Colorectal cancer: a decade of progress

Over the last decade there has been considerable improvement in the management of metastatic colorectal cancer. Like other cancer patients, people with colorectal cancer have benefited from service reorganizations that have lead to more rapid referral and diagnosis, and enabled more patients to benefit from recent advances in treatment.

In the UK, colorectal cancer is the third most common cancer and the second most common cause of cancer death (Cancer Research UK, 2009). If diagnosed in its early stages, colorectal cancer is curable with primary surgery, but over half of the 36 000 patients diagnosed each year in the UK present with advanced disease (National Institute for Clinical Excellence, 2004).

Diagnosis

Today, nearly all patients referred urgently with suspected colorectal cancer by their GPs are seen within 2 weeks and treated within 62 days (Richards, 2008). Criteria for urgent referral are shown in *Table 1*. While most patients are likely to present to GPs, hospital doctors also have a responsibility to urgently refer patients fulfilling the criteria to a member of the colorectal cancer multidisciplinary team.

Over the last decade, endoscopy (colonoscopy or flexible sigmoidoscopy) has increasingly replaced barium enema as the investigation of choice in suspected colorectal cancer. Some units are now introducing computed tomographic or virtual colonoscopy, which uses a computed tomography scanner to produce two- and three-dimensional images of the entire colon and rectum. Patients with polyps or tumours found on virtual colonoscopy require conventional colonoscopy for biopsy sampling and excision of polyps.

Computed tomography and magnetic resonance imaging are now used to stage colorectal tumours, to plan management and as part of routine surveillance after curative treatment. Positron emission tomography is also increasingly used with computed tomography to aid accurate selection of patients for resection of metastases. The Dukes' classification is still used to stage colorectal cancer, but is slowly being superseded by more precise clinico/pathological staging based on the tumour, node, metastasis (TNM) classification (*Table 2*).

Table 1. Criteria for urgent (2-week) referral for suspected bowel cancer

Aged ≥40 years	Rectal bleeding with change in bowel habit towards looser stools and/or increased stool frequency persisting for ≥6 weeks
Aged ≥60 years	Rectal bleeding persisting ≥6 weeks without change in bowel habit and without anal symptoms
	Change in bowel habit to looser stools and/or more frequent stools persisting for ≥6 weeks without rectal bleeding
All ages	Right lower abdominal mass consistent with involvement of the large bowel
	Palpable rectal mass (intraluminal and not pelvic) (refer pelvic mass outside to bowel urgently to urologist or gynaecologist)
Men of any age	Unexplained iron-deficiency anaemia and haemoglobin of ≤11 g/100 ml
Non-menstruating women	Unexplained iron-deficiency anaemia and haemoglobin of ≤10 g/100 ml

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Individualizing treatment

Choice of treatment depends on the stage of the patient's presenting disease, influenced by performance status and comorbidities.

While early-stage disease may simply require surgical resection (with or without radiotherapy in the case of rectal cancer), the treatment of advanced disease is more complex, potentially involving surgery, radiotherapy and chemotherapy. In metastatic colorectal cancer the aims of treatment are to maximize survival and improve presenting symptoms, while maintaining quality of life during treatment and allowing treatment breaks.

Table 2. Staging of colorectal cancers

TNM	Description	Dukes'
Stage 0	Carcinoma in situ	A
Stage 1	No nodal involvement, no distant metastases	
	Tumour invades submucosa (T1, N0, M0)	
	Tumour invades muscularis propia (T2, N0, M0)	
Stage 2	No nodal involvement, no distant metastases	B
	Tumour invades into subserosa (T3, N0, M0)	
	Tumour invades into other organs (T4, N0, M0)	
Stage 3	Nodal involvement, no distant metastases	C
	1–3 regional lymph nodes involved (any T, N1, M0)	
	≥ 4 regional lymph nodes involved (any T, N2, M0)	
Stage 4	Distant metastases (any T, any N, M1)	D

T = tumour; N = node; M = metastasis

Surgery

About 80% of colorectal cancer patients undergo some form of surgery (National Institute for Clinical Excellence, 2004). By the 1980s, there was increasing evidence that surgeons were underestimating the circumferential resection margin needed in rectal cancer and that this was a cause of local recurrence. Over the last decade, total mesorectal excision has become routine treatment for middle and lower-third rectal cancers.

Total mesorectal excision may be performed as an open or laparoscopic procedure. Laparoscopic total mesorectal excision results in less blood loss, quicker return to normal diet, less pain, less narcotic use and lower immune response, but is associated with longer operative time and higher costs. Long-term impact on survival is also unclear, and awaits the results of randomized studies.

Chemotherapy

Chemotherapy should be used selectively for patients with stage II (Dukes' B) colorectal cancer, but over the last decade it has become increasingly apparent that chemotherapy should be made available following surgery for stage III (Dukes' C) and stage IV (Dukes' D) colorectal cancer if patients are well enough to tolerate it.

Adjuvant chemotherapy

Patients with node-positive disease (stage III) treated with adjuvant chemotherapy have an approximate benefit of 10% in overall survival at 8 years, while node-negative patients have 5% benefit (Gray et al, 2004; Sargent et al, 2009). Although it is unclear which stage II patients should be offered chemotherapy, there are high risk factors where this should be considered. These criteria have not been prospectively verified, but they include T4 disease, perforation, serosal involvement, poorly differentiated lymphovascular invasion and positive circumferential resection margin.

The benefits of adjuvant chemotherapy for rectal cancer are less clear, but randomized trials have shown significant improvement in disease-free survival (Dube et al, 1997), and the National Institute for Clinical Excellence (2004) does not differentiate between colon and rectal cancer in its recommendations for adjuvant chemotherapy.

All adjuvant regimens are based on fluoropyrimidines. Weekly bolus 5-fluorouracil with folinic acid is as effective as, and less toxic than, the monthly five consecutive days Mayo regimen (Kerr et al, 2000). Two oral 5-fluorouracil drugs, capecitabine and tegafururacil, are now available. They are as effective as standard 5-fluorouracil, but better tolerated and more convenient for patients (Van Cutsem et al, 2001; Douillard et al, 2002).

Adjuvantly, oxaliplatin in combination with a fluoropyrimidine has been compared with 5-fluorouracil and folinic acid alone, and has shown an improvement in disease-free survival at 3 years of about 6% (Andre et al, 2004). However, there is an increased risk of oxaliplatin-induced neuropathy, and the combination is often used in the fitter and higher-risk population. Irinotecan has not been shown to be of benefit in the adjuvant setting.

Chemotherapy has also been studied in combination with adjuvant biological agents (see below).

Chemotherapy in advanced disease

Chemotherapy can be used to palliate metastatic disease, as well as being used neo-adjuvantly in combination with surgery for metastectomy. It can also be used to shrink existing liver metastases that may have been initially considered as inoperable, before potentially operable hepatic surgery.

Palliative chemotherapy improves survival when compared to best supportive care. There has been an improvement in median overall survival from 10–14 months with fluoropyrimidines alone to 20–24 months for combination regimens of chemotherapy and monoclonal antibodies (Hoff et al, 2001; Douillard et al, 2002; Hurwitz et al, 2004; Tournigand et al, 2004; Van Cutsem et al, 2009).

Fluoropyrimidine monotherapy is usually used in patients who have a poorer performance status and who may not be able to tolerate combination treatment. These drugs may also be used as initial treatment of other patients with relatively asymptomatic advanced disease.

Combination treatment is the standard therapy for fitter patients. The standard duration of chemotherapy has been 6 months in responding patients, followed by a break in treatment and then commencement on progression. More recently, treating until progression, especially with monoclonal antibodies, has come into vogue, most commonly in the USA.

Radiotherapy

Although it may be given as palliative treatment in patients with advanced disease, radiotherapy is rarely used in the primary treatment of colon cancer. In contrast, a short course of preoperative radiotherapy (25Gy in five fractions over 5 days) is now commonly offered to patients with early operable rectal cancers.

The Swedish Rectal Cancer Trial showed an improvement in overall survival (38% *vs* 30%, P=0.008) and reduction in local recurrence (from 26% to 9%, P=0.001) (Folkesson et al, 2005). There were, however, increased early problems (wound healing) and late effects (increased stool frequency, urgency and incontinence). In the Dutch total mesorectal excision trial, although there was no survival benefit with short course, preoperative radiotherapy after 6 years, there was significant reduction in local recurrence (10.9% *vs* 5.6% compared with total mesorectal excision alone) (Peeters et al, 2007).

In patients with disease threatening the circumferential resection margin (<1 mm), a long course of chemoradiotherapy over approximately 5 weeks (45 Gy in 25 fractions) is recommended to down-size the tumour to allow curative surgery. This is either combined with weekly continuous infusional 5-fluorouracil via a pump for 5 weeks, or bolus 5-fluorouracil and folinic acid on days 1–5 and 29–34, or with oral capecitabine throughout the radiotherapy. In very advanced but non-metastatic tumours, 3 months of systemic chemotherapy has been given before chemoradiotherapy with impressive results (Chau et al, 2006).

In some centres, contact radiotherapy or brachytherapy with low-energy X-rays is used for small, early-stage cancers using a direct rectal probe. The technique can also be considered for accessible tumours in patients who are medically inoperable.

Biological therapies

The last decade has seen the introduction of biological agents which target specific molecular features of cancer cells. These treatments represent a new direction, promising more options and marked improvements in efficacy in the treatment of colon cancer.

A humanized IgG1 monoclonal antibody, cetuximab, targets epidermal growth factor receptor which is over-expressed in 60–80% of colorectal cancer (Cunningham et al, 2004). Cetuximab has single-agent activity in patients with metastatic colorectal cancer that is refractory to both oxaliplatin and irinotecan-based regimens. The National Institute for Health and Clinical Excellence (2009) recommends cetuximab in combination with chemotherapy as first-line treatment in metastatic colorectal cancer patients with potentially operable liver metastases and 'wild type' or unmutated KRAS tumours, present in up to 65% of patients (Van Cutsem et al, 2009). Patients may rarely be allergic to the agent, and acneiform skin rash is the most common side effect (which appears to correlate with response rate) (Cunningham et al, 2004).

Panitumumab is a more recently available epidermal growth factor receptor inhibitor and is licensed in Europe as third-line monotherapy for metastatic colorectal cancer. The agent is currently under review by National Institute for Health and Clinical Excellence.

Bevacizumab is a humanized monoclonal antibody that targets vascular endothelial growth factor receptor, an angiogenic factor over-expressed in about 50% of colorectal cancers (Lee et al, 2000). In 2004, a pivotal trial demonstrated an increase in survival when the agent was combined with irinotecan and bolus 5-fluorouracil as first-line treatment (Hurwitz et al, 2004), and it is licensed in combination with chemotherapy for advanced colon cancer. The drug is associated with a number of potentially serious side effects, including hypertension, bleeding, bowel perforation and impaired wound healing, and there currently are no predictive biomarkers to identify patients who might benefit. National Institute for Health and Clinical Excellence does not recommend bevacizumab in advanced colorectal cancer.

Other targeted agents under investigation in advanced colorectal cancer include the tyrosine kinase inhibitors erlotinib, gefitinib, sunitinib, sorafenib, cediranib and vatalanib. Some of these agents are already in clinical use in the treatment of other cancers – such as erlotinib and gefitinib in lung cancer and sunitinib in renal cell carcinoma. HORIZON II and III trials have recently closed. These compare combinations of chemotherapy to a similar treatment with the addition of the oral tyrosine kinase inhibitor cediranib. In the HORIZON II study, adding cediranib improved progression-free survival compared to oxaliplatin and fluropyrimidine alone, but there was no significant improvement in overall survival.

While the introduction of biological therapies has increased choice, their cost and potential adverse effects means that there is an increasing responsibility to select patients who are most likely to benefit. Genetic markers make it possible to refine patient selection for some biologicals. This means that it is possible to screen patients before treatment based on the breast cancer model, in which women undergo testing for genetic characteristics of their tumours before treatment with trastuzumab. This form of pre-treatment testing should make biologicals more cost effective, and increase their adoption in routine clinical practice.

Colorectal cancer screening

Colorectal cancer incidence rates have remained relatively stable for over a decade. In contrast, 5-year survival rates have doubled over the last 30 years (Cancer Research UK, 2009). Hopefully this trend will continue following reorganization of cancer services in the last decade.

Delayed cancer diagnosis remains an issue in the UK, but this should improve following the introduction of the NHS Bowel Cancer Screening Programme. The programme is based on faecal occult blood testing, offered every 2 years to all men and women aged 60–69 years.

Colorectal cancer prevention

Most cases of colorectal cancer are sporadic and influenced by dietary and lifestyle factors (Cancer Research UK, 2009). Although evidence from randomized studies is lacking, it may be possible to reduce the risk of colorectal cancer by lifestyle changes that will have general benefits for individual and population health.

There is also increasing interest in the potential for chemoprevention of colorectal cancer with aspirin and other non-steroidal anti-inflammatory drugs. Aspirin has emerged as the most likely candidate, but it is not currently possible to make definitive recommendations because of insufficient data on the risk-benefit profile in cancer prevention.

Conclusions

The treatment of metastatic colorectal cancer has been revolutionized in the last decade. Clinicians are now able to offer a multitude of sequential therapeutic options, whether by 'gentle' single-agent oral chemotherapy, a conventional intravenous doublet regimen, or more intensive triplets with biological agents often as part of clinical trials. There is, however, much to do in the next 10 years to further individualize treatment to enhance efficacy, tolerability and quality of life for patients, which will in turn improve therapies' cost-effectiveness. **BJHM**

The authors would like to thank Sue Lyon, who provided medical writing services on behalf of Merck Serono UK. The views and statements in this article are those of the authors.

Conflict of interest: none.

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KEY POINTS

- Over the last decade, patients with metastatic colorectal cancer have benefited from general improvements in the organization of cancer services in the UK.
- Total mesorectal excision has become routine surgical practice to reduce the recurrence of middle and lower-third rectal cancers.
- In colon cancer a 6-month course of adjuvant intravenous chemotherapy following surgery is now used to reduce recurrence and improve 5-year survival.
- Fluoropyrimidines (5-fluorouracil, capecitabine and tegafur-uracil) are the basis of both adjuvant and palliative chemotherapy, which may be combined with oxaliplatin or irinotecan.
- Biological therapies have been introduced in the treatment of colorectal cancer in the last 10 years, including cetuximab, bevacizumab and panitumumab.
- The NHS Bowel Cancer Screening Programme promises to improve future patient outcomes by enabling earlier diagnosis of colorectal cancer.