



**Guidelines for the
prevention, early detection
and management
of Colorectal Cancer (CRC)**



NHMRC

National Health and Medical Research Council



Clinical Practice Guidelines

**The prevention, early detection
and management of colorectal
cancer**

Endorsed March 1999

NHMRC

National Health and Medical Research Council

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IMPORTANT NOTICE

This document is a guide to appropriate practice, to be followed only subject to the clinician's judgment in each individual case.

The guidelines are designed to provide information to assist decision making and are based on the best evidence available at time of publication. They are not meant to be prescriptive.

INTRODUCTION

The National Health and Medical Research Council (NHMRC) has identified four primary reasons for the need for clinical guidelines. These are:

- the size of the health burden
- the cost of the health burden
- variations in practice
- the existence of available evidence¹

In view of this, the Clinical Oncological Society of Australia (COSA) and the Australian Cancer Network (ACN), after wide consultation, initiated a process to develop evidence-based guidelines for the management of colorectal cancer, following NHMRC guidelines for the development of clinical practice guidelines.¹ This publication has been produced with the assistance of funding provided by the Commonwealth Department of Health and Aged Care through the National Cancer Control Initiative.

A principal committee was established to oversee the project and an extensive process of consultation was undertaken to involve the entire medical, paramedical and consumer disciplines associated with colorectal cancer.

The process to develop the guidelines has been inclusive and it has received wide cooperation from groups and individuals across Australia, who have worked mostly in working parties, although some have had individual input.

First draft reports were submitted to a public conference in Melbourne in March 1998. This meeting was widely representative of the health care professions and also attended by consumers. The total attendance was 236 persons and the meeting had significant input and guidance from two American visitors: one was a colorectal surgeon and the other a medical oncologist with significant interest in clinical trials and colorectal cancer. The conference, which was held concurrently with the NHMRC's first stage consultation, initiated further submissions.

Following second stage consultation and specialist review of submissions, COSA and ACN representatives further revised and refined the document and forwarded it to the Health Advisory Committee of NHMRC to take the accrediting process further. An external review led to further refinement preceding its final submission for accreditation by NHMRC.

During development of the guidelines, working parties have allocated their own tasks and met in various ways to complete them.

These guidelines are evidence based. They are inclusive, not prescriptive. They aim to provide information on which decisions can be made, rather than dictate a specific form of treatment. They are the result of a comprehensive process involving the careful assessment of evidence (see Appendix B).

A rating system has been used to identify the evidence base for key decision points. The rating system used, which is undergoing further development by the NHMRC,

has been adapted from the system developed by the United States Preventative Services Task Force. The version used in these guidelines is listed below.

Levels of evidence ratings

Level I	Evidence obtained from systematic review of all relevant randomised controlled trials.
Level II	Evidence obtained from at least one properly designed randomised controlled trial.
Level III	Evidence obtained from a well-designed control trial without randomisation; or from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group; or from multiple time-series with or without the intervention.
Level IV	Opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees; this level signifies the need for further research.

Level I evidence represents the 'gold standard'. However, this does not mean that treatments based on other levels of evidence cannot be used in appropriate circumstances.

While level I evidence is the best scientific evidence, it is not always available. In these circumstances, it is appropriate to base treatment on other levels of evidence. This guidelines document details current understandings, and is predicated on a plan to review it at regular intervals not exceeding five years.

During the final revision of these guidelines, the committee became aware that a new NHMRC guideline *A Guide to the Development, Implementation and Evaluation of Clinical Practice Guidelines*² was imminent, which no longer supports the concept of expert opinion as constituting level IV evidence. Reference to level IV evidence has, therefore, been avoided in these colorectal cancer guidelines. The majority of such information has been included in the text. However, when consensus opinion has been deemed appropriate, it has been presented in boxes in the body of the guidelines without a level of evidence being indicated.

These guidelines highlight areas of knowledge. They also highlight areas where our knowledge is poor and provide guidance for further research. The guidelines will be evaluated to determine their degree of use by practitioners and their effects on patient outcomes. They will be revised in accordance with NHMRC recommendations.

The individual working parties that prepared the various sections of the guidelines have used a range of search strategies, supported by their own expert knowledge and the pooling of their individual resources. These have provided extensive rather than exhaustive resources.

Thus, the review underpinning these guidelines should be regarded as expert rather than systematic in a formal sense: this distinction may be of value to those who may later seek to update the guidelines. It is noted that the 1998 Annual Report of the

Cochrane Colorectal Cancer Group³ details their progress towards comprehensive systematic reviews. These should assist in any later revision of the guidelines.

A consideration of resource implications of guidelines is an integral part of guideline development. Implementation of guidelines requires monitoring and review of relevant resource use, as evidence-based guidelines enable clinicians and managers to identify appropriate resource use. To this end, it is important to note that evidence-based guidelines are not a rationing device, but rather they enable a measure of appropriate resources that should be available. The most appropriate resources are not necessarily the least expensive.

However, where the evidence shows that alternative interventions produce similar health outcomes, with similar levels of acceptability to patients and practitioners, but differ markedly in cost, the guidelines should recommend the cheaper alternative. Some of the subjects where economic issues are relevant to colorectal cancer guidelines include:

- type of screening
- age and frequency of screening
- role of adjuvant therapy
- choices after surgery — radiotherapy and chemotherapy
- location of care

Clinical appraisal of the effectiveness of colorectal cancer guidelines should incorporate economic appraisal, where this is available.

The Commonwealth Department of Health and Aged Care is funding the development, dissemination and evaluation of these guidelines, through a contract with the Australian Cancer Society. The National Cancer Control Initiative is now responsible for managing the project. Consumer guides for colorectal cancer will be derived from these guidelines, as will a guide for general practitioners. Practitioners are encouraged to enter into informed dialogue with patients and their families about the management of colorectal cancer.

Professor Robert Thomas
Chair, Principal Committee

References

1. National Health and Medical Research Council. Guidelines for the Development and Implementation of Clinical Practice Guidelines. Canberra: AGPS, 1995.
2. National Health and Medical Research Council. A Guide to the Development, Implementation and Evaluation of Clinical Practice Guidelines. Canberra: AGPS, 1999.
3. Cochrane Colorectal Cancer Group. 1998 Annual Report (www.afdkbbh-hosp.dk/cccg).

SUMMARY AND GUIDELINES

Colorectal cancer is a major health problem in the Australian community and one in twenty Australians are likely to develop the disease. The risk increases from the age of 40 years onwards but rises sharply and progressively from the age of 50 years.

These guidelines are intended for use by all practitioners and health workers who require information about management of patients with colorectal cancer. They are wide ranging in scope, covering prevention, screening, diagnosis and psychosocial matters as well as the clinical aspects of surgery, radiotherapy and chemotherapy.

The guidelines have been produced by an exhaustive process of consultation and review encompassing all interested parties in Australia. The guidelines are based on evidence, which has been rated as level I, II or III according to the National Health and Medical Research Council (NHMRC) scale. Level IV (expert opinion) was formerly included in the scale but is no longer used since the publication of a revised NHMRC guide in 1999 (*A Guide to the Development, Implementation and Evaluation of Clinical Practice Guidelines*) during the preparation of these colorectal cancer guidelines. Statements that would have been included under this category are included as advice related to recommended practice for which there is no published evidence. Such advice is indicated in the main text as a guideline with no level of evidence (in the summary table below this is designated by ‘-’). There are no formal guidelines based on expert opinion alone. Further research is required to provide evidence in these areas.

The background and clinical significance of each of the recommendations is fully discussed in the chapter that relates to them.

The guidelines will be accompanied by a related document designed for the consumer.

Guidelines

The following tables provide a list of the evidence-based guidelines detailed in the text of the document. Readers should refer to the appropriate chapters when considering application of these recommendations in the care and management of patients with colorectal cancer.

Section I: Early colorectal cancer

Chapter	Guidelines	Level of evidence ¹ for prevention of		Page
		Cancer	Adenoma	
2	PRIMARY PREVENTION			
	Energy intake			
	Restrict energy intake in most males to <2500 kilocalories (10,480 kJ) per day and in most females to <2000 kilocalories (8360 kJ) per day.	III	III	8
	Dietary fat			
	Reduce dietary fat to <25% of calories as fat.	III	II	9
	Fruit and vegetables			
	Eat five or more portions per day of a variety of vegetables and fruits all year round.	III	III	10
	Fibre			
	Select poorly soluble cereal fibres (eg wheat bran), especially if at high risk of colorectal cancer.	III	II	11
	Calcium			
	Ensure a dietary calcium intake of 1000–1200 mg/day.	III	III	11
	Selenium			
	Selenium supplementation for chemoprevention is promising and requires confirmation.	II		13
	Antioxidant vitamins			
	Antioxidant vitamin supplementation is not advised at present to protect against colorectal cancer.	III	II	14
	Anti-inflammatory drugs			
	Aspirin and nonsteroidal anti-inflammatory drug chemoprevention is consistently protective in case-control and cohort studies, but is not recommended until dosage and balance between risk and benefit is evaluated in randomised controlled trials.	III	III	16
	Physical activity			
	Be physically active to protect against colon cancer.	III		17

¹ Throughout these summary tables, ‘–’ indicates advice based on expert opinion (ie recommended practice for which there is no published evidence).

Chapter	Guidelines	Level of evidence ^a for prevention of		Page
		Cancer	Adenoma	
2 (contd)	Smoking Avoid smoking.	III	III	18

Chapter	Guidelines	Level of evidence	Page
3	POPULATION SCREENING FOR COLORECTAL CANCER		
	Population screening		
	Reductions in mortality from colorectal cancer can be achieved through a program of population screening using faecal occult blood test.	I	26
	Screening asymptomatic individuals over 50		
	The minimum effective program is the performance of faecal occult blood tests (FOBT) on three serial stools at least every second year (biennially), but preferably annually. Evidence from controlled trials suggests this approach will lead to a reduction in mortality of about 40% in participants. It must be pointed out to these individuals that it is not a diagnostic test, but a selection process for those who should undergo colonoscopy. The process would be expected to detect 40–80% of cancers, depending on the actual FOBT used and the frequency of use. It is strongly recommended that the subject commit to repeating the FOBT in subsequent years. It is conceivable that a curable cancer, even if missed at the time of initial test, would be detected at the next round of screening and still be at a curable stage. Naturally, this is not guaranteed.	I	27
	In addition, it is acceptable to offer screening flexible sigmoidoscopy on a five-yearly basis, as the case-control studies suggest that an interval of five years is adequate. FOBT and sigmoidoscopy are complementary in that FOBT has the potential to detect lesions proximal to the reach of the sigmoidoscope.	III	27
	Provided there has been a full discussion of the risks involved, it is recommended that FOBT be performed from the age of 50 in asymptomatic individuals who do not have a positive family history.	I	27

Chapter	Guidelines	Level of evidence	Page
4	<p>COMMUNICATION WITH THE PATIENT</p> <p>Patient information</p> <p>Information for patients with colorectal cancer should include:</p> <ul style="list-style-type: none"> • causes of colorectal cancer and the extent of disease; • proposed approach to investigation and treatment, including information on expected benefits, the process involved, common side effects, whether the intervention is standard or experimental and who will undertake the intervention; • the likely consequence of choosing a particular treatment, or no treatment; • the time involved; • the costs involved; • the effect of cancer and its therapy on interpersonal and sexual relationships; • typical emotional reactions; • appearance after surgery; • how to obtain special items such as colostomy devices and wigs; • entitlements to benefits and services, such as subsidies for travel or prostheses; and • access to cancer information services. <p>Clinical trial participation</p> <p>Doctors should encourage patients with colorectal cancer to consider participating in appropriate clinical trials for which they are eligible.</p> <p>Quality of life</p> <p>Quality-of-life measurements must be integrated into future studies of treatment for colorectal cancer.</p> <p>Physicians involved in the management of patients with colorectal cancer should be aware of the potential impact of treatment on quality of life and should include this in the decision making.</p> <p>Patients need to be informed of the likely impact of treatment alternatives on their quality of life.</p>	<p>–</p> <p>–</p> <p>–</p> <p>III</p> <p>III</p>	<p>34</p> <p>35</p> <p>36</p> <p>36</p> <p>36</p>

Chapter	Guidelines	Level of evidence	Page
6 (contd)	Screening (category 2 risk)		
	Offer colonoscopy every five years starting at age 50, or at an age 10 years younger than the age of first diagnosis of colorectal cancer in the family, whichever comes first. Sigmoidoscopy plus double-contrast barium enema is an acceptable alternative for colonoscopy if the latter is unavailable.	III	46
	Consider faecal occult blood testing in intervening years. Colonoscopic follow up (or sigmoidoscopy plus double-contrast barium enema if colonoscopy is unavailable) is necessary for those with a positive faecal occult blood test.	I	46

Chapter	Guidelines	Level of evidence	Page
7	HIGH-RISK FAMILIAL SYNDROMES		
	Management of familial colorectal cancer		
	Working diagnoses should be achieved through the integration of clinical, pathological and genetic information that is standardised and fully validated.	III	56
	Genetic testing should be undertaken under the supervision of a clinical genetics or cancer genetics specialist, and supported by appropriate counselling.	III	56
	The surgical management of familial adenomatous polyposis (FAP) is by total colectomy and ileorectal anastomosis or restorative proctocolectomy.	III	56
	The role of nonsteroidal anti-inflammatory drugs, such as sulindac, in the prevention of cancer in FAP is unclear; their routine use cannot be recommended.	III	56
	Screening of at-risk members of proven hereditary nonpolyposis colorectal cancer (HNPCC) families should be by annual or two-yearly colonoscopy, commencing around the age of 25 years. Annual screening should be offered to individuals carrying a germline mutation.	III	56

Chapter	Guidelines	Level of evidence	Page
8	<p>DIAGNOSTIC TESTS AND PREOPERATIVE ASSESSMENT</p> <p>Investigations</p> <p>All people with suspicious large bowel symptoms or rectal bleeding should be investigated, especially if other risk factors (such as older age or family history) are present, or in any patient over 40 years of age.</p> <p>People under 40 years of age should be investigated if there is a positive family history, if there is not an identified cause of symptoms, or if symptoms are persistent.</p> <p>Stoma siting</p> <p>Stoma siting should be performed preoperatively by an experienced stomal therapist or the surgeon if a stoma is planned or is considered likely.</p>	<p>–</p> <p>–</p> <p>III</p>	<p>61</p> <p>61</p> <p>68</p>

Chapter	Guidelines	Level of evidence	Page
9	<p>MANAGEMENT OF EPITHELIAL POLYPS</p> <p>Management of epithelial polyps</p> <p>Consideration should be given to at least sampling, but preferably removing, all polyps seen at endoscopy. Synchronous polyps should be sought and removed. All patients with colorectal cancer should then be considered for colonoscopic surveillance according to the following protocols:</p> <ul style="list-style-type: none"> • <i>at three months</i> following piecemeal removal, or excision of a malignant adenoma, or a large adenoma that may have been excised incompletely; • <i>within a year</i> following incomplete or possible inadequate examination, for example in a subject with multiple adenomas; • <i>at three years</i> for subjects with large adenomas (>1 cm), adenomas with high-grade dysplasia, villous change in adenomas, three or more adenomas, or aged 60 or more with a first-degree relative with colorectal cancer; and • <i>at four to six years</i> in subjects without the preceding risk factors. <p>Malignant adenomas may be managed safely by endoscopic polypectomy, providing strict criteria for patient selection and histopathological assessment are adhered to. In particular, malignant adenomas should be well or moderately differentiated and excision should be complete.</p>	<p>III</p> <p>III</p>	<p>77</p> <p>77</p>

Chapter	Guidelines	Level of evidence	Page
10	PREPARATION FOR SURGERY		
	Postoperative stoma		
	All patients who have a reasonable chance of a postoperative stoma should be informed about this possibility. This includes a visit, where possible, by the stomal therapy nurse.	III	82
	Bowel preparation		
	Randomised trials do not demonstrate a benefit from routine bowel preparation.	II	83
	If bowel preparation is to be used, then both polyethylene glycol preparation and sodium phosphate preparations are effective, but polyethylene glycol is more acceptable and has lower postoperative complication rates.	II	83
	Blood transfusion		
	If a transfusion is required, then autologous blood is preferable to allogeneic blood for reasons of infection control and resource use.	III	83
	Thromboembolic prophylaxis		
	All patients undergoing surgery for colorectal cancer should receive prophylaxis for thromboembolic disease. Unfractionated heparin, low molecular weight heparin, and intermittent calf compression are effective in reducing the incidence of thromboembolism.	I	84
	Prophylactic antibiotics		
	All patients undergoing colorectal cancer surgery require prophylactic antibiotics.	I	84
	A single preoperative dose of intravenous second or third generation cephalosporin and metronidazole is an effective regime.	II	84
	Perioperative normothermia should be maintained.	III	84

Chapter	Guidelines	Level of evidence	Page
11	ELECTIVE SURGERY FOR COLON CANCER		
	Resection		
	Resection of colon cancer should be based on the appropriate excision of the lymphovascular drainage of the segment of the colon in which the cancer is situated. Resection, where feasible, should be to the origin of the major segmental blood vessels. The amount of colon resected should correspond to the extent of vascular and lymphatic clearance.	–	88

Chapter	Guidelines	Level of evidence	Page
11 (contd)	Synchronous primary carcinoma of the colon Extended segmental colectomy, separate segmental resection or subtotal colectomy should be performed in the management of synchronous primary carcinoma of the colon. The decision between these options will be made on the basis of anatomical situation of the tumours, patient factors and the surgeon's experience.	–	88
	Fixed tumours For fixed tumours, <i>en bloc</i> resection of primary colonic cancer, together with the attached organ or the abdominal wall, should be performed in an attempt to obtain a curative resection.	–	89
	No attempt should be made to assess if the attachment is benign or malignant at the time of surgery.	–	89
	Oophorectomy Bilateral oophorectomy should be performed if there is obvious malignant disease of one or both ovaries. Prophylactic bilateral oophorectomy for colon cancer cannot be supported by the available evidence.	–	90

Chapter	Guidelines	Level of evidence	Page
12	ELECTIVE SURGERY FOR RECTAL CANCER Laparoscopic surgery Laparoscopic surgery for the curative treatment of colorectal cancer should be performed only under the auspices of a randomised controlled trial.	–	95
	Stomal therapy All patients who may require a temporary or permanent stoma should be seen by a stomal therapy nurse before the operation where this facility is available. The stomal therapy nurse assesses the patient's educational needs and, in consultation with the patient or carer, formulates a realistic plan of care and selects an appropriate site for the stoma before the operation.	–	95
	Local excision Local excision of T1 rectal cancer is effective.	III	97

Chapter	Guidelines	Level of evidence	Page
12 (contd)	Local excision of rectal cancers can only be a curative procedure if there are no lymph node metastases. Predicting nodal involvement remains difficult, therefore radical transabdominal resection remains the treatment of choice in patients with rectal cancer.	III	97
	In less fit patients, or where the alternative is abdominoperineal resection and permanent colostomy, local excision has a role in managing rectal cancer. However in such patients, only a small percentage (5–10%) of rectal cancers meet recommended guidelines for local therapy. These guidelines are: <ul style="list-style-type: none"> • mobile tumour <3 cm • T1 on endoanal ultrasound • well-differentiated on histology (biopsy) 	III	97
	Sphincter-saving operation Sphincter-saving operations should be preferred to abdominoperineal resection except in the presence of: <ul style="list-style-type: none"> • low-level infiltrating tumours with unfavourable histological grade • tumours such that adequate distal clearance (>2 cm) cannot be achieved (often an operative decision) • the sphincter mechanism is not adequate for continence • access to the pelvis makes restoration technically impossible (rare) 	III	98
	Distal clearance As it is uncommon for spread to extend more than 1 cm beyond the primary neoplasm, 2 cm of distal clearance should be more than adequate in most instances.	III	100
	Total mesorectal excision Total excision of distal mesorectum beyond the transection of the rectal wall is not recommended as a routine procedure when resecting rectal cancer until more evidence is available to establish its efficacy.	–	101

Chapter	Guidelines	Level of evidence	Page
12	Irrigation of the rectal stump		
(contd)	The rectal stump can be irrigated with normal saline immediately before anastomosis for rectal and sigmoid tumours in an attempt to eradicate malignant cells from the perianastomosis zone.	III	102
	Colonic pouch		
	Where technically feasible, the colonic pouch may be the preferred form of reconstruction after low anterior resection of tumours of the lower half of the rectum to improve short-term postoperative neorectal function.	II	102
	The ideal length of the pouch lies between 5 cm and 8 cm.	III	102
	Anastomosis drains		
	There is no evidence that drains to coloanal and colorectal anastomoses are either beneficial or harmful. They should be used at the surgeon's discretion.	II	103

Chapter	Guidelines	Level of evidence	Page
13	EMERGENCY SURGERY		
	Diagnosis of large bowel obstruction		
	A clinical diagnosis of large bowel obstruction is to be confirmed by a plain radiograph of abdomen and a limited gastrografen enema and sigmoidoscopy (preferably flexible) to exclude pseudo-obstruction.	III	112
	Surgery for bowel obstruction		
	For left-sided obstructing cancer, the lesion is resected, either as a Hartmann's procedure with an end colostomy or as a subtotal colectomy and ileocolic or ileorectal anastomosis. Segmental resection and anastomosis may be performed, if preceded by intraoperative on-table colonic lavage.	II	113

Chapter	Guidelines	Level of evidence	Page
14	STAGING AND REPORTING		
	Staging data		
	ACPS staging, TNM staging and the data required to stage the patient should all be recorded to allow national and international comparisons.	III	119

Chapter	Guidelines	Level of evidence	Page
15	ADJUVANT THERAPY FOR COLON CANCER		
	Adjuvant therapy		
	People with resected node-positive colon cancer should be offered adjuvant therapy.	I	133
	5-FU plus low-dose leucovorin for six months is the preferred option. Other adjuvant therapy regimens with similar reductions in the rate of relapse and mortality (30–40%) include:	II	133
	<ul style="list-style-type: none"> • 5-FU plus low-dose leucovorin plus levamisole for six months; and • 5-FU plus levamisole for one year. 		
	The value of adjuvant therapy in Dukes B (stage II) colon cancer has not been demonstrated uniformly. Adjuvant therapy in this group is not recommended except for patients with 'poor prognosis' stage II disease who, after discussion, wish to have treatment of entry into appropriate clinical trials, which is recommended.	II	133

Chapter	Guidelines	Level of evidence	Page
16	ADJUVANT THERAPY FOR RECTAL CANCER		
	Combined modality therapy		
	Postoperative 5-FU-based chemotherapy and radiotherapy (combined modality therapy) is recommended for patients with high-risk rectal cancer.	II	139
	When chemotherapy is given postoperatively in combination with radiotherapy, protracted venous infusion of 5-FU chemotherapy may offer further benefits in survival when compared to bolus 5-FU therapy. It is the recommended way of delivering combined modality therapy.	II	139

Chapter	Guidelines	Level of evidence	Page
17	FOLLOW UP AFTER CURATIVE RESECTION FOR COLORECTAL CANCER Follow up Follow up of patients after curative resection for colorectal cancer is recommended as it allows practitioners to monitor patient outcomes arising from their treatment and it is consistent with patients' desires. All patients who have undergone surgery for colorectal cancer should have specialist follow up in conjunction with the patient's general practitioner. Randomised controlled trials do not support a survival benefit for more intensive follow-up investigations.	– – II	148 148 148

Chapter	Guidelines	Level of evidence	Page
18	PSYCHOSOCIAL CARE Psychosocial care Attention to psychosocial care is important, and is achieved through appropriate information provision, effective communication, early recognition of those at increased risk of maladaptive adjustment, active treatment of established psychiatric disorder and sustained support for the patient and their care givers. Psychological interventions Psychological interventions improve the quality of life of patients with colorectal cancer.	III I	154 155

Chapter	Guidelines	Level of evidence	Page
19	RECURRENT AND ADVANCED RECTAL CANCER: GENERAL APPROACH AND LOCAL MANAGEMENT Operable advanced rectal cancer Preoperative radiation therapy, possibly with chemotherapy, is recommended in rectal cancers fixed or tethered within the pelvis if it is felt down-staging will enable successful resection.	II	162

Chapter	Guidelines	Level of evidence	Page
19 (contd)	Inoperable advanced rectal cancer		
	Radiation therapy should be considered in patients with locally advanced rectal cancer not amenable to surgery.	III	163
	Radiotherapy for metastatic disease		
	Short courses of radiotherapy are as effective as longer courses for painful bone metastases.	I	163
	Short courses of radiotherapy are as effective as longer courses for cerebral metastases.	II	163

Chapter	Guidelines	Level of evidence	Page
20	THE ROLE OF SYSTEMIC CHEMOTHERAPY		
	Systemic chemotherapy		
	First-line 5-FU-based chemotherapy prolongs life when compared to best supportive care and should be offered to patients with advanced colorectal cancer.	II	169
	The timing of commencement of chemotherapy in asymptomatic patients is unclear, although one study suggests it is best administered early.	II	169
	5-FU plus leucovorin, 5-FU plus methotrexate, and continuous infusion 5-FU are all associated with an improvement in response rate over 5-FU alone. Survival advantages in the palliative setting may exist, but are small with no clear quality-of-life benefits over 5-FU alone.	I	169
	After failure of 5-FU therapy, second-line treatment with irinotecan prolongs life and improves quality of life when compared to best supportive care.	II	169

Chapter	Guidelines	Level of evidence	Page
21	MANAGEMENT OF LIVER METASTASES		
	Resection of liver metastases		
	Patients with up to four lesions that can be safely removed with an adequate margin and have no evidence of extra hepatic disease should be considered for resection.	III	174
	Hepatic arterial infusion		
	Hepatic arterial infusion (HAI) has shown survival benefit compared with best supportive care.	II	177

Chapter	Guidelines	Level of evidence	Page
21 (contd)	HAI shows higher response rates but little evidence of survival advantage compared with systemic chemotherapy.	I	177
	HAI and intravenous chemotherapy should be regarded as acceptable alternatives.	I	177

Section I

Early colorectal cancer

CHAPTER 1

SETTING THE SCENE

1.1 Colorectal cancer in Australia

Colorectal cancer is unequivocally a major health problem in Australia. It is the most common cancer reported to Australian cancer registries and was responsible for 14% of cancer deaths in 1990,¹ the latest year for which national figures are available. Only lung cancer, which caused 20% of deaths, was a more common cause of cancer death.

In 1995 there were 10,615 cases of colorectal cancer and 4508 deaths. About 1 in 21 Australians is likely to develop colorectal cancer during his/her lifetime, with the risk increasing after the age of 40, and rising sharply and progressively from the age of 50 years.

In 1990, premature death from colorectal cancer was responsible for an estimated 26,778 life-years lost before 75 years of age, which made it second only to lung cancer as a cause of lost life-years.¹

In the same year, colorectal cancer was the invasive cancer most commonly diagnosed, after nonmelanocytic skin cancers. Some 13.6% of all invasive cancer diagnoses were accounted for by colorectal cancer.¹ Australian incidence rates are towards the higher end of the scale internationally, alongside those for North America and New Zealand.^{1,2}

The lifetime risk of colorectal cancer before age 75 years is about 1 in 18 for males and 1 in 26 for females,¹ with incidence and mortality increasing progressively with age. Fewer than 1% of cases are diagnosed in people under 35 years of age.¹

Australian data for the period 1983 to 1990 show:

- for females, a slight decline in age-standardised (world population) colorectal cancer mortality, but little evidence of a change in incidence; and
- for males, an increase in incidence, but a comparatively stable mortality rate.¹

In South Australia, where age-standardised incidence and mortality rates are similar to national rates (within 3% for 1986–90), time-trend data for 1977–94 showed increases in incidence of 28% in males and 12% in females.³ This probably reflects, at least in part, an increase in detection of early lesions. Age-standardised mortality rates were relatively stable in males, particularly during 1981–94, but showed a 13% decline in females.³ The risk of developing a colorectal cancer varied with the individual's baseline age and sex, and the time period. The older the person and the longer the time period, the greater the risk. For example, a 65-year-old man's risk of developing colorectal cancer within 20 years was 1 in 13. The corresponding risk for a 65-year-old woman was 1 in 19.

1.2 Aetiology and pathogenesis

Colorectal cancer is a malignant tumour that starts in the bowel wall and is confined locally for a relatively long period before spreading through the bowel wall and metastasising to lymph nodes and other parts of the body. Survival rates are significantly improved where the disease is detected and treated early.

The aetiology of colorectal cancer is complex and appears to involve interactions between inherited susceptibility and environmental factors.⁴⁻⁶

Most colorectal cancers are thought to develop from benign precursor lesions, or adenomas,⁷ which may vary from tiny nodules to tumours up to 12 cm across.⁸ Colorectal cancers can arise in a pre-existing adenoma or de novo, but the relative importance of these two pathways is unclear. Colorectal cancer develops from areas of dysplasia. Adenomas and carcinomas often coexist, and adenomatous remnants are frequently found in carcinomas.⁹ De novo cancers have, however, been observed to arise in flat mucosa,¹⁰ and flat elevated cancers may originate from a pathway different from the adenoma–carcinoma sequence.¹¹

Adenomatous polyps (adenomas) are benign tumours that develop on the lining of the bowel. Some become malignant over time and most evidence suggests that adenomas are precursors for a substantial proportion of colorectal cancers. This has prompted considerable interest in removal of adenomas to prevent development of colorectal cancer.¹² However, the development of colorectal cancer from small adenomas takes many years.¹³

1.3 Treatment

There are a number of treatment options for colorectal cancer, and the evidence for these is presented in subsequent chapters. Usual treatment options consist of resection of the colon or rectum (or both), with or without adjuvant chemotherapy or radiotherapy. In very advanced stage disease, surgical treatment may not be appropriate. Efforts over recent years to improve survival have focused on earlier (presymptomatic) diagnosis, adjuvant chemotherapy, intensive follow up and modifications of surgical technique.

1.4 Case survival

Case-survival rates in Australia, as in the United States and the Netherlands, exceed those reported from most European countries, ranging from about 90% five-year survival for cancers detected at the earliest (localised) stage, to 7% for people diagnosed with distant metastatic cancer.

South Australian data for 1977–94 show a five-year survival from colorectal cancer of 53%.³ Based on United States SEER (surveillance, epidemiology and end results) data, it is estimated that 15-year survival would be about 47%.¹⁴ For the 1977–85 diagnostic period, the five-year case survival was 50%, rising to 56% for the 1986–94 diagnostic period.³ The South Australian figures, and the upward trend, are similar to data from the United States¹⁴ and the Netherlands.¹⁵

The earlier the stage at diagnosis, the higher is the chance of survival. While population-based cancer registries in Australia do not collect data on Dukes stage or Australian clinicopathological stage (ACPS) (see Chapter 14), hospital-based registries for teaching hospitals in South Australia show that five-year colorectal cancer case survival varies with the ACPS: 88% for stage A, 70% for stage B, 43% for stage C (regional nodal involvement), and 7% for stage D (distant metastases).¹⁶ This equates with international experience. Only 15% of these cancers in South Australia were diagnosed at stage A, suggesting that significant improvement in survival and a concomitant reduction in mortality could be achieved by a shift in diagnosis to the earlier, localised stage. Significantly lower survival from colorectal cancer has been found in lower socioeconomic groups in the South Australian population,¹⁷ and delay in seeking care has been proposed as a major contributing cause of such differences.¹⁸

1.5 References

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CHAPTER 2

PRIMARY PREVENTION

Studies on the primary prevention of colorectal cancer encompass a range of disciplines including molecular genetics, cell biology, animal models, and human nutrition and epidemiology. Endpoints also vary from gene expression, cell proliferation and apoptosis, aberrant crypt formation, adenomas (benign tumours) and colorectal cancer. This chapter will be biased towards human epidemiology — both observational and interventional.

Most data exist for colorectal cancer as an endpoint, but adenomas also provide useful information. As most colorectal cancers develop through adenomas, epidemiological studies using adenomas as an endpoint can provide information about environmental influences on early colorectal carcinogenesis. A variety of evidence supports this adenoma–carcinoma sequence. It is based on the following:

- strong circumstantial evidence of the association of adenomas with carcinoma (such as frequent synchronous occurrence, depth of malignant invasion varies inversely with adenomatous remnants in cancer and reduced cancer incidence in cohorts subjected to polypectomy);
- the clinical genetic model of the sequence seen in familial adenomatous polyposis (FAP); and
- the relationship of accumulating genetic mutations with increasing size of adenomas and ultimately malignant transformation with invasion.^{1,2}

De novo cancer pathways independent of a precursor adenoma also exist. Once definitive markers of this pathway can be identified, it may be possible to achieve a firmer understanding of colorectal cancer aetiology by virtue of stronger associations in epidemiological studies.

This chapter will focus principally on the endpoint of colorectal cancer, but where appropriate, extra information relating to colorectal adenomas will also be highlighted.

2.1 Dietary factors

The proportion of colorectal cancer attributed to dietary factors has been estimated to be about 50%.³

The most recent comprehensive overview of diet and cancer estimates that 66–75% of colorectal cancer could be prevented by diet and physical activity.⁴ For those already treated for colorectal cancer, an appropriate diet can maintain health in an attempt to prevent further malignancy.

2.1.1 Macronutrients

Energy

Case-control studies consistently show a positive association with energy intake and colorectal cancer risk. As fat intake is closely associated with energy intake, it has been difficult to differentiate between the two. Attempts to correct for energy in multivariate analysis in cohort studies have been moderately convincing, and indicate energy derived from fat sources predominates in risk, focusing attention then on fat intake itself.⁵

On the other hand, a meta-analysis of 13 case-control studies of colorectal cancer and dietary practice concluded there was little evidence of any energy-independent effect of either total fat or saturated fat.⁶ It also concluded that substitution of fat by other sources of energy is unlikely to reduce meaningfully the risk of colorectal cancer.⁶

Notwithstanding the controversy over the importance of energy, the evidence is sufficient to recommend reducing energy intake, both to prevent colorectal cancer and for other reasons.

Guideline — energy intake	Level of evidence for prevention of	
	Cancer	Adenoma
Restrict energy intake in most males to <2500 kilocalories (10,480 kJ) per day and in most females to <2000 kilocalories (8360 kJ) per day.	III	III

Fat

The incidence of colorectal cancer and adenomas has been correlated with high dietary fat intake (greater than 40% of total caloric intake). As well, a dietary fat intake of less than 15% of total caloric intake has been correlated with a low frequency of colorectal adenomas and cancers.

Increased dietary fat has been shown in experimental animals to lead to increased hepatic synthesis of cholesterol and bile acids, and their increased presence in the colon and faeces. Bacterial flora (particularly anaerobes) can convert these sterols into cholesterol metabolites and oxidised bile acids, which have tumour-promoting activity in animal models. Cross-cultural studies of colorectal cancer risk and faecal concentrations of bile acids support this aetiological hypothesis. Summarising the case-control and cohort studies of fat and colorectal cancer risk, Potter⁷ found six of ten (three null and one inverse) were positively associated.

Two randomised controlled trials have studied, inter alia, fat reduction using adenoma as an endpoint in people with previous adenomas removed. The Toronto Polyp Study showed no benefit, though the results were not differentiated by adenoma size at outcome.⁸ The Australian Polyp Prevention Project demonstrated a marginally statistically significant result for low fat diets (<25% calories as fat) after two and four years of intervention on the occurrence of adenomas of 1 cm in size.⁹ This result was complemented, and became more clearly significant ($P < 0.03$), in the group randomised to low fat and added wheat bran (25 g wheat bran supplement). This effect was seen despite there being no change in the weight of participants during the

trial, suggesting an effect on carcinogenesis intrinsic to dietary fat, rather than associated energy (see above). Further trials of fat reduction are in progress.¹⁰

An important exception to the relationship of dietary fat to colorectal cancer is omega-3 fatty acids. Fish and fish oil correlate inversely in international incidence data for colorectal cancer, especially the ratio of fish oil to animal fat intake.¹¹ Fish oil also reduces rectal epithelial cell proliferation. Case-control studies also demonstrate an inverse relationship.

Guideline — dietary fat	Level of evidence for protection against	
	Cancer	Adenoma
Reduce dietary fat to <25% of calories as fat.	III	II

Meat

Cohort studies have shown an inconsistent association between red meat intake and colorectal cancer.^{4,12-14} While a majority showed a positive association, most of these associations were weak and in only two studies was the trend towards increasing risk with increasing intake statistically significant.^{5,15} These two studies showed a reduction in risk of colon cancer with increasing intake of chicken, which was statistically significant in one.⁵

Separating effects of dietary fat intake from those of red meat is difficult in observational epidemiology. The report of The American Institute for Cancer Research and World Cancer Research Fund⁴ attributed observed increases in risk more to red meat than to fat. This report did not take into account the qualitative higher rating of evidence from randomised controlled trials. In the Australian Polyp Prevention Project,⁹ fat reduction was achieved by design without reduction in red meat intake. On this evidence it is fair to conclude that inhibition of adenoma growth was due to fat reduction rather than red meat reduction.

On the other hand, one effect of high temperature cooking (such as barbecuing) of red meat is the production of heterocyclic amines.¹⁶ Metabolism of heterocyclic amines includes oxidation and acetylation and eventual formation of carcinogens, which are measurable as DNA (deoxyribonucleic acid) adduct formation. N-oxidation (a P4501A2 catalysed step in the liver) and acetylation (NAT2) are genetically controlled and readily phenotyped. Rapid CYP1A2 and rapid NAT2 phenotypes produce more DNA adducts; indeed, acetylator status has been shown to correlate with colorectal cancer risk, particularly when taking red meat into account as a covariable.¹⁷ Some subsequent studies,^{18,19} but not others,²⁰ support this observation. There is inconsistent evidence that increased intake of heavily browned meat per se, or high values of other indicators of intake of heterocyclic amines produced as a result of cooking meat, increases risk of colorectal cancer.^{16,20,21}

Fibre

Fibre is a heterogeneous group of plant nonstarch polysaccharides and noncarbohydrates that is resistant to digestion in the upper digestive tract. Epidemiological and experimental animal studies have been complicated by the different types and mix of actual fibres. In eight of ten case-control or cohort studies the risk of adenomatous polyps decreased with higher consumption of plant food.⁷ In

another combined analysis of 13 case-control studies, risk decreased with fibre intake increase in 12 of 13 studies examined.²² Fibre may act by increasing bulk (and decreasing carcinogen concentration), reducing transit time (and thus carcinogen exposure time), or through its bacterial fermentation products — short chain fatty acids.

Vegetables and fibre

Case-control and cohort studies have shown more consistent protection from vegetables than from cereals,⁷ but this may be due to nonfibre vegetable components such as phytonutrients. Vegetable intake seems particularly important, especially from cruciferous vegetables, which includes bok choy, broccoli, brussels sprouts, cabbage, cauliflower, Chinese cabbage, collards, kohlrabi, mustard greens, swedes and turnips. The results of antioxidant trials using betacarotene indicate that although betacarotene is the most prevalent carotenoid antioxidant in cruciferous vegetables, it does not appear to be responsible for tumour suppression. Characterising the active components of protective vegetables is one of the most promising scientific avenues of pursuit currently, given the strong epidemiological data on protection.

Guideline — fruit and vegetables	Level of evidence for protection against	
	Cancer	Adenoma
Eat five or more portions per day of a variety of vegetables and fruits all year round.	III	III

Cereal fibre: soluble or insoluble

Recent animal studies focus on the relative solubility of different cereal fibres and support the hypothesis that poorly soluble fibres, such as wheat bran, continue to be fermented throughout the colon. Short chain fatty acids including butyrate are released along the length of the colon, including the distal colon and rectum.²³ This distal region carries the highest risk for colorectal cancer in humans. The production of short chain fatty acids decreases luminal pH, inhibits bacterial enzymes capable of carcinogen production, and also acts as an important fuel for the colonocyte. Butyrate can induce differentiation in malignant cell lines, slow proliferation and increase apoptosis, and is associated with inhibition of tumorigenesis in vivo. Butyrate can also hypermethylate DNA, counterbalancing the loss of methyl groups which is one of the early steps in the molecular progression to cancer.²

This line of basic science enquiry is supported also by those human studies that have clearly defined fibre sources. The Freudenheim et al²⁴ study of rectal cancer showed greater protection from insoluble than soluble cereal fibre, as well as fibre from vegetables. The Australian Polyp Prevention Project used 25 g wheat bran (poorly soluble) as its fibre intervention. De Cosse et al²⁵ showed an effect of Kellogg's All Bran[®], which is also wheat bran derived, in patients with familial adenomatous polyposis in a randomised control trial.

The World Cancer Research Fund report,⁴ while recognising a protective effect of cereal fibre, deemphasised the effect. The report did not take into account the more rigorous proof afforded by randomised controlled trials, which increase substantially the quality of supporting evidence in evidence-based assessment.

Guideline — fibre	Level of evidence for protection against	
	Cancer	Adenoma
Select poorly soluble cereal fibres (eg wheat bran), especially if at high risk of colorectal cancer.	III	II

Fruit and fibre

In contrast to the data for vegetable fibre, evidence for a protective effect from fruits is more limited and inconsistent both for colon and rectal cancer, and for adenomas.

Resistant starch

Attention has focused on the possible benefits of those carbohydrates escaping digestion in the small intestine. Although animal data from rat studies have not been supportive, ecological studies suggest otherwise.²⁶ The short chain fatty acid hypothesis should hold as well for resistant starch as for fibre. However, the way in which various forms of resistant starch behave with respect to fermentability in the colon is under active investigation. Strains of maize and wheat have been genetically engineered to resist digestion and promise protective benefit. One such product is under clinical trial in familial adenomatous polyposis and another in hereditary nonpolyposis colorectal cancer (CAPP1 and 2 respectively).

2.1.2 Micronutrients

Calcium and vitamin D

Early studies suggested a modest protective effect for the development of colorectal tumours in the presence of a high calcium diet; however recent analyses do not show a significant effect.^{27,28} Dietary vitamin D appears to have no effect on colorectal tumour development, although most vitamin D is sun related.

Adults should be advised to bring their calcium intake to 1000–1200 mg per day in keeping with general dietary guidelines. No special recommendations can be made at present regarding dietary calcium intake for colorectal cancer prevention over and above this guideline.

Guideline — calcium	Level of evidence for protection against	
	Cancer	Adenoma
Ensure a dietary calcium intake of 1000–1200 mg/day.	III	III

Folate

Folate (folic acid, folacin) is abundant in wheat bran, baker's yeast, cruciferous vegetables and spinach.²⁹ Low folate diets are a risk for colorectal adenomas and colorectal cancer especially in habitual alcohol consumers. Low folate diet enhances the development of chemically-induced colon cancers in rodents.²⁷

This evidence supports recommending a high vegetable diet which includes a high consumption of cruciferous vegetables.

Phytonutrients

It is known that there are several naturally occurring compounds in foods of plant origin (vegetables, fruits and cereals) that have strong anticoloctal cancer properties and that have an independent anticancer effect over and above their fibre content.²⁷

The vegetables of particular importance include members of the brassica family (cabbage, cauliflower, broccoli, brussels sprouts), members of the allium family (garlic, onion, chives), leafy vegetables and tomatoes, as well as fruits and cereals containing carotenoids, vitamin C and vitamin E.²⁷ These phytonutrient compounds include carotenoids, vitamin C, vitamin E, folate, indoles, linolenic acid, allylic sulfides, lycopene and several others.

The evidence at present is epidemiological and underlines the need for a high and varied vegetable, fruit and cereal diet as the most important dietary protective factor for cololectal tumours.²⁷

2.1.3 Alcohol

Total alcohol intake is more consistently associated with cololectal cancer risk than specific types of alcohol.⁴

In cohort studies, significant associations between alcohol intake and risk have been found in four of five colon cancer studies; three of three rectal cancer studies; and two of three studies of colon or rectal cancer (site not distinguished). A United States cohort study of men showed a particularly strong association in individuals with low folate or methionine intakes.¹⁵

In case-control studies, significant associations between alcohol intake and risk have been found in 18 studies of colon cancer and nine of 17 studies for rectal cancer.

The effect is generally stronger in men than women. Australian studies have found the association particularly with beer drinking in men.^{30,31} Wine is less implicated, especially in women. Rectal cancer does not seem to be related to wine drinking.

Mechanisms involving solvent effects, microsomal enzyme induction of procarcinogens, inhibition of DNA repair and concurrent nutritional deficiency are largely speculative.

2.2 Nutritional supplements

Dietary micronutrients and micronutrient supplements should be differentiated, since it is very likely that whole foods will be found to have many more anticancer substances than those identified so far. For this reason, it is a good general principle to promote eating whole foods rather than advocating nutritional supplements, except in certain reasonably well-defined situations.

2.2.1 Calcium

In experimental animals, calcium binds with fatty acids protecting the colonic epithelium from their cytotoxicity. Colonic proliferation is inhibited.

Although some early human studies³² which were uncontrolled or partially controlled trials were encouraging regarding calcium supplementation, two recent randomised, double-blind, placebo-controlled studies did not affect rectal mucosal proliferative activity.^{33,34} Calcium supplementation on current evidence is unlikely to be useful in the prevention of colorectal tumours.

2.2.2 Folate

Folate supplementation protects against chemically-induced colon cancer in rats. Human studies of folate supplementation have not been conducted so far.

2.2.3 Selenium

Selenium is an essential trace element in humans. It is a part of the enzyme glutathione peroxidase which catalyses the removal of intracellular hydrogen peroxide thereby reducing the formation of oxygen radicals and the risk of oxidative damage to DNA. Deficiency of selenium may occur with diets lacking whole grains and vegetables, and from foods derived from soils low in selenium. Populations deficient in selenium have an increased incidence of, and mortality from, colorectal cancer.³⁵

Clark and co-workers from the Nutritional Prevention of Cancer Study Group performed a multicentre double-blind, randomised placebo-controlled cancer prevention trial to test if selenium supplementation decreased the incidence of carcinoma of the skin.³⁶ Among the secondary endpoints of the study were total cancer incidence and incidence of colorectal cancer. The intervention agent was 200 µg of selenium supplied as a 500 mg brewer's yeast tablet or matched placebo per day. After a total follow up of 8271 person-years, there were eight colorectal cancers in the selenium group versus 19 in the placebo group (relative risk [RR], 0.42; 95% confidence interval [CI], 0.18 to 0.95; *P* = 0.03). The total frequency of carcinomas was 59 in the selenium-treated group and 104 in the placebo group (RR, 0.55; 95% CI, 0.40 to 0.77; *P* = 0.001). The selenium dose of 200 µg per day was estimated to be approximately twice the projected typical dietary intake of these patients and was three to four times the recommended daily allowance. No dermatological signs of selenium toxicity were observed. A total of 35 patients complained of adverse effects resulting in their withdrawal from the study, 21 in the selenium group and 14 in the placebo group.

The study provides evidence that selenium supplementation provides a strong protective effect against colorectal cancer. However, because the results relating to colorectal cancer were from a secondary endpoint analysis, the effect requires confirmation in an independent trial of appropriate design before public health recommendations regarding selenium supplementation should be made.

Guideline — selenium	Level of evidence for protection against	
	Cancer	Adenoma
Selenium supplementation for chemoprevention is promising and requires confirmation.	II	

2.2.4 Antioxidants/carotenoids

One population-based case-control study of colorectal cancer found a statistically significant protective effect from the use of vitamin A and vitamin C containing supplements, an effect independent of other dietary risks.³⁰ A prospective cohort study of 35,215 Iowa women did find a protective association for highest compared with lowest quantile of vitamin E intake (RR, 0.3; 95% CI, 0.19 to 0.54).³⁷ Randomised controlled trials of the antioxidant vitamins A, C and E, and betacarotene, have attempted to decrease the production of mutagens in the stool as a way of decreasing colon adenomas and cancers, but these studies have been almost universally negative. The Dartmouth randomised intervention trial (25 mg betacarotene; 1 mg vitamin C and 400 mg vitamin E and placebo),³⁸ a Canadian trial of vitamin A and vitamin E,³⁹ the Australian Polyp Prevention Project (betacarotene) and the De Cosse interventional study in familial adenomatous polyposis (vitamins C and E) all showed no statistical benefit.

Guideline — antioxidant vitamins	Level of evidence for protection against	
	Cancer	Adenoma
Antioxidant vitamin supplementation is not advised at present to protect against colorectal cancer.	III	II

2.2.5 Phytonutrients

Specific phytonutrients which have been tested and found to have anticolo-rectal cancer properties in experimental models include indoles (cruciferous vegetables), *S*-methyl methane thiosulfonate (cruciferous vegetables); garlic extract, green tea and black tea extracts, and curcuma B supplements (from tumeric).²⁷ Epidemiologic studies are consistent with these experimental findings. At present, phytonutrient supplementation is on an experimental basis, and controlled human studies are required.

2.2.6 Fibre supplements

Commercial fibre preparations could be predicted to provide colorectal cancer protection based on their fermentability. Psyllium is poorly fermentable but clinical studies have not been published on colorectal cancer protection.

2.3 Other chemoprevention candidate agents

2.3.1 Aspirin and nonsteroidal anti-inflammatory drugs

Case-control studies

The Melbourne Colorectal Cancer Study studied 715 patients and showed that regular aspirin use was associated with a 40% lower risk of colorectal cancer.⁴⁰ Subsequently there have been at least seven further case-control studies which have consistently shown significant reduction of relative risk for those taking nonsteroidal anti-inflammatory drugs (NSAIDs) regularly.⁴¹ Typically the reduction in relative risk

would suggest that the rate of colorectal cancer is halved by regular NSAID use. However, the retrospective nature of the data collection should be noted. Further, it has been suggested that the effect was achieved because NSAID use led to gastrointestinal bleeding and then to earlier diagnosis.

This latter question was studied in a large case-control study of United States veterans where those taking aspirin for medical reasons, such as ischaemic heart disease, peripheral vascular disease or arthritis, were compared with those taking other anticoagulants for conditions such as atrial fibrillation and thrombophlebitis.⁴² Although all patients should have had an increased risk of bleeding, the results of this study indicated that only the aspirin-treated individuals had a decreased risk of colon cancer.

Cohort studies

Prospective data regarding NSAID intake and subsequent development of colorectal cancer or polyps in the general population have been collected in at least eight studies to date. The initial study performed by Paganini-Hill et al⁴³ actually showed no protective effect. However, all subsequent studies have shown protection, with the relative risk being at 0.6 or lower.

The most significant prospective study of aspirin use and colorectal cancer was performed by Thun and colleagues for the American Cancer Society.^{44,45} Aspirin intake of more than 662,000 adults in the United States was documented and this cohort was then followed for seven years. Death from colorectal cancer and other causes was noted. There was an inverse relationship between the death rates from colorectal cancer and the frequency of aspirin use. A dose-response relationship was noted. For those who took 16 or more aspirin per month for at least 10 years, the relative risk of fatal colon cancer was 0.36. Overall, for those taking aspirin 16 or more times a month for at least a year, the relative risk was 0.60 for men (95% CI, 0.40 to 0.89) and 0.58 for women (95% CI, 0.37 to 0.90). Of additional interest in this study was the finding that other gastrointestinal cancers were also reduced. The relative risk of gastric cancer was found to be 0.53 with frequent aspirin use, and the relative risk of oesophageal cancer was 0.59. Given the large size and prospective design of the study, and the presence of a dose-response relationship, this study strongly supports the view that NSAIDs have a protective effect against gastrointestinal malignancies.

In view of these data it is not surprising that patients with rheumatoid arthritis show a reduced likelihood of colorectal cancer. Prospective cohort studies from Finland and from Sweden have demonstrated that the likelihood of developing colorectal cancer is 30–40% lower in patients with rheumatoid arthritis than in the general population.^{46,47} Adenomatous polyps are also reduced by aspirin. Greenberg and associates reported that of 793 patients who had adenomatous polyps, those who reported any use of aspirin had, at the end of a one-year period, a 48% lower incidence of recurrent polyps than those who used no aspirin.³⁸

Two large prospective cohort studies have been performed by Giovannucci et al.^{48,49} In the Harvard Health Professionals Study,⁴⁸ 47,900 men who were regular users of aspirin (that is, at least twice per week) had a lower risk for colorectal cancer in general (RR, 0.68), and for metastatic or fatal colorectal cancer in particular (RR, 0.51). Adjustment for multiple other variables did not change this association. In the Nurses Health Study,⁴⁹ 551,000 female nurses who documented dose and duration of aspirin

use were followed for eight years. Although small benefit was seen with lesser duration use, those who were regular users of aspirin over a 10–20-year period demonstrated greatest benefit, with a reduction of relative risk to 0.56.

Randomised controlled trial

There has been one prospective randomised clinical trial of aspirin intervention. The United States Physicians Health Study was primarily designed to assess the benefit of aspirin use (325 mg every other day) in the prevention of cardiovascular disease.⁵⁰ Male physicians were randomised for treatment by aspirin or placebo during a 4.7-year period. No benefit from the aspirin treatment was evident from this study (RR, 1.15). The findings are difficult to interpret because of the relatively brief duration of therapy, the low dose of aspirin, and the failure to exclude polyps or cancer at the start of the study. Given a probable presymptomatic phase for colorectal cancer of five to 10 years, treatments initiated at less than five years are unlikely to show benefit.

Summary of epidemiological studies

In summary, the current pool of epidemiological studies provides strong evidence that a 40–50% reduction in colorectal cancer could be anticipated from regular aspirin or NSAID use. The studies however are not consistent. The one prospective randomised study failed to show a benefit and there is a lack of sufficient detail regarding dosage, duration, age for recommended onset, and options regarding different NSAIDs. This latter requirement is crucially important because, in the end, the appropriateness of NSAID chemoprevention will depend largely on the balance between toxicity and benefit.

The risk–benefit ratio for aspirin/NSAID prophylaxis will be more favourable for individuals at high risk for colorectal cancer, but is still difficult to quantify. Adenomatous polyposis coli (APC) and hereditary nonpolyposis colorectal cancer (HNPCC) gene carriers are currently participating in randomised controlled trials on the basis of improved risk–benefit ratio, but results are unavailable. One of the likely mechanisms for the effects of NSAIDs in reducing the risk of colorectal cancer is via inhibition of cyclo-oxygenases (cox-1 and cox-2), which catalyse the formation of prostaglandins. Selective cox-2 inhibitors, which do not have the side effects of classical NSAIDs, have been developed.⁵¹ Future trials will determine if these can replace aspirin and NSAIDs as chemopreventive agents in colorectal cancer.

Guideline — anti-inflammatory drugs	Level of evidence for protection against	
	Cancer	Adenoma
Aspirin and nonsteroidal anti-inflammatory drug chemoprevention is consistently protective in case-control and cohort studies, but is not recommended until dosage and balance between risk and benefit is evaluated in randomised controlled trials.	III	III

2.3.2 Other agents

Hormone replacement therapy

Three of six studies reporting on oestrogen replacement therapy and colorectal cancer risk have shown a reduction in risk whereas none have shown an increase in risk.^{4,52}

Difluoromethylornithine (DFMO)

DFMO inhibits ornithine decarboxylase, an essential enzyme in the process of proliferation. Multiple lines of evidence propel DFMO into chemopreventive candidature but loss of hearing acuity has emerged as a serious drawback to its use in human trials.

Oltipraz

Oltipraz is a compound related to dethiolthionines, which are found in cruciferous vegetables. It is already in use as an antischistosomiasis agent. Oltipraz has reached human clinical trial stage as a chemopreventive agent.

Ursodeoxycholic acid

Ursodeoxycholic acid is a 'trace' bile acid normally present in humans, but it is dominant in bears. It can neutralise the toxic effects of bile and it is under clinical trial in adenoma prevention trials.

HMG-CoA reductase inhibitors

HMG-CoA reductase inhibitors inhibit tumorigenesis in animal models. Their effect on risk of colorectal cancer should emerge from large trials of these agents currently in progress for patients with cardiovascular disease.

Other agents

Other agents under investigation at present, some of which are emerging into clinical trials, are green tea extracts, magnesium hydroxide, curcumin and tumeric, the soy extract genistein and vitamin D.

2.4 Physical activity

The evidence that physical activity protects against colon (as distinct from rectal) cancer is strong and convincing. Seven of nine cohort studies, and 10 of 11 case-control studies show protection⁵³. Occupational studies (reflecting physical activity status) are also consistent. Various mechanistic hypotheses (stimulation of transit, and immune and hormonal changes function) are postulated. The data for rectal cancer are not consistent.^{4,27}

Guideline — physical activity	Level of evidence for protection against	
	Cancer	Adenoma
Be physically active to protect against colon cancer.	III	

2.5 Smoking

Of 51 case-control or cohort studies, 22 show a 50% increase in risk from smoking, and 10 are statistically significant. The evidence is stronger for rectal than colonic cancer, and risk is increased for those who have smoked for a longer period. Data are even more consistent for adenomas: 22 of 27 case-control or cohort studies show at least a 50% increase. Nineteen are significant and nine of 10 have a positive dose response.²⁷ Thus, the main effect of smoking seems to occur early in the process, during adenoma formation.

Guideline — smoking	Level of evidence for protection against	
	Cancer	Adenoma
Avoid smoking.	III	III

2.6 Conclusion

The guidelines and recommendations espoused in this chapter fit into what is currently recommended as a healthy lifestyle in general, with some special emphasis on certain aspects of colorectal cancer prevention which suit certain high-risk groups. It is worth reiterating that appropriate dietary changes, together with regular physical activity and maintenance of healthy weight, could, in time, substantially reduce the incidence of colorectal cancer.

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CHAPTER 3

POPULATION SCREENING FOR COLORECTAL CANCER

The biology of colorectal cancer provides the opportunity for a variety of techniques for primary prevention and early detection. Progression from the precancer phase through the various stages of cancer is normally spread over a number of years.¹ *Certainly, the cancer is potentially curable in its early stages.*¹

3.1 Age as a risk factor

The risk of colorectal cancer increases with age, as shown in Table 3.1 in absolute terms for the general population.

Table 3.1 Absolute risk of colorectal cancer

If a person is aged:	Risk over the next...			
	5 years	10 years	15 years	20 years
30	1 in 7000	1 in 2000	1 in 700	1 in 350
40	1 in 1200	1 in 400	1 in 200	1 in 90
50	1 in 300	1 in 100	1 in 50	1 in 30
60	1 in 100	1 in 50	1 in 30	1 in 20
70	1 in 65	1 in 30	1 in 20	1 in 15
80	1 in 50	1 in 25		

Note: Absolute risk is the observed or calculated likelihood of the occurrence of an event in a population under study.

Source: AIHW 1996²

The table gives only the absolute risk for an average member of the population. If that person develops symptoms, obviously his or her risk will increase until the cause of the symptoms is clarified.

Similarly, if a person has a relative who has or who develops colorectal cancer, that person's risk is modified in accordance with the categories outlined in Chapter 6.

For example, a 50-year-old woman with no family history of colorectal cancer is at about *average risk*. As shown on the table, her chance of developing colorectal cancer is about 1 in 300 over the next five years, and 1 in 30 over the next 20 years.

If her father were diagnosed with colorectal cancer at age 68 (that is, 55 years or older), that would place her in the second part of category 1 (see Chapter 6). Her *risk approximately doubles* to 1 in 150 over the next five years and 1 in 15 over the next 20 years.

If her grandmother as well as her father had colorectal cancer, or if her father was diagnosed at age 48, that would place her in category 2. Her risk would be *three to six*

times average. It would be between 1 in 100 and 1 in 50 over the next five years; and between 1 in 10 and 1 in 5 over the next 20 years.

3.1.1 Age as a determinant of screening

Recent randomised controlled clinical trials at the population level indicate that screening tests based on faecal occult blood, in populations selected on the basis of age, reduce overall mortality from colorectal cancer.³

The question of screening for colorectal cancer in Australia has been systematically reviewed in a report from the Australian Health Technology Advisory Committee (AHTAC).³ The committee's deliberations are summarised in Box 3.1 at the end of this chapter. In brief, the report concluded that the efficacy of screening based on the faecal occult blood test (FOBT) has been demonstrated, but that the best approach to mass screening of the Australian population has not yet been defined and pilot studies are warranted.⁴⁻⁶ Assuming this is established, issues such as recruitment, participation and compliance, quality assurance, assessment, and potential adverse physical effects would need to be considered.

3.1.2 Potential psychological consequences of screening

A further important consideration is the role of adverse psychological effects on individuals. Potential adverse psychological effects associated with screening for colorectal cancer range from the trauma of identification of disease in symptom-free, healthy individuals through to stress among people in whom cancer is suspected but later discounted, to the more subtle concerns of participants during the screening process.⁷ Health care professionals must recognise the potential adverse psychological effects of screening.

3.2 The asymptomatic patient aged 50 or over

The individual asymptomatic subject aged 50 or over who has concerns about the possible presence of colorectal cancer presents a particular situation that warrants careful consideration.

Where the issue of prevention or risk for colorectal cancer is raised in a subject over 50, the following procedure is recommended:

1. Take a thorough history focusing on risk factors, namely:
 - symptoms;
 - family history;
 - individual history of colorectal adenomas (note that not all polyps are adenomas and not all adenomas pose a risk);
 - individual history of colorectal cancer; and
 - individual history of inflammatory colorectal disease (eight or more years).

While diet is a risk factor for colorectal cancer, it is not clear at this stage how a simple dietary history can reasonably quantify risk and determine further action.

2. Perform a physical (including abdominal) examination looking for:
 - palpable abdominal masses or enlarged liver; and
 - low rectal cancer (digital rectal examination) — note that this will detect approximately 35% of rectal cancers but less than 10% of all colorectal cancer.
3. Once it is clear that there are no relevant risk factors apart from age, and the person is otherwise healthy, the following sequence is appropriate:
 - explain to the person their absolute and relative risk for colorectal cancer using the information provided above;
 - providing the person desires to proceed with preventive measures, explain what constitutes a healthy diet;
 - explain the nature and value of the screening tools available; and
 - indicate that it is acceptable to undertake a screening test because such tests have been demonstrated to reduce mortality.

3.2.1 Screening for colorectal cancer

The screening process is a sequence of risk refinement leading to a final decision as to whether or not one should undertake the definitive diagnostic test.

More specifically, the approach is to use a simple, affordable and acceptable screening tool or test to identify whether a particular individual is more likely to have a significant lesion such as an adenoma or cancer (preferably early stage and curable) in whom it is justifiable to go ahead and perform an invasive, perhaps slightly risky, diagnostic test such as colonoscopy.³ In the context of the present discussion, the case is already predicated on an individual living in a high-risk country such as Australia, having reached an age where the chance is increasing (namely 50 years), and conditions indicating high risk having been excluded.

In this context, the simple, affordable and acceptable screening tool could be an FOBT or sigmoidoscopic examination (flexible or rigid).

Faecal occult blood testing

Two main types of faecal occult blood test (FOBT) are available³ — guaiac tests and immunochemical tests. Guaiac tests are based on the pseudoperoxidase activity of haem. Immunochemical tests utilise antibodies against human haemoglobin.

In screening programs, a person with a positive FOBT has a 30–45% chance of having an adenoma and a 3–5% chance of colorectal cancer.³

Traditional guaiac tests (Hemoccult[®]) will detect 40–80% of asymptomatic colorectal cancer.³ In other words, a Hemoccult test will miss at least 20% of colorectal cancer under ideal testing conditions, and it can miss in excess of 50% if the appropriate protocol is not followed (see below for correct usage). When dietary restrictions are followed, a test such as Hemoccult is highly specific — 98–99% of healthy subjects will have a negative FOBT.³

The newer guaiac test (eg Hemoccult SENSE[®]) and immunochemical tests (eg HemeSelect[®] and Hemolex[®]) are more sensitive than the earlier guaiac tests such as Hemoccult. Under ideal circumstances, they may detect 80–90% of cancers and

60–75% of large adenomas. Their specificity of 95–98% is slightly lower than that of the earlier guaiac tests, but immunochemical tests are not affected by diet and dietary restriction is unnecessary.

Another way to view these results is to point out that somebody with a positive FOBT is 12–40 times more likely to have a colorectal cancer than somebody with a negative test.³ **Thus, it should never be assumed that a positive test is due to dietary interference, as it may reflect bleeding from neoplasia. All positive tests need investigation and follow up.**

Guideline — population screening	Level of evidence
Reductions in mortality from colorectal cancer can be achieved through a program of population screening using faecal occult blood test.	I

Sigmoidoscopy

Sigmoidoscopy has been shown to have value in screening.

Flexible sigmoidoscopy has a higher diagnostic sensitivity than rigid sigmoidoscopy, as more colon is examined. It is capable of reaching 50–55% of colorectal cancers and a similar proportion of larger adenomas (those of 6 mm or more).³

However, controlled population studies of screening flexible sigmoidoscopy have not yet been conducted with mortality as the endpoint. There are some concerns about the acceptability of flexible sigmoidoscopy to a significant proportion of the community at large. Also, the equipment is more expensive to purchase and maintain than a rigid sigmoidoscope.

Nonetheless, a number of case-control studies have now demonstrated that subjects who undergo screening with flexible sigmoidoscopy do show a reduction in mortality.⁹ Depending on the study and the interval involved, the reduction in mortality for participants is between 50% and 80% for lesions which would be within reach of the instrument.

Provided the full process of risk evaluation and explanation defined above is followed, it is acceptable to proceed with screening. It is also acceptable to offer screening flexible sigmoidoscopy on a five-yearly basis.

It is important to advise participants that if they develop symptoms, they should seek medical advice. Also, if any risk factors become apparent, they should return for re-evaluation of their program.

The issue of occasional colonoscopy, for example at the age of 55, as a ‘once only’ screening process is controversial and not yet proven either in terms of effect on mortality, or from the perspective of cost-effectiveness. A way of directing limited endoscopic resources to those more likely to benefit is through FOBT.

Guidelines — screening asymptomatic individuals over 50	Level of evidence
<p>The minimum effective program is the performance of faecal occult blood tests (FOBT) on three serial stools at least every second year (biennially), but preferably annually. Evidence from controlled trials suggests this approach will lead to a reduction in mortality of about 40% in participants. It must be pointed out to these individuals that it is not a diagnostic test, but a selection process for those who should undergo colonoscopy. The process would be expected to detect 40–80% of cancers, depending on the actual FOBT used and the frequency of use. It is strongly recommended that the subject commit to repeating the FOBT in subsequent years. It is conceivable that a curable cancer, even if missed at the time of initial test, would be detected at the next round of screening and still be at a curable stage. Naturally, this is not guaranteed.</p>	I
<p>In addition, it is acceptable to offer screening flexible sigmoidoscopy on a five-yearly basis, as the case-control studies suggest that an interval of five years is adequate. FOBT and sigmoidoscopy are complementary in that FOBT has the potential to detect lesions proximal to the reach of the sigmoidoscope.</p>	III
<p>Provided there has been a full discussion of the risks involved, it is recommended that FOBT be performed from the age of 50 in asymptomatic individuals who do not have a positive family history.</p>	I

3.2.2 Correct usage of screening tools

It is important that screening tests be undertaken in a careful manner with attention to quality assurance and quality control, and that those conducting the tests are experienced in their use.

Faecal occult blood testing

At present, there is considerable research being undertaken to determine the most appropriate FOBT to be used. Recent evidence indicates that certain immunochemical tests are a little easier for the subject to use than the typical chemical (guaiac) tests, and they may have some clinical advantages in terms of sensitivity and specificity.

The manufacturer's instructions on how to use these tests should be followed, and it is recommended that three serial stools be tested, no matter which type of test is being used. It is mandatory that any positive FOBT (including just one of three samples) be appropriately investigated by diagnostic tests as described above.

If a subject fails to follow dietary restrictions, it is dangerous to assume that a positive result is a result of dietary noncompliance.

Where guaiac tests are to be used, then the following straightforward dietary requirements are indicated.³ They are not required for the immunochemical tests. The modifications involve exclusion of:

- red meat (beef, lamb);
- rockmelon (cantaloupe) and other melons;
- raw turnips, raw radishes (especially horseradish) and raw broccoli or cauliflower;
- vitamin C supplements, which can produce false negative results; and
- aspirin or anti-inflammatory drugs (except low doses for cardiovascular indication and provided it is clinically feasible), which can produce low-grade gastric bleeding.

Patients should start the modified diet three days before they take the first faecal sample, and continue the diet through the testing period.

Delaying the development of the guaiac test for 72 hours after the patient has sampled the stools can further minimise the possibility of plant peroxidases causing false positive reactions.⁹ It may also avoid the need to restrict specific fruits and vegetables.

Sampling stools

Participants should be given sample cards/devices in order to take the faecal sample themselves. Several precautions are necessary because haem and haemoglobin degrade in moist faeces, and because haemoglobin may be leached out of stools by toilet bowl water.

1. Sample the stool from a normally passed bowel action. Avoid contamination with water by, for example, putting a paper towel or plastic wrap on top of the water in the bowl.
2. Sample from the surface or where you think blood might be present.
3. Prepare a thin smear, which will dry quickly, on the specimen card.
4. Follow the manufacturer's instructions if you use other types of test kit — such test kits should stabilise the haem or haemoglobin.
5. Sample at least three stools, as bleeding may be intermittent.

Reading of results

The FOBT is generally thought to be simple, but inexperienced readers may miss faintly positive results.¹⁰ It is important to read guaiac tests in a good light. Any blueness, no matter how transient, signifies a positive test.

Performing flexible sigmoidoscopy

It is obviously important that screening endoscopic examinations be carried out under optimal conditions by appropriately experienced endoscopists. Patients should be advised that this procedure is quite simple, does not require bowel washout or elaborate preparation (although an enema is needed) and does not require sedation. It has been demonstrated to be acceptable to participants and can involve only a small disruption to the normal working day.

Box 3.1

Recommendations of the Australian Health Technology Advisory Committee on Colorectal Cancer Screening, 1997³

1. On the basis of published evidence, and subject to favourable preliminary testing, it is recommended that Australia develop a program for the introduction of population screening for colorectal cancer (CRC) by faecal occult blood testing (FOBT) for the average risk population (well population aged over 50).
2. Given the uncertainties relating to the most effective means of implementing such a program and to the feasibility, acceptability and cost-effectiveness of such a program in the Australian setting, the program should commence with preliminary testing involving a number of pilot and feasibility studies.
3. Pilot and feasibility study should investigate the effects on likely cost-effectiveness, compliance rates and safety, of varying the upper age limit of the population offered screening.
4. Pilot and feasibility studies should investigate:
 - which method(s) of FOBT achieves the best balance between sensitivity, specificity and costs; and
 - whether the detection rate of significant lesions is improved by the addition to FOBT of other screening modalities such as flexible sigmoidoscopy or double contrast barium enema, and if so, what is the effect of such an addition on the participation rate, feasibility and likely cost-effectiveness of the program.
5. At this time, there is insufficient evidence either to accept or reject screening for colorectal cancer using other modalities. Further investigation of the relative effectiveness of alternative approaches should be encouraged.
6. Pilot and feasibility studies should investigate the effect of frequency of testing (annual or biennial) on compliance rates and likely cost-effectiveness.
7. Pilot and feasibility studies should investigate the best method of achieving high quality and efficient follow up of positive FOBT.
8. It is recommended that data are obtained through pilot and feasibility studies to determine the effectiveness of the different strategies for screening for CRC in Australia. These studies should focus on the relative advantages and disadvantages of using a program:
 - based on general practitioner testing and recall; or
 - involving a central register and recall system, with screening overseen by general practitioners; or
 - where recall and screening are carried out under a centralised system, with secondary involvement of general practitioners for information, counselling and on-going management.
9. Pilot and feasibility studies should investigate the potential workforce and resource issues relating to screening for CRC in Australia.
10. Pilot and feasibility studies should investigate whether it is possible to achieve adequate participation and compliance, detection rates and cost-effectiveness in Australia at this time.

11. Pilot and feasibility studies should investigate the most cost-effective method of consistently collecting high quality specimens, transporting them reliably and achieving high quality laboratory testing and reporting of results.
12. Pilot and feasibility studies should investigate the magnitude and significance of the adverse physical and psychological effects of the screening program.
13. It is recommended that one or more steering groups should be established to develop, in coordination with the State anti-cancer councils, programs for education of the public and medical profession.
14. It is recommended that one or more steering groups be established to:
 - oversee the planning of the pilot and feasibility studies relating to population screening of the average risk population;
 - oversee the development and coordination of programs and registers for the high-risk population;
 - regularly review the scientific international and national literature relating to potential further developments in the field for possible incorporation into the program; and
 - evaluate the success and acceptability of the pilot program(s).
15. Subjects at high risk of CRC should be identified and individualised programs of surveillance developed.
16. A nationally coordinated approach to familial adenomatous polyposis (FAP) is required with a systematic program for identification, genetic testing, counselling, endoscopic surveillance and treatment of affected individuals.
17. A nationally coordinated program should be developed for hereditary nonpolyposis colorectal cancer (HNPCC) based on services for affected families, including registries of affected persons, counselling, genetic testing, endoscopic surveillance and treatment of affected individuals.
18. One or more steering groups should be established to oversee the development and coordination of programs and registers for the high-risk population.
19. People with one first-degree relative diagnosed over age 55 with CRC should be managed in the same way as the general population, as there is currently insufficient evidence to accept or reject the use of sigmoidoscopy in surveillance for this age group.

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CHAPTER 4

COMMUNICATION WITH THE PATIENT

4.1 The initial consultation

Patients and their carers often seek information about their cancer at the time of diagnosis, but studies have shown that only part of the initial consultation is remembered.¹ Therefore, the provision of information should not end with the initial consultation. Patients and their families and carers should be given time to assimilate information and the opportunity to ask questions at a subsequent visit. It is not necessary to make all treatment decisions at the initial consultation. Interpreter services should be ensured for nonEnglish-speaking patients. The interpreter should be a professional and not a family member.

4.2 Breaking bad news

Breaking bad news in language the patient understands should be the responsibility of the senior clinician. It should not be delayed unduly and, wherever possible, it should take place privately. A qualified and appropriate interpreter is important if the patient does not understand English.

The NHMRC recommends the following approach, adapted from the New South Wales Cancer Council²

- give bad news in a quiet, private place
- allow enough uninterrupted time in the initial meeting
- assess the individual's understanding
- provide information simply and honestly
- encourage individuals to express feelings
- respond to individual's feelings with empathy
- give a broad time-frame for the prognosis
- avoid the notion that nothing can be done
- arrange a time to review the situation
- discuss treatment options
- offer assistance to tell others
- provide information about support services
- provide documented information

4.3 How much should the patient be told

There is evidence to suggest that most cancer patients wish to be fully informed of all available information, and they usually want a close relative or friend present at the initial interview.³ They report that subsequent discussions about actions to be taken

and what the diagnosis means, are at least, if not more, important than the disclosure of the initial diagnosis.⁴ Cancer patients appreciate and use communication aids such as audiotapes or personalised letters from the consultation when these are available.⁵ An assessment of a patient's previous experiences and expectations is needed so that information giving can be individualised. The terminology used in communicating about cancer affects patient anxiety. Vagueness and obscurity make a difficult situation worse.⁶

The NHMRC states that patients are entitled to make their own decisions about treatments or procedures and should be given adequate information on which to base those decisions.

- Information should be provided in a form and manner which helps patients understand the problem and treatment options available, and which is appropriate to the patient's circumstances, personality, expectations, fears, beliefs, values and cultural background.
- Doctors should give advice, but should not coerce.
- Patients should be encouraged to make their own decisions.
- Patients should be frank and honest in giving information about their health, and doctors should encourage them to be so.⁷

Guidelines — patient information	Level of evidence
<p>Information for patients with colorectal cancer should include:</p> <ul style="list-style-type: none"> • causes of colorectal cancer and the extent of disease; • proposed approach to investigation and treatment, including information on expected benefits, the process involved, common side effects, whether the intervention is standard or experimental and who will undertake the intervention; • the likely consequence of choosing a particular treatment, or no treatment; • the time involved; • the costs involved; • the effect of cancer and its therapy on interpersonal and sexual relationships; • typical emotional reactions; • appearance after surgery; • how to obtain special items such as colostomy devices and wigs; • entitlements to benefits and services, such as subsidies for travel or prostheses; and • access to cancer information services. 	–

4.4 Keeping the patient's other doctors informed

The main method of communication between consultants and general practitioners in Australia is the letter of referral to the consultant and the reply to the general practitioner. Surveys of referring doctors show that the letters to them from the consultant should cover diagnosis, clinical findings, future tests/test results, treatment recommendations, likely side effects and prognosis.⁸

4.5 Second opinion

Patients have the right to obtain a second opinion at any time. Having a second opinion may help clarify questions, can help them decide which doctor they prefer to manage their condition and which course of treatment to follow. It can also reinforce that advice already given was accurate and enhance confidence. Doctors should cooperate fully in providing a referral and all relevant information.

4.6 Coordination of care

Treatment of colorectal cancer requires the input of multiple disciplines including clinicians with specialist knowledge in the areas of surgery, radiation therapy, chemotherapy and general practice. Coordination and continuity of care ensure high quality treatment for individuals with colorectal cancer. The choice of the person to coordinate this care should be made by the patient in conjunction with their general practitioner and specialists. The coordinator may not necessarily be a health professional but rather a well-informed friend or relative.

4.7 Clinical trials

Clinical trials are essential to finding better treatments for colorectal cancer. In Australia, clinical trials are conducted on a large scale through national and international collaborations. They are designed to define optimum management programs and test appropriate modifications to these programs. Doctors should encourage patients with colorectal cancer to consider participating in appropriate clinical trials for which they are eligible. Protocols should be approved by appropriate ethics committees. Patients must be provided with relevant and complete information about the trial protocol and must provide their written consent before taking part.

Guideline — clinical trial participation	Level of evidence
Doctors should encourage patients with colorectal cancer to consider participating in appropriate clinical trials for which they are eligible.	–

4.8 Quality of life

Up to 50% of patients report psychological distress, depression or anxiety following a diagnosis of colorectal cancer.⁹ The prevalence of psychological dysfunction is greater for those with stomas as compared to patients with intact sphincters. Anxiety and depression levels tend to decline, and overall quality of life improves in the months following treatment.¹⁰ Psychological dysfunction associated with loneliness, stigma and low self-esteem and disturbed body image are also reported and more prevalent in stoma patients than in nonstoma patients.^{11,12} In general, the psychological functioning of younger, female patients is more impaired than that of older male patients.¹¹ Patients reporting psychological distress function less well in their usual roles and activities than patients without distress.¹⁰

Colorectal cancer and its treatment clearly can have adverse effects on social functioning, including work and productive life, relationships with friends, relatives, and partners, and other social activities and interests.¹³ Although both stoma patients and nonstoma patients report restrictions in their level of social functioning, such problems are more prevalent among stoma patients.

Bowel function usually improves and stabilises during the first year following surgery, although bowel problems may persist.¹⁴ Both stoma and nonstoma patients report frequent bowel movements.^{12,15} Stoma patients report more problems with gas and urinary function, whereas patients with intact sphincters report more constipation.

The overall prevalence of sexual dysfunction is consistently higher in stoma patients than in patients with intact sphincters (66–100% compared with 30–75% respectively).^{15,16} The principal sexual problems in men pertain to erectile function and ejaculation.

Abdominoperineal resection appears to result in most severe reduction of sexual activity and functioning. Based on the few studies that have assessed female sexual functioning, sexual dysfunction (dyspareunia, cessation of sex) is also more prevalent among female stoma patients than among female nonstoma patients.^{15,17} It is estimated that one fifth of women who have stomas suffer from dyspareunia. Body image problems appear to be greater in women.

Guidelines — quality of life	Level of evidence
Quality-of-life measurements must be integrated into future studies of treatment for colorectal cancer.	—
Physicians involved in the management of patients with colorectal cancer should be aware of the potential impact of treatment on quality of life and should include this in the decision making.	III
Patients need to be informed of the likely impact of treatment alternatives on their quality of life.	III

4.9 Counselling and support

There is evidence that some cancer patients who receive psychological support in formal treatment groups experience psychological benefit as a result.^{18,19} Appropriate counselling has the potential to improve quality of life.¹⁸

A number of people involved in the patient's care may be involved in providing counselling and support in either a formal or informal manner. These can include family, friends, doctors, nurses, and other health care professionals or a cancer support service (a national telephone contact number for all such services is **13 11 20**; or **1300 361 366** in Queensland). These services provide peer and professional support to people with cancer. This support may be specific, for example, an ostomy support group, or general, and is usually coordinated by volunteers.

Educational pamphlets are available from regional cancer councils and are particularly informative for individuals with stomas and their carers.

Enterostomal therapy nurses are usually hospital based and are an important resource for patients who require a stoma. Services provided by them include preoperative counselling and teaching, selection of stoma site, selection of skin care and pouching systems, postoperative patient teaching and long-term follow up for rehabilitation.

Sexual counselling may be appropriate for selected patients, and can be provided by trained enterostomal therapy nurses and/or referral to sexual and relationship counsellors. Sperm storage should be considered in men undergoing rectal surgery where fertility is an important consideration.

Guidelines — support	Level of evidence
Support needs for individuals with colorectal cancer and their families may include: <ul style="list-style-type: none">• counselling, including sexuality and fertility• access to a cancer support service and/or ostomy support group• education and assistance with stomal therapy• assistance with care of children or other family members• assistance with transport• dietary advice	—

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CHAPTER 5

THE PATIENT WITH SYMPTOMS

There are three main sets of symptoms and signs that raise the possibility of colorectal cancer. They are:

- certain nonspecific bowel or abdominal symptoms
- iron deficiency anaemia
- rectal bleeding

This chapter provides guidance on how these situations might be approached, with the goal of reducing morbidity and mortality from colorectal cancer.

5.1 The patient with bowel or abdominal symptoms

The principal relevant symptoms include:

- bleeding from the rectum, mixed with or separate from the faeces ('rectal bleeding')
- symptoms of anaemia
- a change in bowel habit, especially a recent one
- abdominal pain, especially if of recent onset

Other symptoms may be the presenting complaint such as bloating, loss of weight, malaise or mucus in the faeces. While each of these symptoms can be associated with more common and relatively benign conditions such as irritable bowel syndrome or haemorrhoids, it should not be assumed too readily that this is the case.¹ This can make the decision about when to investigate quite difficult. Age over 40 years, and recent onset of symptoms (say within the last 6–12 months) should raise suspicion for colorectal cancer. Although uncommon, colorectal cancer can occur below the age of 40 and persistent symptoms in younger people demand full investigations. In addition, the presence of any risk factors for colorectal cancer should also raise the level of suspicion. These risk factors are:

- age
- a personal history of colorectal cancer or adenoma
- a family history of colorectal cancer or adenoma
- a personal history of inflammatory bowel disease²

Rectal bleeding is the most important symptom. It is not possible to be certain from the patient's description of the bleeding that it necessarily originates from a simple lesion such as haemorrhoids, rather than a colorectal adenoma or cancer. Indeed, lesions such as haemorrhoids may coexist with colorectal cancer.

An Australian survey has shown that a high proportion of adults never examine their stools, the toilet paper, or the toilet bowl adequately to be able to identify whether or not blood is present.³ Prompt medical attention for rectal bleeding does facilitate earlier diagnosis of colorectal cancer.³

Rectal bleeding requires investigation, especially when it is of recent onset (within the previous 6 to 12 months). However, the patient should be reassured that the cause is likely to be benign.

People over 40 years of age should be encouraged to look for blood with the bowel motions on a regular basis.

5.1.1 Investigation

Investigation must be tailored to the circumstances. It is re-emphasised that recent onset of symptoms in a patient over 40 years of age raises the index of suspicion for colorectal cancer and investigation is important in this situation.

Guidelines — investigation	Level of evidence
When a decision is made to investigate, it is appropriate to perform a thorough examination of the anus, rectum and colon. Proctosigmoidoscopy is helpful, as this enables haemorrhoids to be more easily identified. If actively bleeding haemorrhoids or another obvious anorectal cause for bleeding is found, one needs to be very careful in attributing the bleeding to that source, even if the anorectal lesion is treated.	III
Colonoscopy is the investigation of choice, but air contrast barium enema and sigmoidoscopy is an alternative to colonoscopy. Barium enema must be included with colonoscopy if colonoscopy is incomplete. See Chapter 8 for a more detailed discussion.	III

5.2 The patient with iron deficiency anaemia

There is always a cause for iron deficiency and, in nonmenstruating patients, gastrointestinal bleeding is the most common pathophysiology.⁴ It is usually occult. In nonmenstruating patients over 40, colorectal cancer is a common cause.⁵

It is important to confirm iron deficiency before embarking on gastrointestinal investigation. In this context, an isolated low serum ferritin is not adequate evidence,⁴ and it needs to be confirmed by microcytosis or low iron saturation and other abnormalities in iron studies.

Investigation of patients with iron deficiency must include full colonic evaluation. Colonoscopy is preferred, as lesions such as angiodysplasia are not recognisable by radiology. If colonoscopy is incomplete or unavailable, an air contrast barium enema is required.

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CHAPTER 6

SCREENING BASED ON FAMILY HISTORY (FAMILIAL CLUSTERING) OF COLORECTAL CANCER

Colorectal cancer occurs in some families more than others.¹⁻⁷ It is possible to divide the population's risk of colorectal cancer into three main categories, according to relative risk, for unaffected members of the family. These categories are below.

6.1 Taking a family history

Experience demonstrates that accurate and complete family histories are rarely taken. As family history is a significant determinant of risk for colorectal cancer and of the required investigative action, it is important that the information gathered is accurate. It may be necessary to get more detailed information from other family members, from death certificates or from medical records.

6.2 Quantifying risk based on family history

Individuals can be placed in one of three categories of relative risk based on their family history (see also Table 6.1).

Category 1 — those at or slightly above average risk

This covers about 98% of the population. Asymptomatic people fit into this category if there is:

- no personal history of colorectal cancer or ulcerative colitis and no confirmed family history of colorectal cancer; or
- one first-degree or second-degree relative with colorectal cancer diagnosed at age 55 or older.¹⁻⁶

In the latter case, relative risk may be up to *double* the average risk,⁵ but this risk is expressed after the age of 60.

Category 2 — those at moderately increased risk

This covers 1–2% of the population. Asymptomatic people fit into this category if there is:

- one first-degree relative with colorectal cancer diagnosed before the age of 55 years (without the potentially high-risk features listed below); or
- two first or second-degree relatives on the same side of the family with colorectal cancer diagnosed at any age (without the potentially high-risk features listed below).⁵⁻⁷

Relative risk in these cases is increased *three to six-fold*.

Category 3 — those at potentially high risk

This covers less than 1% of the population. Asymptomatic people fit into this category if there are:

- three or more first or second-degree relatives on the same side of the family diagnosed with colorectal cancer (suspected hereditary nonpolyposis colorectal cancer, or HNPCC).
- two or more first-degree or second-degree relatives on the same side of the family diagnosed with colorectal cancer, including any of the following high-risk features:
 - multiple colorectal cancers in the one person
 - colorectal cancer before the age of 50 years
 - at least one relative with endometrial or ovarian cancer (suspected HNPCC);
- at least one first-degree or second-degree relative with colorectal cancer, with a large number of adenomas throughout the large bowel (suspected familial adenomatous polyposis or FAP);
- somebody in the family in whom the presence of a high-risk mutation in the adenomatous polyposis coli (APC) or one of the mismatch repair (MMR) genes has been identified.^{8–11}

The relative risk for people in these groups, without genetic testing, reaches a maximum lifetime risk of 1 in 2. The risk may rise even further if such people are shown to have a high-risk mutation.

The approach to managing people in category 3 will be considered in detail in Chapter 7.

Table 6.1 Familial clustering of the common forms of colorectal cancer

Family history	Relative risk
One first-degree or second-degree relative with colorectal cancer diagnosed at 55 or over (category 1)	up to 2-fold
One first-degree relative with colorectal cancer diagnosed under 55 (category 2)	3 to 6-fold
Two first-degree or second-degree relatives on the same side of the family with colorectal cancer diagnosed at any age (category 2)	3 to 6-fold

Note: Relative risk is the ratio of the risk of getting colorectal cancer in a particular exposed group to the average risk in the whole population (cf absolute risk; see Table 3.1).

6.3 Category 1 risk — those at or slightly above average risk

This covers the majority of familial occurrence of colorectal cancer.

The yield of surveillance colonoscopy in subjects having just one affected relative, diagnosed when 55 years or older, is low.^{12–16}

A number of national bodies, including the Australian Gastroenterology Institute, the Australian Cancer Society, the American Cancer Society and the American Gastroenterological Association, do not consider the slight increase in degree of risk for this group, namely an increase of up to twice the average risk, justifies a more intensive screening program than that recommended for the general population.¹⁷⁻¹⁹ While further deliberations are required on this matter, an Australian Health Technology Advisory Committee (AHTAC) Working Party concluded that people in this category should be treated as for the standard-risk population.²⁰

Guidelines — screening (category 1 risk)	Level of evidence
Faecal occult blood testing annually from the age of 50.	See Chapter 3 and AHTAC recommendations (Box 3.1)
Consider sigmoidoscopy (preferably flexible) every five years from the age of 50.	See Chapter 3

6.4 Category 2 risk — those at moderately increased risk

In these people, the risk for colorectal cancer *is increased approximately 3 to 6-fold*.⁵⁻⁷ Members of such families have a moderately increased risk of colorectal cancer, but 70-90% of people in this group will never get colorectal cancer.

It is recommended that these people be referred for colonoscopy at five-yearly intervals from age 50, or 10 years younger than the age of the earliest diagnosis of colorectal cancer in the family, whichever comes first.^{9,11-13,16-19}

It is important to point out that colonoscopy is not totally without risk as it is an invasive procedure. The risks associated with screening colonoscopy are low: in one study, perforation occurred at a rate of 4 in 12,000, serious bleeding at a rate of 11 in 12,000, while there were no deaths.²¹ The risks would be largely associated with polypectomy.

If colonoscopy is unavailable, then it is appropriate to offer flexible sigmoidoscopy (or rigid sigmoidoscopy if the latter is unavailable) and double-contrast barium enema.²⁰ It is worth considering annual FOBT in the intervening years as a few studies have demonstrated that this occasionally picks up interval or missed cancers. It also has the benefit of keeping subjects associated with the ongoing program.²⁰

A number of steps are important in managing people within this group.

1. A complete family history should be taken and the accuracy of the diagnoses checked carefully.
2. People at category 2 risk should be advised that, at present, genetic testing is not appropriate. Genetic testing should be considered when any of the Bethesda criteria²¹ are met (see Chapter 7, Table 7.1).

3. As with all forms of surveillance screening, the patients should be carefully checked for the presence of symptoms that might be due to colorectal cancer. Where these are present, appropriate diagnostic steps should be taken and entrance into a screening or surveillance program deferred.
4. As with patients at normal risk, colonoscopic follow up (or sigmoidoscopy plus double-contrast barium enema if colonoscopy is unavailable) is necessary.²⁰

Guidelines — screening (category 2 risk)	Level of evidence
Offer colonoscopy every five years starting at age 50, or at an age 10 years younger than the age of first diagnosis of colorectal cancer in the family, whichever comes first. Sigmoidoscopy plus double-contrast barium enema is an acceptable alternative for colonoscopy if the latter is unavailable.	III
Consider faecal occult blood testing in intervening years. Colonoscopic follow up (or sigmoidoscopy plus double-contrast barium enema if colonoscopy is unavailable) is necessary for those with a positive faecal occult blood test.	I

6.5 Category 3 risk — those at potentially high risk

Fewer than 5% of colorectal cancers occur under category 3 conditions.

Members of families with either FAP or definite or suspected HNPCC are at high risk for colorectal cancer.⁸⁻¹¹ Members of these families require careful surveillance and consideration for genetic testing. See Chapter 7 for details.

People with three (or more) relatives with colorectal cancer may be difficult to categorise, especially if all cases of colorectal cancer occur at an advanced age, are confined to one generation of the family, and if no one in the family has had any of the extracolonic cancers associated with HNPCC. It may be appropriate to provisionally classify such families as having a moderately increased risk (ie category 2), while keeping the possibility of HNPCC under review. New diagnoses of cancer in the family or results of microsatellite instability (MSI) or genetic testing may clarify the situation.

Recommendations for this category are to be found in Chapter 7.

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CHAPTER 7

HIGH-RISK FAMILIAL SYNDROMES

The occurrence of colorectal cancer in families encompasses distinct syndromes in which there is a well-defined inherited genetic basis, as well as families showing clustering of colorectal cancer that is without a known genetic cause. The possibility of a high-risk syndrome is suggested when at least two close relatives are affected (see Chapter 6). This definition may be relaxed if other warning features are present, including young age of onset or certain syndrome-specific characteristics (see below).

The two most important known syndromes are familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC). Both are inherited as autosomal dominant traits. Constructing separate guidelines for the management of FAP, HNPCC and family clusters of colorectal cancer may give the misleading impression that these entities are easily distinguished and diagnosed. This is generally true for FAP but more difficult for the majority of HNPCC families.

7.1 Principles of management

The management of familial colorectal cancer will depend on the assignment of the correct diagnosis, or at least of a provisional or working diagnosis. This is important because risk assessment, genetic counselling, cancer preventive strategies and surgical treatment will differ according to the diagnosis.

Diagnosis should be based upon meticulously verified clinical and pathological data from a representative segment of the family pedigree. This diagnosis may be confirmed ultimately by the demonstration of a germline mutation in the causative gene.

A family-based approach to the problem is facilitated by providing family members with clear and complete information, and by inviting them to participate actively in their own management. Care is focused on the family as well as the individual family member, and it aims to reduce cancer morbidity and mortality within an environment that is both supportive and fully apprised of the rapid developments in this complex area.

There is firm evidence that cancer mortality is reduced in members of FAP families who are registered in regular surveillance programs.¹⁻³ Colonoscopic screening and removal of adenomas in at-risk members of HNPCC families leads to a reduction in cancer incidence. Cancers that are not prevented by polypectomy are detected while still at an early stage.^{4,5}

7.2 Multidisciplinary approach

FAP and HNPCC are inherited disorders associated not only with an increased risk of colorectal cancer, but also with proliferative disorders in a variety of extracolonic sites.

The principal life-threatening extracolonic lesions in FAP are periampullary adenocarcinoma and intra-abdominal fibromatosis (desmoid tumours).⁶ Additional extracolonic features include papillary carcinoma of the thyroid, epidermal cysts and mandibular osteomas. Retinal pigmentation (congenital hypertrophy of retinal pigmented epithelium, or CHRPE) is observed commonly and is of diagnostic value.⁷

In HNPCC, extracolonic cancer may affect the endometrium, ovary, stomach, small intestine, renal pelvis and ureter, brain, skin and possibly pancreas.⁸ Management of these multisystem disorders does not fall within the traditional boundaries of any clinical discipline, but it requires the input of surgeons, gastroenterologists, gynaecologists, oncologists and clinical geneticists. Equally important is the expert support from the laboratory-based disciplines including anatomical pathology, cytogenetics and molecular genetics. Registries provide a useful focal point for coordinating the management of these complex disorders.¹⁻⁵ It is difficult for any individual practitioner to offer comprehensive management (encompassing diagnosis, cancer screening and treatment) that is family-based with continuity of support to successive generations.

7.3 Colorectal cancer family registries

All published data from cancer prevention programs that have reduced cancer incidence in family members with either FAP or HNPCC have used family registries.¹⁻⁵ These registries facilitate the management of familial colorectal cancer by providing or supporting the following services:

- ascertainment of families
- construction of extended pedigrees
- verification of clinical and pathological data
- collection of tissue and blood samples
- maintenance of a meticulous, confidential and secure database on behalf of the family and future generations
- liaison with relevant health care professionals
- liaison with sister registries
- educational support and counselling
- identification of at-risk family members
- coordination of cancer screening
- coordination of genetic testing
- facilitation of multidisciplinary clinical management
- documentation of extended follow up
- provision of resources for legitimate research (translating ultimately into improved patient care).

7.4 Genetic testing

Genetic testing provides the ultimate diagnosis of a specific hereditary condition, although it is often not required to achieve a working diagnosis that is likely to be correct. However, a genetic diagnosis is required if at-risk members of a particular family are to be tested for a mutation. There is also evidence in the case of FAP that the site of the mutation will influence the disease phenotype.^{9,10} In turn, this may be relevant for the optimisation of surgical intervention. In addition, screening by colonoscopy rather than sigmoidoscopy may be required in families with atypical or attenuated FAP.

Genetic testing should be undertaken after the family history has been established in detail (just as special investigations *follow* the taking of a history and examination of an individual). Genetic testing should be conducted under the supervision of a clinical geneticist, specialist in cancer genetics or ethically approved clinical research group, and it should be supported by appropriate counselling.¹¹

An individual who believes that he or she is at risk for an inherited cancer may for obvious reasons wish for a 'genetic test'. Isolated testing is inappropriate since it is likely to be negative, and a proportion of these will be false negative results that fail to exclude a genetic risk. This can give the individual, and possibly the individual's family, a false sense of security.¹¹ Furthermore, harmless genetic variation (polymorphism) may be interpreted falsely as a positive result.

The most appropriate series of steps is to:

- establish a working diagnosis;
- define the causative mutation in an affected individual;
- develop a predictive test for the family;
- offer predictive testing to at-risk members of the family; and
- provide appropriate genetic counselling and support for affected and unaffected family members.

This is appropriate for each member of a family who has not yet had genetic testing.

In summary, although genetic testing is possible and has been achieved for many FAP¹¹ and HNPCC¹²⁻¹⁴ families, it is a time-consuming and often expensive procedure associated with many pitfalls. It can be recommended only after a family has been thoroughly investigated, and with the involvement of an accredited clinical genetic or cancer genetic service or an ethically approved clinical research group.

7.5 Diagnosis and management of FAP

FAP is an autosomal disorder caused by a germline mutation in the APC gene.^{15,16} If people who have the APC mutation are not treated, the development of colorectal cancer approaches 100% by the age of 50 years. FAP accounts for less than 1% of colorectal cancer. In Finland, FAP accounts for only 0.2% of colorectal cancer, which reflects the success of prophylactic colectomy in cancer prevention in that country.

The diagnosis of a new case is usually made when an individual develops colorectal cancer at a relatively early age in a background of colorectal adenomatous polyposis

(usually considerably more than 100 adenomas). At this stage unaffected family members can be identified who are 'at risk'.

All at-risk individuals require the following sigmoidoscopy screening:

- flexible sigmoidoscopy annually from age 10–15 years to 30–35 years, depending on likely compliance (sigmoidoscopy is done yearly to establish rapport and continuity of care); and
- sigmoidoscopy every three years after the age of 35 years, in view of the diminishing risk.¹⁷

The causative APC gene mutation can be identified in the majority, but not all, of FAP families. Genetic testing may then be used to distinguish mutation positive and mutation negative family members. Individuals testing negatively no longer require intensive screening, with their risk reverting to that of the general population. Children are generally tested when they would be commencing flexible sigmoidoscopy (for example in early teens). Those testing positively will require annual sigmoidoscopy. A representative sample of the polyps should be confirmed by histology as being adenomas. Lymphoid polyps can simulate adenomas and they are sometimes large and numerous in children. It is usual to proceed to surgery once there is an endoscopic diagnosis with pathological confirmation.

Appropriate surgical options for prophylactic management include total colectomy and ileorectal anastomosis and restorative proctocolectomy.^{17,18} The usual age for these procedures is in the teenage years.

Rare atypical forms of FAP may be mistaken for HNPCC and they have been reported erroneously as such.¹⁹ This has led to the dissemination of false information regarding the presentation of flat, right-sided adenomas in HNPCC²⁰ when, in fact, this is a feature of some families with atypical FAP.²¹

The role of regular upper gastrointestinal endoscopy in the prevention of upper gastrointestinal malignancy in affected members of FAP families is unclear, but annual endoscopy is widely practised from the age of 30–35. One study has shown that surveillance of the upper gastrointestinal tract leads to a moderate gain in life expectancy.²²

The role of nonsteroid anti-inflammatory drugs (NSAIDs) such as sulindac as cancer chemopreventive agents is suggested by a number of clinical studies, but these are not yet supported by randomised controlled trials and such treatments cannot be recommended firmly.²³ There are reports of subjects developing colorectal cancer while on NSAIDs, despite the fact of polyp regression.²⁴

7.6 Diagnosis and management of HNPCC

HNPCC is an autosomal dominant disorder caused by a germline mutation in one of a family of DNA mismatch repair (MMR) genes — *hMSH2*, *hMSH6*, *hMLH1*, *hPMS1* and *hPMS2* and probably others.^{25–30} The majority of mutation positive families have mutations of either *hMLH1* or *hMSH2*. The contribution of HNPCC to all colorectal cancer is probably in the range of 1% to 4%.⁸

HNPCC is characterised by early age of onset of colorectal cancer, a predilection for proximal colonic malignancy and a tendency to develop multiple colorectal cancers.^{8,31} It is generally accepted that, when men and women are considered together, about 70% of people with HNPCC will develop colorectal cancer by the age of 65 years.³² For women alone, however, a lower risk (30%) has been described.³³ One risk estimate for endometrial cancer was 42%,³³ emphasising the need to screen this extracolonic site.

HNPCC is distinguished clinically from FAP by the paucity of adenomas and other pathological features.

A high proportion of families fulfilling the Amsterdam criteria (probably between 60% and 95%) will have HNPCC.^{34,35} The Amsterdam criteria, which identify families that should be considered for a diagnosis of HNPCC, are:

- at least three cases of colorectal cancer in the family
- one case a first-degree relative to the other two
- at least two successive generations affected
- at least one case diagnosed before the age of 50
- exclusion of FAP³⁶

Some families which meet these criteria or which have a very strong family history of cancer suggestive of a dominant pedigree do fall outside the syndrome of HNPCC.^{35,37,38} Conversely, some families that do not meet these strict criteria do have HNPCC.^{39,40} Modifications to the Amsterdam criteria are now being discussed. The Bethesda guidelines include families with two affected first-degree relatives and one of the cancers may be an HNPCC-related extracolonic cancer (see Table 7.1). One cancer must also be from a subject aged below 45 years.⁴¹ The Bethesda guidelines (like the Amsterdam criteria) are not a definition of HNPCC; they merely identify families or individuals requiring further evaluation to specifically test tumour samples for DNA microsatellite instability.⁴¹

Table 7.1 Bethesda guidelines for testing colorectal cancer for microsatellite instability⁴¹

Individuals with cancer in families that meet the Amsterdam criteria.
Individuals with two HNPCC-related cancers, including synchronous and metachronous colorectal cancers or associated extracolonic cancers. ^a
Individuals with colorectal cancer and a first-degree relative with colorectal cancer and/or HNPCC-related extracolonic cancer and/or a colorectal adenoma: with one of the cancers diagnosed before the age of 45, and the adenoma diagnosed before the age of 40.
Individuals with colorectal cancer or endometrial cancer diagnosed before the age of 45.
Individuals with right-sided colorectal cancer with an undifferentiated pattern (solid/cribriform) on histopathology diagnosed before the age of 45. ^b
Individuals with signet-ring-cell-type colorectal cancer diagnosed before the age of 45. ^c
Individuals with adenomas diagnosed before the age of 40.

a Endometrial, ovarian, gastric, hepatobiliary, or small-bowel cancer or transitional cell carcinoma of the renal pelvis or ureter.

b Solid/cribriform defined as poorly differentiated or undifferentiated carcinoma composed of irregular, solid sheets of large eosinophilic cells and containing small gland-like spaces.

c Composed of >50% signet ring cells.

A molecular marker phenotype in the form of tumour DNA microsatellite instability (MSI) is helpful for corroborating the diagnosis of HNPCC, particularly in small families.^{35,37,39} MSI can be demonstrated by comparing normal and cancer DNA obtained from formalin fixed tissue, and this should precede the expensive step of formal genetic screening of a family. When there is a family history of colorectal cancer, the presence of MSI in the DNA of one or more cancers is a good indicator of a germline mutation in one of the MMR genes.³⁹ It is desirable that cancers occurring in subjects aged 45 or less be tested for DNA MSI, as this has led to the identification of HNPCC in small families.³⁹

Colorectal cancer in HNPCC is more likely to be mucinous, lacking in glandular differentiation and characterised by the presence of tumour infiltrating lymphocytes.⁴² Greater diagnostic precision is achieved by a combination of clinical, pathological and genetic variables.⁴³

As in FAP, identification of the causative germline mutation in an affected individual allows other at-risk family members to be offered predictive testing. Genetic testing is not a simple matter, and it should not be carried out in isolation. For full information on the ethical issues surrounding genetic testing, see the draft Australian Cancer Network/NHMRC document *Guidelines on Familial Aspects of Cancer*.⁴⁴

If genetic testing is carried out, those carrying the high-risk gene can be targeted for cancer screening or preventive measures whereas family members who lack the mutation revert to the population risk.¹²

Screening of at-risk individuals in HNPCC families should be by full colonoscopy performed 1–2 yearly and beginning at the age of 25 years or five years earlier than the youngest affected member of the family (whichever is the earliest).⁸ Faecal occult blood testing may be offered in alternate years or to subjects unwilling to accept colonoscopy. Rapid evolution of the adenoma–carcinoma sequence or other routes of morphogenesis may account for the relatively high frequency of interval cancers.⁴⁵ For

this reason, annual colonoscopy is recommended for subjects who are shown to carry a germline mutation.

Consideration should be given to screening for extracolonic malignancy in affected and at-risk individuals. The efficacy of screening sites outside the colon and rectum has not been determined, but it is expected to be greater in families with an increased burden of extracolonic malignancy. The most common extracolonic site of cancer is the uterus (endometrium), and this applies to both *hMSH2* and *hMLH1* families.⁴⁶ Uterine screening has been advocated from the age of 30–35 years.^{8,46} Additional extracolonic sites may be affected more frequently in families with the *hMSH2*⁴⁶ and *hMSH6*^{30,47} genes.

The risk of metachronous colorectal cancer is increased in HNPCC. For this reason, extended surgery, for example total colectomy or proctocolectomy, has been recommended for subjects with proven HNPCC. Age, state of health and the wishes of the patient, together with the site of the cancer, will influence the choice of surgical procedure. Annual endoscopic surveillance of remaining large bowel mucosa is then required.⁴⁸ Long-term compliance and access to such surveillance will also influence the choice of surgical procedure. Consideration should be given to offering women with proven HNPCC a hysterectomy and possibly oophorectomy at the time of surgery for colorectal cancer.⁸

Prophylactic colectomy in either at-risk individuals or even those known to be mutation carriers cannot be recommended generally, but may be an option in particular instances. Under such circumstances, consideration should be given to prophylactic hysterectomy and possibly oophorectomy from the age of 30–35 years or when child bearing is complete.

7.7 Management of familial clusters of colorectal cancer

Since there is evidence that HNPCC can affect families that do not meet the Amsterdam criteria, the possibility that a family cluster of colorectal cancer may be due to HNPCC should be taken seriously using the diagnostic criteria described above. There should be a full review of the clinical and pathological data as well as tests of tumours for DNA microsatellite instability. When a working diagnosis of HNPCC cannot be justified, screening recommendations for familial clusters of colorectal cancer should be followed (see Chapter 6).

Members of proven FAP and HNPCC families who test negatively for the mutation are no longer at high risk and revert to the average risk group.

Extended cancer surgery, for example total colectomy or proctocolectomy, should be considered in subjects with proven HNPCC because of the increased risk of metachronous neoplasia. Remaining large bowel mucosa will require annual endoscopic surveillance.

Consideration should be given to screening extracolonic sites in HNPCC, especially in families with clusters of extracolonic cancers.

Guidelines — management of familial colorectal cancer	Level of evidence
Working diagnoses should be achieved through the integration of clinical, pathological and genetic information that is standardised and fully validated.	III
Genetic testing should be undertaken under the supervision of a clinical genetics or cancer genetics specialist, and supported by appropriate counselling.	III
The surgical management of familial adenomatous polyposis (FAP) is by total colectomy and ileorectal anastomosis or restorative proctocolectomy.	III
The role of nonsteroidal anti-inflammatory drugs, such as sulindac, in the prevention of cancer in FAP is unclear; their routine use cannot be recommended.	III
Screening of at-risk members of proven hereditary nonpolyposis colorectal cancer (HNPCC) families should be by annual or two-yearly colonoscopy, commencing around the age of 25 years. Annual screening should be offered to individuals carrying a germline mutation.	III

A family history should be obtained in all patients presenting with colorectal cancer. Familial colorectal cancer should be managed with the support of clinical genetics/cancer genetics services underpinned by family registries.

Consideration should be given to microsatellite instability (MSI) testing in all subjects who meet the Bethesda criteria.

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CHAPTER 8

DIAGNOSTIC TESTS AND PREOPERATIVE ASSESSMENT

A right-sided colon cancer usually presents with anaemia and abdominal pain, and occasionally it is a palpable mass. A left-sided lesion usually presents with a change in bowel habit, abdominal pain or the passage of blood or mucus per rectum.

Many rectal cancers produce no symptoms initially, and they are discovered as part of a routine anorectal examination. Bleeding is the most common symptom of rectal cancer. Any rectal bleeding should be investigated. Typical anal outlet bleeding can be adequately investigated with a sigmoidoscopy. If actively bleeding haemorrhoids or another obvious anorectal cause for bleeding is found, one needs to be very careful in attributing the bleeding to that source, even if the anorectal lesion is treated.

The presence of any of these symptoms may be an indication for investigation of the colon and rectum. However, these typical clinical features are present in only 40% of people with colon cancer,¹ as outlined in Chapter 5.

The risk of colorectal cancer increases with age and with a strong family history of colorectal and other cancers. The presence of these added risk factors should be included in the consideration of investigations.

Guidelines — investigations	Level of evidence
All people with suspicious large bowel symptoms or rectal bleeding should be investigated, especially if other risk factors (such as older age or family history) are present, or in any patient over 40 years of age.	—
People under 40 years of age should be investigated if there is a positive family history, if there is not an identified cause of symptoms, or if symptoms are persistent.	—

8.1 Methods of investigation

8.1.1 Digital examination

Digital rectal examination enables detection and assessment of the size and fixation of mid and low rectal cancer. This should be the first and most important assessment in any patient with an anorectal symptom. While digital assessment of the extent of local disease is imprecise, it provides a rough estimate of the local staging of the rectal cancer² and of the state and strength of anal sphincters. The adequacy of the anal sphincters would influence a surgical decision regarding whether to perform an ultra-low anterior resection.

8.1.2 Sigmoidoscopy

Sigmoidoscopic examination facilitates diagnosis and biopsy of rectal cancer. It should allow the collection of helpful information such as:

- distance from the lower edge of the cancer to the anal verge
- which wall the cancer is located on
- whether or not the lesion is annular

The flexible sigmoidoscopy is superior to the rigid sigmoidoscope in terms of extent of bowel examined and patient comfort.³ Sigmoidoscopy, whether rigid or flexible, is mandatory in the diagnosis and assessment of rectal cancer.^{3,4}

Equivocal lesions seen on a contrast barium enema can be confirmed if they are within reach of the flexible sigmoidoscope. Sensitivity and specificity for flexible sigmoidoscopy for lesions in the rectosigmoid region are similar to those for colonoscopy (see below). Most studies do not have any complications⁴ and the perforation rates are less than 2 in 10,000 examinations.⁵

8.1.3 Barium enema

The sensitivity of double-contrast barium enema for colon cancer is 90%, with a range of 65% to 95%.⁶⁻⁸

Barium enema is more likely to miss a Dukes A cancer (see Chapter 14) than colonoscopy.⁶ In a review,⁸ the best result of double-contrast barium enema for detecting polyps smaller than 1 cm was 70–95%, compared with 90% for colonoscopy.

The rectum and rectosigmoid region are not well visualised on double-contrast barium enema. These regions should be examined by sigmoidoscopy, rigid and/or flexible, or by colonoscopy.

Lesions are more commonly missed in the sigmoid colon because of underlying diverticular disease. They are also often missed in the caecum because of inadequate imaging.^{9,10} If visualisation of the sigmoid colon is difficult because of severe diverticular disease, supplementary examination by flexible sigmoidoscopy or colonoscopy may be needed. Combined or supplementary examination by flexible sigmoidoscopy or colonoscopy may be needed.¹¹

Colonic redundancy in the ascending colon can also mask neoplastic lesions.

Reports of barium enema are often vague due to a technically inadequate examination or medicolegal concerns by the radiologist. All barium enema reports should contain an indication as to the completeness, quality and limitations of the examination.

Complications

Barium enema is done as an outpatient procedure. Sedation is not used. Serious complications are rare and have been estimated at 3 per 10,000 tests, with a death rate of 3 in 100,000 tests.⁵

Quality issues

The accuracy of the double-contrast barium enema is, in large part, dependent on quality issues. Five to 10% of barium enemas are judged unsatisfactory.^{12,13}

The American College of Radiology has outlined the quality issues associated with double-contrast barium enema.¹³ Good quality bowel preparation is necessary. Double-contrast barium enema should be carried out under the supervision of a radiologist experienced in the technique and the results should be reported by two independent radiologists. This is known as 'double-reporting'.¹⁴ A suggested aim for quality control is that barium enema should detect more than 90% of colorectal cancers and more than 80% of polyps greater than 1 cm in size.

8.1.4 Colonoscopy

The sensitivity of colonoscopy for colon cancer is 95%, with a range of 70% to 95%.⁶⁻⁸ Colonoscopy allows biopsy and histologic confirmation of the diagnosis. It also allows identification and endoscopic removal of synchronous polyps.

However, even meticulous colonoscopy has a significant miss rate for small adenomas. When evaluated by one or two colonoscopists by performing back-to-back (tandem) colonoscopies on the same day, there is a miss rate of 15% for polyps <1 cm and 6% for polyps ≥ 1 cm.^{15,16} Improved effectiveness of colonoscopy is achieved with practice,^{17,18} sedation¹⁹ and better preparation of the colon.¹⁷

Complications

Colonoscopy is performed as a day-case procedure and usually needs sedation. Diagnostic colonoscopy is associated with a complication rate of 0.14%, compared with a rate of 2% for therapeutic colonoscopy.²⁰ In a review of six prospective studies of colonoscopy, about 1 in 1000 patients suffer perforation, 3 in 1000 suffer major haemorrhage, and between 1 and 3 in 10,000 die as a result of the procedure.⁵ A review of Australian data gives a slightly higher figure of 0.17% for perforation and similar figures for haemorrhage and death.²¹ There are other occasional serious complications associated with bowel preparation or the use of sedation.

Care should be taken to avoid complications, and guidelines have been issued by the Gastroenterological Society of Australia.²²

Quality issues

Training or experience in colonoscopy has an important impact on the efficacy of colonoscopy. Trained endoscopists regularly achieve caecal intubation in over 90% of cases.^{3,23} However, self-trained colonoscopists have reported caecal intubation rates as low as 54%, which did not improve with continued performance of colonoscopy.²⁴

The sensitivity of colonoscopy is lowest in the splenic flexure and caecum.⁶ The colonoscopist must recognise if a total colonoscopy is done by unequivocally identifying the caecum and terminal ileum. If this has not been done, then a barium enema will be required in some cases to ensure complete visualisation of the colon.

Investigation for suspected colorectal cancer should include a digital rectal examination, a rigid sigmoidoscopy and a colonoscopy. A double-contrast barium

enema plus flexible sigmoidoscopy may replace the colonoscopy if there are difficulties with local availability or expertise, or if the patient prefers.

8.2 Preoperative staging

8.2.1 Locoregional staging of colon cancer

Most patients do not require preoperative staging. The extent of the tumour is better evaluated during laparotomy and by histologic examination of the specimen.

In selected cases, such as patients with a large and fixed tumour, a preoperative computerised tomography (CT) scan will help identify contiguous structures that may be involved such as the duodenum, spleen, kidney, bladder and ureter.

There is no evidence that routine preoperative CT scan is cost-effective or alters the treatment plan.³² A careful clinical assessment may be more valuable by identifying those patients with a bulky cancer who may benefit from CT imaging.²⁵ Magnetic resonance imaging (MRI) has no advantage over CT scan in locoregional staging of colon cancer.^{26,27}

Colonoscopic ultrasonography uses an ultrasound transducer incorporated in the tip of the colonoscope.²⁸ It is unlikely to be of practical use because surgery for colon cancer is not stage-dependent.

Routine preoperative locoregional staging with a CT scan or MRI does not usually alter treatment plan. However a CT scan should be considered if there are clinical indications of a locally advanced cancer or of systemic metastases which might alter operative or other management strategies.

8.2.2 Locoregional staging of rectal cancer

Preoperative locoregional staging of rectal cancer is much more important than for colon cancer, both to plan for surgery and to consider the possible need for preoperative adjuvant chemoradiotherapy (see Chapter 16).

Endorectal ultrasound

Endorectal ultrasound provides a high resolution image of the individual layers of the rectal wall and it can visualise the disruption of one or more of these layers by tumour. It can also detect adjacent nodal and other pelvic organ involvement. Endorectal ultrasound is generally performed by the colorectal surgeon rather than by the radiologist.

Accuracy rates for depth of cancer invasion through the rectal wall range from 85% to 95%. Comparative studies have shown endorectal ultrasound to be superior to CT²⁹⁻³² and MRI.³² The overall accuracy for detecting lymph node metastases is about 80%.³³⁻³⁵

While endorectal ultrasound is the most accurate method to preoperatively stage the rectal cancer locally, it is not necessarily indicated for all rectal cancers. Its main role will be:

- for advanced (T3–4) rectal cancers where neoadjuvant therapy is being considered;³⁶
- for small cancers in the distal rectum where a local transanal excision may be an alternative to abdominoperineal excision of the rectum with a permanent colostomy, so accurate assessment of the depth of local tumour invasion and state of the lymph nodes is essential;³⁴ and
- if neoadjuvant chemoradiotherapy or a transanal local excision is planned.

The accuracy of endorectal ultrasound is strongly dependent on the expertise of the operator.³⁷ Preferably it should be performed by the surgeon who has assessed the tumour by digital rectal examination and sigmoidoscopy, and who will be making the decisions on management. Currently there are few specialists who are experienced with the use of endorectal ultrasound in Australia. There is a long and steep learning curve with the techniques. Establishment of endorectal ultrasound services may need to be limited to major centres, where supervised training and audit are essential. Table 8.1 gives details of an endorectal ultrasound staging system.

Table 8.1 Endorectal ultrasound staging

uT0	Submucosa intact (benign lesion)
uT1	Tumours confined to the mucosa and submucosa
uT2	Tumours confined to the rectal wall and muscularis propria, leaving the third hyperechoic layer intact
uT3	Tumours penetrating into perirectal fat
uT4	Tumours penetrating into surrounding organs
uN0	No nodal involvement on ultrasound
uN1	Nodes involved on ultrasound

CT scan

CT scan is rarely helpful in the early stages of primary rectal cancer.³⁸ It is not sensitive enough to accurately assess the depth of invasion within the bowel wall and to detect metastases in normal-sized lymph nodes.

However, for patients with a large bulky rectal cancer, and especially a stenosing cancer that precludes an endorectal ultrasound, CT scan is useful in assessing the extent of pelvic disease. It may also give information about metastatic disease (see below).

Endorectal MRI

MRI using an endorectal coil showed promising results in preliminary studies. Subsequent studies have shown that endorectal MRI is disappointing in the locoregional staging of rectal cancer.³⁹

Endorectal ultrasound is more accurate than either CT or MRI for assessing the depth of invasion and lymph node status. It is the preferred initial method of locally staging a rectal cancer preoperatively.

8.2.3 Staging for distant metastases

The purpose of staging is three-fold, namely to assist treatment decision making, to provide information on prognosis and to define disease groups for comparison of results.

The United Kingdom Colorectal Cancer Working Party has recommended a routine chest X-ray and liver scan by CT or ultrasound.⁴⁰ This may help determine prognosis,⁴¹ although there is no evidence that it alters prognosis.

Preoperative identification of liver and/or lung metastases may be useful in:

- frail, elderly patients who may not need resection of a relatively asymptomatic colorectal cancer;
- patients suspected to have extensive liver metastases (>50% of liver volume) since, in these people, resection of the primary colorectal cancer is associated with a high postoperative mortality and morbidity with little benefit;⁴²
- patients suspected to have unresectable liver metastases, where an infusaport for chemotherapy treatment of liver metastases may be inserted during laparotomy for the primary cancer; and
- identifying a few selected cases where synchronous liver resection may be performed with colorectal resection.

Staging for intra-abdominal and liver metastases may involve one or more of a number of methods.

Transabdominal ultrasound

This is often capable of detecting liver metastases, but is not sufficiently sensitive (sensitivity 40–70%) to exclude them.^{43,44} However, it is widely available, relatively cheap and used as an initial screening investigation if a CT scan is not readily accessible.

Dynamic sequential contrast-enhanced CT scan

This investigation is 70–80% sensitive in diagnosing intra-abdominal and liver metastases.⁴⁵ Helical (spiral) CT is likely to be significantly more sensitive, particularly for small lesions. However, a large series with state-of-the-art CT has not yet been published.

CT (or helical CT) during arterial portography (CTAP)

CTAP is the most sensitive preoperative method of assessment, with a sensitivity rate of greater than 90%.⁴⁶ However, histological confirmation is not available in most studies.⁴⁷

CTAP is hampered by a fairly high rate of false positives due to artefacts and lack of specificity. Usually, these may be clarified by correlation with other imaging or in combination with CT during hepatic arteriography.

The complexity and invasiveness of these newer techniques have prevented their widespread adoption.

Magnetic resonance imaging (MRI)

MRI is considerably more expensive, less readily available and no more sensitive than CT scan in a multicentre prospective study on staging for locoregional or distant metastases.²⁶ There is also no advantage in using both MRI and CT scan in the same patient.²⁶

New MRI techniques, including fast scanning techniques, use of blood-pool contrast agents (gadolinium chelates) and development of liver-specific contrast agents for MRI may further augment the sensitivity of MRI in liver imaging in the future.

Intraoperative ultrasound

When combined with surgical palpation of the liver, intraoperative ultrasound is the most sensitive examination for liver metastases, and it changes the staging of the disease in 11% of the cases in which it is used. However, the surgical management is rarely altered.⁴⁸

Intraoperative ultrasound does not detect liver metastases less than 5 mm in size, and there is a false negative rate of 15% among patients who later develop overt liver metastases.^{49,50}

Thus even with the most sensitive test for liver metastases, a negative test does not fully exclude occult metastases.

8.2.4 Other investigations

Intravenous urography

Routine intravenous urography is not appropriate because of the low sensitivity.⁵¹ If clinical or CT scan suggests urinary tract involvement, intravenous urography may be indicated for further evaluation and for determining function in the other kidney.

Cystoscopy

The bladder may rarely be involved by a large sigmoid cancer. Urological symptoms such as haematuria, recurrent urinary tract infection, pneumaturia and faecaluria may be present. Cystoscopy and CT scan are complementary in this situation.

Carcinoembryonic antigen (CEA)

While high preoperative CEA levels may suggest the presence of occult systemic disease, the test is not sufficiently sensitive or specific to be used for routine staging or for the early diagnosis of colorectal cancer.⁵²

Preoperative assessment for comorbid factors

A careful clinical evaluation of the entire body system and a careful family history are essential to highlight the need for appropriate investigations.

A complete blood count may reveal the presence of anaemia. Urea and electrolytes should be monitored for safe anaesthesia, especially as many patients shall also undergo mechanical bowel preparation. Abnormal liver function tests may suggest the presence of liver metastases.

Chest x-ray, electrocardiogram (ECG) and tests of cardiac function should be performed if there are relevant cardiorespiratory comorbid factors. Rarely, chest x-ray may reveal pulmonary metastases.

8.2.5 Counselling and stoma siting

The feelings and fears of the patient and the family must be addressed in a suitable setting and with adequate time allowed. Repeat consultations may be necessary to convey information and allow questions.

Where a stoma may be needed, careful counselling and siting should be done preoperatively whenever possible,⁵³ with stomal therapy nurses involved in the planning and counselling process. Preoperative counselling is an integral part of the surgical management.

Cancer information services and support groups provide invaluable resources for the patient and the family. Support is also available from each State/Territory cancer information service (telephone no **13 11 20**; or **1300 361 366** in Queensland).

Guideline — stoma siting	Level of evidence
Stoma siting should be performed preoperatively by an experienced stomal therapist or the surgeon if a stoma is planned or is considered likely.	III

8.3 References

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CHAPTER 9

MANAGEMENT OF EPITHELIAL POLYPS

A polyp is a circumscribed mass projecting above an epithelial surface. The principal types of epithelial polyp found in the large bowel are:¹

- adenoma or neoplastic polyp
- hyperplastic polyp
- hamartoma (juvenile and Peutz–Jeghers)
- inflammatory

The term ‘polyp’ is not synonymous with adenoma. The commonest polyps are the adenoma and the hyperplastic polyp. Although these tend to coexist within individual patients, only adenomas have a significant malignant potential. Adenomas occur throughout the bowel, whereas hyperplastic polyps are more frequent in the distal colon and rectum. Although distal hyperplastic polyps have been considered to be markers of more proximal adenomas,^{2–8} the larger and better controlled studies have not found them to be clinically useful in this regard.^{9–14} The only situation in which the hyperplastic polyp may be a marker for cancer risk is in subjects with hyperplastic polyposis.¹⁵ In this condition hyperplastic polyps are large, often exceeding the usual limit of 5 mm, and they occur throughout the bowel. It has been suggested that the polyps occurring in hyperplastic polyposis are actually serrated adenomas. The term ‘serrated adenomatous polyposis’ is probably synonymous with hyperplastic polyposis.¹⁶

Solitary juvenile polyps are not precancerous. However, juvenile polyposis, a rare condition which may occur as an autosomal dominant trait, is associated with an increased risk of malignancy.¹⁷ Malignancy in the Peutz–Jeghers syndrome is usually extracolonic, but there is a small increased risk of colorectal cancer.¹⁸

Adenomas are usually elevated, and may be sessile or pedunculated. A minority are relatively flat and these may be slightly raised, flat or slightly depressed.^{19,20} Adenomas are typed according to histological architecture as tubular, tubulovillous and villous. They may be diminutive (1–4 mm), small (5–9 mm) or large (10 mm or more). They are also classified according to the grade of epithelial dysplasia as mild, moderate and severe or alternatively as showing low and high-grade dysplasia.¹ Severe or high-grade dysplasia are terms used in preference to carcinoma-in-situ. The latter term has aggressive connotations that are unwarranted.

Evidence for the precancerous nature of the adenoma is well documented in standard texts¹⁸ as follows:

- adenomas show a spectrum of changes ranging from mild dysplasia through to severe dysplasia;
- longitudinal studies show malignant progression in (villous) adenomas with time;
- adenocarcinoma may occur at the same time as adenoma;

- epidemiology of adenoma matches adenocarcinoma;
- genetic changes in adenomas fit with the evolutionary mechanism underlying carcinogenesis;²¹
- removal of adenomas results in a reduced incidence of adenocarcinoma;^{22,23} and
- adenomas in familial adenomatous polyposis (FAP) are identical to sporadic adenomas. FAP patients with adenomas invariably develop cancer.

9.1 Natural history of adenomas

Based on adenoma prevalence studies from autopsy data and the lifetime cumulative incidence of colorectal cancer, it appears that only about 5% of colorectal adenomas undergo malignant transformation.¹⁸ Adenomas more likely to harbour cancer are those that are large and that have a villous architecture and/or high grades of dysplasia.²⁰ Flat adenomas may possibly be more aggressive or give rise to more aggressive adenocarcinomas.^{24,25}

The clinical context may also influence progression. For example, adenomas occurring in the context of hereditary nonpolyposis colorectal cancer (HNPCC) characteristically show an accelerated evolution.²⁶ Adenomas may be larger and more numerous in subjects without HNPCC or classical FAP but with a strong family history of colorectal cancer.^{27–29}

Adenomas appear to grow slowly. Small polyps may be observed endoscopically for several years before they are removed and diagnosed histologically.³⁰ Adenomas under 1 cm, and particularly those measuring 5 mm or less, may remain the same size for years or even regress.³⁰ The cumulative risk for developing a cancer in polyps (mainly adenomas) greater than 1 cm has been estimated to be 3% at five years, 8% at 10 years and 24% at 20 years.³¹ Studies conducted in different nations have shown that the majority of polyps can be diagnosed from the surface morphology of their pit openings using magnifying endoscopy coupled with indigocarmine dye spraying.^{19,32} This approach should yield additional insight into the natural history of adenomas in the future. It should also eliminate the removal of non-neoplastic polyps.

9.2 Polypectomy

In the absence of magnifying endoscopy combined with dye spraying, it is often not possible to determine the histological type of a polyp by endoscopic inspection. Diminutive hyperplastic polyps and adenomas (<5 mm) may be indistinguishable. The unusual large hyperplastic polyp may mimic an adenoma. For this reason, all polyps should be considered for removal.

Diminutive polyps may be too numerous to be cleared completely. In subjects with multiple small polyps, a sample of at least three should be biopsied for histological study.^{33,34} Hot biopsy and electrocoagulation have been used to eradicate diminutive polyps, but these may leave residual polyp tissue behind.^{35–38} Cold snare polypectomy is an effective alternative.³⁹

Polyps should be removed by total excision. Sessile polyps may require piecemeal removal, but this will make histological evaluation difficult or impossible.⁴⁰ The area may be tattooed with India ink to facilitate follow-up evaluation.⁴¹ Tattooing will also identify the site for subsequent surgical resection.

9.3 Malignant polyps

The term malignant polyp applies to an adenoma containing a focus of malignancy. Management of malignant adenomas by polypectomy alone is now standard practice. It is generally acknowledged to be safe, providing there is a strict policy of case selection and histopathological assessment.^{42–45} For example, polyps containing poorly differentiated adenocarcinoma are not suitable for curative local excision in view of the high risk of associated lymph node metastasis.⁴⁶

Three key factors that are indicative of lymph node spread, local recurrence and prognosis and that are linked to favourable outcomes have been identified in patients treated by polypectomy for malignant adenoma and then managed by either follow up alone or surgical resection. These three factors are:

- a clear margin of excision;
- well or moderately differentiated cancer; and
- absence of lymphatic or venous invasion.

The usefulness of lymphatic invasion⁴⁴ and venous invasion^{43,44,47} as markers has been questioned, and they are rarely found in the absence of other unfavourable features. However it is advisable that vessel invasion continue to be regarded as an adverse marker.^{43,48–50}

Three factors — polyp size, a sessile base, and the extent of replacement by cancer — may impede complete local excision and definitive histopathological assessment. However, only demonstrable complete or incomplete excision serves as an independent predictor of outcome.^{43,44} The pathologist can make this determination only by examining multiple step sections through the polyp base. If this is undertaken with care, the majority of cases can be classified as being either completely or incompletely excised. A specific clearance margin of 1 mm⁴³ or 2 mm⁴⁴ has been advocated, but the importance of achieving such margins has not been evaluated. In one study, nine subjects had a clear margin, but cancer was within 2 mm of the line of excision. Only one of these patients turned out to have residual cancer, but it was not stated if this was within the polyp base or a lymph node.⁴⁴ Pathologists are generally comfortable with reporting a surgical margin as either clear or not clear.

Malignant adenomas with unfavourable features may require further treatment, but this decision should be individualised on the basis of the age, health and wishes of the patient. Treatment decisions will also be influenced by site, particularly in the case of low rectal lesions for which radical surgery would involve abdominoperineal excision and colostomy.

9.4 Follow-up surveillance for adenomas

Patients developing adenoma or carcinoma are at increased risk of developing additional (metachronous) neoplasms in the future.

9.4.1 Adenoma follow up

There are no internationally agreed recommendations for following up patients with adenomas.

In a British study, 1618 patients were treated for rectosigmoid adenomas using rigid-instrument sigmoidoscopy. These patients were not initially followed up, and the study retrospectively assessed their long-term risk of developing colorectal cancer. The results showed that the incidence of rectal cancer for these patients was similar to that of the general population. Most rectal cancers occurred in subjects with incompletely excised adenomas and the risk of colon cancer depended on the type, size and numbers of rectosigmoid adenomas removed initially, as follows:

- an increased standardised incidence ratio of 3.6 was observed in subjects with large adenomas (>1 cm) or with adenomas with a villous component;
- the ratio was increased to 6.6 if, in addition, subjects had multiple adenomas; and
- in the remaining subjects with small (<1 cm) excised tubular adenomas, the risk of cancer was not increased, even in subjects with multiple adenomas (standardised incidence ratio of 0.5).⁵¹

This study suggests that a sizeable subset of patients is not at increased risk of developing significant colorectal cancer in the future if they have only small (<1 cm) tubular adenomas which have been removed. However, it was not a prospective study and it relates only to patients with excised adenomas of the distal large bowel.

The United States National Polyp Study has confirmed that risk factors for metachronous colorectal cancer include adenoma size, presence of villous change and multiplicity.⁵² This study also advocates an interval of at least three years before re-endoscopy, as adenoma recurrence rates were no higher when intervals of three years were compared to one year. A longer follow-up interval of six years has been proposed for subjects *other* than those:

- who have three or more adenomas at initial colonoscopy; or
- who are 60 years of age or over and have a parent with colorectal cancer.

We have recommended a screening interval of 4–6 years for this low-risk group and three years for the two high-risk groups. The relative risk of developing a significant adenoma (>1 cm or having high-grade dysplasia or invasive cancer) was 5.2 and 4.3 for the high-risk groups respectively. These two groups comprised 27% of the subjects in the study, and they accounted for 69% of significant adenomas.⁵³

In summary, a three-yearly follow-up period is safe provided colonoscopy is complete, and the endoscopist has removed all polyps seen and is confident of having achieved adequate visualisation. It may be extended further for subjects lacking high-risk features.^{33–35,51–54}

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CHAPTER 10

PREPARATION FOR SURGERY

Most people with colorectal cancer will undergo surgery. Routine preoperative assessment includes a full medical history and physical examination, with particular interest in cardiorespiratory assessment. Appropriate haematological and clinical chemistry investigations are also performed. Other preoperative anaesthetic investigations may be appropriate.

Surgery should be avoided where the potential risks would appear to outweigh the potential benefits of the surgical procedure. This applies to patients who:

- are medically unfit for surgery — medical and/or anaesthetic consultations may be appropriate; and
- have advanced disease which is not amenable to surgery — note that this situation does not preclude palliative surgery.

The decision not to operate depends on highly individual factors, so specific guidelines cannot be provided. It is important that the patient (and possibly relatives) is involved in the making of such a decision and that the reasoning for such a decision is clear to all concerned.

10.1 Informed consent

It is important to explain in detail to the patient the reasons for the proposed procedure, the likely outcome of the procedure, the probability of the procedure producing undesirable results, possible outcomes if the procedure is not carried out, any alternatives to the proposed procedure, and the prognosis.

A full and detailed preoperative discussion with the surgeon and the anaesthetist is essential in order for the patient to give their informed consent.

This may involve provision of written material. The patient must be in as settled a condition as possible prior to giving informed consent. Frequently, more than one consultation is necessary. The patient (and relatives) must be given the opportunity to ask any questions they feel are relevant.

10.2 Preparation for stoma

Any patient undergoing surgery for colorectal cancer may require a stoma, so all patients should be warned of the relative likelihood of this possibility by the surgeon. The difference between a temporary and permanent stoma needs to be explained clearly. If there is a reasonable chance of a stoma, the patient should preferably be seen preoperatively by the stomal therapy nurse. This visit serves a number of purposes, including:

- identification of the role of the stomal therapy nurse
- assessment of physical, social, psychological and cultural factors
- initiation of patient teaching
- selection of stomal sites
- patient reassurance

A retrospective study has shown that patients who were visited preoperatively by the stomal therapy nurse had less adverse outcomes than those who were not visited by the stomal therapy nurse.¹

Guideline — postoperative stoma	Level of evidence
All patients who have a reasonable chance of a postoperative stoma should be informed about this possibility. This includes a visit, where possible, by the stomal therapy nurse.	III

10.3 Bowel preparation

In patients undergoing elective surgery for colorectal cancer, who do not have a bowel obstruction, mechanical bowel preparation is usually administered. Care should be taken to ensure adequate hydration and intravenous therapy, especially in the elderly.

As a result of pressure for hospital beds, restraints on the health care budget, and sometimes individual patient wishes, preoperative bowel preparation is often administered as an outpatient. A retrospective study comparing outpatient and inpatient bowel preparation has demonstrated that outpatient preparation is safe and effective, except for patients with multiple medical problems.²

A number of different mechanical bowel preparations are used. Polyethylene glycol and sodium phosphate preparations are the two used most frequently. Both usually produce adequate bowel preparation, and a number of randomised trials have demonstrated this.

A randomised study comparing polyethylene glycol to Ringer's lactate and sodium phosphate solution found no significant differences in bowel cleansing, but an increased instance of postoperative complications in the sodium phosphate group. Polyethylene glycol was better tolerated than Ringer's lactate.³ Sodium phosphate solutions should not be used in the elderly or in those with multiple medical problems.⁴

A controlled trial in dogs has demonstrated that the absence of a mechanical bowel preparation in colonic resection and primary anastomosis does not cause an increased risk of anastomotic dehiscence.⁵ Randomised trials do not demonstrate a benefit from routine bowel preparation.^{6,7}

Guidelines — bowel preparation	Level of evidence
Randomised trials do not demonstrate a benefit from routine bowel preparation.	II
If bowel preparation is to be used, then both polyethylene glycol preparation and sodium phosphate preparations are effective, but polyethylene glycol is more acceptable and has lower postoperative complication rates.	II

10.4 Cross matching

About 50% of patients undergoing surgery for colorectal cancer are given a blood transfusion over the perioperative period.^{8–10} The requirement for transfusion will depend on the preoperative haemoglobin and the extent of intraoperative blood loss. It would appear that many clinicians now transfuse at lower haemoglobin levels than previously. Blood transfusion requirements will depend on the preoperative haemoglobin and the extent of intraoperative blood loss.

A ‘group and hold’ is usually adequate preparation, as blood can be obtained within five to 10 minutes of a request for cross match, as long as pathology staff are on site. This will obviously depend on the proximity of the transfusion service to the operating theatres.

A number of studies have demonstrated an increased risk of infection following blood transfusion during colorectal cancer surgery.^{11–15} The use of autologous blood has been demonstrated to cause fewer postoperative infections than transfusion of homologous blood.¹⁵ According to the patient’s wishes and the likelihood of a transfusion, autologous blood collection should be considered.

It is unclear whether or not there is an increased risk of colorectal cancer recurrence following transfusion during colorectal cancer surgery. Some prospective and retrospective studies have found an increased incidence of recurrence, while others have not.^{11,16–22}

Guideline — blood transfusion	Level of evidence
If a transfusion is required, then autologous blood is preferable to allogeneic blood for reasons of infection control and resource use.	III

10.5 Thromboembolism prophylaxis

Cancer has been shown to be an independent risk factor for the development of thromboembolism.²³ People undergoing surgery for colorectal cancer are at moderately high risk of deep venous thrombosis and pulmonary embolism. A meta-analysis of appropriate trials in general surgical patients has demonstrated that prophylactic use of subcutaneous unfractionated heparin reduces the risk of deep venous thrombosis, pulmonary embolus and death.²⁴

A randomised trial comparing low molecular weight heparin with unfractionated heparin in patients undergoing elective abdominal surgery found low molecular weight heparin to be more effective than unfractionated heparin in the prevention of deep venous thrombosis.²⁵

In patients having abdominal surgery for cancer, low molecular weight heparin has been shown to lead to a greater reduction in the risk of deep venous thrombosis than unfractionated heparin.²⁶

Intermittent calf compression intraoperatively is effective in reducing the incidence of deep venous thrombosis in the presence of malignant disease.²⁷

Guideline — thromboembolic prophylaxis	Level of evidence
All patients undergoing surgery for colorectal cancer should receive prophylaxis for thromboembolic disease. Unfractionated heparin, low molecular weight heparin, and intermittent calf compression are effective in reducing the incidence of thromboembolism.	I

10.6 Antibiotic prophylaxis

Prophylactic administration of antibiotics decreases morbidity, shortens hospital stay and reduces infection-related costs.²⁸ Many different antibiotic regimes have been shown to be effective. Most surgeons would now appear to favour the use of preoperative parenteral antibiotics over the oral route. In cases where intravenous cephalosporin and metronidazole are used, there is evidence from one randomised control trial that a single immediately preoperative dose is as efficacious as a three-dose regime in preventing wound infection.²⁹

10.7 Body temperature

A randomised trial comparing perioperative normothermia to perioperative hypothermia has demonstrated a significant reduction in the incidence of wound infection rate and length of hospital stay.³⁰

Guidelines — prophylactic antibiotics	Level of evidence
All patients undergoing colorectal cancer surgery require prophylactic antibiotics.	I
A single preoperative dose of intravenous second or third generation cephalosporin and metronidazole is an effective regime.	II
Perioperative normothermia should be maintained.	III

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CHAPTER 11

ELECTIVE SURGERY FOR COLON CANCER

11.1 Operative technique

The objective of surgical treatment of colon cancer is to remove the primary tumour and any regional spread that may have already occurred without causing further dissemination of tumour, while at the same time preserving a reasonable quality of life for the patient.

The technique of colonic cancer resection has been debated widely throughout this century. Features emphasised include high ligation of the lymphovascular pedicle before manipulating the tumour,¹ wide excision,^{2,3} and early securing of the lymphovascular pedicle with minimal manipulation.^{1,2} In a review of the literature, Sugarbaker and Corless⁴ concluded that high ligation of the mesenteric pedicle did not produce substantial improvement in survival.

Wiggers et al⁵ have reported a prospective randomised trial comparing the no-touch isolation technique with standard methods of colon cancer resection. No significant difference was noted in postoperative morbidity or mortality. There was a reduction in the number of patients developing liver metastases, and an increase in the time to the occurrences of liver metastases in the no touch group, although the differences were not statistically significant. After five years follow up, overall and corrected survival did not differ between the two treatment groups, although in every subgroup analysis, survival in the no-touch group was superior.

There are very few prospective randomised trials comparing limited segmental resection versus more extensive resection. The French Association for Surgical Research⁶ published a prospective randomised trial comparing median and actuarial survival in 270 consecutive patients after left hemicolectomy or left segmental colectomy for cancers located between the left third of the transverse colon and (but not including) the colorectal junction. Left hemicolectomy involved high ligation of the inferior mesenteric artery, and segmental resection left intact the origin of the inferior mesenteric artery, but divided the left colic artery at its origin. The length of colon resected was greater in the hemicolectomy group.

Complications and operative mortality were not significantly different. Patients were followed up for approximately 10 years, and it was equivalent in both groups. Actuarial survival curves for all patients and for Dukes C patients (see Chapter 14) were similar.

The available evidence supports extensive lymphovascular resection to the origin of the major blood vessels, with the accompanying bowel resection corresponding to the extent of vascular mesenteric clearance. There is no evidence that prophylactic omental resection influences survival following surgery for colon cancer.

Guideline — resection	Level of evidence
Resection of colon cancer should be based on the appropriate excision of the lymphovascular drainage of the segment of the colon in which the cancer is situated. Resection, where feasible, should be to the origin of the major segmental blood vessels. The amount of colon resected should correspond to the extent of vascular and lymphatic clearance.	—

11.2 Synchronous colonic cancer

The reported incidence of synchronous carcinoma of the colon varies from 2% to 9%.^{7,8} The most appropriate surgical approach for synchronous tumours depends principally on the location of the tumours. The options available are extended segmental colectomy, separate segmental resections, and subtotal or total colectomy with ileorectal anastomosis. The choice for individual patients must be based on both the position of the synchronous tumours and the age of the patient.

Total or subtotal colectomy may be appropriate for younger patients with synchronous carcinoma. In fact, Demeter and Freeark⁹ have recommended this option because of concern over the relatively high risk for metachronous carcinomas in younger patients. However, there is no evidence to support the superiority of subtotal or total colectomy under such circumstances as compared with extended or separate segmental resections with close lifelong surveillance of the large intestine.

Guideline — synchronous primary carcinoma of the colon	Level of evidence
Extended segmental colectomy, separate segmental resection or subtotal colectomy should be performed in the management of synchronous primary carcinoma of the colon. The decision between these options will be made on the basis of anatomical situation of the tumours, patient factors and the surgeon's experience.	—

11.3 Fixed tumours with contiguous organ attachment

Adherence of tumours to nearby structures occurs in about 10% of patients with colorectal cancer.¹⁰ Up to 43% of such attachments are inflammatory, and 40% of patients who have tumours adherent to other organs subsequently are proven to have a Dukes B lesion,¹⁰ which underlines the potential for cure. If the patient is to be offered the best chance of cure, an en bloc resection of the primary tumour and the attached organ should be performed.

McGlone et al¹¹ and Gall et al¹² have reported markedly reduced survival prospects for patients who have had division of dense adhesions between colorectal cancer and a contiguous organ compared with patients who underwent en bloc resection. Attachment to the abdominal wall by tumour mandates wide discontinuity excision of both tumour and abdominal wall.

Guidelines — fixed tumours	Level of evidence
For fixed tumours, <i>en bloc</i> resection of primary colonic cancer, together with the attached organ or the abdominal wall, should be performed in an attempt to obtain a curative resection.	–
No attempt should be made to assess if the attachment is benign or malignant at the time of surgery.	–

11.4 Synchronous resection of liver metastases

Between 10% and 20% of patients having resection of primary colorectal cancer will have liver metastases evident. Hepatic resection remains the only potential for cure for such metastases. Most liver resections will necessitate an anatomical resection of liver tissue, which would most appropriately be performed several months postoperatively.¹³ A small proportion of patients have hepatic metastases which are potentially curable by wedge resection at the time of the primary operation.¹⁴

Hughes et al¹⁵ have espoused five basic requirements for safe simultaneous resection of a hepatic metastasis at the time of large bowel resection, as follows:

- a solitary metastatic lesion which can be removed by a limited resection;
- minimal blood loss or contamination in an uncomplicated bowel resection;
- the presence of an appropriate incision for hepatic resection;
- medical status that would permit both procedures; and
- a surgeon who is comfortable in proceeding with hepatic resection.

Provided the wedge resection encompasses 1 cm of normal liver tissue beyond the metastasis, there is no survival advantage with a wider hepatic resection.^{16,17}

Most liver resections for metastases will necessitate an anatomical resection at a time after the initial bowel resection, when investigations have shown that the resection is feasible. Simultaneous wedge resection for a solitary hepatic metastasis at the time of colonic operation may be appropriate provided a 1 cm margin of normal liver tissue beyond the metastasis is obtained.

11.5 Ovarian metastases

The incidence of synchronous metastatic ovarian disease is between 2% and 8%. Blamey et al¹⁸ have reported that 1.4% of female patients required re-operation for ovarian recurrence after colonic cancer resection. Morrow and Enker¹⁹ have recommended bilateral oophorectomy if only one ovary is involved, because of the risk of bilateral ovarian metastatic disease. Cutait et al,²⁰ in a nonrandomised study, were not able to demonstrate a survival advantage for those patients undergoing prophylactic bilateral oophorectomy. Young-Fadok et al²¹ have presented preliminary results of a prospective randomised trial examining the influence of prophylactic oophorectomy on recurrence and survival in patients with Dukes B and C colorectal

cancer. No case of ovarian metastasis has been observed in control subjects on short-term follow up.

Guideline — oophorectomy	Level of evidence
Bilateral oophorectomy should be performed if there is obvious malignant disease of one or both ovaries. Prophylactic bilateral oophorectomy for colon cancer cannot be supported by the available evidence.	—

11.6 Laparoscopic surgery for colon cancer

There are no prospective randomised studies that are suitable to support the case for or against laparoscopic-assisted procedures for colon cancer.

Only two prospective randomised studies have been published. In total these have randomised 80 patients, 40 in each group, and follow up has been short term only.^{22,23} Follow up of several larger case-control studies has now been between 18 months and five years.^{24–27} No survival difference or trocar site recurrences have been noted in these studies.

Such studies are complicated by methodologic difficulties. Open surgery is often performed by one group of surgeons and laparoscopic-assisted surgery by another group: many studies have placed laparoscopic colectomy for benign and malignant disease together, making interpretation of results difficult. Laparoscopic surgery for colorectal cancer cannot be recommended outside the conduct of properly designed randomised controlled trials.

11.7 References

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CHAPTER 12

ELECTIVE SURGERY FOR RECTAL CANCER

Rectal cancer surgery has the potential for worse clinical outcomes than colon cancer surgery. Quality of life, local recurrence and survival are generally worse after rectal cancer surgery. Much debate has occurred about the extent of resection, the type of reconstruction and the training of a rectal surgeon.

This chapter aims to summarise, evaluate and quantify the best levels of evidence of some of the contentious clinical aspects of elective surgery for rectal cancer. Unfortunately, for most technical aspects of rectal cancer surgery, the level of evidence on which to base decision making is poor.

12.1 Who should perform elective cancer surgery?

Optimal treatment of rectal cancer is a special challenge, which calls for the best possible clearance of the tumour in association with preservation of the anal sphincter mechanism and avoidance of injury to the pelvic autonomic nerves. Further, it requires the coordination of care of the surgeon, stomal therapist and medical and radiation oncologist.

It could be expected that such results would best be achieved only at specialist multidisciplinary centres. Evidence for this, however, is lacking. McArdle and Hole¹ performed a prospective audit of 645 patients and demonstrated unacceptably high variation in outcomes between surgeons. They concluded that patients would be better treated by surgeons with a special interest in colorectal surgery, but the authors had not specifically tested that proposition in their data collection. The study is sufficient, however, to support the need for national outcome norms and expectations against which individual surgeon performance should be measured.

The question of whether the colorectal-trained surgeon achieves better results than the experienced general surgeon remains unresolved. Comparative audits have generally not shown important differences.²⁻⁴ A more recent study by Porter and co-workers⁵ appears to indicate better outcomes by colorectal surgeons. They compared the outcomes achieved by five colorectal-trained surgeons with 47 general surgeons. Local recurrence rates were lower and survival figures were better for those either with colorectal training or a case load of more than 21 patients. Surprisingly however, even the colorectal-trained surgeons had a local recurrence rate of approximately 14% and on average, for the duration of the study, the colorectal-trained surgeons treated less than three patients with rectal cancer per year. As the specialty of colorectal surgery becomes better established, undoubtedly better data will become available in due course.

These various studies, however, do support two significant observations. Firstly, there are major variations in outcomes between different individuals and different groups. Secondly, there appears to be a correlation between clinical experience in the

treatment of rectal cancer and outcome. Until better data are available to permit more refined definition, we should ensure that our training surgeons have access to the best training. We should require that those performing rectal surgery maintain an accurate audit of their personal outcomes to be compared with national norms and we should encourage the development of specialist interests so that the surgeons treating rectal cancer maintain an adequate level of clinical experience.

In summary, elective surgery for rectal cancer should be carried out by a surgeon who has undergone a period of special exposure to this form of surgery during surgical training and who has satisfactory experience in the surgical management of rectal cancer. All surgeons treating patients with rectal cancer should be aware of their own outcomes as derived from appropriate audits.

12.2 The role of laparoscopic-assisted resection for rectal cancer

Although the feasibility and safety of laparoscopic surgery has been established,⁶ several issues about the application of these techniques for colorectal cancer are still of concern. In particular, we are yet to determine properly the problem of port site metastases, the effect on immune function, long-term survival and the potential for increased cost.

Several prospective studies⁶⁻⁹ and one randomised controlled trial¹⁰ have been published regarding laparoscopic colorectal resections for cancer. However, very few have included patients with rectal cancer, so it may not be appropriate to extrapolate these outcomes to the treatment of rectal cancer.

In these studies, an abdominoperineal excision has generally been performed. Low anterior resections have been performed laparoscopically for selected rectal cancers, but the techniques are not widely applicable, largely due to the lack of suitable stapling instruments that can articulate to 90 degrees.

While the problem of cancer recurrence at the site of a surgical wound is not new, the phenomenon of recurrence at the site of cannula insertion following laparoscopy has been reported increasingly, and reported rates have ranged from 0% to 4%. Prospective results from laparoscopic colorectal registries suggest the true incidence may be closer to 1.1%.¹¹

In comparison, two large series of wound recurrence after open colectomy have reported incidences of 1%¹² and 1.5%.¹³ A closer estimate of the true incidence of wound recurrences after either laparoscopic or open surgery may be obtained after adequate duration of follow up of randomised trials or meta-analysis of several trials.

Furthermore, several experimental reports have suggested that laparoscopic surgery is associated with less tumour growth stimulation than open surgery.¹⁴ It is also associated with better preservation of immune function.¹⁵ It remains, however, to be seen if any of these advantages will be manifest in the clinical setting.

Guideline — laparoscopic surgery	Level of evidence
Laparoscopic surgery for the curative treatment of colorectal cancer should be performed only under the auspices of a randomised controlled trial.	–

It is reasonable to perform palliative laparoscopic surgical procedures in patients with proven inoperable distant metastases. This may include defunctioning stomas for patients with locally advanced pelvic tumours.

12.3 Preoperative stomal therapy consultation

One of the aims of stomal therapy nurse intervention in Australia is that all patients who potentially require a stoma are seen by a stomal therapy nurse and the site of the stoma is marked.¹⁶ There have been no randomised controlled trials carried out on this ideal, but a retrospective qualitative study stated that outcomes of patients who had access to stomal therapy nursing were better than those who had not received this specialist care.¹⁷ Stomal therapy nurses are a credible authority who have the expert knowledge to facilitate patient coping and adaptation to having a stoma. They can do this by facilitating education, counselling and support and by giving a sense of order to the whole process.¹⁸

A study carried out in the United Kingdom shows that 80% of patients who had stomal sites marked by the stomal therapy nurse, but had the site moved by the surgeon, had problems.¹⁶ A retrospective study carried out in the United States showed that 43.5% of patients who were not sited for elective stomal surgery had problems, compared to 32.5% of patients who were sited preoperatively.¹⁹ This indicates that preoperative siting by the stomal therapy nurse is beneficial for improved outcomes of patients with stomas.^{20,21}

Guideline — stomal therapy	Level of evidence
All patients who may require a temporary or permanent stoma should be seen by a stomal therapy nurse before the operation where this facility is available. The stomal therapy nurse assesses the patient's educational needs and, in consultation with the patient or carer, formulates a realistic plan of care and selects an appropriate site for the stoma before the operation.	–

12.4 The role of local excision and transanal endoscopic excision of rectal cancer

Local treatment of rectal cancer can be curative only if there is no spread to regional lymph nodes.²² The incidence of nodal metastases is associated with depth of tumour invasion, tumour differentiation, and lymphatic or venous invasion.^{23–25} Tumour size is not a strong predictor.^{23,24}

Well and moderately differentiated tumours confined to the submucosa (T1) metastasise to lymph nodes in only 3–5% of patients.^{23,24} The preoperative

identification of patients with nodal metastases is difficult, as up to two thirds of nodal metastases are micrometastases.²⁶

Intrarectal ultrasonography is currently the most accurate way of defining tumour depth of invasion and nodal status. Centres with experience in this technique report negative predictive values from 70% to 95% in determining depth of invasion and nodal involvement.^{27,28}

Preoperative assessment of histological grade based on random biopsy is unfortunately unreliable, underestimating the degree of anaplasia in 18% of patients when compared with operative specimens.²⁹

Published series on highly selected patients undergoing curative local excision for rectal cancer report five-year cancer-specific survivals between 88% and 100% (absolute five-year survivals vary from 30% to 100%). Local recurrence rates are reported at between 12% and 27% in those series with more than five years follow up. Half of the patients with local recurrence were salvaged by additional resectional surgery.^{25,30–35}

A prospective randomised study published in 1997 has provided evidence (level II) in support of local excision of T1 rectal cancer.³⁶

Pathological features associated with reduced survival were positive surgical margins, moderately and poorly differentiated histopathology, and increasing depth of invasion (T2 and T3).²² Local excision is associated with a complication rate of between 5% and 18% and a mortality of 1%.²²

Buess et al has recently championed the use of transanal endoscopic microsurgery in the management of early rectal cancers.³³ Transanal endoscopic microsurgery can be performed on lesions from the dentate line to around 20 cm. It allows for suturing and direct closure of full thickness defects. Buess published the results of a case series of 74 patients who had undergone local excision for rectal cancer. There were only two recurrences with a mean follow up of 14 months.

Patients with early rectal cancers (T1 and T2) undergoing abdominoperineal resection have a five-year cancer-specific survival between 85% and 98%, and a local recurrence rate of between 5% and 10%. The mortality associated with performing radical resectional surgery (either abdominoperineal or anterior resection) varies between 1% and 5%.³⁴ This mortality rises markedly in patients over 70 years of age (7% mortality in patients aged 70 to 79, and 17% in those aged over 80 years).

Guidelines — local excision	Level of evidence
Local excision of T1 rectal cancer is effective.	III
Local excision of rectal cancers can only be a curative procedure if there are no lymph node metastases. Predicting nodal involvement remains difficult, therefore radical transabdominal resection remains the treatment of choice in patients with rectal cancer.	III
In less fit patients, or where the alternative is abdominoperineal resection and permanent colostomy, local excision has a role in managing rectal cancer. However in such patients, only a small percentage (5–10%) of rectal cancers meet recommended guidelines for local therapy. These guidelines are: <ul style="list-style-type: none"> • mobile tumour ≤ 3 cm • T1 on endoanal ultrasound • well-differentiated on histology (biopsy) 	III

Local excisions may also afford reasonable palliation in patients with metastatic disease. There is insufficient evidence to accept or reject transanal endoscopic microsurgery in the management of rectal cancer.

There is some evidence that endorectal radiotherapy can be used as definitive treatment or as an adjunct to local excision.³⁶

12.5 The role of abdominoperineal versus sphincter-saving anterior resection

It is assumed that any benefit from adjuvant therapy would be equal irrespective of the type of operation for rectal cancer performed with curative intent. Numerous studies have shown similar outcomes for sphincter-saving resection and abdominoperineal resection with curative intent in terms of survival and local recurrence, and that reconstructive surgery has not compromised oncological outcome.^{35,37} The size of the tumour has often been considered an indication for abdominoperineal resection, but the United States National Surgical Adjuvant Breast and Bowel Project (NSABP) has not shown an adverse outcome even for tumours smaller than 6 cm treated by sphincter-saving resection.³⁷

A study by Williams and Johnston revealed a 25% incontinence rate (usually minor) with a sphincter-saving resection, compared to 66% leak rate from the stomal therapy appliance after abdominoperineal resection, although more modern appliances may have reduced this figure. The authors concluded that patients having low anterior resection have a quality of life superior to those treated by abdominoperineal resection.³⁸ Other studies have also suggested that functional results are satisfactory after low anterior resection,³⁹ although a reduction in rectal sensation related to loss in reservoir capacity probably contributes to incontinence.⁴⁰ However, rectal function improves with time in most cases and with colonic pouch reconstruction.

The incidence of sexual dysfunction after low and very low anterior resection is comparable to abdominoperineal resection (58% compared to 66%).⁴¹

The margin of distal clearance (see above) has been revised from the historical 5 cm to 2 cm based on reviews comparing local recurrence rates and survival which show no advantage in outcome beyond a margin of 2 cm.^{42,43}

Guideline — sphincter-saving operation	Level of evidence
<p>Sphincter-saving operations should be preferred to abdominoperineal resection except in the presence of:</p> <ul style="list-style-type: none"> • low-level infiltrating tumours with unfavourable histological grade • tumours such that adequate distal clearance (>2 cm) cannot be achieved (often an operative decision) • the sphincter mechanism is not adequate for continence • access to the pelvis makes restoration technically impossible (rare) 	III

12.6 The role of high ligation of the inferior mesenteric vessels

There is no demonstrated survival advantage for high ligation.

No studies have evaluated the widely held views that:

- there are potential technical advantages of high ligation in providing additional mobility of the left colon to facilitate low colorectal anastomoses or colonic J-pouch construction;
- there are differences in functional outcome between the two techniques; or
- ischaemic complications in the elderly or atheromatous patient are a contraindication of high ligation.

Although no significant survival advantage has been demonstrated for high ligation of the inferior mesenteric artery, its continued use may be justified on the grounds that it does not result in increased morbidity or mortality, it technically facilitates low colorectal anastomosis and colonic J-pouch construction, and it may improve postoperative bowel function by allowing descending rather than sigmoid colon to be used for anastomoses.^{44,45}

12.7 Distal margin for adequate excision

Since the turn of the century, surgeons have preferred radical surgery when dealing with colorectal carcinoma despite early reports that intramural spread was minimal. Nevertheless, in a small study on intramural spread, Connell and Rottino in 1949⁴⁶ supported the radical approach. In fact, by the 1950s, Grinnell⁴⁷ had suggested a '5 cm rule'. This idea was subsequently supported by the work of Enker et al⁴⁸ and of

Hermanek and Gall⁴⁹, who showed an increased recurrence of cancer when the distal margin was too short.

A substantial body of evidence has since failed to show a relationship between anastomotic recurrence and the length of the distal margin. The implication of these findings is that many patients with low rectal cancers may be reasonably considered for sphincter-saving operations instead of abdominoperineal resection of the rectum with permanent colostomy.

The length of the distal margin may vary depending on whether the specimen is measured fresh, fresh and pinned out, fixed in formalin or fixed in formalin and pinned out. The affect of fixation is minimal if the specimen is pinned out first.⁵⁰

Well-designed quasi-experimental studies (level III) reveal that 81–95% of all carcinomas have either no spread or intramural extension of less than 1 cm.^{47,50-53} Interestingly, one of these was Grinnell's 1954 study.⁴⁷ In all these studies, rectal carcinomas that were associated with intramural spread beyond 1 cm were almost always advanced (high grade, stage C) tumours, or even lesions already associated with distant metastases.⁴⁷⁻⁵² Therefore, in the majority, a distal margin of 2 cm would remove all microscopic disease.

In the remainder, the presence of microscopic intramural disease becomes irrelevant because, in these stages, the resection is ultimately palliative because of the advanced stage of the disease. The large descriptive study by Penfold of 546 abdominoperineal resections endorses these conclusions (level III).⁵³

A number of retrospective studies have related length of distal margin to recurrent cancer. Willams et al⁵¹ reviewed 79 anterior resections, 48 with a distal margin <5 cm (61%) and 31 with a margin >5 cm (39%). Although there were over twice as many advanced (Dukes C; see Chapter 14) lesions in the group with the shorter margin (54% compared to 23%), there was no difference in local recurrence [<5 cm — seven (15%); >5 cm — three (10%)].

Hojo⁵⁴ studied 273 anterior resections, 22 with distal margins less than 2 cm. In this study, there were more Dukes C lesions in the group with margins greater than 2 cm (20% compared to 51%). Nevertheless, anastomotic recurrences still occurred with the same frequency in each group [<2 cm — two (9%); >2 cm — 28 (11%)].

Wilson and Beahrs⁵⁵ analysed 902 anterior resections. Forty-four had distal margins <2 cm. For all anterior resections (high and low), the anastomotic recurrence rate was 7% (three of 44) for the short (<2 cm) margin group and 5% (99 of 858) when the distal margin exceeded 2 cm. Local pelvic recurrence was 16% and 12% respectively.

Pollett and Nicholls⁵⁶ reviewed 334 anterior resections and found no difference between distal margins of <2 cm (55 patients), 2–5 cm (177 patients) and >5 cm (102 patients) with respect to local recurrence (7.3%, 6.2% and 7.8% respectively).

McDermott et al⁵⁷ had 505 anterior resection patients and assessed the distal margin in 1-cm increments (<1 cm, 13 patients; 1–2 cm, 37 patients; 2–3 cm, 88 patients; 3–4 cm, 132 patients; 4–5 cm 89 patients; 5–6 cm, 72 patients; >6 cm, seven patients), but there was no difference in local recurrence among the groups (23%, 22%, 16%, 25%, 16%, 15% and 20% respectively).

Vernava et al⁵⁸ looked at 243 anterior resection cases. Local recurrence was, again, no different in the group <2 cm (28 of 124 patients — 23%) and the group >2 cm (20 out of 115 patients — 17%). However, these workers did observe that, when the distal margin was less than 0.8 cm (20 patients), anastomotic recurrence was greater (six out of 20 patients — 30%) compared to the group with a margin >0.8 cm (23 of 219 patients — 11%).

Finally, Heald⁵⁹ performed 192 anterior resections: 152 were 'curative' with distal margins >1 cm in 110 patients and <1 cm in 42 patients. There were four local recurrences in the first group, but none in the group with margins <1 cm (0 of 42).

Guideline — distal clearance	Level of evidence
As it is uncommon for spread to extend more than 1 cm beyond the primary neoplasm, 2 cm of distal clearance should be more than adequate in most instances.	III

12.8 Total mesorectal excision

Total mesorectal excision for rectal cancer is a sharp dissection in the extrafascial plane between the fascia propria of the rectum and the presacral fascia. Two separate procedures are possible:

- lateral (radial or circumferential) resection of the mesorectum, which should extend at least to the endopelvic fascia to ensure, as often as possible, that the margin of resection is not involved; and
- total excision of distal mesorectum beyond the transection of the rectal wall.

In 1951 Sauer and Bacon⁶⁰ were probably the first surgeons to emphasise the importance of adequate lateral clearance when excising carcinoma of the rectum. Quirke et al⁶¹, in a prospective study, found involved lateral margins in 12.8% of curative resections. In these patients the local recurrence rate was 80%, leading to the hypothesis that inadequate margins were the main cause of local recurrence.

Chapman et al⁶², in a prospective study, showed a decreased five-year survival in those patients whose resected specimens were found to have an involved lateral margin. In 1982 Heald and Ryall⁶³ reported metastatic carcinoma in the adjacent mesorectum in five resection specimens where the spread was distal to the lower extent of the primary tumour. In these three specimens, there were deposits of carcinoma more than 2 cm distal to the caudal limit of the carcinoma. Based on these findings, the recommendation was made that total excision of *distal* mesorectum should be performed when resecting rectal cancer.

This recommendation is supported by two prospective clinicopathological studies. Scott et al⁶⁴ studied distal mesorectal spread in 20 patients where total mesorectal excision was performed. Two patients (10%) had mesorectal spread equal to or greater than 2 cm beyond the lower level of cancer. Both patients developed distant metastases, so that radical treatment of the mesorectum did not improve survival. Reynolds et al⁶⁵ studied mesorectal spread in 50 resected specimens and found

metastatic deposits more than 2 cm below the tumour in five cases (10%). Such findings had a significant relationship to tumours larger than 5 cm in diameter.

Heald and Ryall⁶⁶ published the lowest local recurrence rates (2.6%) for anterior resection of rectal cancer. Pollett and Nicholls⁶⁷ have reported a local recurrence rate of 6.9% in 334 patients treated at St Mark's Hospital, London. Bokey reported a local recurrence rate of 6.5% in 260 treated in the Colorectal Unit at Concord Hospital, Sydney, and Killingback⁶⁸ found a local recurrence rate of 6.6% in 340 patients treated by sphincter-saving resections.

McCall et al⁶⁹, in a review of local recurrence rates, reported pooled results of 1033 patients where the total mesorectum excision technique was used, with a local recurrence rate of 7.3% for all curative resections for rectal cancer. Arbman et al⁷⁰ reported a historically controlled series suggesting a reduction in recurrence and improved survival following total mesorectal excision.

Guideline — total mesorectal excision	Level of evidence
Total excision of distal mesorectum beyond the transection of the rectal wall is not recommended as a routine procedure when resecting rectal cancer until more evidence is available to establish its efficacy.	–

12.9 Rectal washout during elective anterior resection

Exfoliated malignant cells have been demonstrated in the bowel lumen in patients with primary colorectal cancer.⁷¹⁻⁷⁸ The viability of these cells has been confirmed, and reduction in their viability by application of a variety of chemical constituents has been established.⁷¹⁻⁷⁴

Experimentally-induced anastomotic implantation of luminal cells has been demonstrated in an animal model.⁷⁹ Cases of implantation metastases in anal wounds from occult proximal tumours have been reported.⁸⁰ Therefore, it seems logical that elimination of viable exfoliated malignant cells from the vicinity of the anastomosis may prevent implantation metastases, and so reduce the risk of locoregional tumour recurrence. This has not been investigated by a clinical trial to date.

However, irrigation of the rectal stump with normal saline immediately before anastomosis for rectal and sigmoid tumours has been shown to eliminate malignant cells from the perianastomosis zone.⁷⁸

Thorough rectal irrigation probably eliminates malignant cells by mainly mechanical means, even when a cytocidal agent is employed, and should be considered in rectal cancer surgery as a means of reducing locoregional recurrence.

Irrigation of the rectal stump prior to anastomosis should be considered in all patients undergoing restorative resection for rectal cancer.

Guideline — irrigation of the rectal stump	Level of evidence
The rectal stump can be irrigated with normal saline immediately before anastomosis for rectal and sigmoid tumours in an attempt to eradicate malignant cells from the perianastomosis zone.	III

12.10 The role of colonic pouches after elective anterior resection

Three prospective randomised controlled trials comparing coloanal anastomoses with and without a colonic pouch have been reported, each demonstrating significantly improved rectal function persisting from the time of stoma closure to at least one year.⁸¹⁻⁸⁴

All studies demonstrated a significant reduction in stool frequency, from a median of six stools per day to three stools per day. There was at least a trend to improvement in other functional measures in each study, including rectal compliance, urgency and continence, but small numbers reduced the power of these studies to demonstrate a significant difference in every measured parameter.

A high incidence of incomplete rectal emptying has been observed in patients with pouches 8–10 cm in length.⁸⁵⁻⁸⁸ In the largest series of 162 patients, with a maximum follow up of seven years, 25% of patients required an enema or suppository to empty the pouch.⁸⁸ A pouch length of 8–10 cm was calculated in a mathematical model to produce an ideal pouch capacity⁸⁹ although the risks of impaired emptying were not factored into this model. In a randomised clinical trial, 5-cm pouches were found to have similar physiologic function to the 10-cm pouch. There was some sacrifice in reservoir capacity, but a significantly better ability to evacuate.⁹⁰ The long-term function of pouches remains to be fully assessed.

It has been demonstrated that there is a significantly reduced blood flow within the colonic wall at the end of a straight end-to-end coloanal anastomosis, relative to that at the site of a pouch–anal anastomosis.⁹¹ This may explain the anecdotal reports of a reduction in leakage seen after pouch–anal anastomosis.⁸⁴

Guidelines — colonic pouch	Level of evidence
Where technically feasible, the colonic pouch may be the preferred form of reconstruction after low anterior resection of tumours of the lower half of the rectum to improve short-term postoperative neorectal function.	II
The ideal length of the pouch lies between 5 cm and 8 cm.	III

12.11 The role of drains to coloanal and colorectal anastomoses

The routine use of pelvic drains after colorectal or coloanal anastomosis remains controversial. Proponents of drainage argue that drains allow the egress of postoperative fluid collections that have the potential to become infected and, therefore, may predispose to anastomotic complications. It has also been suggested that an anastomotic dehiscence may be more readily recognised, and perhaps controlled, if a drain has been inserted. Studies in animal models have shown that the use of drains near colonic anastomosis is associated with an increased incidence of anastomotic leakage, morbidity and mortality.⁹² Randomised controlled trials have demonstrated no benefit for the use of routine drains for intraperitoneal colonic anastomoses, and their use has largely been abandoned.^{93,94} Many surgeons continue to drain rectal anastomoses which lie below the peritoneal reflection within the pelvis, in which haematoma and fluid collections may accumulate.

It has been demonstrated that the quantity of fluid removed by a drain in the pelvis increases as the distance of the anastomosis from the anus decreases, suggesting that it is dependent, at least in part, upon the extent of pelvic dissection, rather than to local reaction to the drain.⁹⁵

There has only been one randomised controlled clinical trial of pelvic drainage after rectal resection in which a 'no drain' arm was included.⁹⁶ This study compared the use of a high pressure closed-suction drain with no drain in patients undergoing rectal resection. There was no difference in postoperative morbidity or mortality, or in the size of the pelvic fluid collection as measured by ultrasound in the two groups. It has been shown that the duration of drainage has no effect on the development of pelvic sepsis and that when anastomotic leakage does occur, the presence of a drain does not permit its earlier recognition.⁹⁵⁻⁹⁷

Despite this, the use of pelvic drainage after rectal resection is widely practised, and there is no evidence to indicate that it has a detrimental effect on anastomotic healing.⁹⁷

Guideline — anastomosis drains	Level of evidence
There is no evidence that drains to coloanal and colorectal anastomoses are either beneficial or harmful. They should be used at the surgeon's discretion.	II

12.12 References

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CHAPTER 13

EMERGENCY SURGERY

In population-based studies, about 30% of people with colon cancer and 10% of people with rectal cancers present as emergencies. Most of these (80%) have obstruction and most of the others (15%) have perforation.^{1,2} Massive bleeding from colorectal cancer is an uncommon presentation.³

A clinical diagnosis of bowel obstruction is confirmed by a plain abdominal radiograph, and a limited gastrografenema. Sigmoidoscopy is performed to exclude pseudo-obstruction.⁴

Most perforations occur at the site of the cancer. A less common presentation is a perforated caecum due to an obstructing cancer of the left colon.⁵ Perforation leads to either a localised abscess or generalised peritonitis.

13.1 Investigations for emergency presentations

13.1.1 Erect chest x-ray

This helps assess any concomitant cardiorespiratory disease and lung metastases, and demonstrates the presence of free subdiaphragmatic gas, which would indicate intraperitoneal perforation. An abdominal decubitus film should be performed for this latter purpose if it is not possible to obtain an erect chest x-ray.

13.1.2 Abdominal x-ray

Supine and erect plain radiographs of the abdomen will usually show typical features of large bowel obstruction. Right-sided colonic obstruction may present appearances similar to a distal small bowel obstruction. True mechanical obstruction may be impossible to distinguish from pseudo-obstruction.⁶ The degree of caecal distension depends on the competence or otherwise of the ileocaecal valve, and should be determined on plain abdominal radiograph.

13.1.3 Contrast enema

For patients with a suspected large bowel obstruction the examination is undertaken without bowel preparation using dilute barium or gastrografen. This helps determine the presence and level of mechanical large bowel obstruction.⁶ If there is any clinical suspicion of perforation, a water-soluble contrast (gastrografen or others) should be employed.

13.1.4 Sigmoidoscopy

In patients with a distal large bowel obstruction, a sigmoidoscope may be used to visualise the obstructing lesion. This is of greater value for detecting rectal or

rectosigmoid lesions than colonic lesions, and it will help plan the surgery (see Chapter 8).

13.1.5 CT scan of the abdomen and pelvis

This is useful when there is clinical suspicion of a local perforation and in very elderly and/or immobile patients where a contrast enema can not be tolerated.⁷ A CT scan may sometimes differentiate diverticular disease from a neoplasm.

Guideline — diagnosis of large bowel obstruction	Level of evidence
A clinical diagnosis of large bowel obstruction is to be confirmed by a plain radiograph of abdomen and a limited gastrografenema and sigmoidoscopy (preferably flexible) to exclude pseudo-obstruction.	III

13.2 Timing of surgery

Unless perforation is overt (shown by free gas under the diaphragm) or imminent (shown by a distended caecum), surgery for a large bowel obstruction can be regarded as an urgent rather than an emergency procedure. It is preferable to schedule surgery during the day with a full complement of experienced medical and nursing staff. If there is overwhelming sepsis or, rarely, severe bleeding, urgent surgery is performed after optimisation.

Emergency surgery should be carried out during daytime hours, whenever possible, by experienced surgeons and anaesthetists. Less commonly, patients present with imminent or overt perforation and should undergo surgery more urgently after initial stabilisation. In general, patients presenting as emergencies should be optimised before surgery. The need for a stoma should be considered, discussed and sited preoperatively by a stomal therapy nurse or surgeon whenever possible.

13.3 Preparation for surgery

Patients presenting in the emergency department should be prepared carefully for surgery, with adequate fluid and electrolyte resuscitation and monitoring of hydration and urine output. Antibiotic⁸ and deep vein thrombosis (DVT)^{9–11} prophylaxis are administered (see also Chapter 10).

Mechanical bowel preparation is generally not used. However, in patients with subacute large bowel obstruction where there is an interval of several days between presentation and surgery, bowel rest and gentle enema are helpful.

All patients should have a rectal examination and sigmoidoscopy (preferably flexible) to exclude a synchronous rectal lesion. Discussion on siting of a stoma should be performed preoperatively, preferably by a stomal therapy nurse.

The support of an intensive care or a high dependency unit may be needed postoperatively, and occasionally preoperatively as well. Many patients have other comorbid medical conditions and require careful anaesthetic assessment and medical

optimisation. In appropriate cases, autologous blood should be stored or blood should be cross matched preoperatively.

13.4 Surgery

13.4.1 Bowel obstruction

For right-sided cancers, unless there is overwhelming sepsis with generalised peritonitis or the patient is very frail and sick, a primary ileocolic anastomosis is usually performed.¹²

For left-sided obstructing lesions, the cancer is usually resected, either as a Hartmann's procedure with an end colostomy, or, when certain criteria are fulfilled (see below), with primary resection with anastomosis.¹³ However, Kronborg¹⁴ reported a randomised controlled trial which showed little difference between staged and immediate resection. For right-sided lesions presenting as obstruction or perforation, primary resection should be carried out.

With primary anastomosis, the following options are available:

- appropriate resection and a primary anastomosis accompanied by on-table lavage¹⁵ or a modified bowel preparation (for subacute bowel obstruction); or
- subtotal colectomy with ileorectal anastomosis.¹⁶

The morbidity and outcome of these two restorative procedures are comparable, although the long-term bowel function is better with a more limited resection.¹⁷ Occasionally, a diverting loop ileostomy is used to protect the anastomosis after a segmental resection.¹⁸ A subtotal colectomy is preferred in the presence of caecal perforation¹⁹ or in the presence of synchronous neoplasms.

Guideline — surgery for bowel obstruction	Level of evidence
For left-sided obstructing cancer, the lesion is resected, either as a Hartmann's procedure with an end colostomy or as a subtotal colectomy and ileocolic or ileorectal anastomosis. Segmental resection and anastomosis may be performed, if preceded by intraoperative on-table colonic lavage.	II

13.4.2 Perforated cancer

The principles of surgery for a perforated cancer follow those for an obstructing cancer. The main points in management are treatment of sepsis and resection of the perforated cancer or colon.⁵ With a left-sided perforated cancer, an anastomosis is best avoided in the presence of generalised peritonitis and significant sepsis. A stoma is performed whenever it is clinically indicated (overwhelming sepsis, frail and sick patients, problematic anastomosis or unresectable cancer — see below). If there is any doubt whether a diversion should be performed or not, then the procedure is

generally indicated. In these circumstances, the siting of the stoma will usually be done by the surgeon, the location to be as appropriate as possible in the circumstances.

13.4.3 Colonic bleeding

When a patient presents with massive rectal bleeding, consideration should be given to other more common causes such as diverticular disease or angiodysplasia. The principle of surgery for a bleeding colon cancer is similar to that for an obstructing cancer.

13.4.4 Nonoperative relief of obstruction

More recently, laser therapy has been used in acute obstructing left colon cancers as a pre-resection strategy, allowing for a formal bowel preparation and a definitive one-stage resection and anastomosis. Self-expandable metallic stents have also been used to relieve left colon obstruction by cancer, enabling mechanical bowel preparation, elective resection and anastomosis.²⁰ The experience with either pre-resection laser therapy or stenting is limited to isolated case reports only.

In high-risk patients with major comorbid factors, the quickest and safest surgical option is preferred.

13.5 Outcome

13.5.1 Morbidity and mortality

Patients presenting as emergencies tend to be older and have other comorbid illness.^{21,22} The duration of hospitalisation tends to be longer and there is a higher incidence of a permanent stoma.²¹ Perioperative morbidity and mortality (19% compared to 8%) are higher and survival poorer (29% compared to 39% at five years), compared with patients undergoing elective surgery.²³

The operative mortality following emergency/urgent surgery for colorectal cancer has been consistently less than 20% in most recent audits of major centres.^{24,25} Subgroup analysis, however, revealed a higher (35% vs 15%) operative mortality after surgery for perforated than obstructed colorectal cancer,^{22,26,27} especially if major sepsis is present.

13.5.2 Cancer-related survival

Patients presenting as emergencies tend to have a more advanced-staged cancer.^{21,22,26,27} The only variable of prognostic significance in emergency surgery for obstructing colorectal cancer is the stage of the cancer.²⁸

With malignant large bowel obstruction, after taking into account 30-day operative mortality, obstruction as initial presentation *per se* does not appear to be an independent predictor of longer-term survival.

Perforation with generalised peritonitis is associated with a higher incidence of tumour recurrence and it is an independent adverse prognostic factor.^{22,26,29,30} Five-year

survival may also be adversely affected by inadvertent perforation of the colon or rectum,³¹ or spillage³² during 'curative' resection for cancer.

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CHAPTER 14

STAGING AND REPORTING

Staging of colorectal cancer refers to the classification of the tumour according to the extent of spread in a manner that has a clinically useful correlation with prognosis.

Applications of staging include patient management, quality assurance and research.

There are a number of imaging techniques, including endorectal ultrasound, that will define the extent of tumour spread at the time of diagnosis. There is, however, no known reliable preoperative staging system that correlates accurately with patient survival.

14.1 Development of postsurgical staging

The first well-documented and tested staging system was that of Dukes.¹ This system was based entirely on the extent of direct tumour spread and the presence or absence of lymph node metastases in the resected specimen of bowel. Although Dukes staging was originally described for rectal cancer, it has been shown to also be applicable to colon cancer. Dukes stages A, B and C correlated well with patient survival, and they were easy to recall and apply. For these reasons the system was widely adopted. However, the Dukes system did not seek to address the issue of residual tumour, whether local, due to tumour transection, or due to known distant metastases.

The Dukes A, B, C system was broadened by Turnbull et al, who added a stage D for cases with known distant metastases and locally advanced tumour.² Thus, Turnbull introduced the concept of clinicopathological staging in which distant metastases, found by the surgeon at the time of bowel resection, could determine the assigned stage. Clinicopathological staging has now gained wide acceptance as the preferred method of staging.

14.2 Selection of a clinicopathological staging system

The two main clinicopathological staging systems available, the Australian clinicopathological staging (ACPS) system and pathological staging (pTNM — tumour, node, metastasis), may both be seen as extensions of the original Dukes staging method.

The ACPS system was recommended for use in Australia following two workshops on staging held in Brisbane in 1981.³ The system was validated using prospectively collected data from the Concord Hospital Colorectal Cancer Project. The ACPS is essentially a simplified version of the system used at Concord Hospital since 1971.^{4,5} the ACPS and Concord systems are shown in Table 14.1.

Table 14.1 Clinicopathological staging systems

Maximum spread	ACPS	Concord substage
Mucosa	A0	A1
Submucosa	A	A2
Muscularis propria		A3
Beyond muscularis propria	B	B1
Free serosal surface		B2
Local nodes involved	C	C1
Apical nodes involved		C2
Tumour transected (histological)	D	D1
Distant metastases (clinical or histological)		D2

Source: Davis and Newland¹⁸

A pTNM system acceptable to both the Union Internationale Contre Le Cancer and the American Joint Committee for Cancer was agreed in 1986 with the aim of attempting to achieve uniformity in staging of colorectal cancer (Tables 14.2 and 14.3).^{6,7}

Table 14.2 Pathological TNM staging nomenclature

T — spread of primary tumour	
Tis	Carcinoma in situ
T1	Submucosa
T2	Muscularis propria
T3	Subserosa, nonperitonealised pericolic/perirectal tissues
T4	Other organs or structures/visceral peritoneum
N — regional lymph nodes	
NO	No regional lymph node metastases
N1	1–3 positive regional nodes
N2	4 or more positive regional nodes
M — distant metastasis	
MO	No distant metastasis
M1	Distant metastasis

Source: AJCC¹⁹

Table 14.3 Pathological TNM staging

Stage	Tis	N	M
0	Tis	NO	MO
I	T1	NO	MO
	T2	NO	MO
II	T3	NO	MO
	T4	NO	MO
III	Any T	N1	MO
	Any T	N2	MO
IV	Any T	Any N	M1

Source: Hermanek²⁰

Apart from the symbols used to designate the stages, the two clinicopathological systems differ only in their definition of known residual tumour. The ACPS stage D requires the presence of tumour in a line of resection (histological) and/or distant metastases (clinical or histological), while pTNM stage IV applies only to cases with known distant metastases (clinical or histological). The pTNM includes an optional R classification for local residual tumour but does not assign a stage for such cases.

Data have been published supporting the inclusion of tumour in a line of resection in ACP stage D and others have also documented the importance of this histological parameter.^{8,9} Should the histological assessment of lines of resection be made essential for pTNM staging and involvement by tumour be a criterion for stage IV classification, then the two systems would be identical.

The ACPS system embodies the simplicity of Dukes staging. It comprehensively defines known residual tumour, it is based on a small number of key variables (direct spread, lymph node metastases and known residual tumour) and it has been validated by a large prospective series.

Guideline — staging data	Level of evidence
ACPS staging, TNM staging and the data required to stage the patient should all be recorded to allow national and international comparisons.	III

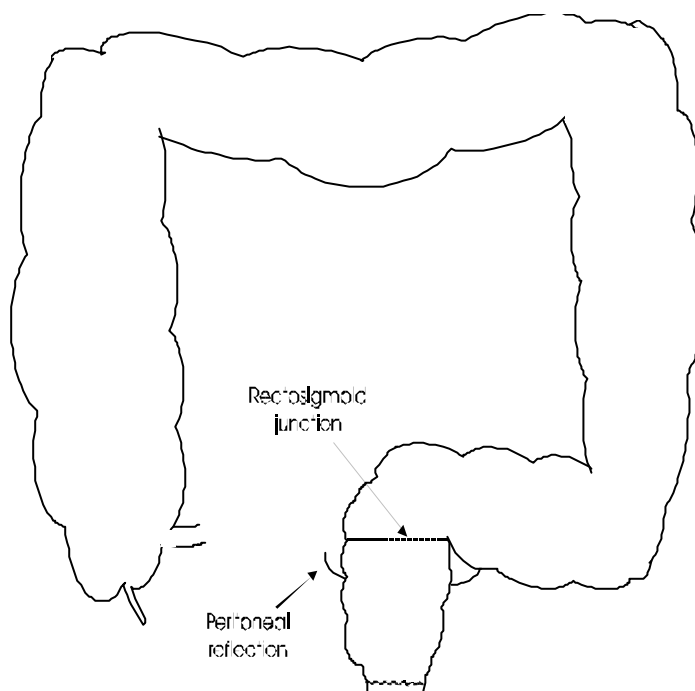
14.3 Clinical input

The use of a clinicopathological staging system requires that the surgeon make the operative findings known to the pathologist. A convenient proforma for conveying this information is attached as Figure 14.1. Should this information be unavailable to the pathologist, the report should indicate that the ACPS has been assigned on the assumption that there were no known distant metastases present at the time of the resection.

CANCER OF THE COLON AND RECTUM — INFORMATION FOR THE PATHOLOGIST

The following special information should be recorded for the pathologist in addition to the usual information supplied when requesting histopathological examination. This special information will enable the pathologist to use the Australian Clinicopathological Staging System in this report.

Name		Age	Sex	File no.
<ul style="list-style-type: none"> • Mark location of tumour on diagram • Mark lines of resection on diagram 				
Name of operation performed:				
Was operation: <input type="checkbox"/> curative (<i>no obvious tumour remaining</i>) <input type="checkbox"/> palliative (<i>tumour remaining</i>)		If palliative, the reason was: <input type="checkbox"/> tumour transected <input type="checkbox"/> metastases remaining <input type="checkbox"/> both		
If distant metastases present:				
State site(s)	Biopsy taken <input type="checkbox"/> yes <input type="checkbox"/> no	Was adjacent organ(s) or tissue excised with bowel <input type="checkbox"/> yes <input type="checkbox"/> no		



M.O. Signature.....

Figure 14.1 Cancer of the colon and rectum — information for the pathologist

14.4 Translation between staging systems

A matrix for the purpose of translating between staging systems was developed by a working party on staging, which reported in 1990.¹⁰ The international comprehensive anatomical terminology (ICAT) for colorectal cancer and matrix for staging conversion is shown in Table 14.4.

14.5 Additional information on pathology

Apart from tumour stage, the importance of including information on a range of other variables in the histopathology report is recognised. These variables include the components of stage and some other factors, which have been shown to have a bearing on prognosis. The independent prognostic effects of many of these variables has been assessed within the ACPS system and have been demonstrated to be stage dependent.^{8,11,12}

The pTNM staging system uses an alphanumeric shorthand method of defining the extent of tumour spread. This terminology is detailed but it does not permit the separate designation of cases where tumour spread specifically involves a free serosal surface. This aspect of tumour spread has been shown to be an important prognostic variable.¹¹⁻¹³ As has been mentioned, the code for local residual tumour (the R classification) is optional.

14.5.1 Reporting on colorectal cancer specimens

The following list of variables should be addressed when reporting on colorectal cancer specimens:

1. **Extent of direct spread** of tumour (submucosa, muscularis propria, subserosa, free serosal surface, adjacent organ/structure, surgical lines of resection).
2. **Lymph node involvement** (number of involved nodes, apical node involved or not). The number of nodes examined should be recorded as a guide to the adequacy of the lymph node harvest.
3. **Venous invasion** present or absent.
4. **Perineural invasion** present or absent.
5. **Tumour histology**
 - tumour type (adenocarcinoma, mucinous adenocarcinoma*, signet ring cell*, large cell undifferentiated*)
 - grade of differentiation (well, moderately or poorly differentiated)
 - margin (expanding or infiltrating)
 - peritumoural and tumour infiltrating lymphocytes*
6. **Histology of any biopsy material.**

* Histological variables are useful diagnostic markers for hereditary nonpolyposis colon cancer (HNPCC) and sporadic cancers showing microsatellite instability (MSI).^{14,15}

14.5.2 Microsatellite instability

It is now apparent that DNA microsatellite instability falls into a high category (MSI-H) in which at least 30% or more loci tested show instability and a low category (MSI-L).^{16,17} Only the MSI-H category shows distinctive clinical, pathological and molecular characteristics. These include:

- proximal location
- lower stage
- lower frequency of distant spread
- improved survival
- increased frequency of cancer multiplicity
- diploidy
- poor or mucinous differentiation and tumour infiltrating lymphocytes

Between 9% and 16% of colorectal cancers are MSI-H. By contrast, MSI-L cancers are indistinguishable from microsatellite stable cancers.^{16,17}

It is likely that further studies on tumour markers will provide more information on the expected behaviour of colorectal cancers.

Table 14.4 International comprehensive anatomical terminology (ICAT) for colorectal cancer and matrix for staging system conversion

Line #	Feature in 1 cat	pTNM	Line #	pTNM		ACPS		Concord Hospital		Dukes and Bussey 1958		Astler-Coller		Japanese Research Society	
				Stage	Line #	Stage	Line #	Stage	Line #	Stage	Line #	Stage	Line #	Stage	Line #
	Microscopic description of tumour depth			0	3	0	3	A-1	3	A	4,5	A	3	1	3–5
1	– Primary tumour cannot be assessed	pTX	1		12		12		12		12		12		12
2	– No evidence of primary tumour	PT0	2		15,16		15,16		15,16		15,16		15,16		15,16
3	– Cancer in situ; severe dysplasia	pTis	3		18,19		18,19		18,19		18,19		18,19		18,19
4	– Tumour invades submucosa	pT1	4		22		22		22						22
5	– Tumour invades muscularis propria	pT2	5				25		25	B	6–8	B-1	4,5		
6	– Tumour invades through muscularis propria into the subserosal connective tissue or non-peritonealised pericolic or perirectal tissue	pT3	6	I	4,5						12		12	II	6,8
		pT4	7,8		12	A	4,5	A-2	4		15,16		15,18		12
					15,16		12		12		18,19		18,19		15,16
		pNX	9		18,19		15,16		15,16						18,19
7	– Tumour directly invades other organs or structures	pN0	12		22		18,19		18,19	C-1	4–8	B-2	6–8		22
		pN1	13,15,16,18,19				22		22		13,14		12		
8	– Tumour to and invading free (serosal) surface of the specimen	pN2	14,15,16,18,19	II	6–8		25		22		15–17		15,16	III	7 or 4–8
		pN3	17,20		12				25		18,19		18,19		12 or 13,14
					15,16	B	6–8	A-3	5						15,16 or 15,16

Table 14.4 (contd)

Line #	Feature in 1 cat	pTNM	Line #	pTNM		ACPS		Concord Hospital		Dukes and Bussey 1958		Astler-Coller		Japanese Research Society	
				Stage	Line #	Stage	Line #	Stage	Line #	Stage	Line #	Stage	Line #	Stage	Line #
	Regional lymph node status	(p)MX	21		18,19		12		12	C-2	4–8	C-1	4,5		18,19 or 18,19
9	– Cannot be assessed	(p)M0	22		22		15,16		15,16		13,14		13,14		22 or 22
10	– Number of lymph nodes examined	(p)M1	23				18,19		18,19		15–17		15–17		
11	– Number of nodes positive for tumour			III	1–8		22		22		20		18–20	IV	4–8
12	– Line 11=0	RX	24		13,14		25		25						13,14
13	– Line 11=1–3 positive nodes	R0	25		15–17							C-2	6–8		17
14	– Line 11 >3 positive nodes	R1/R	26–28		18–20	C	1–8		B-1	6,7			13,14		20
		2			22		13,14		12				15–17		22
	Status of nodes on vascular trunk						15–17		15,16				18–20		
15	– Not recorded			IV	1–8		18–20		18,19						
16	– Negative for tumour				9,12–14		22		22					V	1–8
17	– Positive for tumour				15–17		25		25						9,12–14
					18–20										15–17
	Apical node status				23	0	1–8	B-2	8						18–20
18	– Not recorded						9,12–14		12						23
19	– Negative for tumour						15–17		15,16						
20	– Positive for tumour						18–20		18,19						
							23		22						
	Distant metastasis: status before definitive treatment						24–28		25						
21	– Cannot be assessed							C-1	1–8						

Table 14.4 (contd)

Line #	Feature in 1 cat	pTNM	Line #	pTNM		ACPS		Concord Hospital		Dukes and Bussey 1958		Astler-Coller		Japanese Research Society	
				Stage	Line #	Stage	Line #	Stage	Line #	Stage	Line #	Stage	Line #	Stage	Line #
22	– None								13,14						
23	– Present								15–17						
									18,19						
	Residual tumour: status after definitive treatment								22						
									25						
24	– Cannot be assessed														
25	– None							C-2	1–8						
26	– Locally in line of bowel resection only (shown histologically)								13,14						
									15–17						
27	– Distant only (histologically or clinically)								20						
28	– Both local and distant								22						
									25						
								D-1	1–8			Notes			
									9,12–14						
									15–17			(1)	Distant metastasis (line 21–23) is not considered in Dukes-Bussey and Astler-Coller system		
									18–20						
									22						
									26						
								D-2	1–8			(2)	Residual tumour status (line 24–28) is considered in ACPS stage and Concord Hospital system only. It may be recorded in the TNM system by the additional R classification.		
									9,12–14						
									15–17						
									18–20						
									23			(3)	All data are of proven prognostic significance.		
									24–28						

pTNM = pathological staging (tumour, node, metastasis); ACPS = Australian clinicopathological stage; Source: Dukes and Bussey²¹, Astler and Collier²², Jinnai²³

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CHAPTER 15

ADJUVANT THERAPY FOR COLON CANCER

Carcinoma of the colon is a major cause of cancer death. More than a third of patients with colon carcinoma present with lymph node metastases and more than half of these patients, initially treated for cure, relapse and later die of the disease.

There have been recent advances in the use of adjuvant therapy in patients with colon cancer following curative resection, but questions remain regarding appropriate adjuvant therapy, its value and indications.¹

15.1 The research evidence

Buyse et al summarised the data on randomised trials of adjuvant therapy for colorectal cancer up to 1987.² Results of this meta-analysis will be discussed subsequently. In addition, the Australian Cancer Network and Clinical Oncological Society of Australia working party on adjuvant therapy for colon cancer (see Appendix A) considered only randomised controlled trials published after 1987 comparing adjuvant treatments with observation or other treatments after curative surgery in patients with Dukes C colon cancer. That evidence will be considered now.

15.1.1 Early adjuvant trials

This group of three trials predates modern treatment schedules. The South Western Oncology Group (SWOG) compared chemotherapy using 5-fluorouracil (5-FU) plus semustine (MF) with MF plus BCG immunotherapy or BCG alone. The negative result of the SWOG trial (no survival benefit detected) was consistent with previous reports.³

The NSABP trial C-01 was the first large adjuvant trial in colon carcinoma to detect a benefit for adjuvant therapy. It found a borderline significant 8% absolute improvement in survival for Dukes C (but not B) patients treated with either chemotherapy (semustine, vincristine, 5-FU) or BCG.⁴

The third trial in this group was a cooperative study from Japan in which patients with either colon or rectal cancer were randomised, after stratification, to observation or one of two regimens of chemotherapy.⁵ The Japanese study used chemotherapy not widely used in Australia: mitomycin C by portal and peripheral vein injections plus oral 5-FU. Survival results favoured adjuvant therapy over observation, but only in the subgroup of Dukes C patients.

15.1.2 5-fluorouracil plus levamisole

These trials inaugurated the modern era of adjuvant treatments involving the use of the 'immunomodulator' levamisole or the biochemical modulator of 5-FU, leucovorin (folinic acid).

In the initial Leicester trial,⁶ patients were randomised after curative surgery to either observation, 5-FU, or 5-FU plus levamisole. 5-FU was administered intravenously for three days following surgery, and then orally once weekly for six months; levamisole was administered for only three postoperative days. After five years of follow up, the survival of patients randomised to 5-FU plus levamisole was significantly prolonged compared with 5-FU alone ($P = 0.02$) or observation ($P = 0.045$).

Levamisole alone, given intermittently for one year, did not produce a survival benefit in the European Organization for Research and Treatment of Cancer (EORTC) trial with Dukes C colon cancer patients,⁷ and its effect was inferior to the combination with intravenous 5-FU in the North Central Cancer Treatment Group (NCCTG) trial in Canada with Dukes B and C colorectal cancer patients.⁸

Intergroup trial #0035 detected a significant survival advantage for 5-FU plus levamisole compared with observation.⁹ This benefit, amounting to a 30–40% reduction in the rates of recurrence and death, occurred only in Dukes C,¹⁰ but not in Dukes B, colon cancer patients.¹¹ The United States Consensus Conference in 1990 recommended this one-year combination of 5-FU plus levamisole as standard care for Dukes C colon cancer patients.¹

15.1.3 5-fluorouracil plus leucovorin

Using an individual patient data meta-analysis, the IMPACT (International Multicentre Pooled Analysis of Colon Trials) investigators pooled the results from 1493 randomised patients across three similar trials (Italian, French and Canadian) in patients with Dukes B or Dukes C colon cancer.¹² These trials compared postoperative observation with adjuvant 5-FU modulated by leucovorin (folinic acid).

A significant reduction in the rate of recurrence was detected for patients randomised to 5-FU plus leucovorin treatment compared with control (hazard ratio [HR] 0.65; 95% CI, 0.54 to 0.78; $P < 0.0001$). After a median follow up of 3.5 years, there was also a reduction in the risk of death favouring treatment (HR 0.76; 95% CI, 0.61 to 0.96; $P = 0.018$). The benefits were confined to patients with Dukes C disease. Survival at three years was 76% versus 64% favouring treatment in Dukes C patients, and 90% versus 88% in Dukes B.

A similar observation was reported by Francini et al¹³ In this trial, 239 patients with Dukes C or high-risk Dukes B colon cancer were randomised to either observation or 5-FU plus leucovorin following resection. With a median follow up of 4.5 years, the relative reduction in recurrence rate was 35% (95% CI, 18% to 52%) and in mortality rate 34% (95% CI, 23% to 45%) favouring treatment. At five years, survival was 79% for adjuvant therapy compared with 65% for control ($P = 0.0044$). When analysed by stage, the benefit was confined to patients with Dukes C disease.

For patients with Dukes C disease, five-year survival was 69% compared to 43% for adjuvant therapy and control respectively ($P = 0.0025$); recurrence-free survival was 66% and 41% respectively ($P = 0.0016$). A preliminary report in abstract form of intergroup trial #0089 also detected an overall significant reduction in recurrence rate (77% compared to 64% at 3.5 years; $P = 0.004$), but no improvement in survival (75% compared to 71%; $P = 0.13$) favouring 5-FU plus low-dose leucovorin compared with observation, but the analysis was not stratified by stage.¹⁴

15.1.4 Portal vein infusion

The most reliable evidence upon which to make treatment recommendations comes from a recently published individual patient data meta-analysis of trials of portal vein infusion in colorectal cancer.¹⁵ The analysis of 3499 patients from 10 trials detected an 18% reduction in the annual odds of death for all patients treated with portal vein infusion ($P = 0.0004$), which translates into an absolute reduction in death rate at five years of 6% ($P = 0.001$). When analysed by stage, patients with Dukes C disease experienced a 5% absolute improvement in survival at five years (46.9% compared to 51.7%; $P = 0.2$) corresponding to a 17% reduction in the odds of death for patients with Dukes C disease alone (not significant). An important large negative study ($n = 1200$), of portal vein infusion has subsequently been published.¹⁶

When portal vein infusion was compared with systemic chemotherapy with 5-FU alone, there was a 14% reduction in the odds of death with portal vein infusion. However the difference did not approach conventional levels of significance ($P = 0.4$) and the systemic therapy regimen (5-FU alone) would be considered inadequate by today's standards.

In the individual patient data meta-analysis, portal vein infusion was associated with a 28.2% reduction in the odds of hepatic recurrence as the first event for all patients ($P = 0.001$), which was due mainly to the first hypothesis-generating trial involving 271 patients.¹⁷ For the other nine trials combined, involving 2817 patients, there was a 14% reduction in the odds of hepatic recurrence as the first event, which was not significant ($P = 0.2$).¹⁵ However, a meta-analysis of all portal vein infusion-treated patients detected an overall 25% decrease in deaths compared with observation ($P = 0.0002$).¹⁸

15.1.5 Trials without no-treatment control arm

The NSABP trial C-03 compared MOF (semustine, vincristine and 5-FU) with a combination of 5-FU plus leucovorin.¹⁹ A significant improvement in disease-free and overall survival was reported for patients treated with 5-FU plus leucovorin. The survival benefit was mainly in Dukes C patients (27% relative reduction in deaths).

Three trials, published in abstract form only and presented at the 1996 meeting of the American Society of Clinical Oncology (ASCO),²⁰⁻²² compared the standard control recommended in 1990¹ (one year of 5-FU plus levamisole) with a variety of regimens including 5-FU plus leucovorin and/or levamisole. NSABP C-04 compared 5-FU plus levamisole with 5-FU plus high-dose leucovorin, either alone¹⁸ or added with levamisole.²⁰

Patients randomised to 5-FU plus leucovorin for one year had a significantly better survival than those randomised to 5-FU plus levamisole for one year. The addition of levamisole to 5-FU plus leucovorin did not improve outcomes, but did increase toxicity. Treatment effect was similar in Dukes B and C patients.

An intergroup trial (#0089) also compared standard therapy of one year of 5-FU plus levamisole to three regimens of 5-FU at two different dose levels of leucovorin, administered for six months.²¹ In the final analysis, four of the five potential treatment comparisons were equivalent for disease-free and overall survival. These were 5-FU plus leucovorin in low dose versus high dose; 5-FU plus levamisole versus 5-FU plus

high-dose leucovorin; and 5-FU plus low-dose leucovorin with and without levamisole. The comparisons of 5-FU plus levamisole with 5-FU plus low-dose leucovorin without levamisole remain blinded for future analysis. Significant differences in treatment effect were not detected for Dukes B and III patients.

The third of these recently presented studies is a collaboration between the NCCTG and the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG).²⁰ In a two-by-two factorial design, standard 5-FU plus levamisole was compared with a three-drug regimen of 5-FU plus low-dose leucovorin plus levamisole, and either regimen given for six or 12 months. Although no difference in disease-free survival was observed, a significant overall difference in survival was noted ($P = 0.04$). In pairwise comparisons, the only significant survival advantage was for patients receiving the three-drug regimen for six months compared to patients receiving the standard one year 5-FU plus levamisole regimen ($P = 0.005$). Subgroup analyses according to stage have not yet been reported. Overall, these three studies suggest that six to eight months of 5-FU plus leucovorin is at least as good as 12 months of 5-FU plus levamisole.

15.1.6 Other trials

Chemotherapy delivered by the intraperitoneal route has been tested in two trials of adjuvant therapy.^{23,24} Intraperitoneal treatment involves the infusion of drug into the peritoneal cavity, with catheter placement. Both trials used no-treatment control groups, with one trial using a placebo.²⁴

Clinical outcomes related to recurrence and survival were reported in only one trial involving 121 randomised patients with Dukes C or high-risk Dukes B disease.²³ At a median follow up of 4.6 years, both disease-free survival and overall survival favoured treatment (disease-free survival 75% compared to 58%; $P = 0.06$; overall survival 78% compared to 63%; $P = 0.05$); but the effect was confined to patients with Dukes C disease. Because of the trial design, it cannot be determined whether this route of therapy is superior to the more conventional intravenous route.

Passive immunotherapy with BCG, with or without chemotherapy, has been tested in several trials.^{3,4} No benefit compared with chemotherapy alone has been observed.

More recently, Isenberg et al²⁵ tested preoperative immunostimulation with bacterial products compared with a no-treatment control in 101 patients with colon and rectal cancer. At 76 months follow up for all patients, immunostimulation was associated with improved overall survival (91% compared to 63%), including 42 Dukes C patients (38% compared to 30%). Formal significance tests were not reported, and the sample size was small.

Hoover et al²⁶ tested active specific immunotherapy with autologous tumour cells and BCG against observation alone in 80 evaluable patients with high-risk Dukes B and Dukes C colon and rectal cancer. At a median follow up of 93 months, the main analysis could not detect a benefit for treatment, but in subset analysis there was a survival benefit for the 47 patients with colon cancer (47.8% compared to 16.7%; HR 3.97; $P = 0.02$). Rectal cancer patients also received postoperative radiotherapy, whereas colon cancer patients did not. Analyses were not formally stratified and reported by stage. The results suggest the need for further trials.

In a German study, 189 Dukes C patients with resected colon and rectal cancer were randomised to observation alone or to receive five injections of monoclonal antibody 17-1A.²⁷ Treated patients had a significant improvement in disease-free and overall survival at both five years and seven years, although the trial was too small for separate analysis of patients with colon ($n = 96$) and rectal ($n = 70$) cancers. A larger trial evaluating this approach is ongoing.

15.1.7 Buyse meta-analysis

In the meta-analysis by Buyse et al in 1988,² chemotherapy compared with observation showed no significant difference in the odds of death. However, in the subgroup of patients treated with 5-FU for at least one year, the odds of death were significantly reduced when compared with untreated controls (OR 0.83, $P = 0.03$). On further analysis of this subgroup, the risk reduction for death was more pronounced for rectal than for colon cancer patients (38%, $P = 0.02$ compared to 8%, nonsignificant). Stage could not be examined due to lack of standardisation. The authors cautioned about the significance of these findings in subgroup analysis, which could only suggest hypotheses to be tested in clinical trials.

In 1990, a United States National Institutes of Health consensus conference¹ reviewed the available evidence and recommended that one year of 5-FU plus levamisole be offered to all patients with resected Dukes C colon cancer. Since then, adjuvant trials have abandoned the no-treatment control and have substituted the 5-FU plus levamisole regimen. Through a computer-simulated model, it has been estimated that this adjuvant therapy costs US\$2094 per year of life saved.²⁸

Guidelines — adjuvant therapy	Level of evidence
People with resected node-positive colon cancer should be offered adjuvant therapy.	I
5-FU plus low-dose leucovorin for six months is the preferred option. Other adjuvant therapy regimens with similar reductions in the rate of relapse and mortality (30–40%) include: <ul style="list-style-type: none"> • 5-FU plus low-dose leucovorin plus levamisole for six months; and • 5-FU plus levamisole for one year. 	II
The value of adjuvant therapy in Dukes B (stage II) colon cancer has not been demonstrated uniformly. Adjuvant therapy in this group is not recommended except for patients with 'poor prognosis' stage II disease who, after discussion, wish to have treatment of entry into appropriate clinical trials, which is recommended.	II

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CHAPTER 16

ADJUVANT THERAPY FOR RECTAL CANCER

Adjuvant therapy is any treatment that is given in addition to a standard cancer treatment. For early rectal cancer, the standard treatment is surgery to remove the cancer. Radiotherapy and chemotherapy have both been extensively studied to see if they may reduce the risk of cancer recurrence. They may be used alone or in combination, preoperatively or postoperatively.

16.1 Radiotherapy

Radiotherapy uses ionising radiation to kill cancer cells. Only those tissues within the treatment beam are affected. Radiotherapy achieves high cell kill but only within the treatment field. It may also affect the normal tissues within the field. It aims to reduce the incidence of recurrent cancer within the pelvis. Recurrent pelvic cancer is nearly always incurable and often causes pain, bleeding and sometimes blockage of the kidneys.

16.2 Chemotherapy

Chemotherapy is cytotoxic drug treatment. Chemotherapy affects the entire body, and is given with the aim of killing circulating cancer cells that may grow in distant organs such as the liver and lungs. Distant recurrence is almost always fatal. It may also have some radiosensitising action.¹

16.3 Benefits of adjuvant therapy

Patients whose tumours have penetrated the wall of the rectum and/or involved lymph nodes are at risk of recurrent cancer in the pelvis or in distant organs. There have been many trials² that seek to improve the results of surgery for rectal cancer in this group. There may also be a high risk of local recurrence when the surgical resection margins (either radial or longitudinal) are close or positive.³

The optimum strategy to improve the outcome of treatment of rectal cancer must address the problems of local and distant recurrence.

Patients are at high risk of relapse locally and/or distantly if they have localised rectal cancer that has either penetrated the rectal wall and/or involved lymph nodes by metastatic cancer, or that has involved an excision margin.

16.4 Can the results of trials be applied in the Australian setting?

Patients in clinical trials have tumours of high enough risk to warrant the risks of extra treatment. They also have to be fit enough to withstand further treatment in addition to major surgery. A review of the entry criteria for studies of the combined modality therapy (CMT), comprising both radiotherapy and chemotherapy, have not shown them to be restrictive. For patients who received surgery alone (as for the control group in the NSABP randomised study of CMT),⁴ the five-year survival data are comparable to a large cohort study performed by a colorectal unit in Australia³. For lymph node-positive patients, the five-year survivals for the NSABP and Concord groups were 35% and 32% respectively. Corresponding survival for tumours that had penetrated the bowel wall were 57% and 62%.

16.5 The role of combined chemotherapy and radiotherapy

There have been eight randomised studies of CMT.⁴⁻¹⁰ Postoperative CMT has been most extensively studied. The Gastrointestinal Tumour Study Group (GITSG) study⁶ performed a study for which the four components were:

- surgery
- surgery and postoperative radiotherapy
- postoperative chemotherapy with semustine and 5-FU
- postoperative CMT

Disease-free survival was improved in the CMT treatment when compared with surgery alone (67% compared to 45%). However, overall survival was not significantly different between the treatments. This study has been criticised because of the small numbers in each treatment group (about 50).

Only one other study has compared CMT with surgery alone.¹⁰ In this study 144 patients were randomised to receive postoperative radiotherapy and synchronous bolus chemotherapy, or no further treatment. Local recurrence in the CMT treatment was 12% compared with 30% in the surgery alone treatment. Survival was also significantly increased (64% vs 46%, $P = 0.01$).

Krook et al⁸ randomised 204 patients with high-risk rectal cancer to postoperative radiotherapy alone or CMT. The CMT treatment group experienced lower recurrence rates, both locally and distantly. The rates of cancer-related deaths and deaths from any cause were also significantly reduced with CMT.

Two further studies have addressed refinements of chemotherapy when used in combination with radiotherapy. GITSG⁷ randomised 210 patients to postoperative radiotherapy with either semustine plus 5-FU or 5-FU alone. There was no survival advantage to the addition of semustine and, given its known leukemogenic activity, they recommended that 5-FU alone be used.

O'Connell et al⁹ examined the effectiveness of altered schedules of chemotherapy and different delivery methods in 660 patients with high-risk rectal cancer. Patients were

randomised to receive 5-FU as a bolus or by protracted venous infusion during radiotherapy. They were also randomised to receive systemic 5-FU chemotherapy with and without semustine. Protracted venous infusion conferred a significant advantage in time to relapse and survival. When compared with bolus 5-FU, there was a 10% absolute increase in survival at four years for the infusion patients. Again, semustine gave no benefit over 5-FU alone.

Guidelines — combined modality therapy	Level of evidence
Postoperative 5-FU-based chemotherapy and radiotherapy (combined modality therapy) is recommended for patients with high-risk rectal cancer.	II
When chemotherapy is given postoperatively in combination with radiotherapy, protracted venous infusion of 5-FU chemotherapy may offer further benefits in survival when compared to bolus 5-FU therapy. It is the recommended way of delivering combined modality therapy.	II

Only one study has examined the use of preoperative CMT, and compared it with preoperative radiotherapy and surgery (RT/S) only.⁵ There was a nonsignificant trend to better survival in the RT/S group with 59% survival, compared to 46% for the CMT group ($P = 0.06$). The radiotherapy in both arms of the study covered the para-aortic region and the pelvis, with opposed anterior and posterior portals. Such a technique has been shown in subsequent randomised studies to be associated with any excessive risk of late small bowel damage.^{11,12} Preoperative chemotherapy and radiotherapy requires further clinical trials using modern radiotherapy and chemotherapy techniques.

16.6 The role of adjuvant radiotherapy without chemotherapy

The evidence for the value of radiotherapy comes from two meta-analyses of more than 8000 patients randomised to receive either radiotherapy and surgery, or surgery alone.^{2,13} Radiotherapy alone does not affect the rates of death from distant metastasis but, as is discussed below, it may significantly reduce local relapse. This may have a flow-on effect on survival, as local relapse is rarely salvaged.

16.7 Preoperative radiotherapy without chemotherapy

There is strong and consistent evidence from meta-analysis of 18 trials involving 4000 patients that preoperative radiotherapy reduces local recurrence in the pelvis by about 50%, whether given in one week or five.² Effective schedules include 20–25 Gy in five fractions and 40–45 Gy in 20–25 fractions. No reduction in local recurrence was seen with 20 Gy in 10 fractions or 5 Gy in one fraction.

Similar benefit was seen with both fixed and mobile tumours. There was no evidence of either increased or decreased operability in any of the studies. The proportion of benefit was not affected by stage of disease: 41%, 43% and 45% for Dukes stage A, B and C, respectively. There was no difference in terms of complication rates between the short and long schedules.²

There was no significant reduction in the rate of out-of-field failure with preoperative radiotherapy. Similarly, there was significant improvement in overall survival with a nonsignificant trend of 4% in favour of radiotherapy. There was a significant improvement in deaths from colorectal cancer with preoperative radiotherapy (18%, $P = 0.001$). In absolute terms, the reduction in the number of curatively resected patients dying of colorectal cancer was 6.5% (38.4% compared to 44.9%). This was partly counterbalanced by an increase in deaths from other causes, predominantly within the first year after randomisation, and it was only seen in studies using now obsolete two-field radiotherapy techniques that irradiated large volumes of normal tissue.²

Two recent studies^{14,15} not included in the above meta-analysis have shown a significant survival advantage. Patients (1168) under 80 years of age with rectal cancer were randomised to receive either 25 Gy in five fractions and surgery, or surgery alone. Postoperative mortality was equal in each treatment. Local recurrence was reduced from 27% to 11% ($P < 0.001$) and survival was significantly increased in the radiotherapy arm (58% compared to 48%, $P = 0.004$). This improvement was found in all Dukes stages.

16.8 Postoperative radiotherapy without chemotherapy

There have been eight trials of surgery and postoperative radiotherapy versus surgery alone. Meta-analysis shows that postoperative radiotherapy significantly reduces local recurrence by one third ($P = 0.003$).² There is no evidence, however, that overall survival is improved by postoperative radiotherapy.

16.9 Preoperative versus postoperative radiotherapy

There is good evidence that preoperative radiotherapy using modern techniques (more than two fields) can moderately improve survival for curatively resected patients.² Even without a survival improvement, the avoidance of the morbidity and costs associated with local recurrence of rectal cancer would make preoperative radiotherapy worthwhile.

The reduction in rectal cancer mortality is greater for preoperative radiotherapy (14%, $P = 0.002$) than postoperative radiotherapy (7%, not significant). Similarly, the reduction in local recurrence is greater in the preoperative studies than in the postoperative studies, but a formal test of interaction was not significant.² Therefore, there is no statistically convincing evidence from indirect comparisons between studies of greater benefit from preoperative radiotherapy. The better results seen in preoperative RT studies may be due to the selection of clinically staged patients with

earlier tumours than those pathologically staged before entry into a postoperative RT trial.

There has been one direct comparison where patients were randomised into two groups to receive either 25.5 Gy preoperatively or 60 Gy postoperatively.¹⁶ There were significantly fewer local recurrences in the preoperative radiotherapy group (13% compared to 22%, respectively; $P = 0.02$), but there was no difference in overall survival between the two groups. Late radiotherapy complications were reported for each treatment and were higher with postoperative radiotherapy than either preoperative radiotherapy or surgery alone (41%, 20% and 23%, respectively). After accounting for the effect of different fraction size of radiation, the postoperative dose was biologically about 50% higher than the preoperative dose,¹⁷ and a much greater rate of late effects would be expected. However, when the results were analysed by intention-to-treat, then the rate of complications in the postoperative group fell to 31%, which was not significantly different from the preoperative rate. This suggests that a policy of preoperative radiotherapy for all patients with rectal cancer would yield a similar absolute number of complications to a policy of selective postoperative radiotherapy. Better preoperative patient selection by endorectal ultrasound may improve this ratio to clearly favour preoperative radiotherapy.

Preoperative radiotherapy may be preferred over postoperative radiotherapy if radiotherapy alone were to be used, because of the higher rate of local control. Preoperative radiotherapy may also have value in attempting to preserve the anal sphincter with low rectal cancers.¹⁸ In some circumstances, this may not be feasible, such as in emergency operations due to obstruction or perforation. However, there has been no direct comparison with postoperative CMT, and the role of preoperative radiotherapy alone remains uncertain, as radiotherapy alone does not affect the rate of distant failure.

16.10 The role of chemotherapy without radiotherapy

Postoperative adjuvant chemotherapy alone has only been tested in rectal cancer in one study, where it was compared with surgery alone, surgery plus radiotherapy, and surgery plus CMT.⁶ There was a nonsignificant trend to higher cancer-free survival in patients receiving postoperative adjuvant chemotherapy. However, there is an extensive body of evidence examining the role of chemotherapy in colon cancer. Some of these studies may have included rectal cancer patients. This evidence is reviewed elsewhere in these guidelines (see Chapter 15). It appears that there is a significant survival benefit from 5-FU-based chemotherapy for patients with lymph-node positive colon cancer. There is no biological reason to expect that the response of rectal cancer to chemotherapy should differ from the response of colon cancer, but it has not been proven.

16.11 Possible complications of adjuvant therapy and how they can be reduced

All radical anticancer treatments are associated with specific morbidities. These must be weighed up against the morbidity and risk of death associated with cancer

persistence or recurrence. This balance will be different for each patient and will also need to include an assessment of his or her preferences and general condition.

Overall quality of life has not been directly assessed in any published randomised trial of adjuvant therapy for rectal cancer, but it is being addressed, along with functional endpoints, in current studies. An indirect assessment of quality of life using Q-TWiST (quality adjusted time without symptoms or toxicity) methodology supports adjuvant therapy.¹⁹

16.11.1 Radiotherapy

Short-term (acute) complications of pelvic radiotherapy include lethargy, mild nausea, diarrhoea, tenesmus and skin erythema or desquamation. All of these acute effects develop in most patients to some degree during the treatment, and all of them usually resolve within weeks of completion.

Long-term side effects are usually permanent, but affect only small numbers of patients. They include small bowel damage (bleeding, stricture, perforation and malabsorption) and rectal damage (reduced reservoir capacity, urgency, frequency, bleeding, incontinence and fistula formation). These severe effects are seen in 3–11% of cases.¹⁶ All premenopausal women receiving pelvic radiotherapy will undergo a premature menopause. Fertility is not usually affected in men, but potency may be.

Preoperative radiotherapy has been associated with an increase in postoperative complications in some studies.^{2,15} Mortality from noncancer causes was greater in the radiotherapy treatments of older studies than those that used two-field techniques (see above). Modern series report postoperative mortality rates of 3–5%.¹⁶ Long-term morbidity and mortality are significantly increased in patients over 75 years of age. Technique is important and multiple fields are mandatory. Manoeuvres that reduce the amount of small bowel in the treatment volume are associated with lower morbidity. These include the prone treatment position, belly boards and occasionally surgical procedures such as omental slings or dextron meshes.¹²

16.11.2 Chemotherapy

Acute complications of 5-FU-based chemotherapy are mouth ulcers, diarrhoea and nausea. Marrow suppression is usually mild, but may be severe in a small number of patients. Uncommonly, palmar plantar erythema or skin photosensitivity may develop. Complete hair loss (alopecia) is very uncommon.

16.11.3 Combined modality

Both acute and late morbidity are increased with CMT. This should be considered when giving advice about treatment recommendations to individual patients. In the GITSG study,⁶ severe nonhaematological toxicities occurred in 35% of patients receiving CMT, compared to 16% for radiotherapy alone or 15% for chemotherapy alone. Leukopenia (white cell count <2000/mL) occurred in 26% of the CMT group, compared with 2% for radiotherapy alone and 13% for chemotherapy alone groups.

Krook et al⁸ also found haematological toxicity to be increased when CMT was compared with radiotherapy alone. Protracted venous infusion has been associated

with significantly more diarrhoea (24%) than bolus 5-FU (14%, $P<0.01$), but less leukopenia (2% compared to 11%, $P<0.01$).⁹

Rectal function may also be adversely affected by CMT. In a survey of patients entered into the Mayo randomised trial,²⁰ those who received CMT had significantly higher rates of occasional and frequent incontinence (39% compared to 7% and 17% compared to 0% respectively). There was also an increased frequency of bowel motions, loose stools and urgency. Future studies of adjuvant therapy should include quality of life and rectal function in the trial endpoints.

16.12 Costs of adjuvant therapy

Simulation methods have been used to model the costs and benefits associated with adjuvant chemotherapy for colorectal cancer. In general, these studies show that there is a favourable cost-utility for adjuvant chemotherapy. Cost estimates per quality adjusted life-year (QALY) gained vary from A\$370/QALY to A\$17,500/QALY for the one Australian study.²¹

There is one study that addresses adjuvant radiotherapy for rectal cancer.²² The marginal cost of radiotherapy and 5-FU was US\$8700 per life-year gained, and the extra cost for infusional chemotherapy was US\$950 per life-year gained. This compares favourably with many widely accepted health care interventions.

The need to rely on secondary estimates and modelling techniques highlights the need to improve the data collection on costs, treatment effects, and quality of life in future trials of adjuvant therapy.

16.13 Is adjuvant therapy necessary with good surgery?

The body of randomised trials covers a long period in which both surgical and adjuvant techniques have evolved considerably. It has been suggested that very low local recurrence rates can be achieved by expert surgery employing total mesorectal excision. The evidence is from one historical uncontrolled series.²³

Analysis of the effect of surgeon variation was performed on patients entered into the randomised Stockholm study.²⁴ They found that some centres had lower rates of recurrence, but that these rates of recurrence and survival could be further improved by the addition of preoperative radiotherapy. This question is the subject of an ongoing randomised trial in the Netherlands of surgery with total mesorectal excision with or without radiotherapy.

16.14 Conclusions and future directions

There are clear benefits for patients with high-risk rectal cancer in having adjuvant therapy. The nature of the optimum treatment is still uncertain. Postoperative chemotherapy and radiotherapy significantly improves survival and local control by about 10% in absolute terms. The major area of improvement in survival with

protracted venous infusion has been a reduction in deaths from metastases. Any adjuvant therapy program should include chemotherapy and radiotherapy. Currently there are good data only for postoperative CMT. Preoperative radiotherapy alone may also improve survival. There has not been any direct comparison with postoperative CMT, nor any modern study reported on the effects of preoperative CMT. These studies are ongoing, and their completion will necessitate a revision of these guidelines.

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CHAPTER 17

FOLLOW UP AFTER CURATIVE RESECTION FOR COLORECTAL CANCER

17.1 Rationale for follow up

17.1.1 Detection of second primary tumours

Following curative surgery for colorectal cancer, patients have an increased incidence of metachronous primary colorectal cancers and adenomatous polyps.¹ In one series, the rates of development of new primary cancers and adenomas at four years were 7.7% and 62%, respectively.²

Colonoscopic surveillance and the removal of any adenomas may reduce the incidence of subsequent primary colorectal cancer.

17.1.2 Early detection of recurrence

About one in three patients who have curative surgery for colorectal cancer will die as a result of recurrent disease.³ Follow up is performed to improve on this outcome by detecting recurrence at an earlier and potentially curable stage. In general, this will mean detecting recurrence in an asymptomatic person with resectable suture-line recurrence, or resectable liver and lung metastases. There is evidence of benefit in terms of *cure* by further surgery for about 1% of such patients.⁴

However, three randomised studies of follow up have not shown any significant survival benefit over either less intensive or no follow up.⁵⁻⁷ The main explanation for this is that recurrences had low resectability and cure rates regardless of the amount of follow up, even when recurrences were detected earlier. In the first study, only 1.7% and 0.6% of cases in the follow up and control treatments were cured of local and distal recurrences, respectively. An Australian randomised controlled trial supports this conclusion. Yearly colonoscopy, liver CT and chest radiography did not improve survival from colorectal cancer when added to symptom and simple screening review.⁸ The studies did not have statistical power to detect a small but meaningful difference in survival.^{6,7}

17.1.3 Audit

Follow up provides information on clinical outcomes for clinicians to evaluate their practice against professional standards.⁹ It is essential for participation in clinical trials.¹⁰ Follow up is also required in order to produce national outcomes data to assess the impact of new guidelines and the introduction of alternative therapies.

17.1.4 Patient preference

An observational study on colorectal cancer patients undergoing follow up indicated that the visits had no direct effect on quality of life. However, they may provide

reassurance. Subjects expressed a positive attitude and indicated a strong preference to be followed up.^{10,11}

17.1.5 Cost

No studies have examined the cost of scheduled follow up after surgery for colorectal cancer. However, there have been studies of follow up of people with other diseases. One study of follow up of women who had curative treatment for breast cancer found that if American doctors had followed a minimalist surveillance strategy, they would have saved the United States health system US\$636 million in 1990.¹² There have been two clinical trials in breast cancer, involving more than 2000 women, which show that intensive follow up provides no survival benefit over a minimalist approach.^{13,14}

Guidelines — follow up	Level of evidence
Follow up of patients after curative resection for colorectal cancer is recommended as it allows practitioners to monitor patient outcomes arising from their treatment and it is consistent with patients' desires.	—
All patients who have undergone surgery for colorectal cancer should have specialist follow up in conjunction with the patient's general practitioner.	—
Randomised controlled trials do not support a survival benefit for more intensive follow-up investigations.	II

Qualifying statement

Most recurrences detected on follow up are still too advanced to be curable using currently available technology. Further large randomised studies using improved detection strategies may eventually show a survival advantage with follow up.

17.2 Which patients should be followed up?

Because there are no reliable indicators of an individual's risk of synchronous or metachronous lesions, nor of treatable recurrence, all patients who have undergone *curative* surgery and are fit for further intervention if disease is detected should be offered follow up.

Those who are unfit for further surgery or who have advanced disease require appropriate follow up directed to psychological support and symptom relief.

17.3 Who should perform the follow up?

The requirement for audit and sigmoidoscopy confirms the current practice of the operating surgeon or associated gastroenterologist performing the follow up, together with the general practitioner.

However, there is no evidence that intensive hospital based follow up is associated with a survival advantage over general practitioner based care. Further studies are needed to determine whether community-based follow up can be adequately performed without decreasing patient survival, and to define the optimal balance between the general practitioner and the specialist in follow up.

17.3.1 Investigations

Colonoscopy is the most appropriate investigation for detection of synchronous, recurrent or metachronous cancers and polyps.

A number of studies have clearly shown that colonoscopy should be performed at the time of diagnosis of the primary lesion in order to exclude synchronous lesions.^{15,16} Ideally, the colonoscopy which visualises the entire colon should be prior to the surgery for the primary lesion.

However, if this is not achievable for technical or other reasons (such as an obstructing left-sided cancer), then colonoscopy should be performed in the postoperative period. It is recommended that the procedure should be performed within three to six months of the surgery.¹⁷

Studies have shown that metachronous cancers may be detected no earlier than three years following surgery for colorectal malignancy, but it is most likely to be five years after the initial operation.^{18,19} Consequently, it is recommended that colonoscopy be performed three to five years after the initial operation.⁸

Sigmoidoscopy may be useful as an adjunct to rectal digital examination for patients who have had an anterior resection in order to detect early suture-line recurrence.

Faecal occult blood tests (FOBTs) should be performed annually in accord with the recommendations regarding the surveillance of high-risk patients.

Serum carcinoembryonic antigen (CEA) levels have been used to alert presence of recurrent or metastatic cancer. In one meta-analysis of nonrandomised studies,²⁰ some of which used historical controls, it was postulated that a rise in CEA is associated with improved survival as it allows 'pick up' of resectable hepatic metastases. However, there is little other high level evidence to support this practice.²¹ Consequently, surveillance using serum CEA levels is not favoured routinely for all patients. It is recognised as the marker of choice and its selective use is appropriate, as outlined in the American Society of Clinical Oncology protocols, for the use of tumour markers in breast and colorectal cancer.^{22,23} Evidence in favour of other serum oncological markers is less encouraging; hence none can be recommended for routine clinical use.

CT scan of the liver has been shown to be effective in the early detection of liver metastases, and may define a small group where hepatic resection is indicated (see Chapter 22). However, there is no evidence that early detection of hepatic metastases results in improved outcome for a larger group of patients in a trial setting.⁸ The routine use of CT scan of the liver in follow up is not supported.

Ultrasonographic screening for liver metastases has not been investigated in prospective randomised trials. However, the sensitivity and specificity of this investigation are no better than CT scanning.

Chest x-ray is a sensitive investigation for detecting lung metastases. Although chest x-ray will detect metastatic lung disease, there is no evidence to support its routine use as a screening investigation.⁸

The Adelaide study⁸ showed clearly that a regular planned clinical review, along with routine haematological and faecal tests, was effective in detecting both resectable and nonresectable recurrences and metastases.

A person developing clinical symptoms of disease requires full investigation.

17.4 Suggested schedule

There should be an early postdischarge review, followed by a review six monthly for two years, and yearly thereafter.¹¹

The review should consist of history and examination, including examination of the rectum, and sigmoidoscopy in patients who had an anterior resection of the rectum.

Colonoscopy should be performed three to five years after the initial operation in order to detect any metachronous tumour, and repeated at three to five-yearly intervals thereafter.

The follow up should continue until an age at which comorbidities preclude further intervention.¹⁷ It is difficult to place an actual age limit to follow up as 'biological age' varies between individuals.

17.5 Summary

The debate regarding the rigour and intensity of follow up investigations is complex. The benefits from follow up include:

- the provision of audit and survival data;
- patient support;
- the ability to remove metachronous polyps and to detect early metachronous cancers; and
- the detection of potentially curable recurrent disease.

However in studies undertaken, no survival advantage has been demonstrated, and costs and complications of follow-up investigations can be considerable.

Large-scale trials are recommended in two areas. The first is to accurately define whether or not there is a survival advantage from intensive follow up. The second is to compare specialist follow up with general practitioner follow up, and to compare both of these with no formal follow up.

These recommendations are for asymptomatic patients. All patients who develop symptoms should be investigated rigorously.

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CHAPTER 18

PSYCHOSOCIAL CARE

The diagnosis and treatment of cancer presents a major stressful life event necessitating an adaptive adjustment to sustain quality of life. A fundamental goal is to enhance quality while striving to prolong life. Attention to psychosocial aspects is vital to achieve this goal.

Sprangers et al¹ reviewed nine studies assessing psychological dysfunction in patients with colorectal cancer. Prevalence estimates for depression ranged from 7% to 50%, with significantly higher rates for ostomates than nonostomates.^{2,3} Anxiety was problematic in 25%.^{4,5} Psychological functioning was more impaired in younger, female patients.^{6,7}

In general, people with a stoma reported greater impairment of social functioning, including problems with work, frequency of social contacts and quality of relationships, including marriages.¹

In a large Australian study of patients with advanced cancer in the palliative care setting, up to half of the patients (20% of whom had colorectal cancer), one third of their spouses and one quarter of their offspring showed evidence of substantial psychological distress warranting specific support.⁸ The distress reverberates through the family in the setting of palliative care such that both patient and family-centred models of care need to be adopted.

Prevalence estimates of sexual dysfunction after surgery for colorectal cancer range from 62% to 88% when pelvic autonomic nerves have been damaged, and include problems with erectile function and ejaculation in men.¹ Dyspareunia has been reported in up to one third of women.⁹ Age may play an important role in impairment of sexual functioning.

A range of physical symptoms also interfere with the quality of life of colorectal patients: one third of patients report more than five bowel movements per day, half have problems with flatus, odour, diet, diarrhoea or constipation, and stoma-related problems remain substantial. Spillage and accidents in the 1960s ranged from 50% to 86% and, despite technical advances in ostomy equipment, more recent studies also report significant problems with leakage, odour and late complications.¹⁰⁻¹²

Systematic studies of patients with cancer have shown that clinicians frequently fail to identify psychological problems. There are generic risk factors applicable to all patients with cancer, as well as specific factors in the setting of colorectal cancer. The latter have been identified as:

- younger patients^{2,6,13}
- women^{2,6,7}
- ostomates¹
- patients who have experienced cumulative losses
- socially isolated

- those who have been widowed, separated or divorced
- those with a history of psychiatric disorder
- those in financial difficulty
- those with social deprivation

All these people have an increased risk of poor adjustment to the diagnosis and treatment of colorectal cancer.

Consumer satisfaction surveys of patients with cancer repeatedly identify information provision as a major unmet need. Research has shown that the provision of adequate information is related to increased psychological well-being.¹⁴ Effective communication skills ensure that this information is clearly explained and understood.^{15,16}

Relevant principles about information provision for colorectal cancer patients are that:

- treatment options should be explained clearly with realistic information about potential effectiveness and adverse effects;
- patients should be invited to guide the clinician over the level of detail they wish and over their desire for active involvement in decision making;¹⁷
- clinicians should review both the understanding of and reaction to the information as a means of increasing integration and providing emotional support;
- written materials should be provided and tape recording of key consultations offered;¹⁸
- information should be made available over time, and review appointments, which allow time for further integration of information, should be scheduled;
- patients' carers and families should also be kept well informed; and
- well-informed patients feel more in control and achieve a better psychological adjustment over time.

Guideline — psychosocial care	Level of evidence
Attention to psychosocial care is important, and is achieved through appropriate information provision, effective communication, early recognition of those at increased risk of maladaptive adjustment, active treatment of established psychiatric disorder and sustained support for the patient and their care givers.	III

18.1 Psychological treatments

There is incontrovertible evidence from three meta-analyses of the benefits of psychological interventions in patients with cancer. Such interventions improve emotional adjustment (including anxiety and depression, sense of control, self-esteem), functional status (including activities of daily living, social and role functioning and vocational activities), knowledge of the disease and its treatment,

treatment and disease-related symptoms (eg nausea, vomiting, pain etc) and overall quality of life.^{14,19,20}

There are wide benefits from relaxation-based therapies in reducing anxiety, treatment-related phobias, conditioned nausea and vomiting, and insomnias.¹⁴ Both cognitive-behavioural and supportive-expressive therapies are effective in countering existential fears of dying, aloneness, meaninglessness and unrealistic fears about processes of treatment.^{14,19,20} Early referral for specialist support from a clinical psychologist or liaison psychiatrist is worthwhile when symptoms of distress or high risk become evident.

Randomised controlled studies of early versus late referral to palliative care services show strong evidence of the benefits of early referral in reducing time spent in hospital, enhancing symptom control, increasing family satisfaction and permitting death to occur in the desired location.²¹⁻²³ Early referral to community-based domiciliary palliative care services, where available, may have several benefits and enhance quality of life.

Guideline — psychological interventions	Level of evidence
Psychological interventions improve the quality of life of patients with colorectal cancer.	I

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Section II

Advanced colorectal cancer

CHAPTER 19

RECURRENT AND ADVANCED RECTAL CANCER: GENERAL APPROACH AND LOCAL MANAGEMENT

19.1 General approach

The patient with advanced colorectal cancer may present with local recurrence and/or systemic recurrence of disease. Typical sites of recurrence include the pelvis, intraperitoneal disease, the liver and other distant organs.

The prognosis of patients with advanced colorectal cancer depends in part on the biology and the extent of the disease in each individual. It is not possible to generalise and predict the prognosis of this cohort of patients as if they were a homogeneous group. Even in the context of inoperable metastatic liver disease, prognosis may vary from a few months to several years, independent of the impact of any treatment.

A decision regarding treatment will depend upon the performance status of the patient and the extent of metastatic disease. If active treatment is appropriate, then a number of options will need to be considered. For example, the treatment of multiple liver metastases may include one or several of the following modalities — surgery, systemic chemotherapy, intra-arterial chemotherapy or image controlled destruction. There is a lack of good quality clinical trials in which these various alternatives have been compared, often making the decision about the appropriate option complex and difficult.

Patients with advanced cancer suffer from a variety of symptoms and disturbances that are common to all cancers, and not specific to colorectal cancer. The management of these symptoms, such as pain,¹ anorexia, cachexia and psychological problems, among others, requires therapeutic measures that are part of the general care of patients with advanced cancer. These matters will not be described further in these guidelines. This exclusion in no way underestimates the crucial significance of the control of these symptoms to the wellbeing of the patient. Management of these matters is the first priority of any clinician caring for a patient with advanced colorectal cancer.

The coordinated efforts of a team of professionals is likely to be helpful in managing such patients. The precise membership of the team will depend upon the patient, the stage of the disease, the goals of management and the particular problem. However, medical oncologists and radiation oncologists, palliative care physicians, surgeons and nurses, including oncology, palliative care, stomal therapy and domiciliary nursing staff, may all play a critical role in patient management. Of particular importance is the involvement of the general practitioner in the management of both the patient and the family. In selected cases, support of the patient and family may require the assistance of psychiatrists or psychologists.

There are some specific principles that can be applied in the management of people with colorectal cancer when the disease is advanced. The following chapters discuss

some of the various and often complex therapeutic options available to such a patient with advanced colorectal cancer.

19.2 Local recurrence

The incidence of local recurrence following resection of rectal cancer varies. It depends on tumour factors including stage, grade and vessel invasion, and external factors such as surgical technique and use of adjuvant therapies.²⁻⁴ Local recurrence may be asymptomatic or may cause pain, bleeding, mucus discharge, neurological symptoms and ureteric obstruction. Local recurrence rates of 3–50% have been reported following apparently curative resection of rectal cancer.^{5,6} Median recurrence rates for T1, T2–3 and node-positive tumours were 8.%, 16.3% and 28.6% respectively.⁶

There are no randomised, prospective trials to act as guides for the management of locally recurrent rectal cancer. We have to rely on less robust evidence, such as retrospective analyses and uncontrolled prospectively documented series.

19.2.1 Assessment of the extent of local recurrence

There are three established methods of assessing the extent of local recurrence of rectal cancer: CT scan, MRI scan and endorectal ultrasound (ERUS).

CT scan is probably the most widely evaluated modality, with recent studies suggesting lesions as small as 2 cm can be detected reliably.⁷ While initial reports claimed a remarkable 95% sensitivity at detecting local recurrence,⁸ later series show the sensitivity to be considerably lower at 69–88%.⁹⁻¹¹

There are difficulties in differentiating the appearance of normal postoperative changes (particularly in patients having had previous radiotherapy)¹² from recurrent cancer.¹³ Serial scans showing changes from a baseline are more sensitive than one-off scans.^{7,13}

MRI scans were reported initially to be able to distinguish postoperative fibrosis from tumour recurrence more effectively than CT scans,¹⁴ but this has not been confirmed by more recent studies.¹⁵

ERUS has been found to be at least as good as CT at detecting local recurrence.¹⁶ Small extrarectal recurrences can be detected before any symptoms develop or there is luminal evidence of recurrence.¹⁷ Unfortunately, like CT and MRI, ERUS is unable to differentiate between normal perirectal lymph nodes and those harbouring recurrent cancer.¹²

19.2.2 Management of local recurrence

About 50% of patients with local recurrence of rectal cancer have disease confined to the pelvis.^{6,18} The vast majority of local recurrences are inoperable and incurable. Their management is palliative and it should include consideration of radiotherapy and/or chemotherapy as well as adequate pain relief.

Radiotherapy

Local relapse is a major cause of morbidity. A minority of pelvic recurrences may be resectable, but the majority are incurable. Recurrent rectal cancer in the pelvis can lead to disabling pain, tenesmus and bleeding — symptoms often difficult to palliate. The use of radiation therapy can relieve these symptoms in the majority of cases, but the duration of relief is often short lived.^{19–22}

The benefits of palliative radiation in these patients may translate into improved quality of life with reduced requirements for analgesia and other medications. Such radiation may be combined with chemotherapy, either given concurrently or sequentially with radiation treatment. These patients are often in severe discomfort with cachexia and a limited life expectancy. There are no randomised trials to assess survival or improved quality of life, but there have been a number of reports showing symptomatic relief with the use of palliative radiation.^{19–22}

Surgery

A small number of local recurrences, mainly anastomotic, may be salvaged by further local treatment.

When local recurrence is not resected, five-year survival is negligible.¹⁸ With major ablative surgery in selected cases, five-year survival rates can be as high as 37%.²³ Therefore, in the absence of distal disease or disabling comorbidities, surgical resection should be considered.

In cases where radiotherapy has not been administered previously to maximum tolerable doses, and the recurrence is deemed to be resectable, the routine use of adjuvant preoperative radiotherapy is to be recommended. In patients deemed not to be resectable, a course of preoperative chemoradiation may result in the tumour shrinking to a resectable size in a significant proportion of patients, although it is unclear as to whether this results in a significant survival benefit.²⁴ Even in the face of early metastatic disease, local treatment should be considered in order to prevent the development of the symptoms of uncontrolled pelvic cancer that can be very difficult to control medically.

When local recurrence starts to invade surrounding structures, resection becomes more difficult and the benefits of re-resection less clear-cut. Rarely is major resectional surgery indicated. In carefully selected patients, however, five-year survivals of up to 50% have been reported.^{25–27} Major resectional surgery can result in a permanent end colostomy and ileal conduit. Despite this, improvement in quality of life has been reported following surgical removal of all pelvic organs (pelvic exenteration) in such patients.²⁸ Although the above mentioned reports support the use of radical surgical procedures, the lack of randomised controlled trial-based evidence of their benefit precludes the issuing of broad recommendations regarding their use. Where contemplated, these procedures should be performed in specialised centres.

19.3 Advanced rectal cancer deemed potentially operable

Such advanced cancers (T4) are often inoperable due to local extension and fixity. Preoperative radiotherapy may shrink bulky tumours and mobilise those tethered within the pelvis, enabling successful resection in such cases previously deemed inoperable. In addition, improved pelvic control has been noted, as has a survival advantage in some cases.

Two randomised trials^{29,30} and an uncontrolled study³¹ have shown the benefit of preoperative radiation therapy in such cases. As well, new reports suggest that combining radiation with chemotherapy delivered preoperatively can enhance the effect of treatment without increasing surgical morbidity, and this may be considered in locally advanced cases.³² Such chemotherapy, if employed, should consist of a 5-FU-based regimen.

For locally advanced rectal cancers where there is a risk of incomplete resection, the technique of intraoperative radiotherapy has been successfully used, improving both local control and overall survival.^{33,34} However it remains experimental and it should be properly evaluated in randomised studies.

Guideline — operable advanced rectal cancer	Level of evidence
Preoperative radiation therapy, possibly with chemotherapy, is recommended in rectal cancers fixed or tethered within the pelvis if it is felt down-staging will enable successful resection.	II

19.4 Advanced rectal cancer deemed inoperable

In patients with regionally advanced cancers deemed inoperable, radiation therapy may offer excellent palliation with a small group (less than 10%) showing long-term control.³⁵ Even in the presence of metastatic disease, significant symptom relief can be obtained with radiation therapy in 50–90% of patients with rectal bleeding, discharge or pain.^{19–22}

Such radiation needs to be fractionated appropriately, with multiple fields and manoeuvres undertaken to minimise small bowel presence within the irradiated volume. The dose delivered to the designated tumour volume needs to be of the order of 50–60 Gy.²⁰ With such measures, the risk of radiation-induced bowel injury is small.

The use of brachytherapy (often combined with laser treatment) in locally advanced rectal cancers can contribute to improved local control and symptom relief in patients not amenable to surgery. Such brachytherapy can be used as a boost to external beam radiotherapy to increase the cytotoxic dose delivered to the tumour, or delivered as sole therapy for palliation in patients with a short life expectancy.^{36,37}

Guideline — inoperable advanced rectal cancer	Level of evidence
Radiation therapy should be considered in patients with locally advanced rectal cancer not amenable to surgery.	III

19.5 Metastatic disease

Local treatment with radiation therapy to sites of symptomatic involvement in patients with metastatic disease has an important role to play in the alleviation of:

- pain arising from skeletal secondaries³⁸
- symptoms from obstructed viscera such as bowel or ureter
- distress from cerebral metastases³⁹

Patients with severe liver capsule pain can be relieved by a short course of external beam radiation therapy. Experimental procedures include implantation with remote after-loading catheters, and brachytherapy delivered to retard progression of secondaries.

Meta-analysis has shown that short courses of radiotherapy are as effective as long courses in the relief of bone pain³⁸ and similar results were found in the treatment of cerebral metastases.³⁹

In view of the shortened life expectancy of such patients, palliative radiation is given via larger fractions over shorter periods of time than conventional radical courses of treatment.

Guidelines — radiotherapy for metastatic disease	Level of evidence
Short courses of radiotherapy are as effective as longer courses for painful bone metastases.	I
Short courses of radiotherapy are as effective as longer courses for cerebral metastases.	II

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CHAPTER 20

THE ROLE OF SYSTEMIC CHEMOTHERAPY

20.1 First-line chemotherapy

There are few studies comparing chemotherapy with supportive care alone (Table 20.1). Scheithauer et al¹ compared 5-FU plus leucovorin to supportive care alone, finding a significantly better survival (median survival of 11 months compared to 5 months, $P = 0.006$).

Beretta et al² compared 5-FU plus leucovorin to supportive care, finding an improvement in survival (median survival of 7.5 months compared to 5.5 months). Treatment was well tolerated.

As many of the patients on the control arms of both these studies may have received chemotherapy later on, it is possible that the survival benefit has been underestimated.

Table 20.1 Studies of chemotherapy and supportive care versus supportive care alone

Study	Treatment	Patients eligible	Median survival time (months)
Scheithauer et al (1993) ¹	5-FU + LV + CP + supportive care	24	11
	supportive care	12	5
Beretta et al (1994) ²	5-FU + LV + supportive care	80	7.5
	supportive care	83	5.5

5-FU = 5-fluorouracil; LV = leucovorin; CP = cisplatin

20.2 Second-line chemotherapy

After failure of initial therapy based on 5-FU, there is evidence that chemotherapy with irinotecan is superior to best supportive care alone in terms of survival duration and quality of life.³

20.3 Toxicity

In the study reported by Beretta et al,² fewer than 20% of patients suffered from myelosuppression or diarrhoea. In all cases, these conditions were reversible, and no patient had grade 4 toxicity. However, based on a meta-analysis involving over 1200 patients, haematologic toxicity, mainly neutropenia, was more frequent with 5-FU bolus than with 5-FU by continuous infusion (31% and 4%, respectively; $P < 0.0001$), while hand-foot syndrome was less frequent with 5-FU bolus than with continuous infusion (13% and 34%, respectively; $P < 0.0001$). There was no difference between

the two treatment groups in terms of other nonhaematologic toxicities. Independent prognostic factors for nonhaematologic toxicities were age, sex and performance status; performance status and schedule of administration for haematologic toxicities; and age, sex, and schedule were predictors for hand-foot syndrome⁴.

20.4 Quality of life

Scheithauer et al¹ addressed quality of life and found it improved in the group receiving first-line chemotherapy. The benefits were noted in those with symptoms from the tumour burden. This suggests a real benefit from chemotherapy compared with the group receiving supportive care alone. A similar benefit in quality of life was reported for second-line irinotecan³.

20.5 Timing of chemotherapy

An important question to answer when considering chemotherapy is timing. Should chemotherapy be used when signs of advanced colorectal cancer appear, or should it wait until symptoms appear or are distressing?

The Nordic group⁵ compared early with delayed (until symptoms) chemotherapy, administering 5-FU, leucovorin and methotrexate to 183 patients with advanced but asymptomatic colorectal cancer. The study found improved symptom-free survival (median 10 compared to 2 months, $P < 0.001$) and nonsignificantly longer survival (median 14 compared to 9 months, $P = 0.13$) in the group treated early. Sixty per cent of the delayed group received chemotherapy (level II).

Because of the fact that only 60% of the delayed group received chemotherapy, an Australian and Canadian group⁶ is currently examining this question using 5-FU plus leucovorin. The study will also measure quality of life.

20.6 Which chemotherapy?

While 5-FU plus leucovorin has become the standard treatment for advanced colorectal cancer, the question of which chemotherapy is best has been subject to several large meta-analyses.

The Advanced Colorectal Cancer Meta-analysis Project⁷ reviewed data on 1381 patients in nine trials of 5-FU plus leucovorin.⁸⁻¹⁶ The National Health Service Centre for Reviews and Dissemination, University of York¹⁷ has analysed a further five studies.¹⁸⁻²²

These data⁷ show a highly significant increase in response rate for the combination of 5-FU plus leucovorin over 5-FU alone (23% compared to 10%, $P < 0.0001$), but without any survival advantage (11.5 compared to 11 months). Two studies not included in this meta-analysis have shown large survival benefits.^{18,21}

The Advanced Colorectal Cancer Meta-analysis Project also reviewed data on 1178 patients in multiple randomised trials^{9,15,22–28} of 5-FU plus methotrexate compared to 5-FU alone²⁹. The response rate again was doubled (19% compared to 10%, $P < 0.001$) and survival was moderately improved (median survival 10.7 compared to 9.1 months $P = 0.02$).

The Meta-analysis Group in Cancer³⁰ has reviewed studies of continuous infusion 5-FU compared to bolus, and the review has also found a doubling of response rates and a slight improvement in survival.^{31–36}

The addition of interferon to 5-FU or 5-FU plus leucovorin has not consistently improved response or survival.³⁷

The oral administration of 5-FU, using the same formulation and clinical entity, appears inferior to intravenous 5-FU, though several orally available 5-FU prodrugs are undergoing clinical evaluation.^{38–40}

Among other newer agents, raltitrexed (Tomudex®) has demonstrated activity comparable to 5-FU plus leucovorin.⁴¹

Guidelines — systemic chemotherapy	Level of evidence
First-line 5-FU-based chemotherapy prolongs life when compared to best supportive care and should be offered to patients with advanced colorectal cancer.	II
The timing of commencement of chemotherapy in asymptomatic patients is unclear, although one study suggests it is best administered early.	II
5-FU plus leucovorin, 5-FU plus methotrexate, and continuous infusion 5-FU are all associated with an improvement in response rate over 5-FU alone. Survival advantages in the palliative setting may exist, but are small with no clear quality-of-life benefits over 5-FU alone.	I
After failure of 5-FU therapy, second-line treatment with irinotecan prolongs life and improves quality of life when compared to best supportive care.	II

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CHAPTER 21

MANAGEMENT OF LIVER METASTASES

Fifty per cent of patients with colorectal cancer will develop liver metastases within five years. In 20–40% of cases, this will be the only (or first) site of failure.

21.1 Surgical resection

There are no controlled trials of liver resection, but the natural history of liver metastases from colorectal cancer is well described,¹ and several authors have retrospectively assessed the outcome of potentially resectable diseases. In three studies of patients with apparently resectable lesions, survival at three years and five years was 12% and 3%, 14% and 2% and 10% and 0%. Even solitary lesions had a uniformly bad outcome.^{2–4}

Early attempts at liver resection led to high rates of morbidity and mortality. However, the mortality of liver resection in noncirrhotic patients is now well under 5% in most major units.^{4–6}

In more recent series of highly selected patients, five-year survival following liver resection for liver metastases from colorectal cancer of between 15% and 50% has been described.^{2,3,7,8,10,11,21,31}

Retrospective studies of patients who had liver resection have attempted to define good and bad prognostic indicators for long-term outcomes. In addition, bilobar liver metastases do not appear to influence outcome, provided they are resectable.^{7,9,11}

The characteristics of metastases disease that correlate with poor outcome appear to be:

- more than three metastases^{13,14}
- tumour size¹³
- a positive surgical margin^{9,13}

Two studies have suggested that the level of preoperative carcinoembryonic antigen (CEA) may correlate with outcome.^{15,16}

In multivariate analyses, the most consistent predictors of long-term outcome have been the stage of the primary tumour, total volume of liver involvement and completeness of resection.¹⁷ However, Hughes³ has shown that a number of patients with poor prognostic indicators survived five years after liver resection, and it was concluded that each case must be assessed individually on its merits.

One can certainly identify groups at lower risk. Patients with a CEA of less than 200 ng/mL, 1 cm resection margin and less than 1000 g liver resection had a greater than 50% chance of five-year survival.¹⁵

There are a number of reports of repeat hepatic resection for recurrent colorectal liver metastases, with results comparable to those after initial resection.^{2,18–20}

Guideline — resection of liver metastases	Level of evidence
Patients with up to four lesions that can be safely removed with an adequate margin and have no evidence of extra hepatic disease should be considered for resection.	III

21.2 Imaging controlled destruction

Cryotherapy is the best established technique of imaging controlled destruction and it has now been performed in about 2000 patients, with published results in almost 1000.²¹ It is usually performed as an open technique, although there is laparoscopic and percutaneous experience. Postoperative morbidity is relatively limited and a mortality of 14 in 869 (1.6%) has been seen.

Few series have five-year survival data, which limits comparison of cryotherapy to resection, but there are five-year survivors in many series.^{22–29} There is one small and limited randomised study of cryotherapy against liver resection, with the two approaches achieving very similar results.³⁰

Important prognostic factors for long-term survival following cryotherapy are a smaller initial lesion and complete destruction of the tumour/s, and a normalisation of CEA.³¹

Alcohol injection has been a very successful treatment for small hepatomas. For metastatic colorectal cancer, it was significantly less effective than laser in a control trial because of the limited diffusion of alcohol within the rather fibrous lesions,³² although prolonged survival has been described.³³ However, the percentage of patients in whom the CEA returns to normal is low.³⁴

Laser photocoagulation is an easier method than cryotherapy to use percutaneously but it has, to date, been of limited value because of the small volume of destruction achieved around the tip. Clinical data on tumour marker normalisation and survival are both very limited. One of the best results was a 66% 'local tumour control' at six months in lesions under 2 cm diameter, and 35% 'local tumour control' in larger lesions.³⁵

Further research is required in the use of other techniques. Laser therapy may achieve similar long-term results and can be done percutaneously, while alcohol injection is less effective than laser.³¹

21.2.1 Hepatic arterial infusion

Hepatic arterial infusion (HAI) involves the administration of chemotherapy agents directly into the liver through a surgically implanted catheter into the hepatic artery.

There are two theoretical advantages for HAI over intravenous chemotherapy in the treatment of liver metastases where there are no signs of extrahepatic spread.

First, delivery of chemotherapy through the hepatic artery results in a mean hepatic drug concentration approximately 15-fold higher than can be achieved with intravenous chemotherapy.³⁶ Furthermore, established liver metastases derive their blood supply mainly from the hepatic artery rather than the portal vein.

Second, almost all (94–99%) administered floxuridine (FUDR), an effective drug for the treatment of colorectal cancer, is metabolised by the liver during the first pass, which reduces systemic drug concentrations and resulting toxicity.³⁷⁻³⁹ Because of this high first pass metabolism, the systemic concentration of FUDR achieved from HAI would be insufficient to treat extrahepatic metastases. For this reason, HAI is a suitable option only for those people who have metastatic colorectal cancer confined to the liver. In addition to these criteria, selected patients need to be able to tolerate a laparotomy for catheter insertion.

21.2.2 Procedural aspects of treatment

The surgical implantation of the drug delivery system, which comprises a subcutaneous pump or port linked to the catheter, has a low complication rate if performed by a surgeon who has previously performed this procedure at least 10 times.³⁶

The procedure routinely includes a cholecystectomy to prevent chemical cholecystitis. Meticulous attention to the ligation of branches of the hepatic artery perfusing the stomach, common bile duct and pancreas is necessary to prevent postoperative complications, particularly peptic ulceration resulting from inadvertent perfusion of the stomach.

Complete hepatic perfusion should be confirmed intraoperatively as well as postoperatively.

21.2.3 Potential complications

Technical complication rates from this procedure include:

- an operative mortality below 1%;
- mechanical problems related to the catheter such as leakage, kinks, migration or breakage (5%);
- vascular complications from the catheter such as thrombosis or aneurysm formation (5%); and
- problems associated with implantable pumps (8%).³⁶

Toxicities from intrahepatic chemotherapy include: sclerosing cholangitis (10%) which is occasionally fatal, chemical gastritis (10%), peptic ulceration (5%), or diarrhoea (5%).³⁷

21.3 Efficacy of hepatic arterial infusion

Randomised controlled trials comparing HAI with intravenous chemotherapy have consistently shown dramatically and significantly higher response rates in favour of HAI, but so far this has not been translated into a survival benefit.⁴⁰

Most studies were also performed using a sample size that is too small to detect a meaningful survival advantage. For instance, the NCCTG trial only had statistical power to rule out a doubling of survival for HAI over intravenous chemotherapy.³⁹

Two trials comparing HAI with an ad libitum control treatment (managed with supportive care that could include intravenous chemotherapy) have both shown a significant survival benefit for HAI.^{41,42} However, only 20%⁴¹ and 50%⁴² of patients in the control groups of these studies received any chemotherapy.

Pooled data from a meta-analysis of six of seven randomised studies on HAI published between 1988 and 1993 confirmed the significantly higher response rate (41% compared to 14%) for HAI compared with intravenous chemotherapy. The effect on survival is less certain — no significant survival benefit could be observed when the studies comparing HAI with intravenous chemotherapy were pooled. Although the Northern California Oncology Group (NCOG) study³⁷ was excluded from this meta-analysis as individual data were not available, its inclusion would be unlikely to change the final result because the median survival for both treatments were virtually identical in this trial. Only when two positive studies comparing HAI with ad libitum controls were included did the pooled survival results achieve statistical significance.

21.3.1 Efficacy of symptom palliation

The effects of HAI on improving the quality of survival is an important issue, particularly when its effects on prolonging survival are limited. For intravenous chemotherapy as well as HAI, any potential improvement in quality of life gained from a treatment response may be negated by treatment toxicities.

Only limited information is available in this area. The NCCTG study was the only trial comparing HAI with intravenous chemotherapy to report any quality-of-life comparisons. It found no difference in symptoms, performance status or weight gain between the two treatments.³⁹

The British Hepatic Artery Pump Test evaluated quality of survival as a primary endpoint. No significant differences in symptom, anxiety or depression scores were found between the HAI and ad libitum treatment options. However, patients in the HAI treatment group had a significantly higher number of days of survival without symptoms, anxiety or depression.⁴¹ The design of this study does not allow comparison of quality of life between HAI and intravenous chemotherapy.

Future studies should incorporate quality-of-life measurements as a major endpoint.

21.4 Newer treatments

More recent, but uncontrolled, studies have shown superior response rates with the addition of systemic leucovorin to FUDR.⁴² One randomised study evaluated the addition of dexamethasone to FUDR in an attempt to decrease biliary toxicity and unexpectedly found higher response rates, as well as improved survival, on the dexamethasone.⁴³

The role of HAI as an 'adjuvant' treatment following a potentially curative liver resection is currently unknown. However a large randomised trial, performed by the Eastern Cooperative Oncology Group, comparing hepatic resection with or without postoperative HAI has now completed accrual, and it will eventually help answer this question.

Guidelines — hepatic arterial infusion	Level of evidence
Hepatic arterial infusion (HAI) has shown survival benefit compared with best supportive care.	II
HAI shows higher response rates but little evidence of survival advantage compared with systemic chemotherapy.	I
HAI and intravenous chemotherapy should be regarded as acceptable alternatives.	I

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Appendixes

APPENDIX A COMMITTEE MEMBERSHIP AND CONTRIBUTORS TO GUIDELINES

Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer has benefited enormously from the work, knowledge and input of many, many people. Among those the Clinical Oncological Society of Australia and the Australian Cancer Network would like to thank are all those who served on committees, who attended the conference held in Melbourne on 27–28 March 1998, and who provided comments on the draft guidelines presented at that conference. A list follows.

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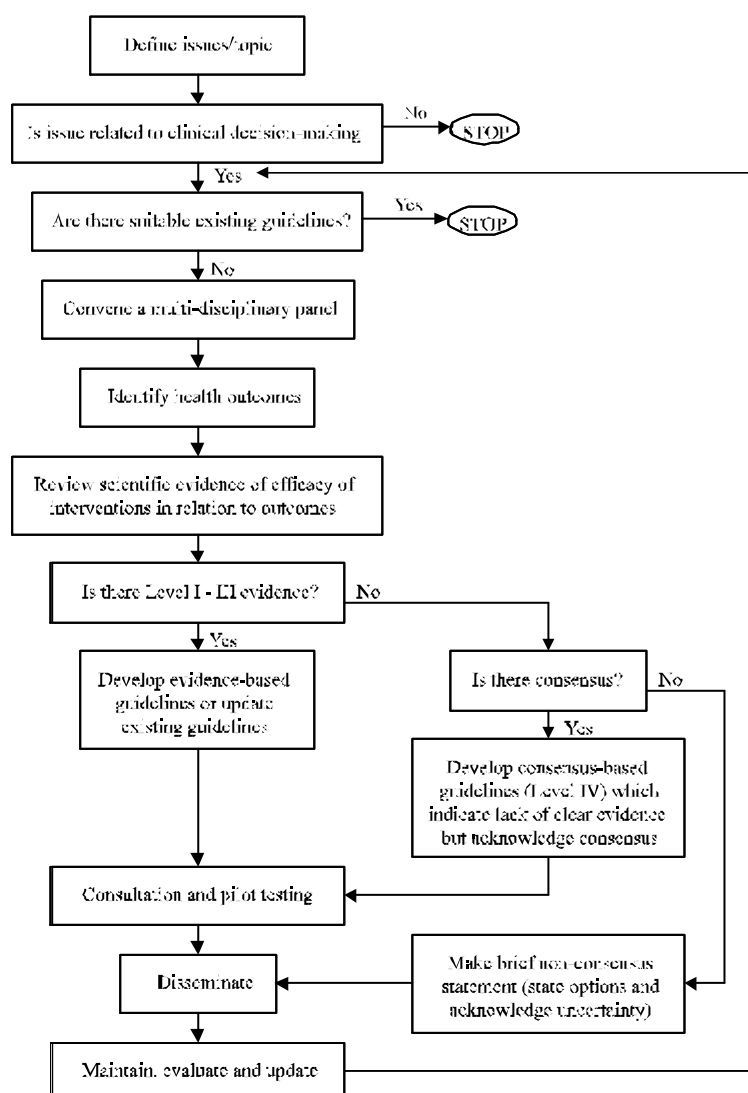
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APPENDIX B GUIDELINE DEVELOPMENT PROCESS

The National Health and Medical Research Council (NHMRC) has given four primary reasons for the need for clinical practice guidelines:

- the size of the health burden;
- the cost of the health burden;
- variations in practice; and
- the existence of available evidence.

In view of this, the Clinical Oncological Society of Australia and the Australian Cancer Network, after wide consultation, initiated a process to develop evidence-based guidelines for the management of colorectal cancer. The process followed was in accordance with the guidelines of the NHMRC. A principal committee was established to oversee the project. The process followed for development of the guidelines is shown in the flowchart below.



Source: Guidelines for the Development and Implementation of Clinical Practice Guidelines. NHMRC, Commonwealth Department of Human Services and Health, October 1995, Australian Government Publishing Services, p40

Consultative group

An extensive process of consultation was undertaken to involve the many medical, paramedical and consumer disciplines associated with colorectal cancer. The groups involved include:

1. Royal Australasian College of Surgeons
2. Royal Australasian College of Physicians
3. Royal Australasian College of General Practitioners
4. Royal Australian and New Zealand College of Radiologists and the Faculty of Radiation Oncologists
5. Royal College of Pathologists of Australasia
6. Colorectal Surgical Society of Australia, which made a major contribution to the process of developing these guidelines
7. Medical Oncology Group of Australia
8. Gastroenterology Society of Australia
9. Australian Gastroenterological Institute
10. The Gut Foundation
11. Clinical Oncology Nurses Group of COSA
12. Australian Association of Stomal Therapy Nurses
13. Commonwealth Department of Health and Aged Care
14. National Health and Medical Research Council
15. Consumers from Consumer Health Forum and by public advertisement
16. All the various components of the Australian Cancer Network, comprising 70 groups and societies concerned with cancer care across Australia.

Representatives from these groups formed the Principal Committee.

This committee met in December 1996. Agreement was reached about the desirability of the project and the methodology to be followed. It was decided to construct the draft guidelines through establishment of a number of working groups. Each working group produced a draft document relating to their area of concern. Each group was provided with resources; format documents; examples of other evidence-based guidelines. Each group has also had contact with the Cochrane Collaboration for technical support.

The first draft reports were reviewed at a public conference held in March 1998, following which the guidelines have been revised, taking into consideration the contributions from that conference and from individuals and professional groups. The first stage of the NHMRC consultation process was carried out concurrently. Consideration of the submissions and conference proceedings informed the development of the second stage consultation draft.

Second stage consultation was held during August 1998 to 14 September 1998. The NHMRC Health Advisory Committee established a small expert working party to

consider the submissions received. A list of submissions received is provided below. Recommendations arising from deliberations of these submissions were referred to the ACN for action.

The document was revised in light of these recommendations and the final document was forwarded to the Health Advisory Committee to consider NHMRC Council's endorsement. In accordance with Health Advisory Committee protocols, the draft was sent out for external review. The review indicated that some technical and editorial work be undertaken. This was subsequently undertaken and the final document referred to the NHMRC for final endorsement.

These guidelines are evidence based. They are inclusive, not prescriptive. They aim to provide information on which decisions can be made, rather than dictate a specific form of treatment. They are the result of a comprehensive process involving the careful assessment of evidence.

Submissions received

First stage consultation

Ms Doreen Akkerman	Anti-Cancer Council of Victoria
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Dr Geoff Bowers	Australian and New Zealand Association of Physicians in Nuclear Medicine
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Dr Phillip Childs	Duncraig, WA
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Dr Graeme Dickie	Royal Australasian College of Radiologists
Dr Roger Down	Newcastle, NSW
Dr G Fisher	Bunbury, WA
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Dr Clive Glover	Sutherland, NSW
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Dr Andrew Kneebone	Liverpool Health Centre Cancer Service
Ms Vanessa Lambert	Highgate, SA
Dr S Leung	East Melbourne, Vic
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Dr Jack McLeish	Monash Medical Centre, Clayton, Vic
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Dr Richard Mendelson	Royal Perth Hospital, WA
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Ms Robyn Middleton	Medical Oncology Group of Australia
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Professor Pierre H. Chapuis	University of Sydney
Dr Graeme Dickie	Royal Australasian College of Radiologists
Ms Jan Duke	Australian Nursing Council Inc
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Dr Julianne Grace	Royal College of Pathologists of Australasia
Dr Daniel G Haller	University of Pennsylvania Cancer Center, USA
Ms Heather Hill	Concord Repatriation Hospital, NSW
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Ms Vanessa Lambert	Highgate, SA
Mr W G Lawrence	Australian College of Health Service Executives
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ABBREVIATIONS

5-FU	5-fluorouracil
ACPS	Australian clinicopathological stage
APC	adenomatous polyposis coli
ASCO	American Society of Clinical Oncology
BCG	Bacillus Calmette-Guerin (tuberculosis vaccine)
CEA	carcinoembryonic antigen
CI	confidence interval
CMT	combined modality therapy (comprising both radiotherapy and chemotherapy)
CT	computerised tomography
CTAP	computerised tomography during arterial portography
DFMO	difluoromethylornithine
EORTC	European Organization for Research and Treatment of Cancer
ERUS	endorectal ultrasound
FAP	familial adenomatous polyposis
FOBT	faecal occult blood test
FUDR	floxuridine
GITSG	Gastro-Intestinal Tumour Study Group
HAI	hepatic arterial infusion
HNPCC	hereditary nonpolyposis colorectal cancer
HR	hazard ratio
MF	semustine plus 5-FU
MMR	mismatch repair genes
MRI	magnetic resonance imaging
MSI	microsatellite instability
MSI-H	microsatellite instability — high
MSI-L	microsatellite instability — low
NCCTG	North Central Cancer Treatment Group, United States
NHMRC	National Health and Medical Research Council
NSABP	National Surgical Adjuvant Breast and Bowel Project, United States
NSAID	nonsteroidal anti-inflammatory drugs
QALY	quality adjusted life-year gained
Q-TWiST	quality adjusted time without symptoms or toxicity

RR	relative risk
RT/S	preoperative radiotherapy and surgery
SEER	surveillance, epidemiology and end results (data collection program of the National Cancer Institute in the United States)
SWOG	South Western Oncology Group
TNM	tumour, node, metastasis staging system
pTNM	pathological staging

The National Health and Medical Research Council

The National Health and Medical Research Council (NHMRC) is a statutory authority within the portfolio of the Commonwealth Minister for Health and Aged Care, established by the *National Health and Medical Research Council Act 1992*. The NHMRC advises the Australian community and Commonwealth, State and Territory Governments on standards of individual and public health, and supports research to improve those standards.

The NHMRC advises the Commonwealth Government on the funding of medical and public health research and training in Australia and supports many of the medical advances made by Australians.

The NHMRC also develops guidelines and standards for the ethical conduct of health and medical research.

The Council comprises nominees of Commonwealth, State and Territory health authorities, professional and scientific colleges and associations, unions, universities, business, consumer groups, welfare organisations, conservation groups and the Aboriginal and Torres Strait Islander Commission.

The Council considers and makes decisions on reports prepared by committees and working parties following wide consultation on the issue under consideration.

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