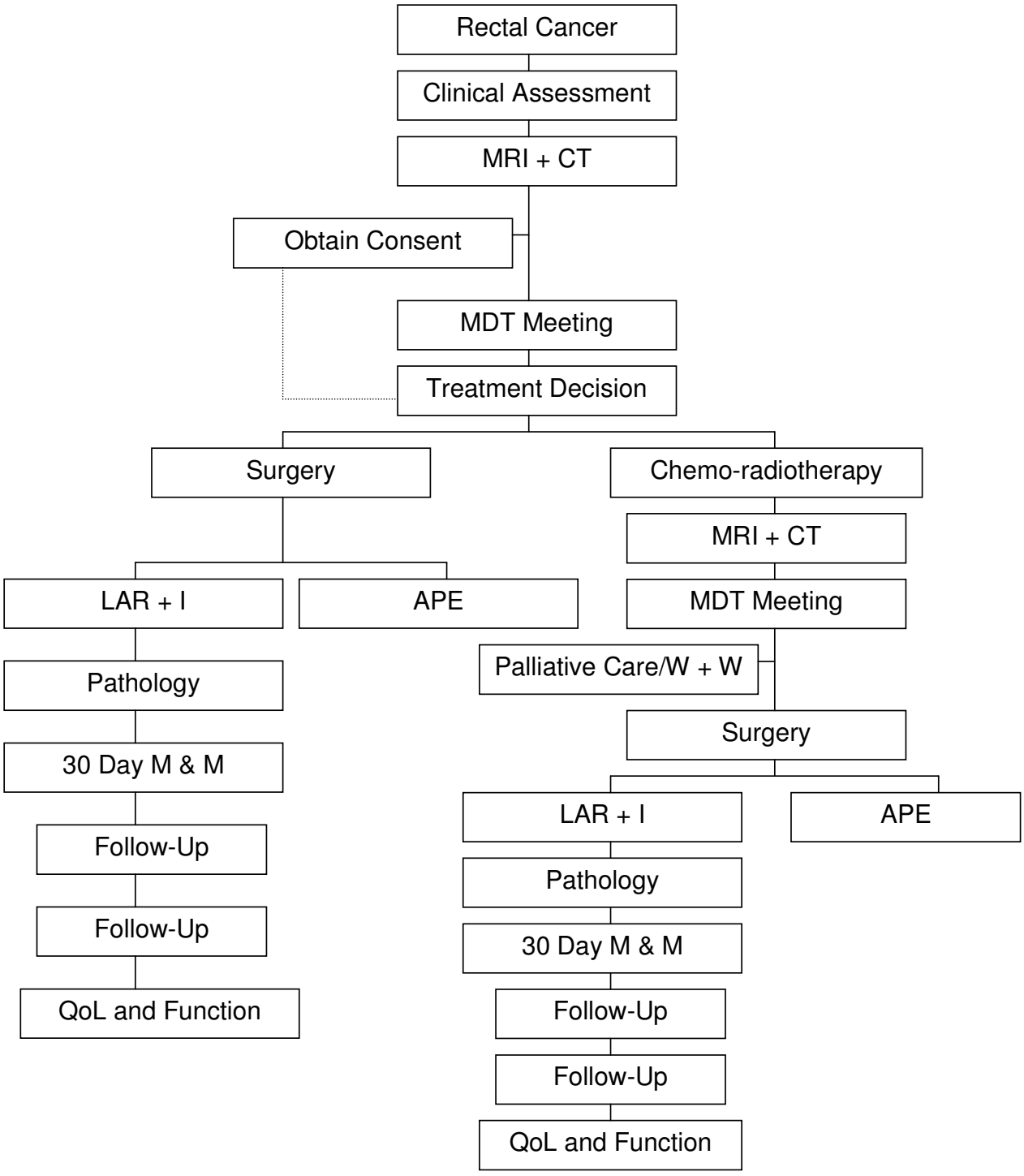
Appendix 2: MRI Methods - pp 50-59

Appendix 3: Pathology Protocol - pp 60-78

Appendix 4: Radiotherapy Planning Details - pp 79-80

Appendix 5: Suggested Follow-Up Policy – p 81

Appendix 1: Steps of Data Collection



Appendix 2: MRI Methods

Method

Indications and patient preparation The examination should be performed in those patients with histologically proven rectal carcinoma who present for disease staging. Ensuring that the patient is comfortable and pain free will ensure a good quality examination free from unwanted motion artifact. Patients need to be fully informed about the length of time of the scans, be positioned comfortably within the scanner and pain-free. There is no role for purgative bowel preparation or enemas. Small bowel movement is not a problem in our experience, therefore anti-peristaltic agents are not indicated. The patient is placed supine on the table and the flexible 4-element phased array body/pelvic coil is placed firmly around the pelvis to ensure good compression and to minimise the possibility of motion. A full bladder is unnecessary and is uncomfortable with the compression from the body coil. The referring surgeon should indicate the tumour position (in terms of height above the anal verge) and any history of past pelvic pathology and surgery. The imaging must be performed before the multidisciplinary meeting to aid in the preoperative decision making process.

Hardware

Magnet

A 1.0T/1.5T system can be used. All of the images presented here have been produced with a 1.5T machine. The main consequence of using a 1.0T magnet is the longer image acquisition times. Equally good images can be produced on these magnets.

Phased array coils:

These coils gain the advantages of the surface coil by obtaining higher signal but with greater coverage than a single surface coil and improved homogeneity.

Sequences recommended in the local staging of rectal cancer:

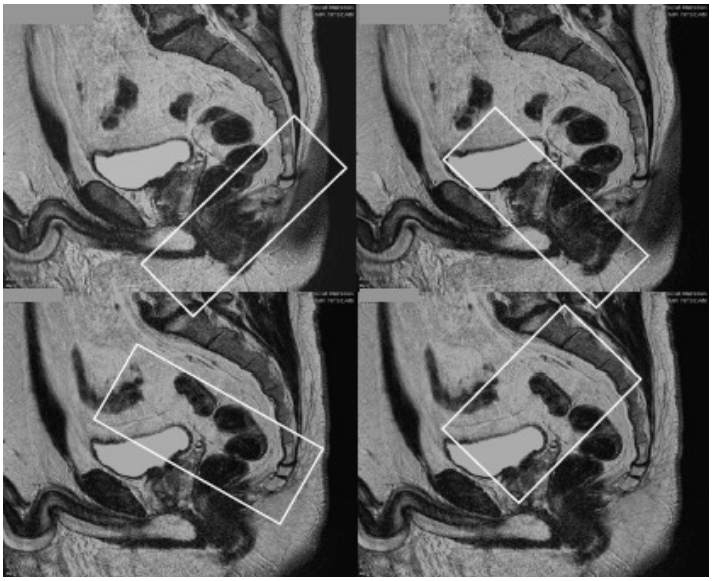
The initial sequences performed are the localisation images, in the coronal and sagittal planes to image the tumour and plan the high resolution images that are performed axial to the rectum.

- The first series is the sagittal T2W-FSE, which enables identification of the primary tumour
- The second series - large field of view axial sections of the whole pelvis from the iliac crest to the symphysis pubis

Sequence 3:

While the second series is being acquired, the high-resolution images can be planned. The sagittal T2 weighted images obtained are used to plan T2-weighted thin-section axial images through the rectal cancer and adjacent peri-rectal tissues. It is critical that these images are performed perpendicular to the long-axis of the rectum (figure 2).

Figure 2:



The images are obtained by using a 16cm field of view and 3mm section thickness.

Sequence 4:

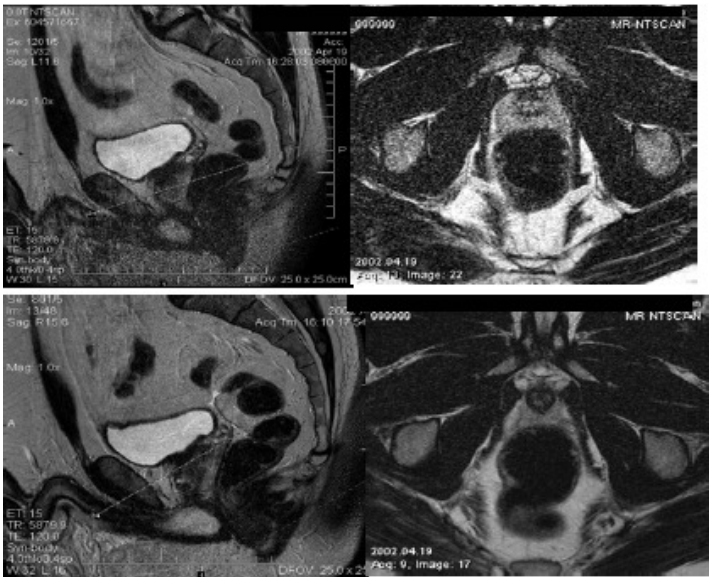
The rapid change in calibre of the rectal lumen at the level of the anorectal junction limits the usefulness of oblique axial imaging alone. At this level axial images may not show the rectal wall in its entirety and clear delineation between the outer edge of the rectal wall and the levator muscle may not be possible. This can potentially lead to overstaging. It is therefore useful to utilise a high spatial resolution coronal imaging sequence which will show the levator, the sphincter complex, the intersphincteric plane and the relationship to the rectal wall most optimally (figure 2).

Potential factors that may impair the quality of images

Coil Positioning.

In order to prevent poor signal to noise from the anorectal junction (figure 3), Figure 3 it is important that the phased array coil is centred optimally to ensure adequate coverage of the rectum, mesorectum and anal sphincter complex.

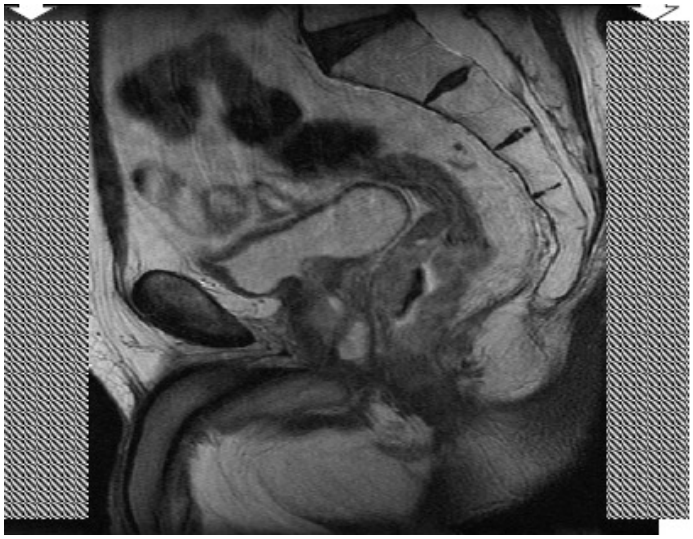
Figure 3:



It is important that the phased array coil is centred optimally to ensure adequate coverage of the rectum, mesorectum and anal sphincter complex.

Thus there should be adequate coverage from the level of the sacral promontory to below the symphysis pubis (figure 4).

Figure 4:

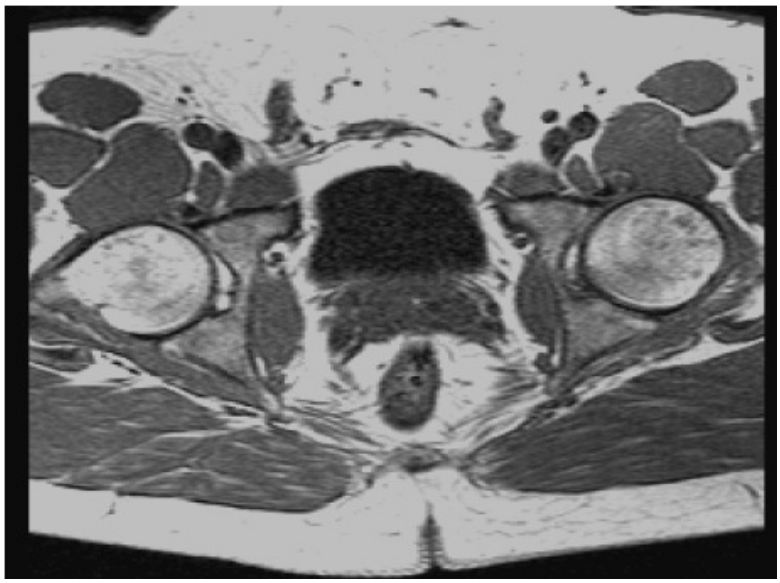


Choice of sequences

T1 weighted imaging

Although the availability of short TR/TE volume imaging can provide images of high spatial resolution, images obtained fail to show adequate contrast to depict either tumour or the layers of the bowel wall (figure 5).

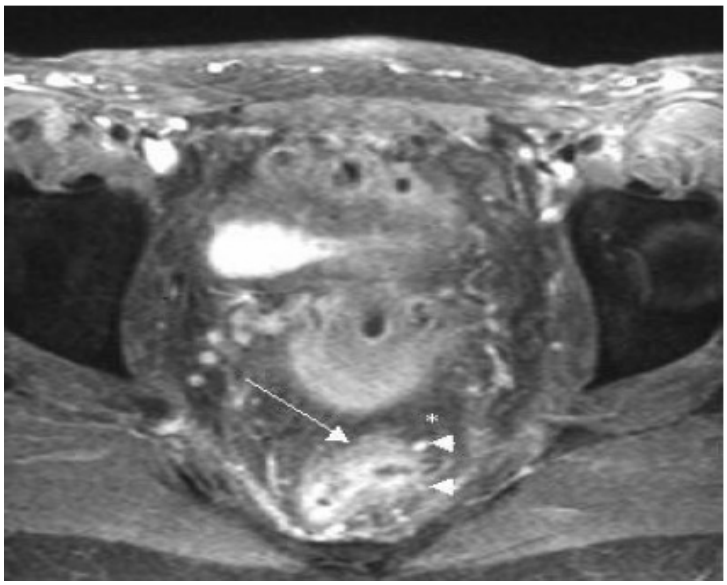
Figure 5:



Fat saturation and contrast enhancement.

Contrast enhancement has not been shown to be an effective method for the local staging of rectal cancer. A contrast-enhanced technique requires the high signal from surrounding perirectal fat on T1 weighted images to be suppressed to permit visualisation of high signal enhancement of tumour. This results in a further reduction in signal to noise ratio and potential overstaging of tumours due to enhancement of adjacent non-tumour tissue (figure 6).

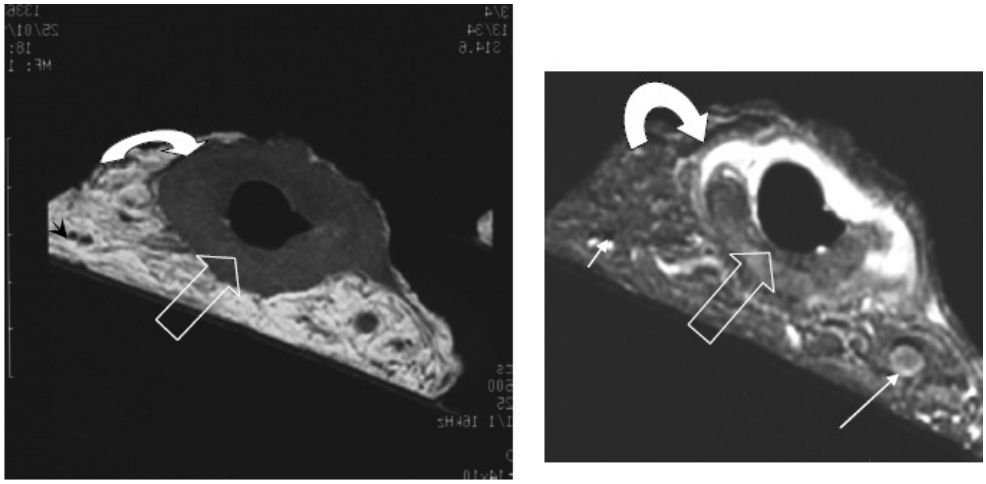
Figure 6:



T2 Weighted Fast spin-echo (T2 FSE)

T2 weighted images of the rectal wall and pararectal tissues result in visualisation of individual bowel wall layers and tumour returns a brighter signal than the muscle coat but low signal intensity than perirectal fat and thus superior depiction of tumour when compared with T1 weighted images (figure 7).

Figure 7:

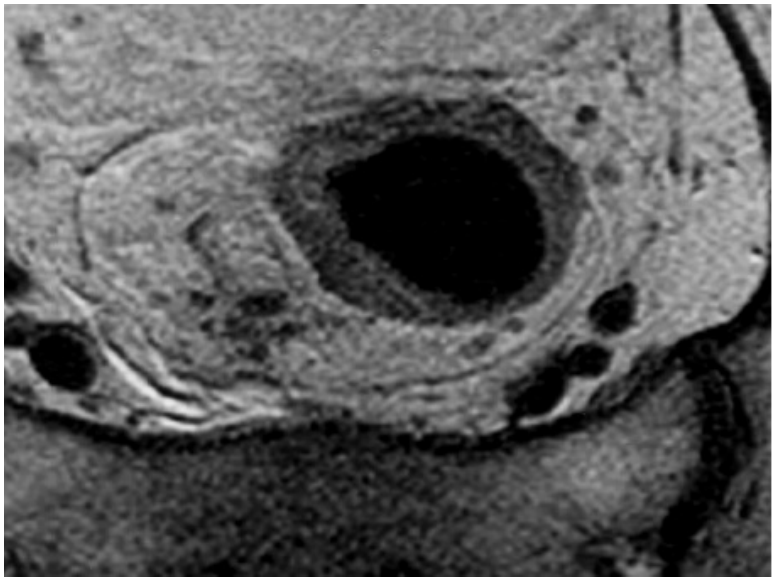


Thus T1, fat saturated or STIR imaging of the rectum and perirectal tissues offers no additional staging information and should not be used.

Cross-talk

This varies with machines and patients and is manifested on the images obtained as loss of signal and unexpected loss of detail (figure 8).

Figure 8:



This is overcome by interleaving slices during the high resolution acquisition or increasing the slice gap.

Tumour not seen on initial sagittal sequences

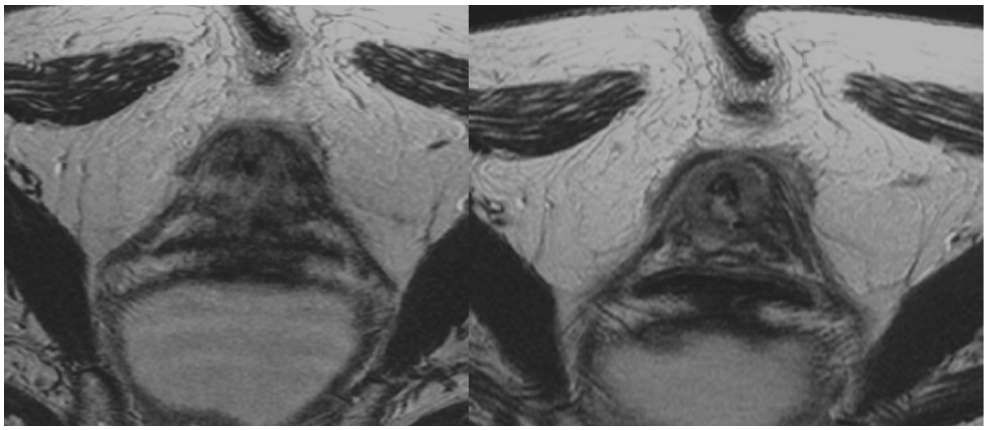
On occasion, lack of clinical detail or the presence of a small tumour prevents the tumour being seen on the sagittal images. In these instances, tumour may only be visible on the high resolution images. In order to ensure that the tumour has not been missed it will be necessary to perform high resolution scans along the entire length of the rectum (as shown in figure 2).

Patient unable to tolerate long scan.

Some patients (<5%),either due to co-existing medical conditions or claustrophobia, find

the scan impossible to tolerate, some of the sequences may be omitted. A combination of patient discomfort, excessive motion of the anterior abdominal wall may result in motion artefact. This is seen as horizontal bands across the image (figure 9).

Figure 9:



Of all of the sequences the oblique high resolution scans are the most important. The sagittal views can be shortened by altering the parameters; the large field of view axials are performed last and may even be omitted if the patient is in considerable discomfort.

Appendix 3: Pathology Protocol

Low rectal cancer study Pathology protocol

Abdomino-Perineal Excisions

In a recent study we have demonstrated that the CRM is involved in 36.5% of abdominoperineal resections (APs) compared to 22.3% of anterior resections (ARs). This was also seen in the MRC CLASICC study where 21% APs showed margin involvement vs 10 % ARs. In the Mercury study, 33% of APs vs 13% of ARs below 6cm showed CRM positivity, in the Dutch TME/RT study 29% APs had margin involvement vs 13% of ARs and in the Norwegian national audit of curative excisions of rectal cancer 12% APs and 5% ARs had positive margins. In series with follow-up, the increased rate of margin positivity always equated with an increased rate of local recurrence and a poorer survival. Thus when pathologically assessing APs always look carefully for CRM positivity in the area of the low mesorectum and sphincter.

There is also a much higher rate of tumour perforation in APs than in ARs in the Dutch study 13.7% of APs were perforated vs 2.5% ARs and in the Norwegian study 16% APs vs 4% ARs.

Abdomino-perineal excisions have a higher rate of recurrence because of the smaller amount of tissues at the height of the levators and thought should be given to treating these as a high-risk category as the tumour is closer to the CRM. Their margin positivity rates are much higher and their survival worse than anterior resections. It should be

recognised that the anatomy of the levator/anal canal area varies between individuals.

With this data it became apparent that there was a wide variation in the quality of the AP resections and a new quality classification was derived. This was similar to the mesorectal grading system in that it describes the surgical plane of dissection.

Pathology dissection for the study

The pathology is critical for this study as the primary endpoint is CRM positivity. We also have an important role to play in identifying perforation and the planes of surgery of the mesorectum and the levator/anal sphincter. We must also identify response to therapy, substantial numbers of lymph nodes, extramural venous invasion and peritoneal involvement to the highest standards. We are using TNM5 for this study not TNM7. This is because of the poor reproducibility of the TNM7 definitions of extramural vascular invasion and lymph nodes. Thus we use the 3mm rule for nodal involvement. This allows this study to be consistent with other trials such as the Dutch TME trial, CR07 etc. Thank you for your efforts and for participating.

Preparation of the specimen

The specimen must be photographed prior to dissection. Preferably this is on receipt in the department. Digital photographs should be taken of the front and back of the specimen and preferably close up images of the front and back of the levator/anal sphincter. The quality of the surgery should then be graded by the local pathologist for the mesorectum and the levator/anal sphincter area.

The specimen can then be opened from the proximal margin down to 2-5 cms above the tumour. The distal end should be kept intact. If fresh material is to be taken for local use then it should be taken at this stage. A piece of foam/paper soaked in formalin can be inserted through the tumour if felt appropriate. The specimen can then be placed in formalin.

It is acceptable to inflate the specimen with formalin and then fix and take the photographs prior to dissection but this should be before opening the specimen.
THE AREA OF THE TUMOUR MUST NEVER BE OPENED AS THIS DESTROYS THE ANTERIOR CRM.

Dissection

Anterior and posterior non-peritonealised surfaces are painted with ink. It should be remembered that the circumferential margin only applies to the surgically incised mesorectal planes and not the peritonealised surfaces. The mesorectal surface is larger posteriorly and extends up to a higher level than it does anteriorly. After the resection surfaces have been inked the specimen is fixed in formalin for a minimum of 2 days (48 hours).

The macroscopic description should be completed specifically noting the presence of a perforation of the tumour or mucosa and the place of the perforation. It should be specifically stated whether the tumour perforation is present in an area covered by peritoneum or a surgical margin, and whether it is above or at the height of the sphincters. The presence or absence of levator ani on the specimen should be

described. The descriptions of grading are given below.

The specimen should be sliced as thinly as possible starting from the distal margin to 2-5cms above the tumour. These slices should be laid out in good light starting with the most distal slice at the top left hand corner and the most proximal slice ending up as the last slice. The face presented to the camera should be consistent in all the slices. These slices should then be photographed. The photograph must include a cm scale.

The minimum distance of the tumour to the CRM should be described, as should the maximum depth of invasion through the muscularis propria.

If the CRM is free of tumour it should be note whether there is normal tissue at the margin or whether it is fibrotic tissue following tumour regression.

If the CRM is involved (confirmed on histology) then the mode of involvement should be stated, as well as the distance of involvement.

It is preferable to sample the main tumour by embedding each tumour bearing slice and cutting a large mount section.

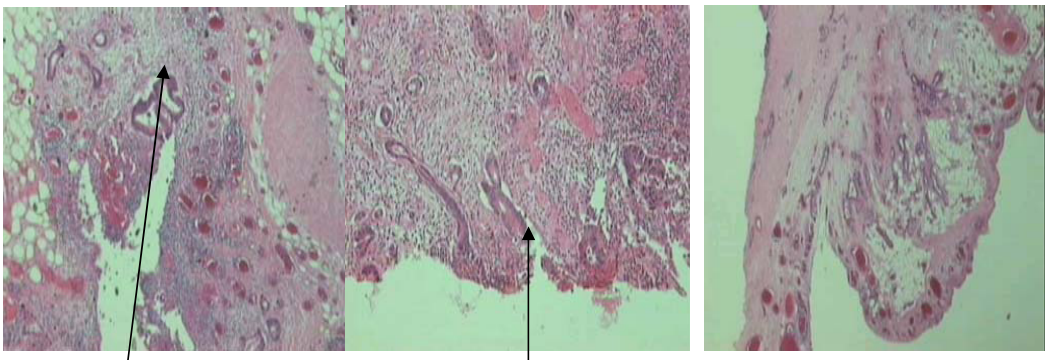
As many lymph nodes as possible should be dissected and a running mean of fifteen is to be expected in cases not undergoing preoperative neoadjuvant therapy. Involvement of the peritoneum is defined as per Shepherd and extramural vascular invasion when involvement of a vascular structure with smooth muscle in the wall is apparent. This should be looked for closely and if tumour is present close to an arterial structure without

an accompanying vein have a high level of suspicion. Involvement of the CRM is defined as tumour within 1 mm of the CRM. The digital photographs (front, back and slices) and a duplicate set of sections should be cut for sending to Leeds for curation and scanning. If a duplicate set is not available please send all the original slides and these will be scanned and returned within 2 weeks.

T staging of low rectal cancers

The T-staging of cancers above the sphincters is straightforward, however many of these cancers have a proportion of the lesion within the region of the sphincters. T-staging of adenocarcinoma in the area of the sphincters is unsound. TNM 6 states that such tumours should be staged as anal cancers by tumour size. In TNM 7 there is a proposal to call both internal and external sphincter involvement T4. In the absence of a robust staging system the only solution is to describe the anatomical extent of spread both above the sphincter and at their height separately to allow subsequent analysis. We propose that the maximum level of invasion above the sphincter and at the level of the sphincter be separately recorded by extent of maximal spread.

Peritoneal involvement should be assessed by the method of Shepherd et al 1995.



Yes Yes No

Peritoneal involvement with tumour penetrating the peritoneum

Assessment of Quality of Surgery - Grading

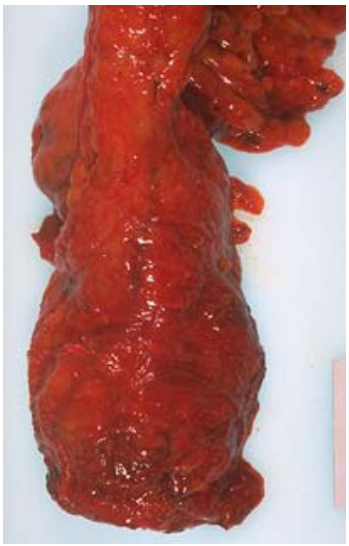
The mesorectum and the levator canal should be graded separately. Thus for an anterior resection there will only be one grade - the grade for the mesorectum. For Abdomino-Perineal Excisions there will be a grade for the mesorectum and a further grade for the levator canal area below the mesorectum.

Quality of resection of the mesorectum

The quality of a mesorectal resection can be easily assessed.

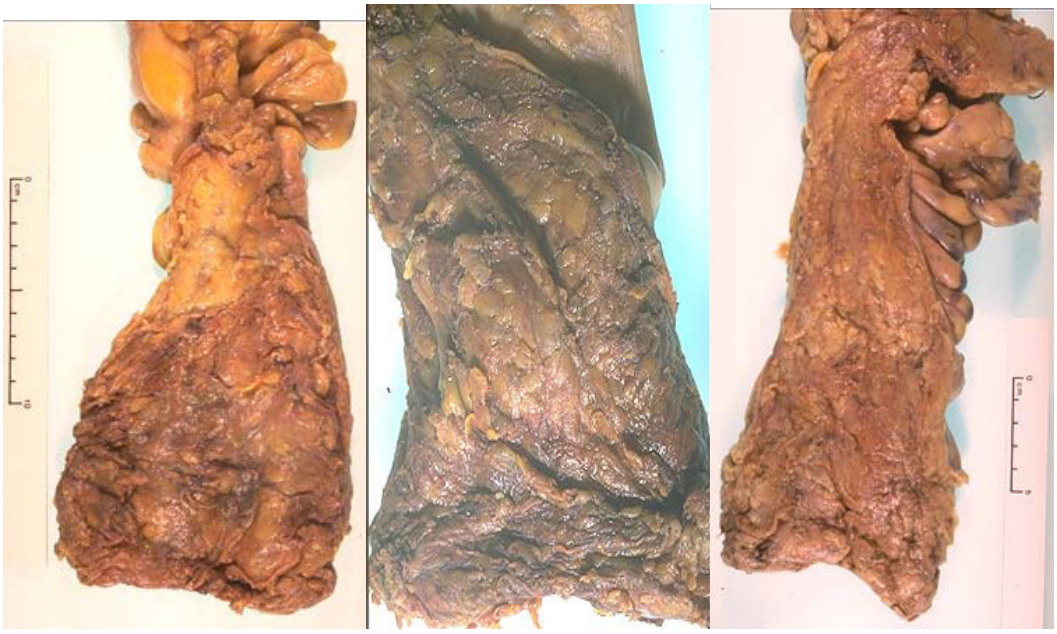
Mesorectal plane

For a good resection the mesorectum should be smooth with no violation of the fat, good bulk to the mesorectum anteriorly and posteriorly and the distal margin should appear adequate with no coning near the tumour. No defect should be more than very superficial or 5mm deep. These sections show high quality surgery (**Mesorectal plane**).



Intramesorectal plane

The images below demonstrate an intramesorectal plane. This is defined by superficial incursions into the mesorectum, areas of mesorectum missing, coning of the mesorectal dissection and most importantly, in no area is the muscularis propria exposed (**intramesorectal plane**).



Intramesorectal plane

Superficial incisions **Superficial incisions and coning** **Coning**

Muscularis propria surgery

Muscularis propria surgery shows many areas of substantial loss of mesorectal tissue, area(s) of the muscularis propria are seen, and deep cuts and tears down onto the muscularis propria may also be present.

Muscularis propria surgery

–irregular mesorectum with defects > 1 cm2 or incision down to muscularis propria.

Irregular CRM with little bulk and little clearance anteriorly

This classification has been used in CR07 and CLASSIC trials and shown to predict a higher risk of local recurrence in the Dutch data (14). The frequency of CRM involvement can also be determined and it is likely that this is a good early determinant of the quality of surgery and subsequent risk of local recurrence (12). The ease of high quality surgery after chemoradiotherapy also needs to be determined.

Summary of Grading

Mesorectal fascial plane: the mesorectum should be smooth with no violation of the fat, good bulk to the mesorectum anteriorly and posteriorly and the distal margin should appear adequate with no coning near the tumour. No defect should be more than superficial or 5mm deep.

Intramesorectal plane: Moderate bulk to mesorectum but irregularity of the mesorectal surface. Moderate coning of the specimen towards the distal margin. At no site is the muscularis propria visible with the exception of the area of insertion of levator muscles. Moderate irregularity of the CRM.

Muscularis propria plane: There will be areas of substantial loss of mesorectal tissue. Deep cuts and tears down onto the muscularis propria will be present. On cross section there will be a very irregular CRM with little bulk to the mesorectal fat and the muscularis propria will form the CRM in places.

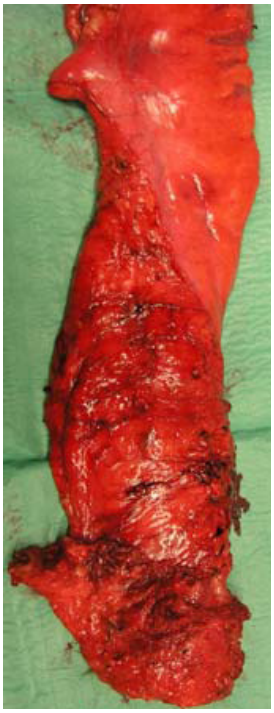
Quality of resection - abdomino-perineal

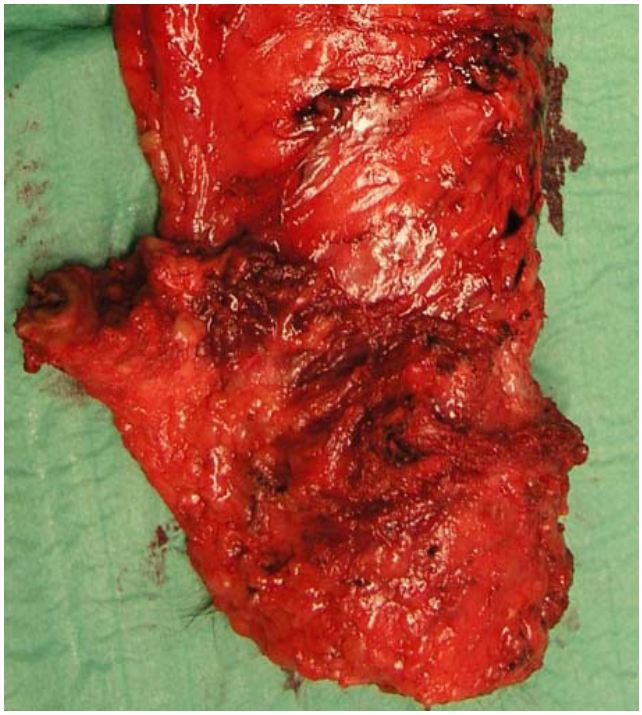
Thus the quality of surgery of the levator/anal canal area below the mesorectum can be assessed as:

Levator plane

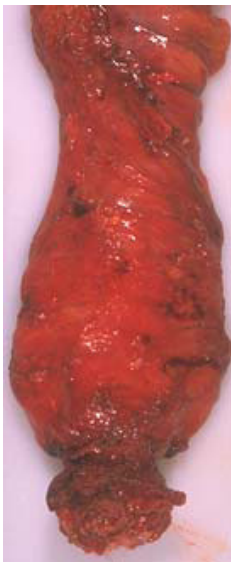
The surgical plane lies external to the levators with them being removed en bloc with the specimen. This creates a cylindrical specimen with the levators forming an extra protective layer on the sphincters.

Levator plane

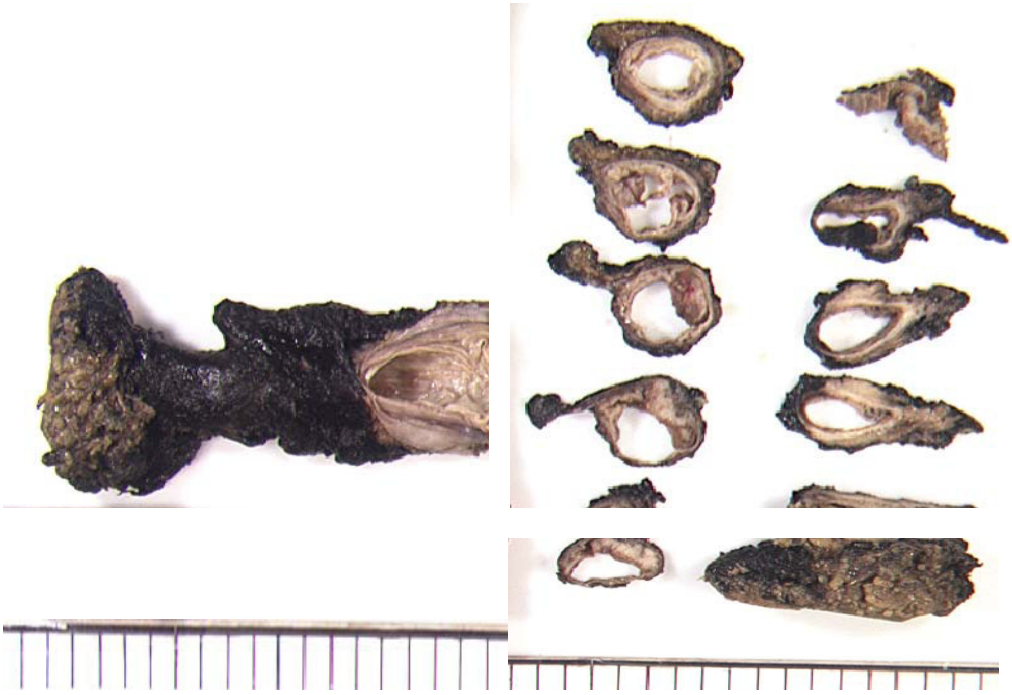




Sphincteric plane: Either there are no levator muscles attached to the specimen or only a very small cuff and the resection margin in on the surface of the sphincters. The specimen has a waisted/apple core appearance.

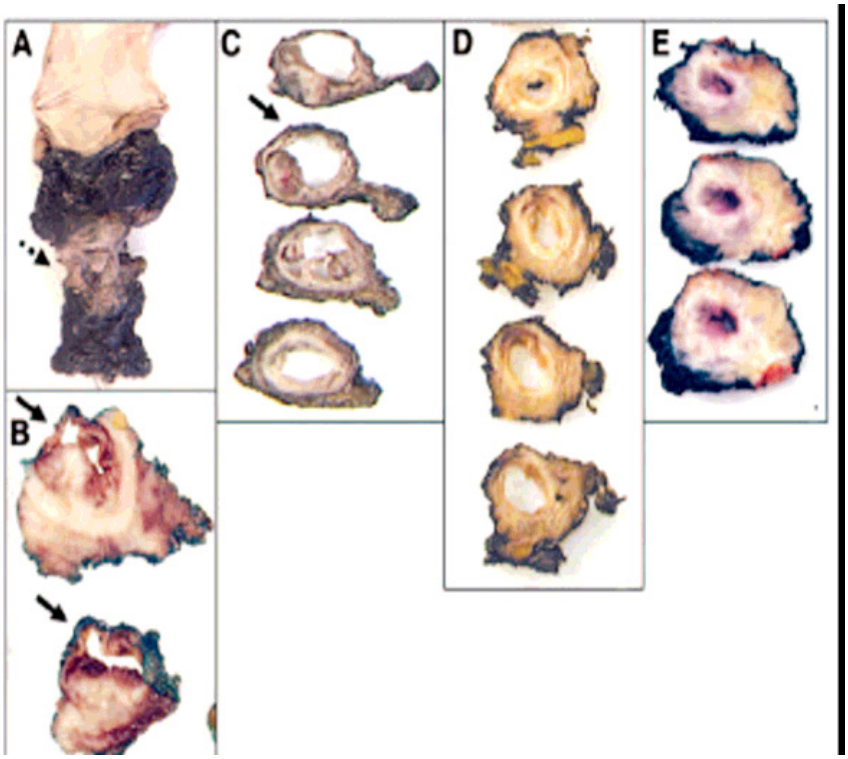


Intrasphincteric/submucosal plane: The surgeon has inadvertently entered the sphincters or even deeper into the submucosa or perforated the specimen at any point.



Intrasphincteric/submucosal plane: APE with areas of failure to excise all of the muscularis propria in the area of the levators and no levator excision.

Cross sections of AP



A: Perforation B,C: Submucosa D: Sphincter E: Levator

Thus for an AR there will be a single grade and for an APE there will be two grades;

Chemoradiotherapy response scoring

Dworak scoring

- **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 5 blocks of tumour the whole area of the tumour will be embedded. Should no further tumour cells be seen then three levels will be taken and examined from each tumour block. If after these assessments no tumour cells are identified then the tumour should be considered to have undergone a complete response. Further levels should not be taken as it is important to standardise the degree of effort made to find the presence of tumour.

Definitions used in Pathology

Position of the tumour

The position of the tumour should be accurately noted. Initially this involves documentation of the surface involvement ? i.e. anterior quadrant, posterior quadrant, lateral quadrant and combinations of the above. However, to correlate the position with the MRI report the tumour should be reported from the distal resection margin with the mesorectum posterior and the peritoneal reflection anterior. This can be documented as a relationship to a clock-face on the reporting proforma.

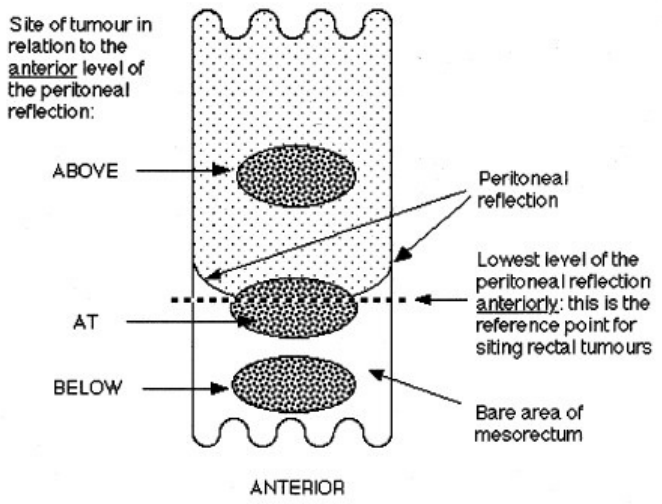
ALL POSITIONS SHOULD BE REPORTED FROM THE PATIENTS

PERSPECTIVE TO CORRELATE WITH THE MRI

Relationship to the peritoneal reflection

The crucial landmark for recording the site of rectal cancers is the 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:

1. Entirely above the level of the peritoneal reflection anteriorly
2. Astride (or at) the level of the peritoneal reflection anteriorly
3. Entirely below the level of the peritoneal reflection anteriorly



Relationship to the CRM

Anteriorly the upper rectum is covered by peritoneum. Only the area below the peritoneal reflection is at risk of surgical circumferential margin involvement. Posteriorly this area, and the area above it, a triangular shaped bare area running up to the start of the sigmoid mesocolon, is at risk not only from direct tumour spread but also metastatic deposits in lymph nodes that lie against the circumferential margin.

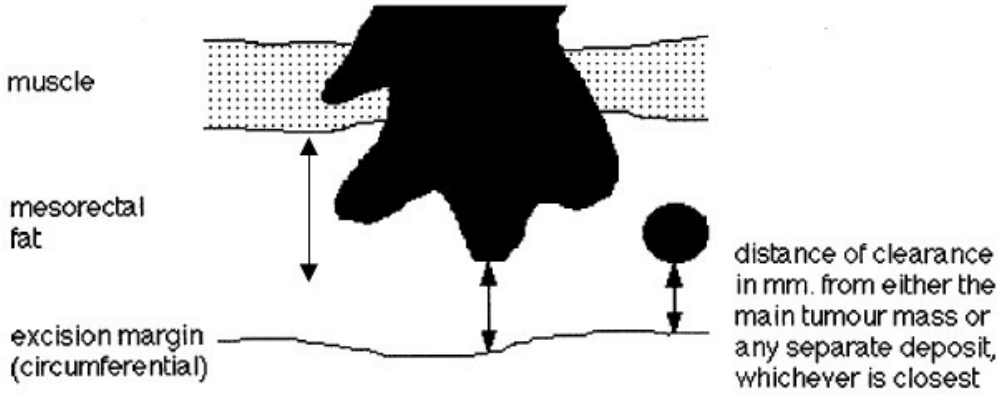
It is recommended that the whole of this margin (i.e. the mesorectum) be painted with a marker such as silver nitrate or India Ink before dissecting the specimen. The tumour is then best sliced serially at 3-4 mm intervals to select blocks form the area above and below the tumour to look for metastatic deposits. If lymph nodes lie against the circumferential margin then these should be included in the block.

Relationship to extra-mural invasion

When assessing the relationship to the CRM, on the whole-mount section the corresponding relationship between the outer muscle coat and the maximum depth of extra-mural invasion needs to be measured. This is performed using the Vernier scale on the microscope.

Lymph nodes

All lymph nodes found in the specimen should be sampled and counted, regardless of heir site and size.



The number of positive lymph nodes must be equal to or less than the number of lymph nodes sampled.

Extramural tumour deposits measuring # 3 mm are counted as involved lymph nodes even if no residual lymph node structure can be identified.

Extra-mural invasion

Smaller deposits are regarded as apparent discontinuous extensions of the main tumour.

In the TNM staging system, pN1 corresponds to involvement of 1-3 nodes and pN2 to involvement of 4 or more nodes.

Distance to the distal resection margin

Measured from the nearest cut-end of the specimen, not the circumferential margin. It is only necessary to examine the margins histologically if tumour extends macroscopically to within 30mm of one of these. For tumours further than this 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 or show extensive vascular or lymphocyte permeation or are undifferentiated carcinomas.

Relationship to the Dentate Line

This can only be measured for low rectal tumours in abdomino-perineal excision of the rectum (APE) specimens. The dentate line should be defined as the level of the limit of the internal sphincter.

If the tumour has perforated into the peritoneal cavity or is clearly present in tissue beyond the edge of the mesorectal fascia then these cases should be recorded as a perforation.

Tumour Differentiation

The differentiation of the tumour should be defined on the dominant area of tumour. Other types of differentiation, i.e. mucinous adenocarcinomas, signet ring, undifferentiated and high-grade dysplasia should be documented.

Proforma

Please complete the histopathology proforma and return to the study centre along with

the digital photographs and copies of the slides or the original slides marked clearly FOR RETURN TO CENTRE AFTER SCANNING.

WE WOULD ALSO LIKE ONE BLOCKOF TUMOUR AND ONE BLOCK OF NORMAL MUCOSA TO BE SENT TO THE CENTRE TO ALLOW FURTHER STUDY. This should be material that is not required for diagnosis locally.

Retention of Tissue

All patients, as part of the consent process, will be asked to donate a piece of their cancer and normal tissue for tissue-based cancer research. Tissue will be kept in wax blocks and stored separately for future studies. Use of this tissue will be addressed in separate Study applications to the Steering Committee.

Appendix 4: Radiotherapy Planning Details

Long Course Radiotherapy

Phase 1 Target Volumes

Inferior: The CTV is defined as the GTV + 1.5 cms.

Superior: The nodal volume will depend on N staging.

N0 : 2 cm superior to inferior SI joint

All other nodal status (N1 / N2 / Pelvic sidewall nodal disease) L5 / S1.

Lateral: To include pelvic sidewall nodes.

Posterior: To include the entire sacrum inferiorly but excluding the posterior half of the sacrum at the level of S1 / S2.

Phase II

The CTV is the imagable disease with a 2cm margin which is modified to ensure that the volume remains within the bony pelvis.

Inferior: To be kept the same as phase I

Short Course Radiotherapy

Target Volumes

Inferior: The CTV is defined as the GTV + 1.5 cms

Superior: The nodal volume will depend on N staging.

N0: 2 cm superior to inferior SI joint

All other nodal status (N1 / N2 / Pelvic sidewall nodal disease)

L5 / S1

Lateral: To include pelvic sidewall nodes.

Posterior: To include the entire sacrum inferiorly but excluding the posterior half of the sacrum at the level of S1 / S2.

The dose will be 25Gy in 5 fractions.

Appendix 5: Suggested Follow-Up Policy

(modified from suggested CR07 follow-up protocol)

The suggested follow-up protocol is as follows:

4 Weeks	To assess immediate morbidity and mortality
3 Months	Follow-up and rigid sigmoidoscopy
6 Months	Follow-up and rigid sigmoidoscopy
9 Months	Follow-up and rigid sigmoidoscopy
12 Months	CT of liver and pelvis, CEA, and Colonoscopy
18 Months	Follow-up and rigid sigmoidoscopy
24 Months	CT of liver and pelvis, CEA, and rigid sigmoidoscopy
30Months	Follow-up and rigid sigmoidoscopy
36 Months	CT of liver, CEA, and rigid sigmoidoscopy
48 Months	CT of liver and pelvis and rigid sigmoidoscopy
60 Months	CT of liver and pelvis and rigid sigmoidoscopy

Endpoints are the development of recurrence (local or distant).

If distant recurrence continued re-assessment for local disease.

Appendix 6: Case Report Forms

Please see separate Patient Pack v2.6.