MRC CR07

Pathology-guided Treatment in Rectal Cancer

A randomised trial comparing pre-operative radiotherapy and selective post-operative chemoradiotherapy in rectal cancer

CLINICAL PROTOCOL
January 1998

MRC COLORECTAL CANCER WORKING PARTY

A Medical Research Council Colorectal Cancer Working Party randomised trial comparing pre-operative radiotherapy and selective post-operative chemoradiotherapy in rectal cancer

This document describes a Medical Research Council trial in rectal cancer, and provides information about procedures for entering patients. The protocol is not intended for use as an aide-memoire or guide to the treatment of other patients. Amendments may be necessary; these will be circulated to known participants in the trial, but centres entering patients for the first time are advised to contact the MRC Cancer Trials Office, Cambridge to confirm details of the protocol in their possession.

Clinical Coordinators

Surgery

Professor Robert Steele
Department of Surgery
Ninewells Hospital
Dundee
DD5 4RA
Tel: 01382 660111
Fax: 01382 641795

Professor Colin McArdle
University Department of Surgery
Western General Hospital
Crewe Road, Edinburgh
EH4 2XU
Tel: 0131 537 1567
Fax: 0131 537 1767

Radiotherapy

Dr Roger James
Dept of Clinical Oncology
Christie Hospital
Withington
Manchester M20 4BX
Tel: 0161 446 3000
Fax: 0161 446 3352

Dr Tim Maughan
Dept of Clinical Oncology
Velindre Hospital
Whitchurch
Cardiff CF4 7XL
Tel: 01222 615 888
Fax: 01222 694 179

Dr David Sebag-Montefiore
Cookridge Hospital
Leeds
LS16 6QB

Tel: 0113 292 4244
Fax: 0113 292 4214

Chemotherapy

Dr Matt Seymour
Cookridge Hospital
Leeds
LS16 6QB

Tel: 0113 292 4307
Fax: 0113 292 4361

Professor David Kerr
Dept of Clinical Oncology
Clinical Research Block
Queen Elizabeth Hospital
Birmingham B15 2TH
Tel: 0121 414 3802
Fax: 0121 414 5376

Dr Jonathan Ledermann
Dept of Oncology
UCL Medical School
91 Riding House Street
London W1P 8BT
Tel: 0171 380 9430
Fax: 0171 436 2956

Histopathology

Professor Philip Quirke
Division of Clinical Sciences
Algernon Firth Building
University of Leeds
Leeds LS2 9JT
Tel: 0113 233 3412
Fax: 0113 292 2834

MRC Cancer Trials Office:

Trial Manager

Anne Holliday (+44 (0)20 7670 4747, email: ath@ctu.mrc.ac.uk)

Data Managers

Tom Cullum (+44 (0)20 7670 4744, email: tc@ctu.mrc.ac.uk)

Shama Hassan (+44 (0)20 7670 4760, email: shh@ctu.mrc.ac.uk)

Statistician

Gareth Griffiths (+44 (0)20 7670 4704, email: gg@ctu.mrc.ac.uk)

MRC Clinical Trials Unit
Cancer Division
222 Euston Road
London
NW1 2DA

Tel: +44 (0)20 7670 4700
Fax: +44 (0)20 7670 4818

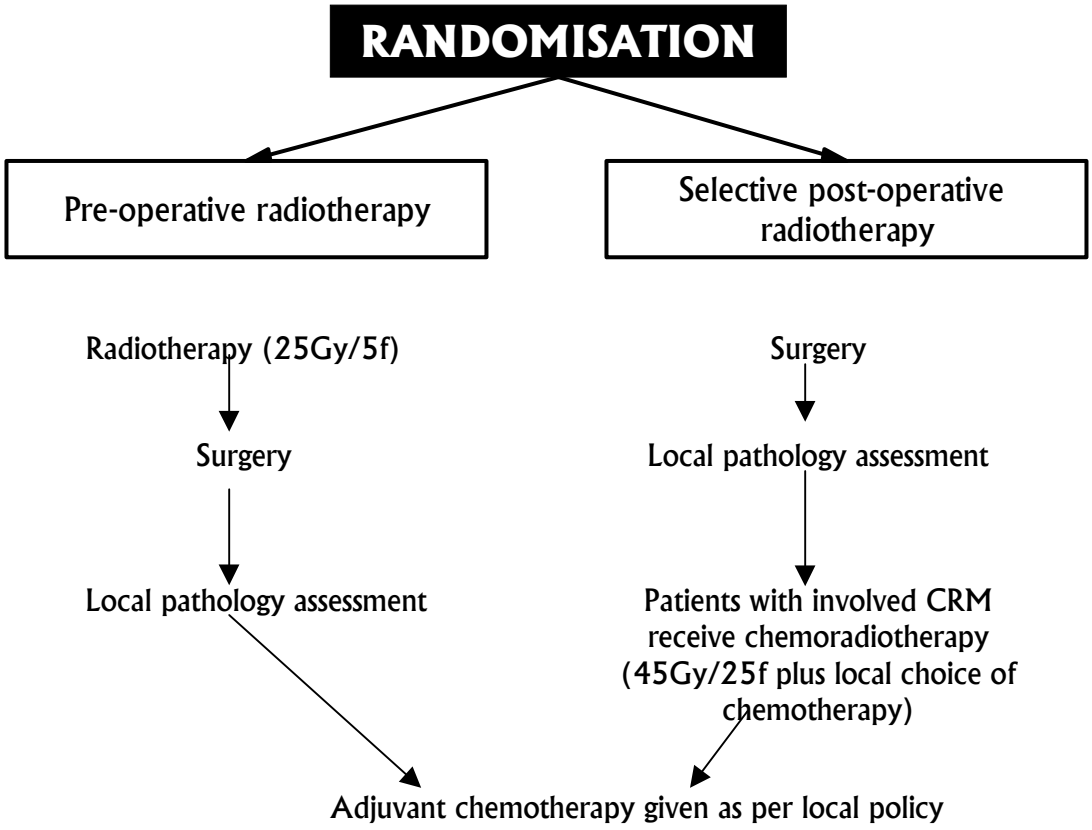
RANDOMISATIONS

Telephone the MRC Clinical Trials Office on:
+44 (0)20 7670 4777
between 0900 and 1700 hours, Monday to Friday

Contents

1. Outline

Clinically operable adenocarcinoma of the rectum



Forms to be completed

- Randomisation
- Surgery
- Pathology
- 1 month - includes post-operative morbidity
- 3 months - includes details of radiotherapy when applicable
- 6 months - includes details on which patients are receiving adjuvant chemotherapy
- 9 months - includes details of chemotherapy when applicable
- Follow-up -1 year, then 6-monthly to 3 years and annually thereafter

Quality of life assessments at baseline, 3-monthly to 1 year, then 6-monthly to 3 years

Primary endpoint: Local recurrence

2. Introduction

Over 10,000 new cases of rectal cancer are reported in the UK each year. For many patients, local recurrence following surgery for rectal cancer is a significant problem, causing intractable pelvic pain, which does not respond well to treatment. Radiotherapy has been used widely with the aim of preventing local recurrence, and two main approaches are available: (a) short course pre-operative radiotherapy and (b) selective post-operative radiotherapy.

Despite 13 major prospective randomised trials comparing surgery alone with surgery plus various radiotherapy regimens, the precise role of radiotherapy has yet to be defined. Four early studies using low dose radiation pre-operatively showed no significant effect on locoregional recurrence or survival (1–4), and three trials of post-operative radiotherapy (5–7), were similarly disappointing. However, four more recent randomised trials using pre-operative radiotherapy have shown significant reductions in local recurrence (8–11), although only one has shown a clear effect on survival (11). In addition, the results of two large MRC trials have just become available. In one of these, CR02, patients with clinically fixed rectal tumours were randomised to surgery alone or pre-operative radiotherapy (12). In the other, CR03, patients with mobile rectal tumours were randomised to surgery alone or post-operative radiotherapy (13). Both studies showed a significant reduction in local recurrence rates - of approximately 50% - associated with radiotherapy. Neither study, however, showed a clear improvement in survival.

Pre-operative radiotherapy

The Swedish Rectal Cancer trial (SRCT) randomised 1168 patients to surgery alone or short course pre-operative radiotherapy (25Gy in 5 fractions) followed by surgery (14). After 5 years follow up the overall local recurrence rate was reduced from 27% following surgery alone to 11% when radiotherapy was given prior to surgery. This trial is the first pre-operative radiotherapy trial to show an improvement in overall survival without the use of adjuvant chemotherapy, with overall 5 year survival rates of 58% for radiotherapy plus surgery vs 48% for surgery alone ($p = 0.004$). The previous reports of increased operative mortality using high daily fraction sizes of radiotherapy appear to have been overcome in the SRCT by the use of planned volumes using 3 or 4 portals (15). The disadvantage of the use of short course pre-operative radiotherapy, however, is that this approach is not selective. This policy requires that all patients with mobile rectal cancer should receive radiotherapy. There is no information on any subgroups of patients who might benefit from this approach and

its benefits in association with improved surgical techniques remain uncertain and the subject of at least one recently launched randomised trial in the Netherlands.

Post-operative radiotherapy

The recently published MRC CR03 trial (13) randomised 469 patients with Dukes' B and C rectal cancer after curative resection to four weeks of post-operative radiotherapy or no further treatment. The crude local recurrence rate after surgery alone of 34% fell to 21% for those patients randomised to post-operative radiotherapy. This trial did not demonstrate any clear difference in overall survival.

Randomised trial of pre-operative radiotherapy vs post-operative radiotherapy

One randomised trial has compared short course pre-operative radiotherapy to all patients against post-operative radiotherapy to patients with Dukes' B and C histology (16). This trial demonstrated a local recurrence rate of 13% using short course pre-operative radiotherapy compared with 22% using the post-operative policy ($p=0.22$). This trial can be criticised as the post-operative radiotherapy would be regarded today as suboptimal due to the 1–1.5 week gap in radiotherapy after 4 weeks.

Post-operative chemoradiotherapy

The post-operative trials analysed by the NCI for the Consensus statement (GTSG-7175 and NCCGT 79-47-51) showed a survival advantage for post-operative radiotherapy plus chemotherapy, using a combination of concomitant and sequential techniques, over respectively surgery alone and post-operative radiotherapy (17, 18). A North Central Cancer Treatment Group trial (NCCTG 86-47-51) compared the enhancement of post-operative radiotherapy by concomitant 5FU delivered by either bolus injection or continuous infusion (19). Both groups received in addition post-operative sequential bolus chemotherapy. After a median of 46 months follow up patients who received continuous infusion had a significantly improved ($p=0.01$) survival and time to relapse.

The advantages of the above trials were obtained at the expense of increased acute toxicity. In GITSG 7175 (17) severe non-haematological toxicity was reported in 35% of patients receiving chemoradiotherapy compared with 16% of those receiving radiotherapy alone. In the NCCTG 79-47-51 trial (18) comparable figures were 20% versus 5%. Modulation of 5FU with low dose folinic acid may also increase toxicity. The NSABP R03 trial (20) used post-operative radiotherapy with low dose folinic acid and 5FU 325mg/m^2 with a reported 28% of patients having more than 7 bowel movements per day and 6% having an overall toxicity of at least grade 4. The NCCTG

86-47-51 trial (19) reported a 24% incidence of severe/life threatening diarrhoea using continuous infusion 5FU (225 mg/m^2/day) with 50.4 Gy of irradiation. These data would suggest that it is important both to reduce the toxicity of chemoradiotherapy regimens and to carefully select those patients who will benefit from it.

Systemic adjuvant chemotherapy

Studies addressing the effect of systemic adjuvant chemotherapy in rectal cancer are complicated by the interaction with post-operative radiotherapy. Fewer trials of adjuvant chemotherapy have been conducted in rectal cancer, however the available data to date strongly suggest that, as with colon cancer, chemotherapy improves relapse-free and overall survival in high-risk patients (17-19).

Histopathology

The work of Quirke's group (21-24) has demonstrated that examination of the circumferential resection margin (CRM) can predict patients at high risk of local recurrence due to residual microscopic disease. The involvement of the CRM is independent of Dukes' stage, and both are important prognostic factors. Adam et al (21) demonstrated that 36% of patients who the surgeon felt had all macroscopic tumour removed had involvement of the CRM with a local recurrence rate of 64% whereas the 64% of patients with a clear (uninvolved) CRM had a local recurrence rate of 9%. The use of an involved CRM as the selection criterion for post-operative chemoradiotherapy will result in fewer patients receiving chemoradiotherapy.

Surgical technique

The major criticism of the previous adjuvant radiotherapy trials is that improvements in surgical technique are likely to lower the expected recurrence rates after surgery alone. Total mesorectal excision (TME) as described by Heald (25) has been reported in selected series (reviewed by McCall et al, 26) to result in low local recurrence rates. The value of adjuvant radiotherapy has not previously been tested combined with TME in a randomised trial. It is therefore not possible to define which groups of patients might benefit from either pre-operative or post-operative radiotherapy.

Synthesis of progress: optimising surgery, histopathology and adjuvant therapy

The Dutch Colorectal Group have recently launched a randomised trial where all surgery is conducted by accredited TME surgeons and patients are randomised between pre-operative short course radiotherapy and post-operative radiotherapy if there is involvement of the circumferential resection margin. In the UK there is an opportunity to conduct a randomised trial comparing short course pre-operative radiotherapy and best post-operative therapy (chemoradiotherapy) for those patients with involvement of the CRM. In addition the influence of the type of surgery on outcome will be investigated, although this will not be done in a randomised fashion.

3. Trial objective

The aim of the trial is to address the key question surrounding the use of radiotherapy in operable rectal cancer:

Are local recurrence-free rates and QL optimised by giving all patients short course pre-operative radiotherapy, or is a preferable option to give post-operative chemoradiotherapy only to those at high risk of recurrence (i.e. with involved margins following surgery)?

4. Endpoints

Primary endpoint

- Local recurrence (defined as +ve biopsy, +ve imaging, or equivocal imaging and a +ve CEA result (see detailed algorithm in Appendix I))

Secondary endpoints

- Local recurrence-free survival
- Overall survival
- Time to appearance of distant metastases
- Disease-free survival
- Morbidity
- Quality of life
- Economic implications

5. Quality of Life

The aim of assessing quality of life (QL) in this trial is to build up a complete picture of all the 'costs' and 'benefits' of these 2 treatments. However, during the treatment period a complex mix of therapies will be taking place. The individual effects of each are well documented and the major effects will be recorded by the clinicians. The aim therefore will be to compare the longer term effects of these policies: are patients now able to get on with their day to day activities, are they suffering any long term symptoms, has their sex life been affected?

The aim also, in this large trial, is to collect good quality data on as many patients as possible, and not to overburden clinicians and patients. We have chosen to combine the SF36 and the EORTC QLQ CR38 (colorectal module) to cover both the long-term effects and the relevant symptoms. It will be administered at baseline (pre-randomisation), 3, 6, 9 and 12 months and then at 6-monthly intervals to 3 years.

To ensure optimal compliance, guidelines for administering QL forms will be provided by the CTO, and each centre should nominate one person to hand out, collect and check the forms in the clinic.

6. Pathology training

The local pathologist is the key person in this trial. Thus pathologists must attend a training day where the full method for assessing rectal cancer specimens and the quality of surgery will be explained and demonstrated. A booklet will also be available.

A network of regional pathologists will be established to handle any queries, and to provide further pathology training if required. Difficult queries can be referred to Professor Philip Quirke (see inside front cover for contact details).

A system of quality assurance will be implemented to ensure uniformity of pathological reporting.

7. Health Economics

A health economic assessment will be made in a subgroup of centres. This will take into account the relative costs of short course pre-operative radiotherapy for all patients compared with a longer post-operative course in a selected group of patients, in addition to the costs of treating recurrent disease.

The final health economic balance will be very dependent on the proportion of patients allocated to post-operative radiotherapy who in fact require it.

The assessment of Health Economics will be the subject of a separate project grant proposal.

8. Trial entry

8a. Administration

This trial requires close collaboration between local surgeons, clinical oncologists, and pathologists. Before any centre can start to enter patients the 'Surgeon Checklist' (Appendix II) must be completed and returned to the CTO. This will entail:

- Each participating surgeon informing the CTO of the clinical oncologist(s) and pathologist with whom he will be collaborating.
- One pathologist in each centre being nominated to attend a training session (see section 6).
- Local policies for chemoradiotherapy and adjuvant chemotherapy being agreed at each centre to ensure that patients in both arms of the trial are treated and assessed consistently.

8b. Eligibility

- Histologically confirmed adenocarcinoma of the rectum (defined as lower edge of tumour within 15 cm of anal verge).
- Tumour considered potentially operable (i.e. not fixed).
- No evidence of metastases indicated by i) liver ultrasound or CT scan, ii) chest Xray, or iii) renal, liver and bone profiles. (Patients whose metastases are only discovered at surgery will continue in the trial for follow-up, but are treated at clinician's discretion.)

- Patients should be considered sufficiently fit to receive all the treatment in either arm of the trial. It is unlikely that many patients aged over 75 years will be fit. If in doubt, it is important to consult the clinical oncologist prior to randomisation.
- No concurrent uncontrolled medical illness (e.g. uncontrolled heart failure, angina, infection, etc.).
- No other previous or current malignant disease likely to interfere with the protocol treatments or comparisons.
- Informed consent obtained (see Appendix III).
- First QL questionnaire completed.

8c. Randomisation

After pre-treatment evaluation complete the Randomisation Form and telephone the MRC Cancer Trials Office (0900-1700 hours, Monday to Friday) on:

randomisation line: +44 (0)20 7670 4777

stating that the patient is to be entered into the CR07 trial. The patient will be allocated a regimen and a trial number. A copy of the confirmation letter will be faxed by the CTO to the surgeon, clinical oncologist, pathologist, and person responsible for QL administration.

To ensure balance between the 2 groups, patients will be stratified by a number of factors including surgeon.

N.B. Once randomised all patients remain in the trial, even if patients withdraw from treatment, and full documentation is required.

9. Protocol treatment

Schedule for patients allocated **pre-operative radiotherapy:**

- Radiotherapy (see sections 9c and 9d)
- Surgery (see section 9a)
- Pathology review (see section 9b)

Schedule for patients allocated **post-operative radiotherapy:**

- Surgery (see section 9a)
- Pathology review (see section 9b)
- Patients with histologically confirmed involved CRM then receive chemoradiotherapy (see sections 9c and 9e)

Patients in **both groups** may receive adjuvant chemotherapy (see section 9f) epending on local policy, which must apply to both arms of the trial.

9a. Surgery

Prior to randomisation the surgeon must ascertain that the tumour is rectal, and this is defined as the lower margin of the tumour being at or below 15 cm from the anal verge as measured by rigid sigmoidoscopy with the patient in the left lateral position. The surgeon must also consider that the tumour is resectable, i.e. that it is not fixed to the pelvis and that complete excision is feasible. If it is impossible to determine operability by digital examination in the clinic, examination under anaesthetic supplemented where appropriate by pelvic CT or MRI scanning or endoluminal ultrasound should be carried out.

After randomisation and after pre-operative radiotherapy in patients randomised accordingly, the patient will undergo anterior resection, abdomino-perineal resection or Hartmann's resection of rectum as deemed appropriate by the surgeon. Any metastatic disease seen at operation should be biopsied, and if local residual disease is thought to have been left, this too should be biopsied and the disease extent marked by metal clips. Although the aim of the operation will be to achieve complete local excision of the tumour, the performance of a formal total mesorectal excision will be left to the surgeon's discretion. Likewise, the construction of a defunctioning stoma at anterior resection will be an individual surgical decision.

9b. Pathology

All specimens will be assessed by the local pathologist using a standardised procedure (see Appendix IV for details).

9c. Radiotherapy

All radiotherapy should be administered from supervoltage radiotherapy machines, preferably a linear accelerator. All treatments must be computer planned and use a minimum of three treatment portals (two laterals and posterior). Patients should be treated in the prone position and the treatment volume localised using a combination of clinical examination, sigmoidoscopic findings, barium and CT/MRI films as available. Both conventional simulator planning films or CT planning are acceptable techniques.

Sperm storage should be discussed with men and hormone replacement therapy with premenopausal women, as pelvic radiotherapy will sterilise.

9d. Pre-operative radiotherapy

Selection. Pre-operative radiotherapy is given to **ALL** patients randomised to this policy in the trial.

Volume. The clinical target volume encompasses the posterior pelvis to include all the identified tumour plus the adjacent tissues. The superior border is usually level with the sacral promontory. The inferior border depends on the location of the tumour in the pelvis. The inferior margin should be 3-5 cm below the inferior tumour margin. For mid or upper third tumours the anal canal can be spared. The posterior border lies one cm behind the anterior border of the sacrum. The anterior border usually lies 2-3 cm anterior to the sacral promontory. Some upper third rectal cancers may extend further anteriorly than this and reference to imaging data for these tumours is vital. The lateral borders lie 1 cm lateral to the pelvic wall. Clinical oncologists are encouraged to review the detailed description of the radiotherapy planning used in the Swedish trials (Frykholm et al, 27).

Dose, fractionation. The ICRU reference dose administered to a point central within the tumour volume is 25 Gy. This is delivered in 5 fractions of 5 Gy in one week. Using the linear quadratic time formula, this is equivalent to 21 x 2 Gy fractions for both acute and late effects assuming α/β = 10 Gy for acute effects and 3 Gy for late effects. Using the CRE formula, the dose equivalence is the same for acute effects, but increased to 25 x 2 Gy for late effects (Frykholm et al, 27).

Timing. This treatment should be scheduled to be delivered such that surgery is undertaken within 7 days of the last fraction of radiotherapy.

Note: Patients who have received pre-operative radiotherapy **must not** be treated with further radiotherapy post-operatively even if the CRM is involved.

9e. Post-operative chemoradiotherapy

Radiotherapy

Timing. Post-operative radiotherapy should be commenced after healing of the operative scars, synchronously with the commencement of concurrent chemotherapy. This should optimally be at 4-6 weeks from surgery, but a window up to 12 weeks post-operatively is permissible.

Selection. Post-operative radiotherapy is given to those patients randomised to selective post-operative radiotherapy whose pathology report indicates tumour is within 1 mm of the CRM. (Patients who have received pre-operative radiotherapy **must not** be treated with further radiotherapy post-operatively even if the CRM is involved.) If no comment is made on the pathology form regarding CRM involvement then ask the trial pathologist to review their report.

Volume. The clinical target volume is similar to that described above and encompasses a posterior pelvic volume. The superior border is level with the sacral promontory. The inferior border depends on the operation performed and the location of the primary tumour. In patients with lower third rectal cancer who have had an AP resection, the perineal scar should be included with a margin of 1-2 cm. In those with AP resections whose cancer was not in the lower third, the perineum need not be included. In patients with anterior resections, the inferior margin should be 3-5 cm below the anastomosis or at the inferior aspect of the obturator foramen whichever is the more inferior. The posterior border lies 1 cm behind the anterior border of the sacrum. The anterior border usually lies 2-3 cm anterior to the sacral promontory and encompasses the posterior two-thirds of the femoral heads. The lateral margins lie 1 cm lateral to the pelvic side wall.

Dose, fractionation. The standard tumour dose should be 45 Gy in 25 fractions in 5 weeks treating 5 days per week, giving 1.8 Gy per fraction to the ICRU reference dose point. A boost dose of a further 5.4 Gy in 3 fractions in a further week of radiotherapy should be considered in patients in whom macroscopic residuum has been left and identified with surgical clips. Surgeons have been encouraged to place clips at the site of any residual disease. This boost should be given using a 3 or 4 field plan to the site of residual disease.

Chemotherapy

During post-operative radiotherapy, patients should receive chemotherapy. Each centre should select their own protocol, but one of the following options is advised. Alternative schedules should be discussed with one of the clinical coordinators. If patients are considered unfit to receive chemoradiotherapy after surgery, then the chemotherapy may be omitted at the treating oncologist's discretion.

(i) Continuous infusional 5FU. Fluorouracil 200 mg/m^2/d continuously during post-operative radiotherapy using ambulatory pump and central venous catheter. This is a 25 mg/m^2/d reduction from the NCCTG dose and has been safe in unpublished UK usage. Give warfarin 1 mg/d while catheter is in situ.

(ii) Bolus 5FU 300 mg/m^2 and folinic acid 20 mg/m^2 once weekly. This is the regimen used in the QUASAR trial and, although toxicity does occur, it has been widely used in the UK.

(iii) A 5 day bolus schedule of 5FU and folinic acid is being piloted. Once data from this is available it may be introduced as an alternative as a planned protocol amendment.

9f. Adjuvant chemotherapy

The trial is not designed to test the effect of systemic chemotherapy, but following protocol treatment, patients may receive adjuvant chemotherapy either within an appropriate randomised trial (eg QUASAR1) or using a standard regimen according to local policy. Advice on the selection of patients for systemic chemotherapy, and suitable standard regimens, are given in Appendix V.

Each centre will be asked to state their local policy, which must not depend on the arm of the trial, and must adhere to it for all patients in the trial. On the 'Surgeon Checklist' (Appendix II), define which subgroup of patients (if any) will be treated routinely with adjuvant chemotherapy and which regimen will be used.

Timing. Patients receiving adjuvant chemotherapy only should commence once post operative recovery is sufficient: scars are healed, optimally 4-6 weeks after operation. Patients receiving chemoradiotherapy and adjuvant chemotherapy, undergo chemoradiotherapy first (see section 9f), then proceed, 4 weeks after completion of chemoradiotherapy with cycle 1 of adjuvant chemotherapy.

10. Additional treatment

Treatment for recurrent disease is at the clinician's discretion. Entry of eligible patients into trials for advanced disease is encouraged. The CTO can provide information about ongoing trials.

11. Clinical follow-up

It is vital that all patients are followed and assessed consistently so that no bias in the reporting of local recurrence occurs. The timing of follow-up visits can be according to local practice but must be the same regardless of the treatment randomised. There are no mandatory follow-up investigations. However, all patients should have the anastomosis inspected and palpated at each follow-up visit.

The primary endpoint is confirmed local recurrence and therefore it is vital that the date of confirmation is recorded. Please also record the date when the first symptoms suspicious of local recurrence were noted, and arrange for radiological investigations (CT scan) to confirm this. Ideally, even if distant metastases have been confirmed, monitoring should continue for local recurrence.

12. Assessments and forms

The following forms (copies in Appendix IX) should be completed:

- **Randomisation Form**
- **Surgery Form**
- **Pathology Form**. After assessing the specimen, the pathologist should complete the Pathology form, which includes Dukes' and TNM staging. The situation of the tumour should be reported as this is of interest as anterior tumours should have a higher CRM positive rate. The completed form should be sent to the surgeon, with copies (fax if possible) to the clinical oncologist, and the CTO. Colour 2x2 slides (if taken), digital photographs, or photocopies of the specimen should be sent to the CTO.
- **1 month Follow-up Form**. This should be completed by the surgeon and includes information on surgical morbidity.

- **3 month Follow-up Form**. This should be completed by the clinical oncologist for all patients. It includes details of all radiotherapy (and chemoradiotherapy) received, as well as radiotherapy toxicity.
- **6 month Follow-up Form**. This should be completed for all patients and includes information on which patients are receiving adjuvant chemotherapy.
- **9 month Follow-up Form**. This should be completed for all patients, and includes details of any adjuvant chemotherapy received.
- **Subsequent Follow-up Forms**. Complete follow-up forms for all patients at 1 year from the date of randomisation, then at 6-monthly intervals for a further 3 years, and yearly thereafter.
- **Quality of Life** assessments should be performed at baseline, 3, 6, 9 and 12 months and then 6-monthly to 3 years.

Once randomised all patients remain in the trial and forms relating to all the above assessments are required even if patients withdraw from treatment. All patients will be followed to death.

13. Analysis plan

In all analyses the treatments will be compared on the intention-to-treat basis. No formal subgroup comparisons are planned, but the prognostic value of surgical technique will be evaluated.

Primary endpoint

Local recurrence. The time to the first confirmation of local recurrence will be recorded, and the regimens compared using the Mantel-Cox version of the log-rank test. Patients with no confirmed local recurrence will be censored at date of death or date last seen. Confidence intervals will be calculated for the corresponding hazard ratios.

Secondary endpoints

Local recurrence-free survival. Isolating local recurrence from survival can potentially give misleading results as the group with the longer survival will have more

time in which to recur. Therefore considering local recurrence-free survival is an effective way of dealing with this potential bias, and is also clinically relevant - the aim of treatment being to keep patients alive and free of disease for as long as possible. The 'event' will be time from randomisation to confirmation of local recurrence or death, which ever occurs first, survivors with no local recurrence being censored at the date last seen.

Overall survival. Survival will be measured from the date of randomisation to the date of death, survivors being censored at the date last seen.

Time of appearance of distant metastases. The 'event' will be time from randomisation to confirmation of distant metastases, patients without confirmation of distant metastases being censored at the date of death or date last seen.

Disease-free survival. The 'event' will be time from randomisation to confirmation of local recurrence, distant metastases, or death, whichever occurs first, disease-free survivors being censored at the date last seen.

Morbidity. The treatments will be compared in terms of the proportion of patients with post-operative morbidity, grade 3 or 4 symptoms at 3, 6, 9 and 12 months, and long term complications at 12 and 24 months.

Quality of life. The use of the SF-36 will allow us to compare the overall QL of patients in the 2 treatment groups: using the 9 subscales to assess their general health, physical and social functioning, vitality, bodily pain etc. In addition the EORTC QLQ-CR38 will concentrate on specific disease and treatment related symptoms. The treatments will be compared longitudinally and at 3 monthly intervals from randomisation in the first year and 6 monthly thereafter.

14. Statistical considerations

Local recurrence rates following pre-operative radiotherapy have been estimated at approximately 10% at 2 years, though it is possible that the increasing use of TME may reduce this even further. A slightly higher recurrence rate overall would be acceptable in patients in the selective post-operative radiotherapy group, in whom only 25-35% would be expected to receive radiotherapy, however a difference of more than 5% would generally be considered unacceptable. Thus the trial is designed to have 90% power to show that there is less than a 5% difference in local recurrence rates at 2 years (2-tailed $\alpha = 0.05$). This will require the randomisation of approximately 1800 patients.

This number of patients would also provide >85% power to detect a 7% difference in local recurrence-free or overall survival rates at 5 years (ie from 55% to 62%, or from 60% to 67%). However the power to detect a 5% difference would only be 60%.

15. Data Monitoring Committee

An independent data monitoring committee (DMC) will be established consisting of two clinicians not entering patients in the trial, and an independent statistician. It is anticipated that this DMC will meet at approximately yearly intervals; the exact frequency will depend upon accrual, recurrence and death rates. At their first meeting, the DMC will advise on the nature and frequency of subsequent interim analyses.

16. Publication

The results from different centres will be analysed together and published as soon as possible. Individual clinicians must not publish data concerning patients entered into the trial which are directly relevant to questions posed by the trial until after the Working Party has published its report. The main trial result will be published as a CR07 Trial Steering Committee report. All contributors will be acknowledged.

17. Ethical considerations

The protocol has been approved by the Scottish Multicentre Research Ethics Committe (MREC) and must be approved by each centres Local Research Ethics Committee (LREC) prior to entering patients. The patient's consent to participate in the trial should be obtained after a full explanation has been given of the treatment options, including the conventional and generally accepted methods of treatment. A suggested patient consent form and patient information leaflet are attached (Appendix III and VI). These may be modified to comply with LREC requirements. A copy of the LREC approval letter must be sent to the CTO.

The right of the patient to refuse to participate in the trial without giving reasons must be respected. After the patient has entered the trial the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the patient's best interest, but the reasons for doing so should be recorded and the patient will remain within the trial for the purposes of follow-up and data analysis according to the treatment option to which he/she has been allocated. Similarly, the patient must remain free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing his/her further treatment.

A statement of MRC policy on ethical considerations in the clinical trial of cancer therapy, including the question of informed consent, is available from the CTO, and may be used to give guidance to participating investigators and to accompany applications to the LREC.

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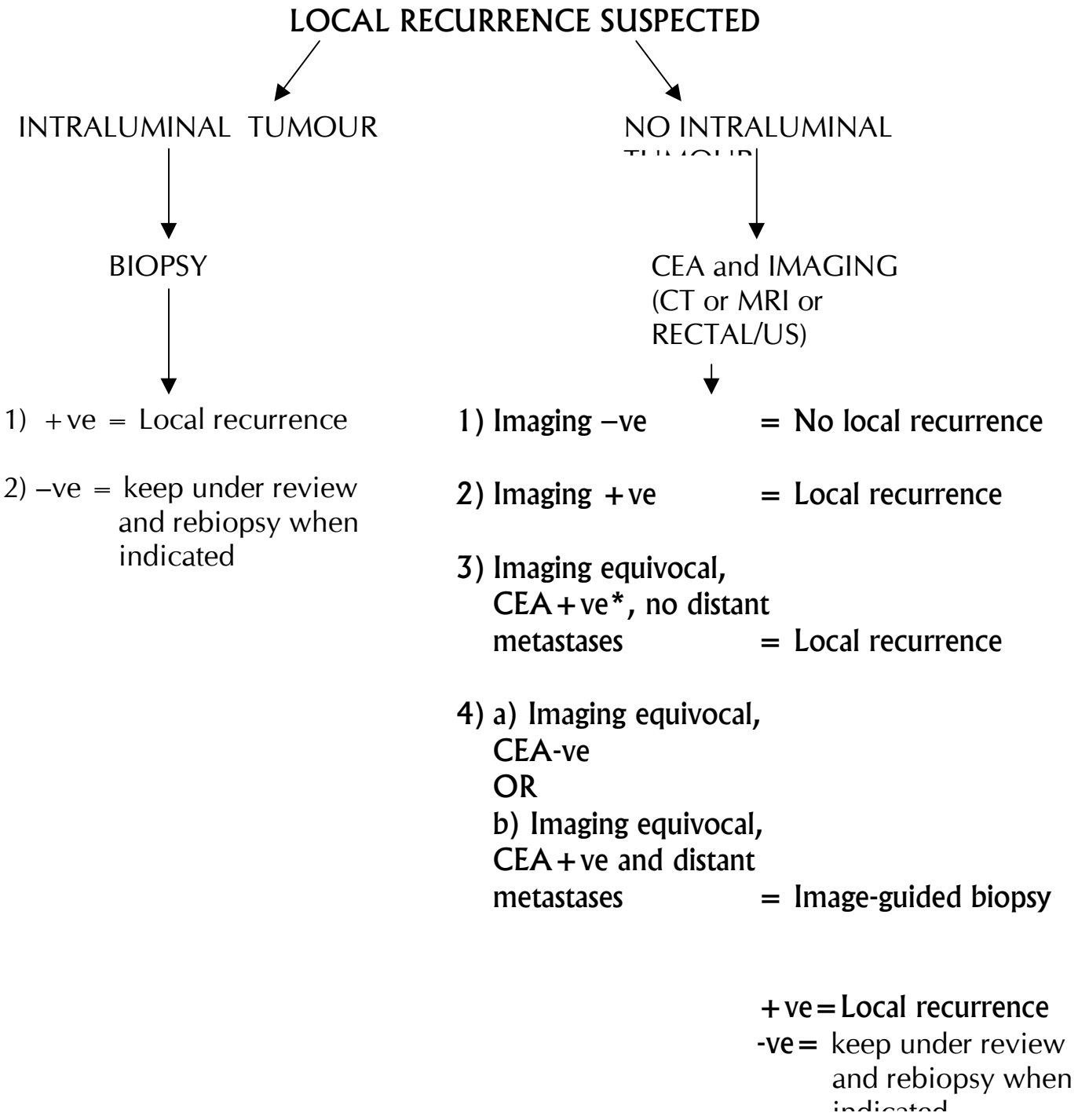
Appendix II

ALOGORITHM FOR DEFINING LOCAL RECRRENCE

Note: as local recurrence is the primary endpoint, continue monitoring for local recurrence even if distant metastases have been confirmed.



**Note: CEA+ve defined as > upper limit of local normal value*

Surgeon Checklist

Surgeon

Centre

Telephone **Fax** **Email**

1. Participating clinical oncologists:

Name	Tel	Fax	Email

2. Nominated local pathologist:

Name	Tel	Fax	Email

3. Confirm nominated pathologist has attended CR07 training session: ☐ (tick)

4. Local coordinator(s) responsible for data collection and quality of life administration:

Name	Tel	Fax	Email

5. Confirm local ethics approval gained (send copy of confirmation to the Cancer Division): ☐ (tick)

6. Agreed local policy for post-operative chemoradiotherapy:

7. Agreed local policy for adjuvant chemotherapy for all patients:

Send to: CR07, Cancer Division, MRC Clinical Trials Unit, 222 Euston Road, NW1 2DA.

Appendix III

PATIENT CONSENT FORM
MEDICAL RESEARCH COUNCIL COLORECTAL CANCER TRIAL (CR07)

Patient's name _____

Address _____

_____

I have received an explanation of the trial and read the information sheet and understand:

- what the trial involves
- that if I decide not to participate my future treatment will not be affected in any way
- that I may withdraw from the trial at any time.

I agree to take part in the trial.

Signature _____ Date

I have been present while the trial has been explained to the patient and have witnessed his/her consent to take part.

Signature _____ Date

Clinician's signature _____ Date

Appendix IV

PATHOLOGICAL ASSESSMENT OF A RECTAL CANCER SPECIMEN

The pathological assessment of a rectal cancer specimen has been described previously (Quirke & Dixon, Quirke & Scott) but minor modifications are presented here. Where possible specimens should be received fresh and opened by the pathologist. If this is not possible, then the surgeon should open the bowel in the way described below and pin it out on a cork board for fixation. If neither of these are possible then the specimen should be placed in an adequate volume of formalin, usually 20 times the volume of the specimen.

We now open the rectum anteriorly apart from the area 2 cm above and below the tumour where the anterior part of the rectum is left intact. This change is because of the importance of the anterior quadrant with respect to local spread. Below the peritoneal reflection the surgeon can usually remove between 0.5 and 1.0 cm anteriorly, thus tumours involving this area are at greater risk of circumferential resection margin (CRM) involvement. In tumours above the peritoneal reflection, involvement of the peritoneal surface can occur, and it is best to avoid destroying this area and the pathologist's ability to sample it by avoiding opening the site of the tumour. If possible a macroscopic photograph of the posterior and anterior sides of the specimen is valuable.

The opened specimen should then be pinned to a cork board and fixed for 48-72 hours. After fixation the specimen should be removed from the board and the non-peritonealised surfaces painted with ink by the method in use locally.

The macroscopic description of the specimen is then performed. Failing to open the specimen does cause a problem with recording the tumour characteristics but the length, width and area of the tumour are not prognostic whereas CRM and peritoneal involvement are. The best estimate possible should be made after slicing the tumour. The macroscopic description should assess the quality of the mesorectum on the specimen. There are 3 grades:

3 – Good: Intact mesorectum with only minor irregularities of a smooth mesorectal surface. No defect is deeper than 5 mm. No coning on the specimen. Smooth CRM on slicing.

2 – Moderate: 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 the insertion of levator muscles. Moderate irregularity of CRM.

1 – Poor: Little bulk to mesorectum with defects down onto muscularis propria and/or very irregular CRM.

The area of the tumour that has been left intact is now sectioned transversely as thinly as possible. If the specimen is not well fixed (i.e. 48-72 hours in formalin) then this process is more difficult.

The fixed slices are laid out under good light and photographed (if possible) and then inspected macroscopically. Measurements: i) the maximum depth of extension of the tumour from the muscularis propria, ii) the distance from the CRM to the tumour. If the tumour is within 1 mm on histological sections then CRM involvement is said to have occurred. This distance was chosen by analysis of previous studies (Quirke et al , Adam et al). If any lymph nodes abut the CRM then these should be taken in continuity with the CRM so that involvement by this route can be identified, similarly if there is any evidence of isolated deposits or thickening/fibrosis in this area it should be sampled. Again, if tumour is less than 1mm from the CRM, the CRM is said to be involved. Any peritumoral lymph nodes will be collected at this time. If the tumour approaches the peritoneal surface this must also be sampled to exclude malignant cells on the surface or ulceration of the serosa by tumour (Shepherd et al). Four blocks of the primary tumour must be taken to assess the peritoneum and tumour characteristics. These may be the same blocks as those for the CRM, if there is adequate tumour represented.

After assessing the primary tumour attention should be turned to the lymph nodes. Starting at the vascular resection margin the lymph nodes should be visualised by cross cutting the vessels and mesorectum. The highest lymph node (Dukes C2) should be identified. All other lymph nodes should be identified and embedded. If any lymph nodes lie against the circumferential margin then they should be taken in continuity with the margin to exclude CRM involvement. Again if tumour is <1 mm, CRM involvement is said to occur. The distal margin should then be sampled and the doughnuts examined. The proximal margin does not need to be examined unless within 5 cm of the tumour. Any mucosal lesions seen should be sampled. The status of the background mucosa can be obtained from the distal margin.

Standard histological examination of the haematoxylin and eosin sections should then be performed. If tumour is within 1 mm of the CRM then it should be deemed to be involved. This measurement should be made on the glass slide using the Vernier scale. If tumour is close to the margin but greater than 1 mm then deeper levels should be cut to exclude involvement. If fibrosis has led to a mistaken impression of the depth of invasion from the muscularis propria then this measurement should be corrected from the slide.

References

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Appendix V

GUIDELINES ON USE OF ADJUVANT CHEMOTHERAPY

Each centre must agree a local policy for the criteria they will use in deciding whether to recommend systemic adjuvant chemotherapy. These criteria must not depend on which arm of the trial the patient is allocated to, and must apply to all patients in the trial.

Suggested schema

	CR07 Allocation: Pre-op Radiotherapy	**CR07 Allocation: Selective post-op radiotherapy**
Node –ve CRM -ve	CR07: pre-op RT and surgery then: no further treatment*	CR07: surgery alone then: no further treatment*
Node –ve CRM +ve	CR07: pre-op RT and surgery then: adjuvant chemotherapy	CR07: surgery and post-op CRT then: adjuvant chemotherapy
Node +ve CRM -ve	CR07: pre-op RT and surgery then: adjuvant chemotherapy*	CR07: surgery alone then: adjuvant chemotherapy*
Node +ve CRM +ve	CR07: pre-op RT and surgery then: adjuvant chemotherapy	CR07: surgery and post-op CRT then: adjuvant chemotherapy

* or consider trial of chemotherapy vs no further treatment (eg QUASAR)

Suggested adjuvant chemotherapy regimens

There is no single "standard" adjuvant chemotherapy regimen, so for this trial two alternative regimens are suggested, both with a range of doses, which will suit different oncology units, and which appear from available evidence to be of similar efficacy and toxicity.

Treatment

Patients should receive a total of 6 months of chemotherapy, thus if they have already received chemoradiotherapy, the duration of adjuvant chemotherapy should be reduced.

i. **5 day bolus** 5FU and low dose folinic acid regimen

Folinic acid, 20 mg/m^2, iv bolus, D1-5, q28d

Fluorouracil, 370-425 mg/m^2, iv bolus 5 min, D1-5, q28d

6 cycles to be administered (4 cycles if chemoradiotherapy already given)

ii. **Weekly** 5FU and low dose folinic acid regimen

Folinic acid, 20 mg/m^2, iv bolus, D1, q7d

Fluorouracil, 370-500 mg/m^2, iv bolus 5 min, D1, q7d

24 cycles to be administered (16 cycles if chemoradiotherapy already given)

Treatment Delay. The FU/FA course should be delayed for a week, until completely recovered, in the event of either: low blood counts (neutrophils $< 2.0 \times 10^9$/l or platelets $< 100 \times 10^9$/l) or any persistent mucositis or diarrhoea.

5FU Dose Reductions for Toxicity. Patients who develop Grade 2 Common Toxicity Criteria (CTC) toxicity (see below) during the 5 day chemotherapy schedule should have the remainder of the 5FU and folinic acid withheld for that cycle. In the event of toxicity between courses (on either schedule), the dose level of 5FU for subsequent doses should be reduced depending on the worst grade of toxicity observed following the preceding course. The table below shows the percentage of the 5FU dose used in the preceding course which should be given for all further courses of therapy, i.e. the dose of 5FU should remain at the reduced level, or lower if further toxicity occurs, for the remainder of the treatment. NB: dose reductions apply only to 5FU.

Non-haematological toxicity (diarrhoea, stomatitis)

See Appendix VIII for CTC grades of diarrhoea and stomatitis

	CTC Grade	0–1	2	3	4
Haematological	0–2 (P 50 and N 1.0)	100%	80%	50%	NFT
platelets (P) &	3 (P = 25–49 or N = 0.5–0.9)	80%	70%	50%	NFT
neutrophils (N)	4 (P < 25 or N < 0.5)	50%	50%	50%	NFT

(NFT = No further treatment recommended)

Appendix VI

SUGGESTED PATIENT INFORMATION SHEET

You have been invited to consider taking part in a clinical study conducted by the Medical Research Council. This is a large clinical trial that is being carried out in several hospitals across the country. In total, 1800 patients are required to take part. This sheet explains the background to the study and is intended to supplement your discussion with your doctors.

Your surgeon has discovered that you have a growth in your back passage or rectum. This has been shown to be a malignant growth, or in common terms, a cancer.

The standard treatment for cancer of the rectum is to remove it surgically and this remains the most important part of any treatment. However, for some patients we know that the addition of radiotherapy, or X-ray treatment, to the area of the tumour in the pelvis can improve the outcome of the surgical treatment. We are trying to establish whether this radiotherapy is required for all patients, and when it should be given.

One approach (Policy A) is to remove the lower part of the bowel surgically and to examine the removed specimen under the microscope in the pathology laboratory. If the tumour has been completely removed and there is no evidence of cancer near the edge of the removed tissues, then you do not receive radiotherapy as there is little risk of the cancer recurring. If however, the examination under the microscope reveals cancer cells at the edge of the removed tissues, then you do receive a course of radiotherapy to the pelvis to try and eradicate any cells that might have been left behind. This treatment would be given over 5 weeks treating you with a small dose of radiotherapy once a day as an outpatient 5 days a week. During your radiotherapy treatment you will also receive chemotherapy which is thought to improve the results of radiotherapy and is generally well tolerated. We would expect between a quarter and a third of patients to receive radiotherapy and chemotherapy using this approach.

A different approach (Policy B) to the use of radiotherapy has been carefully evaluated in Sweden and shown to be of benefit, and we wish to see whether it is also of benefit in the UK in combination with surgery. This approach is to give every patient who is going to have an operation to remove a cancer of the rectum a short one week course of radiotherapy to the rectum before the operation. This treatment is very quick and therefore will not delay the operation date. The information from Sweden suggests that this is a safe way to give radiotherapy.

We therefore wish to compare the benefits of these 2 policies:

Policy A – radiotherapy given after surgery for those patients whose cancer is seen at the edge of the removed tissues

or

Policy B – a 1 week course of radiotherapy given before surgery for all patients.

In order to be sure that the results of this comparison are not biased, we need to allocate patients to Policy A or Policy B randomly. This is done by a central computer and neither your consultant nor you yourself are able to choose which treatment policy you prefer. You therefore need to be happy to receive either of the 2 possible treatment policies if you are going to be involved in this study.

The side effects of the 2 treatment policies will be slightly different. Patients allocated Policy A who receive radiotherapy and chemotherapy after the operation are likely to experience tiredness, diarrhoea, possibly some skin redness and maybe soreness. Rarely, the small bowel may become inflamed giving rise to colicky abdominal pain. Very rarely, this may result in a narrowed segment of small bowel, which may need to be removed at a later date. Patients allocated Policy B all receive radiotherapy before the operation. This is very well tolerated in the short term but may lengthen the time taken to heal up after the operation. Because this is a relatively recent treatment, we are not aware of any longer term problems that may arise, but these are likely to be very rare.

Pelvic radiotherapy as given in either policy will sterilise both men and women. If this is an issue with you, please raise this with your specialist.

In addition to the treatments explained above, some patients in both policies will be advised to received some gentle chemotherapy as part of their treatment. This may be advised for patients whose cancers have spread to the lymph glands alongside the bowel and those whose cancers have spread to the edge of the tissues that are removed at the operation. This will be discussed with you further after the operation when the full report is available from the pathology laboratory.

In addition to information from the doctor treating you, we also wish to know about how you are feeling, physically and emotionally, before and after your treatment. In order to collect this information you will be asked to complete a "Quality of Life Questionnaire" each time you attend the hospital for treatment. These questionnaires

refer to how you have been feeling during the past week and are designed to assess the effect of your treatment on your general health, and to monitor any side effects you may be experiencing. They remain confidential at all times.

If you decide to participate in this trial, your GP will be informed. All information about you and your treatment will remain strictly confidential and no individual patients will be identified when the results of the trial are published.

Specimens from all tumours are routinely saved by the hospital since it may be helpful for your management in the future. These specimens may also be useful for finding new tests, which in future may improve the treatment of this disease. In asking you to take part in this study, we are also requesting your permission to use stored material from your operation in future scientific studies. These possible extra studies will not affect your treatment in any way.

IMPORTANT: If, after deciding to take part in the trial, your condition changes and your doctor feels that the treatment decision which has been made should be changed, or if you simply change your mind, the decision may be reversed without affecting your subsequent treatment, and without detracting from your contribution to the research.

This trial uses no experimental treatments, all aspects are standard hospital practice and therefore any claims for negligence remain the responsibility of your hospital.

If you have any further questions about your disease or clinical trials, please contact your doctor or if you prefer you can contact BACUP (an independent patient advisory group).

Freephone 0800 181199
or
Write to : BACUP
3 Bath Place
Rivington Street
London
EC2A 3JR

Appendix VII

CTC TOXICITY SCALE

Symptom	Grade				
	0	1	2	3	4
Nausea	none	able to eat reasonable intake	intake significantly decreased but can eat	no significant intake	-
Vomiting requiring support	none	1 episode in 24hrs	2-5 episodes in	6-10 episodes in 24hrs	>10 episodes in 24hrs 24hrs or parenteral
Diarrhoea	none	increase of 2-3 stools per day over pre-Rx	increase of 4-6 stools/day, or nocturnal stools, or moderate cramping	increase of 7-9 stools/day, or incontinence or severe cramping	increase of >10 stools/day, or grossly bloody diarrhoea, or grossly bloody colostomy output or loose watery colostomy output requiring parenteral support; dehydration
Stomatitis	none	painless ulcers, erythema or mild soreness	painful erythema, oedema or ulcers but can eat	painful erythema, oedema or ulcers and cannot eat	requires parenteral or enteral support
Genitourinary	no change	frequency of urination or nocturia twice pretreatment habit/dysuria, urgency not requiring medication	frequency of urination or nocturia which is less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anesthetic (eg Pyridium)	frequency with urgency and nocturia hourly or more frequently/dysuria, pelvis pain or bladder spasm requiring regular, frequent narcotic/ gross haematuria with/without clot passage	haematuria requiring transfusion/acute bladder obstruction not secondary to clot passage, ulceration or necrosis
Mucositis	no change over baseline	injection/may experience mild pain not requiring analgesic	patchy mucositis which may produce an inflammatory serosanguinitis discharge/may experience moderate pain requiring analgesia	confluent fibrinous mucositis/may include severe pain requiring narcotic	ulceration haemorrhage or necrosis
Haemoglobin	>11	10.0 - 11.0	8.0 - 9.9	6.5 - 7.9	<6.5
WBC	>=4.0	3.0 - 3.9	2.0 - 2.9	1.0 - 1.9	<1.0
Neutrophils	>=2.0	1.5 - 1.9	1.0 - 1.4	0.5 - 0.9	<0.5
Platelets	>100	75.0 - 100	50.0 - 74.9	25.0 - 49.9	<25.0

Appendix VIII

TNM STAGING

T - Primary tumour

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria
T1	Tumour invades submucosa
T2	Tumour invades muscularis propria
T3	Tumour invades through muscularis propria into subserosa or into non-peritonealized pericolic or perirectal tissues
T4	Tumour directly invades other organs or structures and/or perforates visceral peritoneum

N - Regional lymph nodes

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1 to 3 pericolic or perirectal lymph nodes
N2	Metastasis in 4 or more pericolic or perirectal lymph nodes

M - Distant metastasis

MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

	Stage grouping			Dukes' Stage
Stage 0	Tis	N0	M0	
Stage I	T1-2	N0	M0	A
Stage II	T3-4	N0	M0	B
Stage III	Any T	N1-2	M0	C
Stage IV	Any T	Any N	M1	