# Chemotherapy and radiotherapy for colorectal cancers

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## Abstract

Surgery remains the cornerstone of the curative treatment of localized colorectal cancer (CRC), but both radiotherapy and chemotherapy play an important role in the management of these patients to help improve survival. Treatment of locally advanced and metastatic disease often requires multimodality therapy. Advances in both surgical techniques and non-surgical oncology have led to a reduction in the mortality rate over the last 40 years.

**Keywords** Chemotherapy; colon cancer; radiotherapy; rectal cancer

## Introduction

Colorectal cancer (CRC) is the third most common cancer in the UK, accounting for 13.6% and 11.2% of all cancers in men and women respectively in England.[1] Incidence continues to rise, with around 30,000 cases diagnosed in the UK in 2011/2012.[2] Nearly three quarters of those newly diagnosed are aged 65 years and over and although incidence rates continue to increase, mortality has halved for women and decreased by 38% for men since the early 1970s.[1]

The introduction of bowel cancer screening has allowed earlier detection and treatment and has led to a reduction in the mortality rate.[3,4] Despite this, many patients still present with signs and symptoms associated with CRC and emergency admissions continue to account for around 20% of cases diagnosed in England and Wales.[2] The five-year survival varies significantly with stage at presentation, but overall survival is around 55%.[5]

## Investigation and staging

To ensure that patients receive the optimal treatment, it is vital that they are staged adequately preoperatively and discussed fully in the multidisciplinary team (MDT) meeting. Full clinical, endoscopic and radiological evaluation should be undertaken where possible. This should include:

- clinical examination and examination under anaesthetic (EUA), if applicable
- documentation of performance status and co-morbidities
- colonoscopy – flexible sigmoidoscopy or CT colonography for patients with major comorbidity
- CT scan of the thorax, abdomen and pelvis
- MRI pelvis for rectal cancers
- Transrectal ultrasound (TRUS) – this may be performed to give further information on depth of invasion and nodal status for low rectal cancers.

### Pathological staging of CRC

Colorectal cancer is most commonly staged using the TNM classification but the Modified Duke's staging may still be used (See Tables 1 and 2).

## Management

Oncological treatments may be offered before surgery (neoadjuvant), after curative surgery (adjuvant) or in the palliative setting to help alleviate symptoms and prolong progression free survival.

The role of the MDT is to identify those patients who may benefit from neoadjuvant or adjuvant therapy, and also to consider palliative treatment options if appropriate.

All treatment strategies can be associated with significant short- and long-term morbidity and therefore these risks should be considered and discussed with patients.

## Rectal cancer – localized disease

Selection of patients suitable for multimodality therapy is guided by the risk of local recurrence if surgery alone were offered. The widespread adoption of total mesorectal excision (TME) has lead to lower recurrence rates and improved survival in rectal cancer,[6] but locoregional recurrence following surgical resection of rectal cancer still occurs and is difficult to treat. Presence of microscopic tumour within 1 mm of the circumferential resection margin (CRM) has been shown to be associated with higher rates of local recurrence.[7,8] A trial by the MERCURY Study Group established the importance of MRI in the imaging and staging of bowel cancer. It showed that the accuracy of predicting a positive circumferential margin was 92% for MRI compared with 70% for DRE.[9] In addition, MRI can help to predict possible involvement of the levators and the depth of extramural invasion. Nodal status both inside and outside the mesorectal envelope is also important to identify. MRI can therefore be used to help identify those patients who may be at higher risk of local recurrence and has become routine in preoperative staging in the UK.

### Preoperative (neoadjuvant) treatment

The aim of neoadjuvant treatment is to help reduce the risks of local recurrence in operable rectal cancer. In some cases it may downstage locally advanced disease that is inoperable or of borderline operability.

The choice of which preoperative treatment to offer remains a matter of some debate. It is broadly divided into short-course preoperative radiotherapy (SCPRT) and chemoradiation (CRT). Typically SCPRT delivers 25Gy in five fractions over 1 week whereas CRT delivers 45Gy in 25 fractions over 5 weeks combined with chemotherapy. The two approaches developed in parallel and a number of trials now show good evidence for the use of both strategies.

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### Preoperative radiotherapy versus surgery alone

The pivotal Swedish rectal cancer trial[10] addressed the question of whether the addition of SCPRT improved outcome compared to surgery alone. Patients with resectable rectal tumours (cT1-3) were randomized to receive 25Gy in five fractions of radiotherapy over 1 week followed by surgery, or surgery alone. This showed a significant reduction in local recurrence (11% vs 27%) and is also the only trial to show a significant improvement in overall survival (58% vs 48% at 5 years). Surgery within the trial was not standardized and would now be considered suboptimal.

Two main European trials have supported the use of preoperative radiotherapy versus surgery alone in the TME era. The Dutch rectal cancer trial[11] and the Medical Research Council (MRC) CR07 trial[12] also compared an approach of upfront surgery with the addition of SCPRT. These trials incorporated routine assessments of the circumferential resection margin and the quality of the macroscopic surgical specimen. The two trials enrolled a total of 3155 patients and both showed a statistically significant reduction in the rate of local recurrence.

The Dutch study standardized surgery and mandated TME showing an improvement in rates of local recurrence (5.6% vs 10.9%) with no difference in overall survival.

The MRC CR07 trial randomized patients to either SCPRT or selective postoperative CRT (with concurrent 5-fluorouracil [5-FU]) only if microscopic tumour extended to less than 1 mm from the circumferential resection margin. Adjuvant chemotherapy was given as per the participating institution's local policy. The results show an absolute risk reduction in local recurrence of 6.2% at 3 years and disease-free survival (DFS) of 6.0%. There was no significant difference in overall survival. A criticism of the trial has been that surgery in the mesorectal plane was achieved in only half of the patients.

### Neoadjuvant chemoradiotherapy

Adjuvant radiotherapy alone and combined chemoradiotherapy has been the focus of a number of studies since the 1980s, with the addition of chemotherapy leading to an improvement in local control compared to radiotherapy alone.[13] Local recurrence rates and late toxicity were relatively high with postoperative treatment and that led to interest using preoperative radiotherapy/CRT.

In 2004, results of the German Trial CAO/ARO/AIO-94 were published. In this trial a total of 823 patients with clinically staged T3/T4 or node positive rectal cancer were randomized to receive either preoperative or postoperative chemoradiotherapy. The treatment schedule was the same, delivering 50.4 Gy in 28 fractions with 5-FU over 5 days on the first and fifth week of treatment, although the postoperative group were given an additional 5.4Gy boost. All patients had surgery with TME and then adjuvant 5-FU chemotherapy.[14] The 5-year local recurrence rate was 6% in the preoperative group and 13% in the

## TNM staging of colorectal cancer

**Primary tumour (T)**

| | |
|---|---|
| **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 the muscularis propria into the pericolorectal tissues |
| T4a | Tumour penetrates to the surface of the visceral peritoneum |
| T4b | Tumour directly invades or is adherent to other organs or structures |
| Regional lymph nodes | |
| Nx | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastasis |
| N1 | Metastasis in 1–3 regional lymph nodes |
| N1a | Metastasis in 1 regional lymph node |
| N1b | Metastasis in 2–3 regional lymph nodes |
| N1c | Tumour deposit(s) in the subserosa, mesentery, or non-peritonealized, pericolic or perirectal tissues without regional nodal metastasis |
| N2 | Metastasis in four or more lymph nodes |
| N2a | Metastasis in 4–6 regional lymph nodes |
| N2b | Metastasis in seven or more regional lymph nodes |
| Distant metastasis | |
| M0 | No distant metastasis |
| M1 | Distant metastasis |
| M1a | Metastasis confined to one organ or site (eg, liver, lung, ovary, non-regional node) |
| M1b | Metastases in more than one organ/site or the peritoneum |

**Table 1**

## Anatomical and prognostic staging

| Stage | T | N | M | Duke's | MAC |
|---|---|---|---|---|---|
| 0 | Tis | N0 | M0 | – | – |
| I | T1 | N0 | M0 | A | A |
| | T2 | N0 | M0 | A | B1 |
| IIA | T3 | N0 | M0 | B | B2 |
| IIB | T4a | N0 | M0 | B | B2 |
| IIC | T4b | N0 | M0 | B | B3 |
| IIIA | T1–T2 | N1/N1c | M0 | C | C1 |
| | T1 | N2a | M0 | C | C1 |
| IIIB | T3–T4a | N1/N1c | M0 | C | C2 |
| | T2–T3 | N2a | M0 | C | C1/C2 |
| | T1–T2 | N2b | M0 | C | C1 |
| IIIC | T4a | N2a | M0 | C | C2 |
| | T3–T4a | N2b | M0 | C | C2 |
| | T4b | N1–N2 | M0 | C | C3 |
| IVA | Any T | Any N | M1a | | |
| IVB | Any T | Any N | M1b | – | – |

MAC, modified Astler-Coller staging.

**Table 2**