Management of colorectal cancer

A Leslie, R J C Steele

Colorectal cancer is the second most common cause of cancer death in the UK. Prompt investigation of suspicious symptoms is important, but there is increasing evidence that screening for the disease can produce significant reductions in mortality. High quality surgery is of paramount importance in achieving good outcomes, particularly in rectal cancer, but adjuvant radiotherapy and chemotherapy have important parts to play. The treatment of advanced disease is still essentially palliative, although surgery for limited hepatic metastases may be curative in a small proportion of patients.
Screening of high risk groups

Family history

In general, patients with a family history of colorectal cancer constitute a high risk group. Precise recommendations for follow up are difficult to prescribe but it is generally agreed that individuals at moderate risk of developing colorectal cancer on the basis of their family history should be advised to undergo a single colonoscopy at the age of 50 years. There are, however, two conditions, inherited as autosomal dominant traits, which put the patient at very high risk of developing the disease. The first of these, familial adenomatous polyposis, accounts for approximately 1% of all colorectal cancer cases and is due to a germline mutation in the APC gene.\(^1\) The condition is characterised by the appearance of multiple polyps throughout the colon and the inevitable development of colorectal cancer at a mean age of about 40 years. The age at which polyps first appear is highly variable but it is usually in the late teens and early 20s. It is now possible to identify mutations of the APC gene of an affected individual and the offspring of such an individual can be offered genetic counselling and screening.\(^2\) If an offspring does not carry a mutation then no further investigations are required. However, carriers of the mutation should be offered early sigmoidoscopy and colonoscopy every two to three years. When polyps begin to develop the patient should undergo either proctocolectomy or ileorectal anastomosis depending on the degree to which the rectum is affected.

The second inherited condition, hereditary non-polyposis colorectal cancer accounts for around 5% of colorectal cancer cases. The diagnosis of this condition is made using the following clinical criteria:\(^3\):

1. The affected individual should have at least three relatives with a confirmed colorectal cancer (one of whom should be a first degree relative of the other two).
2. At least two consecutive generations should be affected.
3. Colorectal cancers should be diagnosed at less than 50 years of age.

It is now known that the majority of individuals with this condition have a germline mutation in one of the DNA mismatch repair genes\(^4\) and, in some specialist centres, it is possible to offer genetic screening to individuals who appear to be at risk on the basis of their family history. Once an individual is identified as carrying a mismatch repair gene mutation or fulfils high risk criteria, colonoscopy should be offered every two to three years starting at about the age of 20.

Sporadic adenomatous polyps

Patients who have had colonscopic removal of adenomatous polyps are at higher risk than the general population of developing further polyps (approximately 40% risk at three years)\(^5\) and presumably, therefore, of developing colorectal cancer. The strongest evidence for this contention is the recent finding that screening for colorectal cancer can reduce the incidence of the disease, most probably as a result of removal of adenomas at colonoscopy.\(^6\) However, enthusiasm for colonoscopic follow up of patients with colorectal adenomas must be tempered with a realistic approach to the use of endoscopy services. There has been one randomised trial showing that three yearly colonoscopy is as effective as one yearly colonoscopy in detecting significant lesions after polypectomy,\(^7\) and it is generally agreed that patients should be offered follow up colonoscopy at three to five years after polypectomy. It is reasonable to defer for five years if there are one or two tubular adenomas without severe dysplasia. If, however, there are multiple polyps or a polyp with a villous component or severe dysplasia, colonoscopy should be repeated at three years. If no adenomas are found at follow up colonoscopy then five yearly examination is indicated but if further adenomas are detected repeat colonoscopy at three years is advisable.

Inflammatory bowel disease

Patients with long standing ulcerative colitis or Crohn’s colitis are known to be at higher risk of developing colorectal cancer than the general population.\(^8\) In ulcerative colitis the cumulative risk of developing invasive cancer appears to be 2% at 10 years, 8% by 20 years, and 18% by 30 years.\(^9\) Thus, it seems reasonable to offer patients with left sided colitis or pancolitis of 10 years’ duration colonoscopy every three years with mucosal biopsies plus biopsy of any lesions which are suspicious of cancer. This regimen should be increased to yearly colonoscopy when the disease has been present for 20 years or when indeterminate dysplasia has been diagnosed. If, on the other hand, high grade dysplasia is found, colectomy should be advised as there is a 40% chance of such a patient harbouring an invasive colorectal cancer.

Population screening

As colorectal cancer is a common condition, particularly after the age of 50, and because there is a well defined premalignant lesion which is amenable to treatment, the disease would seem to be a prime candidate for population screening. The most widely used screening tests are faecal occult blood testing, flexible sigmoidoscopy, and colonoscopy. However, only faecal occult blood testing has been shown to be effective in reducing colorectal cancer mortality in population based randomised trials. Such trials are essential in order to eliminate biases such as lead bias, which can give a false impression of an improved prognosis in screen detected disease. The trials of faecal occult blood testing carried out in Minnesota, USA, Nottingham, UK, and Funen, Denmark\(^10\) have all shown significant reductions in disease specific mortality, and in the UK a demonstration pilot of faecal occult blood test screening for colorectal cancer is in progress.\(^11\) If this pilot demonstrates that introduction of this type of screening is feasible then it is hoped that a national programme will be forthcoming.

STAGING

Once the diagnosis of colorectal cancer has been made it is important to establish the extent of the disease both locally and in terms of distant spread. All patients should have preoperative chest and liver imaging, and there is good evidence that computed tomography is the most sensitive modality for both liver and distant metastases.\(^12\) As rectal cancer is not infrequently inoperable due to its confinement within the pelvis, many surgeons also use preoperative computed
but is less widely available. As synchronous tumours occur in subcutaneous heparin.

Surgery

There is now a great deal of interest in imaging rectal tumours with a view to planning preoperative radiotherapy, and there is no doubt that MRI is the most accurate modality for predicting histological spread of the tumour through the rectal wall and surrounding mesorectum. However, its significant cost in this respect has yet to be fully established. Endoluminal ultrasound is also widely used but this is more valuable in distinguishing between benign rectal adenomas and invasive carcinoma. Endoluminal MRI has a similar role but is less widely available. As synchronous tumours occur in about 5% of patients with colorectal cancer it is also very important to ensure the entire colon has been imaged before surgery if at all possible. Although this can be achieved by DCBE, colonoscopy is preferable as this will also allow removal of any benign adenomatous polyps remote from the malignant tumour. If preoperative colonoscopy is not feasible because of anatomical reasons or with subtotal colectomy and primary anastomosis. However, one randomised trial has shown that the latter procedure is associated with poorer functional outcome. Clinical anastomotic dehiscence rates after colonic resection should be less than 5% but there is no consensus as to the best method of anastomosis. Randomised trials of stapling versus hand sutured anastomosis show no difference, but the technique associated with the lowest anastomotic dehiscence rates in the literature is the interrupted seromucosal technique as described by Matheson.

Rectal cancer

In recent years it has emerged that the most important concept in rectal cancer surgery is mesorectal excision. This involves careful dissection in the plane immediately outside the mesorectum (fatty tissue surrounding the rectum in the pelvis) so that the rectum and tumour can be removed as a package and damage to the pelvic nerves is minimised. There is some debate as to whether a total mesorectal excision right down to the pelvic floor is necessary for all rectal cancers. It is generally agreed that for tumours of the upper third of the rectum it is safe to transect the mesorectum at 5 cm below the tumour, whereas for tumours of the lower two thirds of the rectum total mesorectal excision is necessary. Abdominoperineal excision of the rectum should only be necessary for very low tumours and should account for no more than 40% of all rectal cancer operations, and indeed, in specialist centres this figure can be reduced further. Providing a small rectal stump can be preserved an anastomosis is possible using stapling techniques. Unfortunately, however, this type of very low anastomosis is associated with a high anastomotic leakage rate (in the region of 20%) and many surgeons advise the use of a defunctioning loop ileostomy in order to minimise the effects of leakage.

If the principles in mesorectal excision are adhered to then overall local recurrence rates after rectal cancer surgery should be below 10%. As local recurrence is difficult to treat and ultimately fatal, good surgery also translates into better long term survival for patients with rectal cancer.

Adjuvant therapy

Adjuvant therapy can be subdivided into adjuvant chemotherapy and adjuvant radiotherapy.

Adjuvant chemotherapy

As a result of many randomised trials it is now accepted that patients with Dukes's stage C carcinoma of the colon should be offered 5-fluorouracil based adjuvant chemotherapy if they are fit to receive it. Other newer chemotherapy agents may be more effective but their use outside the setting of a randomised trial is not yet justifiable. There is some debate about the use of adjuvant chemotherapy in rectal cancer but it is generally agreed that the same rules apply as for colon cancer. It is more doubtful, however, whether or not patients with Duke's stage B cancer should receive chemotherapy and this question is still being addressed by randomised studies.
Currently, chemotherapy is not advised for patients with Duke's stage A cancer.

**Adjuvant radiotherapy**

Adjuvant radiotherapy can only be recommended for rectal cancer as the morbidity associated abdominal radiotherapy is prohibitive. Within the pelvis, however, it has an important part to play. In North America the emphasis has been on postoperative radiotherapy and there is evidence that this is more effective when combined with 5-fluorouracil based chemotherapy. However, in Europe emphasis has been on preoperative radiotherapy, and there is at least one randomised study indicating that preoperative treatment is associated with less morbidity and better disease control than postoperative radiotherapy.

In general, preoperative radiotherapy can be divided into two categories. The first category is radiotherapy for the fixed rectal cancer in an attempt to render it operable. In these cases most radiotherapists would recommend 45 Gy in 25 fractions over five weeks followed by an interval of about a six weeks before surgery is attempted. While this can be effective, the results of this approach are often disappointing. The second strategy for preoperative radiotherapy is to use it on clearly operable disease in an attempt to reduce the risk of local recurrence. The most persuasive randomised trial examining this approach was the Stockholm 2 trial which demonstrated that 25 Gy in five fractions the week before surgery reduced local recurrence rates from 27% to 11% and was associated with improved survival.

However, there was concern over the high local recurrence rate in the surgery only arm of this trial and for this reason a study based in the Netherlands randomised patients undergoing total mesorectal excision to preoperative radiotherapy or no preoperative radiotherapy. This demonstrated a reduction in local recurrence from 8% to 2%, which was statistically significant. These results indicate that in order to benefit six patients it is necessary to treat 100 patients and it is known that this schedule of preoperative radiotherapy is associated with significant morbidity. Thus, until the long term results of the Dutch trial are available, the precise role of radiotherapy in operable rectal cancer will remain unclear. In the meantime there is an ongoing Medical Research Council study (CR07) in which patients are randomised to have preoperative radiotherapy or postoperative radiotherapy only if the circumferential margins of the mesorectal excision are involved. This study is steadily accruing patients and will inform this debate.

**Follow up**

There is little consensus regarding the follow up of patients treated for colorectal cancer, which varies from no follow up at all to lifelong scrutiny with regular carcinoembryonic antigen estimations, cross sectional imaging, and colonoscopy. In essence there are four reasons for follow up. The first is to detect the development of metastatic disease at an early stage when treatment may be more effective. This is particularly true of liver metastases which may be suitable for resection. The second reason is to detect metachronous polyps or cancers, and it is generally agreed that patients should undergo colonoscopy at three years after a successful bowel resection. If this colonoscopy is negative then colonoscopy every five years is indicated. The third reason to follow up patients with colorectal cancer is to facilitate audit, and the fourth is to provide psychological support for the patients. Previously there was no evidence of any benefit accruing from intensive follow up but a recent meta-analysis of randomised trials has indicated that intensive follow up with computed tomography and carcinoembryonic antigen estimation does result in improved survival,

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**MANAGEMENT OF ADVANCED DISEASE**

**Surgery for metastatic disease**

There is now good evidence, although not from randomised studies, that survival may be prolonged by liver resection in patients with operable hepatic metastases. The precise indications for surgical resection are not clear but it is generally accepted that if all disease can be removed while retaining sufficient functioning liver then resection should be attempted providing the patient is fit enough to withstand the surgery. If the disease is not resectable then it may be possible to destroy metastases using in situ techniques such as cryoablation and radiofrequency ablation. Again there is evidence that this may prolong survival, although it is weaker than that for liver resection. Pulmonary resection for isolated lung metastases has also been reported but opportunities to carry out this surgery are infrequent.

**Surgery for locally advanced disease**

When considering the treatment of locally advanced disease, either primary or recurrent, it must be remembered that surgical excision provides the only realistic hope of cure. Thus when the primary tumour is invading adjacent structures such as the duodenum, stomach, kidney, ureter, or bladder consideration should be given to en-bloc resection of the tumour with an adequate portion of the adjacent organ. As far as advanced rectal cancers are concerned, a prolonged course of preoperative radiotherapy as described above should be considered prior to attempting resection.

**Treatment of inoperable advanced disease**

When colonic cancer is truly inoperable then surgical defunctioning or bypass may alleviate symptoms. Palliative radiotherapy is worth considering in patients with advanced rectal cancer as this may reduce symptoms. Recently there has been interest in stenting rectal and left sided inoperable cancers in order to alleviate obstructive symptoms but this will do little to reduce bleeding and mucus discharge. Palliative chemotherapy is the mainstay of the treatment of inoperable advanced colorectal cancer and the Mayo regimen of bolus 5-fluorouracil and folinic acid has been widely used. However, this regimen appears to be the least effective and most toxic of the regimens that have been widely tested in randomised trials. The De Gramont regimen of intermittently infused

**Box 5: Adjuvant therapy**

- Patients with stage C colorectal cancer should be considered for 5-fluorouracil based adjuvant chemotherapy.
- Preoperative radiotherapy for rectal cancer seems to be preferable to postoperative treatment.
- Preoperative radiotherapy reduces the risk of local recurrence of rectal cancer, but its role in conjunction with total mesorectal excision has yet to be fully established.

**Box 6: Follow up**

Follow up is carried out for:
- Early detection of metastases.
- Detection of metachronous polyps or cancers.
- Psychological support.
- Audit.

There is, however, little consensus as to how follow up should be conducted.

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5-fluorouracil and folinic acid and the Lokich regimen of continuously infused 5-fluorouracil appear to be more effective.\textsuperscript{53} Raltitrexed is also an effective treatment but there have been recent concerns regarding toxicity with this drug.\textsuperscript{56} A promising new approach is the use of oral capecitabine, and this also has been made in recent years and in terms of improved survival advantage can only be stressed, however, that chemotherapy can only be viewed as a primary treatment increases the response rate and may the feasibility of molecular screening for the disease. N Engl J Med 1998;338:1481–7.

Conclusion
Significant advances in the treatment of colorectal cancer have been made in recent years and in terms of improved survival the most important areas appear to be early detection and high quality surgery, particularly in the pelvis. The role of adjuvant therapy has been partially clarified but the treatment of advanced disease remains inadequate; as our understanding of the genetic and biochemical basis of cancer improves it is hoped that new biological modifiers and gene therapy may have a part to play in the future.

Authors’ affiliations
A Leslie, R J Steele, Department of Surgery and Molecular Oncology, University of Dundee, Ninewells Hospital and Medical School, Dundee, UK

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