Improving outcomes in colonic cancer

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Many of the symptoms of colon cancer do not start until the tumour has spread outside the bowel, and treatment at this stage has reduced chances of cure. Early detection and the optimum combination of surgery and adjuvant treatment can make a significant impact on outcome.

Colorectal cancer is the second most common cause of cancer deaths in the UK. There are 28 000 new cases and 19 000 deaths per annum (Office of Population Censuses and Surveys, 1992). The overall relative 5-year survival rate is 35%. The main factor responsible for this poor outcome is advanced stage at presentation.

Less than 25% of colorectal cancers arise in patients with known risk factors (inflammatory bowel disease, strong family history and hereditary polyposis and non-polyposis syndromes). Careful screening of these groups is clearly indicated and worthwhile but will not make a significant impact on overall mortality from colorectal cancer. Colorectal cancer usually arises from a pre-existing adenomatous polyp (Hill et al, 1978). These increase in size and undergo a number of genetic changes (Fearon and Vogelstein, 1990), with a small percentage becoming overtly malignant. One of the keys to improving outcome is likely to be the identification and treatment of these premalignant polyps.

SCREENING

Despite the fact that annual mortality from colorectal cancer exceeds both breast and cervical cancer there is no national screening programme for colorectal cancer in the UK.

Colonoscopy is the gold standard for imaging the whole colon, but it would be prohibitively expensive as a screening tool and carries a risk of colonic perforation of between 1 in 200 and 1 in 500 procedures. The other two options are faecal occult blood testing (FOBT) and flexible sigmoidoscopy.

FOBT relies on testing for small amounts of blood lost into the stool from colonic polyps and colonic cancers. The techniques available are very sensitive but have a low specificity and therefore produce a high false positive rate.

The aim of flexible sigmoidoscopy is to identify and treat left-sided colonic polyps. The rationale for using one-off flexible sigmoidoscopy in patients in the 55–60-year age group is:

- Ninety per cent of colorectal cancers are diagnosed after the age of 55 years
- Distal colonic adenomas appear to be an indicator of increased risk of lesions in the proximal colon (American Society for Gastrointestinal Endoscopy, 1988)
- Treatment of these polyps reduces the incidence of the development of colorectal cancer (Winamer et al, 1993).

Large studies of FOBT screening have been undertaken in Nottingham and Funen, Denmark. These assessed two populations of approximately 150 000, half of each population was randomized to receive FOBT and there was a 60% compliance rate (Hardcastle et al, 1996; Kronborg et al, 1996). The screened group had a reduced colorectal-related mortality of between 15 and 18%. If introduced on a population scale this would reduce annual mortality from colorectal cancer in the UK by between 2800 and 3500 cases.

A colorectal cancer screening pilot study commenced in April 2000. This aims to screen a population of 1 million over 2 years in Dundee and Coventry. This pilot consists of offering FOBT to all 50–69-year-olds in the study population; positive tests will be investigated and treated. The feasibility of a national FOBT screening programme will be considered on the basis of the results of this pilot.

A national study of one-off flexible sigmoidoscopy has been undertaken by the Imperial

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Cancer Research Fund in centres in the UK. These centres undertook over 40 000 flexible sigmoidoscopies in people between 55 and 60 years old. The results of this study are not yet fully reported. The preliminary data showed a compliance rate of approximately 45%, adenomatous polyps in 9% and colorectal cancer in 0.3%. The results comparing the screened group with the control population for colorectal-related mortality are not likely to be available for a further 2–3 years.

Both the FOBT studies and the flexible sigmoidoscopy study will ultimately yield data on whether patients who have had polyps removed have a lowered risk of developing colorectal cancer. These data will not be complete for between 10 and 15 years.

ASSESSMENT OF SYMPTOMATIC PATIENTS

The 2-week rule for the assessment of patients with symptoms suggestive of colorectal cancer (e.g. rectal bleeding with change in bowel habit, abdominal mass, palpable rectal mass and anaemia) is being introduced across the UK this year. The purpose of this is to shorten the time from presentation to a primary care physician to definitive diagnosis and treatment. This cannot work unless the appropriate hospital infrastructure is developed to allow rapid access to flexible sigmoidoscopy, barium enema and colonoscopy. There is no evidence at present to support the belief that this accelerated diagnostic system will have any effect on long-term outcome.

SURGERY AND PATHOLOGY

Surgical resection still provides the only chance of cure in invasive colonic carcinoma. Our understanding of best surgical techniques has developed over the last 80 years alongside our understanding of the pathology.

Dukes' classification of rectal carcinoma (Dukes, 1930), which was subsequently applied to colonic carcinoma (Simpson and Mayo, 1939), has provided both prognostic information and an insight into adequate surgical resection margins.

The principal aim of resection should be to remove the primary tumour in its entirety with its lymphatic drainage. Sometimes the tumour appears to either be adherent to or be invading adjacent structures. It is not always easy to differentiate whether this is caused by cancer or an inflammatory reaction. Even if it is caused by tumour, if the cancer turns out to be node negative on histology then there is evidence that removal of the adjacent area is associated with an improved prognosis (Durdey and Williams, 1984).

It is possible that laparoscopic-assisted colorectal resection may carry advantages of reduced hospital stay, accelerated recovery and cosmesis. However, the risk of portsite recurrence remains uncertain (Wexner and Cohen, 1995). The British CLASSIC trial, in which conventional surgery is compared with laparoscopic-assisted surgery, is ongoing.

ADJUVANT TREATMENT

A study of adjuvant therapy for colon cancer published by Moertel et al (1990) suggested significant reductions in local recurrence (41%) and death (33%) using a combination of 5-fluorouracil and levamisole. There were a number of flaws in this study but it provided part of the stimulus for the Quasar study in the UK. In this study patients with colorectal cancer have been randomized to receive one of several regimens of chemotherapy if their cancers are Dukes stage C and randomized to either a chemotherapy or no chemotherapy arm if their tumours are Dukes stage B. The Dukes B arm of this study continues to recruit patients. The early results show no benefit from the addition of levamisole to 5-fluorouracil and folinic acid and no benefit from the use of high dose folinic acid (Quasar Collaborative Group, 2000). No outcome data on recurrence or death will be available for 2–3 years.

There are some data to support a role for radiotherapy in colonic cancer but these benefits need to be carefully balanced against the morbidity caused by irradiation of the small bowel (Willett et al, 1987).

TREATMENT OF METASTATIC DISEASE

The commonest sites for distant metastases of colorectal cancer are in the liver and lungs.

A study by the Gastrointestinal Study Group in the USA (Gastrointestinal Study Group, 1984) showed a statistically significant benefit from liver resection when the patients had clear resection margins on histology. Five-year survival rates of 25% or more can be achieved from liver resection with very low operative mortality.

Few patients with pulmonary metastases are suitable for surgical resection, but in selected groups operative mortality is low and 5-year survival rates are as high as 44% (Scheele et al, 1989).

FOLLOW-UP

There is no consensus among surgeons as to the ideal follow-up after colonic resection for can-

cer. The aim of follow-up in the first 3 years is to initially exclude synchronous cancer and then to identify recurrence. After this period the aim is to identify metachronous polyps.

Studies from Scandinavia have shown no improvement in treatment of recurrent disease in a no follow-up *vs* an intensive follow-up group (Ohlsson et al, 1995; Kjeldsen et al, 1997).

Purely from a practical point of view, ultrasound will detect liver metastases, colonoscopy synchronous and metachronous lesions in the colon and computed tomography scanning may be helpful in the diagnosis of local recurrence. Intensive outpatient follow-up is not helpful for the diagnosis of recurrent or metachronous disease but provides psychological support for the patient.

THE FUTURE

Diagnosis of early colonic cancer provides the key to improving outcomes in the future. Population screening by FOBT or flexible sigmoidoscopy seem the most practical methods.

The mapping of the human genome may help identify much larger groups of people at increased risk of colorectal malignancy, thus allowing targeted surveillance.

Studies of immunotherapy and new adjuvant chemotherapy agents are already in progress, the results of these and Quasar are eagerly awaited. **HM**

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KEY POINTS

- A high proportion of patients present with advanced disease and therefore poor prognosis.
- Population screening by faecal occult blood testing is associated with a significant reduction in colorectal cancer-related mortality.
- En-bloc resection of colonic cancer with adjacent involved tissues provides the best chance of cure.
- 5-fluorouracil in combination with low-dose folinic acid is as effective as 5-fluorouracil in combination with levamisole or high-dose folinic acid.
- Hepatic and pulmonary resection for metastases is worthwhile in selected patients.