Management of colorectal cancer

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Introduction

This paper summarises a series of interlinked systematic reviews of research evidence carried out to inform guidance on commissioning cancer services published by the English National Health Services Executive.¹ These formed the basis of an *Effective Health Care* bulletin.²

These reviews involved, at a minimum, searching MEDLINE from 1980, checking reference lists of papers retrieved, and consulting experts in the various fields. Meta-analysis of data from individual patients in randomised trials was carried out where appropriate. Further information on the review process, including the specific questions considered, is given in *Improving outcomes in colorectal cancer: the research evidence*.³

Incidence and risk

Colorectal (large bowel) cancer was responsible for over 15 000 deaths in England and Wales in 1996 (68% colon, 32% rectal cancer). Age standardised incidences in 1992 were 4/100 000 among people under 50 years old, 100/100 000 among those aged 50–69, and over 300/100 000 among people over 70.⁴

Two genetic syndromes lead to cancer at a relatively early age: hereditary non-polyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP). The HNPCC mutation, which affects 2%–5% of patients with colorectal cancer, is associated with an 80% lifetime risk. Without treatment, people with FAP (1% of patients) would usually die of bowel cancer before the age of 40.^{5–6}

As well as these rare genetic syndromes, close relatives of people diagnosed with colorectal cancer are at increased risk, but the disease is so common that 10% of people over the age of 50 will have an affected relative. The risk is greater, the larger the number of relatives affected, the closer the family relationship, and the younger they are at the time of diagnosis (figure).^{5–7–9} Overall, about 25% of patients with colorectal cancer have a positive family history.

Early detection, diagnosis, and staging

The effectiveness of treatment and prospects for survival depend crucially on the stage of the cancer at diagnosis, usually described in terms of a modified Dukes' classification (table 1).^{10–12}

EARLY DETECTION

Three randomised controlled trials have shown that population screening of people over 50 years old for blood in faeces can reduce the

death rate from colorectal cancer.^{13–15} High quality case-control studies suggest that screening with endoscopy may also be effective.^{16–17}

Of young people at substantial risk of colorectal cancer because of genetic syndromes routine surveillance with invasive methods to examine the colon (colonoscopy), can prevent death from colorectal cancer.^{5–6–18–21} However, genetic screening of the whole population to identify the small percentage with HNPCC would be very expensive relative to the small impact on survival.²² Of people over 50 with a strong family history (more than one affected first degree relative) surveillance with faecal occult blood testing and sigmoidoscopy is also likely to be cost effective.^{23–24}

SYMPTOMS

The most common presenting symptoms of colorectal cancer include change in bowel habit, rectal bleeding, abdominal pain, and anaemia. These are non-specific, occur relatively often in the population, and have a wide variety of causes. This varied symptomatology may lead to problems with diagnosis and referral to a wide range of hospital specialties.

Studies from Holland, Australia, and the United States have shown that visible rectal bleeding in older people is an important indicator of possible colorectal cancer. Around 20% of patients over 60 and 10% of those over 40 who report rectal bleeding of recent onset have colorectal cancer or polyps.^{25–27}

Studies from the United Kingdom report combined patient and professional delays between the onset of symptoms and treatment of colorectal cancer totalling around 10 months.^{28–36} Misdiagnosis can lead to delay when it is assumed that symptoms are caused by haemorrhoids. There is little evidence that such delays affect health outcomes.^{11–28–32–37–39}

DIAGNOSIS

In cases of suspected colorectal cancer, the large bowel can be completely examined by one of two methods: colonoscopy, or sigmoidoscopy plus double contrast barium enema. A United States randomised controlled trial⁴⁰ and studies from the United Kingdom and Sweden^{41–42} found that these diagnostic methods have similar yields and costs. This equivalence depends, however, on operator competence. Colonoscopy is a technically difficult procedure which can yield reliable results if the tip of the colonoscope reaches the caecum, or proximal end of the colon completion.

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Table 1 Colorectal cancer staging, stage distribution, and survival*

Dukes' stage (modified)	Definition	Approximate frequency at diagnosis (%)	Five year survival (%)
A	Cancer localised within the bowel wall	11	83
B	Cancer which penetrates the bowel wall	35	64
C	Cancer spread to lymph nodes	26	38
D	Cancer with distant metastases (most often in the liver)	29	3

*Data from St Vincent's Hospital, Dublin. These figures should be taken as illustrative only, as stage frequency and survival statistics vary between published series from different centres.

Although published series, mainly from the United States, report completion rates of 85% or more,⁵ audit data from the Trent Region and Wales suggest that completion rates in many British hospitals may be below 50%.

Colonoscopy technique improves with practice.⁴³⁻⁴⁶ A study of training in colonoscopy found that physicians are normally able to achieve completion 80% of the time after 50 colonoscopies, rising to 95% after 200.⁴⁷ Competence in flexible sigmoidoscopy can be achieved after 24 to 30 examinations.⁴⁸ A United States study found that trained nurses were as likely to discover cancers by sigmoidoscopy as were gastroenterologists, and patients were more willing to return for a repeat procedure after examination by a nurse.⁴⁹

A range of imaging techniques, including ultrasound, computed tomography (CT), immunoscintigraphy, and magnetic resonance imaging (MRI), can provide information on stage of cancer, but none seems to be very accurate.⁵⁰⁻⁵¹ Ultrasound examination of the liver correctly identifies around 52%–58% of patients who have metastatic cancer.⁵² Both CT or MRI of the liver is more reliable, with sensitivities of 62% and 70% (and specificities of 97% and 94%), respectively.⁵³ Because ultrasound is cheap and readily available, it may be most appropriately used as the first of a possible series of investigations; more expensive technologies can be used when initial findings are negative.⁵²

Risk of colorectal cancer by age and family history (relative to risk in 45 year olds with no family history). Family history category: 0= no family history; 1= one affected first degree relative over 45 at diagnosis; 2= one affected first degree relative under 45 at diagnosis; 3= two affected first degree relatives.

Management

SURGERY

About 80% of patients undergo surgery, usually with the hope of cure. Fewer than half survive more than five years.⁵⁴⁻⁵⁵ (Also found by the Yorkshire Cancer Registry, unpublished data.)

Prospective and retrospective studies have reported substantial variability between surgeons in the outcomes they achieve. This is partly explained by chance variation but persists after differences in patient case mix and surgeon grade are taken into account.⁵⁷⁻⁶¹ For example, a study in Scotland of patients managed by 13 consultant surgeons found a threefold variation between surgeons in five year mortalities after controlling for Dukes' stage, local spread of tumour, differentiation, age and sex of patient, and emergency admission.⁵⁹

Long term survival is only likely when the tumour is completely removed. Microscopic cancer cells left behind after surgery in tissue close to the rectum (the mesorectum) can become foci of incurable local recurrence. These are especially common around the circumference of the segment of bowel where the cancer originated.⁶²⁻⁶³ In a prospective series from Leeds, 90% (95% confidence interval (95% CI) 84% to 96%) of patients had no local recurrence at five years when the circumferential margin of tissue removed during surgery was clear of cancer cells, compared with 22% of patients with margin involvement (95% CI 6% to 38%).⁶⁴

The role of pathologists in reporting surgical margin status is important both for decisions on adjuvant treatment and to give feedback to surgeons. However, many pathologists do not report on involvement of the crucial circumferential margin.⁶⁵

Total mesorectal excision is an approach to surgery in which meticulous care is taken to remove all the tissue surrounding the tumour. There is some evidence from studies with historical controls⁶⁶ and non-randomised comparative studies⁶⁷ that total mesorectal excision may reduce recurrence rates and improve survival. However, there have been no randomised trials comparing total mesorectal excision with conventional surgery.

When surgery involves removal of the anal sphincter, the patient is left with a stoma; this can impair the quality of life.⁶⁸ If the tumour is very low in the rectum, there may be no alternative to abdominoperineal resection, which necessitates stoma formation; however, the wide range of reported rates of abdominoperineal resection (9%–68%) suggests that it may be possible to avoid stoma formation in many cases.⁶⁹⁻⁷⁰

Effects of specialisation and volume

There is contradictory evidence on whether specialisation and increased patient throughput improves outcomes. No volume or specialisation effects were found in a Scottish study,⁵⁹ in a small study comparing teaching and district general hospitals,⁷¹ nor in an analysis of outcomes for around 2000 of the patients included in the Trent/Wales audit of colorectal

cancer.⁵⁸ A Finnish study found better five year survival in regions served by university hospitals than in those served by non-university hospitals, but it is not clear whether this is due to the presence of a radiotherapy unit in some hospitals, teaching hospital status, or degree of specialisation.⁷² Unpublished data from East Anglia and from Northern and Yorkshire cancer registries suggest that survival rates are higher when patients are treated in larger hospitals or oncology centres.

Three United States observational studies looked for associations between mortality in hospital and volume of surgery.⁷³⁻⁷⁵ Of the two which adequately adjusted for case mix, one found lower mortality in hospitals where the number of patients treated for colorectal cancer was higher than the median, compared with lower volume hospitals (standardised mortality ratio (SMR) 0.94 *v* 1.14, $p < 0.05$);⁷³ the other found no effects of volume.⁷⁴

There is some evidence that volume of activity and specialisation may be associated with better surgical technique or practice. Surgeons who carry out more operations have been shown to be more likely to rejoin the bowel successfully after removing the tumour (4.2% of junctions (anastomoses) created by higher volume surgeons leaked, compared with 14% of those by lower volume surgeons, $p < 0.05$).⁷⁶ In Oxford, surgical teams headed by specialists were more likely to perform primary resection (potentially curative surgery) and immediate anastomosis in emergency situations than those not headed by specialists (67% *v* 41%, $p < 0.05$).⁷⁷

RADIO THERAPY FOR RECTAL CANCER

The effectiveness of radiotherapy was assessed in a series of meta-analyses by the Colorectal Cancer Collaborative Group. This included data on 6000 individual patients in 12 studies of preoperative radiotherapy⁷⁸⁻⁸⁹ and 2000 patients in eight studies of postoperative radiotherapy.^{82 90-96}

Preoperative radiotherapy was associated with 14% (SD 4%, $p = 0.002$) fewer deaths from colorectal cancer: 43.9% *v* 49.2% dead. This was counterbalanced by an increase in deaths from other causes, but only in studies with obsolete irradiation techniques. The benefit is greater in patients who go on to have curative resections.

Postoperative radiotherapy leads to a 33% (SD 11%, $p = 0.003$) reduction in local recurrence but no clear evidence of improved survival. A randomised study showed that preoperative radiotherapy is more effective in improving survival than postoperative radiotherapy, takes one week rather than four or five weeks, and causes less long term morbidity.⁹⁷

It is not clear whether routine preoperative radiotherapy is sufficiently beneficial to justify the costs and risks when surgeons consistently achieve low rates of local recurrence.⁹⁸ This will be investigated in a future trial (CRO7).

Palliative radiotherapy can be highly effective to reduce symptoms due to locally advanced rectal cancer in patients who have not previously had radiotherapy.⁹⁹

CHEMOTHERAPY

Adjuvant chemotherapy

The effectiveness of adjuvant chemotherapy was assessed in a meta-analysis by the Colorectal Cancer Collaborative Group of individual five year survival data for 12 000 patients in 33 randomised controlled trials, supplemented by an additional meta-analysis of published data on 6000 patients from 17 other studies. This suggests that for every 100 patients with Dukes' stage C cancer treated for six months with 5-fluorouracil/folinic acid (FUFA), six deaths can be avoided (95% CI 2% to 10%).³ A one week postoperative infusion of 5-FU directly into the liver may also be effective.¹⁰⁰ It is not yet clear whether smaller potential benefits for patients with Dukes' stage B cancer outweigh the toxicity of chemotherapy; such patients should be entered into trials such as the QUASAR study.

Two economic evaluations suggest that adjuvant chemotherapy for stage C colorectal cancer, either given intraportally¹⁰¹ or systemically¹⁰² are relatively cost effective, with a cost per discounted life year gained of around \$1000 to \$2000. However, because of the adverse effects of adjuvant chemotherapy on quality of life, the costs per quality adjusted life year (QALY) gained are higher.¹⁰³

Chemotherapy for advanced or recurrent colorectal cancer

Five randomised trials compared chemotherapy given immediately on diagnosis of advanced or recurrent disease with chemotherapy reserved for the palliation of symptoms. These show that early chemotherapy increases median survival by three to six months and that symptom free survival increases from a median of two months to 10 months ($p < 0.001$).¹⁰⁴⁻¹⁰⁸

Meta-analyses of relevant randomised controlled trials suggest that improved response rates can be achieved by supplementing 5-FU with methotrexate or folinic acid and that continuous infusion of 5-FU is more effective than bolus administration.³ Supplementation of 5-FU with folinic acid is more effective than the addition of methotrexate.¹⁰⁹ However, the gains of supplementation are modest and its cost effectiveness is not established.

A meta-analysis of hepatic arterial infusion³ suggests that this is associated with better response rates than systemic treatment,¹¹⁰⁻¹¹⁴ and possibly improved survival in patients with liver metastases.¹⁰⁷

FOLLOW UP

Patients who have had surgery with the intention of cure are often followed up to detect recurrences of the cancer in the hope that they will be resectable. The nature, extent, and frequency of follow up varies widely. Tests may include colonoscopy; laboratory analysis of carcinoembryonic antigen, liver function, and faecal occult blood; radiological investigations such as chest and colonic x ray films; liver ultrasound and CT.^{54 115-117} However, even with follow up as often as every three months, most recurrences are discovered as a result of

Table 2 Randomised trials of different follow up schedules after surgery for colorectal cancer (crc)

Study, country, grade	Aims of study	Study design	Patient characteristics	Outcome measures	Results	Comments
Lennon <i>et al</i> 1995 ¹²⁴ UK 1a	To assess the value of surgical intervention for recurrent crc based on rising concentrations of CEA.	RCT, 5 year follow up. CEA monitored monthly (blind), years 1–3, 3 monthly years 4–5 after primary resection, in 1447 patients; randomised 1982–93 if CEA rose significantly. Aggressive (A) group (n=108): rise in CEA led to investigation before second look surgery. Conventional (C) group (n=108): clinician not informed of CEA rise.	All apparently disease free at clinical examination before CEA rise noted; symptomatic patients excluded.	5 year survival; number undergoing second look surgery.	Survival: group A: 20.4% at 5 years; group C: 22%;. Survival hazard ratio for conventional to aggressive 0.84 (95% CI: 0.62 to 1.13). 62% in aggressive, 23% in conventional group had second look surgery.	More detailed questioning showed that some apparently disease free patients did have symptoms. Trial closed after recommendation that survival advantage for second look surgery highly unlikely.
Ohlsson <i>et al</i> 1995 ¹²² Sweden 1b	To compare intensive follow up with no follow up after curative surgery for crc.	RCT, 5 year follow up. 107 patients randomised 1983–6, 3 months after primary surgery and colonoscopy to remove polyps. Intensive follow up (FU) group (n=53): frequent clinical examination for >5 years, plus colonoscopy, CT (in patients who underwent APER), lung x ray film, liver function tests, CEA and FOBT monitoring. Control group (n=54): no follow up.	Mean age 66, 33% tumour in rectum, 66% colon. Exclusions: patients with distant metastases, also those in whom age or severe illness might preclude treatment of recurrent disease.	5 year and cancer specific survival. Tumour recurrence. Test that first signalled recurrence.	5 year survival, 75% in FU group, 67% in controls (p>0.05); corresponding cancer specific survival rates 78% and 71%. Tumour recurred in 33%. FU group: recurrence first signalled by symptoms in 47%, CEA in 41%. Controls: symptoms first sign of recurrence in 83%. Cumulative 5 year survival 59% in intensive group, 54% in controls (p=0.5). Recurrence identified earlier in intensive group (mean 10 v 15 months) Endoscopy and ultrasound useful, not CT. Reresections on 22% of intensive group, 14% of conventional group. Over half asymptomatic when recurrence diagnosed.	Authors conclude that intensive follow up did not improve survival. However, the study was too small to be conclusive.
Makela <i>et al</i> 1995 ¹²³ Finland 1b	To assess the value of intensified follow up after curative surgery for crc.	RCT, 5 year follow up. 106 consecutive patients randomised after primary surgery, 1988–90. All seen in outpatient clinic 3 monthly for 2 years, then 6 monthly; FOBT and CEA tests, chest x ray film, cbc count. Intensified follow up group (n=52): yearly colonoscopy, sigmoidoscopy 3 monthly for rectal or sigmoid cancer. Liver ultrasound 6 monthly, CT yearly. Conventional group (n=54): barium enema yearly, rigid sigmoidoscopy 3 monthly if rectal cancer.	Mean age 66, no information on exclusions. 26% stage A, 45% stage B, 28% stage C. 29% had rectal tumours, 71% colon (including sigmoid).	Time of detection of recurrence, resectability and survival.	Time of detection of recurrence, resectability and survival.	Authors conclude that more intensive follow up does not improve survival. However, the study was too small to be conclusive.

RCT=randomised controlled trial; CEA=carcinoembryonic antigen; APER=abdomino-perineal excision of the rectum; FOBT=faecal occult blood test. cbc count=complete blood cell count.

symptoms reported by patients, and even those discovered by testing are rarely amenable to cure.^{54 118–121}

Three randomised controlled trials have evaluated more intensive follow up with carcinoembryonic antigen and other tests.^{122–124} Taken together, they suggest that more intensive follow up leads to more surgery with no evidence of benefit to the patient (table 2). A large cohort study also found little difference in survival.¹²⁵ A meta-analysis of data from non-randomised studies suggested a slight, but not significant, survival advantage of more intensive follow up, possibly caused by selection bias.¹²⁶

Four studies looking at the costs and potential benefits of patient follow up after potentially curative colorectal cancer treatment conclude that, for most patients, follow up leads to a significant increase in costs without an increase in life expectancy.^{127–130}

Conclusions

Many aspects of services for patients with colorectal cancer could be improved. This paper does not include discussion of issues that are general to all types of cancer—such as the benefits of clear information for patients and the need for effective delivery of palliative care; these have been covered in previous publications.¹³¹

Early detection of colorectal cancer in members of high risk groups, through screening or

surveillance, can reduce mortality. The case for the introduction of screening for colorectal cancer in England is being considered by the National Screening Committee.

Improvements in diagnostic and surgical technique in many British hospitals may be expected to produce significant improvements in both duration and quality of life. The guidance suggests that surgery should be concentrated in the hands of those surgeons who can show the best outcomes.

Preoperative radiotherapy is effective for patients with rectal cancer, and should become routine practice unless surgeons can show low (<10%) local recurrence rates. Chemotherapy should be considered for patients with Dukes' stage C and recurrent or metastatic cancers.

There is insufficient evidence to justify routine intensive follow up after primary treatment. Reducing intensity of follow up may result in considerable savings with no reduction in quality of care.

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