

Recent advances in the management of rectal cancer

Recently there have been significant advances in the management of patients with rectal cancer, attributed mainly to advances in surgical techniques and pre- and postoperative therapy. This review addresses some of these advances and their impact on the prognosis for rectal cancer patients.

Approximately 13 000 new cases of rectal cancer are diagnosed every year in the UK leading to 5477 deaths (Cancer Research UK, 2004). The main objectives of management of patients with rectal cancer are curative excision, preventing local and systemic recurrence, improving quality of life and prolonging survival.

Management of rectal cancer is marred by a high incidence of local recurrence and low 5-year survival figures; 5-year survival for curative resections is 40–50% with local recurrence between 15–50% (Heriot and Jumar, 2002). Thirty per cent of treatment failure is a result of local recurrence with only 30% of recurrences deemed curable. Low rectal cancers are generally regarded as a challenge both in terms of local recurrence and sphincter preservation.

During the last few decades, improvements in survival and reduced local recurrence rates (Dahlberg et al, 1999) have been observed, mainly because of changes in treatment strategies. Imaging techniques like magnetic resonance imaging (MRI) for locoregional staging have improved the ability to predict tumour and nodal staging and hence accurately plan treatment. The most important surgical development has been the widespread and uniform adoption of total mesorectal excision, reducing local recurrence from around 34% to 5–8%. Advances in pathological reporting of surgical specimens have contributed significantly to the correct assessment of specimens and predictability regarding the rate of local recurrence and need for any additional treatment.

This review discusses the effect of these changes on outcomes after treatment of rectal cancer.

Definition and staging of rectal cancer

The rectum is unique with respect to its position in the pelvis and outside of the peritoneal cavity, as well as the intimate association with the pelvic nerves, urogenital organs and anal sphincters; it presents significant challenges to the surgeon planning excision of a rectal cancer. The precise length of the rectum has also been debated between surgeons, anatomists and pathologists. It is clear that the rectum is the part of the large bowel distal to the sigmoid colon and commences at the level of the sacral promontory. The Association of Coloproctology of Great Britain and Ireland (2007) defined rectal cancer as a tumour with a distal margin at 15 cm or less from the anal verge seen with a rigid sigmoidoscope.

Modern multimodality treatment of rectal cancer is based on the ability of preoperative imaging to accurately determine the stage, status of nodes, circumferential margin status and other features like penetration of the peritoneum by the tumour. The tumor, node, metastasis (TNM) staging system (*Table 1*) of the American Joint Committee on Cancer (2002) and the International Union Against Cancer is the standard for colorectal cancer staging recommended by the College of American Pathologists and the Royal College of Pathologists. The TNM staging system is also widely used by national, regional and local tumour registries in the UK and internationally. This system has the advantage that it is multidisciplinary in design and is pertinent to all modern techniques of stage evaluation.

High resolution MRI provides a very accurate means of ascertaining the above. Brown et al (2003) used MRI to preoperatively and prospectively assess 98 patients undergoing total mesorectal excision. There was a 94% agreement between MRI and pathological assessment of the T stage, 85% agreement between MRI and histological node status and MRI prediction of circumferential margin status in 92% of patients. In the last few decades, the increasing improvement in the quality of MRI and its use for locoregional staging has significantly improved the ability to predict the T and N stage of rectal tumours, and identify patients at risk of circumferential margin involvement, thereby helping to decide whether to proceed to surgery, to offer short course radiotherapy or to recommend downstaging or downsizing long-course chemoradiotherapy. Computed tomography on the other hand is the gold standard for the evaluation of hepatic metastasis from rectal cancer and often can identify local spread of rectal cancer to adjacent organs.

Transrectal ultrasound is used for staging rectal cancer, reported to have a high sensitivity and specificity both for T staging and nodal status. This is the preferred choice for staging rectal cancer in the USA and is not used routinely in the UK.

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Table 1. Tumour, node, metastasis (TNM) staging of rectal cancer

Primary tumour (T)	TX – Primary tumour cannot be assessed or depth of penetration not specified
	T0 – No evidence of primary tumour
	Tis – Carcinoma in situ (mucosal); intraepithelial or invasion of the lamina propria
	T1 – Tumour invades submucosa
	T2 – Tumour invades muscularis propria
	T3 – Tumour invades through the muscularis propria into the subserosa or into non-peritonealized pericolic or perirectal tissue
	T4 – Tumour directly invades other organs or structures and/or perforates the visceral peritoneum
Regional lymph nodes (N)	NX – Regional lymph nodes cannot be assessed
	N0 – No regional lymph node metastasis
	N1 – Metastasis in one to three pericolic or perirectal lymph nodes
	N2 – Metastasis in four or more pericolic or perirectal lymph nodes
	N3 – Metastasis in any lymph node along the course of a named vascular trunk
Distant metastasis (M)	MX – Presence of metastasis cannot be assessed
	M0 – No distant metastasis
	M1 – Distant metastasis

From Association of Coloproctology of Great Britain and Ireland (2007)

Resection of rectal cancer: total mesorectal excision

Adequate lymphadenectomy during resection of rectal cancer is fundamental to the surgical approach to management of rectal cancer. The mesorectum is the lymph-containing fatty tissue surrounding the rectum encased in the endopelvic fascia. As the mesorectum contains the majority of lymphatic drainage from the rectal bowel wall, adequate lymphadenectomy depends on adequate mesorectal excision. Excision of the rectum along with its blood vessels and surrounding lymph nodes within an intact visceral fascial envelope, preserving the integrity of the mesorectal fascial envelope and obtaining a negative circumferential margin, are the key elements in minimizing pelvic recurrence. Resection of fewer than 14 lymph nodes has been identified as an independent prognostic factor for local recurrence (Sasson and Sigurdson, 2000).

Traditionally, mesorectal dissection and excision were carried out in a blunt and often blind fashion. This technique is associated with a local recurrence rate ranging from 12–45% as well as an increased incidence of urinary and sexual dysfunction (Ruo and Guillem, 1998; Sasson and Sigurdson, 2000). In 1979, Heald et al developed and popularized total mesorectal excision and reported a significant decrease in both local recurrence and adverse genitourinary side effects, which has been supported by numerous subsequent studies (Heald and Ryall, 1986; Kapiteijn and van de Velde, 2002).

Total mesorectal excision requires precise, sharp dissection under direct vision in the plane of areolar tissue between the fascia propria of the rectum and the parietal

endopelvic fascia extending down to the levator muscles of the pelvic floor (Heald and Ryall, 1986). It allows for a characteristic bilobed specimen with complete extirpation of the surrounding perirectal lymph nodes, along with visualized avoidance of the autonomic plexus innervating the pelvis, and improves the ability to obtain an adequate circumferential margin. Sharp, adequate mesorectal excision extending to the endopelvic fascia achieves negative circumferential margins in up to 93% of cases. The well-documented improvement in local recurrence rates and genitourinary complications has made this technique the standard of care whether abdominoperineal resection or low anterior resection is chosen for the patient.

Heald reported his 20-year experience with total mesorectal excision in 519 consecutive operations for rectal cancer within 15 cm of the anal verge (Heald et al, 1998); the local recurrence rate in 405 patients who underwent curative anterior resection was 3% at 5 years, and the overall recurrence rate was 6%. Only 49 patients received preoperative radiotherapy, usually for fixation or inoperability. The cancer-specific survival rate was 80% at 5 years and 78% at 10 years for patients treated for cure.

The remarkably low recurrence rates reported by Heald, achieved without radiation therapy, have focused attention on the value of embracing established surgical oncological techniques, and attempts have been made to standardize total mesorectal excision as the operative treatment for appropriately selected cancers of the low and mid rectum. Wibe et al (2002) reported the initial results of the Norwegian Rectal Cancer Project, followed by an update (Wibe et al, 2003). This project was initiated in 1993 with the goal of improving the outcome of patients with rectal cancer by implementing total mesorectal excision as the standard rectal resection technique on a national level. Courses were arranged to teach surgeons the total mesorectal excision technique and pathologists were trained to assess resected specimens in a systematic and standardized manner. Between 1986 and 1988, 28% of patients with rectal cancer, having undergone resection with curative intent, had developed local recurrence. Rapid implementation of total mesorectal excision was instituted and 78% of patients underwent total mesorectal excision in 1994 and 96% in 1998. Remarkably, the local recurrence rate from December 1993 to December 1999 fell to 8% with a mean follow up of 39 months. Similar programmes in the Netherlands and Sweden also demonstrated a decrease in local recurrence rates (Kapiteijn et al, 2002; Martling et al, 2002).

Tumours in the mid to upper third of the rectum may be more appropriately treated by preserving the mesorectum distal to the tumour. Once an appropriate distal margin is achieved, the mesorectum can be divided at 90° to the rectum. As mesorectal spread is rarely greater than 4 cm, 'wide mesorectal excision' describes the appropriate technique for upper rectal lesions, and refers to the recommendation that sharp mesorectal excision should only extend 5 cm distal to the lesion, preserving

the blood supply to the distal rectal stump in proximal lesions without compromising local recurrence rates. Critics of total mesorectal excision have noted an increased anastomotic leak rate, reported as high as 17%. This has been attributed to the devascularization of the distal stump of the reconstructed rectum that occurs when mesorectal dissection is taken to the pelvic floor.

Total mesorectal excision is recommended for tumours in the lower two-thirds of the rectum, either as part of a low anterior resection or an abdominoperineal resection. In tumours of the upper rectum the mesorectum should be divided no less than 5 cm below the lower margin of the tumour.

Pathological reporting of rectal cancer specimens

Proper pathological evaluation of the resected surgical specimen is vital to total mesorectal excision surgery. The integrity of the mesorectal envelope can only be assessed if surgical specimens are assessed by pathologists familiar with the concept of total mesorectal excision surgery (Quirke et al, 1986). Any breaches in the mesorectum identified by the pathologist means an increased risk of local recurrence and possibly subsequent need for adjuvant therapy. A proper pathological evaluation of the total mesorectal excision specimen can also help guide the surgeon, audit his/her total mesorectal excision practice and suggest any technical improvements needed. The Royal College of Pathologists (2007) recommends a minimum data set for reporting colorectal cancers to ensure thorough and standardized reporting (Table 2).

Laparoscopic total mesorectal excision surgery

Laparoscopic surgery offers a range of potential benefits for patients, and is being used increasingly for colorectal surgery. Less pain, smaller scars, better cosmetics, early feeding, shorter hospital stay, earlier return to work, fewer adhesions and reduced morbidity are the consistently reported advantages over open surgery.

The most significant trial comparing laparoscopic *vs* open surgery for rectal cancers is the UK MRC CLASSIC trial (Guillou et al, 2005), which compared conventional *vs* laparoscopic-assisted surgery in patients with both colon and rectal cancers. The long-term outcomes (Jayne et al, 2007), 3-year overall survival, disease-free survival, local recurrence and quality of life from this trial have shown no differences between the laparoscopic and open groups. The trial concluded that successful laparoscopic-assisted surgery for colon and rectal cancer is as effective as open surgery in terms of oncological outcomes and preservation of quality of life.

The Clinical Outcomes of Surgical Therapy (COST) study group, a multicentre, randomized controlled trial, has shown that the lymph node harvest is similar in both laparoscopic and open colorectal cancer resections (Clinical Outcomes of Surgical Therapy study group,

2004). Moreover, recurrence rate, overall survival, time to recurrence, rate of complications and rate of re-operations were similar in both groups.

A meta-analysis of short-term outcomes after laparoscopic resection for colorectal cancer has shown that convalescence is more rapid in laparoscopic surgery, mainly as a result of shorter hospital stay, less pain, less blood loss and rapid return to usual activities (Abraham et al, 2004). The duration of operation was longer in laparoscopic resections, but lymph node harvest, quality of life and occurrence of complications were similar. Most importantly, there was no evidence of a difference in the number of recurrences (including wound recurrences), disease-free survival and overall survival.

A recent systematic review has concluded that there are no oncological differences between laparoscopic and open resections for treatment of primary rectal cancer (Anderson et al, 2008). This meta-analysis contained data on 1403 laparoscopic and 1755 open rectal resections from 24 publications. Overall 3-year survival was not statistically different between the two groups, the mean local recurrence rates were 7% for the laparoscopic group and 8% for open procedures and there were no differences in radial margin positivity between groups.

Based on these findings, the National Institute for Health and Clinical Excellence changed its guidance in 2006, and laparoscopic resection is now an accepted alternative to open resection in the UK.

Neoadjuvant and adjuvant therapy for rectal cancer

Neoadjuvant (pre-surgery) and adjuvant (post-surgery) therapy has been suggested as an adjunct to surgery in treating rectal cancer for over 25 years. This treatment mainly exists in the form of chemotherapy, radiotherapy and/or a combination of both. There has been a transatlantic divide as to the neoadjuvant and adjuvant timing of therapy, with neoadjuvant preferred in mainland Europe. Although surgery remains the cornerstone of treatment for adenocarcinomas of the rectum, the use of chemoradiation has significantly altered the therapeutic paradigm and been clearly shown to reduce the risk of local recurrence after rectal cancer surgery.

Neoadjuvant radiotherapy

Preoperative radiotherapy is usually delivered by short-course preoperative radiotherapy or long radiotherapy

Table 2. Criterion for reporting colorectal cancers

Measurement of the extent of extramural spread beyond lamina propria
Record of the tumour involvement of 'non-peritonealized circumferential resection margin'
Grading of plane of surgical resection margin in rectal cancer specimens
Recording of the extent of tumour regression post treatment
Recording whether tumour perforation is serosal or retro/infraperitoneal

From Royal College of Pathologists (2007)

alone and/or in conjugation with chemotherapy. Short-course preoperative radiotherapy delivers a lower dose of 25 Gy, but in a short duration (five daily fractions over 1 week). Surgery is performed the following week, before the onset of acute radiotherapy side effects, so short-course preoperative radiotherapy does not lead to significant tumour shrinkage before surgical resection. It is, therefore, appropriate only for patients with rectal cancers that are felt to be clinically and radiologically resectable.

Long-course radiotherapy consists of doses from 45–50 Gy in 25 daily fractions over 5 weeks followed by surgery 4–8 weeks after completion of radiotherapy, allowing maximal tumour shrinkage. This is more effective with the use of synchronous 5-fluorouracil (5FU)-based chemotherapy otherwise known as chemoradiotherapy.

The major trial which influenced surgical and oncological practice with regards to adjuvant therapy was the Swedish Rectal Cancer Trial (1997), which randomized 1168 patients with resectable rectal cancer to receive short-course preoperative radiotherapy followed by surgery or surgery alone. The use of short-course preoperative radiotherapy reduced the risk of local recurrence from 27% to 11% at 5 years and improved the 5-year overall survival from 48% to 58%. These benefits were maintained for a prolonged period (median follow up 13 years).

To evaluate the role of short-course preoperative radiotherapy with total mesorectal excision, the Dutch Colorectal Cancer Group randomized 1861 patients to short-course preoperative radiotherapy followed by total mesorectal excision surgery or total mesorectal excision surgery alone (Kapiteijn et al, 2001). Patients who were found to have an involved circumferential resection margin following total mesorectal excision alone were to receive postoperative radiotherapy. This trial showed that the addition of short-course preoperative radiotherapy to total mesorectal excision reduced the risk of local recurrence from 8.2% to 2.4% at 2 years and from 11.4% to 5.8% at 5 years. There was no difference in overall survival.

The UK MRC CR07 trial was a further landmark trial in this direction (Sebag-Montefiore et al, 2006). Although similar in design to the Dutch total mesorectal excision trial, total mesorectal excision was performed in 93% of the patients randomized. A total of 1350 patients were recruited. The early data (median follow up of 3 years) from CR07 confirm that the addition of short-course preoperative radiotherapy to total mesorectal excision reduces local recurrence from 11.1% to 4.7% at 3 years and improves disease-free survival from 74.9% to 79.5%. The benefit was consistent for lower, mid and upper rectal tumours.

However, if short-course preoperative radiotherapy is offered to all eligible patients for a moderate reduction in local recurrence (6%), there is a risk of long-term toxicity associated with radiotherapy. Whether short-course preoperative radiotherapy should be offered to all patients with operable rectal cancer is a difficult question and the balance between benefit and toxicity must be considered.

Long-course preoperative chemoradiotherapy and adjuvant chemotherapy

For locally advanced rectal cancers preoperative chemoradiotherapy seems to be effective both for downstaging and downsizing the tumour and hence for reducing local recurrence after surgery. The German GAO/ARO/AIO-94 trial randomized 421 patients with resectable T3–4 rectal cancers to chemoradiotherapy given either preoperatively or postoperatively (Sauer et al, 2004). All patients were to have total mesorectal excision surgery. Patients receiving preoperative treatment had fewer local recurrences and a lower risk of late toxicity.

The EORTC 22921 trial randomized 1011 patients with resectable (clinically staged T3–4) mid and lower rectal cancers to receive preoperative 5FU-based chemoradiotherapy or conventional radiotherapy alone with or without four further cycles of adjuvant 5FU chemotherapy postoperatively (Bosset et al, 2005). Total mesorectal excision was not a protocol requirement. There was a significant reduction in local recurrence for patients who received either synchronous or adjuvant chemotherapy as well as preoperative radiotherapy. Local recurrence at 5 years in patients not receiving chemotherapy was 17.1%.

The FFCD 9203 trial randomized 733 patients with resectable palpable (clinically staged T3–4) rectal cancers to preoperative chemoradiotherapy or conventional radiotherapy alone. Total mesorectal excision was not a protocol requirement. All patients received four cycles of 5FU chemotherapy postoperatively (Gerard et al, 2006). The results are similar to corresponding arms of the EORTC trial (local recurrence of 8% *vs* 16.5% at 5 years).

For postoperative adjuvant therapy, the histopathological status of the resected tumour is important in determining the need for and effectiveness of adjuvant therapy. In node-positive disease, there is clear evidence from randomized trials that postoperative 5-FU modulated by folinic acid regimens increase overall survival by 13% from 51% to 64% (National Institute for Clinical Excellence, 2004). There is growing evidence that combination therapy based on oxaliplatin and 5-FU is also useful. Two trials have shown a reduction in recurrence and increase in disease-free survival (Andre et al, 2004; Lembersky et al, 2006). The Association of Coloproctology of Great Britain and Ireland (2007) guidelines state that there is no distinction between colon and rectal cancer in terms of chemotherapy and that either 5-FU or oxaliplatin with 5-FU or folinic acid should be considered for the adjuvant treatment of patients with node-positive colorectal cancer following potentially curative surgery.

The benefit from adjuvant chemotherapy is less in node-negative disease (Dukes' B colorectal carcinoma). The UK QUASAR group has shown a modest benefit with bolus 5-FU or folinic acid of around 4% improvement in overall survival (Kerr et al, 2000; QUASAR Collaborative Group et al, 2007). Based on this, patients with node-negative disease are currently not routinely

offered adjuvant chemotherapy, but this can be an option in young patients with adverse pathological parameters and needs to be determined on an individual basis.

Conclusions

Rectal cancer remains a significant health risk and poses a challenge to the team managing the patients. The last few decades have shown that the treatment of rectal cancer requires a multimodality approach. The best outcome is achieved by high quality total mesorectal excision, preceded by either short-course preoperative radiotherapy or chemoradiotherapy, and selective use of adjuvant chemotherapy. However, the use of short-course preoperative radiotherapy has to be balanced against the toxicity caused by its use. The widespread adoption of total mesorectal excision has led to a significant decrease in local recurrences. It is hoped that in combination with appropriate adjuvant therapy, there will be better locoregional control and improvement in overall survival. **BJHM**

Conflict of interest: none.

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KEY POINTS

- The incidence of local recurrence for rectal cancer has reduced significantly with total mesorectal excision. This is now regarded as standard practise for resection of mid to low rectal cancers.
- Laparoscopic colorectal resection for cancer is an accepted alternative to open surgery, with comparable outcomes.
- Short-course preoperative radiotherapy further reduces local recurrence for rectal cancer and improves disease-free survival.