Effective Health Care

Bulletin on the effectiveness of health service interventions for decision makers

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The management of colorectal cancer

- Colorectal (bowel) cancer is the second most common cause of cancer death in the UK. The disease is curable when not too far advanced and UK survival rates could be substantially improved with better management.
- Quality of diagnostic procedures should be monitored, particularly the completeness of the examination of all of the large bowel using colonoscopy, and associated complications. Training should be given, if necessary, to improve standards.
- Substantial variability in outcomes achieved by surgeons suggests that concentrating surgery in the hands of those with better results could improve survival.
- Histopathologists should provide detailed information on the nature and extent of the cancer and give feedback to surgeons.

- Sugeons should aim, wherever posssible, to use operations which conserve the anal sphincter and avoid the need for a stoma.
- Pre-operative radiotherapy should be routinely offered to patients with rectal cancer unless surgeons demonstrate low (<10%) local recurrence rates.
- Chemotherapy can be beneficial in more advanced cancers but agents other than 5-FU+ folinic acid (FUFA) should not be used outside the context of trials until their benefits have been clearly established.
- There is no evidence that routine intensive follow-up after primary treatment benefits patients.
 Reducing the intensity of follow-up could conserve NHS resources without compromising quality.

A. Background

A.1. Incidence and mortality:

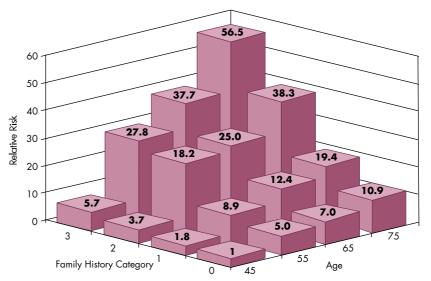
Colorectal (large bowel) cancer was responsible for over 15,000 deaths in England and Wales in 1996 (68% colon, 32% rectal cancer).1 The incidence rate per 100,000 (all ages) is 53.5 for men and 36.7 for women.

Incidence rises sharply with age. Age-standardised rates in 1992 were 4 per 100,000 among people aged under 50, 100 per 100,000 among those aged 50-69, and over 300 per 100,000 among people over the age of 70.

A.2 People at raised risk: 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 colorectal cancer patients, 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 40.2,3

In addition to these rare genetic syndromes, close relatives of people diagnosed with colorectal cancer are at increased risk. 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 (Fig. 1).2,4-6 However, the disease is so common that 10% of people over the age of 50 will have an affected relative.

Those with a single relative diagnosed over the age of 60 have



Family History Category

- 0 No family history
- One affected first-degree relative, over 45 at diagnosis
- One affected first-degree relative, under 45 at diagnosis
- Two affected first-degree relatives

Fig. 1 Risk of colorectal cancer by age and family history (relative to risk in 45 year olds with no family history)

the same risk as the general population. About 25% of patients with colorectal cancer have a positive family history.

A.3 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).7-9

The overall 5-year survival rate in England is 35%.10 Within Britain, there is evidence of wide variations in treatment and outcomes.

A.4 The Guidance on

In order to improve the standard of care for patients with colorectal

Commissioning Cancer Services:

Table 1 Colorectal cancer staging, stage distribution and survival*

Dukes' Stage (modified)	Definition	Approximate frequency at diagnosis	5-year survival
Α	Cancer localised within the bowel wall	11%	83%
В	Cancer which penetrates the bowel	35%	64%
С	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, since stage frequency and survival statistics vary between published series from different centres.

cancer, the Department of Health's Clinical Outcomes Group (COG) commissioned the production of guidance. This was distributed with EL(97) 66 and is now available as a series of three related publications: *Improving* Outcomes in Colorectal Cancer: The Manual; The Research Evidence; and Guidance for General Practitioners and Primary Health *Teams*. 11–13 These may be obtained free of charge by calling the NHS Response Line on 0541 555 455.

This bulletin summarises the research evidence which informed the guidance, based on a series of interlinked systematic reviews of the research evidence. These reviews involved, at a minimum, searching MEDLINE from 1980, checking reference lists of papers retrieved and consulting experts in the various fields. For some topic areas, a meta-analysis which combined data on individual patients from several trials (individual patient data metaanalysis) was carried out. Further information on the review process, including the specific questions considered, is given in Improving Outcomes in Colorectal Cancer: The Research Evidence.13

B. Diagnosis

B.1. Early detection: Three randomised controlled trials have demonstrated that population screening of people over 50 years old for non-visible (occult) blood in faeces can reduce the colorectal cancer death-rate.14-16 High quality case-control studies of screening with endoscopy suggest that this is also effective;^{17, 18} this is being further evaluated in a UK trial. The case for the introduction of colorectal cancer screening is being considered by the national screening committee.

Routine surveillance of young people who are at substantial risk of colorectal cancer because of genetic syndromes, using invasive methods to examine the colon (colonoscopy), can prevent death from colorectal cancer.^{2, 3, 19–22} 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.²³ Surveillance of people aged over 50 with a strong family history (e.g. >1 affected first-degree relative) using faecal-occult blood testing and sigmoidoscopy is likely to be cost-effective.24, 25

B.2. 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 frequently in the population and have a wide variety of causes. This varied symptomatology may lead to problems with diagnosis and to referral to a wide range of hospital specialities.

Dutch, Australian and US studies have shown that visible rectal bleeding in older people is an important indicator of possible colorectal cancer. Around 20% of patients aged over 60,26 and 10% of those aged over 40²⁷ reporting visible rectal bleeding had colorectal cancer. In the US study

none of the cancers occurred in people aged under 50.28

B.3 Delay in diagnosis: UK studies report delays of around 10 months between the onset of symptoms and treatment of colorectal cancer.29-33 Median patient delay is approximately three months, usually because patients do not think the symptoms signify serious illness.29, 34-37 Professional delay may be the result of mis-diagnosis, often due to the assumption that symptoms are caused by haemorrhoids. There is little evidence that such delays affect health outcomes.8, 29-33, 38-40

B.4 Diagnostic methods: 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. In colonoscopy, a flexible tubular device (endoscope) is inserted into the anus and threaded along the whole of the large bowel. In sigmoidoscopy, a shorter instrument (rigid or flexible) is used to examine the lower part of the bowel (Fig. 2). The whole bowel is then visualised using X-rays.

A US randomised controlled trial41 and UK and Swedish studies42,43 found that these diagnostic methods have similar yields and costs. This equivalence depends, however, on operator competence.

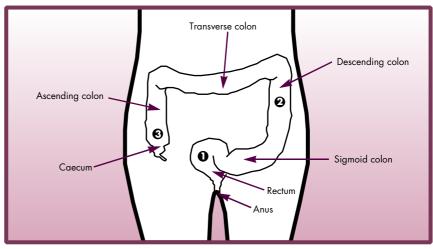
B.5 Achieving competence in **endoscopy:** Colonoscopy is a technically difficult procedure which can yield reliable results if the tip of the colonoscope reaches the caecum (or proximal end) of the colon – 'completion' (Fig. 2). Although published series, mainly from the US, report completion rates of 85% or more,2 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.44-47 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 200.48

Competence in flexible sigmoidoscopy can be achieved after 24 to 30 examinations. 49 A US study found that trained nurses were as likely to discover cancers by sigmoidoscopy as gastroenterologists (and patients were more willing to return for a repeat procedure after examination by a nurse).50 Further research on nurse endoscopy is being commissioned by the NHS Health Technology Assessment Programme.

B.6 Pre-operative staging:

Patients diagnosed with colorectal cancer should undergo further investigation to provide information on cancer stage unless



The large intestine: 1. Limit of rigid sigmoidoscope; 2. Limit of flexible sigmoidoscope; 3. Limit of colonoscope

the findings are unlikely to influence management. More accurate staging (e.g. detection of liver metastases) facilitates more appropriate treatment.

A range of imaging techniques is available - ultrasound, CT scanning, immunoscintology and MRI – but none of them appear to be very accurate.^{51,52} Ultrasound examination of the liver correctly identifies around 52-58% of patients who have metastatic cancer.53 CT or MRI of the liver is more accurate, with detection rates of 62% and 70% and true negative rates of 97% and 94%, respectively.54 Because ultrasound is relatively cheap and readily available, it may be most appropriately used as the first of a possible series of investigations, only progressing on to more expensive technologies in the case of a negative finding.53

C. Management

Surgery

About 80% of patients undergo surgery, usually with the hope of being cured. Fewer than half survive more than 5 years. 55-57

C.1. Effectiveness of surgery:

Surgery is the first-line treatment and its effectiveness has been demonstrated, for example, by trials of early detection and treatment by surgery.^{14–16} The quality of surgery has been shown to affect its impact on local recurrence and survival.

C.2. Variability between

surgeons: Prospective and retrospective studies have shown substantial variability between surgeons in the outcomes they achieve, which persists after chance variation and differences in patient case-mix and surgeon grade are taken into account. ⁵⁸⁻⁶² For example, a study in Scotland of patients managed by 13 consultant surgeons shows up to a 3-fold variation between surgeons in 5-year mortality rates after

controlling for local spread of tumour, Dukes' stage, differentiation, age and sex of patient and emergency admission.⁶⁰

C.3 Surgery for rectal cancer:

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.^{63,64} In a prospective series from Leeds, 90% (95% CI: 84%, 96%) of patients had no local recurrence at 5 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%, 38%).65

Pathologists can play an important role in reporting surgical margin status, 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.⁶⁶

Total mesorectal excision (TME) 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 using historic controls⁶⁷ and non-randomised comparative studies⁶⁸ that TME may reduce recurrence rates and improve survival. However, there have been no randomised trials comparing TME with conventional surgery.

An advantage of TME is that it can preserve the anal sphincter. This avoids the need for a stoma (a new opening of the bowel at the abdominal surface for the evacuation of bowel contents) which impairs patients' quality of life. When the tumour is very low in the rectum, there may be no alternative to abdominoperineal resection (APER), which necessitates stoma formation. However, the wide range of

reported APER rates (from 68% to 9%) suggests that some stomas could be avoided.^{70,71}

C.4 Emergency surgery:

Outcomes are worse after emergency surgery. $^{55,\,59,\,61,\,72-75}$ The Trent/Wales and Wessex audits reported 20% and 14% emergency rates respectively.^{55, 59} Analysis of case-mix adjusted data from the Trent/Wales audit shows that the odds of death within 30 days for emergency admissions was 3.5 times higher (95% CI: 1.9, 6.6) than for elective surgery for colon cancer, and 13.3 times higher (95% CI: 3.5, 50.1) for rectal cancer. However, after exclusion of perioperative deaths, long term mortality was not affected.⁵⁹ It is not clear from the research evidence how such emergencies could be avoided or how the poorer outcomes associated with emergency admission could be improved.

C.5. Effects of specialisation and

volume: There is contradictory evidence that specialisation and increased patient throughput improves outcomes. No volume or specialisation effects were found in either McArdle's Scottish study,60 nor in an analysis of outcomes for around 2,000 patients included in the Trent/Wales audit of colorectal cancer,59 or in a small study comparing teaching and district general hospitals.⁷⁶ On the other hand, a Finnish study found improved 5-year survival in regions served by university hospitals compared with those served by non-university hospitals, although 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.⁷⁷ Unpublished data from East Anglia and from Northern and Yorkshire cancer registries suggest that patients treated in larger hospitals or oncology centres have improved survival.

Three US observational studies looked for associations between inhospital mortality and volume of surgery.^{78–80} Of the two studies

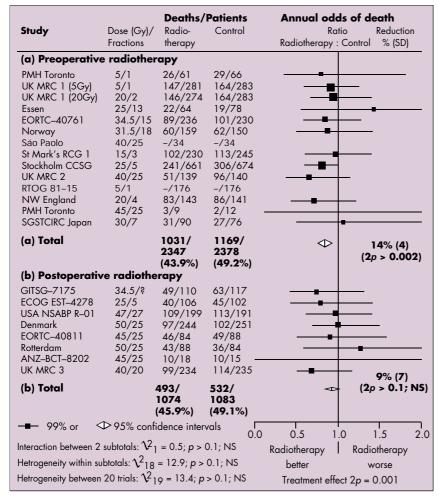


Fig. 3 Mortality from colorectal cancer in trials of radiotherapy versus the same management without radiotherapy in rectal cancer

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 (SMR 0.94 vs. 1.14, p < 0.05); the other found no volume effects.79

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 re-join the bowel successfully after removing the tumour (4.2% of the junctions (anastomoses) created by 5 highervolume surgeons leaked, compared with 14% of those by 23 lower-volume surgeons, p < 0.05).81 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% vs. 41%, p < 0.05).82

Radiotherapy

cancer: The effectiveness of radiotherapy was assessed in a series of meta-analyses by the Colorectal Cancer Collaborative Group. This included individual

C.6. Radiotherapy for rectal

data on 6,000 patients in 12 studies of pre-operative radiotherapy^{83–94} and 2,000 patients in eight studies of post-operative radiotherapy.87,95-101

Pre-operative radiotherapy was associated with 14% (SD 4, p = 0.002) fewer deaths from colorectal cancer: 43.9% vs. 49.2% dead (Fig. 3). This was

counterbalanced by an increase in deaths from other causes, but only in studies using obsolete techniques. The benefit is even greater in those patients who went on to have curative resections.

Post-operative radiotherapy leads to a reduction in local recurrence but no clear evidence of improved survival (Fig. 3). A randomised study showed that pre-operative radiotherapy is more effective than post-operative in improving survival and only takes one week rather than four or five, and causes less long-term morbidity. 102

Where surgeons, working with pathologists, consistently achieve clear margins (see C.3) and therefore, low rates of local recurrence, it is not clear whether routine pre-operative radiotherapy is sufficiently beneficial to justify the costs and risks.103 This will be investigated in a future trial (CRO7).

Radiotherapy can be highly effective in reducing symptoms (palliation) due to locally advanced rectal cancer in patients who have not previously had radiotherapy.104

Chemotherapy

C.7 Chemotherapy for primary **colorectal cancer:** The effectiveness of adjuvant chemotherapy (i.e. after surgery) was assessed in two meta-analyses. The Colorectal Cancer Collaborative Review Group pooled individual five-year survival data for 12,000 patients in 33 randomised controlled trials. This was supplemented by a metaanalysis of published data on 6,000 patients in 17 other studies.13

The results of 25 studies evaluating prolonged chemotherapy using 5-fluorouracil/folinic acid (5-FU/FA) are shown in Fig. 4. This suggests that for every 100 patients with Dukes' stage C cancer treated for six months with 5-FU/FA, six deaths can be avoided (95% CI: 2%, 10%).13 A one-week post-operative infusion of 5-FU directly into the liver may also be

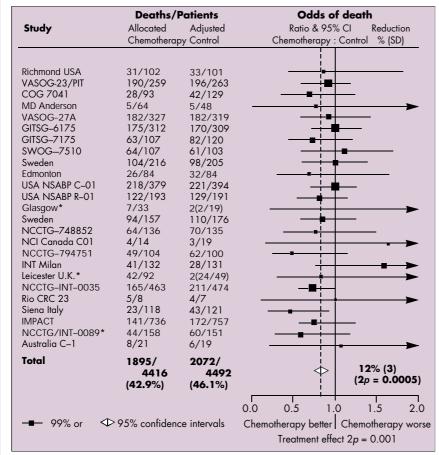


Fig. 4 Mortality in trials of prolonged (3 months) 5–Fluorouracil-based adjuvant chemotherapy regimens versus control with no chemotherapy.

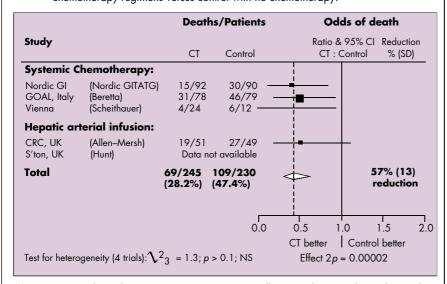


Fig. 5 Active chemotherapy (CT) versus symptom palliation only (control) in advanced colorectal cancer; six month survival.

effective. 105 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 intraportally¹⁰⁶ or systemically¹⁰⁷ are relatively costeffective, with a cost per discounted life year gained of around \$1,000 to \$2,000.

However, because of the adverse effects of adjuvant chemotherapy on quality of life, the cost of each quality adjusted life year (QALY) gained may be much greater. 108

C.8. Chemotherapy for advanced or recurrent colorectal cancer:

Five randomised trials compared chemotherapy given immediately on diagnosis of advanced or recurrent disease with chemotherapy for the palliation of symptoms. These show that early chemotherapy increases median survival (Fig. 5) and that symptom-free survival increases from a median of two months to ten months (p < 0.001). ^{109–113}

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.¹³ Supplementation of 5-FU with folinic acid is more effective than the addition of methotrexate.114 However, the gains of supplementation compared with 5-FU alone are modest and cost-effectiveness is not established.

A meta-analysis of hepatic arterial infusion¹³ suggests that this is also associated with improved response rates^{115–119} and possibly improved survival in patients with liver metastases.¹¹²

D. 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, leading to better overall survival. The nature, extent and frequency of follow-up varies widely. Tests may include: colonoscopy; laboratory analysis of carcinoembryonic antigen (CEA), liver function and faecal occult blood; and radiological investigations such as chest and colonic X-ray, liver ultrasound and

Table 2 Randomised trials of different follow-up schedules after surgery for colorectal cancer

Study country	Aims of study	Study design	Patient characteristics	Outcome Measures	Results	Comments
Lennon, 1995 ¹²⁹ UK Ia	To assess the value of surgical intervention for recurrent colorectal cancer based on rising carcinoembryonic antigen (CEA) levels.	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 work-up prior to "second look" surgery. "Conventional" (C) group (n=108): clinician not informed of CEA rise.	All apparently disease-free at clinical examination before CEA rise observed; symptomatic patients excluded.	5 year survival; number undergoing 2nd 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, 1.13). 62% in aggressive, 23% in conventional group had 2nd look surgery.	More detailed questioning showed some apparently disease free patients did have symptoms. Trial closed following recommendation that survival advantage for second-look surgery highly unlikely.
Ohlsson 1995 ¹²⁷ Sweden Ib	To compare intensive follow-up with no follow-up after curative surgery for colorectal cancer.	RCT, 5-year follow-up. 107 patients randomised 1983–6, 3 months after primary surgery & 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, liver function tests, CEA & 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%.	Authors conclude that intensive follow-up did not improve survival. However the study was too small to be conclusive.
Makela 1995 ¹²⁸ Finland Ib	To assess the value of intensified follow-up after curative surgery for colorectal cancer.	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 & CEA tests, chest x-ray, cbc count. Intensified follow up group (n=52): yearly colonoscopy, sigmoidoscopy 3 monthly for rectal or sigmoid cancer. Liver ultrasound 6 monthly, CT scan 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, re- resectability & survival.	Cumulative 5 year survival 59% in intensive group, 54% in controls (p=0.5). Recurrence identified earlier in intensive group (mean 10 vs. 15 months) Endoscopy & ultrasound useful, not CT. Reresections on 22% of intensive group, 14% of conventional group. Over half asymptomatic when recurrence diagnosed.	Authors conclude that more intensive follow-up does not improve survival. However the study was too small to be conclusive.

CT scanning. 55, 120-122 However, even with follow-up as frequent as every 3 months, most recurrences are discovered as a result of symptoms reported by patients, and even those discovered by testing are rarely amenable to cure. 55, 123-126

Three randomised controlled trials have evaluated more intensive follow-up using CEA and other tests.127-129 Taken together, they suggest that more intensive followup leads to more surgery with no evidence of patient benefit (Table 2). A large cohort study also found little difference in survival.130 A meta-analysis of data from non-randomised studies suggested a slight, but not statistically significant, survival advantage of more intensive

follow-up, possibly caused by selection bias.131

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. $^{132-135}$

E. Implications

The research evidence has the following implications which include the six key recommendations identified in the COG guidance.11 If implemented, they would make a major contribution to improving quality

of care. The first of these, on patient focus, is general to all cancer sites. The evidence for this can be found in a previous bulletin (Effective Health Care 1996, Vol. 2 No. 6, The Management of Primary Breast Cancer) and in the research evidence document.13

Patient focus

Patients should be offered full verbal and written information about their condition and about any treatment that may be offered. This should take the individual needs of patients into account. Patients should have continuing access to a member of the core team who can offer guidance and support.

• Multi-disciplinary teams

The management of colorectal cancer in the UK is highly varied and sometimes poorly coordinated. Management by multi-disciplinary teams which work to agreed protocols is likely to facilitate improved quality and co-ordination of care. The establishment of co-ordinated teamwork may be a necessary condition for delivering services in a way that is compatible with the research evidence, and for monitoring and improving standards. These teams should include clinicians with up-todate knowledge of diagnosis and treatment of colorectal cancer, and specialised nursing staff who can support and advise patients.

Endoscopy facilities

Adequate endoscopy facilities should be provided to help ensure accurate and timely diagnosis. The quality of diagnostic procedures – particularly colonoscopy completion and complication rates – should be monitored and staff should be given additional training when necessary to improve standards. Results of diagnostic tests should be audited and further training in colonoscopy should be given when completion rates are below 85%.

Surgery for rectal cancer

Surgery for rectal cancer should be concentrated in the hands of surgeons who can demonstrate good results, particularly in terms of low recurrence rates. These surgeons should monitor their performance by working closely with histopathologists.

Pathology reporting Pathology reporting Pathology reporting should be sufficiently detailed to give comprehensive feedback on the adequacy of surgery, particularly for rectal cancer. Reports on surgical specimens should include data on the size, type, grade and Dukes' stage of tumour, and the involvement of lymph nodes and surgical margins. This information is important to guide treatment

decisions, for routine collection

of data on case-mix by cancer registries, and for monitoring long-term outcomes.

Adjuvant therapies

Pre-operative radiotherapy should be available for patients with rectal cancer particularly where surgeons do not achieve low rates of local recurrence. Adjuvant chemotherapy can improve survival in some groups of patients and should be more widely available. Large scale, nationally or internationally coordinated randomised controlled trials should be supported in order to determine the best management of patients with colorectal cancer.

• Follow-up

There is insufficient evidence to justify routine intensive follow-up. A reduction in intensity of follow-up may result in considerable savings with no reduction in quality of care.

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