Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised clinical trial

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Summary

Background Local recurrence rates in operable rectal cancer are improved by radiotherapy (with or without chemotherapy) and surgical techniques such as total mesorectal excision. However, the contributions of surgery and radiotherapy to outcomes are unclear. We assessed the effect of the involvement of the circumferential resection margin and the plane of surgery achieved.

Methods In this prospective study, the plane of surgery achieved and the involvement of the circumferential resection margin were assessed by local pathologists, using a standard pathological protocol in 1156 patients with operable rectal cancer from the CR07 and NCIC-CTG CO16 trial, which compared short-course (5 days) preoperative radiotherapy and selective postoperative chemoradiotherapy, between March, 1998, and August, 2005. All analyses were by intention to treat. This trial is registered, number ISRCTN 28785842.

Findings 128 patients (11%) had involvement of the circumferential resection margin, and the plane of surgery achieved was classified as good (mesorectal) in 604 (52%), intermediate (intramesorectal) in 398 (34%), and poor (muscularis propria plane) in 154 (13%). We found that both a negative circumferential resection margin and a superior plane of surgery achieved were associated with low local recurrence rates. Hazard ratio (HR) was 0.32 (95% CI 0.16–0.63, p=0.0011) with 3-year local recurrence rates of 6% (5–8%) and 17% (10–26%) for patients who were negative and positive for circumferential resection margin, respectively. For plane of surgery achieved, HRs for mesorectal and intramesorectal groups compared with the muscularis propria group were 0.32 (0.16–0.64) and 0.48 (0.25–0.93), respectively. At 3 years, the estimated local recurrence rates were 4% (3–6%) for mesorectal, 7% (5–11%) for intramesorectal, and 13% (8–21%) for muscularis propria groups. The benefit of short-course preoperative radiotherapy did not differ in the three plane of surgery groups (p=0.30 for trend). Patients in the short-course preoperative radiotherapy group who had a resection in the mesorectal plane had a 3-year local recurrence rate of only 1%.

Interpretation In rectal cancer, the plane of surgery achieved is an important prognostic factor for local recurrence. Short-course preoperative radiotherapy reduced the rate of local recurrence for all three plane of surgery groups, almost abolishing local recurrence in short-course preoperative radiotherapy patients who had a resection in the mesorectal plane. The plane of surgery achieved should therefore be assessed and reported routinely.

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Introduction Outcomes in operable rectal cancer show wide variation, with local recurrence ranging from less than 6% to more than 50% and survival from 45% to 80% at 5 years.1–3 Two methods for improving outcomes are preoperative radiotherapy4–6 (alone or in combination with chemotherapy) and better surgical techniques.7–9 For preoperative radiotherapy, both short-course treatment, as proposed by radiotherapists in Sweden,4–6 and long-course radiotherapy or chemoradiotherapy10 improve local recurrence rates4–6,10–12 and overall survival.4–6 However, radiotherapy increases the cost of the management of these patients13 and has well described long-term toxic effects.14,15 Surgical training, including total mesorectal excision, also reduced local recurrence rates and improved survival in populations from Norway,16 Sweden,17 and Netherlands.18 Removed resection specimens differ in their appearance, and macroscopic grading might be a way to assess and classify the plane of surgery achieved.1 A study19 of 180 cases that adopted this grading showed that surgery in the mesorectal plane lowered local recurrence rates and improved survival compared with other planes of surgery. However, the plane of surgery achieved and its effect on local recurrence rates have not been routinely assessed by local pathologists in large clinical trials. Furthermore,
the relative improvements in surgical techniques and radiotherapy are unclear. We prospectively assessed the importance of circumferential resection margin and the grading of the plane of surgery achieved from data obtained in the international multicentre CR07 and NCIC-CTG CO16 trial.

Our aim was to answer these key questions: does the data support the use of circumferential resection margin as a prognostic factor for local recurrence? Is the prospective histopathological assessment of the plane of surgery achieved an independent prognostic factor for local recurrence? Is the relative benefit of preoperative radiotherapy inversely related to the plane of surgery achieved (ie, does preoperative radiotherapy lead to greater benefit with poorer plane of surgery achieved)?

Methods
Procedures
The Medical Research Council (MRC) CR07 and NCIC-CTG CO16 trial is a large, international, multicentre randomised controlled trial, done between March, 1998, and August, 2005, that compared 5-day short-course preoperative radiotherapy with immediate surgery and reserving postoperative chemoradiotherapy for high-risk circumferential resection margin positive patients. We assessed a total of 1156 patients for plane of surgery achieved. This protocol was approved in the UK by the Multicentre Research Ethics Committee for Scotland. Local approval was obtained at all participating institutions, and written informed consent was obtained from all patients. The MRC Clinical Trials Unit coordinated the trial in the UK and analysed the data. The National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG), and one centre in South Africa and one in New Zealand also participated.

In this trial, local histopathologists assessed the resected specimen in two ways: by the tumour involvement of the surgical circumferential resection margin (an involved circumferential resection margin was defined as tumour within or equal to 1 mm or less from the circumferential resection margin) and by the plane of surgery achieved by the surgeon. The trial protocol defined the histopathological assessment. Training classes, where grading of the specimen, dissection, and reporting were demonstrated, were held for pathologists who were taking part in the study in the UK, Canada, and South Africa. We used a pathology proforma based on the TNM system version 5 to record data and other important pathological features, including site of tumour, completeness of excision, distance of extramural spread, distance to circumferential resection margin, extramural vascular invasion, and peritoneal invasion. The panel shows grading of the specimen to identify the plane of surgery achieved.

Panel: Grading of specimen
Mesorectal plane (good plane of surgery achieved)
Intact mesorectum with only minor irregularities of a smooth mesorectal surface; no defect deeper than 5 mm; no coning; and smooth circumferential resection margin on slicing
Intramesorectal plane (moderate plane of surgery achieved)
Moderate bulk to mesorectum, with irregularities of the mesorectal surface; moderate distal coning; muscularis propria not visible with the exception of levator insertion; and moderate irregularities of circumferential resection margin
Muscularis propria plane (poor plane of surgery achieved)
Little bulk to mesorectum with defects down onto muscularis propria; very irregular circumferential resection margin; or both

![Figure 1: Circumferential resection margin positivity rate during trial recruitment](image)

![Figure 2: Effect of treatment on circumferential resection margin and plane of surgery subgroups](image)
Outcome measures
We defined local-recurrence-free interval as the time from randomisation to a confirmed local recurrence. Confirmation of local recurrence came from: positive biopsy, positive imaging, or positive carcinoembryonic antigen (if imaging was equivocal and there was no evidence of distant metastases). Patients without a confirmed local recurrence were censored at the time of last follow-up.

We defined disease-free survival as the time from randomisation to the time of confirmed local recurrence, metastases, or death related to disease or treatment, whichever occurred first. Patients who were alive and disease-free, or died of other causes, were censored at the time of last follow-up.

Statistical analysis
All analyses were by intention to treat. We compared Kaplan-Meier curves of local-recurrence-free interval and disease-free survival with a two-sided log rank test. We compared proportions with the χ² test, and ordered categories with the Mann-Whitney test.

We used a logistic regression model to study the association between an involved circumferential resection margin and clinical, surgical, and pathological factors in a multivariate analysis. We used a Cox regression model with fractional polynomials to study the association between time to local recurrence and clinical, surgical, and pathological factors in a multivariate analysis to allow for possible non-linearity of any associations. In both multivariate analyses, all factors were forced into the model to allow the relative importance of individual factors to be assessed, taking into account all other factors.

Role of the funding source
The sponsor of the trial had no role in the design or conduct of the study, or analysis of the data. The corresponding author had full access to the data and had final responsibility for the decision to submit for publication.

Results
1350 patients were randomised (674 to short-course preoperative radiotherapy and 676 to selective postoperative chemoradiotherapy) from 80 centres (69 in UK, nine in Canada, one in South Africa, and one in New Zealand). Patient characteristics, treatment received, and overall results are described in the accompanying paper. Overall, the median age of patients was 65 years, 981 (73%) were male, 1069 (79%) were WHO performance status 0, resection was done in 1237 (97%), with an anterior resection in 792 (62%) and an abdominoperineal excision in 404 (32%). Of the patients allocated to short-course preoperative radiotherapy, 614 (96%) received 25Gy/5f preoperative radiotherapy, and of those allocated to selective postoperative chemoradiotherapy who were reported as having a positive circumferential resection margin, 53 (69%) received postoperative chemoradiotherapy. 99 (7%) patients had a local recurrence.

Short-course preoperative radiotherapy reduced the 3-year local recurrence rate from 10·6% with selective postoperative chemoradiotherapy to 4·4% with short-course preoperative radiotherapy (hazard ratio [HR] 0·39, 95% CI 0·27–0·58, p<0·0001) and improved the 3-year disease-free survival from 71·5% with selective postoperative chemoradiotherapy to 77·5% with short-course preoperative radiotherapy (HR 0·76, 95% CI 0·62–0·94, p=0·013), with only minor short-term morbidity.

Patients assessed for plane of surgery achieved were similar to the trial population. Of 1156 patients assessed (table 1), 835 (72%) were male, 930 (80%) were WHO performance status 0, anterior resection was done in 700 (64%) and abdominoperineal excision in 356 (32%) and 78 (7%) patients have been reported as having had a local recurrence.

An involved circumferential resection margin occurred in 128 (11%) patients (10% with short-course preoperative radiotherapy and 12% with selective postoperative chemoradiotherapy). During the trial, the circumferential resection margin positivity rate decreased (p<0·001) (figure 1) and the median distance from the tumour to the circumferential resection margin increased from 5 mm in patients recruited in 1998–99 to 8 mm in those recruited in 2004–05 (p=0·038). Although this reduction was seen in patients who had an anterior resection (18% in 1998 and 8% in 2005), it was not seen in patients who had an abdominoperineal excision (17% in 1998 and 31% in 2005). An involved circumferential resection margin was associated with the surgical procedure (abdominoperineal excision: 16%; anterior resection: 7%, p<0·0001), tumour position (distal extent 0–5 cm
from the anal verge: 15%; 5.1–10 cm: 9%; 10.1–15 cm: 9%, p=0·004), higher tumour (T) stage (p<0·0001) and nodal (N) stage (p<0·0001), and those tumours with an anterior component (involved: 13%; not involved: 7%, p=0·001). We showed, with a multivariate analysis including all the above factors, that T stage, N stage, and tumour position were independently associated with an involved circumferential resection margin.

Local recurrence rate and disease-free survival were different in patients who had a negative or positive circumferential resection margin (3-year local recurrence: 6% negative, 17% positive; HR 0·32, 95% CI 0·16–0·63, p=0·0011; 3-year disease-free survival: 79% negative, 50% positive; HR 0·19, 95% CI 0·13–0·28, p<0·0001).

Overall, patients allocated to short-course preoperative radiotherapy showed an improvement of local recurrence rate and disease-free survival. Although we showed that circumferential resection margin is a prognostic factor, there was no evidence that the benefit of short-course preoperative radiotherapy differed with circumferential resection margin status. For local recurrence, the p value for the circumferential resection margin and treatment interaction was 0·27, and for disease-free survival 0·34. Figure 2 shows the effect of short-course preoperative radiotherapy in the subgroups of circumferential resection margin.

Of the 1156 patients with pathological data available, surgery was achieved in the mesorectal plane in 604 (52%), in the intramesorectal plane in 398 (34%), and in the muscularis propria plane in 154 (13%). The plane of surgery achieved improved over the course of the trial (figure 3). Table 1 shows characteristics associated with the three planes of surgery. The plane of surgery achieved was worse in abdominoperineal excisions than in anterior resections (p<0·001), was related to circumferential resection margin positivity (p=0·001), but was not related to the TNM stage of tumour (p=0·68). There was no indication that the plane of surgery achieved was associated with the median lymph node yield (median yields: 11, 12, and 12 for mesorectal plane, intramesorectal plane, and muscularis propria plane, respectively; p=0·71).

The plane of surgery achieved was strongly associated with local recurrence (figures 2 and 4A), with a 3-year local recurrence rate of 4% (mesorectal plane), 7% (intramesorectal plane), and 13% (muscularis propria plane) (log rank p=0·0039). This pattern was repeated for 3-year disease-free survival (figures 2 and 4B) (79% [mesorectal plane], 75% [intramesorectal plane], and 70% [muscularis propria plane]), although it did not reach statistical significance (log rank p=0·14).

The plane of surgery achieved was similar in the two treatment groups of the trial. The effect of short-course preoperative radiotherapy did not differ with the plane of surgery achieved (p for trend=0·30; figure 2). Local recurrence was almost abolished in patients who received short-course preoperative radiotherapy and in whom mesorectal plane surgery was achieved (1% at 3 years; table 2).

Analyses to investigate the association between plane of surgery achieved and circumferential resection margin status indicated that, for all three planes of surgery achieved, circumferential resection margin positive cases showed a higher rate of 3-year local recurrence (table 2 and figure 5) and a decreased 3-year disease-free survival (table 3 and figure 5) than did negative cases.

| Operation                  | Muscularis propria (n=154) | Intramesorect al (n=398) | Mesorectal (n=604) |
|----------------------------|----------------------------|--------------------------|-------------------|
| Anterior resection         | 69 (48%)                   | 224 (58%)                | 407 (71%)         |
| Abdominoperineal excision  | 70 (48%)                   | 152 (39%)                | 134 (24%)         |
| Hartmann’s                 | 5 (3%)                     | 6 (2%)                   | 20 (4%)           |
| Other                      | 1 (1%)                     | 5 (1%)                   | 9 (2%)            |
| Missing                    | 9                          | 11                       | 34                |
| TNM stage                  |                            |                          |                   |
| I                          | 44 (29%)                   | 95 (24%)                 | 164 (27%)         |
| II                         | 41 (27%)                   | 126 (32%)                | 182 (30%)         |
| III                        | 67 (44%)                   | 172 (43%)                | 250 (41%)         |
| IV                         | 1 (1%)                     | 4 (1%)                   | 7 (1%)            |

CRM=circumferential resection margin.

Table 1: Factors associated with plane of surgery achieved.
We did a multivariate analysis with time to local recurrence as the outcome measure, including plane of surgery achieved, age, sex, WHO performance status, circumferential resection margin status, T stage, N stage, number of lymph nodes sampled, involvement of the anterior quadrant, type of surgery, distal extent, and treatment allocation. The analysis indicated that N stage, treatment, T stage, tumour involving the anterior quadrant, and plane of surgery achieved were independent and significantly associated with the risk of local recurrence taking into account all other variables (table 4). The following factors were not significantly associated with local recurrence: age (p=0·76), sex (p=0·71), WHO performance status (p=0·22), distal extent (p=0·43), type of operation (anterior resection: p=0·78; abdominoperineal excision: p=0·25), circumferential resection margin status (p=0·79), and lymph nodes examined (p=0·66). When all factors were taken into account, circumferential resection margin was not a significant indicator of risk of local recurrence.

Discussion
Preoperative short-course (5 days) radiotherapy has beneficial effects on local recurrence.4–7 The results presented here suggest that an assessment of plane of surgery achieved by an appropriately trained pathologist can be used to identify the risk of local recurrence. In this trial, we used the involvement of the circumferential resection margin to identify patients in the selective postoperative chemoradiotherapy group regarded as high risk of local recurrence. Such patients subsequently received adjuvant chemoradiotherapy. In univariate analyses, involvement of the circumferential resection margin predicted a higher rate of local recurrence and a poorer disease-free survival in both treatment groups. The overall circumferential resection margin positive rate of 11% was better than the rate of nearly 19% reported in a Dutch study,22 and the 13% reported for rectal cancer in the CLASICC trial of laparoscopic versus open surgery.23 We also confirmed the high rate of local recurrence and the poor survival with circumferential resection margin positive tumours seen in previous studies.18,22,24–26 However, in multivariate
analyses, which take into account all variables, the circumferential resection margin status was not independently associated with local recurrence.

In contrast, in both univariate and multivariate analyses, the plane of surgery achieved, as assessed by local pathologists in routine clinical practice, was associated with local recurrence. This result suggests that the plane of surgery achieved should be assessed as one of the main prognostic factors. Our multivariate analysis identified previously reported tumour characteristics (N stage, T stage, and involvement of the anterior quadrant), and two treatment factors that can affect outcomes (radiation treatment and the plane of surgery achieved), emphasising the importance of the surgeon and multidisciplinary team discussion.

We also showed that, for any plane of surgery achieved, the use of short-course preoperative radiotherapy reduces the local recurrence rate by more than 50%. Our data suggest that the plane of surgery achieved and short-course preoperative radiotherapy have additive effects, indicating that preoperative radiotherapy is beneficial whatever plane of surgery is achieved. Indeed, in patients who received short-course preoperative radiotherapy and in whom a mesorectal plane resection was achieved, local recurrence was almost abolished.

Plane of surgery achieved did not deteriorate with advancing TNM stage, suggesting that it is not the late stage that determines the plane of resection, but the ability of the surgeon to stay in the mesorectal plane. Although we could not identify the relative contributions of the skill of the surgeon and the plane of surgery achieved, our results suggest that excellent surgery and improvement of plane of surgery achieved can be important in all rectal cancer surgery. These can be achieved through education and surgical tuition, which are an essential aspect of the basic care of rectal cancer patients. Tuition is cost effective,” especially considering the costs of treatment for disease recurrence.

During the trial, surgeons received informal feedback on the planes of surgery achieved and circumferential resection margin positive rates. Furthermore, multidisciplinary teamwork was introduced in the UK, along with an emphasis on MRI staging. The fact that more surgeons received short-course preoperative radiotherapy and in whom a mesorectal plane resection was achieved, our results suggest that excellent surgery and improvement of plane of surgery achieved can be important in all rectal cancer surgery. These can be achieved through education and surgical tuition, which are an essential aspect of the basic care of rectal-cancer patients. Tuition is cost effective,” especially considering the costs of treatment for disease recurrence.

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to change surgical approach for abdominopерineal excision to improve the surgical plane of excision and reduce incomplete resection of these tumours.8,29 West and colleagues29 have proposed that there should be complete resection of the levators when this operation is performed.

Our approach could be useful in other surgical operations that generate large surgical margins, such as the colon11 and oesophagus,12,13 and should be considered in the pancreas, head and neck dissections, and sarcoma surgery. Our approach might explain some of the wide variations in clinical results and provide a method for the improvement of cancer surgery at other sites. Additional prospective studies of these operations based on our approach are needed.

Overall, we showed an additive effect of the plane of surgery achieved and short-course preoperative radiotherapy, leading to a 3-year local recurrence rate in patients receiving such radiotherapy and in whom surgery in the mesorectal plane is achieved of only 1% at 3 years. We also showed that pathologists from 80 centres, from four countries, can routinely identify the plane of surgery and the groups of patients with different risks of local recurrence. At present, only 50% of rectal cancer surgery is done in the mesorectal plane, suggesting that a further decrease in local recurrence rates might be obtained by improving the plane of surgery achieved. Survival could be further improved by the use of surgical and multidisciplinary team training, such as those programmes completed (Norway,3464–85. Stockholm,35 England, and British Columbia in Canada) or underway (Belgium, Jutland, Copenhagen, and Hong Kong). Assessment of the quality of surgery, for example, using the surgical plane achieved, should become part of the routine assessment of rectal cancers and could be important to improve patient outcomes.

Contributors
All authors were members of the CR07/CO16 trial management group, participated in the discussion and interpretation of data, and in writing the report. PQ designed the study and advised on the pathological aspects of the study. RS and JM advised on the surgical aspects of the study. BG and SK advised on the radiotherapy aspects of the study. LT and RS analysed the data.

Conflict of interest statement
LT, MP, and RS are employed by the Medical Research Council, who sponsored and funded the CR07 trial. All other authors declare that they have no conflict of interest.

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