Clinical Practice Guidelines

FOR THE PREVENTION, EARLY DETECTION AND MANAGEMENT OF COLORECTAL CANCER

APPROVED BY

Australian Government

National Health and Medical Research Council

Clinical Practice Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer

APPROVED BY THE NHMRC ON 8 DECEMBER 2005

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NHMRC approval

These guidelines were approved by the National Health and Medical Research Council at its 159th Session on 8 December 2005, under section 14A of the National Health and Medical Research Council Act 1992. Approval for the guidelines by the NHMRC is granted for a period not exceeding five years, at which date the approval expires. The NHMRC expects that all guidelines will be reviewed no less than once every five years. Readers should check with the Australian Cancer Network for any reviews or updates of these guidelines.

Disclaimer

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

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

Conflict of interest

The development of these clinical practice guidelines has been undertaken by a non-remunerated working party of the Australian Cancer Network, with further support from The Cancer Council Australia, the Clinical Oncological Society of Australia, and a grant-in-support from the Australian Government Department of Health and Aging to the National Cancer Control Initiative for editing and review services.

Some members have received sponsorship to attend scientific meetings, been supported in the conducting of clinical trials, or have been involved in an advisory capacity by pharmaceutical and biochemical companies.

Periodic updates

New information arising in areas considered to be of importance will be posted periodically on the ACN website (www.cancer.org.au/guidelines). This information will not yet have been approved by the NHMRC but will be included as appropriate in future editions of the document.

These guidelines can be downloaded from the Australian Cancer Network website at www.cancer.org.au/guidelines or from the National Health and Medical Research Council website: www.nhmrc.gov.au

Copies of this Guideline document can be ordered through the Australian Cancer Network on (02) 9036 3120 or email: acn@cancer.org.au

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Foreword

This document is a revision and update of the 1999 Guideline publication *"Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer"*.

It has been developed by the multidisciplinary ACN Colorectal Cancer Guidelines Revision Working Party, not only because it was timely, but because of numerous enquiries as to when a new edition would be released.

The 1999 Guidelines have been widely used as a reference and in several reviews which have demonstrated that concordance between guidelines and practice has been achieved, but that there is still a distance to travel before it is complete.

There have been significant changes in relation to practice in that multidisciplinary care is being widely incorporated into the management of malignancy, and the principles involved in its introduction are expected to be carefully followed. It is promoted and expected that in areas of doubt, physicians and surgeons will encourage their patients to be involved in randomised clinical trials.

Whereas in the past, intensive follow up after treatment was not promoted, it has now been shown that intensive follow up leads to earlier detection of recurrence and a Cochrane Review found such a programme to improve survival (17.1.2). The Guidelines encourage this change in practice towards optimal care.

There has been considerable discussion about Practice Recommendations and the Working Party made the decision to use them in the development of this document. Practice Recommendations were derived from overseas documentation (ref 2, page xiv). The NHMRC is developing its own grades for implementation by future guideline developers.

The Working Party submitted a draft document for public consultation and received 32 submissions from a variety of sources (Appendix 4). These were carefully reviewed by members of the Working Party. There were a number of phone discussions, two of which included non-working party members. It is agreed that the quality of submissions from the public review had led to refinement and increased clarity in some areas of the document.

The draft guidelines were on The Cancer Council Australia – Australian Cancer Network's website: www.cancer.org.au/guidelines since the beginning of the consultation period. There were a large number of hits – including unique downloads, on this site.

Another exciting development is that CSSA (Colorectal Surgical Society of Australia) used the draft document as a core reference for its advanced trainees and Fellows and in examinations for advanced trainees of that organisation.

Professor Robert Thomas / Professor Michael Solomon
Joint Chairs, ACN Colorectal Cancer (CRC) Working Party

Executive Summary

- Colorectal Cancer continues to be a major health problem for Australians, being the commonest Cancer in Australia (excluding non-melanoma skin cancer). From age 40 there is increased risk for individuals which rises sharply after age 50. The latest national figures available in 2000, reveal Colorectal Cancer as being responsible for 13% of cancer deaths. (Australian Institute of Health and Welfare, Australasian Association of Cancer Registries. Cancer in Australia 2000. Canberra: Australian Institute of Health and Welfare, 2000)
- The Guidelines for the prevention, early detection and management of Colorectal Cancer (CRC) are evidence-based. They have been produced by a multidisciplinary team and are proposed as basic for sound decision making. They are guidelines not rules and carry no sense of prescription.
- The guidelines are intended to provide a resource for all medical practitioners and health workers who require sound information directed toward the management of patients with Colorectal Cancer. These guidelines are wide-ranging in scope and provide information which covers prevention and screening, diagnosis and psychosocial matters, as well as the clinical aspects of surgery, radiotherapy and chemotherapy. High quality surgery is proposed as a gold standard and the Guidelines address training to this end.
- Emphasis is placed on good history taking and early investigation of the patients with symptoms.
- Familial CRC is addressed and the genetic background and assessment discussed. A directory to the Hereditary Bowel Cancer Registers in Australia and New Zealand is included.
- A time frame for follow-up for the management of epithelial polyps is proposed.
- Advanced Colorectal Cancer should be managed by a multidisciplinary team and includes a number of difficult issues, including the selection of patients for treatment who have liver metastases.
- Whole patient consideration is the basis of each recommendation for management after consideration of all and optimal use of the available modalities. The careful recording of comprehensive and consistent data and outcomes and encouragement of participation in well designed clinical trials is necessary to provide future strategies in prevention and reduction of mortality from Colorectal Cancer.

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 (see Appendix 2).

The guidelines are based on evidence obtained through an exhaustive literature review process. Individual studies have been rated as level I, II, III-1, III-2, III-3 or IV according to the National Health and Medical Research Council (NHMRC) scale (see below). Each recommendation has also been further evaluated according to the level, quality and statistical precision of the included studies (strength of evidence), and the overall size and clinical importance of the effect. The levels of evidence and strengths of recommendations are described in detail in Appendix 3. Detailed summations of the studies supporting each recommendation are included in the text of each chapter.

Guidelines to be used in the interpretation of tables

The following tables provide a list of the evidence-based recommendations 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.

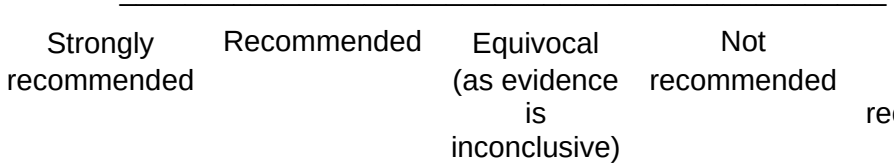
The clinical question is in bold. The recommendations of the advisory panel and working party follow in italics. These provide options for the clinician to discuss with the patient; they are not prescriptive but should be considered during the decision making process. The following columns provide the level of evidence (I-IV) of the key studies and the strength of the recommendation determined by the expert advisory panel taking into account the strength of the evidence from the included studies and the overall size and clinical importance of the effect. The key references that underpin the recommendation (included studies) are provided in the last column.

LEVELS OF EVIDENCE[1]

I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly designed randomised controlled trial
III-I	Evidence obtained from well-designed pseudo randomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test/post-test

STRENGTH OF RECOMMENDATIONS[2,3]

The strength of recommendations are determined by the expert advisory panel taking into account the level of evidence, quality of studies, size of effect and clinical importance for all the included studies, and ranges from Strongly recommended to Strongly not recommended. These levels of recommendation are modified from The Canadian Task Force on the Periodic Health Examination and are explained in further detail in Appendix 3.



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2. Woolf SH, Battista RN, Anderson GM, Logan AG, Wang E. Assessing the clinical effectiveness of preventive manoeuvres: analytic principles and systematic methods in reviewing evidence and developing clinical practice recommendations. A report by the Canadian Task Force on the Periodic Health Examination. J Clin Epidemiol 1990; 43: 891-905.

3. Grimes DA, Schulz KF. An overview of clinical research: the lay of the land. Lancet 2002; 359: 57-61.

SECTION I: EARLY COLORECTAL CANCER

Chapter	Recommendations	Level of evidence		Practice recommendation		Refs
2	**PRIMARY PREVENTION**	**Cancer**	**Adenoma**	**Cancer**	**Adenoma**	
	Should physical activity and weight control be advised to reduce the risk of Colorectal Cancer? ***"****Engage in moderate to vigorous physical activity for 30–60 minutes/day, and avoid excessive weight gain.* *Weight should be maintained in the healthy weight range of BMI."*	III-2 III-2	III-2 III-2	Recommended Recommended	Recommended Recommended	2,3,4,5, 6,12 2,6,7, 8,9,10,11, 13
	Should alcohol intake be restricted to reduce Colorectal Cancer risk? ***"****Alcohol consumption should be limited or avoided. For people who do drink alcohol, recommended amounts for men are no more than 2 standard drinks per day and for women no more than one standard drink a day."*	III-2	III-2	Strongly recommended	Recommended	9,14, 17-20
	Does smoking tobacco increase the risk of Colorectal Cancer? *"Avoid tobacco smoking."*	III-2	III-2	Recommended	Recommended	2,21-24
	Should energy intake be restricted to reduce Colorectal Cancer risk? *"Limit energy intake in most men to <2500 calories (10,480 kJ) per day and in most women to <2000 calories (8360 kJ) per day."*	III-2	-	Strongly recommended	-	9,29, 30
	Should dietary fat be restricted to reduce Colorectal Cancer risk? ***"****Reduce dietary fat to <25% of calories as fat."*	III-2	II	Recommended		29,30,36-38,40,42, 43

	Should red meat intake be altered to reduce Colon Cancer risk? *"Moderate intakes of lean red meat can be eaten as part of a mixed diet including carbohydrates (breads and cereals), vegetables and fruit, and dairy products. Charring of red meat is best avoided. Consumption of processed meats should be limited."*	III-2	III-2	Equivocal	Equivocal	9,29, 36,41, 49, 50
	Should fresh fruit and vegetable intake be increased to reduce Colorectal Cancer risk? *"Eat five or more serves per day of a variety of vegetables. National nutrition guidelines also advise two serves of fruit daily ("Go for 2 and 5")."*	III-2	-	Equivocal	-	32,36,41, 43,63,64, 68
	Should cereal fibre be selected to reduce Colorectal Cancer risk? *"Select poorly soluble cereal fibres (e.g. wheat bran), especially if at increased risk of Colorectal Cancer."*	III-2	II	Equivocal	Equivocal	9,41,51,73-76
	Does calcium supplementation reduce Colorectal Cancer risk? *"Ensure a total calcium intake of 1000–1200 mg/day in keeping with general dietary guidelines."*	III-2	II	Equivocal	Equivocal	83-87
	Does selenium supplementation reduce Colorectal Cancer risk? *"Selenium supplementation for chemoprevention is promising but requires confirmation."*	II	-	Equivocal	Equivocal	106-109

	Does antioxidant vitamin supplementation reduce Colorectal Cancer risk? *"Antioxidant vitamin supplementation is **not** advised at present to protect against Colorectal Cancer."*	II	II	Recommended	Recommended	41,77, 109,111, 112
	Do anti-inflammatory drugs reduce Colorectal Cancer risk? *"Aspirin should be considered as prophylaxis against further adenoma development in those with a previous removal of an adenoma."*	II	II	Recommended	Recommended	113-119,124-126
	Should hormone replacement therapy be recommended to reduce risk of Colorectal Cancer? *"HRT **cannot be recommended** as prophylaxis against Colorectal Cancer because of its possible collateral risks, including breast cancer."*	III-2	III-2	Equivocal	Equivocal	128-132

Chapter	Recommendations	Level of evidence	Levels of recommendations	Refs
3	**SCREENING FOR COLORECTAL CANCER**			
	Should screening be recommended? **Faecal Occult Blood Testing** *"Organised screening with FOBT, performed at least once every two years, is recommended for the Australian population over 50 years of age."*	I	Strongly recommended	13
	Flexible Sigmoidoscopy *"Screening with flexible sigmoidoscopy on a five-yearly basis from the age of 50 years."*	III-2	Equivocal	38, 39

Chapter	Recommendations	Level of evidence	Practice recommendation	Refs
4	**COMMUNICATION WITH THE PATIENT**			
5	**THE PATIENT WITH SYMPTOMS**			
	What investigations need to be included? *"In symptomatic patients aged over 40 years, referral to a specialist should be considered and consideration of full examination of the colon with colonoscopy is recommended."*	III-3	Equivocal	4-8
6	**FAMILY HISTORY OF COLORECTAL CANCER**			
	What recommendations are there for those at category 1 risk? *"Faecal occult blood testing (FOBT) every second year from the age of 50 years."*	Refer to Chapter 3 & AHTAC recomms (Box 3.1)	Recommended	3-6, 21, 28-31
	"Consider sigmoidoscopy (preferably flexible) every five years from the age of 50."	Refer to Chapter 3 & AHTAC recomms III-3	Recommended	3-6, 21, 28-31
	What recommendations are there for those at 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 bowel 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-2	Recommended	4-6, 35, 36
7	**HIGH RISK FAMILIAL COLORECTAL CANCER SYNDROMES**			
	How should genetic testing be undertaken for high risk CRC family syndromes? *"After counselling, genetic testing should be undertaken under the supervision of a cancer genetics specialist."*	III-2	Recommended	14
	What is the role of NSAIDs in the prevention of colorectal neoplasia? *"The role of NSAIDs such as sulindac in the prevention of cancer in FAP is unclear. High dose celecoxib (400mg twice daily) has been shown to reduce polyp numbers and its use may facilitate the control of polyps, but carries significant cardiovascular morbidity."*	II	Equivocal	14, 32, 33, 35, 36

Chapter	Recommendations	Level of evidence	Practice recommendation	Refs
	What is the surgical management of FAP? *"The surgical management of FAP is by total colectomy and ileorectal anastomosis or restorative proctocolectomy."*	III - 2	Recommended	14, 25
	When should large bowel surveillance begin in FAP and what should be offered? *"Surveillance in FAP is by sigmoidoscopy from 12-15 years of age (the later age is recommended), except in attenuated FAP where surveillance is based on colonoscopy."*	III - 2	Recommended	1-3,19
	Is duodenal surveillance recommended in FAP? *"Duodenal surveillance in FAP is recommended, from 25 years of age or earlier should there be a family history of duodenal cancer at an earlier age."*	III-2	Recommended	14, 26-31
	How should FAP family members not carrying their family mutation be advised? *Members of proven FAP families who test negatively for the family APC mutation are no longer at high risk.*	III - 2	Recommended	24
	When should large bowel surveillance screening of at-risk members in proven HNPCC families be offered? *"Screening of at-risk members of proven HNPCC families should be by annual or two yearly colonoscopy, commencing around the age of 25 years or five years before the earliest age of cancer diagnosis in the family, whichever comes first. Annual screening should be offered to individuals carrying a germline mutation and for clinically affected individuals in Amsterdam families where mutation status is unknown."*	III-2	Recommended	4-6, 9, 14
	What surveillance is recommended for extra-colonic cancers in HNPCC? *Consideration should be given to screening extracolonic sites in HNPCC, especially in families with clusters of extracolonic cancers. Surveillance of uterus and ovaries should begin at around 30-35 years or five years earlier than the youngest relative affected with uterine or ovarian cancer, whichever comes first.*	III -3	Recommended	9

Chapter	Recommendations	Level of evidence	Practice recommendation	Refs
	How should tumour testing (MSI and IHC) be used in affected individuals from families suspected to have HNPCC? *"The Revised Bethesda Guidelines could be applied to the selection of cancers for microsatellite instability (MSI) testing and immunohistochemical staining."*	III-2	Recommended	76
	How should HNPCC family members not carrying their family mutation be advised? *"Members of proven HNPCC families who test negatively for the family mismatch gene mutation do not have an additional risk associated with this mutation."*	III-2	Recommended	14
	What surveillance is recommended in hyperplastic polyposis and for MSI-variable cancers? *"Affected subjects in familial clusters characterised by mixtures of MSI-H, MSI-L and MSS cancers and/or the finding of multiple/large hyperplastic polyps should be screened by colonoscopy according to HNPCC recommendations, though first degree relatives unaffected by cancer may be screened according to intermediate risk guidelines."*	IV	Equivocal	92,93
8	**DIAGNOSTIC TESTS AND PREOPERATIVE ASSESSMENT**			
	Who should be investigated? *"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."*	III-3	Equivocal	4-7
	What are the investigations for symptoms of Colorectal Cancer? *"Investigation should include a digital rectal examination, a rigid sigmoidoscopy and a colonoscopy. A double-contrast barium enema plus sigmoidoscopy or CT colonography may replace the colonoscopy if there are difficulties with local availability, expertise or an incomplete colonoscopy."*	III-3	Equivocal	6, 9, 10, 13-16

Chapter	Recommendations	Level of evidence	Practice recommendation	Refs
	What role does FDG-PET scan have in assessing recurrent Colorectal Cancer? *"FDG-PET scan facilitates management of probable or proven recurrent Colorectal Cancer."*	III-2	Recommended	10
9	**MANAGEMENT OF EPITHELIAL POLYPS**			
	What is the management of epithelial polyps? *"All polyps should be at least sampled, and preferably removed. Synchronous polyps should be sought and removed."*	III-2	Recommended	25-34
	What is the general management of all patients with colorectal neoplasia completely removed at colonoscopy? *All patients with colorectal neoplasia completely removed at colonoscopy should then be considered for colonoscopic surveillance according to the following protocols.* • *Within a year following incomplete or possible inadequate examination, for example in a subject with multiple adenomas.* • *At three years 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 with colorectal neoplasia* • *At four to six years in subjects without the risk factors outlined above.*	II II III-3	Recommended Recommended Equivocal	45-48
	What is the management of malignant adenomas? *"Malignant adenomas may be managed safely by endoscopic polypectomy provided 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."*	III-2	Recommended	35-43
10	**PREPARATION FOR SURGERY**			
	What is the role of the stomal therapist? *"All patients who have a reasonable chance of a postoperative stoma should be prepared for this possibility. This includes a visit, where possible, by the stomal therapy nurse."*	III-2	Recommended	1

Chapter	Recommendations	Level of evidence	Practice recommendation	Refs
	Should bowel preparation be given routinely preoperatively? *"Bowel preparation is current standard practice prior to elective colorectal operations. However recent randomised controlled trials have not demonstrated any conclusive benefit from this procedure. Accordingly the previous guideline has been revised. As follows:* *mechanical bowel preparation is not indicated in elective colorectal operations unless there are anticipated problems with faecal loading which might create technical difficulties with the procedure. Eg. Laparoscopic surgery, low rectal cancers. "*	I	**Not** recommended	11
	What happens if a blood transfusion is required perioperatively? *"Perioperative blood transfusion is to be avoided whenever possible as there may be a detrimental association between transfusion and recurrence."* *"If a transfusion is required, then autologous blood is preferable to allogeneic blood for reasons of infection control and resource use."*	III-2	Recommended	27
	Should thromboembolic prophylaxis be given? **"***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. Low molecular weight heparin has not been shown to be superior to low dose heparin in colorectal surgical patients."*	I II	Strongly recommended Strongly recommended	29 30
	Should prophylactic antibiotics be given? *"All patients undergoing Colorectal Cancer surgery require prophylactic antibiotics."* *"A single preoperative dose of intravenous cephalosporin and metronidazole, or gentamicin and metronidazole is an effective regime."*	II I	Recommended Strongly recommended	33 34
	Should normal body temperature be maintained? *"Perioperative normothermia should be maintained."*	II	Recommended	36

Chapter	Recommendations	Level of evidence	Practice recommendation	Refs
11	**ELECTIVE SURGERY FOR COLON CANCER**			
	Does high ligation provide any benefit? *"High ligation of the lymphovascular pedicle does not confer any oncological benefit. Resection where feasible should extend to the origin of segmental vessels."*	III - 3	Equivocal	4
	Does no-touch isolation technique have any benefit? *"No-touch isolation technique has no oncologic benefit."*	II	**Not** recommended	5
	Is segmental and extended resection equivalent in outcome? *"Segmental resection is equivalent to extended resection in outcome."*	II	Equivocal	7
	Do sutured and stapled anastomosis have equivalent outcomes? *"Sutured and stapled anastomosis have equivalent outcomes."*	I	Strongly recommended	8, 9
	Does omental wrapping of intestinal anastomoses have any benefit? *"Omental wrapping of anastomosis has no benefit."*	III-2	Strongly **not** recommended	11
	When should oophorectomy be performed in association with colectomy for colon cancer? *"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."*	III-3 II	Recommended **Not** recommended	23, 24 26
	Is laparoscopic colonic surgery as effective as the conventional approach? *"In experienced hands, laparoscopic surgery for colon cancer has equivalent outcome to conventional surgery."*	I	Recommended	36
12	**ELECTIVE SURGERY FOR RECTAL CANCER**			
	Who should perform elective rectal cancer surgery? *"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."*	III-2	Recommended	1-7

Chapter	Recommendations	Level of evidence	Practice recommendation	Refs
	When should local excision of rectal cancer be performed? *"Local excision of T1 rectal cancer may be used in selected cancer patients according to the following guidelines.* *mobile tumour ≤3 cm* • *T1 on endorectal ultrasound or MRI* • *not poorly differentiated on histology (biopsy)"*	III-3	Equivocal	8–12, 16–21
	What is an adequate distal clearance of resection? *"2 cm (fresh) and 1cm (fixed) of distal clearance is recommended in most instances."*	III-2	Recommended	30–35
	What factors influence sphincter preservation? *"Sphincter saving operation is preferred to abdominoperineal resection except in the presence of:* • *tumours such that adequate distal clearance (> 1 - 2 cm) cannot be achieved* • *the sphincter mechanism is not adequate for continence* • *access to the pelvis makes restoration technically impossible (rare)."*	III - 3	Equivocal	10,22, 25–30
	• **What is recommended for the extent of mesorectal excision (TME)?** • *"For mid to low rectal tumours, the principles of extra fascial dissection and total mesorectal excision (TME) are recommended."*	III-2	Recommended	31,35, 43–55
	Should a colonic reservoir be constructed? *"Where technically feasible, a colonic reservoir is recommended for anastomosis within 2cm from ano-rectal junction."*	II	Strongly recommended	56,57, 59,61, 65-67, 69-71, 74
	Should drainage be considered? *"Routine drainage should be considered only for rectal cancers."*	II	Equivocal	76,77, 79–81
13	**EMERGENCY SURGERY**			
	What surgery is recommended for bowel obstruction? *"Primary resection of obstructing carcinoma is recommended unless the patient is moribund."*	II	Recommended	14-21

Chapter	Recommendations	Level of evidence	Practice recommendation	Refs
	When should primary anastomosis be considered? *"Primary anastomosis should be considered as a colectomy, with an ileocolic or ileorectal anastomosis."* *"Primary colonic and rectal anastomoses could be considered and may need to be preceded by on table colonic lavage."*	III - 2 III - 2	Equivocal Equivocal	14, 15, 17-20 18,19, 21
14	**STAGING AND REPORTING**			
	What staging data should be recorded? *"TNM staging, ACPS staging and the data required to adequately prognose should all be recorded to allow national and international comparisons. (ACPS staging embodies the simplicity of Dukes)."*	III-3	Equivocal	9, 10
15	**ADJUVANT THERAPY FOR COLON CANCER**			
	Who should be considered for adjuvant therapy? *"People with resected Dukes C i.e. node positive colon cancer should be considered for adjuvant therapy."*	I	Strongly recommended	3-5
	What is the value of adjuvant therapy in Duke's B colon cancer? "*The value of adjuvant therapy in Dukes B colon cancer has not been demonstrated unequivocally. Adjuvant therapy in this group is not recommended except for patients with features of 'poor prognosis'."*	II	Recommended	46
16	**ADJUVANT THERAPY FOR RECTAL CANCER**			
	When should adjuvant therapy be considered for rectal cancer? *"Adjuvant preoperative or postoperative radiotherapy should be considered for the high-risk rectal cancer."*	I	Strongly recommended	26
	Does preoperative therapy reduce late morbidity compared with postoperative? *"Preoperative therapy may lower the incidence of late morbidity."*	II	Recommended	22, 34

Chapter	Recommendations	Level of evidence	Practice recommendation	Refs
	What postoperative chemotherapy should be administered if radiotherapy is indicated? *"Where postoperative radiotherapy is indicated, 5-FU based chemotherapy should be administered."*	II	Recommended	6
17	**FOLLOW-UP AFTER CURATIVE RESECTION FOR COLORECTAL CANCER**			
	What are the recommendations for follow up? *"Intensive follow up for Colorectal Cancer should be considered for patients who have had potentially curable disease. Although future investigations and pathways are yet to be firmly established. "*	I	Recommended	12, 13
18	**PSYCHOSOCIAL CARE**			
	How important is psychosocial care in patients with cancer? *"Psychosocial care is important. Psychological interventions should be* **a component of care as they can improve the quality of life for the patients with cancer.**	I	Strongly recommended	17, 22
SECTION II ADVANCED COLORECTAL CANCER				
19	**RECURRENT AND ADVANCED COLORECTAL CANCER: GENERAL APPROACH AND LOCAL MANAGMENT**			
	What are the recommendations for recurrent and advanced rectal cancer? *"Radiotherapy, generally combined with chemotherapy is recommended in rectal cancers fixed or tethered within the pelvis."*	II	Recommended	2, 3
	What are the recommendations for inoperable rectal cancer? *"Radiotherapy alone or chemoradiation should be considered in patients with locally advanced rectal cancer not amenable to surgery."*	IV	Recommended	6-9, 16
20	**THE ROLE OF SYSTEMIC CHEMOTHERAPY IN METASTATIC DISEASE**			
	Should chemotherapy be offered to patients with metastatic disease? *"First-line FU based chemotherapy prolongs life when compared to best supportive care and should be offered to patients with advanced Colorectal Cancer."*	I	Strongly recommended	1

Chapter	Recommendations	Level of evidence	Practice recommendation	Refs
	When is the optimal time to commence chemotherapy? *"The optimal time to commence chemotherapy in patients that are initially asymptomatic is unclear."*	II	Equivocal	6, 7
	What is the response rate in regimes of 5-FU chemotherapy? *"After failure of 5-FU therapy, second-line treatment with irinotecan prolongs life and improves quality of life when compared to either best supportive care or an alternative regimen of 5-FU."*	II	Recommended	4,5
21	**MANAGEMENT OF LIVER AND OTHER DISTANT METASTASES**			
	Should imaging controlled destruction be considered? *"Radiofrequency ablation is an alternative to surgery in selected cases."*	II	Equivocal	37
	Should adjuvant chemotherapy be considered? *"Adjuvant chemotherapy should be considered following resection of liver metastases."*	II	Equivocal	27-30
	Does combination systemic chemotherapy have any benefits? *"Combination systemic chemotherapy regimens that incorporate irinotecan or oxaliplatin have response rates, survival outcomes and safety profiles that are superior to those achieved with hepatic artery infusion chemotherapy."*	III-2	Recommended	48, 51-55
	When should surgical resection of unresectable liver metastases be considered? *"Patients with liver metastases that are initially considered unresectable and achieving a response to systemic chemotherapy could be reconsidered for surgical resection."*	III-3	Equivocal	56
	What is the role of cytoreductive surgery with hyperthermic intra-peritoneal chemotherapy? *"Cytoreductive surgery with or without chemotherapy should be performed on an appropriate randomised controlled trial."*	II	Equivocal	70-82

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 13% of cancer deaths in 2001,[1] the latest year for which national figures are available. Only lung cancer, which caused 19% of deaths, was a more common cause of cancer death.

Each year there are about 12,600 new cases of Colorectal Cancer and 4,700 deaths. About one in 21 Australians is likely to develop Colorectal Cancer during his or her lifetime, with the risk increasing after 40 years of age, and rising sharply and progressively from the age of 50.[1]

In 2001, premature death from Colorectal Cancer was responsible for an estimated 29, 058 life-years lost before 75 years of age. This made it second only to lung cancer as a cause of lost life-years.[1]

In the same year, Colorectal Cancer was the most commonly diagnosed invasive cancer after non-melanocytic skin cancers, accounting for some 14% of all invasive cancer diagnoses.[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 the age of 75 is about one in 17 for males and one in 26 for females,[1] with incidence and mortality increasing progressively with age. (Table 3.1) Fewer than 1% of cases are diagnosed in people under 35 years of age.[1]

Australian data for the period 1999–2001 show:

- for females, little evidence of a change in incidence (+0.1% per annum), but a slight decline in age-standardised (world population) Colorectal Cancer mortality (-1.6% per annum)
- for males, an increase in incidence (+0.3% per annum), and a slight decrease in the mortality rate (-1.2% per annum).[1]

A national Colorectal Cancer care survey in Australia has reviewed all cases registered at each cancer registry within Australia between February and April 2000. This study gives a snapshot of the management plan currently used in Australia. The results show a high concordance of current practice with evidence-based NHMRC guidelines.[3]

1.2 Aetiology and pathogenesis

Colorectal Cancer is a malignant tumour that starts in the bowel wall and is usually, but not always, 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 when 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. 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 the development of Colorectal Cancer.[12] However, it usually takes many years for Colorectal Cancer to develop from small adenomas.[13]

1.3 Treatment

There are a number of treatment options for Colorectal Cancer, and the evidence for these will be presented in subsequent chapters. Usual curative treatment options consist of surgical resection with or without adjuvant chemotherapy or radiotherapy. In advanced-stage disease, neoadjuvant therapy for T4 rectal tumours may allow subsequent resection. Palliative care programs provide benefit for patients with advanced disease (Chapter 19). 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. They range from about 90% five-year survival for people whose cancers were detected at the earliest (localised) stage, to 7% for people diagnosed with distant metastatic cancer.

South Australian data for 1977–94 showed a five-year survival from Colorectal Cancer of 53%;[14] 1993–2001 data showed a survival rate of 58% (Colin, Luke. (2004) personal communication). Based on United States SEER (surveillance, epidemiology and end results) data, it is estimated that 15-year survival would be about 47%.[15] For the 1977–85 diagnostic period, the five-year case survival was 50%, rising to 56% for the 1986–1994 diagnostic period.[14] The South Australian figures, and the upward trend, are similar to data from the United States[15] and the Netherlands.[16]

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 (confined to the bowel wall), 70% for stage B (confined to the bowel wall), 43% for stage C (regional nodal involvement), and 7% for stage D (distant metastases).[17] 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 socio-economic groups in the South Australian population,[18] and delay in seeking care has been proposed as a major contributing cause of such differences.[19]

1.5 Screening for Colorectal (bowel) Cancer

Screening for bowel cancer based on faecal occult blood testing (FOBT) has been demonstrated to reduce mortality in population studies (Chapter 3). Pilot programs of FOBT for Colorectal Cancer have begun in three Australian states and are being evaluated.

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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 research, human nutrition and epidemiology. Endpoints range from gene expression, cell proliferation, apoptosis, and aberrant crypt formation to adenomas (benign tumours) and Colorectal Cancer. Although the strongest evidence has Colorectal Cancer as an endpoint, adenomas also provide useful information. As most Colorectal Cancers arise from adenomas (see Chapter 9), epidemiological studies that use adenomas as an endpoint can provide information about environmental influences on the early stages of colorectal carcinogenesis.

Several molecular pathways to Colorectal Cancer are now recognised. The chromosomal instability pathway is characterised by proto-oncogenic activation (e.g. K-ras) and suppressor gene loss (APC, P53 and DCC), and the microsatellite instability (MSI) pathway by mismatch repair deficiency.[1] *De novo* cancer pathways, independent of a precursor adenoma, also exist. Dietary protection could well be pathway-specific, quite possibly accounting for differences in findings reported in some observational and interventional studies.

This chapter will focus principally on studies using Colorectal Cancer as an endpoint but, where appropriate, information derived from studies on colorectal adenomas will also be included. Data relating to physical activity and obesity have matured in recent observational studies, so advice relating to these has been prioritized in this edition.

2.1 Physical activity

The evidence that physical activity protects against colorectal cancer is strong but varies by site in the bowel.[2] It is strongest for colonic cancer. In cohort studies, two of six studies not differentiating by site and eight of fourteen colonic cancer studies (two with mortality outcomes) showed protection, but neither of two rectal cancer studies showed benefit. Respective results for case-control studies were three of seven colorectal, ten of fifteen colonic, and one of ten rectal studies. Some of these studies showed statistical benefit restricted to one gender, specific age ranges, intense but not moderate levels of exercise, or only with one of either recreational or occupational exercise categories.[2,3,4] Levels of activity needed to protect against colon cancer are 30–60 minutes per day of moderate to vigorous physical activity, and the relationship is dose-dependent.[5]

Various mechanistic hypotheses are postulated. These include reduced bile acid secretion, stimulation of intestinal transit, immune and hormonal changes, and a reduction in levels of insulin-like growth factor (trophic to the colonic mucosa).[2,6]

2.2 Obesity

Obesity, particularly central obesity, is an independent but not as strong a risk factor for Colorectal Cancer and adenomas.[2,7,8] Obesity interacts with other lifestyle variables in a manner only recently being untangled in epidemiology where it persisted as an independent risk factor.[9]

The 2002 IARC report summarizes the relationship of Colorectal Cancer risk and body mass index. For cohort studies, two of seven studies of colonic cancer showed increased relative risk with obesity, and all but one showed, at least for men, a trend between increasing obesity and Colorectal Cancer risk. There was no such trend in the one rectal cancer cohort study. In case-control studies, four of seven studies had significant increased relative risks for colonic cancer, but none of four rectal cancer studies showed this. Again, some of these significant outcomes were gender restricted, with the risk generally being found more in men than in women.[2] The IARC report concluded that there is sufficient evidence to support a link between weight gain and cancer of the colon, and certain other types of cancer, but inadequate evidence to show that intentional weight loss reduces cancer risk for

any site (data not shown here). The report also concluded that regular physical activity reduces the risk of colon cancer, independently of weight control.

The American Cancer Society Cohort Study of over 900,000 American adults identified relative risks of cancer death in the morbidly obese compared to those of normal weight of 1.52 (CI 1.13–2.05) for men and 1.62 (CI 1.40–1.87) for women. There was also a significant association between body mass index (BMI) and death rates for both colon cancer and rectal cancer.[10] In a Canadian prospective study, the greater risk associated with obesity was mainly in premenopausal women.[11] Intentional weight loss was associated with a reduction in colon cancer risk.[8,12]

Weight gain is also related to adenoma occurrence. [2,13]

Should physical activity and weight control be advised to reduce the risk of Colorectal Cancer?

Guideline — Physical activity and obesity	Level of evidence		Practice recommendation		Refs
	Cancer	Adenoma	Cancer	Adenoma	
Engage in moderate to vigorous physical activity for 30–60 minutes/day, and avoid excessive weight gain.	III-2	III-2	Recommend	Recommend	2,3,4,5, 6,12
Weight should be maintained in the healthy weight range of BMI	III-2	III-2	Recommend	Recommend	2,6,7, 8,9,10, 11, 13

2.3 Alcohol

With some exceptions, total alcohol intake is more consistently associated with Colorectal Cancer risk than specific types of alcohol.[14]

In cohort studies, significant associations between alcohol intake and risk have been found in four of five colon cancer studies;[9] three of three rectal cancer studies;[9] and two of three studies of Colorectal Cancer (sub-site not distinguished).[9] A United States cohort study of men showed a particularly strong association of alcohol intake with the development of Colorectal Cancer and adenomas in individuals with low folate or methionine intakes.[15]

In case-control studies, significant associations between alcohol intake and increased risk have been found in nine of 18 studies of colon cancer and nine of 17 studies for rectal cancer.[9] This effect is generally stronger in men than women. Australian studies have found a similar positive association with beer drinking in men.[16,17] The positive association of alcohol intake and development of colon cancer is not as strong for wine intake, especially in women.[9,18] Rectal cancer does not seem to be related to wine drinking.[18]

A recent pooled analysis of eight cohort studies reports a modest increase in risk for cancer with consumption of three or more drinks per day (RR 1.41, CI 1.16–1.72), a risk that was not site-specific within the large bowel.[14]

Colorectal adenomas, especially advanced adenomas, also are related to high alcohol intake.[19] Postulated mechanisms of action include solvent effects of alcohol, microsomal enzyme induction of pro-carcinogens, inhibition of DNA repair and concurrent nutritional deficiency.

Should alcohol intake be restricted to reduce Colorectal Cancer risk?

Guideline — Alcohol	Level of evidence		Practice recommendation		Refs
Alcohol consumption should be limited or avoided. For people who do drink alcohol, recommended amounts for men are no more than 2 standard drinks per day and for women no more than one standard drink a day.	Cancer	Adenoma	Cancer	Adenoma	9,14, 17-20
	III-2	III-2	Strongly recommend	Recommend	

2.4 Tobacco smoking

Of 51 case-control or cohort studies, 22 show a 50% increase in risk from tobacco smoking, and ten 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.[21,22] Mortality from Colorectal Cancer is also increased.[23] Data are even more consistent for adenomas, with 22 of 27 case-control or cohort studies showing at least a 50% increase in risk. Nineteen are significant and nine of ten have a positive dose response.[2] Thus, the main effect of smoking seems to occur early in the process, during adenoma formation, and applies especially to distal sites in the large bowel.[24]

Smoking is also recognisable as a risk factor in vegetarians.[25]

Smoking may cause specific mutations[26] and may induce metabolic activation (CYP1A2) of heterocyclic amines,[27] particularly in relation to MSI high cancers.[28]

Does smoking tobacco increase the risk of Colorectal Cancer?

Guideline — Tobacco smoking	Level of evidence		Practice recommendation		Refs
Avoid tobacco smoking	Cancer	Adenoma	Cancer	Adenoma	2,21-24
	III-2	III-2	Recommend	Recommend	

2.5 Energy Intake

Case-control studies consistently show a positive association between 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 by multivariate analysis in cohort studies have indicated that energy derived from fat sources predominates in risk, focusing attention on fat intake itself. [29]

However, a meta-analysis of 13 case-control studies of diet and Colorectal Cancer found little evidence of any energy-independent effect of either total fat or saturated fat intake.[30] The authors

concluded that substituting other sources of calories for fat is unlikely to reduce Colorectal Cancer risk.

A role for insulin and/or insulin-like growth factor 1 as an endogenous hormone trophic to colorectal neoplastic lesions has been suggested. Epidemiological studies provide mixed evidence to support this. The Women's Health Study of 39,876 health professionals recently reported a positive association (relative risk (RR) 2.85, 95% confidence intervals (CI) 1.40–5.80) for dietary glycaemic load, ($p = 0.004$ for trend across quintiles), supporting this hypothesis.[31] Total carbohydrate intake was also significantly related (RR 2.41, CI 1.10–5.27), especially with respect to non-fibre carbohydrate ie sugar (RR 2.60, CI 1.22–5.54). However, a United States prospective cohort study of 49,124 women showed no association between Colorectal Cancer incidence and glycaemic load or total carbohydrate or sugar consumption.[32]

Should energy intake be restricted to reduce Colorectal Cancer risk?

Guideline — Energy Intake	Level of evidence		Practice recommendation		Refs
Limit energy intake in most men to <2500 calories (10,480 kJ) per day and in most women to <2000 calories (8360 kJ) per day.	Cancer	Adenoma	Cancer	Adenoma	9,29, 30
	III-2	-	Strongly recommend	-	

2.6 Fat Intake

Many case-control and cohort studies demonstrate a direct relationship between dietary fat intake and Colorectal Cancer risk[33] although this has come into recent question from the Boston group of epidemiologists, who favour red meat rather than fat as the risk factor.[34,35] The incidence of Colorectal Cancer is high when fat intake is high and conversely, low when dietary fat intake is low. Summarising the case-control and cohort studies of fat and Colorectal Cancer risk, Potter found that six of ten studies (three null and one inverse) showed this positive association.[36] Other analyses of case-control studies suggest a null association, pointing more to total energy as the key relationship.[30]

In animal models, a higher intake of dietary fat — whether saturated or polyunsaturated — leads to increased hepatic synthesis of cholesterol and bile acids, elevating their concentration in the colon and faeces. Bacterial flora (particularly anaerobes) can convert these sterols into tumour-promoting cholesterol metabolites and oxidised bile acids, increasing chances of DNA replication errors and modulation of apoptosis and cell proliferation. [37]

High intake of monounsaturated fat, typified by olive oil in the 'Mediterranean diet', may not be associated with increased risk for Colorectal Cancer or may even be beneficial.[38] Evidence for a beneficial effect was found in a randomised controlled trial reporting on the total incidence of cancer.[39]

Three randomised controlled trials have studied the effect of fat reduction using adenoma recurrence as an endpoint. The Toronto Polyp Study showed no benefit, although the results were not differentiated by adenoma size at outcome.[40] The Australian Polyp Prevention Project demonstrated a significant benefit ($p = 0.05$) with low-fat diets (<25% calories as fat) after two and four years of intervention on the occurrence of large (10 mm or more in diameter) adenomas.[41] The result became more significant ($p<0.03$) in the group randomised to low fat and added wheat bran (25 g wheat bran supplement). This effect was seen without any change in the weight of participants, suggesting an effect on carcinogenesis intrinsic to dietary fat intake. However, the National Cancer Institute's trial of a combined low fat (<20% of total calories), high fibre (18 gm per 1000 kcals) and high fruit and

vegetable (3.5 serves/1000 kcals) diet found no difference in the incidence of adenomas after four years of intervention.[42,43]

Omega-3 fatty acids may provide an important exception to the relationship between dietary fat and colorectal neoplasia. There is some evidence of an inverse correlation between intake of fish and fish oil and incidence of Colorectal Cancer, but the epidemiological evidence is inconsistent. The ratio of fish oil to animal fat intake may be important in determination of risk.[44] Fish oil also reduces the proliferation of rectal epithelial cells. [45]

Should dietary fat be restricted to reduce Colorectal Cancer risk?

Guideline — Dietary fat	Level of evidence		Practice recommendation		Refs
Reduce dietary fat to <25% of calories as fat.	Cancer	Adenoma	Cancer	Adenoma	29,30,36-38,40,42, 43
	III-2	II	Recommend		

2.7 Major food groups

2.7.1 Meat

A meta-analysis of studies on red meat and Colorectal Cancer risk showed a modest effect attributable to red meat: 12–17% increase per 100 gm per day of all meat or red meat consumed. Much of the risk was associated with processed meat.[46] In another meta-analysis, relative risk was 1.27 (CI 1.11–1.45) for red meat and 1.39 (CI 1.09–1.76) for processed meat.[47] A combined prospective study of vegetarians showed that the risk for Colorectal Cancer was no different from non-vegetarians, diminishing the likelihood of an association between the intake of red meat and the risk of Colorectal Cancer. [48] A recently published large cohort study bears mention[49]. In this study of 478,040 people across Europe, the adjusted (for many confounding variables) hazards ratio of highest (>160gm per day) vs lowest (<20gm per day) intake of red and processed meat was 1.35 (CI 0.96 to 1.88), with protection from high fish (80gm vs 20gm) intakes where the hazard ratio was 0.69 (CI 0.54 to 0.88), but not from poultry. However, for nearly all sub-analyses, the risk was higher for processed meat than red meat, and lean red meat was not differentiated from overall red meat intake.

Separating the effects of dietary fat intake from those of red meat is difficult in observational epidemiology. The first report of the American Institute for Cancer Research and World Cancer Research Fund[9] attributed observed increases in risk more to red meat than to fat. That report did not take into account the qualitative higher rating of evidence from randomised controlled trials. It has received criticism for the strength of its conclusions about a 'probable' association.[50] In the Australian Polyp Prevention Project,[41] fat reduction was achieved without reduction in red meat intake. The observed inhibition of adenoma growth in this study was therefore attributed to fat reduction rather than red meat reduction. The evidence relating lean red meat to Colorectal Cancer risk remains weak and insufficient to allow the disadvantages of avoiding lean red meat (e.g. decreased intake of iron, calcium, zinc, magnesium, vitamin B12 and other vitamins) to be ignored.

One effect of high-temperature cooking (such as barbecuing) of red meat is the production of heterocyclic amines.[51] 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 — otherwise known as CYP1A2 — catalysed step in the liver) and acetylation (NAT2) are genetically controlled and readily identified. Rapid CYP1A2 and rapid NAT2 phenotypes produce more DNA adducts. Indeed, acetylator status has been shown to positively correlate with Colorectal Cancer risk, particularly when taking red meat into account as a co-variable.[52] Some studies,[27,53-55] but not all,[56-58] 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.[56,59,60] It is less certain whether the increased risk associated with well-done red meat is linked to the presence of known mutagens such as heterocyclic amines. In some studies, the risk relationship survives in the genetically susceptible (rapid phenotype for both NAT and CYP1A2) regardless of measured heterocyclic amines in stool. [61,62]

Should red meat intake be altered to reduce colon cancer risk?

Guideline — Meat	Level of evidence		Practice recommendation		Refs
Moderate intakes of lean red meat can be eaten as part of a mixed diet including carbohydrates (breads and cereals), vegetables and fruit, and dairy products. Charring of red meat is best avoided. Consumption of processed meats should be limited.	Cancer	Adenoma	Cancer	Adenoma	9,29, 36, 41, 49, 50
	III-2	III-2	Equivocal	Equivocal	

2.7.2 Dietary fibre - general

Fibre is a heterogeneous group of plant non-starch polysaccharides and non-carbohydrates that resist digestion in the upper digestive tract. Epidemiological and animal studies have been complicated by the different types and mix of fibres investigated. In a systematic review, Potter found an inverse correlation between plant food intake and cancer risk in eight of ten case-control or cohort studies.[36]Similar findings were observed in a systematic review of case-control studies. Of these studies, 12 out of 13 showed a decreased risk of Colorectal Cancer with increased fibre intake.[63] A cohort study involving United States nurses showed no effect on Colorectal Cancer risk when fibre was analysed by solubility and source.[32] However, overall fibre intake was low and the range of intakes was narrow in that study.

Perhaps the most compelling evidence comes from the EPIC prospective cohort study. A total of 519,978 participants with a wide range of intakes were followed through 1,939,011 person-years; the adjusted relative risk for Colorectal Cancer was 0.58 (CI 0.41–0.85) for highest *versus* lowest quintiles of fibre intake.[64]

Fibre may act by increasing bulk (and decreasing carcinogen concentration), by reducing transit time (and thus carcinogen exposure time), or by acting through its bacterial fermentation products — short chain fatty acids. The production of short chain fatty acids decreases luminal pH, inhibits bacterial enzymes capable of producing carcinogens, and also acts as an important fuel for the colonocyte.[65] Butyrate can induce differentiation in malignant cell lines, slow proliferation and increase apoptosis, and is associated with inhibition of tumorigenesis *in vivo*.[66] Butyrate can also hypermethylate DNA, counterbalancing the loss of methyl groups, which is one of the early steps in the molecular progression to cancer.[67]

2.7.3 Vegetables and fruit

Case-control and cohort studies have shown more consistent protection against Colorectal Cancer from vegetables and fruit compared to cereals.[36] This may be due to non-fibre vegetable components such as phytonutrients. Vegetable intake, especially consumption of cruciferous vegetables (which include bok choy, broccoli, brussel sprouts, cabbage, cauliflower, Chinese cabbage, collards, kohlrabi,

mustard greens, swedes and turnips) appears to be important in conferring this protection.[68] However, the National Cancer Institute trial found that the incidence of adenomas was no lower in those randomised to high fibre/high fruit and vegetable diets when compared to controls.[42,43] Animal models of Colorectal Cancer provide evidence of protection for a range of vegetables[69], including cruciferous vegetables and also juice extracts and berries[70]. However, the evidence is not strong enough at this stage to conclude that preferentially eating cruciferous vegetables will reduce the risk of Colorectal Cancer.[70]

Characterising the active components of protective vegetables continues to be a promising scientific avenue of pursuit, given the strong epidemiological data on protection. The results of antioxidant trials using betacarotene indicate that, although it is the most prevalent carotenoid antioxidant in cruciferous vegetables, betacarotene does not appear to be responsible for tumour suppression.[36] Protection from cancer by fruit and vegetables may be associated with their low energy density, controlling weight gain. Despite the National Institutes of Health randomized controlled trial, the overall conclusion remains that a higher intake of vegetables probably lowers the risk of Colorectal Cancer.[69]

In contrast to the data for vegetables, evidence for a protective effect from fruits is more limited and has been inconsistent both for colon and rectal cancer and for adenomas. However, a recent study on a large cohort of United Kingdom vegetarians pointed more to fruit than to vegetables as being protective, despite finding no overall reduction in cancer in the vegetarians (RR 0.84, CI 0.55–1.32).[25] The protection may be more for MSI-H (high) cancers exhibiting methylated promoter silencing of MLH mismatch repair genes,[71] highlighting the need for more studies on genotypically-characterised cancers and adenomas.[72]

Should fresh fruit and vegetable intake be increased to reduce Colorectal Cancer risk?

Guideline — Fresh vegetables	Level of evidence		Practice recommendation		Refs
Eat five or more serves per day of a variety of vegetables. National nutrition guidelines also advise two serves of fruit daily ("Go for 2 and 5")	Cancer	Adenoma	Cancer	Adenoma	32, 36, 41, 43, 63, 64, 68
	III-2	-	Equivocal	-	

2.7.4 Cereals and bread

Recent animal studies on the relative solubility of different cereal fibres support the hypothesis that poorly soluble fibres, such as wheat bran, continue to be fermented throughout the colon.[73] As cereal fibres are digested, short chain fatty acids, including butyrate, are released along the length of the colon and rectum.[74]

Several human studies have investigated the role of specified fibre sources on the development of Colorectal Cancer. The study of rectal cancer by Freudenheim et al showed greater protection from insoluble than soluble cereal fibre. There was also protection afforded by vegetable fibre in this study.[75] A recent cohort study reported protection with fibre from vegetables, fruit and whole grains.[76] The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, involving 33,971 participants, found fewer adenomas at screening flexible sigmoidoscopy in those in the highest quintile of fibre intake compared to the lowest intake (RR 0.73, CI 0.62–0.86).[51] This association was strongest for grains and cereals and for fruit. As discussed above, the Australian Polyp Prevention

Project used poorly-soluble cereal fibre (25g/day of unprocessed wheat bran) as its fibre intervention.[41] De Cosse et al showed a protective effect of wheat bran (Kellogg's All Bran®) in patients with familial adenomatous polyposis (FAP) in a randomised control trial, but only on the basis of actual intake.[77]

While recognising a protective effect, the report from the World Cancer Research Fund placed less emphasis on the importance of cereal fibre than on other fibre sources.[9] The benefits of wheat bran were null in the Arizona intervention trial,[78] a larger study than the Australian study. This has substantially reduced the strength of evidence for wheat bran. However, all trials and observational studies are still consistent with a synergistic effect of unprocessed wheat bran and a low fat diet in reducing Colorectal Cancer risk.[79]

Should cereal fibre be selected to reduce Colorectal Cancer risk?

Guideline — Cereal fibre	Level of evidence		Practice recommendation		Refs
Select poorly soluble cereal fibres (e.g. wheat bran), especially if at increased risk of Colorectal Cancer.	Cancer	Adenoma	Cancer	Adenoma	9, 41, 51, 73-76
	III-2	II	Equivocal	Equivocal	

2.7.5 Resistant starch

Attention has focused on the possible benefits of those carbohydrates escaping digestion in the small intestine. Although animal data have not been supportive, ecological studies suggest otherwise.[80] The short chain fatty acid hypothesis should hold as well for resistant starch as for fibre. Indeed, resistant starch in the diet produces the highest level of faecal butyrate.[81] 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 selected or chemically modified to resist digestion and promise protective benefit. One such product is under investigation in a phase III clinical trial on FAP (the CAPP1 study)[82] and another on hereditary non-polyposis Colorectal Cancer (HNPCC) (the CAPP2 study).

2.7.6 Dairy foods

At present there is insufficient evidence to advise for or against dairy products with respect to Colorectal Cancer risk. NHMRC dietary guidelines recommend and the Australian Government's Australian Guide to Healthy Eating recommend including milk, yoghurt, cheese, and/or alternatives in a healthy diet.

2.8 Micronutrients

2.8.1 Calcium and vitamin D

Although early studies suggested that in the presence of a high-calcium diet there is a modest protective effect for the development of colorectal tumours, recent systematic reviews do not show a significant effect.[83,84] However, *post hoc* analysis showed that dietary calcium intakes above 1068 mg protected against adenoma recurrence in the Arizona interventional wheat bran trial (RR 0.56, CI 0.39–0.80).[85] In combination, dietary and *supplemental* calcium showed a modest reduction in cancer incidence in a cohort study involving over 125,000 persons (RR 0.87, CI 0.67–1.12, p = 0.02 for trend).[86] The effect was stronger for supplements alone. A threshold of 700 mg/day of dietary calcium

for protection against Colorectal Cancer was suggested in analyses of results of the prospective Nurses Health Study (on women) and the Health Professionals Follow-up Study (on men).[87]

Adults should be advised to bring their calcium intake to 1000–1200 mg per day, in keeping with general dietary guidelines.

Dietary vitamin D intake, as distinct from serum 25-(OH) vitamin D levels, appears to have no effect on the development of colorectal tumours.

Does calcium supplementation reduce Colorectal Cancer risk?

Guideline — Calcium	Level of evidence		Practice recommendation		Refs
Ensure a total calcium intake of 1000–1200 mg/day in keeping with general dietary guidelines.	Cancer	Adenoma	Cancer	Adenoma	83-87
	III-2	II	Equivocal	Equivocal	

2.8.2 Folate

Folate (folic acid, folacin) is abundant in wheat bran, baker's yeast, cruciferous vegetables, spinach, peanuts and liver of all types.[88] A review of prospective and retrospective studies indicated that high folate diets are associated with a decreased risk for colorectal adenomas (RR 0.27 to 0.84) and Colorectal Cancer (RR 0.31 to 1.03),[15] especially in male habitual alcohol consumers.[89-91] One study showed that dietary folate consumption was associated with a greater reduced risk of colon cancer in women having a first-degree relative with colon cancer (RR 0.48 CI 0.28–0.83), compared to those without a family history (RR 0.88 CI 0.62–1.07). Moderate to heavy alcohol consumption increased the familial risk.[92]

Low folate status is associated with increased risk for adenoma formation and cancer.[93] This is enhanced in individuals with the thymine-thymine (TT) genotype for methylenetetrahydrofolate reductase.[94] The effect may be especially relevant to microsatellite unstable Colorectal Cancers, which are characterised by perturbations in methylation.[95,96] Indeed, methyl-poor diets (low folate, low methionine and high alcohol) confer a greater risk compared with methyl-rich diets, the latter perhaps offering a 40% reduction in Colorectal Cancer incidence.[97,98]

At present, no recommendation on folate in terms of Colorectal Cancer risk can be provided.

2.8.3 Phytonutrients

It is known that there are several naturally occurring compounds in foods of plant origin (vegetables, fruits and cereals) that have strong protective effects against Colorectal Cancer over and above effects related to their fibre content.[83] The vegetables of particular importance include members of the cruciferous vegetable 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.[83] These phytonutrient compounds include, among others, carotenoids, vitamin C, vitamin E, folate, indoles, linolenic acid, allylic sulfides, and lycopene. Increasing evidence also points to tea (containing catechins) as being protective.[99,100]

The bulk of the evidence on phytonutrients is epidemiological and underlines the need for a high and varied vegetable, fruit and cereal diet as an important dietary protective factor for colorectal tumours.[83]

2.9 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 anti-cancer substances than those identified so far. For this reason, it is a good nutritional practice to promote eating whole foods rather than advocating nutritional supplements, except in certain well-defined situations.

2.9.1 Calcium

A recent large cohort study has demonstrated protection with supplemental calcium (RR 0.69, CI 0.49–0.96). In an interventional trial conducted by Baron et al, 1.2 g elemental calcium reduced the incidence of new adenomas in the Calcium Polyp Prevention randomised controlled trial.[101] More detailed analysis suggested that the benefit of calcium supplementation was largely in the sub-group with serum 25-(OH) vitamin D levels above the median for the group.[102] These findings are supported by a European trial that also tested the effect of soluble fibre.[103]

2.9.2 Folate

Human interventional studies of folate supplementation have commenced but only on a small scale to date.[104]

2.9.3 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 with foods derived from soils low in selenium. North American studies of populations deficient in selenium have suggested an increased incidence and mortality from Colorectal Cancer, but dietary selenium intakes and serum levels in Australia do not show good correlations, weakening a link Colorectal Cancer risk.[105]

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 whether selenium supplementation decreased the incidence of carcinoma of the skin.[106] Among the secondary endpoints of the study were total cancer incidence and incidence of Colorectal Cancer. The intervention agent was 200 mcg 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 (RR 0.42; CI 0.18–0.95; $p = 0.03$). The total number of carcinomas was 59 in the selenium-treated group and 104 in the placebo group (RR, 0.55; CI, 0.40–0.77; $p = 0.001$). The selenium dose of 200 mcg per day was estimated to be twice the typical dietary intake of these patients and three to four times the recommended daily allowance. 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.

Further support comes from geo-epidemiological observations. Serum selenium levels related inversely to large adenomas in a low soil selenium area in Spain.[107] However, other evidence is not so supportive. Prediagnostic serum selenium levels did not predict recurrent adenomas in a nested case-control study.[108]

Does selenium supplementation reduce Colorectal Cancer risk?

Guideline — Selenium	Level of evidence		Practice recommendation		Refs
Selenium supplementation for chemoprevention is promising but requires confirmation.	Cancer	Adenoma	Cancer	Adenoma	106-109
	II	-	Equivocal	Equivocal	

2.9.4 Antioxidants/carotenoids

One population-based case-control study of Colorectal Cancer found a statistically significant protective effect from the use of multivitamin and vitamin C-containing supplements, an effect independent of other dietary risks.[17] A prospective cohort study of 35,215 Iowa women did find a protective association for highest compared with lowest quartile of vitamin E intake (RR, 0.3; CI, 0.19–0.54).[110] In contrast, randomised controlled trials of the antioxidant vitamins A, C and E and betacarotene have been almost universally negative. The Dartmouth randomised intervention trial (betacarotene 25 mg/day; vitamin C 1 g/day and vitamin E 400 mg/day and placebo),[111] a Canadian trial of vitamin C and vitamin E (vitamin C 400 mg/day; vitamin E 400 mg/day),[112] the Australian Polyp Prevention Project[41] (betacarotene 25 mg/day) and the De Cosse et al interventional study in familial adenomatous polyposis (vitamin C 4 g/day and vitamin E 400 mg/day)[77] all showed no benefit.

Does antioxidant vitamin supplementation reduce Colorectal Cancer risk?

Guideline — Antioxidant vitamins	Level of evidence		Practice recommendation		Refs
Antioxidant vitamin supplementation is ***not*** advised at present to protect against Colorectal Cancer.	Cancer	Adenoma	Cancer	Adenoma	41,77,109, 111,112
	II	II	Recommend	Recommend	

2.9.5 Phytonutrients

Specific phytonutrients, including indoles (cruciferous vegetables), *S*-methyl methane thiosulfonate (cruciferous vegetables); garlic extract, green tea and black tea extracts, and curcuma B supplements (from tumeric) have been found to have anti-Colorectal Cancer properties in experimental models.[83] Some epidemiological studies support these experimental findings. However, at present, phytonutrient supplementation is on an experimental basis and controlled human studies are required.

2.9.6 Fibre supplements

Based on their ability to undergo fermentation, commercial fibre preparations could be predicted to provide protection against Colorectal Cancer. Limited information form human studies is available. The European Cancer Prevention trial showed that psyllium gave weak protection against adenomas.[103]

2.10 Other chemopreventive candidate agents

2.10.1 Aspirin and nonsteroidal anti-inflammatory drugs

The Melbourne Colorectal Cancer Study, which examined 715 patients and 727 controls, was the first to show that regular consumption of aspirin was statistically significantly protective (40% protection) against both colon and rectal cancer in men and in women.[113] Since that report, numerous case-control and cohort studies have supported this association. In addition, several studies have shown protective effects against colorectal adenoma.[114,115]

There have been four prospective randomised clinical trials of aspirin intervention. The first, the Physicians' Health Study, involved use of aspirin in a dose of 325 mg every second day.[116] Although this study showed that aspirin gave no protection against Colorectal Cancer, the findings are difficult to interpret because of the relatively brief duration of treatment and the failure to exclude polyps or cancer at the start of the study. The Dartmouth randomised controlled trial conducted in the USA of aspirin 80 mg/day versus placebo showed a 19% reduction in adenoma incidence. Curiously, aspirin 325 mg/day did not show benefit in the same study.[117] In a parallel study in patients after Colorectal Cancer resection, aspirin 325 mg/day was effective in reducing the incidence of metachronous adenomas during follow up.[118]

Using the less gastrotoxic lysine acetylsalicylate, Benamouzig et al also demonstrated a significantly lower incidence of small and large adenomas at one year in those randomised to aspirin compared with placebo.[119]

Non-aspirin, nonsteroidal anti-inflammatory agents (NSAIDs) have also been found to provide a degree of protection for Colorectal Cancer. With the exception of sulindac,[114] adverse side effects have been a deterrent to large-scale controlled human studies.

Cyclo-oxygenase-2 specific inhibitors have recently been developed to minimise the gastrointestinal side effects of aspirin and of NSAIDs. They have been shown to decrease the number of rectal and duodenal polyps in FAP.[120,121] The rofecoxib "APPROVe" trial was successful in meeting its primary endpoint of reducing the proportion of "higher risk" adenoma patients (mostly those with advanced adenoma features at entry - 78% of the total group) with adenomas over 3 years of treatment (RR 0.75, CI 0.67-0.83). Secondary endpoints evaluating the total group, and cumulative reduction in adenoma number and size were also highly significant. [122] However, both of the two large international trials of COXII inhibitors in sporadic adenoma patients have recently been aborted because of an increased risk of myocardial infarction and stroke emerging after 18 months of treatment, especially in the higher dosage.[122,123] In the rofecoxib trial comparing 25mg vs placebo, there was a relative risk of 1.92 (CI 1.19 3.11; p=0.008)[122] whereas in the celecoxib trial the hazard ratio at 2.8 to 3.1 years was 3.4 (CI 1.4 -7.8) comparing 800mg with placebo, with a non-significant trend apparent with the 400mg arm.[123] Deaths from cardiovascular disease were not significantly different. These have dampened the enthusiasm for chemoprevention with these drugs. Both of these trials recruited in Australia.

Several mechanisms of the action of aspirin and non-aspirin NSAIDs as colorectal tumour chemopreventive agents have been elucidated. These include an anti-proliferative effect, an enhanced apoptotic effect, an anti-angiogenic effect and possibly also, immune modulation.[114,115] This anti-tumour action appears to be related in part to the ability of aspirin and other NSAIDs to inhibit the enzyme COX-2, and in part to mechanisms that appear to be independent of COX-2 inhibition.

Collective evidence of epidemiological studies strongly suggests that a reduction of about 40% in Colorectal Cancer risk can be associated with regular aspirin intake[124] and possibly also with regular NSAID use. Up to now, aspirin has not had broad scientific approval for use as a colorectal tumour chemopreventive in individuals at average risk of because of uncertainties about the optimal dosage,

the optimal duration of use, and adverse side effects. Furthermore, there has not been an assessment of the balance between benefit and risk involved in prolonged aspirin use. This assessment is crucial, as the use of aspirin or NSAID chemoprevention will depend largely on this balance. The lessons apparent from the COXII trials make this especially cogent.

Dosage of aspirin has been informative in two recent studies. In an analysis of the Nurses Health Study, the protective advantage of aspirin was shown to be dose dependent. The analysis showed that 0.5–1.5 standard tablets per week have a RR of 0.80 (CI 0.70–0.93), 2–5 tablets/week have a RR of 0.74 (CI 0.62–0.88), 6–14 tablets per week have a RR of 0.72 (CI 0.61–0.0.85), and more than 14 tablets per week have a RR of 0.49 (CI 0.36–0.65, $p<0.001$ for trend). Increasing duration did not increase the benefit.[125] However, a European cohort study of low-dose use (maximum 150 mg per day) did not show an effect in 29,470 people.[126]

The risk–benefit ratio for aspirin or NSAID prophylaxis is likely to be more favourable for individuals at high risk for Colorectal Cancer, but this risk–benefit ratio is still difficult to quantify. FAP and HNPCC gene carriers are currently participating in randomised controlled trials on the basis of improved risk–benefit ratio,[82] but results are so far unavailable. Several controlled trials are currently in progress, using aspirin alone, aspirin and folate, aspirin and resistant starch, sulindac alone, sulindac and curcumin, and sulindac with difluoromethylornithine (DFMO), as well as COX-2 specific inhibitors alone or in combination with selenium.[106] The results of these studies, to be published over the next few years, should answer some of the unresolved questions. Early indications from a nested case-control study suggest that the benefits may be less, although still significant, when COX-2 inhibitors are compared with non-selective NSAIDs.[127]

For the present, it is reasonable to consider aspirin as prophylaxis in adenoma bearers. The trial by Baron et al showed that a low dose of aspirin may be sufficient.[117]

Do anti-inflammatory drugs reduce Colorectal Cancer risk?

Guideline — Anti-inflammatory drugs	Level of evidence		Practice recommendation		Refs
Aspirin should be considered as prophylaxis against further adenoma development in those with a previous removal of an adenoma.	Cancer	Adenoma	Cancer	Adenoma	113-119,124-126
	II	II	Recommend	Recommend	

2.10.2 Hormone replacement therapy

A meta-analysis of 18 observational studies showed a 20% reduction in colon cancer incidence among women who had ever used hormone replacement therapy (HRT) (RR 0.80, CI 0.74–0.86),[128] a finding supported by the randomised controlled Women's Health Initiative (RR 0.63 CI 0.43–0.92).[129] However, those cancers detected were at a more advanced pathologic stage in the HRT group versus the control group, tempering the observation of reduced incidence in that study.[130] A reduction in incidence may be particularly true for MSI tumours (RR 0.67, CI 0.59–0.77).[131] These results are mirrored by improvements in survival.[97] Risk is also reduced in rectal cancer (RR 0.81, CI 0.72–0.92). HRT protects against colorectal adenomas.[132]

Any benefits must be balanced against the possibly increased risks for breast cancer, stroke, pulmonary embolism and other adverse outcomes.[129]

Should hormone replacement therapy be recommended to reduce risk of Colorectal Cancer?

Guideline — Hormone replacement therapy	Level of evidence		Practice recommendation		Refs
HRT ***cannot be recommended*** as prophylaxis against Colorectal Cancer because of its possible collateral risks, including breast cancer.	Cancer	Adenoma	Cancer	Adenoma	128-132
	III-2	III-2	Equivocal	Equivocal	

2.10.3 Other agents

Difluoromethylornithine inhibits ornithine decarboxylase, an essential enzyme in the process of cell proliferation. Loss of hearing acuity has emerged as a drawback to its use in human trials.[133] Oltipraz is a compound related to dethiolthionines, which are found in cruciferous vegetables. It is already in use as an anti-schistosomiasic agent. Oltipraz has reached the stage of human clinical trials as a chemopreventive agent. Ursodeoxycholic acid is a 'trace' bile acid in humans. It can neutralise some toxic effects of bile and it is under clinical trial for adenoma prevention. There is evidence that it decreases incidence of colorectal neoplasia in ulcerative colitis, and reduces development of adenomas with high grade dysplasia in patients with previous adenomas.[134, 135]

Other agents under investigation as specific extracts rather than foods include green tea extracts, magnesium hydroxide, curcumin, tumeric, genistein (a soy extract), and vitamin D, some of which are being studied in clinical trials.

2.11 Conclusions

Modifiable dietary and life-style factors have been estimated to account for 70% of the attributable risk for Colorectal Cancer in Western populations.[136]

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 that may be relevant to some high-risk groups. It is worth repeating 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 approaches to primary prevention and early detection. Progression from the precancerous phase through the various stages of cancer is normally spread over a number of years.[1] Certainly, Colorectal Cancer has a high cure rate in its early stages.[1] Effective targets for screening are curable cancer (to reduce mortality) and removable adenomas (to reduce incidence) through early detection.

3.1 Concept of screening for Colorectal Cancer

Population screening is the systematic application of a suitable screening test, to identify individuals at risk of a specific condition/disorder to warrant intervention. It is undertaken among asymptomatic individuals. Importantly, population screening is an organised process that involves call and recall of the population to regular screening, as an aid to early detection and appropriate follow up of people requiring further treatment. As such, population screening differs significantly from dealing with symptomatic patients, or even 'individual case finding' in asymptomatic patients with certain risk factors.

The World Health Organization (WHO) has endorsed nine principles of screening[2,3] to assist in determining whether there is sufficient evidence to warrant the consideration of an organised, population-based screening program. In summary, the WHO principles specify that population screening should only be considered where:

- the condition is an important health problem
- there is a recognisable latent or early symptomatic stage
- the natural history of the condition, including the development from latent to declared disease, is adequately understood
- there is an accepted treatment for patients with recognised disease
- there is a suitable test or examination (i.e. for screening purposes)
- the test is acceptable to the population
- there is an agreed policy on who to treat as patients
- the cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole, and
- case finding is a continuing, and not a 'once and for all' project.

As specified by WHO,[3] the process involves offering a simple, affordable and acceptable screening tool or test to identify whether a particular healthy individual is more likely to have a significant lesion such as an advanced adenoma or cancer (preferably early stage and curable) and in whom it is justifiable to go ahead and perform an invasive, perhaps slightly risky, diagnostic test such as colonoscopy.[3] Adequate therapy must be available. The process should be acceptable to a large segment of the at-risk population and high-quality investigation and treatment should be available for those with positive findings. As screening is directed at apparently healthy people and uses expensive and sometimes scarce resources, harm must be minimised and the screening method must have been shown to offer benefit at a population level.

With Colorectal Cancer, screening applies to individuals living in a high-risk country (e.g. Australia) who have reached an age where the chance of neoplasia being present justifies engagement in screening. Any screening program should identify and redirect those with significant symptoms or those with increased risk factors towards more appropriate interventions (see subsequent chapters). It should also advise those with co-morbid conditions or other concerns to seek further medical advice before participating.

3.2 Age as a risk factor

The risk of Colorectal Cancer increases with age, as shown in Table 3.1.

Table 3.1 Absolute risk of Colorectal Cancer

If a person is	Risk over the next …			
aged	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 (*cf* relative risk, which is the ratio of the risk in a particular exposed group to the average risk in the population; see Table 6.1).

Source: AIHW 1996[4]

Table 3.1 gives the absolute risk for an average member of the population. If risk factors apply, then these multiply the chance. Symptoms are a risk factor and, obviously, a person's risk will be increased pending clarification of the cause.

Similarly, if a person has a relative with 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 bowel cancer is at about *average risk* for her age. As shown on the table, her chance of developing bowel 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 bowel 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*[5] to 1 in 150 over the next five years and 1 in 15 over the next 20 years.

If her paternal grandmother as well as her father had bowel cancer, or if her father was diagnosed at age 48 rather than 68, that would place her in category 2. Her risk would be *three to six times average.*[5] 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.

Personal history of advanced adenoma or cancer also increases risk by the relevant multiplier (see Chapter 9).

3.2.1 Age to commence screening

Randomised controlled trials at the population level indicate that screening tests for faecal occult blood (performed once every 12 months, as shown in one trial,[6-8] or once every 24 months, as shown in three trials,[6-12] reduce overall mortality from Colorectal Cancer in populations selected on the basis of age.[6-13] These have shown benefit for people aged 45–50 years and upward. Cost-effectiveness

studies also demonstrate that age influences cost-effectiveness.[14] Together with the observation that risk increases 4-fold between ages of 40 and 50 years (Table 3.1), these lead to the recommendation that screening of average risk people should commence at age 50 years. This is consistent with the deliberations of several major international bodies.[15-20]

3.3 Evidence for benefit from population screening

Randomised controlled trials at the population level show that screening for faecal occult blood reduces overall mortality from Colorectal Cancer on the basis of intention-to-screen by 15–33%[6,7,9-12] and reduces incidence by 20%.[8] Case-control studies (see below) suggest an impact of screening based on sigmoidoscopy and colonoscopy as well. However, these are not population-based studies and, especially in the case of colonoscopy, suffer from several biases that make it impossible to determine the added benefit and cost derived from use of these modalities.

3.3.1 Implementation of population screening for Colorectal Cancer in Australia

The question of screening for Colorectal Cancer in Australia has been systematically reviewed in a report from the Australian Health Technology Advisory Committee (AHTAC).[15] The committee's key recommendations related to population screening are listed in Box 3.1.

The pilot studies recommended in the AHTAC report commenced in November 2002 through the Bowel Cancer Screening Pilot Program (the Pilot) (in Mackay, Melbourne and Adelaide) to address issues such as recruitment, participation and compliance, assessment, choice of faecal occult blood test (FOBT), access to services, quality assurance and potential adverse effects. These are being implemented in the context of the existing health care system and should demonstrate whether such screening is feasible, what barriers exist and whether the program can be rolled out to the Australian population. The Pilot will assess the feasibility, acceptability and cost-effectiveness of faecal occult blood-based screening in the Australian population in both rural and urban areas.

Box 3.1

The first two recommendations of the Australian Health Technology Advisory Committee on Colorectal Cancer Screening,[15] are

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 by faecal occult blood testing 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.

3.3.2 Barriers to population screening with FOBTs

Barriers to participation in FOBT screening fall into several categories, including: inconvenience of the testing process, aversion to manipulating faeces, lack of perceived benefit of screening, fear of a diagnosis of cancer, cost, views about personal invulnerability, and cultural beliefs and attitudes.[21,22] Recent studies have demonstrated that several of these barriers can be at least partially overcome so as to improve participation. Removal of dietary restrictions needed for certain FOBTs, simplifying the method of stool sampling and endorsement of screening by a person's own general practitioner all lead to a significant improvement in participation.[23-25]

3.3.3 Potential psychological consequences of screening

A further important consideration is the role of adverse psychological effects on individuals. These can range from the trauma of identification of disease in symptom-free, healthy individuals, to stress among people in whom cancer is suspected although later discounted, to more subtle concerns of participants during the screening process.[26] Health care professionals must recognise the potential adverse psychological effects of screening, although several studies have shown no evidence of long-term harm after screening.[27-29]

Despite the possibility of adverse psychological consequences of screening, the stress generated by diagnosis of an advanced cancer when there has been no opportunity for early detection by screening also needs to be taken into consideration.

3.4 Screening and case-finding scenarios

Two main scenarios need to be considered:

- an unsolicited offer of screening to individuals in the general population that does not involve any personalised approach (population screening)
- the individual asymptomatic person aged 50 years or over who is concerned about the possible presence of Colorectal Cancer (sometimes referred to as case-finding) due to their age, family medical history, personal medical history or symptoms.

3.4.1 Population screening for Colorectal Cancer

In this scenario the focus is on the general population and WHO criteria should be met. Feasibility, acceptability and cost-effectiveness are vital considerations as pointed out in the AHTAC report. The more people undertaking even the simplest preventive measures, the greater will be the impact at the population level.

Screening tool options could be: FOBT, sigmoidoscopy, FOBT combined with sigmoidoscopy, colonoscopy, and CT colonography. Taking into account WHO criteria, the need for high-level evidence at the population level, and the feasibility of engaging a majority of the population, a simple, affordable and acceptable screening tool could be FOBT (alone) or perhaps sigmoidoscopic examination either alone or combined with FOBT.

FOBT appears likely to be acceptable in Australian populations and the outcomes of the Pilot will establish whether this is the case. Cost-effectiveness calculations based on Australian costs demonstrate that FOBT screening is cost-effective.[30]

It is important to advise people entering a screening program that if they develop symptoms or have a significant family history, they should seek medical advice. Also, if any new risk factors become apparent, then they should return for re-evaluation of their screening protocol. Ideally, screening is not a once-only event and continuing participation increases the likelihood of success.

3.4.2 The asymptomatic individual aged 50 or over

The individual asymptomatic person 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 years, the following procedure is recommended:

1. Take a thorough history focusing on risk factors, namely:
    - present age

- symptoms
- family medical 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
- individual history of extensive inflammatory bowel disease (eight or more years)
- cigarette smoking
- unfavourable diet and/or lifestyle.

Although it is difficult to make a simple assessment of unfavourable diet and lifestyle, body mass index (BMI) could be used as an indicator because of the greater risk for Colorectal Cancer associated with obesity.[31]

2. Perform a physical examination (including abdominal and digital rectal examination), looking for:
   - palpable abdominal masses or enlarged liver
   - low rectal cancer — 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 that 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 dietary lifestyle
   - explain the nature, value, risks, and cost of all screening tools available, and indicate that it is reasonable to choose FOBT-based screening (providing testing is of high quality) as it has been shown to reduce Colorectal Cancer mortality and incidence.

3.5 Screening tests for average risk subjects or general populations

3.5.1 Faecal occult blood testing

Two main types of FOBT are available[32] — guaiac tests and immunochemical tests. Guaiac tests are based on the pseudoperoxidase activity of haem. Immunochemical tests utilise antibodies against human haemoglobin.

In population screening programs, a person with a positive FOBT has a 30–45% chance of having an adenoma and a 3–10% chance of Colorectal Cancer.[15]

Traditional guaiac tests (e.g. Hemoccult®) will detect 40–60% of asymptomatic Colorectal Cancer.[9,11] In other words, a Hemoccult II test will miss at least 40% of Colorectal Cancer under ideal testing conditions. However, when dietary restrictions are followed, a test such as Hemoccult II is highly specific — 97–99% of healthy subjects will have a negative FOBT.[9,11]

The newer guaiac tests (e.g. Hemoccult SENSA®) and immunochemical tests (e.g. HemSp (also known as Bayer detect), OC Hemodia, Hemolex® and InSure (previously known as Inform)) are generally more sensitive than the earlier guaiac tests such as Hemoccult II.[32] Under ideal circumstances, they may detect 60–90% of cancers and many advanced adenomas. Specificity of the more sensitive guaiac tests and the immunochemical tests tends to be lower than that of the earlier guaiac tests. The immunochemical tests are not affected by diet or medications, making dietary and drug restriction unnecessary. Immunochemical tests have now been shown to demonstrate clear population advantages in terms of participation[23] and are being evaluated in the Australian Pilot program. They are also highly selective for colonic bleeding.

FOBTs serve to refine the likelihood of cancer being present. A person with a positive FOBT is 12–40 times more likely to have a Colorectal Cancer than somebody with a negative test.[9,11,33]

It is mandatory that any positive FOBT (even if just one of the samples is positive) be appropriately investigated by diagnostic evaluation of the colon. Colonoscopy is preferred as it allows for biopsy of lesions and therapeutic removal of adenomas. In those who have a positive FOBT, the probability that some type of neoplastic lesion will be present is 35–50%.[9,11,33]

In the absence of iron deficiency or relevant symptoms, positive test results do not warrant follow up by upper GI endoscopy.

3.5.2 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 50–60% of Colorectal Cancers and a similar proportion of larger adenomas (those of 6 mm or more).[34] Although controlled population studies of screening flexible sigmoidoscopy are in progress, final results, with mortality as the endpoint, will not be available for several years.[35-37]

Nonetheless, a number of case-control studies (not population-based) have demonstrated that subjects who undergo screening with flexible sigmoidoscopy do show a reduction in mortality.[38-40] Depending on the study and the interval involved, the reduction in mortality for participants appears to be between 50% and 80% for lesions within reach of the instrument. A five-year interval between examinations should be sufficient, and even longer intervals might be satisfactory.[38]

3.5.3 Colonoscopy and CT colonography

The place of once-only or periodic colonoscopy for population screening remains unproved as there is insufficient high-level, direct evidence to include or exclude this as the primary screening method.[17,18] Colonoscopic resources are limited and the efficacy of colonoscopy is supported by its integral role in FOBT screening. A way of directing limited endoscopic resources to those more likely to benefit is through FOBT screening, a positive test increasing the likelihood of neoplasia being present. At an international level, many recommendations are guarded. They support individual choice of method in the context of case-finding and based on consensus rather than population evidence.[19,20,41] It is unclear whether the increased accuracy of colonoscopy compared to alternative, less invasive screening methods offsets its cost and additional complications, especially when its acceptability to the general population is uncertain.

CT colonography is being evaluated as a diagnostic test compared to colonoscopy (see Section 8.1.5). Encouraging results are being obtained but the data are not yet conclusive. Equipment varies greatly in its usefulness and experience is highly variable. Population-based evaluation for CT colonographic screening is only just beginning[42,43] and the approach must be considered experimental at this time. Colonoscopy will still be necessary for polypectomy and biopsy.

Should screening be recommended?

Guidelines — Screening asymptomatic individuals over 50	Level of evidence	Practice Recommendation	Refs
Organised screening with FOBT, performed at least once every two years, is recommended for the Australian population over 50 years of age.	I	Strongly recommend	6-9, 11, 13, 15
Screening with flexible sigmoidoscopy on a five-yearly basis from the age of 50 years.	III-2	Equivocal	38,39

3.6 Correct usage of screening tools

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

3.6.1 FOBT — guaiac and immunochemical

At present, considerable research is being undertaken to determine the most appropriate FOBT to use. As indicated above, evidence now indicates that some immunochemical tests are easier for the subject to use than guaiac tests.[23] The manufacturer's instructions on how to use these tests should be followed, and it is recommended that the specified number of stools be tested, no matter what type of test is being used.

If a subject fails to follow dietary restrictions for guaiac tests, it is risky to assume that a positive result is due to non-compliance with diet. Dietary restrictions are not needed for immunochemical tests.

Sampling stools

Participants should be given stool 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. Follow the test instructions carefully to have the greatest likelihood of detecting occult bleeding from the large bowel.

2. Sample the number of stools recommended, as bleeding may be intermittent.

3. Collect samples from normally passed bowel actions, carefully following the manufacturer's instructions. For example, with guaiac tests, prepare a thin smear (which will dry quickly) on the specimen card.

4. Sample from the stool surface or where it is thought that blood might be present, or where the test manufacturer recommends.

Reading of results

The guaiac FOBTs are generally thought to be simple, but inexperienced readers may miss faintly positive results.[44] It is important to read guaiac tests with adequate illumination. Any blueness, no matter how transient, signifies a positive test. Automated development of some immunochemical tests avoids subjective aspects of interpretation of test results, thus improving quality assurance.[45,46]

3.6.2 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 very acceptable to participants.[36,47]

3.7 Current status of Bowel Cancer Screening in Australia

In view of the evidence and the AHTAC recommendations (Box 3.1), a pilot feasibility program for population screening, the Bowel Cancer Screening Pilot, ran from November 2002 to June 2004. The key features of the Pilot are described in Box 3.2 and the screening pathway used is shown in Box 3.3.

Box 3.2

Features of the Australian Bowel Cancer Screening Pilot Program*

1 The Central Bowel Cancer Screening Pilot Register (the Register) was located within the Health Insurance Commission in Canberra. It utilised Medicare data to identify those eligible for inclusion in the Pilot.

2 There were three sites — Mackay in Queensland (November 2002 start date); nine postcodes in the western and southern suburbs of Adelaide (February 2003 start date); and ten postcodes in the north-east part of Melbourne (March 2003 start date). Invitations to participate were sent to nearly 57,000 eligible members of the target population.

3 Two immunochemical FOBTs were used at all three sites, with tests randomised by household.

4 The age range for Pilot participants was 55–74 years, as of 1 January 2003.

5 FOBTs were distributed by the Register, by mail, over 12–15 months, up to June 2004.

6 Test results were sent to the Pilot participants and, with their consent, to their general practitioners and to the Register.

7 The relevant state health departments, divisions of general practice, general practitioners, and cancer council education units were closely involved in the conduct of the Pilot and in providing professional and community education about the Pilot.

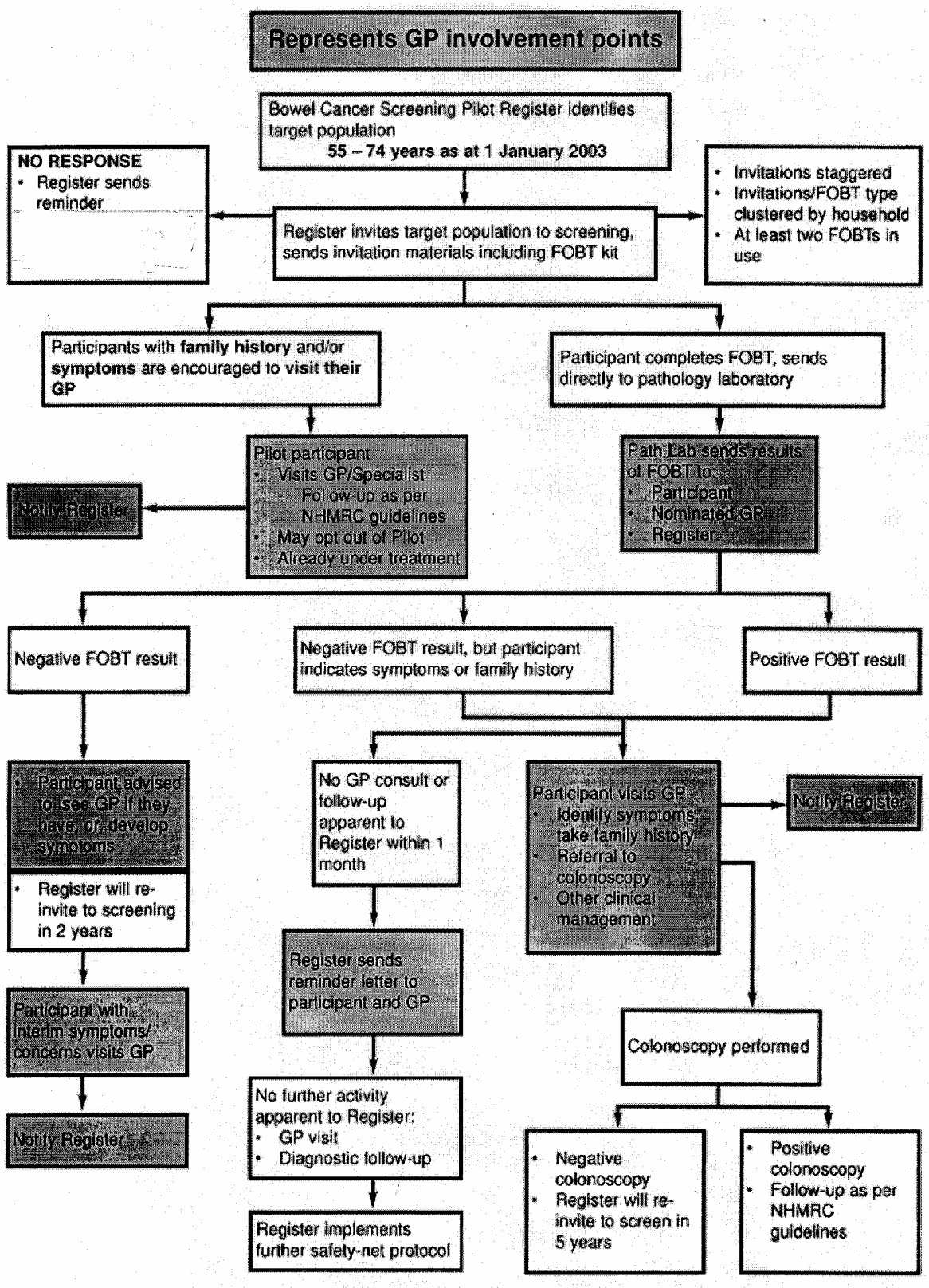
8 Specialists were involved in follow-up of positive tests.

9 Safety net procedures were provided by the Register to fulfil duty-of-care requirements for participants with positive FOBT results who failed to see their general practitioner about follow up, and for participants failing to have appropriate follow up investigation.

* The Pilot evaluation report is available at <www.cancerscreening.gov.au>.

Box 3.3

Screening Pathway used in the Australian Bowel Cancer Screening Pilot Program.



Following the success of the Bowel Cancer Screening Pilot Program, in the 2005-06 Federal Budget the Australian Government allocated $43.4 million over three years to phase in a nationally coordinated, population based, bowel cancer screening program. Initially screening will be offered to people turning 55 and 65 years of age and those who participated in the Pilot program. The results will be fully evaluated in 2007-08 with the aim of extending screening, if successful on clinical grounds, to all Australians over the age of fifty five.

The National Bowel Cancer Screening Program will be run along similar lines to the Pilot Program, with an immunochemical faecal occult blood test being mailed directly to eligible participants by a National Register, to be established and maintained by Medicare Australia (formerly the Health Insurance Commission). Almost one million Australians will be offered bowel cancer screening under this initial phase of the Program, which will commence in May 2006.

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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 a proportion 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 treatment decisions at the initial consultation. Interpreter services should be provided for non-English-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 essential if the patient does not understand English.

The NHMRC recommends the following approach, adapted from the New South Wales Cancer Council:[2]

- give bad news in a quiet, private place
- allow enough uninterrupted time in 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
- Provision of patient-held records are beneficial for patients.[3]

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.[4] They report that the subsequent discussions about actions to be taken, and what the diagnosis means, are at least as, if not more important, than the disclosure of the initial diagnosis.[5] Cancer patients appreciate and use communication aids such as audiotapes or personalised letters from the consultation when these are available.[6] 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.[7]

Most patients want to be given prognostic information because it helps in their decision making. This is regardless of stage of illness. When patients desire information, they want it presented honestly and clearly. They want specialists to explore and negotiate the amount, type and format of prognostic

information to be discussed. It is good practice to present prognostic information in a variety of ways to suit each individual. [8-12]

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 that 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 do so.[13]

Information for patients with Colorectal Cancer should include:

- causes of Colorectal Cancer, 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
- entitlements to benefits and devices, such as subsidies for travel or prostheses
- access to cancer information services (also see Chapter 18).

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.[14]

4.5 Second opinion

Patients have the right to obtain a second opinion at any time. A second opinion may help patients to clarify questions and to decide which doctor they prefer to manage their condition, and which course of treatment to follow. It can also reinforce the accuracy of advice already given, and enhance their confidence. Doctors should cooperate fully in providing both a referral and all relevant information.[15]

4.6 Coordination of care

Treatment of Colorectal Cancer requires the contributions of multiple disciplines, including clinicians with specialist knowledge in 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 where available an experienced oncology nurse can provide support for both patient and family.[16,17]

It may be helpful to both patient and coordinators if the patient is introduced to a prompt list of structural questions to help facilitate acquisition of information during consultation. Such a template is described as having assisted patients in meeting their participation preferences and information needs.[18]

4.7 Clinical trials

Clinical trials are an essential component 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. The benefits of clinical trials are that trial patients with cancer have been observed to have a better outcome.[19-21]

Practice Recommendation

Should clinical trial participation be encouraged?

Clinical trial participation is recommended

- Patients who have cancer and who participated in clinical trials may have a better outcome than patients not included in such trials.
- Doctors should encourage patients with 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.[22] The prevalence of psychological dysfunction is greater for those with stomas compared to patients with intact sphincters. Anxiety and depression levels tend to decline, and overall quality of life improves in the months following treatment.[23] 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 non-stoma patients.[24,25] In general, the psychological functioning of younger, female patients is more impaired than that of older male patients.[24] Patients reporting psychological distress function less well in their usual roles and activities than patients without distress.[23]

Colorectal Cancer and its treatment can have adverse effects on social functioning, including work and productive life; relationships with friends, relatives and partners; and other social activities and interests.[26] Although both stoma patients and non-stoma 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.[27] Both stoma and non-stoma patients report frequent bowel movements.[25,28] 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).[28,29] 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.[28,30] It is estimated that one fifth of women who have stomas suffer from dyspareunia. Body image problems appear to be greater in women.

4.9 Counselling and support

The *Clinical practice guidelines for the psychosocial care of adults with cancer*[17] provide a valuable resource for facilitating the practical psychosocial care of people with cancer.

There is accumulating evidence that psychological therapies improve emotional adjustment and social functioning, and reduce both treatment and disease-related distress in patients with cancer [17].

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. They may be specific, for example, an ostomy support group, or general, and are usually coordinated by volunteers.

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

Stomal therapy nurses are usually hospital-based and are an important resource for patients who require a stoma. The services they provide 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. In studies of patients with other cancers discussions with a specialist nurse has been shown to reduce psychological morbidity, and increase understanding, recall of information and perceptions of support.[17, 31]

Sexual counselling may be appropriate for patients, and can be provided by stomal therapy nurses and/or referral to sexual and relationship counsellors. There is the potential for loss of fertility in both men and women. This may result from surgery or adjuvant therapies such as radiation and chemotherapy. Sperm storage should be considered for men undergoing rectal surgery or chemotherapy and for whom fertility is an important consideration. Referral for specialist advice with regard to ovarian and fertility preservation is recommended if loss of fertility is a possibility and women wish to retain the option of further childbearing.[17] Referral for specialist advice in the setting of premature menopause caused by adjuvant therapies such as pelvic irradiation is also recommended.

Support needs for individuals with Colorectal Cancer and their families may include:

- counselling, including sexuality and fertility
- access to a cancer support service and/or stomal support group
- education and assistance with stomal therapy

- assistance with and 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:

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

This chapter provides guidance on how these signs and symptoms might be approached, with the goal of reducing morbidity and mortality from Colorectal Cancer.

5.1 The patient with rectal bleeding bowel, or abdominal symptoms

The principal relevant symptoms include:

- bleeding from the rectum, with or separate from the faeces, which should be appropriately investigated regardless of age,
- symptoms of anaemia, (haemoglobin less than 10g/100ml in postmenopausal women)
- a change in bowel habit, especially a recent one and towards loose stools,
- 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 (see Chapter 13 for urgent Colorectal Cancer presentation). 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] Age over 40 years, and recent onset of symptoms (say within the past 6–12 months) should raise concern 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.

Risk factors for Colorectal Cancer

The principal risk factors for Colorectal Cancer are:

- age >40 years
- a personal history of Colorectal Cancer or adenoma
- a family history of Colorectal Cancer, adenoma or gynaecological cancer
- a personal history of inflammatory bowel disease.[2]

See Table 3.1 for a summary of the absolute risk of colorectal cancer by age and time interval.

Rectal bleeding is the most important symptom. It is not always 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, haemorrhoids may coexist with colorectal neoplasia.

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 blood is present.[3] Prompt medical attention for rectal bleeding facilitates diagnosis of Colorectal Cancer.[3]

Rectal bleeding requires investigation, especially when it is of recent onset (within the previous 6–12 months).

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

5.1.1 Investigation

Investigation must be tailored to the circumstances. 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.

In all patients, a thorough examination of the anus, rectum and colon should be performed including digital rectal examination. Proctosigmoidoscopy is recommended, as this enables haemorrhoids to be more easily identified. However, failure of symptoms to settle should lead to full colonoscopic examination[4-9] barium enema or CT Colonography, which is becoming preferred to barium enema (see Sections 8.1.3, 8.1.4 and 8.1.5). This in spite of evidence that the prevalence of Colorectal Cancer in patients with colonic symptoms who have no evidence of bleeding 'is low and is comparative with the prevalence in an asymptomatic population'.[10]

Complete colonoscopy has been shown in a two-cohort study to exhibit a high level of accuracy. A cohort of 8 486 patients had a clear colonoscopy. Of these, 496 had repeat studies with an average of 3.1 years follow up. Subsequent malignancy was observed in 0.6%.[4] This degree of accuracy can be achieved very safely in diagnostic colonoscopy.[5]

It should also be recognised that with flexible sigmoidoscopy, colonoscopy and double contrast barium enema it is possible to miss a cancer during the examination. Should there be a deficiency of 'correlation between clinical and investigational findings', the matter should be carefully reviewed.[11]

What investigations need to be included?

Guidelines — Investigation	Level of evidence	Practice recommendation	Refs
In symptomatic patients aged over 40 years, referral to a specialist should be considered and consideration of full examination of the colon with colonoscopy is recommended.	III-3	Equivocal	4-8

5.2 The patient with iron deficiency anaemia

There is always a cause for iron deficiency and, in non-menstruating patients, gastrointestinal bleeding is the most common cause.[7] It is usually occult. In non-menstruating patients over 40, Colorectal Cancer is a common pathology.[8]

It is important to confirm iron deficiency before embarking on gastrointestinal investigation. An isolated low serum ferritin is not adequate evidence,[7] 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, a double contrast barium enema is required[8], or CT Colonography

considered (see 8.1.5). Double contrast barium enema has a known false-negative perception error which has been shown to be effectively reduced if the images are submitted to multiple radiologists for reading[11] (see Section 8.1.4).

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CHAPTER 6 SCREENING BASED ON FAMILY HISTORY OF COLORECTAL CANCER

Interest in hereditary predisposition to Colorectal Cancer has increased greatly over the past 15 years, largely because of identification of the genes associated with familial adenomatous polyposis (FAP) and hereditary non-polyposis Colorectal Cancer (HNPCC). Both disorders have an autosomal-dominant mode of transmission within families and carry a very high risk for cancer. In untreated FAP, mutation carriers have a lifetime risk for Colorectal Cancer close to 100%. In HNPCC, their risk for colorectal or other syndrome cancers is 70–90%. (See Chapter 7 for further information.)

This chapter discusses cancer risk and recommendations for screening for the large number of people in the community who have a family history of Colorectal Cancer, but whose family history does not have the clinical features suggestive of either FAP or HNPCC.

6.1 Cancer risk in relatives of patients with common Colorectal Cancer or adenoma

Early cancer mortality studies indicated that first-degree relatives of patients with common Colorectal Cancer (i.e. Colorectal Cancer that is not associated with FAP, HNPCC, chronic ulcerative colitis, or other recognised causes) themselves have a three- to four-fold increase in lifetime risk for Colorectal Cancer.[1,2] However, studies of cancer incidence, in which there were appropriately matched control groups and stringent methods for collection of family cancer data in relatives, reported only a doubling of this lifetime risk.[3–6] Relative risk was increased 1.6-fold for women and 1.9-fold for men in the Danish study, 1.8-fold for those with just one affected relative in the Australian study, and 1.7-fold and 2.2-fold in the United States studies.

In contrast to those modest levels of increased risk, Colorectal Cancer risk was shown to be substantially (three- to six-fold) greater for those who have a first-degree relative with Colorectal Cancer diagnosed at an early age (below 45 or 55 years) or when two close relatives have had Colorectal Cancer, irrespective of the age at diagnosis.[4–6]

The observed increases in risk may be due in part to shared dietary and lifestyle factors (see Chapter 2), either alone or in combination with predisposing genetic factors. Genetic epidemiological studies indicate that inherited genetic predisposition accounts for familial clustering of Colorectal Cancer in at least some of these families, even though the mode of transmission and risks associated with the putative low-penetrance genes remain uncertain.[7,8]

Several studies have shown that colorectal adenomas are also a marker for risk of Colorectal Cancer in other family members.[9–11] Risk appears to be greater when adenomas are detected at an early age[9,10] and when adenomas have advanced histological features (see Chapter 9).[11] Although this is a cause for concern, information from prospective studies is needed before confident recommendations can be made about special screening protocols for relatives of adenoma patients.

6.2 Practical issues related to assessment and screening

All too frequently, clinicians fail to inquire about family history of cancer. In a Swedish population-based audit of patients with Colorectal Cancer, a family medical history was documented in only 1% of the cases at the time of first presentation with symptoms.[12]

Medical information that patients provide about their relatives is often inaccurate.[4,13–16] Given its potential importance, every effort should be made to collect reliable information. When there is uncertainty, more detailed information should be obtained from other family members, from death certificates, or from medical records. If a family medical history appears to be significant but

diagnoses prove difficult to confirm, it may be appropriate to seek expert help from a familial cancer clinic.

When discussing cancer risk and screening, it may help to combine estimates of relative risk with absolute risk for the general population, as shown in Chapter 3. Calculations based on present age and applying to the next 5–10 years puts risk into better perspective than calculations limited to life-time risk.

6.3 Quantifying risk based on family history

Individuals can be placed in one of three categories of relative risk based on their family history.

Category 1 — those at or slightly above average risk

Asymptomatic people fit into this category if they have:

- no personal history of bowel cancer, advanced adenoma, or chronic ulcerative colitis, and
- either no close relatives with bowel cancer or one first-degree or second-degree relative with bowel cancer diagnosed at age 55 years or older.[4–6,17]

For those with an affected first-degree relative, risk is *double* the average risk, although most of that extra risk is expressed after the age of 60 years. When the affected relative is second-degree (e.g. a grandparent, uncle or aunt), lifetime risk is increased only 1.5-fold.[6]

Category 2 — those at moderately increased risk

Asymptomatic people fit into this category if they have:

- one first-degree relative with bowel cancer diagnosed before the age of 55 years (without the potentially high-risk features listed below),[4,6,18–20] or
- two first-degree *or* one first- and one second-degree relative(s) on the same side of the family with bowel cancer diagnosed at any age (without the potentially high-risk features listed below).[19–21]

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

Category 3 — those at potentially high risk

Asymptomatic people fit into this category if they have:

- three or more first-degree or a combination of first-degree and second-degree relatives on the same side of the family diagnosed with bowel cancer (suspected HNPCC),[22] or
- two or more first-degree or second-degree relatives on the same side of the family diagnosed with bowel cancer, including any of the following high-risk features:
  - multiple bowel cancers in the one person
  - bowel cancer before the age of 50 years
  - at least one relative with cancer of the endometrium, ovary, stomach, small bowel, renal pelvis, ureter, biliary tract or brain (suspected HNPCC, see Chapter 7),[22] or

- at least one first-degree relative with a large number of adenomas throughout the large bowel (suspected FAP),[23] or

- somebody in the family in whom the presence of a high-risk mutation in the APC (adenomatous polyposis coli) gene or one of the mismatch repair (MMR) genes has been identified.[23,24]

Without genetic testing and in the absence of phenotypic features of FAP, the lifetime risk for cancer in these groups is at, or close to, 1 in 2 (relative risk increased about 15-fold). For those shown to carry a high-risk genetic mutation or to have polyposis or other features of FAP, the risk rises even further without medical intervention.

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

Table 6.1 Familial clustering of the common forms of bowel cancer

Family history	Relative risk
One first-degree relative with bowel cancer diagnosed at 55 years or over (included in category 1)	up to 2-fold
One first-degree relative with bowel cancer diagnosed under 55 years	3 to 6-fold
Two first-degree relatives with bowel cancer diagnosed at any age	3 to 6-fold

Note: Relative risk is the ratio of the risk of developing Colorectal Cancer in a particular exposed group to the average risk in the whole population (*cf* absolute risk; see Table 3.1).

6.4 Screening recommendations

It should be noted that the following recommendations are based on studies of cancer risk and on yield of lesions in screening studies, not on randomised controlled trials with Colorectal Cancer mortality as the outcome.

Category 1 — those at or slightly above average risk

Most people with a family history of Colorectal Cancer are in this category. Their levels of risk are similar to those associated with cigarette smoking, high alcohol intake or obesity.[25–27] In subjects who have just one affected relative, diagnosed when 55 years or older, the yield of clinically significant lesions at screening colonoscopy is low.[21,28–31]

A number of organisations, including the American Cancer Society and the American Gastroenterological Association, do not consider that the slight increase in degree of risk for this group justifies more invasive screening than that recommended for the general population.[32,33] The Australian Health Technology Advisory Committee (AHTAC) Report on Colorectal Cancer Screening concluded that recommendations for people in this category should be the same as for the average-risk population.[34]

What recommendations are there for bowel cancer screening for those at category 1 risk?

Guidelines — Screening (category 1 risk)	Level of evidence	Practice recommendation	Refs
Faecal occult blood testing (FOBT) every second year from the age of 50 years.	See Chapter 3 and AHTAC recommendations (Box 3.1)	Recommend	3–6, 21, 28–31
Consider sigmoidoscopy (preferably flexible) every five years from the age of 50 years — average risk	See Chapter 3 and AHTAC recommendations III-3	Recommend	3–6, 21, 28–31

Category 2 — those at moderately increased risk

In category 2, the risk for Colorectal Cancer is increased approximately three- to six-fold.[4,6,18–21] People in this situation are classified as having a moderately increased risk of Colorectal Cancer. Despite that, 70–90% of people in the group will never develop Colorectal Cancer.

It is recommended that the at-risk relatives be referred for colonoscopy at five-yearly intervals starting at age 50, or ten years younger than the age of the earliest diagnosis of Colorectal Cancer in the family, whichever comes first.[34] The recommendation that some should start colonoscopy before age 50 years needs to be kept under review. In one Australian audit, few significant lesions were found in category 2 subjects under 50 years of age despite the diagnosis of cancer at an early age in many index cases in that study.[35] Similarly, a recent Scottish study on category 2 subjects has also questioned the value of colonoscopic screening before the age of 50 years.[36]

Family members should be advised that colonoscopy is not without risk as it is an invasive procedure (see Chapter 8 for details). Flexible sigmoidoscopy and double contrast barium enema[34] or CT colonography may be offered if colonoscopy is contra-indicated for some reason.[37]

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

1. Because of the possibility of HNPCC, a complete family history should be taken and updated regularly, and the accuracy of the cancer diagnoses and polyp pathology should be checked carefully.

2. People at category 2 risk should be advised that genetic testing is not appropriate at present. Tumour testing for HNPCC-related changes, using immunohistochemistry and microsatellite instability, should be considered when any of the revised Bethesda criteria are met (see Chapter 7).

3. As with all forms of screening, those at risk should be carefully checked for the presence of symptoms that might be due to colorectal neoplasia. Where symptoms are present, appropriate diagnostic steps should be taken before entry into a screening program.

What recommendations are there for bowel cancer screening for those at category 2 risk?

Guidelines — Screening (category 2 risk)	Level of evidence	Practice recommendation	Refs
Offer colonoscopy every five years starting at age 50, or at an age ten years younger than the age of first diagnosis of bowel cancer in the family, whichever comes first. Flexible sigmoidoscopy and double contrast barium enema[34] or CT colonography may be offered if colonoscopy is contraindicated for some reason.	III-2	Recommend	4–6, 35,36

Category 3 — 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 potentially high risk for bowel cancer and, depending on the syndrome, for cancer at certain other sites.[23,24,38,39] Members of these families should be considered for genetic testing. Those shown to carry their family-specific mutation or having uncertain genetic status require careful cancer screening (see Chapter 7 for details).

The risk for some people with three (or more) relatives with bowel cancer may be difficult to categorise, especially if all cases of bowel 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 extra-colonic cancers associated with HNPCC.[40] Family size should be taken into account when assessing these families. If there is uncertainty about their status, it may be safer to categorise multi-case families as having suspected (or possible) HNPCC. New diagnoses of cancer in the family or results of microsatellite instability (MSI), immunohistochemical staining (IHC) or genetic testing may clarify the situation.

Recommendations for category 3 are to be found in Chapter 7.

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CHAPTER 7 HIGH-RISK FAMILIAL COLORECTAL CANCER SYNDROMES

Familial Colorectal Cancer includes syndromes in which there is a well-defined inherited genetic basis, as well as those families showing clustering of Colorectal Cancer in which no genetic cause has yet been found. Suspicion of a high-risk syndrome should be raised when two or more close relatives are affected, Colorectal Cancer has been diagnosed at an early age, (the earlier the age, the higher the degree of suspicion), or certain syndrome-specific characteristics are present.

The two best-characterised inherited syndromes are familial adenomatous polyposis (FAP) and hereditary non-polyposis Colorectal Cancer (HNPCC), (also known as Lynch syndrome). Both are inherited as autosomal dominant traits. FAP can usually be diagnosed on the basis of clinical findings alone, but the diagnosis is more difficult in the case of HNPCC. FAP and HNPCC have special significance because of their important contribution to Colorectal Cancer diagnosed before the age of 50 years. The chapter also considers families with a family history of Colorectal Cancer that may indicate a potentially high risk, though not strictly meeting HNPCC criteria. Such families are more numerous than those matching classical diagnostic criteria, and these form a large part of the referrals to family cancer clinics. These families and their management overlap with those considered in Chapter 6, to which the reader is also referred.

7.1 Principles of management

The correct management of individuals with, or at risk of, familial Colorectal Cancer is dependent upon determining which syndrome is present. This is important because risk assessment, genetic counselling, genetic testing, cancer preventive strategies and surgical treatment will differ according to the syndrome.

The diagnosis should be based upon meticulously verified clinical and pathological data concerning representative cancer-affected members of the family pedigree. This diagnosis may ultimately be confirmed by the demonstration of a germline mutation in the causative gene by testing an appropriate family member.

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. It aims to reduce cancer morbidity and mortality within an environment that is both supportive and fully appraised of the rapid developments in this complex area.

Cancer mortality is reduced in members of FAP[1,2,3] and HNPCC[4,5,6] families who actively participate in regular screening and surveillance programs.

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. In FAP, the principal life-threatening extracolonic lesions are periampullary adenocarcinoma and intra-abdominal fibromatosis (desmoid tumours).[7] Additional extracolonic features may 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 can support the clinical phenotypic diagnosis of FAP.[8]

In HNPCC, extracolonic cancer may affect the endometrium, ovary, stomach, small intestine, renal pelvis and ureter, brain**,** skin and possibly pancreas.[9,10] Management of these multi-system disorders does not fall within the traditional boundaries of any clinical discipline, but requires the input of surgeons, gastroenterologists, gynaecologists, oncologists, general practitioners and clinical geneticists. Equally important is expert support from the laboratory-based disciplines, including anatomical pathology,[1,2,3,4,5,6] and molecular genetics. Registries provide a useful focal point for coordinating the management of these complex disorders. It is difficult for any individual practitioner to offer comprehensive management that is family-based and provides continuity of support to successive generations, encompassing diagnosis, genetic counselling/testing, cancer screening and treatment. Hence the emergence of multidisciplinary familial cancer services.

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. [1,2,3,4,5,6] These 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 present and future generations of a family
- liaison with relevant health care professionals
- liaison with other regional registries
- educational support and counselling
- identification of at-risk family members
- coordination of genetic counselling and testing
- coordination of cancer screening
- facilitation of multidisciplinary clinical management
- documentation of extended follow up
- resource for legitimate research translating ultimately into improved patient care.

State-based familial cancer registers have been established in Australia, and are listed in Table 7.4 at the end of this chapter.

7.4 Genetic testing

Genetic testing may provide the ultimate diagnosis of a specific hereditary condition, but it is often not required to achieve a correct working diagnosis. However, a genetic diagnosis (i.e. the identification of a causative mutation) is required if at-risk members of a particular family are to be

offered predictive genetic testing. In FAP, the site of the mutation can also influence the disease phenotype.[11,12] This may be relevant when considering surgical management.

Genetic testing usually 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). Occasionally, blood is taken for DNA extraction and storage on clinical suspicion if the sole surviving affected member is frail or very elderly. Genetic testing should be conducted under the supervision of a clinical geneticist, specialist in cancer genetics, or ethically approved clinical research group, and should be supported by appropriate counselling.[13,14] Informed consent is mandatory for genetic testing.

An individual believing him/herself to be at risk for an inherited cancer may wish to have a 'genetic test', for obvious reasons. Isolated testing is inappropriate as it is likely to be negative, a proportion of these being false negative results that fail to exclude a genetic risk factor. This can engender a false sense of security with respect to the individual and the individual's family.[13] Furthermore, a harmless genetic variation (polymorphism) may be incorrectly interpreted as a positive result.

The most appropriate series of steps is to:

- establish a working diagnosis
- consider pre-genetic testing (microsatellite instability and immunohistochemistry) where the pedigree suggests HNPCC but is not clear-cut
- 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
- provide appropriate genetic counselling and support for affected and unaffected family members

Although genetic testing is possible and has been achieved for many FAP[13] and HNPCC[15,16,17] 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.[18,19] Penetrance of an APC mutation, as manifested by the development of Colorectal Cancer, approaches 100% by the age of 50 years in untreated subjects. FAP, however, accounts for less than 1% of all Colorectal Cancer cases. This translates to about 2000 affected and at-risk family members in Australia. In Finland, FAP now accounts for only 0.2% of bowel cancer, which reflects the success of prophylactic colectomy in cancer prevention in that country.[20]

The diagnosis of a new case is usually made when an individual develops Colorectal Cancer at a relatively early age on a background of colorectal adenomatous polyposis (usually, but not always, considerably more than 100 adenomas). Attenuated FAP is also being increasingly recognised. In this condition there are fewer than 100 adenomas present, often only in the proximal colon. Adenomas and cancer tend to develop at an older age than in classic FAP. Careful review of the family history can identify unaffected family members who are at risk, and genetic testing may clarify risk status for individual family members. All 'at-risk' individuals need to be informed that screening sigmoidoscopy (or colonoscopy in the case of attenuated FAP) is recommended.

At-risk individuals include:

- all first degree relatives, and depending on information available on disease status of intermediate relatives, sometimes more distant relatives of affected individuals, until the family APC mutation has been identified

- once the family APC mutation has been identified, relatives who have been found to carry the family specific mutation, as well as untested close relatives.

The recommended protocol for screening is:

flexible sigmoidoscopy annually or biennially from age 12–15 years to 30–35 years until polyposis develops. Depending on likely compliance, sigmoidoscopy is often done yearly to establish better rapport with the individual and continuity of care. Cancers are exceedingly rare in teenage years, guiding the timing of surgery usually to later teenage years. if no family specific mutation has been identified, and no adenomas have developed, sigmoidoscopy as above until 35 years, and then every three years after the age of 35 years, in view of the diminishing likelihood that the person has inherited the APC mutation. Population-based recommendations can then be introduced from 55 years.[21]

- colonoscopic screening is appropriate for families with attenuated FAP, as recto-sigmoid sparing can occur in this variant of the disease.

- Dye spray scattering (chromo-endoscopy) at flexible sigmoidoscopy or colonoscopy increases detection of polyps and enhances information about the phenotype. This may facilitate decision making about which genes to interrogate in the process of a germline mutation search. Dye spray scattering should be considered in investigations to make the initial diagnosis.

Australian experience indicates that the causative APC gene mutation can be identified in over 85% of FAP families .The APC gene is a large gene, spanning 15 exons on chromosome 5.[18,22] Mutations in different families are scattered throughout the gene. Most mutations produce a premature stop codon resulting in an abnormally shortened protein product. Such proteins can be readily identified in the laboratory using the protein truncation test.[23,24] Other mutational analytic strategies may be required to optimise the detection rate (e.g. deletion studies). The exact description of the causative mutation is found by sequencing.

Once a causative APC mutation has been identified for the family, genetic testing may be used to distinguish mutation-positive and mutation-negative family members. Such predictive testing cannot proceed in at-risk members until the specific mutation has been identified in at least one affected family member.[25] Individuals shown not to carry the family-specific mutation no longer require intensive screening, with their risk reverting to that of the general population. Since the mutation (and disease) cannot skip generations, there is no need to test the children of such individuals. When a causative gene mutation is identified, at-risk children are generally offered testing when they would otherwise be commencing flexible sigmoidoscopy (e.g. in early to mid teens). Those testing positively will require annual sigmoidoscopy. It is important to check the histological features of a representative sample of any polyps found, because lymphoid polyps are sometimes large and numerous in children and can be mistaken for adenomas. It is usual to plan surgery once there is an endoscopic diagnosis with pathological confirmation.[14]

Appropriate surgical options for prophylactic management in FAP include total colectomy and ileorectal anastomosis, or restorative proctocolectomy with pouch formation.[21,26] The usual age for these procedures is in the later teenage years, or early adulthood at the latest. Lifetime follow up of the rectum every 6 to 12 months after ileorectal anastomosis, or a pouch (after restorative proctocolectomy), is required; development of cancer, severely dysplastic adenomas or

endoscopically uncontrollable numbers of adenomas in the rectum are indications for proctectomy.[14] Pouch surveillance frequency is uncertain; one guideline adopted in Victoria follows Spigelman guidelines (as below, Table 7.1).

Regular upper gastrointestinal endoscopy (particularly side-viewing duodenoscopy) in the prevention of upper GI malignancy in affected members of FAP families is widely practised from the age of 25 years.[27] Upper gastrointestinal endoscopy need not be done in screening of at-risk family members as colorectal adenomas will almost invariably precede duodenal adenomas. Significant duodenal polyposis is uncommon before 40 years of age and is staged using the Spigelman criteria (see Table 7.1).[28] The frequency of subsequent surveillance endoscopy is dependent on the stage of polyposis, as per the proposed EuroFAP guidelines (see Table 7.2).[29,30] Several centres managing FAP are now intervening with endoscopic mucosal resection of duodenal adenomas, at a time when polyps do not extend over more than two duodenal folds. Side-viewing endoscopy is needed to manage the typical polyp in the periampullary region. Consideration should be given to temporary stenting of the pancreatic duct if there is any risk of disturbing it during resection or ablation of polyps. Post-polypectomy haemorrhage is common, so endoscopic skills (such as endoscopic clipping) should be available to manage bleeding polypectomy sites.

It is reasonable to offer gastroduodenoscopy,[30] to check the ampulla and the periampullary region, before proceeding to colectomy for treatment of colorectal polyposis, and to then follow the guidelines as above.

Table 7.1 Spigelman staging of duodenal polyposis

Score	1	2	3
Number	1–4	5–20	>20
Max size mm	1–4	5–10	>10
Worst histology	Tubular	tubulovillous	Villous
Dysplasia	Mild	moderate	Severe

Stage 1 = score 1–4; Stage 2 = score 5–6; Stage 3 = score 7–8; Stage 4 = 9–12
Source: Spigelman et al[28]

Table 7.2 Proposed program for screening, surveillance and treatment for duodenal adenomatosis

Spigelman Stage 0 and I:	Endoscopy at intervals of 5 years
Spigelman Stage II:	Endoscopy at intervals of 3 years
Spigelman Stage III:	Endoscopy at intervals of 1–2 years Consider celecoxib 800 mg daily Consider endoscopic ultrasonography (EUS)
Spigelman Stage IV	Endoscopic ultrasonography (EUS) Consider surgery: Pancreas-sparing or pylorus-sparing duodenectomy

Source: Bulow et al[30]

One study has shown that screening and surveillance of the upper gastrointestinal tract leads to a moderate gain in life expectancy.[31] Another, at St Mark's Hospital, London, showed no benefit from surveillance endoscopy, apart from confirming the utility of the above staging system in identifying those for whom prophylactic surgery should be considered.[32] A European study provided support for surveillance utilising the Spigelman staging system, demonstrating that most duodenal cancers

developed through a progression of the stages. Their screening and surveillance recommendations are as noted above (EuroFAP Surveillance protocol).[30]

The role of non-steroidal anti-inflammatory agents (NSAIDs) such as sulindac and celecoxib as cancer chemopreventative agents has been suggested by a number of clinical studies.[33] However, there are reports of subjects developing Colorectal Cancer while on NSAIDs, despite evidence of polyp regression.[34] Nevertheless, the specific COX-2 inhibitor celecoxib has been shown to reduce the number of colorectal and duodenal adenomas in a randomised controlled study[35] and may therefore have a role as an adjunct to surgical management.[36] The large sporadic adenoma trials have reported an increased risk of myocardial infarction and stroke in patients taking polyp suppressive doses of COX-2 inhibitors, and therefore the place of these agents in chemoprevention has come under close clinical and regulatory scrutiny (see Chapter 2). On the other hand, sulindac failed to prevent the onset of adenomas in another randomised controlled trial.[37]

7.6 MYH-associated polyposis (MAP)

MYH-associated polyposis (MAP) is a recently described condition that results from biallelic germline mutations in the base excision repair gene, mutY homologue (MYH)[38],MAP has a phenotype that is very similar to classical or attenuated familial adenomatous polyposis (FAP), but MAP is inherited as a recessive condition, whereas FAP (above) is a dominantly inherited disease caused by germline APC mutation. It is postulated that MYH mutations may act by increasing the frequency of somatic APC mutations. Carriers of biallelic MYH mutations have the multiple polyposis phenotype without a family history in the generations above and below the proband. Biallelic MYH mutation carriers should be treated and followed up as for FAP patients. Relatives of such patients should be counselled as for any other recessive condition, although it is possible that carriers of mono-allelic mutations are at a modestly increased risk of Colorectal Cancer.

7.7 Diagnosis of HNPCC

HNPCC is an autosomal dominant disorder caused by a germline mutation in one of a family of DNA mismatch repair (MMR) genes — principally *hMLH1*, *hMSH2*, *hMSH6* and *hPMS2*.[39,40,41,42,43,44] The majority of mutation-positive families have mutations in either *hMLH1* or *hMSH2*.[45] HNPCC probably accounts for about 1–4% of all Colorectal Cancers.[9,45,46,47,48]

In conjunction with family history, molecular tests have been developed to improve the diagnosis of HNPCC and assist in cancer risk assessment. When the family history suggests HNPCC, the presence of high levels of microsatellite instability (MSI) in the DNA of one or more cancers, or the lack of expression of MMR proteins by tumour testing, especially where that cancer occurs at an early age, may be a good indicator of a germline mutation in one of the MMR genes

7.7.1 Diagnosis based on family history

HNPCC is characterised by an early age of onset of Colorectal Cancer, a predilection for proximal colonic malignancy, and a tendency to develop multiple Colorectal Cancers.[9,49] It is generally accepted that risk estimates calculated from clinic-based series of HNPCC families place the Colorectal Cancer risk at about 70–90% for men and women by the age of 65 years,[50] although a lower risk of 30% for women with HNPCC has been described.[51] However, in population-based studies of early onset Colorectal Cancer in Australia, penetrance for Colorectal Cancer by 65 years for males was reported to be only 45% (95% Confidence Intervals 29-62%) and for females 38% (95% CI 19-51%); for any HNPCC related cancers, the risks were 67% (95CI 47-84%), and 72% (CI 48-85%) respectively. (Jenkins MA, personal communication). Another risk estimate for endometrial cancer was 42%,[51] emphasising the need to screen this extracolonic site, especially in hMSH6

mutation carriers.[52] There is also an increased risk of ovarian cancer in female carriers, estimated to be up to 10% over a lifetime.

Cancers may occur at other sites as detailed below. Carriers of an *hMSH2* mutation are at a higher risk of cancer than *hMLH1* mutation carriers.[53]

HNPCC is distinguished clinically from FAP by the paucity of adenomas and by additional pathological features (see below). Adenomas do occur in HNPCC, often at an early age of onset.[54,55,56]

The original Amsterdam-1 criteria[57] are clinical criteria formulated to help identify families that should be considered for a diagnosis of HNPCC. A high proportion of families fulfilling the Amsterdam criteria (probably between 60–95%) will have HNPCC.[58,59] These criteria are:

- at least three cases of Colorectal Cancer in the family (verified)
- 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 FAP.

A memory aid is the *3,2,1* rule: *3* first-degree relatives affected, over *2* generations, with *1* under the age of 50 years.

The Amsterdam II criteria[60] were introduced in an attempt to increase the sensitivity of diagnosing an HNPCC family, with minimal loss of specificity. These criteria allow 'extracolonic malignancy' to be substituted for 'colorectal malignancy'. The sites of extracolonic malignancies included are: endometrium, small bowel, ureter and renal pelvis. Very rarely, there may be families with these malignancies but no Colorectal Cancer.

However, some families that meet these criteria, or have a very strong family history of cancer suggestive of a dominant susceptibility to bowel cancer, do not have a demonstrable MMR germline mutation. Therefore, they do not have HNPCC as defined by the finding of an MMR germline mutation, based on current knowledge and available technology. Conversely, some families that do not meet the Amsterdam criteria do have HNPCC.[61,62,63] Families meeting Amsterdam criteria, regardless of molecular information, are usually managed as for HNPCC. However, emerging evidence suggests that in families with a family history that fulfils the Amsterdam –1 criteria, but where tumour testing shows no evidence to suggest MMR deficiency (see 7.7.2), the risk of Colorectal Cancer may be less than for proven HNPCC, and the risk of extracolonic cancers may be absent.[64] Further evidence may eventually change clinical practice in the management of such families.

7.7.2 Diagnosis based on tumour testing

In conjunction with family history, molecular tests have been developed to improve the diagnosis of HNPCC. When a diagnosis of HNPCC is being considered in an index case, based on a suspicious family or clinical history, testing of tumour tissue using microsatellite instability testing and immunohistochemistry testing may help determine which patients should proceed to formal germline genetic testing.

Microsatellite instability testing (using tumour tissue)

Microsatellites are made up of tandem repeats of short sequences of DNA, 1–5 bases in length. They are found throughout the genome, both in coding and non-coding regions. During DNA replication, errors can occur at these sites, causing a change in size of the microsatellite in the daughter cells — this is termed microsatellite instability (MSI).[65] Normally these errors are recognised and repaired by the DNA mismatch repair (MMR) system. When the DNA MMR system is defective as in HNPCC, due to a germline mutation in one of the MMR gene alleles coupled with mutation, loss or inactivation of the other normal allele, MSI occurs and can be demonstrated by comparing normal and cancer DNA. Tumours are described as microsatellite stable (MSS), where there is no instability; MSI-high (MSI-H), where two or more of the National Cancer Institute -recommended panel of microsatellites are unstable, or MSI low (MSI-L), where only one of the panel is unstable.[65] Instability with mononucleotide repeat sequences alone suggests an underlying hMSH6 mutation.

The great majority of Colorectal Cancers in HNPCC are MSI-H and the presence of high levels of microsatellite instability can help corroborate the diagnosis of HNPCC, particularly in small families.[59,60,62,66,67] Approximately 70% of adenomas in HNPCC will also exhibit MSI-H and show immunohistochemical loss of expression of a DNA mismatch repair protein concordant with the underlying germline mutation.[59]

It is important to note, however, that about 10–15% of the large number of sporadic Colorectal Cancers also exhibit MSI-H.[68,69] Therefore the finding of MSI-H should be considered in the context of the family history and, importantly, the age of the patient. MSI-H occurs in sporadic Colorectal Cancer as a result of acquired hypermethylation and epigenetic silencing of *hLMH1* [70]

MSI-H Colorectal Cancers in HNPCC are likely to be mucinous, poorly differentiated and characterised by the presence of tumour infiltrating lymphocytes.[71] However, there is some evidence that mucinous differentiation and poor glandular differentiation are more typical of sporadic MSI-H Colorectal Cancer, whereas lymphocytic infiltration is more marked in HNPCC-associated MSI-H cancers.[72] Greater diagnostic precision is achieved by analysis of a combination of clinical, pathological and genetic variables.[73] Further molecular approaches may eventually allow a distinction between HNPCC and sporadic MSI-H Colorectal Cancer. For example, a specific BRAF mutation occurs in the majority (but not all) of sporadic MSI-H cancers, but virtually never occurs in HNPCC-associated MSI-H cancers.[74] Thus, presence of the specific BRAF mutation in a MSI-H tumour makes a sporadic aetiology very likely, but absence of the BRAF mutation is not helpful in this differentiation. Currently, tumour BRAF mutation analysis is not generally available in diagnostic laboratories. Another approach is to assess the degree of methylation (silencing), or more accurately, allele specific methylation of mismatch repair genes shown to lack expression of mismatch repair gene proteins in tumours. Silencing of the promoter of, especially hMLH1, is the dominant mechanism of development of MSI-H Colorectal Cancers. Tumour methylation studies can therefore reveal the pathogenesis of MSI-H cancers, and guide the need for a search for a germline mutation where a MSI-H cancer is identified in a family. Methylation studies of mismatch repair genes may be important in the future, but are currently not generally available in clinical practice.

MSI testing and/or immunohistochemistry (see below) should usually precede the expensive step of formal germline genetic screening of a family (commencing with mutation search in an affected family member). When a family history suggests HNPCC, the presence of MSI-H in the DNA of one or more cancers, especially where that cancer occurs at an early age, is a good indicator of a germline mutation in one of the MMR genes.[61]

The Bethesda guidelines were developed to provide selective criteria for testing tumours for MSI *in an individual affected by Colorectal Cancer*.[75,76] The guidelines were modified after experience was gained in their application (Table 7.3). The Revised Bethesda Guidelines[77] should be regarded as the

standard for consideration of MSI and/or immunohistochemistry testing. Changes from the original Bethesda Guidelines include no longer recommending testing for patients with endometrial cancer (alone) under 45 years (as the new guidelines refer specifically to testing of colorectal tumours), testing of tumours in families meeting Amsterdam criteria (many centres would move straight to germline mutation testing in an affected member in these families), and adenomas diagnosed in persons under 40 years (as this has proved a poor marker of MSI). The specificity of the new guidelines[77] has been questioned and tighter guidelines are likely to emerge from this debate[78]

The revised guidelines recommend testing patients with synchronous or metachronous HNPCC-related cancers *regardless of age of onset*, a wider definition of HNPCC-related cancers, increasing the age at diagnosis below which MSI/immunohistochemistry testing should be considered routinely to 50 years, and to 60 years where there are histopathological features suggesting microsatellite instability.

The purpose of the Bethesda criteria is to assist in increasing the yield of HNPCC beyond what may be achieved through the application of the Amsterdam criteria, and help distinguish *individuals* with MSI-H cancers who are likely to have an underlying germline mutation (HNPCC) from the more numerous individuals with sporadic MSI-H cancer, for whom germline screening for a mutation is not warranted. The experience has been that they are sensitive, but not especially specific.

Table 7.3 Revised Bethesda Guidelines for testing colorectal tumours for microsatellite instability

Tumours from individuals should be tested for microsatellite instability (MSI) in the following situations*:*

1. Colorectal Cancer diagnosed in a patient who is less than 50 years of age.
2. Presence of synchronous, metachronous Colorectal Cancer, or other HNPCC-associated tumours[a] regardless of age.
3. Colorectal Cancer with the MSI-H[b] histology[c] diagnosed in a patient who is less than 60 years of age.[d]
4. Colorectal Cancer diagnosed in one or more first-degree relatives with an HNPCC-related tumour, with one of the cancers being diagnosed under age 50 years.
5. Colorectal Cancer diagnosed in two or more first- or second-degree relatives with HNPCC-related tumours, regardless of age.

[a] Hereditary nonpolyposis Colorectal Cancer (HNPCC)-related tumours include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, brain (usually glioblastoma as seen in Turcot syndrome) tumours, sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome, and carcinoma of the small bowel.

[b] MSI-H (microsatellite instability — high) in tumours refers to changes in two or more of the five National Cancer Institute-recommended panels of microsatellite markers.

[c] Presence of tumour-infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern.

[d] There was no consensus among the Workshop participants as to whether to include the age criteria in guideline 3 above; participants voted to keep less than 60 years of age in the guidelines. Sporadic MSI-H cancers are uncommon below the age of 60,[72]and MSI testing should be considered in subjects up to this age when the morphological features of MSI-H cancers are present.

Source: Umar et al[77]

Clearly, the various guidelines are not exclusive, and overlap. They are relevant for different clinical scenarios — family consultations versus individual presentations. All are presented here for information.

Immunohistochemistry testing using tumour tissue

Immunohistochemistry (IHC) testing uses antibodies to measure expression of the various MMR proteins in a tumour. Loss of expression of a specific protein produced by one of the relevant genes (hMLH1, hMSH2, hMSH6 or hPMS2) may be an indicator of a germline mutation in the gene coding for that protein. Immunostaining is sensitive and highly specific.[79] The technique pinpoints the gene that is implicated and therefore facilitates the search for the underlying germline mutation.

The Revised Bethesda Guidelines[77] could also be applied to the selection of cancers for immunohistochemical staining. Indeed, clinical practice world wide is recognizing the value of testing tumours by immunohistochemistry as the first line tumour test, reserving microsatellite instability testing for situations where the family history is highly indicative of HNPCC, but where immunohistochemistry is normal.

7.7.3 Diagnosis by germline genetic testing

Identification of the causative germline mutation in an affected individual allows for other at-risk family members to be offered predictive testing. Genetic testing is not a simple matter, and should not be carried out in isolation. Mutations may occur in any of the four MMR genes. If a causative mutation is found, those carrying the high-risk gene mutation can be targeted for cancer screening or preventive measures. Germline mutational testing of the index case in the family, generally the youngest affected member in a family meeting Amsterdam criteria, or an individual with tumour testing indicative of a mismatch repair mutation, begins the process of characterising the family specific mismatch repair mutation at the molecular level.

7.8 Screening and surgical management of HNPCC

Screening of mutation carriers or individuals affected with HNPCC-related tumours in Amsterdam-positive families should be by full colonoscopy performed annually or at least once every two years, beginning at the age of 25 years or five years earlier than the age of diagnosis of the youngest affected member of the family (whichever is the earliest).[9] Rapid evolution of the adenoma–carcinoma sequence or other routes of morphogenesis may account for the relatively high frequency of interval cancers.[80]

Screening first-degree relatives of affected members in Amsterdam positive families where the mutation status is unknown is similar, although colonoscopy can be reduced to two-yearly. More distant relatives can be offered 5-yearly colonoscopy. This recommendation is a compromise between a policy to offer all relatives annual screening (to protect them from rapidly growing tumours if they do carry the family specific mutation) and the diminishing risk of carriage as the proximity of the relative to the potential carrier recedes with the degree of relationship. Consideration should be given to screening for extracolonic malignancy in affected and at-risk individuals, particularly gynaecological screening. The efficacy of screening any sites outside the colon and rectum has not been determined, but 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).[81] Those to be considered for gynaecological screening would include women with proven MMR mutations and their first-degree relatives who have not been gene tested, women affected by bowel cancer (if uterus or ovaries *in situ*) from Amsterdam–positive families where no mutation has been identified, and untested first- and second-degree relatives of affected members in MSH6 families.[82]

The Cancer Council of Victoria's VCOG Gynaecological Committee recommends that a screening program should include annual transvaginal ultrasound (TVUS) of the ovaries and uterus in premenopausal women, commencing at age 30–35 or five years before the age at diagnosis of the youngest affected family member. In postmenopausal women, annual CA125 measurement may be

added to transvaginal ultrasound.[83] Endometrial sampling and full investigation is required in symptomatic women and those with abnormal endometrial findings as assessed on TVUS during the proliferative phase of the menstrual cycle. Endometrial biopsy is indicated if endometrial thickness is ≥9 mm in the proliferative phase of the premenopausal menstrual cycle or if there is endometrial thickness ≥4 mm in the postmenopausal woman. Such screening is based on expert evidence but has not been established as reducing either incidence or mortality from endometrial or ovarian cancer.

Screening for other HNPCC-associated cancers in at-risk family members (e.g. gene carriers or untested individuals) should be influenced by the profile of cancers occurring in the family. One guideline is to introduce such screening when there are two or more of a particular tumour type in the family (H Vasen, Netherlands Hereditary Tumour Institute, personal communication). Renal tract screening with urine cytology is particularly non-invasive and cheap. Additional extracolonic sites may be affected more frequently in *hMSH2*[81] and *hMSH6*[44,84] families. This is particularly pertinent with respect to gastric cancer, which dominated the original (Family G) description of HNPCC by Warthin.[85]

The risk of metachronous Colorectal Cancer is increased in HNPCC. For this reason, extended surgery, for example total colectomy, has been recommended for subjects with proven HNPCC.[86] However, this is not widely accepted, especially in some parts of Europe, where a controlled surgical trial is being mounted to address the question. In newly suspected cases of HNPCC, MSI testing or immunohistochemical staining of a preoperative biopsy may assist in development of a management plan, including surgery. 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 the remaining large bowel mucosa is then required.[87] Long-term compliance and access to such screening will also influence the surgical procedural choice. Consideration should be given to offering women with proven HNPCC a hysterectomy and possibly an oophorectomy at the time of surgery for Colorectal Cancer, if childbearing is complete.[9, 14]

Prophylactic colectomy in either at-risk individuals or even those known to be mutation carriers cannot be recommended generally, but is an option in particular instances, especially when screening has led to detection of more than one advanced adenoma.[14] Under such circumstances, consideration should also be given to prophylactic hysterectomy and oophorectomy from the age of 30–35 years or when childbearing is complete. Because the efficacy of gynaecological screening is uncertain, prophylactic gynaecological surgery should be discussed whether or not prophylactic colectomy is being considered as an option.

7.9 Familial clusters of Colorectal Cancer

Since there is evidence that HNPCC can affect some families not meeting the Amsterdam criteria, the possibility that a family cluster of Colorectal Cancer may be due to HNPCC should be reviewed using the Australian Cancer Network[88] family history guide with review of the clinical and pathological data and testing of tumours for DNA microsatellite instability and/or loss of an MMR protein by immunohistochemistry. These guidelines recommend referral of families for consideration of risk assessment, tumour testing or genetic testing to familial cancer services where:

- three or more first- or second-degree relatives on the same side of the family are diagnosed with bowel cancer, or
- two or more first- or second-degree relatives on the same side of the family are diagnosed with bowel cancer plus any of the following high-risk features:
  - multiple bowel cancers in a family member
  - bowel cancer before age 50 years

  - a family member has or has had an HNPCC-related cancer (endometrial, ovarian, stomach, small bowel, renal pelvis or ureter, biliary tract, brain cancer), or

- at least one first- or second-degree relative diagnosed with bowel cancer with a large number of synchronous adenomas (suspected FAP), or

- there is a member of a family in which a gene mutation that confers a high risk of bowel cancer has been identified.

When a working diagnosis of HNPCC cannot be justified, screening recommendations for familial clusters of Colorectal Cancer should be followed (see Chapter 6).

Increasing evidence points to a diminished risk for colorectal and especially extracolonic cancers, where there is no evidence of deficient mismatch repair in tumours occurring in the family, despite strong, even Amsterdam positive, family histories of cancer[64] Screening of at risk relatives in these families may eventually warrant a reduced screening strategy, as the evidence evolves.

7.10 Hyperplastic polyposis and MSI-variable cancers

A particular type of familial clustering of Colorectal Cancer may closely mimic HNPCC and the resemblance may extend to the demonstration of one or more Colorectal Cancers showing evidence of MSI.[89-91] However, further investigation of such families may show clinical, pathological and molecular features that cannot be explained on the basis of a germline mutation in a DNA MMR gene. These features may include: (i) mixtures of MSI-H, MSI-L and MSS cancers in different family members or even in the same individual; (ii) presence of hyperplastic polyps that may be numerous and/or large (associated adenomas might also be present); (iii) a relatively older age at onset of cancer; (iv) absence of extracolonic HNPCC-associated tumours. [89,90]

A likely explanation for the finding of MSI-H cancers in such families is silencing of *hMLH1* as a result of somatic DNA methylation. There is now evidence that DNA hypermethylation is involved in the pathogenesis of a subset of hyperplastic polyps, including those found in association with sporadic MSI-H cancers.[92,93,94,95] Hyperplastic polyps with DNA methylation are likely to be multiple, relatively large (≥ 1cm) and located in the proximal colon. In these serrated polyps, a specific somatic *BRAF* gene mutation can occur, as seen in sporadic MSI-H Colorectal Cancers which also have promoter methylation of hMLH1.[74] In some instances hyperplastic polyps may occur in sufficient numbers (>20) to warrant a diagnosis of hyperplastic polyposis.[96]

It is possible that the familial clustering of Colorectal Cancer in the context of the previous observations may be explained in part by a familial predisposition to somatic DNA methylation. A polymorphism in the methyltetrahydrofolate reductase gene may be important in this regard.[97]Screening for a germline mutation in a DNA MMR gene is likely to be unproductive in such families.

Disruption of a DNA MMR gene by inherited mutation is thought to accelerate the development of Colorectal Cancer. It is likely that epigenetic silencing of *hMLH1* or other DNA repair genes such as *MGMT* by DNA methylation may also accelerate cancer progression.[98,99] When such a 'methylator' family is suspected, expert opinion suggests that colonoscopic screening should be the same as for HNPCC in the case of family members affected by either cancer or multiple and/or large hyperplastic polyps (J Jass, personal opinion). Most subjects with hyperplastic polyposis (with or without associated Colorectal Cancer) do not have a family history of Colorectal Cancer. Any genetic basis for this condition is unlikely to be highly penetrant. Therefore, screening of first-degree relatives of affected subjects could be as for subjects in the moderate-risk category (5 yearly colonoscopy -

category 2, see Chapter 6) but may be more intensive if adenomas or multiple small hyperplastic polyps are detected.

7.11 Peutz-Jeghers syndrome and juvenile polyposis

The risk of Colorectal Cancer and some other cancers is also increased in the rarer Peutz-Jeghers syndrome (mucocutaneous pigmentation and multiple hamartomatous polyps)[100] and juvenile polyposis[101] (multiple gastrointestinal juvenile polyps). These patients and their families should also be referred to specialist family cancer clinics for advice and coordination of management.

7.12 Summary of recommendations

How should genetic testing be undertaken for high-risk CRC family syndromes?

Guideline — High familial risk syndromes	Level of evidence	Practice recommendation	Refs
After counselling, genetic testing should be undertaken under the supervision of a cancer genetics specialist.	III-2	Recommend	14

What is the role of NSAIDs in the prevention of colorectal neoplasia in high-risk familial syndromes?

Guideline — High familial risk syndromes	Level of evidence	Practice recommendation	Refs
The role of NSAIDs such as sulindac in the prevention of cancer in FAP is unclear. High-dose celecoxib (400 mg twice daily) has been shown to reduce polyp numbers and its use may facilitate the control of polyps, but carries significant cardiovascular morbidity.	II	Equivocal	14, 33, 35, 36

What is the surgical management of FAP?

Guideline — High familial risk syndromes	Level of evidence	Practice recommendation	Refs
The surgical management of FAP is by total colectomy and ileorectal anastomosis or restorative proctocolectomy.	III-2	Recommend	14, 25

When should large bowel screening begin in FAP and what should be offered?

Guideline — High familial risk syndromes	Level of evidence	Practice recommendation	Refs
Screening in FAP is by sigmoidoscopy from 12–15 years of age (the later age is recommended), except in attenuated FAP, where screening is based on colonoscopy, or where there is a family history of very early age of onset of Colorectal Cancer in the family.	III-2	Recommend	1-3, 14

Is duodenal screening recommended in FAP?

Guideline — High familial risk syndromes	Level of evidence	Practice recommendation	Refs
Duodenal screening in FAP is recommended perioperatively at the time of colectomy, from 25 years of age, or earlier should there be a family history of duodenal cancer at an early age.	III-2	Recommend	14, 26-32

How should FAP family members not carrying their family mutation be advised?

Guideline — High familial risk syndromes	Level of evidence	Practice recommendation	Refs
Members of proven FAP families who are documented to NOT carry the family specific APC mutation are no longer at high risk.	III-2	Recommend	25

When should large bowel screening of at-risk members in proven HNPCC families be offered?

Guideline — High familial risk syndromes	Level of evidence	Practice recommendation	Refs
Screening of at-risk members in proven HNPCC families should be by annual or 2-yearly colonoscopy, commencing around the age of 25 years or five years before the earliest age of cancer diagnosis in the family, whichever comes first. Annual screening should be offered to individuals carrying a germline mutation and for clinically affected individuals in Amsterdam families where mutation status is unknown.	III-2	Recommend	4-6, 9, 14

What screening is recommended for extracolonic cancers in HNPCC?

Guideline — High familial risk syndromes	Level of evidence	Practice recommendation	Refs
Consideration should be given to screening extracolonic sites in HNPCC, especially in families with clusters of extracolonic cancers. Routine screening of the uterus and ovaries (see text) should begin at around 30–35 years, or five years earlier than the youngest relative affected with uterine or ovarian cancer, whichever comes first. Referral to a gynaecological oncologist is advised for women in these families. Gastroscopy should be added to colonoscopy (on the same day, where possible, for patient convenience) if there is any family history of gastric cancer. Annual urine cytology and renal ultrasound is recommended in families with tumours of the renal collecting system.	III-3	Recommend	9

How should tumour testing (MSI and IHC) be used in affected individuals from families suspected to have HNPCC?

Guideline — High familial risk syndromes	Level of evidence	Practice recommendation	Refs
The Revised Bethesda Guidelines could be applied to the selection of cancers for microsatellite instability (MSI) testing and immunohistochemical staining.	III-2	Recommend	77, 78

How should HNPCC family members not carrying their family mutation be advised?

Guideline — High familial risk syndromes	Level of evidence	Practice recommendation	Refs
Members of proven HNPCC families who test negatively for the family mismatch gene mutation do not have an additional risk associated with this mutation.	III-2	Recommend	14

What surveillance is recommended in hyperplastic polyposis and for MSI-variable cancers?

Guideline — High familial risk syndromes	Level of evidence	Practice recommendation	Refs
Affected subjects in familial clusters characterised by mixtures of MSI-H, MSI-L and MSS cancers and/or the finding of multiple/large hyperplastic polyps should be screened by colonoscopy according to HNPCC recommendations, though first-degree relatives unaffected by cancer may be screened according to intermediate risk-guidelines.	IV	Equivocal	92, 93

Table 7.4 Hereditary Bowel Cancer Registers in Australia and New Zealand

FamilialCancer@yahoogroups.com		
NSW and ACT Hereditary Cancer Registers (FAP, polyposis syndromes and HNPCC)	Cancer Council NSW 153 Dowling Street Woolloomoolloo, NSW 2011 PO Box 572 Kings Cross NSW 1340 Australia	Tel: 02 9334 1807 Fax: 02 9334 1867 Email: hcr@nswcc.org.au Website: <www.nswcc.org.au> Cancer Helpline: 13 11 20 or 1800 422 760
Queensland Familial Bowel Cancer Registry inc Queensland Familial Adenomatous Polyposis Register (FAP and polyposis syndromes) and HNPCC	C/- Queensland Familial Bowel Cancer Registry QLD Clinical Genetic Service Block 65 via Back Road, Royal Brisbane Hospital HERSTON QLD 4029	Tel: 07 3636 5117 Fax: 07 3636 9164 Website: www.cancersa.org.au FAP: Ngaire_knight@health.qld.gov.au IHNPCC: Vivianne_geldard@health.qld.gov.au
Familial Cancer Unit (FAP, polyposis syndromes and HNPCC and other familial cancers)	Familial Cancer Unit SW7 Women's and Children's Hospital 72 King William Road NORTH ADELAIDE SA 5006	Tel: 08 8161 6995 Fax: 08 8161 7984 Email: famcancer@mail.wch.sa.gov.au
Victorian Family Cancer Register/ FAP Registry	The Cancer Council Victoria I Rathdowne Street CARLTON VIC 3053	Tel: 03 9635 5374 03 9635 5414 03 9635 5176 Fax:03 9635 5270 Email: enquiries@cancervic.org.au Website: <www.cancervic.org.au>
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CHAPTER 8 DIAGNOSTIC TESTS AND PREOPERATIVE ASSESSMENT

A right-sided colon cancer usually presents with iron deficiency anaemia, or as a palpable abdominal mass. In contrast, left-sided and rectal cancer usually presents with rectal bleeding, and/or a change in bowel habit. The change in bowel habit may include an increased frequency, altered consistency, altered calibre, or worsening constipation. Unfortunately, by the time a Colorectal Cancer becomes symptomatic, a majority of these patients will have either nodal or distant metastases at diagnosis. The diagnosis of Colorectal Cancer based upon symptoms may be difficult because these typical clinical features are present in only 40% of patients[1] with cancer. Similar symptoms (especially bleeding and abdominal pain) may arise from other causes.

An attempt may be made to stratify how urgently patients with symptoms should proceed to evaluation. This stratification should include other risk factors for Colorectal Cancer such as increasing patient age, (esp. over 40 years) and a strong family history of colorectal and other cancers. Urgent referral should be considered in patients with:

- unexplained iron deficiency anaemia
- a palpable rectal mass
- persistent rectal bleeding
- persistent changes in bowel function.

Rectal bleeding is a particularly common symptom in the community. All such patients should be evaluated and investigated. All patients over 40 years of age should undergo a colonoscopy.[2] For younger patients with typical anal outlet bleeding a sigmoidoscopy is a reasonable first approach. However, if the bleeding recurs or persists despite treatment of an apparent anal cause of bleeding, then a colonoscopy is indicated.[3]

Who should be investigated?

Guideline — Preoperative assessment	Level of evidence	Practice recommendation	Refs
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.	III-3	Equivocal	4-7

8.1 Methods of investigation

8.1.1 Digital rectal examination

A digital rectal examination should be the first assessment in any patient with anorectal symptoms. It enables detection and assessment of the size and fixation of mid and low rectal tumours. While digital assessment of the extent of local disease is imprecise, it provides a rough estimate of the local staging of the rectal cancer[8] and of the state and strength of anal sphincters. The adequacy of the anal sphincters may influence a surgical decision about whether to perform sphincter-preserving surgery.

8.1.2 Sigmoidoscopy: rigid versus flexible

Rigid sigmoidoscopy is usually performed in conjunction with the digital rectal examination. It facilitates the diagnosis of anal pathologies (fissure, haemorrhoids) and rectal neoplasm. In assessing neoplasm, it allows assessment of: (i) the distance from the lower edge of the neoplasm to the anal verge, and (ii) the location of the neoplasm.

Flexible sigmoidoscopy is superior to rigid sigmoidoscopy in that more of the large bowel up to the sigmoid colon is examined.[9] It requires a basic preparation in the form of an enema, and is usually performed in a diagnostic unit without sedation. Sigmoidoscopy, whether rigid or flexible, is important in the diagnosis and assessment of rectal neoplasm.[9,10]

Sensitivity and specificity for flexible sigmoidoscopy for lesions in the rectosigmoid region are similar to those for colonoscopy.[11] The procedure is safe[10] and the perforation rate is less than 2 in10,000 examinations.[12]

8.1.3 Colonoscopy

Colonoscopy is currently the most accurate investigation for assessing the colon and rectum.[13] The sensitivity of colonoscopy for colon cancer is 95%.[14,15,16] Colonoscopy allows biopsy and histologic confirmation of the diagnosis. It also allows identification and endoscopic removal of synchronous polyps. A study by the United States National Polyp Study found that colonoscopy was significantly more accurate than double contrast barium enema in diagnosing colorectal polyps.[13]

All patients with colorectal neoplasia should have a colonoscopy as part of their preoperative assessment unless there is perforation or significant large bowel obstruction. In 5–10% of patients, the presence of synchronous pathologies (esp. neoplasm) may alter the surgical approach. Patients with colorectal neoplasm who are undergoing emergency procedures should have a completion colonoscopy within three to six months of their surgery.

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 $\geq$1 cm.[17,18]

Improved effectiveness of colonoscopy is achieved with practice,[19,20] sedation,[21] and better preparation of the colon.[19] Use of high-magnification colonoscopy with chromoscopy (i.e. with indigo carmine) demonstrates morphologic detail of diminutive polyps that can readily be used to separate adenomatous from nonadenomatous polyps[22] and might permit early detection of early Colorectal Cancer, in the form of flat or depressed lesions.[23] Attempts at improving the accuracy of colonoscopy for colorectal neoplasia using high-magnification colonoscopy with chromoscopy (i.e. with indigo carmine or crystal violet) are currently under study.[24]

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.[25] In a review of six prospective studies of colonoscopy, about one in 1000 patients suffer perforation, three in 1000 suffer major haemorrhage, and between one and three in 10,000 die as a result of the procedure.[12] A review of Australian data has a similar complication rate.[5] There are other occasional, serious complications associated with bowel preparation or the use of sedation.

Quality issues

Guidelines on training and experience have been issued by the Gastroenterological Society of Australia.[26] Training or experience in colonoscopy has an important impact on the efficacy of colonoscopy. Trained endoscopists achieve a caecal intubation rate of over 90%.[9,27] However, self-

trained colonoscopists have reported caecal intubation rates as low as 54%, which did not improve with continued performance of colonoscopy.[28]

The sensitivity of colonoscopy is lowest in the splenic flexure and caecum.[14] The colonoscopist must recognise that a total colonoscopy requires unequivocal identification of the caecum and terminal ileum. A barium enema or computerised tomography (CT) colonography will be required in some cases to ensure complete visualisation of the colon.

8.1.4 Barium enema

Barium enema is indicated if there are problems with local access to colonoscopy, or when the endoscopist is unable to complete a colonoscopy,

The sensitivity of double contrast barium enema for colon cancer is 90%, with a range of 65–95%.[14-16] Barium enema is more likely to miss a Dukes A cancer (see Chapter 14) than colonoscopy.[14] In a review,[16] the best results of double contrast barium enema for detecting polyps smaller than 1 cm was 70–95%, compared with 90% for colonoscopy. The identification of such lesions necessitates a colonoscopy to remove them.

The rectum and rectosigmoid region are not well visualised on double contrast barium enema. These regions should be examined by sigmoidoscopy, 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.[29] If visualisation of the sigmoid colon is difficult because of severe diverticular disease, supplementary examination by flexible sigmoidoscopy or colonoscopy may be needed.[30] Colonic redundancy can also mask neoplastic lesions.

Reports of barium enema are often vague due to a technically inadequate examination. 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 three per 10,000 tests, with a death rate of three in 100,000 tests.[12]

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.[6,31] The American College of Radiology has outlined the quality issues associated with double contrast barium enema.[6] 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’.[7] 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.

8.1.5 CT colonography (virtual colonoscopy)

CT colonography (virtual colonoscopy) is probably the best test for patients with an incomplete colonoscopy or for those patients who cannot undergo colonoscopy.[32] It is inaccurate for lesions less than 1 cm in size. A good preparation is important for an adequate test. The sensitivity and specificity per patient of CT colonography for lesions 5 mm or greater is 67% and 75% respectively, and for lesions greater than 1 cm, is 90% and 82% respectively.

For radiological imaging of the large bowel, CT colonography caused significantly less discomfort than double-contrast barium enema and is rapidly replacing barium enema (refer to 5.1 and 5.2) as the method of choice for colonic imaging.[33]

Magnetic resonance colonography

Magnetic resonance (MR) colonography is an experimental procedure that is currently being investigated and evaluated.

There is an application before Medical Services Advisory Committee (MSAC) to evaluate CT Colonography. A report can be expected in the near future.

What are the investigations for symptoms of Colorectal Cancer?

Guideline — Investigations	Level of evidence	Practice recommendation	Refs
Investigation should include a digital rectal examination, a rigid sigmoidoscopy and a colonoscopy. A double contrast barium enema plus sigmoidoscopy or CT colonography may replace the colonoscopy if there are difficulties with local availability, expertise or an incomplete colonoscopy.	III-3	Equivocal	6, 9, 10, 13-16

8.2 Preoperative staging

8.2.1 Locoregional staging of colon cancer

Locoregional extent of the tumour is best evaluated during laparotomy and by histologic examination of the specimen, but in selected cases, preoperative CT scan will help identify involved contiguous structures.

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.[34] Magnetic resonance imaging (MRI) has no advantage over CT scan in locoregional staging of colon cancer.[35,36]

Colonoscopic ultrasonography uses an ultrasound transducer incorporated in the tip of the colonoscope.[37] It is unlikely to be of practical use because surgery for colon cancer is not stage-dependent.

A CT scan should be considered if there are clinical indications of a locally advanced cancer or of systemic metastases that might alter operative or other management strategies.

8.2.2 Locoregional staging of rectal cancer

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

Endorectal ultrasound

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 CT scan.[38–39] The overall accuracy for detecting lymph node metastases is about 80%.[40-42]

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,[43] and
- early (T1) rectal cancers that are being considered for local surgery, either by trans-anal local excision or by transanal endoscopic microsurgery (TEMS), rather than by abdominoperineal excision.[41]

The accuracy of endorectal ultrasound is strongly dependent on the expertise of the operator, who should be appropriately trained. Such training and expertise is available in some colorectal units.[44] The learning curve requires more than 50 rectal cancers before optimal accuracy is attained.[45]

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
uT3	Tumours penetrating into perirectal fat
uT4	Tumours penetrating into surrounding organs
uN0	No nodes involved on ultrasound
uN1	Nodes involved on ultrasound

CT scan

CT scan is rarely helpful in the early stages of primary rectal cancer.[46] 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).

Magnetic Resonance Imaging (MRI) for rectal cancers

MRI using a high-resolution phased array technique is the single most accurate tool to demonstrate preoperatively the involvement of mesorectal fascia and hence the likelihood of an involved circumferential resection margin.[47] The value of a preoperative phased array MRI in patient management is being evaluated in larger clinical trails.[48] It might serve as a promising tool to select preoperatively those rectal cancer patients with different risk of recurrence, so that they can be treated according to the risk.

MRI of rectal cancers is currently proposed as a technique for pre-operative staging of rectal cancers and as a technique for re-imaging cancers following pre-operative radiotherapy. Preoperative MRI scans appear most accurate in defining the circumferential margins of locally advanced tumors. This helps determine whether a clear resection margin can be attained. MRI scans are less accurate in defining T and N stages, especially for early tumours (ie. T1 and T2). MRI scans are less accurate in re-staging patients following radiotherapy as the technique can not clearly differentiate cancer from fibrosis.

A meta-analysis of available clinical trials comparing MRI with endoanal ultrasound (US) and CT scan found that US was most accurate in determining local invasion and perirectal tissue involvement. However, MRI and US were comparable in terms of adjacent organ invasion and lymph node involvement. Improving technology in both MRI, US and CT means that these conclusions may well change over the next five years.[49]

8.2.3 Staging for distant metastases

The purpose of staging is three-fold: (i) to assist in treatment decision making, (ii) to provide information on prognosis, and (iii) 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.[50] This may help determine prognosis,[51] although there is no evidence that it alters oncologic outcome.

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[52]
- identifying a few selected cases where synchronous liver resection may be performed with colorectal resection
- patients with high-risk rectal cancer (T3T4N1) where preoperative chemo-radiotherapy might be considered.

Chest x-ray

Chest x-ray has low sensitivity for pulmonary metastasis, which does not justify its routine use in preoperational staging.

Staging for intra-abdominal and liver metastases may involve one or more of a number of methods. These should be used selectively as they rarely alter the proposed management.

Transabdominal ultrasound

This is often capable of detecting liver metastases, but is not sufficiently sensitive (sensitivity 40–70%) to exclude them.[53,54] However, it is widely available, relatively cheap and may be used as an initial screening investigation if a CT scan is not readily accessible.

CT scan

Dynamic sequential contrast-enhanced CT scan is 70–80% sensitive in diagnosing intra-abdominal and liver metastases.[55] Helical (spiral) CT is more sensitive, particularly for small lesions.[56] Recent guidelines published by the Association of Coloproctology of Great Britain and Ireland have proposed that the ideal preoperative work-up for patients with Colorectal Cancer includes the use of CT.[57]

CT (or helical CT) during arterial portography (CTAP) is the most sensitive preoperative method of assessment, with a sensitivity rate of greater than 90%.[58] However, histological confirmation is not available in most studies.[59] CT is, however, 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.

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 distant metastases.[35] There is also no advantage in using both MRI and CT scan in the same patient as far as distant metastases are concerned.[35] However, pelvic MRI (see Section 8.2.2) provides superior anatomic information of the pelvis as compared to CT scan.[56]

Intraoperative ultrasound

When combined with surgical palpation of the liver, intraoperative ultrasound is the most sensitive examination for liver metastases. It changes the staging of the disease in 11% of the cases in which it is used. However, the surgical management is rarely altered.[60]

Intraoperative ultrasound does not detect liver metastases less than 5 mm in size, and there is a false negative rate of 15% of patients who later develop overt liver metastases.[60,61]

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.[62] If clinical or CT scan suggests urinary tract involvement, an intravenous urography may be indicated for further evaluation and for determining function in the other kidney.

Cystoscopy

In rare cases, a large sigmoid cancer might involve the bladder. 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

While high preoperative carcinoembryonic antigen (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.[63] (Refer 17.1.2)

Anorectal physiological testing

In elderly patients where there are concerns of possible faecal incontinence following a low colorectal anastomosis, anorectal physiological testing might be a useful adjunctive test, although it has never been demonstrated to predict functional outcomes.

8.2.5 Preoperative medical assessment

The issue of performing routine preoperative screening tests has yet to be clearly resolved. The preoperative assessment aims to (i) identify patient factors that may increase the risk of surgery, (ii) quantify the risk so that decisions can be made regarding a patient's suitability for major surgery, and (iii) to minimise this risk through appropriate strategies. The first step in risk assessment is to obtain an appropriate history and perform a physical examination.

8.2.6 Preoperative stomal therapy consultation

In Australia, one of the aims of intervention by a stomal therapy nurse is that whenever possible, the nurse sees all patients who potentially require a stoma as soon as a decision is made and again prior to their surgery[64] to mark the site of the stoma.[65] This has not been subject to randomised controlled trials, 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.[66] Stomal therapy nurses are a credible authority with the expert knowledge to help patients cope with and adapt to a stoma. They can do this by facilitating education, counselling and support, and by giving a sense of order to the whole process.[67]

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.

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.[65] 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.[67] This indicates that preoperative siting by the stomal therapy nurse is beneficial for improved outcomes of patients with stomas.[68,69] (See Chapter 10.)

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. [61-66]

Cancer information service and support groups provide invaluable resources for the patient and their family. Support is also available from each state and territory cancer information service through the Cancer Helpline 13 11 20.

8.3 Fluorodeoxyglucose-positron emission tomography (FDG-PET)

FDG-PET scan has an evolving role in the staging of Colorectal Cancer, especially in the follow up of patients after curative surgery. In patients with clinical suspicion or increased CEA, or if the CT scan is equivocal, FDG-PET assessment is the first choice of imaging. A meta-analysis showed that at equivalent specificity, FDG-PET is the most sensitive non-invasive imaging modality for the diagnosis of colorectal liver metastases compared with MRI, CT scan and ultrasound.[70] FDG-PET was also more accurate than CT scan and other conventional imaging in predicting resectability.[71] While FDG-PET scan has altered the management of recurrent Colorectal Cancer, its role in primary Colorectal Cancer is currently unclear.[72]

What role does FDG-PET scan have in assessing recurrent Colorectal Cancer?

Guideline — FGD-PET scan	Level of evidence	Practice recommendation	Refs
FDG-PET scan facilitates management of probable or proven recurrent Colorectal Cancer.	III-2	Recommend	10

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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 co-exist within individual patients, only 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,[2,3] the larger and better-controlled studies have not found them to be clinically useful in this regard.[4,5]

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.[6,7] Adenomas are typed according to histological architecture as tubular, tubulovillous and villous. They may be diminutive (1–4 mm in diameter), 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', which has aggressive connotations that are unwarranted.

Evidence for the precancerous nature of the adenoma is well documented in standard texts.[8]

- 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 in contiguity with adenoma.
- Epidemiology of adenoma matches adenocarcinoma.
- Genetic changes in adenomas fit with the evolutionary mechanism underlying carcinogenesis.[9]
- Removal of adenomas results in a reduced incidence of adenocarcinoma in non-randomised but controlled studies.[10]
- Adenomas in familial adenomatous polyposis (FAP) are identical to sporadic adenomas. FAP patients 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.[8] Adenomas that are more likely to harbour cancer are large and have a villous architecture and/or high grades of dysplasia.[7] Flat adenomas may possibly be more aggressive or give rise to more aggressive adenocarcinomas.[11–13]

The clinical context may also influence progression. For example, adenomas occurring in the context of hereditary non-polyposis Colorectal Cancer characteristically show an accelerated evolution.[14] Adenomas may be larger and more numerous in subjects without HNPCC or classical FAP but with a

strong family history of Colorectal Cancer.[15–17] Serrated polyps showing microsatellite instability may evolve more rapidly to cancer.[18]

Most adenomas appear to grow slowly. Small polyps may be observed endoscopically for several years before they are removed and diagnosed histologically.[19,20] Adenomas under 1 cm, and particularly those measuring 5 mm or less, may remain the same size for years or even regress.[19,21] 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 ten years and 24% at 20 years.[22] 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.[6,23,24] This approach should yield additional insight into the natural history of adenomas in the future, as well as obviating 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.[25] 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. Magnifying endoscopy is likely to become increasingly available and endoscopic diagnosis may reduce the requirement to remove minute polyps in patients with multiple lesions.

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.[26,27] Hot biopsy and electrocoagulation have been used to eradicate diminutive polyps, but may leave residual polyp tissue behind.[28–31] Cold snare polypectomy is an effective alternative,[32] it does not compromise histology but compromises recovery of tissue for histopathology. Cancer risk is related to number of adenomas, so the documentation of polyp type has prognostic value and surveillance implications.

Polyps should be removed. Sessile polyps may require piecemeal removal, but this will make histological evaluation difficult or impossible.[33] The area may be tattooed with sterile India ink to facilitate follow-up evaluation.[34] Tattooing will also identify the site for subsequent surgical resection.

9.3 Malignant polyps

This term applies to an adenoma containing a focus of malignancy. Management of malignant polyps by polypectomy alone is now standard practice and is generally acknowledged to be safe, providing a strict policy of case selection and histopathological assessment is adhered to.[35–38] 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.[39]

Attempts to identify factors indicative of lymph node spread, local recurrence and prognosis in patients treated by endoscopic (colonoscopic) polypectomy for a malignant polyp and then managed by either follow up alone or surgical resection have identified four key factors that are linked to a favourable outcome:

- a clear margin of excision
- well or moderate cancer differentiation
- absence of lymphatic or venous invasion
- endoscopic assessment of total removal.

Although the usefulness of lymphatic invasion[37] and venous invasion[36,37,40] has been questioned, and is a rare finding in the absence of other unfavourable features, it is advisable that vessel invasion continue to be regarded as an adverse marker.[36,41–43]

While polyp size, extent of replacement by cancer and a sessile base are factors that may impede complete local excision and definitive histopathological assessment, it is the fact of demonstrable complete or incomplete excision that serves as an independent predictor of outcome.[36,37] . The pathologist is required to examine multiple-step sections through the polyp base to make this determination. If this is done with care, the majority of cases can be classified as either completely or incompletely excised. A specific clearance margin of 1 mm[36] or 2 mm[37] 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 whether this was within the polyp base or a lymph node.[37] Pathologists are generally comfortable with reporting a surgical margin as either clear or not clear.

Malignant polyps with unfavourable features may require further treatment, but this decision should be made 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. For colonic polyps, excision can be achieved successfully by laparotomy with colonic resection or laparoscopically assisted colectomy.[44] (See also Chapter 11.)

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.

Close endoscopic follow up should follow piecemeal removal or excision of a large adenoma or a malignant polyp that may have been incompletely removed.

In a British study, 1618 patients were treated for rectosigmoid adenomas using rigid-instrument sigmoidoscopy. The long-term risk of developing Colorectal Cancer was assessed in retrospect. The incidence of rectal cancer was similar to that of the general population. Most rectal cancers occurred in subjects with incompletely excised adenomas. The risk of colon cancer depended on the type, size and numbers of rectosigmoid adenomas removed initially. An increased standardised incidence ratio of 3.6 was observed in subjects with large adenomas (>1 cm) or adenomas with a villous component. The ratio was increased to 6.6 if, in addition, subjects had multiple adenomas. In the remaining subjects with small excised tubular adenomas, the risk of cancer was not increased, even in subjects with multiple adenomas (standardised incidence ratio = 0.5).[45] This study suggests that a sizeable subset of patients with small (<1 cm) tubular adenomas that have been removed from the rectosigmoid region is not at increased risk of developing significant colorectal neoplasia in the future. However, it was not a prospective study and 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 neoplasia include adenoma size, presence of villous change and multiplicity.[46] 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:

with three or more adenomas at initial colonoscopy, or

- who are 60 or over and have a parent with Colorectal Cancer.

A screening interval of 4–6 years is recommended for this low-risk group and three years for the two high-risk groups. High-risk subjects should also include those with ≥1 cm adenomas and adenomas with high-grade dysplasia or villous change. 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. The two high-risk groups accounted for 69% of significant adenomas and 27% of the subjects in the study.[47]

In summary, a three-yearly follow-up period is safe, provided colonoscopy is complete, the endoscopist has removed all polyps seen and is confident of adequate visualisation. It may be extended further for subjects lacking high-risk features.[26–28,45–48]

What is the management of epithelial polyps?

Guidelines — Management of epithelial polyps	Level of evidence	Practice recommendation	Refs
All polyps should be at least sampled, and preferably removed. Synchronous polyps should be sought and removed.	III-2	Recommend	25–34

What is the general management of all patients with colorectal neoplasia completely removed at colonoscopy?

Guidelines — Management of epithelial polyps	Level of evidence	Practice recommendation	Refs
All patients with colorectal neoplasia completely removed at colonoscopy should then be considered for colonoscopic surveillance according to the following protocols:			45–48
• within a year following incomplete or possible inadequate examination, for example in a subject with multiple adenomas	II	Recommend	
• at three years 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 neoplasia	II	Recommend	
• at four to six years in subjects without the risk factors outlined above.	III-3	Equivocal	

What is the management of malignant adenomas?

Guidelines — Management of malignant polyps	Level of evidence	Practice recommendation	Refs
Malignant adenomas may be managed safely by endoscopic polypectomy provided 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.	III-2	Recommend	35–43

9.4.2 Other polyposis conditions

A situation in which the hyperplastic polyp may be a marker for cancer risk is one involving subjects with hyperplastic polyposis.[49] In this condition, hyperplastic polyps are large, often exceeding the usual limit of 5 mm, and 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.[50] There is evidence linking hyperplastic polyps, mixed polyps and serrated adenoma (serrated polyps) with a subset of sporadic Colorectal Cancer showing high-level DNA microsatellite instability (MSI-H).[51–54] Sporadic MSI-H cancers are age-related, occur more frequently in females, are mainly located in the proximal colon, and account for about 10% of Colorectal Cancer and some are associated with multiple hyperplastic and/or serrated adenomatous polyps.[55]

Although solitary juvenile polyps are not precancerous, juvenile polyposis, a rare condition that may occur as an autosomal dominant trait, is associated with an increased risk of malignancy.[56] Malignancy in the Peutz-Jeghers syndrome is usually extracolonic, but there is a small increased risk of Colorectal Cancer.[53]

9.5 Hyperplastic polyps and polyposis

Hyperplastic polyps are usually small, innocuous lesions limited to the distal colon and rectum. However, there are 11 reports of Colorectal Cancer arising in sporadic hyperplastic polyps. These polyps have been large and mainly right-sided.[57] It is likely that most of these large hyperplastic polyps are identical to the recently documented entity described as 'sessile serrated adenoma'.[58–60] These variant hyperplastic polyps are over-represented in the condition hyperplastic polyposis.[50] Patients with multiple hyperplastic polyps and/or large hyperplastic polyps and/or hyperplastic polyps of the proximal colon are at increased risk of cancer.[50,61–63] The risk may be further increased if there are co-existing adenomatous lesions that may be traditional adenomas, admixed polyps or serrated adenomas, or if there is a family history of Colorectal Cancer.[64,65] A particular association has been demonstrated between hyperplastic polyps and cancers with microsatellite instability.[51,52,54,66,67] The term 'hyperplastic polyposis' has been applied to two phenotypes: (i) presence of at least 20–30 hyperplastic polyps proximal to the rectosigmoid junction, (ii) at least five hyperplastic polyps proximal to the splenic flexure, of which two are larger than 1 cm.[68,69] However, patients with other combinations of features may also be at increased risk.[70]

Genetic studies are beginning to delineate heterogeneity among hyperplastic polyps.[18,69] DNA methylation, leading to gene silencing, is more frequent when there are large hyperplastic polyps, hyperplastic polyps of the proximal colon and co-existing serrated adenomas.[71,72] When one polyp is found to show DNA methylation, the same usually applies to all (implying a generalised or field defect).[71] K-ras mutation or loss of chromosome 1p is more common in sporadic hyperplastic polyps and in patients with hyperplastic polyposis in which polyps are left-sided, small and there are no associated serrated adenomas.[69,71] Large, right-sided hyperplastic polyps are more likely to have

BRAF mutation, particularly when multiple or having the morphological features of sessile serrated adenoma.[73] BRAF mutation also occurs in traditional serrated adenomas.[74]

It is recommended that patients with hyperplastic polyposis be offered annual colonoscopy. This should also be considered for patients in whom neither of the strict definitions for the diagnosis of hyperplastic polyposis is met in full, but other risk features are present (one coexisting adenomatous lesion or a first-degree relative with hyperplastic polyposis or Colorectal Cancer). Colectomy should be considered when it is not possible to achieve control of polyps endoscopically. There is increasing evidence that sporadic hyperplastic polyps have malignant potential, particularly when they are large, proximally located, and have the morphological appearances associated with sessile serrated adenoma.[58–60,75,76]

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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. Haematological and clinical chemistry investigations should be performed. Other preoperative anaesthetic investigations may be appropriate. In particular, stress cardiopulmonary testing should be considered where any doubts exist about cardiac status.

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 in this situation
- have advanced disease. However palliative surgery or neoadjuvant therapy may be indicated.

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 (see Section 4.3).

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 before giving informed consent. Sometimes, more than one consultation is necessary and this should be made available to the patient when the patient or family desire it.

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 whenever possible 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

What is the role of the stomal therapist?

Guideline — Postoperative stoma	Level of evidence	Practice recommendation	Refs
All patients who have a reasonable chance of a postoperative stoma should be prepared for this possibility. This includes a visit, where possible, by the stomal therapy nurse.	III-2	Recommend	1

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

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, especially in the elderly.

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.

An Australian randomised clinical trial demonstrated that sodium phosphate solution cleanses the colon more effectively than sodium picosulphate.[3,4] Oliveira et al[5] randomly assigned 200 patients having colorectal surgery to either polyethylene glycol or sodium phosphate bowel preparation. There was no significant difference in cleansing, or septic complication rates, however patients who had sodium phosphate reported significantly less trouble drinking the solution and less abdominal fullness and cramping. Due to electrolyte and fluid changes, the use of sodium phosphate is not recommended in the elderly, or in those patients with significant renal, cardiac or hepatic disease.[6]

Uncontrolled prospective trials and retrospective studies looking at the value of mechanical bowel preparation have produced conflicting results. There have been four published randomised studies that have randomly assigned patients to mechanical preparation or no mechanical preparation.[7–10] Most recently, Miettinen et al[10] reported on 267 patients, the largest study to date. There was no significant difference in the anastomotic leak rate (4% vs 2%), surgical site infection rate (6% vs 5%) or restoration of bowel function, between the group that had bowel preparation with polyethylene glycol and the group that had no preparation.

However, a Cochrane Collaboration systematic review of 1159 patients in six randomised controlled trials (RCT) has now been published.[11] The conclusion was that prophylactic mechanical bowel preparation before colorectal surgery has not proven of value to patients. The available evidence fails to demonstrate a reduction in anastomotic leak rates and other complications. Interestingly, more anastomotic leaks were discovered in the patients having bowel preparation who had undergone colonic surgery. However, for a number of reasons, including shortcomings in the RCTs and statistical evaluation issues, no statistical validity could be applied to the question of anastomotic leak. This finding was not seen after rectal surgery. Further well-planned RCTs to address the questions were recommended.

Should bowel preparation be given routinely preoperatively?

Guidelines — Bowel preparation	Level of evidence	Practice recommendation	Refs
Bowel preparation is current standard practice before elective colorectal operations. However, recent randomised controlled trials have not demonstrated any conclusive benefit from this procedure. Accordingly, the previous guideline has been revised as follows: Mechanical bowel preparation is not indicated in elective colorectal operations unless there are anticipated problems with faecal loading that might create technical difficulties with the procedure. Eg. Laparoscopic surgery, low rectal cancers.	I	**Not** recommend	11

10.4 Cross matching and blood transfusion

About 50% of patients undergoing surgery for Colorectal Cancer are given a blood transfusion over the perioperative period.[12–14] The requirement for transfusion 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 ten 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 randomised studies have demonstrated a definitively increased risk of infection following blood transfusion during Colorectal Cancer surgery.[15–19] The use of autologous blood has been demonstrated to cause fewer postoperative infections than transfusion of homologous blood.[19] According to the patient's wishes and the likelihood of a transfusion, autologous blood collection should be considered.

It is unclear whether 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.[15,20–26]

Many patients with Colorectal Cancer are anaemic prior to surgery and autologous blood transfusion is not practical. Retrospective studies of blood transfusion in Colorectal Cancer surgery are complicated by multiple confounding factors and should be interpreted with caution. Patients who are anaemic prior to surgery are more likely to require transfusion, and are more likely to have larger tumours, which can result in technical difficulties. These factors are all stage independent and therefore difficult to control. Immunosuppression is a separate issue that indicates transfusion should be avoided where possible.

A recent meta-analysis of 32 studies (nine prospective) assessed the effect of perioperative blood transfusions on recurrence of Colorectal Cancer. It found a consistently detrimental association between the use of perioperative blood transfusion and recurrence of Colorectal Cancer. The recurrence rate was 38% in the transfused group compared with 26% in the non-transfused group. This yielded an overall odds ratio of 1.68 (95% CI, 1.54–1.83) and a rate difference of 0.13 (95% CI, 0.09–0.17) against patients who received a blood transfusion. Stratified meta-analyses also confirmed these findings when stratifying patients by site and stage of disease.[27]

What happens if a blood transfusion is required perioperatively?

Guideline — Perioperative	Level of evidence	Practice recommendation	Refs
Perioperative blood transfusion is to be avoided whenever possible because there may be a detrimental association between transfusion and recurrence. If a transfusion is required, autologous blood is preferable to allogeneic blood for reasons of infection control and resource use.	III-2	Recommend	27

10.5 Thromboembolism prophylaxis

Cancer has been shown to be an independent risk factor for the development of thromboembolism.[28] In addition, patients undergoing a colorectal resection are at higher than average risk for developing a postoperative deep venous thrombosis (DVT) because these procedures tend to be of long duration, the patients are often in stirrups, and a pelvic dissection is commonly performed. A meta-analysis of appropriate trials in general surgical patients has demonstrated that prophylactic use of subcutaneous unfractionated heparin reduces the risk of DVT, pulmonary embolus and death.[29]

A randomised double-blind trial comparing subcutaneous unfractionated heparin (5000 units calcium heparin every 8 hours and low molecular weight heparin (enoxaparin 40 mg once daily) as thromboprophylaxis in 936 patients undergoing colorectal surgery found low-dose calcium heparin and low molecular weight heparin to be equally effective in preventing thromboembolism in colorectal surgery patients. There were no deaths from pulmonary embolus in either group. The enoxaparin group had a significantly greater bleeding rate compared with the low-dose heparin group, although the risk of major bleeding and re-operation was not significantly different.[30]

A meta-analysis of general surgical patients having intermittent calf compression intraoperatively demonstrates effectiveness in reducing the incidence of DVT in the presence of malignant disease.[31]

Australasian Best Practice Guidelines suggest unfractionated heparin or low molecular weight heparin and graduated compression stockings or intermittent pneumatic compression for high-risk surgical patients, which includes any patient over 40 years of age who is undergoing major abdominal surgery with cancer. [32]

Should thromboembolic prophylaxis be given?

Guideline — Thromboembolic prophylaxis	Level of evidence	Practice recommendation	Refs
All patients undergoing surgery for Colorectal Cancer should receive prophylaxis for thromboembolic disease.	I	Strongly recommend	29
Unfractionated heparin, low molecular weight heparin, and intermittent calf compression are effective in reducing the incidence of thromboembolism.	II	Strongly recommend	32
Low molecular weight heparin has not been shown to be superior to low-dose heparin in colorectal surgical patients.	II	Strongly recommend	30

10.6 Antibiotic prophylaxis

Prophylactic administration of antibiotics decreases morbidity, shortens hospital stay and reduces infection-related costs.[33] The broad results were derived from 26 trials of patients given various antibodies against controls given none. The authors suggest that the effect of antibiotics was shown so clearly that all further trials should employ a proven standard control, not no treatment. Many different antibiotic regimes have been shown to be effective, but in patients undergoing colorectal surgery, the antibiotics used should be broad spectrum**,** have an effective half-life and be active against both aerobic and anaerobic bacteria.

Song, in a recent systematic review and meta-analysis of randomised trials of antimicrobial prophylaxis in colorectal surgery, found no significant difference in postoperative wound infection rates in 17 trials that compared a single dose to a multiple-dose regimen.[34] Reducing the dosage of antibiotics reduces cost, the potential risks of toxicity and adverse side effects, and the risk of developing bacterial resistance.

Frequently-used agents such as cefuroxime and metronidazole, or gentamicin and metronidazole, have been shown in a multicentre prospective randomised trial to be adequate compared to other agents.[35]

Most surgeons would now appear to favour the use of perioperative parenteral antibiotics over the oral route in view of same-day admissions and compliance issues.

Should prophylactic antibiotics be given?

Guidelines — Prophylactic antibiotics	Level of evidence	Practice recommendation	Refs
All patients undergoing Colorectal Cancer surgery require prophylactic antibiotics.	II	Recommend	33
A single preoperative dose of intravenous cephalosporin and metronidazole, or gentamicin and metronidazole, is an effective regime.	I	Strongly recommend	34

10.7 Body temperature

A randomised trial comparing perioperative normothermia to perioperative hypothermia has demonstrated a significant reduction in the rate of wound infection and length of hospital stay with maintenance of normal levels of temperature.[36]

Normal levels of temperature are best achieved by using heated air blankets and fluid warming.

Should normal body temperature be maintained?

Guidelines — Maintenance of normothermia	Level of evidence	Practice recommendation	Refs
Perioperative normothermia should be maintained.	II	Recommend	36

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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 prime question to be answered needs to be directed at the surgical pathology and technical aspects of management. The appropriate surgeon to undertake the surgery is addressed in Section 12.1.

11.2 High ligation

The technique of colonic cancer resection has been debated widely throughout the 20th and now the 21st century . Features emphasised include high ligation of the lymphovascular pedicle before manipulating the tumour,[1] wide excision,[2,3] and early isolation of the lymphovascular pedicle with minimal manipulation.[1,2] In a review of the literature, Sugarbaker and Corless[4] concluded that high ligation of the mesenteric pedicle did not produce substantial improvement in survival. (See also Section 12.6.)

Does high ligation provide any benefit?

Guideline — High ligation	Level of evidence	Practice recommendation	Refs
High ligation of the lymphovascular pedicle does not confer any oncological benefit. Resection where feasible should extend to the origin of segmental vessels.	III-3	Equivocal	4

11.3 No-touch isolation technique

Wiggers et al[5] 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. Garcia-Olmo et al[6] reported a study using reverse transcriptase polymerase chain reaction assessment of blood from the main drainage vein of the tumour and peripheral blood. This research failed to demonstrate that tumour cells were shed into the circulation during standard tumour mobilisation and could not support the use of the no-touch isolation technique.

Does no-touch isolation technique have any benefit?

Guideline — No-touch isolation technique	Level of evidence	Practice recommendation	Refs
The no-touch isolation technique has no oncological benefit.	II	Recommend	5

11.4 Segmental versus extended resection

There are very few prospective randomised trials comparing limited segmental resection versus more extensive resection. The French Association for Surgical Research[7] published a prospective randomised controlled trial comparing median and actuarial survival in 270 consecutive patients after left hemicolectomy or left segmental colectomy for cancers located between the distal third of the transverse colon and (but not including) the rectal sigmoid junction. Complications and operative

mortality were not significantly different. Patients were followed up for approximately ten years. Actuarial survival curves for all patients and for Dukes C patients were similar.

Is segmental and extended resection equivalent in outcome?

Guideline — Segmental and extended resection	Level of evidence	Practice recommendation	Refs
Segmental resection is equivalent to extended resection in outcome.	II	Equivocal	7

11.5 Sutured and stapled anastomosis

Ileocolic, colocolic or colorectal reanastomosis after resection can be achieved by a hand-sewn suture technique or with metal staples. In a meta-analysis, MacRae and McLeod[8] reported a higher rate of anastomotic stricture with a stapled anastomosis, but mortality rate, anastomotic leak rates and locoregional cancer recurrence rates are equivalent between the two techniques. They conclude that both techniques are effective and the choice may be based on surgeon preference.

A recent Cochrane review of stapled versus hand-sewn anastomosis revealed that in a pooled analysis of the results of the 1233 patients studied (9 trials, 622 stapled anastomoses and 611 hand sewn), there was no evidence of superiority of stapled over hand-sewn colorectal anastomes, regardless of anastomotic level.[9]

Do sutured and stapled anastomosis have equivalent outcomes?

Guideline — Sutured and stapled anastomosis	Level of evidence	Practice recommendation	Refs
Sutured and stapled anastomosis have equivalent outcomes.	I	Strongly recommend	8, 9

11.6 Omental wrapping of anastomosis

Wrapping the anastomosis with omentum has long been reported as lowering the leak rate from colorectal anastomoses.[10,11] In a review of the literature, O'Leary[12] found no evidence to support this theory. This technique cannot be supported by available evidence.

Does omental wrapping of intestinal anastomoses have any benefit?

Guideline — Omental wrapping	Level of evidence	Practice recommendation	Refs
Omental wrapping of anastomosis has no benefit.	III-2	Strongly **not** recommend	12

11.7 Synchronous colonic cancer

The reported incidence of synchronous carcinoma of the colon varies from 2% to 9%.[13,14] 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 anatomical 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 Freeark[15] 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 careful lifelong surveillance of the large intestine.

11.8 Fixed tumours with contiguous organ attachment

Adherence of tumours to nearby structures occurs in about 10% of patients with Colorectal Cancer.[16] Up to 43% of such attachments are inflammatory, and 40% of patients who have tumours adherent to other organs are subsequently proven to have a Dukes B lesion, 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 al[17] and Gall et al[18] 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. Tumour attachment to the abdominal wall mandates wide incontinuity excision of both tumour and abdominal wall.

11.9 Synchronous resection of liver metastases

Between 10% and 20% of patients having resection of primary Colorectal Cancer will have liver metastases evident (see also Section 21.1.1). 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.[19] A small proportion of patients have hepatic metastases that are potentially curable by wedge resection at the time of the primary operation.[20] Synchronous resection of liver metastases could be considered at time of primary bowel operation.

Basic requirements[21] for safe simultaneous resection of a hepatic metastasis at the time of large bowel resection are as follows:

- a solitary liver metastases lesion that 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
- availability of surgical expertise for hepatic resection.

Lyass et al[22] reported a prospective study showing that combined colonic and hepatic resection is comparable to staged resection in terms of postoperative morbidity and mortality, length of stay and survival. It is likely that suitable cases will, however, remain the exception rather than the rule.

11.10 Ovarian metastases

The incidence of synchronous metastatic ovarian disease is between 2% and 8%. Blamey et al[23] have reported that 1.4% of female patients required re-operation for ovarian recurrence after colonic cancer resection. Morrow and Enker[24] have recommended bilateral oophorectomy if only one ovary is involved, because of the risk of bilateral ovarian metastatic disease.

Sielezneff et al,[25] in a nonrandomised study, were not able to demonstrate an improvement in local recurrence or liver metastasis rates of survival with bilateral prophylactic oophorectomy, although

microscopic metastases were found in one patient. In a prospective randomised trial[26] 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.

In gynaecological oncology women with a past history of Colorectal Cancer who present with an ovarian mass are most infrequently encountered. The pathology in these patients can be problematic and the opinion of a pathologist who is expert in this area should be sought. Morphologic changes such as garlanding, dirty necrosis etc can be augmented by the use of immunohistochemical stains from cytokeratin 7 and 20.[27]

When should oophorectomy be performed in association with colectomy for colon cancer?

Guideline — Oophorectomy in surgery for colon cancer	Level of evidence	Practice recommendation	Refs
Bilateral oophorectomy should be performed if there is obvious malignant disease of one or both ovaries.	III-3	Recommend	23, 24
Prophylactic bilateral oophorectomy for colon cancer cannot be supported by the available evidence.	II	Strongly **not** recommend	26

11.11 Laparoscopic surgery for colonic cancer

Laparoscopic colectomy, in experienced hands, is a safe and feasible alternative to open resection for benign disease. In all studies,[28-30] laparoscopic techniques might not be possible in some patients, requiring conversion to open surgery. In a recent randomised trial[31] assessing short-term quality of life (QoL) outcomes, laparoscopic colorectal surgery did not seem to confer any advantage.

Concerns regarding the oncological safety of laparoscopic colectomy for cancer can only be answered by large, well-designed randomised trials. Multicentre trials from the United States[32,33] reported equivalent analytic outcome between laparoscopic and conventional colonic resection. A random controlled trial (RCT) from Hong Kong assessed laparoscopic resection of rectosigmoid carcinoma in 403 patients.[34] Several multicentre trials are now in progress in Europe,[35] and Australasia (Australasian multicentre prospective clinical study, comparing laparoscopic and conventional open surgical treatment of colon cancer in adults [ALCCaS]).

A search for relevant articles published to the end of 2002 found a recent meta-analysis assessing short-term outcomes after laparoscopic resection for Colorectal Cancer. The analysis involved the outcomes of 2512 patients in twelve trials. Colorectal Cancer was found to be 'associated with lesser morbidity, less pain, a faster recovery and shorter hospital stay, without compromising oncological clearance'.[36]

Is laparoscopic colonic surgery as effective as the conventional approach?

Guideline — Laparoscopic surgery	Level of evidence	Practice recommendation	Refs
In experienced hands, laparoscopic surgery for colon cancer has equivalent outcome to conventional surgery.	I	Recommend	36

11.12 Self-expanding metal stents for obstructing cancer

Patients presenting with malignant large bowel obstruction require emergency management that usually involves resection without anastomosis or resection, on-table colonic lavage and primary anastomosis. There have been several reports[37-40] of the use of self-expanding metal stents to relieve the colonic obstruction, thereby allowing bowel preparation and subsequent elective resection. A major indication is the palliative treatment of malignant large bowel obstruction in the presence of widespread tumour dissemination or in a patient with significant co-morbidity.[41] The stents can be deployed under fluoroscopic control,[39,40] colonoscopic control,[37] or a combination of the two techniques.[38] A success rate of 80–100% has been reported. The colonic perforation rate of 0–16% is expected to lessen with greater experience and more flexible stents. Stent migration (10%) and occlusion (10%) are other complications. Pain, and less commonly, haemorrhage, might also occur. The technical failure of stent deployment was reported in 8–10%,[42] mainly from access failure, and less commonly from malposition and perforation.

The risk of tumour dissemination caused by stent deployment in an otherwise potentially curative situation has not been adequately assessed and long-term recurrence and survival analysis is required. At present, the use of self-expanding metal stents in curative cases cannot be supported except in prospective trials with ongoing evaluation. (See also Section 13.4.4.)

11.13 Extended colonic resection

Currently, the extent of colonoscopic surgery is based on lymphovascular drainage. Extended resections may be appropriate for proven HPNCC and may be appropriate for cases strongly suspicious of HPNCC where a mutation is yet to be identified.[43] Research will continue into mutational abnormalities in sporadic cancer and may affect standard resection in the future.

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CHAPTER 12 ELECTIVE SURGERY FOR RECTAL CANCER

Rectal cancer surgery has the potential for worse clinical outcomes than surgery for colon cancer. Quality of life, local recurrence and survival are generally worse after rectal cancer surgery. There has been much continuing debate 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 that 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 therapy nurse, and medical and radiation oncologist.

It could be expected that such results would best be achieved only at specialist multidisciplinary centres. A recent editorial concludes there is 'remarkably consistent evidence that the more experienced doctors or health care systems have with the procedure, the better the results'. In regard to cancer, the authors claim that this provides 'striking examples of markedly better outcomes with higher volume' with 123 of 128 published studies showing evidence of a 'volume–quality' relationship.[1]

The relationship of hospital volume to colostomy rate and survival of patients with rectal cancer has recently been assessed in a paper reporting on 7257 Californian patients with rectal cancer treated between 1994 and 1997.[2] Adjusted risk to odds ratios with 95% confidence intervals were as follows:

- permanent stoma = 1.37 (1.10–1.70)
- 30-day mortality = 2.64 (1.41–4.93)
- two-year mortality = 1.28 (1.15–1.44)

All of the odds ratios were greater for low-volume hospitals.

There are at least 22 studies of Colorectal Cancer patients correlating outcome and volume (hospital/surgeon or both) since 1984 that showed clear difference in quality of life indicators such as permanent stoma rates between low-volume and high-volume surgeons.[2]

A further recent study by Schrag et al[3] examined outcomes in 2815 patients with rectal cancer between 1992 and 1996. Survival advantages for high-volume surgeons were statistically significant when adjusted for casemix and for casemix and hospital volume. Relative risk of overall mortality was significantly lower for unadjusted surgeon volume, casemix adjusted surgeon volume, and hospital-volume adjusted surgeon volume. [3]

Most recently, Wibe et al[4] published a before-and-after picture from Norway. Between 1986 and 1988, a 28% local recurrence rate was observed, with a 55% 5-year overall survival rate for patients less than 75 years old with rectal cancer. The Norwegian Rectal Cancer Group was founded in 1994. Surgeons were trained in total mesorectal excision (TME)(). Pathologists were trained in reporting. A rectal cancer registry was established. The Norwegian Surgical Society declared that 'rectal cancer surgery to be done only by specialised surgeons'. Twelve hospitals ceased the performance of rectal cancer surgery. Following these changes, outcomes were measured in 5,382 rectal cancer patients

between 1993 and 1999. The local recurrence rate had dropped to 8% and the five-year overall survival rate for patients less than 75 years of age had increased to 71%.[4]

An Australian study also provides support for specific practice leading to an increase in patient overall survival. Platell (2002) concludes improvement in survival of patients presenting with CRC and also improved survival times for patients who presented with nodal metastasis to a community based teaching hospital.

The question of whether the colorectal-trained surgeon achieves better results than the experienced general surgeon remains contentious. A study by Porter and co-workers[5] 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 fewer than three patients with rectal cancer per year.

In Penninckx's review and audit of surgeon-related variability in the outcome after radical resection for rectal cancer, there was a relative risk of 0.3–0.8 for local recurrence if performed by a subspecialist surgeon, when compared with general surgeons. The relative risk for disease-free survival (0.7–0.8) was also less for subspecialised surgeons.[6]

These various studies, confirmed by the National Colorectal Cancer Care Survey in Australia,[7] support two significant observations:

- there are major variations in outcomes between different individuals and different groups
- there appears to be a correlation between clinical experience in the treatment of rectal cancer and outcome.

Who should perform elective rectal cancer surgery?

Guidelines — Elective surgery	Level of evidence	Practice recommendation	Refs
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 maintained satisfactory experience in the surgical management of rectal cancer.	III-2	Recommend	1–7

12.2 The role of local excision and transanal endoscopic excision of rectal cancer (TEM)

Local treatment of rectal cancer can be curative only if there is no spread to regional lymph nodes.[8] The incidence of nodal metastases is associated with depth of tumour invasion, tumour differentiation, and lymphatic or venous invasion.[9–11] Tumour size is not a strong predictor.[9,10]

Well- and moderately-differentiated tumours confined to the submucosa (T1) metastasise to lymph nodes in only 3–5% of patients.[9,10] The preoperative identification of patients with nodal metastases is difficult, as up to two thirds of nodal metastases are micrometastases.[12]

Endorectal 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.[13–14] Magnetic resonance

imaging (MRI) with external phase arrayed coils is presently more costly and generally less available than endorectal ultrasound. However, its accuracy and sensitivity may eventually prove to be greater than that achieved by most surgeons using endorectal ultrasound, especially in predicting stage T1/ T2 as well as nodal status.[15]

Unfortunately, preoperative assessment of histological grade based on random biopsy is unreliable, underestimating the degree of anaplasia in 18% of patients when compared with operative specimens.[16]

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 of follow up. Half of the patients with local recurrence were salvaged by additional resectional surgery.[11,17–22] A recent overview has cautioned that local excision should probably be restricted to T1 cancer with favourable pathology.

A prospective randomised study published in 1997 has provided evidence (level II) in support of local excision of T1 rectal cancer.[23]

Pathological features associated with reduced survival were positive surgical margins, moderately- and poorly-differentiated histopathology, and increasing depth of invasion (T2 and T3).[8] Local excision is associated with a complication rate of between 5% and 18% and a mortality of 1%.[8]

Banerjee[20] has recently championed the use of transanal endoscopic microsurgery in the management of early rectal cancers. 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. In a published series, in 74 patients who have undergone local excision for rectal cancer there have been only two recurrences, with a mean follow up of 14 months.[20]

There is as yet insufficient evidence to accept or reject transanal endoscopic microsurgery in the management of rectal cancer. This form of surgery is limited to lesions at or beyond the level of insertion of the instrument (<5cm). Referral to skilled centres would seem appropriate.

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%.[21] 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).

Local excisions may also afford reasonable palliation in patients with metastatic disease.

Adjuvant radiotherapy has also been used in patients after local excision, with improved 5-vear actuarial local control (90% vs. 72% local excision alone) and recurrence-free survival rates (74% vs 66%). This was in a study of 99 patients with rectal cancer treated by local excision, with adjuvant therapy given for T2 tumours and T1 tumours with high-risk pathological factors.[24]

There is also some evidence that endorectal radiotherapy can be used as definitive treatment or as an adjunct to local excision.[23]

When should local excision of rectal cancer be performed?

Guidelines — Local excision of rectal cancer	Level of evidence	Practice recommendation	Refs
Local excision of T1 rectal cancer may be used in selected cancer patients according to the following guidelines: • mobile tumour ≤3 cm • T1 on endorectal ultrasound • not poorly differentiated on histology (biopsy)	III-3	Equivocal	8–12, 16–21

12.3 The role of abdominoperineal versus sphincter-saving anterior resection

Numerous studies have shown similar outcomes for sphincter-saving resection and abdominoperineal resection (APR) with curative intent in terms of survival and local recurrence, and that reconstructive surgery has not compromised oncological outcome.[22,25,26] The size of the tumour has often been considered an indication for abdominperineal resection, but the United States National Surgical Adjuvant Breast and Bowel Project (NSABP) has not shown an adverse outcome even for tumours greater than 6 cm treated by sphincter-saving resection.[25]

The margin of distal clearance has been revised from the historical 5 cm to 2 cm, based on reviews comparing local recurrence rates and survival that show no advantage in outcome beyond a margin of 2 cm.[27, 28]

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 effect of fixation is minimal if the specimen is pinned out first.[29]

Well-designed quasi-experimental studies reveal that 81–95% of all carcinomas have either no spread or intramural extension of less than 1 cm.[29–33] 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.[10,29, 30, 31, 32, 33, 34] Therefore, in the majority, a distal margin of 2 cm would remove all microscopic disease.

A number of retrospective and prospective studies have since tried to relate length of distal margin to recurrent cancer. Essentially, all of these studies have shown no difference in local recurrence or survival when comparing 1–2 cm distal margins with greater than 5 cm distal margins.[26, 31, 33]

Hojo[33] 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 Beahrs[34] 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 Nicholls[26] 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 al[35] 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 al[36] looked prospectively 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, Heald[37] 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).

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 use of preoperative radiotherapy may also alter the decision between APR and sphincter preservation. In a prospective study of 35 patients who clinically required APR prior to radiotherapy, 27 (77%) were able to successfully undergo an ultra-low anterior resection with coloanal anastomosis. The five-year local recurrence rate was 21%, with good or excellent function in 23 of the 27 patients (85%).[38]

Function and continence are the other main considerations when deciding between APR and restorative ultra-low anterior resection.

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 APR, 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 APR.[39] Other studies have also suggested that functional results are satisfactory after low anterior resection,[40] although a reduction in rectal sensation related to loss in reservoir capacity probably contributes to incontinence.[41] However, rectal function improves with time in most cases, and with colonic pouch reconstruction (see Section 12.6).

The incidence of sexual dysfunction after low and very low anterior resection is comparable to APR (58% compared to 66%).[42]

What is an adequate distal clearance of resection?

Guideline — Adequate clearance of resection	Level of evidence	Practice recommendation	Refs
A distal distance of 2 cm (fresh) is recommended in most instances, or 1 cm fixed.	III-2	Recommend	30–35

What factors influence sphincter preservation?

Guideline — Factors influencing sphincter preservation	Level of evidence	Practice recommendation	Refs
Sphincter-saving operations are preferred to abdominoperineal resection except in the presence of: • tumours such that adequate distal clearance (>2 cm) cannot be achieved • the sphincter mechanism is not adequate for continence • access to the pelvis makes restoration technically impossible (rare).	III-3	Equivocal	10,22, 25–30

12.4 Total mesorectal excision

Equally as important as the distal margin for rectal cancer, with respect to local recurrence and disease-free survival (DFS), is the mesorectum and the circumferential (lateral) margin.

In 1982, Heald et al[43] 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.

Total mesorectal excision (TME) for rectal cancer refers to a sharp dissection in the extrafascial plane (between the fascia propria of the rectum and the presacral fascia), with complete excision of the mesorectum to the pelvic floor as well as its lateral borders.

Using this technique for all mid and low rectal tumours, Heald and Ryall[44] reported local recurrence rates of 2.6% for anterior resection. However, these figures were after excluding patients not thought to have a curative resection.

Two prospective clinicopathological studies have also looked at distal mesorectal spread. Scott et al[45] studied 20 patients where total mesorectal excision was performed, and found 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 al[46] 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.

However, others have also reported very low local recurrence rates (6.5–7.3%) even when TME was not always performed.[26, 47–49]

In Killingback's series of 340 patients treated by sphincter-saving resections, including patients in whom the lateral margin was possibly involved, he reported a local recurrence of only 6.6%. Total mesorectal excision was only used for low rectal cancers. For mid-rectal lesions, the mesorectum was divided at least 5 cm distal to the tumour.[47]

Although not a randomised trial, perhaps the strongest evidence in support of the importance of surgical technique (and probably TME) was the 50% reduction in local recurrence after the introduction and training of TME to the Swedish Rectal Cancer Trials surgeons.[50]

Comparison between centres where TME is routinely used has also shown a 25% reduction in local recurrence and 30% difference in survival compared with conventional surgery hospitals.[51]

Sauer and Bacon[52] in 1951 were probably the first surgeons to emphasise the importance of adequate lateral clearance when excising carcinoma of the rectum. Quirke et al,[53] 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 hypotheses that inadequate margins were the main cause of local recurrence.

Chapman et al,[54] in a prospective study, showed a decreased five-year survival in those patients whose resected specimens were found to have an involved lateral margin.

As part of a large randomised trial comparing preoperative radiotherapy and TME versus TME alone for rectal cancer in the Netherlands, the circumferential resection margin (CRM) was determined and compared with local recurrence and survival in 656 non-irradiated patients. CRM was found to be a strong predictor for local recurrence after TME, and is independent of TNM classification. A margin of 2 mm or less was associated with a local recurrence of 16% versus 5.8% in patients with more mesorectal tissue surrounding the tumour ($p<0.0001$). Furthermore, patients who had a margin 1 mm or less had an increased risk of distant metastases (37.6% vs.12.7%, $p<0.0001$) as well as shorter survival.[55]

What is recommended for the extent of mesorectal excision (TME)?

Guideline — Extent of mesorectal excision (TME)	Level of evidence	Practice recommendation	Refs
For mid-to-low rectal tumours, the principles of extra fascial dissection and total mesorectal excision (TME) are recommended.	III-2	Recommend	31,35, 43–55

12.5 The role of colonic reservoirs after elective anterior resection

Three prospective randomised controlled trials comparing coloanal anastomoses with and without a colonic reservoir have been reported, each demonstrating significantly improved rectal function persisting from the time of stoma closure to at least one year.[56–59]

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 reservoirs 8 cm to 10 cm in length.[57] In the largest series of 162 patients, with a maximum follow up of seven years, 25%[60–63] of patients required an enema or suppository to empty the reservoir.[58] A reservoir length of 8 cm to 10 cm was calculated in a mathematical model to produce an ideal reservoir capacity[64] although the risks of impaired emptying were not factored into this model. In a randomised clinical trial, 5 cm reservoirs were found to have similar physiologic function to the 10 cm reservoir. There was some sacrifice in reservoir capacity, but a significantly better ability to evacuate.[65] The medium-term results (two years) suggest continued advantages from the colonic reservoir in terms of frequency, but fragmentation and continence were similar after adaptation of the straight coloanal anastomosis. Patients with a large (10 cm) reservoir were also more likely to require medication for constipation and evacuation at long-term follow up, compared with patients with a small (5–6 cm) reservoir.[61,66,67]

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 reservoir–anal anastomosis.[68] This may explain the anecdotal reports of a reduction in leakage seen after reservoir–anal anastomosis.[59]

More recently, a novel approach to the creation of a colonic reservoir, the transverse coloplasty reservoir, has gained some popularity. However the small trials have not shown any advantage regarding bowel function (other than evacuation difficulties), but a higher rate of anastomotic leaks.[69–71]

Should a colonic reservoir be constructed?

Guidelines — Colonic reservoir	Level of evidence	Practice recommendation	Refs
Where technically feasible, the colonic reservoir is recommended for anastomosis within 2 cm from ano-rectal junction.	II	Strongly recommend	56,57, 59,61, 65,67, 69-71,74

12.6 The role of high ligation, drains and rectal washouts

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 (reservoir) construction, and it may improve postoperative bowel function by allowing descending rather than sigmoid colon to be used for anastomoses.[72,73] However, a recent randomised study has found no functional difference between using the sigmoid or descending colon to construct the colonic J-pouch (reservoir).[74]

To drain or not to drain?

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.[75] Randomised controlled trials have demonstrated no benefit for the use of routine drains for intraperitoneal colonic anastomoses, and their use has largely been abandoned.[76,77] Many surgeons continue to drain rectal anastomoses that 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, on the extent of pelvic dissection, rather than on local reaction to the drain.[78]

There have been only two randomised controlled clinical trials of pelvic drainage after rectal resection in which a ‘no drain’ arm was included.[79,80] These studies 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 one of the studies.[79] 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.[78,79,81] A recent Cochrane review also confirms that there is no difference of outcome measures after prophylactic drainage of anastomoses after elective colorectal surgery or no drainage, revealing the lack of scientific evidence for the use of drainage.[82]

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.[81]

Guideline — Drainage	Level of evidence	Practice recommendation	Refs
Routine drainage should only be considered for rectal cancers	II	Equivocal	76,77, 79–81

Rectal washout

Exfoliated malignant cells have been demonstrated in the bowel lumen in patients with primary Colorectal Cancer.[83–90] The viability of these cells has been confirmed, and reduction in their viability by application of a variety of chemical constituents has been established.[81–78]

Experimentally-induced anastomotic implantation of luminal cells has been demonstrated in an animal model.[91] Cases of implantation metastases in anal wounds from occult proximal tumours have been reported.[91] 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.[90]

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

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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 gastrografin enema or endoscopy is performed to exclude pseudo-obstruction.[4] CT scanning may be performed as an alternative or adjunct to contrast enemas.[5]

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.[6] 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.[7] The degree of caecal distension depends on the competence or otherwise of the ileocaecal valve, and should be determined on plain abdominal radiograph.

A clinical diagnosis of large bowel obstruction should be confirmed by a plain radiograph of abdomen and a limited gastrografin enema with and/or endoscopy.[7]

13.1.3 Contrast enema

For patients with a suspected large bowel obstruction, the examination is undertaken without bowel preparation using dilute barium or gastrografin. This helps determine the presence and level of mechanical large bowel obstruction.[7] If there is any clinical suspicion of perforation, a water-soluble contrast (gastrografin 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 cannot be tolerated.[8] CT can identify the site and cause of obstruction in over 90% of cases, and can also provide extra-colonic information, particularly the presence of liver metastases.[5,9,10]

A clinical diagnosis of large bowel obstruction should be confirmed by a plain radiograph of abdomen and a limited gastrografin enema with and/or endoscopy.[6-10] Increasingly, CT scan has gained popularity over contrast enema because of better patient tolerance, and improved sensitivity.

13.2 Timing of surgery

Unless perforation is overt (shown by free gas under the diaphragm) or imminent (shown by a distended or tender caecum), surgery for a large bowel obstruction can be regarded as an urgent rather than an emergency procedure. It is preferable to schedule surgery 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 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. Antibiotic[11] and deep vein thrombosis (DVT)[12,13] prophylaxis are administered; the studies are soundly based on now-classic trial data. (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 Fleet® enema are helpful.

All patients should have a rectal examination and sigmoidoscopy (preferably flexible) to exclude a synchronous rectal lesion. Discussion on and siting of a stoma should be performed preoperatively, wherever possible by a stomal therapy nurse although abdominal distension may make this difficult. (See also Chapter 10.) 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.

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 resection and primary ileocolic anastomosis is usually performed.[14]

For left-sided obstructing lesions, the cancer is usually resected unless the patient is moribund, as randomised controlled trial data have shown no significant benefit from a staged procedure.[15,16]

Resection can be performed either as a Hartmann's procedure with an end colostomy, or, in selected circumstances, with resection and anastomosis.[17]

With primary anastomosis, the following options are available:

- appropriate resection and a primary anastomosis accompanied by on-table irrigation (which suggested better outcome in a case series),[18] or a modified bowel preparation, (for subacute bowel obstruction), or
- subtotal colectomy with ileorectal anastomosis was shown to be safe in a case series.[19]

A subtotal colectomy is preferred in the presence of caecal perforation or in the presence of synchronous neoplasms.[20] This approach provided operative mortality rates in a case series that were equivalent to those achieved in elective surgery. In the absence of these functions, a segmental resection with on-table irrigation has been shown in an randomised controlled trial to be associated with better long-term bowel function.[21]

Occasionally, a diverting loop ileostomy is used to protect the anastomosis after a segmental resection.[22]

What surgery is recommended for bowel obstruction?

Guideline — Surgery for bowel obstruction	Level of evidence	Practice recommendation	Refs
Primary resection of obstructing carcinoma is recommended unless the patient is moribund.	II	Recommend	14–21

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 Colorectal Cancer.[6] With a left-sided perforated cancer, an anastomosis is best avoided in the presence of generalised peritonitis and significant sepsis. Where the sepsis is more confined, an anastomosis might be performed and consideration should be given to a defunctioning stoma above the anastomosis.

A stoma alone is performed when clinically indicated for moribund patients, or unresectable cancer.

In these circumstances, the siting of the stoma will usually be done by the surgeon.

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

Self-expandable metallic stents can be used to relieve left colon obstruction by cancer. This can then allow a mechanical bowel preparation (see Chapter 10), elective resection and anastomosis, or in some cases with advanced metastatic disease or major co-morbidities, it may constitute definitive treatment. Special units equipped to perform stenting report successful stent deployment in 64–100% of cases, however there is a 5% incidence of colonic perforation following colonic stenting.[23] Other complications include stent migration (10%), bleeding (5%), pain (5%) and re-obstruction (10%). (See Chapter 11.12.)

Other means of preoperatively relieving the obstruction to allow bowel preparation and elective resection have been reported, including endoscopic laser ablation.[24] The experience with these modalities is limited.

In high-risk patients with major comorbid factors, the quickest and safest option is preferred, and in most settings this will be surgery.

When should primary anastomosis be considered?

Guideline — Surgery for large bowel obstruction	Level of evidence	Practice recommendation	Refs
Primary anastomosis should be considered as a colectomy, with an ileocolic or ileorectal anastomosis.	III-2	Equivocal	14,15,17–20
Primary anastomosis could be considered for left-sided obstruction and may need to be preceded by on table colonic lavage.	III-2	Equivocal	18,19, 21

13.5 Outcome

13.5.1 Morbidity and mortality

Patients presenting as emergencies tend to be older and have other comorbid illness.[25,26] The duration of hospitalisation tends to be longer and there is a higher incidence of a permanent stoma.[25] Perioperative morbidity and mortality (19% compared to 8%) is higher and survival poorer (29% compared to 39% at five years), compared with patients undergoing elective surgery.[27]

The operative mortality following emergency/urgent surgery for Colorectal Cancer has been consistently less than 20% in most recent audits of major centres.[28,29] Subgroup analysis, however, revealed a higher (35% vs 15%) operative mortality after surgery for perforated Colorectal Cancer than for obstructed Colorectal Cancer,[26,30,31] especially if major sepsis is present.

13.5.2 Cancer-related survival

Patients presenting as emergencies tend to have a more advanced-staged cancer.[25,26,30,31] The only variable of prognostic significance in emergency surgery for obstructing Colorectal Cancer is the stage of the cancer.[32]

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.[26,30,33,34] Five-year survival may also be adversely affected by inadvertent perforation of the colon or rectum,[35] or spillage[36] 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.

A number of imaging techniques, including endorectal ultrasound, 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 also been shown to also be applicable to colonic 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, either local, due to tumour transection, or due to known distant metastases.

The Dukes A, B, C system was broadened by Turnbull, 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 Newland[6]

A pTNM system acceptable to both the Union Internationale Contre Le Cancer and the American Joint Committee for Cancer (AJCC) was agreed in 1986 with the aim of attempting to achieve uniformity in staging of Colorectal Cancer (Tables 14.2 and 14.3).[7,8]

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 nodes 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: AJCC[9]

Table 14.3 Pathological TNM staging

Stage	**Tis**	**N**	**M**	**Dukes**	**MAC** Modified Astler-Coller
0	Tis	N0	M0	-	-
I	T1	N0	M0	A	A
	T2	N0	M0	A	B1
IIA	T3	N0	M0	B	B2
IIB	T4	N0	M0	B	B3
IIIA	T1–T2	N1	M0	C	C1
IIIB	T3–T4	N1	M0	C	C2/C3
IIIC	Any T	N2	M0	C	C1/C2/C3
IV	Any T	Any N	M1	-	D

Source: AJCC[9]

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.[10,11] 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.

What staging data should be recorded?

Guideline — Staging data	Level of evidence	Practice recommendation	Refs
TNM staging, ACPS staging and the data required to stage the patient should all be recorded to allow national and international comparisons. (ACPS staging embodies the simplicity of Dukes.)	III-3	Equivocal	9, 10

14.3 Clinical input

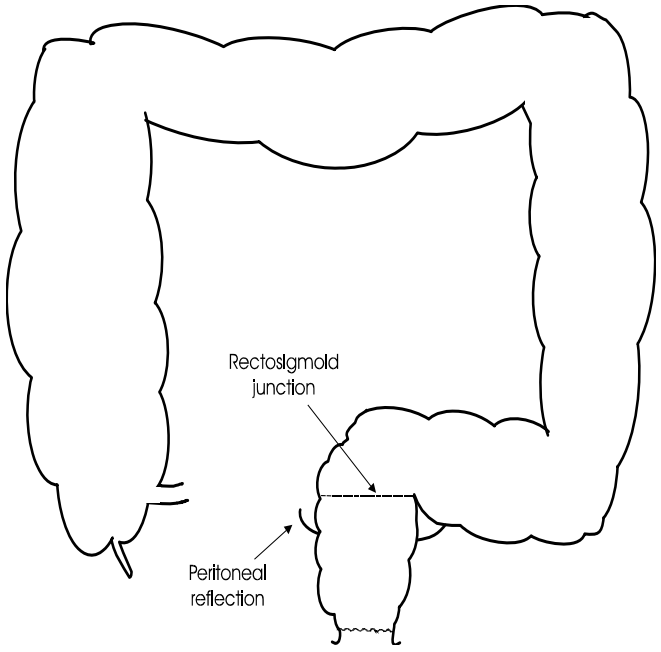
The use of a clinicopathological staging system requires that the surgeon make the operative findings known to the pathologist. A convenient proforma for conveying this information is attached as Figure 14.1. Should this information be unavailable to the pathologist, the report should indicate that the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

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

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.

<table>
<tr><td colspan="2">Name</td><td>Age</td><td>Sex</td><td>File no.</td></tr>
<tr><td colspan="5">Mark location of tumour on diagram
Mark lines of resection on diagram</td></tr>
<tr><td colspan="5">Name of operation performed:</td></tr>
<tr><td colspan="2">Was operation:
☐ curative (no obvious tumour remaining)
☐ palliative (tumour remaining)</td><td colspan="3">If palliative, the reason was:
☐ tumour transected
☐ metastases remaining
☐ both</td></tr>
<tr><td colspan="5">If distant metastases present:</td></tr>
<tr><td>State site(s)</td><td>Biopsy taken
☐ yes
☐ no</td><td colspan="3">Was adjacent organ(s) or tissue excised with bowel
☐ yes
☐ no</td></tr>
</table>



M.O. Signature.....

14.4 Translation between staging systems

A matrix for translating between staging systems was developed by a working party on staging, which reported in 1990.[12] The international comprehensive anatomical terminology (ICAT) for Colorectal Cancer and matrix for staging conversion is shown in Table 14.4.[13]

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, (refer to Table 14.5). These variables include the components of stage and some other factors that have been shown to have a bearing on prognosis. The independent prognostic effects of many of these variables have been assessed within the ACPS system and have been demonstrated to be stage dependent.[12,14,15]

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.[14–16] As has been mentioned, the code for local residual tumour (the R classification) is optional.

Table 14.5 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). Distance of tumour from longitudinal margins, radial margins and anal verge (in those having an abdominoperineal resection).
2. **Lymph node involvement** (number of involved nodes, presence or absence of extracapsular extension, 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. **Lymphovascular 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*
   - presence or absence of necrosis in those patients having preoperative adjuvant therapy
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).[17,18]

14.5.1 Microsatellite instability

It is now apparent that DNA microsatellite instability falls into a high category (MSI-H), in which at least 30% or more of the loci tested show instability and a low category (MSI-L).[19,20] 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.[19,20]

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

			pTNM		ACPS		Concord Hospital		Dukes and Bussey 1958		Astler-Coller		Japanese Research Society	
Line #	Feature in 1 cat	pTNM	Line #	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 Stage	pTNM Line #	ACPS Stage	ACPS Line #	Concord Hospital Stage	Concord Hospital Line #	Dukes and Bussey 1958 Stage	Dukes and Bussey 1958 Line #	Astler-Coller Stage	Astler-Coller Line #	Japanese Research Society Stage	Japanese Research Society 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	pTNM Line #	pTNM Stage	pTNM Line #	ACPS Stage	ACPS Line #	Concord Hospital Stage	Concord Hospital Line #	Dukes and Bussey 1958 Stage	Dukes and Bussey 1958 Line #	Astler-Coller Stage	Astler-Coller Line #	Japanese Research Society Stage	Japanese Research Society 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		(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.				
								D-2	1–8						
									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 Bussey[21], Astler and Coller[22], Jamai[23]

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CHAPTER 15 ADJUVANT CHEMOTHERAPY 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. Adjuvant therapy is any treatment that is given in addition to a standard cancer treatment to improve the chances of cure.

In 1990, an United States National Institute of Health (consensus conference[1] reviewed the available evidence and recommended that one year of 5-fluorouracil (5-FU) plus levamisole be offered to all patients with resected Dukes C colon cancer. Since then, adjuvant trials have abandoned a no-treatment control. There have been recent advances in the use of adjuvant therapy in patients with colon cancer following curative resection, but questions remain regarding the optimal adjuvant therapy regimen and its value in certain clinical contexts, for example, Dukes B colon cancer.

Radiotherapy has a limited role in colon cancer although there are special circumstances where T4 tumours, eg. Adherence to abdominal wall bladder may require adjuvant therapy.

15.1 The research evidence for systemic chemotherapy

Several meta-analyses have been performed to examine the benefits of adjuvant chemotherapy in Dukes C colon cancer. Buyse et al summarised the data on randomised trials of adjuvant therapy for Colorectal Cancer up to 1987.[2] This meta-analysis 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 (CR = 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% vs 8%, p = 0.02). The effect by disease 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.

The Dube meta-analysis of 39 trials performed between 1959 and 1993 in both colon and rectal cancers found a 5% improvement in five-year survival for colon cancer and 9% for rectal.[3] The Cancer Care Ontario Practice Guidelines Initiative (CCOPGI) meta-analysis of 32 trials in 1997 found a mortality odds ratio for adjuvant chemotherapy in stage III colon cancer of 0.69 (0.57–0.85).[4] The Colorectal Cancer Collaborative Group has also presented in abstract form a meta-analysis of 50 studies involving 18,000 patients[5] comparing surgery alone with adjuvant chemotherapy. It found that annualised death rates were reduced by 29% (p = 0.0007) for 5-FU regimens modulated by leucovorin and 22% (p = 0.01) for levamisole modulated regimens. Unmodulated 5-FU schedules led to a 6% reduction (p = 0.11). Overall death rate reduction was 11% for all prolonged systemic chemotherapy treatments.

In addition, the Australian Cancer Network and Clinical Oncological Society of Australia Working Party on Adjuvant Therapy for Colon Cancer (Appendix B) 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 era of adjuvant trials

This group of three trials predates modern treatment schedules. The South Western Oncology Group (SWOG) in the United States compared chemotherapy using (i) 5-FU plus semustine (MF), with (ii) MF plus BCG immunotherapy, or (iii) BCG alone. The negative result of the SWOG trial (no survival benefit detected) was consistent with previous reports.[6]

The NSABP trial C-01 was the first large adjuvant trial in colon carcinoma to detect a benefit for adjuvant therapy, with a borderline statistical significance. It found an 8% absolute improvement in survival for Dukes C (but not B) patients treated with either chemotherapy (semustine, vincristine, 5-FU) or BCG.[7] However, in a recent update of this trial, no benefit from adjuvant chemotherapy was seen at ten years of follow up. However, there was a benefit from the addition of BCG in survival improvement compared to surgery alone (53% vs 46%, p = 0.02).[8] Four other randomised studies have not shown an advantage with BCG[9] and the observed benefit to BCG in the first trial was thought to be most likely due to reduction in deaths from comorbid conditions.

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 either observation or one of two regimens of chemotherapy.[10] 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 and levamisole

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

In the initial Leicester trial,[11] patients were randomised after curative surgery either to 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 when 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 EORTC trial with Dukes C colon cancer patients,[12] and its effect was inferior to the combination with intravenous 5-FU in the NCCTG trial with Dukes B and C Colorectal Cancer patients.[13]

The intergroup trial 0035 detected a significant survival advantage for 5-FU plus levamisole compared with observation.[14] This benefit, amounting to a 30-40% reduction in the rates of recurrence and death, occurred in Dukes C colon cancer patients[15] but not those with Dukes B.[16] 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]

The Netherlands Adjuvant Colorectal Cancer Project (NACCP) also found a significant overall benefit of adjuvant therapy with 5-FU plus levamisole compared with observation in Dukes B and C colon cancer but not for rectal cancer.[17]

In a 1996 meta-analysis of two trials — 5-FU with or without levamisole versus no treatment control arms — the effect of levamisole became non-significant after adjustment for the total planned 5-FU dose.[18] Levamisole is now of historical interest only, as subsequent studies have disproved its efficacy in adjuvant therapy.

15.1.3 5-FU plus leucovorin

These trials compared postoperative observation with adjuvant 5-FU modulated by leucovorin (folinic acid). Folinic acid prolongs the half-life of 5-FU by increasing its enzymatic binding to thymidylate synthetase. Using an individual patient data meta-analysis, the IMPACT (International Mutlicentre 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.[19] A significant reduction in the rate of recurrence was detected for patients randomised to monthly five-day 5-FU plus high-dose leucovorin compared with control (hazard ratio (HR) 0.65; 95% Cl 0.54, 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% Cl 0.61, 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 al.[20] 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% Cl 18%, 52%) and in mortality rate 34% (95% Cl 23%, 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% versus 43% for adjuvant therapy and control respectively (p = 0.0025); recurrence-free survival was 66% and 41% respectively (p = 0.0016).

A United States Intergroup trial in Dukes B and C colon cancer has also detected an overall significant reduction in recurrence rate (74% vs 58% at five years; p<0.01), and overall survival (74% vs 63%; p = 0.02) favouring six months of 5-FU plus low-dose leucovorin compared with observation. The analysis was not stratified by stage.[21]

The National Surgical Adjuvant Breast Project (NSABP) trial C-03 compared MOF (semustine, vincristine and 5-FU) with a combination of 5-FU plus leucovorin.[22] 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).

Clinical trials have proceeded to compare 5-FU plus leucovorin with regimens containing levamisole and to determine duration of therapy. Six studies have matured in the past four years since the year 2000 and these have established that six months of 5-FU-leucovorin provides a similar benefit to twelve months, and that the addition of levamisole provides no further benefit. The NSABP C-04 study compared 5-FU plus leucovorin given for 36 weeks with 5-FU plus levamisole and 5-FU plus leucovorin plus levamisole each given for one year.[23] Amongst 2151 patients there were no significant disease-free survival (DFS) or overall survival (OS) differences between the individual arms, although on pair-wise comparisons, 5-FU plus leucovorin had a significant advantage over 5-FU plus levamisole in terms of DFS (P = 0.04). A collaborative study between the NCCTG and the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG used a two-by-two factorial design where standard 5-FU plus levamisole was compared with a 3-drug regimen of 5-FU plus low-dose leucovorin plus levamisole, and either regimen given for six or 12 months.[24] This study enrolled 891 eligible patients and showed that 12 months of therapy offered no benefit over six months. There was a survival benefit with the addition of leucovorin in patients who received six months treatment with five-year OS 70% vs 60%, p<0.01. The American Intergroup study INT-0089 randomised 3759 patients to 12 months of 5-FU plus levamisole or six months of 5-FU plus low-dose leucovorin (LDLV), 5-FU plus high-dose leucovorin (HDLV) or 5-FU plus LDLV plus levamisole.[25] Twelve months of 5-FU plus levamisole was found to offer no survival benefit over six months of 5-FU plus leucovorin. The largest study to date, the British QUASAR (quick and simple and reliable) Trial, has randomised 4863 patients between levamisole and placebo added to 5-FU plus leucovorin regimens.[26] Survival was non-significantly inferior with levamisole when compared with placebo (odds ratio 1.10, p = 0.07). The German adjCCA-01 trial randomised 680 Dukes C patients to receive either 12 months of 5-FU plus levamisole or 5-FU plus HDLV.[27] At a median follow up of 82 months, the 5FU plus leucovorin combination significantly improved DFS (P = 0.012) and significantly decreased overall mortality (P = .003) in comparison with 5-FU plus levamisole. A recent reported Israeli trial of 398 Dukes B and C patients comparing 12 months of 5-FU plus HDLV to 5-FU plus levamisole found no difference in eight-year survival.[28]

QUASAR has also demonstrated that there is no difference in outcome between the use of high-dose or low-dose leucovorin. QUASAR also incorporated a non-randomised comparison of weekly versus a four-weekly five-day schedule of administering the treatment.[29] This schedule was determined by

clinician preference. Risk of recurrence and survival were identical, but the weekly schedule was associated with much less toxicity. To date there have been no direct randomised trials comparing weekly bolus 5-FU plus LDFA with the schedule of monthly five-day bolus 5-FU plus LDFA (Mayo) or the six-out-of-eight weekly bolus 5-FU plus HDFA (Roswell Park) schedule.

Updated data from the Italian SITAC-01 study, one of the IMPACT trials, has found that the treatment has had no detectable adverse effect on the patients' quality of life.[30] Through a computer-simulated model, it has been estimated that adjuvant therapy with the old regimen of 5-FU plus levamisole costs US$2094 per year of life saved. In an Australian study, cost estimates per quality adjusted life-year (QALY) gained vary from A$370 to A$17,500.[31]

15.1.4 Oral fluoropyrimidines

An individual patient meta-analysis[32] of oral fluoropyrimidines (oral 5-FU, Tegafur and Carmofur) versus surgery alone in curatively resected Colorectal Cancers was presented in abstract form in 2001. Six Japanese trials enrolling 9819 patients were reviewed. A significant overall advantage was found for treatment in terms of disease-free survival and overall survival (relative risk 0.83 and 0.91 respectively). A recent updated meta-analysis[33] of three adjuvant oral fluoropyrimidine trials in 5233 patients, performed by the same group, confirmed that DFS and OS were improved regardless of stage, tumour site, age or sex.

The NSABP C-06 study of oral UFT versus bolus monthly five-day 5-FU plus leucovorin has recently been reported in 1608 patients with Dukes B and C colon cancer.[34] There were no differences in either five-year disease-free or overall survivals. Overall toxicity was similar in both arms, as was quality of life.

Capecitabine given in a two-out-of-three week daily schedule for eight cycles has also been compared to the six cycles of bolus monthly five-day 5-FU plus leucovorin schedule in the X-ACT study[35] of 1987 Dukes C resected colon cancer patients. At 3.8 years median follow up there was a superiority of capecitabine in relapse-free survival ($p = 0.05$) and a trend toward better disease free survival and overall survival. Capecitabine was associated with a better toxicity profile except for more hand-foot syndrome. It also yields a savings in use of medical resources compared to the intravenous therapy.[36] Multivariate analysis found that capecitabine predicted for improved overall survival (HR 0.77, $p = 0.02$).

15.1.5 Oxaliplatin

Interim results of the MOSAIC[37] study of biweekly 5-FU plus leucovorin with or without oxaliplatin in 2246 patients with Dukes B and C colon cancer have shown a superiority of the oxaliplatin in improving disease-free survival at 37-month follow up (78.2% vs 72.9%, $p = 0.002$). Improvement in overall survival is yet to be seen and there are concerns regarding the long-term side effects of neuropathy from the oxaliplatin. However, results to date indicate that severe neurotoxicity does resolve over time to a minor residual grade. A pooled analysis[38] of 15 phase III studies of adjuvant therapy for colon cancer studies utilising individual patient data from 12,915 subjects has shown a high correlation of three-year disease-free survival to the five-year overall survival, except for whether the three-year disease-free survival difference is marginal. The NSABP C07 trial, with the same design as MOSAIC in evaluating oxaliplatin, is now completed and the results are awaited.

15.2 Portal vein infusion

Evidence upon which to make treatment recommendations comes from an individual patient data meta-analysis of trials of portal vein infusion in Colorectal Cancer.[39] The analysis of 3499 patients from ten trials detected an 18% reduction in the annual odds of death for all patients treated with portal vein infusion ($p = 0.0004$). This 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% vs 51.7%; p = 0.2), corresponding to a 17% reduction in the odds of death for patients with Dukes C disease alone (p = ns). 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 meta-analysis of individual patient data, 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). This was due mainly to the first hypothesis-generating trial involving 271 patients.[40] 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).[41] However, a meta-analysis of all patients treated with portal vein infusion detected an overall 25% decrease in deaths compared with observation (p = 0.0002).

Since then, three important negative trials have been presented. The EORTC/GIVIO/JFCR[41] trial (n = 1235), the Swiss SAKK 40/87 (n = 769) trial,[42] and the UKCCCR AXIS[43] (N = 3583) study have all shown no differences in survival of portal vein chemotherapy versus observation. These trials all randomised a combination of colon and rectal cancer patients. The AXIS authors combined their trial data with the above meta-analysis to explore differential treatment effects. They found hazard ratios of 0.82 and 1.00 for colon and rectal patients respectively with PVI. Portal vein infusion, however, is associated with technical difficulties of catheter placement and thrombosis. Therefore portal vein chemotherapy cannot be recommended as a standard adjuvant therapy for high-risk colon cancer after resection.

15.3 Adjuvant therapy in Dukes B colon cancer

The question of the role of adjuvant chemotherapy in Dukes B colon cancer had previously been unresolved because individual trials had been insufficiently powered to exclude a small survival advantage. The NSABP meta-analysis[44] of data from the consecutive C01, C02, C03 and C04 adjuvant studies suggested that the relative mortality reduction in Dukes B patients was 30% versus surgery alone. There was a statistically significant reduction in mortality for patients with Dukes B colon cancer who presented without adverse prognostic factors, but not for those with high-risk prognostic factors. However this meta-analysis has been criticised in that the trials spanned a period between 1977 and 1990, chemotherapy schedules varied, and two of the trials did not have observation arms. An updated meta-analysis of six Japanese oral fluoropyrimidine trials involving 9819 patients also found an overall survival risk ratio of 0.84 (p = 0.017) for Dukes B patients.[32] The recent Dutch NACCP trial found a significant five-year survival difference of 78% versus 70% in patients receiving 5-FU plus levamisole compared to control in Dukes B patients.[17]

The IMPACT B2 investigators,[45] however, found no significant difference in their pooled analysis of five trials accruing 1016 patients. The CCOPGI meta-analysis[4] in 1997 reviewed 31 randomised trials that tested several forms of adjuvant therapy in resected colon cancer, and concluded that treatment neither improved survival nor delayed relapse.

The United Kingdom QUASAR study[46] randomised 3238 patients with uncertain indication for adjuvant therapy to observation or either six five-day four-weekly or 30-weekly treatments of 5-FU (investigators' choice) and either high- or low-dose leucovorin with or without levamisole. As described previously the trial found no difference between high and low-dose leucovorin and no benefit to levamisole. Ninety-one per cent of the patients were Dukes B stage and 71% were colonic primaries. The trial has found a small magnitude of benefit for chemotherapy over observation. The five-year recurrence rate was 22.2% for chemotherapy versus 26.2% for observation (4% absolute benefit, p = 0.02) and overall survivals of 80.3% and 77.4% respectively (3% absolute benefit, p = 0.02). No benefit of chemotherapy was seen in patients over the age of 70 years. A detailed subset analysis will be performed on more mature data and this, combined with meta-analysis, will help to define the groups that receive the most benefit from adjuvant therapy in this setting.

Factors such as poor histological differentiation, aneuploidy, tumour perforation, bowel obstruction and invasion of surrounding structures are associated with a poorer prognosis. It would be appropriate to discuss and consider adjuvant therapy in these patients.

15.4 Adjuvant treatment in elderly patients

The incidence of colon cancer rises with age. A pooled analysis[47] of 3351 patients enrolled in seven randomised studies of adjuvant chemotherapy with either 5-FU plus leucovorin and 5-FU plus levamisole versus observation was recently published. There was no significant interaction found between age and efficacy of therapy. The toxicity of treatment was not increased in the elderly (age greater than 70) except for leucopenia in patients receiving the outdated 5-FU plus levamisole schedule. This is supported by United States SEER and Medicare population-based data showing 5-FU therapy is associated with significantly reduced mortality in elderly node-positive patients and that this hazard reduction does not diminish with increasing age.[48,49] In the absence of significant comorbidities, advanced chronological age should not be used to exclude patients from being offered adjuvant chemotherapy.

15.5 Other trials

A number of other adjuvant therapies or techniques have been investigated or are currently being evaluated and at present cannot be recommended as standard.

15.5.1 Protracted infusional 5-FU

Two recent studies[50,51] have directly compared the administration of protracted venous infusional (PVI) 5-FU with standard bolus monthly five-day 5-FU plus leucovorin for six cycles. Both found a better toxicity profile with PVI 5-FU and similar efficacy. Interestingly, the Saini[51] trial achieved equivalent overall survival and improved time to relapse with only 12 weeks of infusional 5-FU. A five-year update of the later study confirmed no difference in relapse-free or overall survival in the two arms.[52]

15.5.2 Irinotecan

A phase III trial of weekly bolus 5-FU plus leucovorin (FL) versus irinotecan plus 5-FU plus leucovorin (IFL) (CALGB C89803) was conducted on 1264 Dukes C patients.[53] IFL was associated with greater toxicity and in terms of neutropenia, neutropenic fever and death on treatment, with no improvement in overall or failure-free survival over FL. Irinotecan in this schedule is thus not a recommended adjuvant treatment for colon cancer. The results of two randomised studies (PETACC 2 and ACCORD II) of a biweekly schedule of bolus and infusional 5-FU plus leucovorin versus irinotecan plus 5-FU plus leucovorin (FOLFIRI) are awaited. These studies will further define the role of irinotecan in the adjuvant setting.

15.5.3 Intraperitoneal chemotherapy

Chemotherapy delivered by the intraperitoneal route versus surgery alone has been tested in three trials of adjuvant therapy.[54–56] Intraperitoneal treatment involves the infusion of drug into the peritoneal cavity, with catheter placement. One trial[54] used a placebo and was to determine safety and not powered for efficacy. Clinical outcomes related to recurrence and survival were reported in the other two trials involving randomised patients with Dukes C or high-risk Dukes B disease. At a median follow up of 4.6 years in the Scheithauer trial[55], both DFS and overall survival favoured treatment (DFS 75% vs 58%; $p = 0.06$: overall survival 78% vs 63%; $p = 0.05$); but the effect was confined to patients with Dukes C disease. In contrast, Vaillant[56] found no difference in overall survival but a reduced disease-free survival in Dukes B patients.

There has been one trial[55] of intravenous 5-FU plus levamisole versus combined intravenous and intraperitoneal 5-FU plus leucovorin in 241 resected Dukes C and high-risk B colon cancer patients. No difference was found in survival of Dukes B patients at four-year follow up. However, for the Dukes C group, a 45% reduction in estimated mortality was seen for the combined treatment arm. These results require further confirmation.

15.5.4 Passive immunotherapy

Passive immunotherapy with BCG, with or without chemotherapy, has been tested in several trials.[6, 8, 57–59] No definitive benefit compared with chemotherapy alone has been observed.

Isenberg et al[60] compared preoperative immunostimulation with bacterial products 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% vs 63%), including 42 Dukes C patients (38% vs 30%). Formal significance tests were not reported, and the sample size was small.

15.5.5 Active specific immunotherapy

Hoover et al[61] 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 a planned subset analysis there was a survival benefit for the 47 patients with colon cancer (47.8% vs 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. A Dutch study[62] of this treatment in 254 stage II and III colon cancer patients found a significant recurrence-free survival advantage in stage II patients. However, a parallel Eastern Cooperative Oncology Group study E5283[63] that enrolled 412 patients found no difference in disease-free or overall survival for either stage II or III patients, but there was indication that treatment compliance with effective immunisation results in better survivals. A large multinational study is currently in progress.

15.5.6 Alpha interferon

Three randomised studies, the NSABP C-05[64], a Hellenic Cooperative Group trial[65] and the German FOGT-1 trial[66] have shown no benefit from adding the immunomodulator alpha interferon to either adjuvant 5-FU plus leucovorin or 5-FU plus levamisole chemotherapy protocols.

15.5.7 Monoclonal antibody therapy

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-lA (edrecolomab).[67] 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. The results of two large follow-up studies have been conflicting. A three-armed trial of 2761 subjects[68] has shown this monoclonal antibody as monotherapy to be inferior to treatment with 5-FU plus leucovorin and to have no additional benefit to the chemotherapy in adjuvant therapy of Dukes C patients. An American two-armed study of 1839 patients of 5-FU-based therapy (either monthly 5-FU plus LDFA or Moertel 5-FU plus levamisole) with or without edrecolomab found a significant overall survival difference with the addition of the monoclonal antibody.[69] A recent report of CALGB 9581 of edrecolomab versus observation in 1738 patients with Dukes B colon cancer has also found no benefit in overall survival or failure-free survival.[70] The development of this drug has been ceased.

15.5.8 Raltitrexed

Raltitrexed is a specific thymidylate inhibitor synthase active in advanced Colorectal Cancer. The PETACC-1 trial comparing it to a control arm of 5-FU plus leucovorin in the adjuvant setting was terminated early in 1999 when an excess of drug-related deaths in the raltitrexed arm was noted. Thus the specific role of raltitrexed in adjuvant therapy is unknown and it cannot be recommended as standard treatment in this setting.

Who should be considered for adjuvant therapy?

Guidelines — Adjuvant therapy	Level of evidence	Practice recommendation	Refs
People with resected Dukes C, that is, node-positive colon cancer, should be considered for adjuvant therapy.	I	Strongly recommend	3–5

What is the value of adjuvant therapy in Dukes B colon cancer?

Guidelines — Adjuvant therapy	Level of evidence	Practice recommendation	Refs
There is a small but statistically significant benefit for the use of adjuvant chemotherapy in Stage II colon cancer. A decision regarding treatment should be made following a discussion of the relative merits and side effects of chemotherapy. High risk sub-groups are more likely to benefit from adjuvant chemotherapy.	II	Recommend	46

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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 ureteric obstruction. It is associated with a significant deterioration in quality of life.

16.2 Chemotherapy

Chemotherapy is cytotoxic drug treatment. Systemic 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. The addition of chemotherapy may also have some radio-sensitising action when used in combination with radiation.[1]

16.3 Benefits of adjuvant therapy

Patients whose tumours have penetrated the wall of the rectum and/or have metastasised to regional lymph nodes are at increased risk of recurrent cancer in the pelvis or at distant sites. There is also a higher risk of local recurrence when the surgical resection margins (either radial or longitudinal) are close or positive.[2] The optimum strategy to improve the outcome of patients with rectal cancer must address the problems of local and distant recurrence.

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

Patients enrolled in clinical trials have to be fit enough to withstand further treatment in addition to major surgery. A review of the entry criteria of combined modality therapy (CMT) (radiotherapy and chemotherapy) studies have not shown them to be restrictive. For patients who received surgery alone as the control group in the NSABP randomised study of CMT versus surgery alone,[3] the five-year survival data are comparable to a large cohort study performed by an Australian colorectal unit.[2] 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 through the bowel wall were 57% and 62%.

16.5 The role of combined chemotherapy and radiotherapy

The current recommendations are based on a review of randomised trials. There have been ten randomised studies of CMT. Postoperative CMT has been most extensively studied. The Gastro-Intestinal Tumour Study Group (GITSG)[4] performed a study in which the four arms were: surgery, surgery and postoperative radiotherapy, postoperative chemotherapy with semustine and 5-FU, or postoperative CMT.

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

Only one other study has compared CMT with surgery alone.[5] In this study, 144 patients were randomised to receive postoperative radiotherapy and synchronous bolus chemotherapy, or no further treatment. Local recurrence in the CMT arm was 12% compared with 30% in the surgery alone arm. Survival was also significantly increased (64% vs 46%, p = 0.01).

Krook et al[6] randomised 204 patients with high-risk rectal cancer to postoperative radiotherapy alone or CMT. The CMT arm experienced lower recurrence rates, both locally and distantly. The rates of cancer-related deaths and deaths from any cause were also significantly reduced with the combined modality treatment.

Five further studies have addressed refinements of chemotherapy when used in combination with radiotherapy. The GITSG[7] randomised 210 patients to postoperative radiotherapy with either semustine and 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 al[8] examined the effectiveness of alternative 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.

Intergroup 0114[9] was a four-armed study of adjuvant postoperative chemoradiotherapy that compared 5U alone against modulation of 5-FU with levamisole, leucovorin or levamisole plus leucovorin. There were no differences in the different regimens on final analysis in terms of disease-free or overall survival.[10] The Hellenic Cooperative Oncology Group[11] also found no advantage from adding chemotherapy with 5-FU plus leucovorin into a schedule of combination bolus 5-FU plus concomitant radiotherapy.

The preliminary results of a Korean study[12] in 308 patients suggest that early radiotherapy with concurrent chemotherapy (commencing with the first cycle of chemotherapy) after resection of rectal cancer has an advantage in terms of disease-free survival compared to late radiotherapy (commencing with the third cycle of chemotherapy). The PAR Cooperative Study Group,[13] in a trial of 218 Dukes B and C patients, found no difference in 5-year disease-free survival and overall survival when sequential bolus five-day monthly 5-FU with levamisole fortnightly was given in addition to postoperative radiation therapy. The study was, however, underpowered and there was a low (59%) compliance with the chemotherapy due to toxicity.

NSABP R02[14] randomised 694 Dukes B and C patients to receive either postoperative chemotherapy (MOF or 5-FU plus LV) alone or postoperative chemotherapy with radiotherapy. Although radiotherapy conferred no advantage in disease-free or overall survival it reduced the cumulative incidence of locoregional relapse.

Three studies have examined the use of preoperative CMT, and compared it with preoperative radiotherapy alone. In a European Organization on Research and Treatment of Cancer (EORTC) trial[15] there was a non-significant trend to better survival in the RT/S 59% versus 46% CMT (p = 0.06) at five years. 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 an excessive risk of late small-bowel damage.[16,17] The Polish Colorectal Study Group[18] trial using modern techniques enrolled 316 patients, and compared conventional long-course 50.4Gy RT combined with bolus 5-FU plus LV to short-course radiotherapy (25Gy in 5) before TME. There was more acute toxicity in the long course CMT that was associated with a higher pathological shrinkage but not an increased sphincter preservation rate. Preliminary results from the EORTC 22921 trial comparing the addition of two cycles of 5-FU plus LV to

preoperative RT 45Gy over 5 weeks show that the chemotherapy significantly reduced the tumour size and pathological TN staging as well as the incidence of lymphatic, venous or perineural invasion.[19] Acute diarrhoea was increased but compliance with radiation and feasibility of surgical resection were not affected.[20]

No direct comparison between long-course and short-course preoperative radiation has been published. This question is currently being addressed in a Trans Tasman Radiation Oncology Group (TROG)/Australasian Gastrointestinal Trials Group (AGITG) study.

NSABP R03 (closed early by poor accrual) has been completed and compares pre- versus post CMT.[21] Early results of this trial suggested that a larger proportion of the preoperative patients had sphincter-sparing surgery, but also experienced higher toxicity from the treatment.

The recently reported CAO/ARO/AIO-94 trial also compares pre and postoperative CMT[22] and 823 patients were accrued. Grade 3 or 4 acute toxic effects were less in the preoperative (27%) as compared with postoperative (40%) treatment group ($p = 0.001$). A higher sphincter preservation rate was also seen for the preoperative group. Post operative morbidity was not increased by preoperative CMT. The corresponding rates of long-term toxic effects were 14% and 24%, respectively ($p = 0.01$). Chronic anastomotic stenosis rate was seen less following preoperative CMT than postoperatively (4% versus 12%, $p = 0.003$). Five-year pelvic and distant recurrence rates were 6% versus 13% ($p = 0.006$) and 36% versus 38% ($p = 0.84$) respectively. Disease-free and overall survivals are not significantly different. The conclusions of this well-performed RCT was that 'preoperative chemoradiotherapy, as compared with postoperative chemoradiotherapy, improved local control and was associated with reduced toxicity, but did not improve overall survival.'

A similar trial, the Intergroup 0147, has also recently closed due to poor accrual.[23]

16.6 The role of adjuvant radiotherapy without chemotherapy

The best evidence of the value of radiotherapy alone comes from five meta-analyses of more than 8000 patients randomised to receive radiotherapy and surgery, or surgery alone.[24–28] Radiotherapy alone significantly reduces local relapse and also deaths related to rectal cancer, but the impact on overall survival is counterbalanced by early non-cancer deaths. Recent studies suggest a survival benefit from using modern techniques. Even without a survival improvement, the use of radiotherapy can be justified, based on the avoidance of the morbidity and costs associated with local recurrence of rectal cancer. However, radiotherapy itself has certain morbidity.

16.7 Preoperative radiotherapy without chemotherapy

The Colorectal Cancer Collaborative Group overview analysed individual patient data on over 8000 patients from 14 trials, comparing preoperative radiotherapy with no preoperative therapy for rectal cancer.[26] In this analysis, radiotherapy significantly reduced the proportional risk of local recurrence by 46% ($p = 0.00001$) and the absolute risk of death from rectal cancer by 5% (45% vs 50%, $p = 0.003$). Early non-cancer deaths (within a year), however, were increased from 4% to 8% ($p<0.0001$). This counterbalanced the overall survival benefit. A statistically significant correlation ($p = 0.02$) of decreasing benefit of preoperative radiotherapy on mortality was seen with increasing age. The proportional mortality reduction in rectal cancer deaths did not vary by stage. The absolute benefits, however, are larger for the patients with Dukes C cancer as they are at a higher risk of recurrence. In studies where biologically effective doses of ≥30 Gy were used, the reduction in risk of local recurrence was 50%. No significant reductions were seen in those with a dose that was of low or intermediate biological effect (<20 Gy and 20–20.9 Gy).

Two recent studies[29,30] employing modern short-course three- or four-field radiotherapy techniques and included in the above meta-analysis have shown a significant survival advantage. In a Swedish

study, 1168 patients less than 80 years of age with rectal cancer were randomised to receive either 25 Gy in five fractions followed by surgery, or surgery alone. Postoperative mortality was equal in each arm. Local recurrence was reduced from 27% to 11% ($p<0.001$) and survival at five years was significantly increased in the radiotherapy arm (58% vs 48%, $p = 0.004$). This improvement was found across all stages of cancer. The Stockholm II trial[30] of 557 patients at a median of 8.8 years follow up found pelvic recurrence rates reduced from 25% to 12% and overall survival improved from 39% to 46% ($p<0.03$). Cardiovascular death was found to be the main cause of intercurrent death. The toxicities of preoperative radiotherapy are discussed in detail in Section 16.11.1.

The Lyon R90-01 trial examined the interval between completion of pelvic radiotherapy (39 Gy in 13 fractions) and surgery[31]. A long interval (6–8 weeks) was found to be associated with a higher clinical and pathological downstaging compared with a shorter interval (two weeks). No effect was seen on toxicities, local recurrence, anal function or survival after median follow up of six years.[32] The local recurrence rate following anal sphincter preserving surgery was, however, 15% higher than if adominoperineal surgery was carried out. In the Swedish study, no downstaging effect was seen if the interval between radiotherapy and surgery was not more than ten days.[33]

16.8 Postoperative radiotherapy without chemotherapy

There have been eight trials of surgery and postoperative radiotherapy versus surgery alone. The Colorectal Cancer Collaborative Group meta-analysis shows that postoperative radiotherapy significantly reduces local recurrence by about one third ($p = 0.0002$).[26] There is no evidence, however, that overall survival is improved by postoperative radiotherapy alone.

16.9 Preoperative versus postoperative radiotherapy

The Colorectal Cancer Collaborative Group meta-analysis shows the reduction in rectal cancer mortality is greater for preoperative radiotherapy (22%, $p = 0.00002$) than for postoperative radiotherapy (9%, p = NS). The better results seen in preoperative radiotherapy studies may be due to the selection of clinically-staged patients with earlier tumours than those pathologically staged before entry into a postoperative radiotherapy trial.

One direct comparison was performed between 25 Gy in one week preoperatively or 60 Gy in 7-8 weeks postoperatively.[34] There were significantly fewer local recurrences in the preoperative radiotherapy arm (13% vs 22%, $p = 0.02$), but no difference in overall survival. Late radiotherapy complications were reported by treatment given and were higher with postoperative radiotherapy than with either preoperative radiotherapy or surgery alone (41%, 20% and 23% respectively). After accounting for the effect of different fraction size, the postoperative biological dose was about 50% higher than the preoperative dose,[35] and a much greater rate of late effects would be expected. However, when the results are analysed by intention-to-treat, the rate of complications in the postoperative arm falls to 31%, which is not significantly different from the preoperative rate.

The 2004 randomised controlled German rectal trial (CAO/ARO/AIO-94) by Sauer et al[22] of over 800 patients revealed no difference in survival rates. However, the five-year local recurrence was 6% for preoperative chemoradiotherapy and 13% in postoperative ($p = 0.06$). Grade 3 or 4 acute toxic effects were less (27% preoperative as compared with 40% postoperative treatment group, $p = 0.001$) The conclusions of this well-performed RCT was that ‘preoperative chemoradiotherapy, as compared with postoperative chemoradiotherapy, improved local control and was associated with reduced toxicity but did not improve overall survival’.

As already mentioned in Section 16.5, the German rectal trial[22] also showed that preoperative long-course chemoradiotherapy, when compared with postoperative chemoradiation, improved local control without affecting overall survival. Acute and long-term toxicities were also less with preoperative therapy.

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 selection of preoperative patients by endorectal ultrasound or MRI 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. This may not be feasible in some circumstances, such as emergencies due to obstruction or perforation. The United Kingdom MRC CR07 study is currently comparing preoperative radiotherapy with postoperative selective chemoradiotherapy.

When should adjuvant therapy be considered for rectal cancer?

Guideline — Adjuvant therapy for rectal cancer	Level of evidence	Practice recommendation	Refs
Adjuvant preoperative or postoperative radiotherapy is recommended for high-risk (T3/4 or N1) rectal cancer.	I	Strongly recommend	26

Does preoperative therapy reduce late morbidity compared with postoperative?

Guideline — Adjuvant therapy for rectal cancer	Level of evidence	Practice recommendation	Refs
Preoperative therapy may lower the incidence of late morbidity.	II	Recommend	22, 34

What postoperative chemotherapy should be administered if radiotherapy is indicated?

Guideline — Adjuvant therapy for rectal cancer	Level of evidence	Practice recommendation	Refs
Where postoperative radiotherapy is indicated, 5-FU-based chemotherapy should be administered.	II	Recommend	6

16.10 Role of chemotherapy without radiotherapy

Postoperative adjuvant chemotherapy alone for rectal cancer has been tested in several studies. The underpowered study GITSG 7175 compared chemotherapy using 5-FU plus semustine with surgery alone, surgery plus radiotherapy, and surgery plus CMT.[4] There was a non-significant trend to higher cancer-free survival for patients receiving chemotherapy compared to surgery alone. NSABP R-01 compared chemotherapy with MOF (Mitomycin C, Oncovin, 5-FU) to surgery alone or radiation alone in 555 subjects.[3] A significant overall improvement in disease-free and overall survival was found with chemotherapy. A Japanese trial used oral 5-FU combined with mitomycin C for a year and detected a decrease in local failure. A CCOPGI pooled analysis of these trials found a mortality odds ratio of 0.65 ($p = 0.0006$) in favour of chemotherapy, but no significant impact on local recurrence.

A subgroup analysis of rectal patients within a Japanese meta-analysis of three randomised trials of adjuvant oral fluoropyrimidine chemotherapy in Colorectal Cancer following surgery has been reported. This analysis found a mortality risk reduction of 0.86 ($p = 0.05$) and disease free survival risk of 0.77 ($p = 0.0003$) in favour of oral chemotherapy.[36]

In an interim analysis at 3.5 years, the Netherlands Adjuvant Colorectal Cancer Project found no significant difference in disease-free or overall survival for chemotherapy with 5-FU plus levamisole versus surgery alone in a rectal cancer subgroup.[37]

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). There is a significant survival benefit from 5-FU-based chemotherapy for patients with lymph-node positive colon cancer. Data from studies of patients with metastatic disease from these sites would support this. Chemotherapy alone does not appear to affect local recurrence.

16.11 Complications of adjuvant therapy and how they may be reduced

All radical anti-cancer treatments are associated with specific morbidities.[38] 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 methodology supports adjuvant therapy.[39]

16.11.1 Radiotherapy

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

Long-term (late) side effects affect only a small number of patients, but are usually permanent. They include small bowel damage (bleeding, stricture, perforation and malabsorption) and rectal damage (reduced reservoir capacity, urgency, frequency, bleeding, incontinence and fistula formation). These effects are seen in 3–11% of cases.[34] Persisting lumbosacral plexopathy was seen in six patients in the Swedish Rectal Cancer Trial, but this may have been due to incorrect placement of dorsal shields. The Dutch Colorectal Cancer Group preoperative radiotherapy study[40] (to be discussed below) recorded 53 patients as experiencing acute neuropathic symptoms from short-course radiotherapy. With careful evaluation of treatment fields, shielding with adjustments as necessary plus selective treatment interruption, none of these patients had long-lasting symptoms at two years of follow up. Early quality of life data based on 991 Dutch patients indicate that at 1-year post operation, 63% of the radiotherapy group who were sexually active before the operation were still sexually active, compared to 74% for the surgery-alone arm ($p>0.001$). Sexual satisfaction and dyspareunia were worse in the radiotherapy group.[41] All premenopausal women receiving pelvic radiotherapy will undergo a premature menopause. Fertility may be affected in men.

Preoperative radiotherapy has been associated with an increase in postoperative complications in some studies.[28,29] A follow up of patients in the Swedish Rectal Cancer Trial revealed an increase in median bowel frequency, incontinence and urgency as well as emptying difficulties for the irradiated group.[42] Thirty per cent of the irradiated group reported impairment of social life because of bowel dysfunction, as compared to 10% with surgery alone ($p<0.001$). Long-term data from the Stockholm II trial demonstrated an increased risk of death within six months of surgery (5% vs 1%), deep vein thrombosis, cardiovascular events, bowel damage and incontinence in those who had preoperative radiotherapy.[30] The recent toxicity report from the Dutch Colorectal Cancer Group trial of TME with or without preoperative short-course radiotherapy found that irradiated patients that underwent abdominoperineal resection had more blood loss and more complications in perineal wound healing.[40]

Mortality from non-cancer causes was greater in the radiotherapy arms of older studies and those that used two field techniques (see above). Recent series using modern techniques report postoperative mortality rates of 2–4%.[38] Long-term morbidity and mortality are significantly increased in patients over 75. 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 infrequently-used surgical procedures such as omental slings or dexon meshes.[17]

16.11.2 Chemotherapy

Acute complications of 5-FU-based chemotherapy are mouth ulcers, diarrhoea and nausea. Marrow suppression is typically mild, but significant myelo suppression is seen in a small number of patients. Uncommonly, palmar plantar erythema or skin photosensitivity may develop. Complete alopecia is very uncommon.

16.11.3 Combined modality therapy

Both acute and late morbidity are increased with CMT. In the management of individual patients, this should be considered when discussing treatment recommendations. In the GITSG study,[4] severe non-haematological toxicities occurred in 35% of patients with CMT, compared to 16% for radiotherapy alone, or 15% for chemotherapy alone. Leucopoenia (white cell count <2000/ml) occurred in 26% of the CMT group, compared with 2% for radiotherapy alone and 13% for chemotherapy alone.

Krook et al[6] also found haematological toxicity to be increased when CMT was compared with radiotherapy alone. Protracted venous infusion was associated with significantly more diarrhoea (24%) than bolus 5-FU (14%, $p<0.01$), but less leucopoenia (2% vs 11%, $p<0.01$).[8]

Rectal function may also be adversely affected by CMT. In a survey of patients entered into the Mayo randomised trial,[43] those who received CMT had significantly higher rates of occasional and frequent incontinence (39% vs 7% and 17% vs 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 demonstrate 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.[44]

There are two cost-effectiveness studies that address adjuvant radiotherapy for rectal cancer. The marginal cost of postoperative 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.[45] Cost analysis over eight years of 98 patients enrolled onto the Swedish Rectal Cancer trial of short-course preoperative radiotherapy found the cost of a life-year saved was US$3654.[46] With sensitivity analysis for different rates of recurrence and costs related to complications, this figure could vary up to US$15,228. These compare favourably with many widely accepted health care interventions.

16.13 Is adjuvant therapy necessary with optimal resectional 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 optimum expert surgery with clear resection analysis,[47,48] including those series employing total mesorectal excision.[49,50] Analysis of the effect of surgeon variation was performed on patients entered

into the randomised Stockholm study.[51] They found that even for some centres that had lower rates of recurrence, these rates of recurrence and survival could be further improved by the addition of preoperative radiotherapy.

The Dutch Colorectal Cancer Group has published the early results of a randomised study of perioperative short-course radiotherapy combined with total mesorectal excision in rectal cancer. The study enrolled 1805 subjects.[52] In the 1748 patients where a macroscopic complete local resection was carried out, radiotherapy was associated with a local recurrence rate at two years of 2.4% compared to 8.2% with surgery alone ($p<0.001$). This implies treatment of 17 patients to prevent a recurrence. A recent update at three and a half years found respective recurrence rates at 3.4% compared to 10.1%.[41] The preoperative radiotherapy did not compensate for margins less than 1 mm, but for margins greater than 2 mm, the local recurrence rates were 0.4% versus 5.8%. The radiotherapy did not appear to benefit high rectal cancers more than 10 cm from the anal verge. Preoperative radiotherapy reduces the risk of local recurrence in patients with rectal cancer who undergo a total mesorectal excision. "The Dutch trial" included patients with high risk as well as low risk rectal cancer (stages I, II, III and up to 15 cm from anal verge). The benefit of adjuvant therapy is less with better surgery. No differences in distant recurrence rate or overall survival have yet been seen at this interval of follow up.

16.14 Conclusions and future directions

For patients with high-risk rectal cancer there are clear benefits 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 with protracted venous infusion has been a reduction in deaths from metastases. Any postoperative adjuvant therapy program should include radiotherapy and chemotherapy. Currently, there are good data only for postoperative CMT. Preoperative radiotherapy alone using modern techniques at biologically effective doses may also improve survival. Data directly comparing this with postoperative CMT are pending. These studies are continuing, as are others integrating the use of new chemotherapy agents such as the oral fluoropyrimidines, raltitrexed, oxaliplatin and irinotecan into the radiation protocols.

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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 bowel 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]

Proponents of intensive follow up argue that this approach could lead to earlier detection of recurrent and/or metachronous disease, and by improving resectability rates, may improve survival time.

Five single-institution, prospective randomised clinical trials of follow up have compared an intensive follow-up strategy with a less intense strategy.[5-9] All considered overall survival as the main outcome measure. Two of the studies used additional tests in the intensive surveillance arm,[7,8] two looked at the surveillance interval,[5,9] and one looked at both.[6] Although one study[9] found a survival benefit associated with more frequent follow up, the majority of the trials seemed to indicate no survival advantage for intensive follow up — including the one Australian trial.[8] All these studies, however, may be criticised on the basis that they lacked significant statistical power.

Meta-analyses overcome the problems associated with individual studies with regard to sample size and statistical power. However, there are problems with combining dissimilar follow up programs. Four meta-analyses[10-13] have been performed to look at the relationship between intensive follow up and survival after curative resection for Colorectal Cancer. One meta-analyses was based entirely on non-randomised data,[10]and another combined randomised trials with cohort studies.[11]

Two of the studies, however,[12,13] only reviewed published randomised studies.[5-9] They independently reported their results. Both showed a significant improvement in all causes of mortality in patients followed intensively, compared with less follow up (combined risk ratio 0.81, 95% CI 0.70 to 0.94, p = 0.007).[12] No study directly compared specific tests, but in four trials, computed tomography (CT) and frequent carcinoembryonic antigen (CEA) measurements (modalities aimed at detecting extramural disease) were limited to the intensive arms. These four trials, adopting a targeted approach to detecting extraluminal recurrence, showed the greatest effect on mortality (combined risk ratio 0.73, 0.6–0.89, p = 0.002). Little effect was seen in the trial aimed at detecting intramural disease recurrence by intensive colonoscopy surveillance (risk ratio 0.93 0.73–1.18 p = 0.88).[12]

Perhaps this could be improved by a search for occult disease as suggested by Oberg.[14]

Although there was no difference in the rates of recurrence between intensive and control follow up (32% and 33% respectively), recurrences were detected 8.5 months earlier in the intensive group, (95% CI 7.6–9.4 months).

Rates of intraluminal recurrence and detection of metachronous cancers were low (3.2% and 1.3% respectively) in both groups, with no difference in the rates between the two.

The Cochrane review[13] of the same five studies[5-9] found that intensive follow up improves survival, although the studies lacked capacity to infer best follow-up methods or estimate potential harms or cost of intensifying follow up for these patients or adapt a cost-effectiveness approach. Further such trials are necessary.

A more recently published prospective randomised study[15] — aimed at evaluating the diagnostic efficacy and costs of follow up tailored to risk of recurrence, compared with minimal surveillance — appears to support the above. It showed that risk-adapted follow up significantly improved the targeting of curative re-operation and overall survival of patients independently of the risk of recurrence.

17.1.3 Audit

Follow up provides information on clinical outcomes for clinicians to evaluate their practice against professional standards.[16] It is essential for participation in clinical trials.[17] 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

Little data exists on the effect of follow up on quality of life, but it has been suggested that follow up may provide reassurance or conversely, cause anxiety. One study[18] trying to address this issue interviewed Colorectal Cancer patients at different times related to their follow up visit, and found that the timing of the interviews had no effect on the patients' quality of life. They also found patients indicated a strong preference to be followed up. Another study[19] found insignificant differences in quality of life based on intensity of follow up; patients who were followed more intensely also had greater confidence in the utility of follow up.

What are the recommendations for follow up?

Guideline — Follow up	Level of evidence	Practice recommendation	Refs
Intensive follow up for Colorectal Cancer should be considered for patients who have had potentially curable disease, although optimal investigation and pathways are yet to be firmly established.	I	Recommend	12, 13

17.2 Which patients should be followed up?

As 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 at 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.

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

Colonoscopy is the most appropriate investigation for detection of synchronous, recurrent or metachronous cancers and polyps. However, it is not common to find intraluminal recurrences and metachronous cancers irrespective of the intensity of follow up, and intensive follow up with colonoscopy aiming to detect intraluminal recurrences is probably not justified.

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.[20,21] Ideally, the colonoscopy that visualises the entire colon should be performed before 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.[22]

Studies have shown that metachronous cancers are unlikely to be detected earlier than three years following surgery for colorectal malignancy, and are most likely to be detected five years after the initial operation.[23,24] Consequently, it is recommended that colonoscopy be performed three to five years after the initial operation.[8]

Sigmoidoscopy

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.

Serum CEA levels

Serum CEA levels have been used to alert the presence of recurrent or metastatic cancer. In one meta-analysis of nonrandomised studies,[18] some of which used historical controls, it was postulated that a rise in CEA is associated with improved survival as it allowed ‘pick up’ of resectable hepatic metastases. A more recent meta-analysis of randomised controlled trials looking at follow up showed a reduction in mortality with intensive follow up, including frequent measurement of CEA.[12] 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.[25,26] A large number of tumour markers in addition to CEA are currently undergoing evaluation. Although many have shown prognostic importance, none have been evaluated extensively enough in the context of follow up to be recommended for routine clinical use.[27]

The use of regular CEA measurement and CT scans in follow-up protocols is supported by the current available literature. CEA testing is usually arranged 3–6 monthly in conjunction with the patient’s clinical review.

CT scan of the liver

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). Meta-analysis of randomised controlled trials of follow up protocols has shown intensive follow-up protocols aimed at detection of extramural disease using computed tomography to be associated with reduced overall mortality.[12]

Ultrasonographic screening

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, but it does not involve radiation exposure.

Chest x-ray

Chest x-ray (CXR) is a sensitive investigation for detecting lung metastases. Three prospective randomised trials[6-8] that included colon and rectal cancer have suggested that resectable disease can be identified in 1.8–12% of patients through the use of CXR.[27] No study, however has compared differences in survival based on the use of CXR and at present, there is insufficient data to recommend or not recommend the routine use of CXR in follow up of Colorectal Cancer. Further studies are needed to define the role of CXR in this regard.[27]

FOBT

Although FOBT is potentially capable of identifying both local recurrences (if an intraluminal component exists) and metachronous disease, the role of FOBT remains contentious.

PET and monoclonal antibody scans

Although both these investigations have been extensively studied in terms of their role in follow up of other abnormal tests, there is no data currently available that addresses the role of positron emission tomography or monoclonal antibodies scans as first-line investigations in the follow up of colorectal patients.[27]

The Adelaide study[8] showed clearly that a regular, planned clinical review, along with routine haematological and faecal tests, was effective in detecting both resectable and non-resectable recurrences and metastases.

Whatever the choice and frequency of investigations performed, symptoms are the first sign of recurrence for many patients with Colorectal Cancer. Even within carefully performed trials, 16–66% of patients were symptomatic at the time of the diagnosis of their disease recurrence.[27] A person developing clinical symptoms of disease requires full investigation.

17.4 Cost effectiveness of follow up

Cost-effectiveness of follow up has been less well studied for Colorectal Cancer than other diseases. However, a recently published United Kingdom study has addressed this issue by analysing the cost-effectiveness of intensive follow up compared with conventional follow up in patients with Colorectal Cancer.[28] The study looked at incremental cost-effectiveness, recognising differences in follow-up strategies, based on effectiveness data from a meta-analysis of five randomised trials, [5-9] and then at the four trials designed for early detection of extramural recurrence[6-9] — so-called targeted surveillance. For the five trials, the adjusted net (extra) cost for each patient was £2479 (€3550; $A4288), and for each life year gained, it was £3402, substantially lower than the current threshold of NHS cost acceptability (£30,000).[28] Based on United Kingdom 2002 costings, the authors concluded that intensive follow up was economically justifiable (refer 22.8).

While this study justifies current costs of intensive follow up, there is need to evaluate the efficiency of specific surveillance tools that form the basis for economic evaluations in trials.[28]

17.5 Suggested schedule

There should be an early post-discharge review, followed by a review three to six monthly for two years, and six-monthly to yearly thereafter.[18] These intervals are still being discussed as a result of the Cochrane Review,[13] further trials will be necessary to establish optimal protocols.

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

Regular CEA measurement and CT should be considered in follow-up protocols as they may provide useful clinical information.

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 role of FOBT remains contentious. The optimal schedule, including duration, is not yet clear.

Future studies should focus on the cost-effectiveness and efficiency of investigations employed.[29]

17.6 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
- the detection of potentially curable recurrent disease.

Current literature, based on meta-analyses of randomised controlled trials,[12,13] supports small but significant survival advantages for patients who are followed up intensively after curative resection of Colorectal Cancer. Although the costs and complications of follow-up investigations can be considerable, the cost may be economically justified.[28]

Further large-scale trials are recommended to determine cost in the Australian setting, the impact of follow up on quality of life, exactly which tests should be used, and the timing of these tests, and to compare specialist follow up with general practitioner follow up.

The Followup after Colorectal Surgery (FACS) study is in progress in the United Kingdom and is designed to answer these questions.[30]

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 and stressful life event that necessitates an adaptive adjustment to sustain quality of life. A fundamental goal is to enhance quality while striving to prolong life. Quality of life has been reported to predict survival in patients with advanced Colorectal Cancer.[1] Attention to psychosocial aspects is vital to achieve an appropriate level of quality of life.

The importance of psychosocial care is recognised by the recent publication of *Clinical practice guidelines for the psychosocial care of adults with cancer (2003),*[2] which are a useful evidence-based source for practising clinicians.

Sprangers et al[3] 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.[4,5] Anxiety was problematic in 25%.[6,7] Psychological functioning was more impaired in younger female patients.[8,9] Further evidence indicates that 31.6% of colon cancer patients experience psychological distress.[10]

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.[3]

There is also evidence that families of colon cancer patients experience adjustment problems.[10] 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.[11] The distress reverberates through the family in the setting of palliative care in such a way 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.[3,12] Sexual problems experienced by women after surgery include dyspareunia, vaginal dryness and pain interfering with sexual pleasure.[13] 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.[5,14]

Systematic studies of patients with cancer have shown that clinicians frequently fail to identify psychological problems. There are generic factors related to poor adjustment to diagnosis and treatment 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[4,8,15]
- women[4,8,9]
- ostomates[3] (refer 12.1)
- patients who have experienced cumulative losses
- those who are 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.

Surveys of patients with cancer repeatedly identify information provision as a major unmet need.[16] Research has shown that the provision of adequate information is related to increased psychological wellbeing.[17] Effective communication skills ensure that this information is clearly explained and understood.[18,19]

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;[20]
- 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 consideration given to offering tape recording of key consultations.[21] Provision of a specialist nurse or counsellor, a follow up letter and psycho educational programs may also assist in recall of information.[22]
- information should be made available over time and if desired, review appointments that allow time for further integration of information should be scheduled
- patients' carers and families should also be kept well informed
- well-informed patients feel more in control and achieve a better psychological adjustment over time, although many are concerned if they perceive a delay in active treatment.

18.1 Psychological treatments

Surveys of patients with cancer identify psychological support as a major unmet need.[16] 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 daily living activities, social and role functioning, and vocational activities), knowledge of the disease and its treatment, treatment and disease-related symptoms (e.g. nausea, vomiting, pain, etc.) and overall quality of life.[17,23,24] Intensive psychotherapy, consisting of weekly supportive group therapy with self-hypnosis for pain over a 12-month period, has also shown significant survival benefits in women with metastatic breast cancer.[25]

There are wide benefits from relaxation-based therapies in reducing anxiety, treatment-related phobias, conditioned nausea and vomiting, and insomnias.[17] Both cognitive–behavioural and supportive–expressive therapies are effective in countering existential fears of dying, aloneness, meaninglessness and unrealistic fears about processes of treatment.[17,23,24] 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.[26-28] Early

referral to community-based domiciliary palliative care services support and information, where available, may have several benefits and enhance quality of life. Support can be provided by various health disciplines with appropriate training.

Guideline — Psychological interventions	Level of evidence	Practice recommendation	Refs
Psychosocial care is important. Psychological interventions should be a component of care as they can improve the quality of life for patients with cancer.	I	Strongly recommend	17, 22

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Section II

Advanced Colorectal Cancer

CHAPTER 19 RECURRENT AND ADVANCED COLORECTAL CANCER: GENERAL APPROACH AND LOCAL MANAGEMENT

19.1 General approach

Advanced rectal cancer incorporates a wide spectrum of conditions including:

- locally advanced potentially operable
- locally advanced inoperable
- synchronous local and distant disease
- isolated local recurrence
- local and distant recurrence

Decisions regarding management in these groups of patients can be very complex and frequently needs to be individualised according to the extent of disease, the type and severity of symptoms and the health and wishes of the patient. The coordinated efforts of a team of professionals are likely to be helpful in managing such patients. Surgeons, medical and radiation oncologists, palliative care physicians and nurses (oncology, palliative care, stomal therapy and domiciliary) may all play a critical role in patient management. Of particular importance is the role of the general practitioner in the management of both the patient and family. Unfortunately there is a lack of good quality clinical trials in which various treatment 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 (particularly nerve root 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 this chapter. 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.

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 Locally advanced rectal cancer deemed potentially operable

Such advanced cancers (T4) are often initially inoperable due to local extension and fixity. Preoperative radiotherapy or chemoradiation may shrink bulky tumours and mobilise those tethered within the pelvis, enabling successful resection in such cases previously deemed inoperable. This will improve local control, quality of life and may well confer a survival benefit.

In patients with severe obstructive symptoms, it may be appropriate to recommend a defunctioning colostomy before commencing radiotherapy to avoid complete obstruction during therapy and the requirement of an emergency laparotomy.

Two randomised trials[2,3] and an uncontrolled study have shown the benefit of pre-operative radiotherapy in such cases. Recent studies also suggest that combining radiation and chemotherapy preoperatively can enhance the effect of treatment without increasing surgical morbidity, and should

be considered in locally advanced cases.[4–11] Such chemotherapy should consist of a 5-FU-based regimen.

For patients who have had a complete resection, postoperative 5-FU chemotherapy is recommended as per the adjuvant therapy guidelines for high-risk rectal cancer.

For locally advanced or recurrent rectal cancer, the technique of intra-operative radiotherapy may be of benefit.[12,13] This allows the delivery of a single high dose of radiation to the tumour bed or region of post-surgical residual disease. Critical structures such as small bowel can be moved out of the treatment field. Its role, however, is controversial and needs to be evaluated in further clinical trials.[14,15]

What are the recommendations for recurrent and advanced rectal cancer?

Guideline — Preoperative radiotherapy	Level of evidence	Practice recommendation	Refs
Radiotherapy, generally combined with chemotherapy, is recommended in rectal cancers fixed or tethered within the pelvis.	II	Recommend	2,3

19.3 Locally advanced rectal cancer deemed inoperable

In patients with regionally advanced cancers deemed inoperable, radiotherapy may offer excellent palliation with a small group (less than 10%) showing long-term control.[16] The combination of chemotherapy with radiotherapy appears to improve response rates and local control, though its impact on survival is unclear.[6–9]

It is important to deliver relatively high doses of radiotherapy to provide the best opportunity to obtain local control in these patients. Uncontrolled local disease, even in the presence of metastases, is associated with major morbidity that can significantly impair the remaining quality of life of a patient. Symptoms include pain, obstruction, incontinence, bleeding, discharge, neurological compromise and peripheral oedema. Patients with obstruction need to be managed empirically.[17] With the availability of second-line chemotherapy with drugs such as oxaliplatin and irinotecan, local treatments such as surgical resection, cryotherapy, radiofrequency ablation, and hepatic arterial infusion also play a bigger role in achieving effective control of local tumours.

Radiation treatment 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.[18] With such measures, the risk of radiation-induced bowel injury is small. Laser therapy[19] and/or the placement of colonic stents[20] may also be a useful adjunct to radiotherapy in preventing the need for a defunctioning stoma.

The use of brachytherapy 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 to the tumour, or delivered as sole therapy in patients with a short life expectancy.[21,22]

What are the recommendations for inoperable rectal cancer?

Guideline — Inoperable rectal cancer	Level of evidence	Practice recommendation	Refs
Radiotherapy alone or chemoradiation should be considered in patients with locally advanced rectal cancer not amenable to surgery.	IV	Recommend	6–9, 16

19.4 Synchronous local and distant disease

Some of the most difficult decisions on treatment are in those patients diagnosed with both local and distant disease. Accordingly, their treatment often needs to be individualised.

When patients present synchronously with both a colorectal primary and liver secondaries, they can still be considered for potentially curative treatment.[23]

Careful staging is important to accurately select such patients for a radical approach. Such investigations include CT imaging of the chest, abdomen and pelvis, MRI imaging of the pelvis, assessment of the liver with MRI or angio-CT and, where available, PET scanning.[24–26] In these situations, resection of the primary disease generally takes priority, though in certain cases, patients may be considered for synchronous resection of both their primary and liver disease. If all gross disease has been resected, then patients should be considered for adjuvant therapy.

In patients with unresectable metastatic disease, aggressive treatment of the primary disease can often be appropriate to maintain control for the patient's remaining lifetime. Uncontrolled pelvic disease can lead to disabling tenesmus and bleeding, which can often be difficult to palliate. Significant symptom relief can be obtained with radiation therapy in 50–90% of patients with rectal bleeding, discharge or pain.[17,27–29] In a recent series from MD Anderson hospital,[30] 55 patients with synchronous distant metastases from rectal cancer were treated with pelvic chemoradiation and no surgery. Eighty-one per cent had symptomatic pelvic control and 79% remained colostomy-free during their lifetime. Overall, 11% were alive at two years. Newer drugs such as oxaliplatin and capecitabine are under investigation as concurrent therapies with radiation in this setting.

19.5 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.[31–33] Local recurrence rates of 3–50% have been recorded following apparently curative resection of rectal cancer.[34,35] Median recurrence rates for T1, T2–3 and node-positive tumours were 8%, 16.3% and 28.6% respectively.[34]

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.

19.5.1 Assessment of the extent of local recurrence

There are four established methods of assessing the extent of local recurrence of rectal cancer: CT scan, MRI scan, PET scanning 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.[36] While initial reports claimed a remarkable 95% sensitivity at detecting a local recurrence,[37] later series show the sensitivity to be considerably lower at 69–88%.[38–40]

There are difficulties in differentiating the appearance of normal postoperative changes (particularly in patients who have had previous radiotherapy) from recurrent cancer. Serial scans showing changes from a baseline are more sensitive than one-off scans.[41]

MRI scans were reported initially to be able to distinguish postoperative fibrosis from tumour recurrence more effectively than CT scans,[42] and their accuracy has been confirmed by more recent data.[43]

Probably the best currently available method of distinguishing fibrosis from recurrence is with PET scanning. This should be considered where available.[26]

ERUS has been found to be similar in efficacy to CT in detecting local recurrence and can detect small extra-rectal recurrences before symptoms develop or there is endoluminal evidence of disease.[44,45] Unfortunately, like CT and MRI, ERUS is unable to differentiate between normal perirectal lymph nodes and those harbouring recurrent cancer.[41]

19.5.2 Management of local recurrence

About 50% of patients with local recurrence of rectal cancer have disease confined to the pelvis.[35, 46] The vast majority of local recurrences are inoperable and incurable. These patients are often in severe discomfort with cachexia and limited life expectancy. Their management is palliative and it should include consideration of radiotherapy and/or chemotherapy as well as adequate pain relief.

In patients who have not received previous pelvic radiotherapy, the use of palliative radiotherapy can relieve symptoms in the majority of cases, but the duration of relief is often short lived[18,27–29] Such radiation may be combined with chemotherapy, given either concurrently or sequentially. In patients who have had previous pelvic radiotherapy, re-irradiation may be considered in special circumstances.[47] It is important that patients are involved in decision making and that their values are considered when deciding on the role of palliative radiotherapy.[48]

A small number of recurrences may be salvaged with further local treatment. When local recurrence is not resected, five-year survival is negligible.[46] With major ablative surgery in highly selected cases, five-year survival can be as high as 37%.[49,50] Therefore, in the absence of distant disease (after careful staging) or disabling comorbidities, surgical resection should be considered. In cases where radiotherapy has not been administered previously, the use of preoperative chemoradiation is to be recommended.[51]

Major 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.[52] Although the above-mentioned reports support the use of radical surgical procedures, the lack of evidence based on randomised controlled trials as to their benefit precludes issuing broad recommendations regarding their use. Where contemplated, these procedures should be performed in specialised centres.

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CHAPTER 20 THE ROLE OF SYSTEMIC CHEMOTHERAPY IN METASTATIC DISEASE

20.1 To treat or not to treat

First- and second-line chemotherapy should be considered standard treatment for patients with metastatic Colorectal Cancer.

A recent Cochrane review of individual patient data from 13 randomised studies that compared palliative chemotherapy with best supportive care concluded that the use of chemotherapy was associated with a 3.7-month improvement in median survival.[1] This effect was consistent across all age groups. With respect to combination therapy, two randomised studies have demonstrated that the combination of 5-FU plus irinotecan results in superior survival compared to 5-FU alone as first-line treatment.[2,3]

For patients not previously treated with irinotecan, the use of irinotecan as second-line therapy is associated with a significant survival advantage and a significant improvement in quality of life relative to best supportive care.[4,5]

20.2 Timing of chemotherapy

Should chemotherapy be used when signs of advanced Colorectal Cancer first appear (early treatment), or should it wait until symptoms appear (delayed treatment)?

A study by the Nordic group enrolled 183 patients with asymptomatic metastatic Colorectal Cancer to receive either early or delayed 5-FU plus leucovorin.[6] Early chemotherapy resulted in a greater symptom-free survival (median ten months compared to two months, $p<0.001$) and the median survival was improved from nine to 14 months, but this was not statistically significant. Investigators from Australia and Canada recently reported on two almost identical randomised trials that also addressed the question of early versus delayed treatment.[7] In a combined analysis of these two studies, which entered a total of 168 patients, no significant benefit in terms of quality of life or overall survival was evident from the use of early chemotherapy.

While a small but significant survival benefit has not been excluded by these studies, because they were only powered to detect very large difference in overall survival, they now have little relevance to current clinical practice where combination first-line regimens are now available, and second-line chemotherapy is standard.

20.3 Selection of chemotherapy

No single chemotherapy agent or combination regimen can be recommended as standard therapy for all patients presenting with metastatic Colorectal Cancer. Therapy therefore should be individualised, based upon previous treatment, disease extent, organ function, and medical comorbidities.

20.4 Chemotherapy options

20.4.1 Intravenous 5-FU-based chemotherapy

There is no standard method of delivering 5-FU chemotherapy. Options with intravenous 5-FU include bolus administration according to a variety of schedules (with or without leucovorin), and delivery as a continuous infusion. More recently, oral formulations have become available.

The value of adding leucovorin to 5-FU has recently been addressed in a meta-analysis of 18 studies with a total of 2751 patients.[8] The addition of leucovorin significantly increased the response rate

(23% compared to 12%, p<0.0001), and was associated with a small but statistically significant improvement in survival (one-year survival increased from 43% to 48% p = 0.003).[8]

Two standard regimens that combine 5-FU and leucovorin have been developed. The Mayo regimen of 5-FU 425 mg/m^2 plus leucovorin 20 mg/m^2 as an IV push is administered day 1–5 every four weeks. The Roswell Park regimen of 5-FU 500–600 mg/m^2 plus leucovorin 500 mg/m^2 over two hours is given weekly for 6 weeks, with courses repeated every eight weeks. A randomised study that compared these two regimens in 362 patients found similar response rates, palliative effects and survival outcomes.[9] The Mayo regimen was associated with significantly more leucopoenia and stomatitis, but less diarrhoea and fewer hospital admissions. The optimal dose of leucovorin is unclear. Randomised studies looking at low- versus high-dose leucovorin with the Mayo regimen of 5-FU found no significant difference in response rates or survival outcome[10,11] Two similar studies, where the 5-FU was given according to a weekly schedule,[12,13] reported increased response rates in the high-dose leucovorin arms, but survival endpoints were again unaltered, and toxicity and expense were increased.

Only one study has compared a weekly with a monthly 5-FU regimen using the same dose of leucovorin in each arm. Wang et al[14] randomised 94 patients with previously untreated metastatic Colorectal Cancer to receive either weekly treatment (5-FU 400 mg/m^2 plus leucovorin 20mg/m^2) or monthly treatment (5-FU 400mg/m^2 plus leucovorin 20mg/m^2 day 1–5). They reported that the response rate (14.3% vs. 10.6%, p = NS) and median survival (18.4 vs. 15.8 months, p = NS) was similar in both arms. However, the monthly arm produced higher rates of severe diarrhoea (14.9% vs. 2%, p = 0.029) and there was also a trend toward a higher rate of severe stomatitis (8.5% vs 0%, p = 0.054) with monthly treatment.

A potential advantage of weekly treatment is that it permits adjustment of dose if early signs of toxicity appear. When using a Mayo-type regimen, all five doses have typically been administered before significant toxicity is apparent.

The Meta-analysis Group in Cancer performed a review of studies comparing continuous infusion 5-FU with bolus administration. They reported a higher response rate (22% compared to 14%, p = 0.0002) and a slight survival benefit (12.1 compared to 11.3 months, p = 0.04) favouring infusional 5-FU.[15] Bolus 5-FU was associated with more haematological toxicity, mainly neutropenia (31% compared to 4%, p<0.0001), but less hand-foot syndrome (13% compared to 34%, p<0.0001). A randomised study comparing a combination bolus/infusional 5-FU regimen (deGramont) versus bolus 5-FU alone has also recently been reported. The combination arm demonstrated an improved response rate (32.6% compared to 14.4%, p = 0.0004) and less grade 3 and 4 toxicity, but no significant difference in overall survival (median 62 compared to 56.8 weeks, p = 0.067).[16] The disadvantage of infusional 5-FU delivery is the need for indwelling venous access and hence the potential for catheter-related complications.

20.4.2 Oral 5-FU-based chemotherapy

Until recently, the administration of fluoropyrimidines via the oral route was limited by unpredictable bioavailability. Now reliable drug delivery can be achieved by delivery as a prodrug (e.g. capecitabine), and/or in combination with an inhibitor of DPD (dihydropyrimidine dehydrogenase) that prevents GIT metabolism.[17] A survey of 103 patients by Liu et al explored the patients' attitudes to oral therapy.[18] Eighty-nine per cent preferred oral treatment due to the increased convenience of home administration and a preference for a pill rather than intravenous administration. However, 70% were not prepared to accept a lower response rate, indicating that from the patient perspective at least, therapeutic equivalence needs to be demonstrated with these agents.

The most mature and promising data is for capecitabine, a prodrug converted to the active form of 5-FU in the liver and tumour in a multi-step process. Pooled data from two studies that randomised previously untreated patients to receive either capecitabine or standard bolus 5-FU plus leucovorin

have recently been reported.[19] Treatment with capecitabine was associated with a significantly greater response rate (25.7% compared to 16.7%) and significantly less toxicity, but there was no difference in survival endpoints. Capecitabine has a similar toxicity profile to infusional 5-FU.

UFT, a combination of a prodrug (ftorafor) and a DPD inhibitor (uracil), has also been extensively studied.[17] Two randomised studies[20,21] in patients with metastatic Colorectal Cancer, where UFT was compared to a standard 5-FU plus LV regimen, have demonstrated equivalence with respect to response rates, time to progression and overall survival. While UFT, like capecitabine,[19] was associated with a significantly better safety profile, unlike capecitabine there was no improvement in response rate.

20.4.3 Raltitrexed

Raltitrexed, a direct thymidylate synthase inhibitor, has demonstrated equivalent activity to 5-FU plus leucovorin in patients with advanced disease.[22] Raltitrexed is therefore considered an alternative treatment to 5-FU in certain circumstances, including patients experiencing unacceptable toxicity from 5-FU. This drug also has a more convenient schedule (once every three weeks), however this advantage is now less relevant due to the availability of oral 5-FU formulations. A major concern with raltitrexed is the high incidence of adverse events. In the setting of advanced disease, it was significantly more toxic than two 5-FU-based regimens (including an increase in treatment related deaths), and was associated with an inferior quality of life.[23] An adjuvant study of raltitrexed versus the Mayo regimen (PETACC-1) was terminated early due to unacceptable toxicity in the raltitrexed arm.

20.4.4 Irinotecan and oxaliplatin

Irinotecan (a topoisomerase I inhibitor) and oxaliplatin (a platinum analog) have significant single-agent activity in metastatic Colorectal Cancer.[24] These agents have also been widely studied in combination with 5-FU.

In two large randomised studies the combination of irinotecan and 5-FU achieved response rates significantly greater than those achieved with 5-FU alone (35% compared to 21% and 39% compared to 22%).[2,3] Overall survival was also improved (14.8 compared to 12.6 months, and 17.4 compared to 14.1 months). Two first-line studies of the combination of oxaliplatin plus 5-FU also demonstrated a superior response rate over 5-FU alone, (50% compared to 22% and 34% compared to 12%).[25,26] However, in both studies there was no significant improvement in median survival. This may be because these studies were not powered to demonstrate significant differences in median survival and/or the use of second-line therapy was not controlled.

Early results from two studies that explored the optimal sequencing of irinotecan and oxaliplatin-based regimens have been reported. In a European study comparing first-line 5-FU plus irinotecan (FOLFIRI) followed by second-line 5-FU plus oxaliplatin (FOLFOX), or vice versa, response rate and survival data were almost identical for the two arms.[27] In a United States study of bolus 5-FU plus irinotecan (IFL) versus infusional 5-FU plus oxaliplatin (FOLFOX), an improved response rate and superior survival were reported for the patients initially treated with FOLFOX.[28] The FOLFOX regimen had a lower rate of nausea, vomiting, diarrhoea, febrile neutropenia and dehydration. Differences in the 5-FU schedules, and in second-line therapy (patients treated initially with IFL did not routinely receive second-line therapy with oxaliplatin) may account for the apparent superiority of the oxaliplatin-containing regimen as first-line treatment. In this study, the two-drug combination of irinotecan and oxaliplatin (IROX) was inferior to FOLFOX.

On current evidence, with no clearly superior regimen in terms of response rate or survival outcomes, a major consideration becomes the differing metabolism and toxicity profiles of these two agents. An exception may be patients with liver-only metastases that are initially considered inoperable. Preliminary evidence suggests that treatment with an oxaliplatin-containing regimen may result in

more patients having disease down-staged to the point of being surgically resected, although these data are somewhat subjective at present, and may be subject to considerable selection bias.[27] For patients with significantly impaired baseline liver function, where the pharmacokinetics of irinotecan are altered, dose adjustments are required.[29] Abnormal liver function or the presence of significant diarrhoea, which is likely to be exacerbated by irinotecan therapy, are therefore other reasons to favour an oxaliplatin-containing regimen as first-line therapy. For patients with an existing peripheral neuropathy, a common complication of oxaliplatin therapy, first-line treatment with irinotecan is favoured.

20.5 Second line and subsequent chemotherapy

The role of irinotecan alone after failure of initial 5-FU-based therapy has been addressed in two randomised studies. Irinotecan as a single agent was found to be significantly superior to either best supportive care,[4] or an alternative schedule of 5-FU,[5] in terms of survival duration and quality of life. The two commonly used irinotecan regimens (125 mg/m^2 day 1, 8, 15 and 22 of a 6-week cycle, and 350 mg/m^2 day 1 of a 3-week cycle) demonstrate similar efficacy and quality of life, but diarrhoea is significantly less with a 3-weekly schedule.[30]

Where oxaliplatin is used as second-line treatment, it should be given in combination with 5-FU. This is based on the in-vitro synergy of these two agents and the apparently inferior response rates achieved with oxaliplatin alone.[31] Data on oxaliplatin-containing regimens as second-line therapy is emerging. In a single-arm phase II trial of oxaliplatin in combination with 5-FU in 97 patients refractory to 5-FU alone, a response rate of 20.6% and median survival of 10.8 months were reported.[32] An improved performance status was noted in 51% of patients on this study. In separate studies of patients previously treated with 5-FU plus irinotecan, response rates of 10% and 21% were achieved with a combination of oxaliplatin and 5-FU.[27,31]

Given the proven impact of irinotecan as second-line therapy,[4,5] and the limited data regarding oxaliplatin in this context, irinotecan should be considered the standard option for second-line treatment of patients initially treated with 5-FU alone.

20.6 Duration of chemotherapy treatment

Irrespective of the regimen chosen for first-line therapy, the optimal duration of treatment in those patients who achieve at least stable diseases and do not have unacceptable toxicity remains uncertain.

With respect to 5-FU-based regimens, a recent MRC study[33] suggests that routinely continuing therapy indefinitely may have an overall negative impact. In this study, 354 patients who had either partial response or stable disease after 12 weeks were randomised to continue therapy or to stop and then recommence at the time of progressive disease. Patients randomised to continue treatment ultimately received more treatment, experienced more toxicity and had an inferior quality of life without achieving an improvement in either progression-free or overall survival.

A recent study explored the optimal duration of second-line treatment with irinotecan. Patients who responded to treatment were randomised to discontinue treatment after a total of eight cycles of irinotecan 350-mg/m^2 q3w, or to continue until progressive disease. In this small study there was no clear benefit from continuing treatment.[34]

20.7 Other treatment options for patients with metastatic Colorectal Cancer

20.7.1 Bevacizumab

Two recently-reported studies[34,36] have demonstrated that agents targeting angiogenesis are likely to play a major role in the treatment of patients with metastatic Colorectal Cancer. In a study of 815

previously untreated patients, the addition of bevacizumab, a monoclonal antibody to vascular endothelial growth factor, to standard chemotherapy resulted in a significant increase in response rate and overall survival.[35] In patients receiving IFL plus placebo, responses were seen in 35% of patients, in those receiving IFL plus bevacizumab, the response rate was 45% (p = 0.0029). The addition of bevacizumab also improved median survival from 15.6 months up to 20.3 months (p = 0.0003). There was an increased incidence of hypertension in the experimental arm but this was easily controlled with standard medication. Although uncommon, gastrointestinal perforation was limited to the bevacizumab arm. A combined analysis of three studies comparing bevacizumab plus 5-FU plus leucovorin with 5-FU plus leucovorin alone has been reported in abstract form and suggests a similar benefit.[36] However, the available data on the combination of 5-FU plus leucovorin plus bevacizumab in patients who have failed all standard chemotherapy options suggests that bevacizumab may provide little benefit in this context.[37]

20.7.2 Cetuximab

Cetuximab is a chimeric anti-EGFR monoclonal antibody with efficacy against metastatic CRC previously resistant to treatment with irinotecan-based chemotherapy.[38-42] In this context, responses to the combination of cetuximab plus irinotecan were seen in about 23% of patients and to cetuximab alone in about 11% of patients with EGFR-positive tumours. [38-41] In the only randomised study, [42]an impact on survival was not demonstrated, but cross-over was permitted for patients not initially randomised to receive cetuximab. No quality-of-life data are available. Further studies are required to define the role of this promising agent.

20.8 Quality of life

For patients with symptomatic metastatic Colorectal Cancer, an improvement in quality of life has been suggested with first-line 5-FU[1] and clearly demonstrated with second-line irinotecan.[4,5] Preliminary results suggest that the use of 5-FU plus oxaliplatin in patients refractory to IFL results in significant relief of tumour-related symptoms, but the duration of benefit is short.[31]

Should chemotherapy be offered to patients with metastatic disease?

Guidelines — Systemic chemotherapy	Level of evidence	Practice recommendation	Refs
First-line FU-based chemotherapy prolongs life when compared to best supportive care and should be offered to patients with advanced Colorectal Cancer.	I	Strongly recommend	1

When is the optimal time to commence chemotherapy?

Guidelines — Systemic chemotherapy	Level of evidence	Practice recommendation	Refs
The optimal time to commence chemotherapy in patients who are initially asymptomatic is unclear.	II	Equivocal	6,7

What is the response rate in regimes of 5-FU chemotherapy?

Guidelines — Systemic chemotherapy	Level of evidence	Practice recommendation	Refs
After failure of 5-FU therapy, second-line treatment with irinotecan prolongs life and improves quality of life when compared to either best supportive care or an alternative regimen of 5-FU.	II	Recommend	4,5

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CHAPTER 21 MANAGEMENT OF LIVER AND OTHER DISTANT METASTASES

21.1 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. Management of liver metastases can involve one or more of the following treatment modalities:

- surgical resection
- image controlled destruction
- hepatic arterial infusion
- palliative chemotherapy (see Chapter 20)
- palliative radiation therapy.

21.1.1 Surgical resection

Approximately 50% of patients who undergo resection for Colorectal Cancer will develop recurrent disease within 5 years. The liver is the major site of recurrence and the primary determinant of patient survival. Systematic attempts to resect colorectal liver metastasis were commenced some 40 years ago[1,2] and subsequently became more widely accepted. A large number of reports showed that resection for colorectal liver metastasis was safe and potentially curative.[3–6] It is well established that isolated liver metastasis can occur without growth elsewhere and that surgical excision of liver tumours could be performed with low morbidity and mortality.[7]

There have been no controlled studies of surgery versus no treatment or chemotherapy for resectable disease. The studies of the natural history of liver metastases have been quite rightly criticised in regard to the lack of data on extent of liver involvement and comparison with historical controls from an era when clinical examination was the only method of determining metastatic disease to the liver. However, some authors have attempted to assess the natural history of potentially resectable disease that was not resected because of the therapeutic approach at that time. Wood[8] reported on 25 of 113 patients who were thought, retrospectively, to have potentially resectable disease. The survival at one, three and five years was 46%, 12% and 3% respectively. Wagner's study[9] showed three- and five-year survival for untreated, resectable disease was 14% and 2% respectively. Scheele[10] reviewed 62 patients with resectable disease that were not treated and found a three- and five-year survival of 10% and 0% respectively.

The data from these studies indicated that solitary or unilobar disease appeared to have a better prognosis, but had a uniformly bad prognosis when not treated, with 5-year survival consistently below 3%. However, liver metastases are common and most patients will not be helped by resection. As stated by Adson,[11] 'There is a need to distinguish between the limited influence of resection on a total population and the benefits available to a well-defined subgroup that can be treated well'.

The biology of the disease will determine the long-term outcome and better imaging modalities have resulted in better selection of patients to be offered resection. Retrospective studies have attempted to define good and bad prognostic indicators for long-term outcome. There have been conflicting statements regarding age[12] and sex as significant risk factors and similar results have been reported with synchronous or metachronous liver metastases.[3–6,13–15] In addition, bilobar liver metastases do not appear to influence outcome, provided it is resectable.[3,5,6,13] The characteristics of metastatic disease that correlate with poor outcome appear to be more than three metastases,[15,16] increasing tumour size[15] and an involved surgical margin.[5,15] However, recent reports have questioned the upper limit of three

metastases and have shown equivalent results with four or more metastases, provided complete resection with a tumour-free margin is achieved.[17,18] Several studies have suggested that the level of preoperative CEA may correlate with outcome,[18–21] although the critical level has variously been set from 30–200 ug/ml. In multivariate analyses, the most consistent predictors of long-term outcome have been stage of the primary tumour, total of liver involvement and complete resection.[7] However, Hughes[22] and Fong[21] have shown that a number of patients with poor prognostic indicators survived 5 years after liver resection and concluded that each case must be individually assessed on its merits.

In an endeavour to aid the appropriate selection of patients who may benefit from resection for metastatic Colorectal Cancer, Fong and his colleagues,[21] by analysing clinical, pathologic and outcome data on 1001 patients, established a clinical risk score for tumour recurrence. Five clinical criteria available before liver resection — nodal status of the primary; disease-free interval from the primary to discovery of the liver metastases of <12 months; number of tumours >1; preoperative CEA level of >200 ng/ml; and size of the largest tumour >5 cm — were chosen as criteria for a clinical risk score. Each criterion was assigned one point and the total score was compared with the clinical outcome of each patient. The total score was found to be highly predictive of long-term outcome. Such a clinical score may help the surgeon and the patient to be better equipped to make a rational decision about the individual patient.

There are a number of reports of repeat hepatic resection for recurrent colorectal liver metastases with results comparable to those after initial resection.[18,20,21,23–26] What has become evident is that some of the improvement in overall survival has been a result of repeat resection in selected patients, and this may also be applicable with methods using physical ablation.

Most series of liver resection for colorectal metastases have reported five-year survival around 25-35%, with a median survival of greater than two years. While there are no concurrent control groups of resectable but untreated patients, it would be difficult to run a controlled trial with a no-treatment arm. It is imperative that there be a low morbidity and mortality. Mortality of liver resection in most major hepatobiliary units in Australia is less than 2%. The evidence available from the many studies worldwide would support the proposition that liver resection is the only chance of cure in a selected group of patients who fit defined criteria as outlined.

21.1.2 Adjuvant chemotherapy following surgical resection

Four recent randomised studies[27–30] have attempted to define the benefit of adjuvant flouropyrimidine chemotherapy, delivered via a hepatic artery catheter and/or intravenously, following resection of hepatic metastases. A consistent trend toward improved survival outcomes has been demonstrated in each of these studies.

In one study[27] that compared intra-arterial hepatic chemotherapy plus systemic chemotherapy versus systemic chemotherapy alone, a statistically significant survival advantage and reduction of recurrence within the liver was found with combined therapy, but at a cost of higher side effects. Another trial[28] of hepatic arterial infusion with continuous intravenous 5-FU infusion compared to observation found an increased time to recurrence and fewer liver relapses, but median survival was not statistically significant. A Cochrane review of all trials that have randomised patients following liver resection to hepatic artery chemotherapy or any alternative treatment concluded that recurrence in the remaining liver happened less in the hepatic artery chemotherapy group, but that this did not lead to an improvement in overall survival.[31]

The two trials[29,30] that compared systemic bolus 5-FU plus leucovorin to observation alone; each showed only a trend to benefit of chemotherapy. Each study was only powered to show a very large difference. On the basis of these studies it is reasonable to offer adjuvant chemotherapy following surgical resection of liver metastases, but it cannot be considered standard treatment.

21.1.3 Imaging controlled destruction

Local ablative therapies for the treatment of colorectal hepatic metastases have been the focus of much recent research, with most interest being shown in radiofrequency (thermal) ablation (RFA or RFTA). This treatment involves percutaneous (or, less frequently, intraoperative) placement of a metallic probe into a hepatic lesion, using imaging guidance (usually ultrasound, occasionally CT or MRI). Radiofrequency energy passed through the probe causes local ionic excitation resulting in the lesion being 'heated' to a level where cell death occurs. The major technical issues are charring at the needle tip and incomplete treatment, based on the proximity of a lesion to vascular structures which act as a 'heat sink'.[32–34] The procedure may be performed on an outpatient basis using local anaesthetic and intravenous sedation. Most patients can be treated in a single session. Complication rates are as follows: mortality 0.5%, major complications 2%, minor complications 6%.[35,36]

Patient eligibility varies between institutions and individuals. There are no accepted standardised criteria. In general, patients should not be surgical candidates (either because of anticipated technical resection difficulties, or comorbidities), have five or less lesions each less than 5 cm in diameter and be free of other distant metastases.[33] Lesion location may also play a part in selection. Those close to or abutting the gallbladder, hepatic flexure of the colon, diaphragm and hepatic hilum require great care in treatment to avoid heat-related damage and may result in patient exclusion.[33]

As with all relatively new treatment modalities, little robust data is available in the form of randomised controlled trials and long-term survival statistics. A single prospective randomised controlled trial comparing RFA with surgery for solitary colorectal metastasis has been published, demonstrating similar median and 3-year survival rates between the two treatment modalities.[37] The largest published series to date, of 117 patients with hepatic metastases from colorectal carcinoma, reported that technical success (no radiologically detectable tumour at 7–14 days after treatment) was achieved in 98% of patients.[38]

Many other local ablative techniques are under investigation.[33,39–42] These include laser-induced thermotherapy, microwave therapy and high-frequency targeted ultrasound. Cryoablation has been largely abandoned due to a higher rate of major complications than for RFA.

Should imaging controlled destruction be considered?

Guideline — Imaging controlled destruction	Level of evidence	Practice recommendation	Refs
Radiofrequency ablation is an alternative to surgery in selected cases.	II	Equivocal	37

21.2 Chemotherapy for patients with unresectable liver metastases

21.2.1 Hepatic arterial infusion

Hepatic arterial infusion (HAI) involves the administration of chemotherapy agents directly into the liver through a catheter surgically implanted into the hepatic artery.

Potential advantages of this approach include:

- liver metastases mainly derive their blood supply from the hepatic artery rather than the portal vein[43]
- a mean hepatic drug concentration approximately 15-fold higher than can be achieved with intravenous chemotherapy[44]

- almost all (94–99%) administered floxuridine, an effective drug for the treatment of Colorectal Cancer, is metabolised by the liver during first pass, which reduces systemic drug concentrations and resulting toxicity.[45–47] However, this also means the systemic concentration of FUDR is insufficient to treat any extrahepatic metastases.

Technical complications include an operative mortality below 1% in experienced hands, mechanical problems related to the catheter such as leakage, kinks, migration or breakage (5%), vascular complications from the catheter such as thrombosis or aneurism formation (5%), and problems associated with implantable pumps (8%).[44–47] Toxicities from intrahepatic chemotherapy include sclerosing cholangitis (10%), which is occasionally fatal, chemical gastritis (10%) and peptic ulceration (5%).[45]

21.2.2 Efficacy of hepatic arterial infusion

Pooled data from a meta-analysis of six of the seven randomised studies published between 1988 and 1993 confirmed the significantly higher response (41% compared to 14%) for HAI compared with intravenous 5-FU-based chemotherapy.[48] However, this analysis failed to demonstrate a significant survival benefit favouring HAI. In a recent study published by Lorenz et al,[49] 168 patients with unresectable liver metastases were randomised to receive intravenous 5-FU, HAI 5-FU or HAI FUDR. As expected, HAI chemotherapy (5-FU or FUDR) produced a higher response rate than intravenous 5-FU ($p = <.05$), however treatment with HAI FUDR resulted in an increased number of patients developing extrahepatic metastases at six months ($p = <0.05$), and a trend toward increased early deaths and inferior overall survival. In a similar study by Kerr et al[50] comparing intravenous and HAI 5-FU, no differences in progression free or overall survival were demonstrated between the two.

21.2.3 Alternatives to hepatic arterial infusion

In patients with metastatic Colorectal Cancer, randomised studies of combination chemotherapy regimens that include 5-FU plus irinotecan or oxaliplatin have consistently produced response rates in the order of 40–50%, and median survivals approaching 18 months[51–55] (see Chapter 20). Patients with metastases confined to a single organ, such as the liver, will achieve a higher response rate than those with multiple sites of disease.[51,52,54] For patients with liver-only metastases, the combination of 5-FU plus oxaliplatin may be superior to 5-FU plus irinotecan, but this data is somewhat subjective at present.[54–56]

Giachetti et al[56] analysed a series of 151 patients with Colorectal Cancer metastases confined to the liver but considered unresectable due to large tumour size, more than four metastases, or ill-located metastases. All patients received treatment with infusional 5-FU, leucovorin and oxaliplatin. The overall response rate was 59%. Surgery with curative intent was attempted in 77 patients (51%), with complete resections being achieved in 58 patients (38%). Fifty per cent of the 77 operated patients were alive at five years of follow up.

No randomised studies comparing HAI with combination regimens have been or are likely to be performed. However, given the consistently impressive response rates and survival figures achieved with current combination chemotherapy regimens, and the inferior safety profile and minimal effect on subclinical extrahepatic metastases of HAI, HAI should not be considered standard therapy in this context.

Should adjuvant chemotherapy be considered?

Guidelines — Chemotherapy for hepatic metastases	Level of evidence	Practice recommendation	Refs
Adjuvant chemotherapy should be considered following resection of liver metastases.	II	Equivocal	27–30

Does combination systemic chemotherapy have any benefits?

Guidelines — Chemotherapy for hepatic metastases	Level of evidence	Practice recommendation	Refs
Combination systemic chemotherapy regimens that incorporate irinotecan or oxaliplatin have response rates, survival outcomes and safety profiles that appear superior to those achieved with hepatic artery infusion chemotherapy.	III	Recommend	48, 51–55

When should surgical resection of unresectable liver metastases be considered?

Guidelines — Chemotherapy for hepatic metastases	Level of evidence	Practice recommendation	Refs
Patients with liver metastases that are initially considered unresectable and who are achieving a response to systemic chemotherapy should be reconsidered for surgical resection.	III-3	Recommend	56

21.2.4 Palliative chemotherapy

See Chapter 20.

21.2.5 Palliative radiation therapy

Palliative radiation therapy has been used for the management of symptomatic liver metastases for over 30 years. The most common symptoms that may result from liver metastases are pain, sweating, nausea and vomiting. Generally, radiation therapy to the liver results in low toxicity[57,58] and reasonable response rates of symptom relief.[59] Its popularity in recent times has been overshadowed by the development of newer systemic agents and the increasing use of interventional techniques. There has also been the misconception that radiation therapy to the liver results in radiation hepatitis. This is certainly not true provided that high doses are given to only part of the liver[60] or the whole liver dose is restricted to 30 Gy in 15 fractions[61]or 21 Gy in three fractions.[62] More recently, a prospective study in Australia and New Zealand has evaluated 10 Gy in two fractions given on consecutive days.[63] This study reported good relief of symptoms without adverse toxicity.

21.2.6 Treatment of peritoneal carcinomatosis

Peritoneal carcinomatosis from colorectal origin is a common condition facing many surgeons and medical oncologists. It has been estimated that up to 25% of patients die from peritoneal carcinomatosis, even when no other sites of metastases can be found.[70]

Traditional teaching states that once a Colorectal Cancer has disseminated intra-abdominally, no other surgery should be offered apart from resection of the primary tumour and systemic chemotherapy.

This philosophy has come about because of the generally poor prognosis of patients with peritoneal carcinomatosis, with most studies often quoting median survival of six months.

There was only one published randomised controlled trial comparing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC) and systemic chemotherapy. With 50 patients in each arm, the median survival was 12.6 months in the systemic chemotherapy arm and 22.3 months in the surgery arm ($p = 0.032$). The five-year survival rate was 20%. However, this trial was criticised

for using older generation systemic chemotherapy protocols.[70] A recent multi-institutional study with 506 patients from 28 institutions had an overall median survival of 19.2 months, with morbidity and mortality rates of 23% and 4% respectively.[71]

Critics of cytoreductive surgery with HIPEC have two main arguments. The first is that combination systemic chemotherapy using fluorouracil plus leucovorin, irinotecan and oxaliplatin in the treatment of advanced Colorectal Cancer can produce median survival rates of 20 months.[72] However, most patients had liver metastases without peritoneal carcinomatosis and better outcomes in this group of patients would be expected.

The second is the high operative mortality rate, with some centres reporting up to 8% 30-day mortality. This was the reported mortality rate during the early phase or 'learning curve' of cytoreductive surgery with HIPEC. The majority of the deaths were due to intraperitoneal chemotherapy complications during phase II trials. Most units are now reporting 30-day mortality rates of 4%, which is acceptable in major cancer surgery.[73–76]

What is the role of cytoreductive surgery with hyperthermic intra-peritoneal chemotherapy?

Guidelines — Peritoneal carcinomatosis	Level of evidence	Practice recommendation	Refs
Cytoreductive surgery with or without chemotherapy should be performed on an appropriate randomised controlled trial.	II	Equivocal	70–82

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CHAPTER 22 COST EFFECTIVENESS

22.1 Economic burden of Colorectal Cancer in Australia

Colorectal Cancer is a major health concern in Australia. In 2001, it was the most common cancer reported to Australian cancer registries, and the second most common for men and for women following prostate and breast cancer respectively. By age, it was the third and second most common cancer for people aged 15–44 and 45–64 respectively, and the most common cancer for people aged over 65.[1] Colorectal Cancer is also the third most common cause of cancer deaths in both males and females.[1] Treatments for Colorectal Cancer include surgical resection, chemotherapy and radiotherapy. In recent years, efforts to improve survival have focused on pre-symptomatic diagnosis, adjuvant chemotherapy, intensive follow up, and modification of surgical techniques.

The estimated burden of disease attributable to Colorectal Cancer in Australia is outlined in Table 22.1. Years of life lost (YLL) due to Colorectal Cancer are considerably higher than years lost due to disability (YLD). This reflects the fact that the 'burden of cancer is dominated by mortality rather than lengthy periods of disability'.[2]

Table 22.1 Burden of disease attributable to Colorectal Cancer in Australia, 1996

	Total		**Males**		**Females**	
	Number	***Per cent***	***Number***	***Per cent***	***Number***	***Per cent***
Deaths	4973	3.9				
YLL	55372	4.1	29223	3.9	26149	4.4
YLD	11579	1.0	6288	1.0	5291	0.9
DALYs Disability Adjusted Life Year	66951	2.7	35511	2.7	31440	2.7

Source: Mathers et al[2]

The Australian Institute of Health and Welfare has estimated the costs of Colorectal Cancer at a macro level. In 1993–94, cancer was estimated to account for 6% of total health care system costs in Australia. Colorectal Cancer accounted for 10.8% of the total cost of cancer care. It ranked second in terms of the most 'expensive' cancers in Australia, with total health care expenditure on Colorectal Cancer estimated at $204.9 million in 1993–94.[3] Colorectal Cancer ranks as the fifth most costly cancer for females aged 25–44, the first and third most costly cancer respectively for males and females respectively aged 45–64, and the third and second most costly cancer for males and females respectively aged over 65.[3] Total treatment costs per case of Colorectal Cancer were estimated at $A15,374 in 1993–94, which ranks eleventh in terms of the most costly cancer to treat.[3] However, there is relatively little micro-level information available in Australia about treatment patterns and resource use for Colorectal Cancer.

22.2 Economic evaluation

Economic evaluation is the comparative analysis of alternative courses of action in terms of both their costs and consequences. Cost-effectiveness analysis is the form of economic evaluation in which the consequences of interventions, procedures or programs are measured in the most appropriate natural units, such as life-years gained, complications avoided, or cases correctly diagnosed. While many cost-effectiveness evaluations consider a single measure of output, others present an array of output or outcome measures alongside cost, allowing decision makers to form their own view of the relative importance of each measure.

In a cost-utility analysis (CUA), the consequences of an intervention, procedure or program are adjusted by health-state preference scores or utility weights. This means that the quality of the life

years gained can be assessed, which is particularly useful for interventions that extend life at the expense of side effects (such as some chemotherapy for cancer), or produce reductions in morbidity rather than mortality (such as some treatments for chronic conditions, e.g. arthritis).

Whatever form of economic evaluation is used, an intervention, procedure or program can be considered efficient relative to the alternatives if it can be shown to produce a given level of benefit for the minimum cost.

22.2.1 Role of economic evidence in the development of guidelines

The NHMRC has identified two main areas where economic evidence is important in the development of clinical practice guidelines:

- determination of the most cost-effective treatment alternatives
- determination of whether a proposed clinical practice guideline is cost-effective.

In the development of these guidelines, the emphasis has been in the first instance on identifying those interventions for which there is evidence of effectiveness, before addressing questions of cost-effectiveness. There is limited evidence available within Australia to assess the costs and cost-effectiveness of alternatives for screening, early diagnosis and management of Colorectal Cancer. However, there is a range of international literature that provides information about the relative cost-effectiveness of alternatives. This information can be used to inform the development of these guidelines.

The approach taken in reviewing the economic evidence involved:

- identifying those areas where economic evidence is likely to be important
- identifying those areas where economic evaluation evidence is available
- reviewing and summarising the economic evaluation literature.

However, it is important to note that international literature on economic evaluation is limited in its relevance to Australia because of differences in cost structures and reimbursement arrangements, and because the comparator in international studies may not reflect current practice in Australia.

A search was conducted using the databases Pre-Medline, Medline and Embase, covering the period January 1994–December 2004. Economic evaluation literature that pre-dates 1994 was considered to be of limited relevance because of changes in technology, cost structures and management practices. The key words included Colorectal Cancer, colon cancer, rectal cancer, economic evaluation, cost-effectiveness analysis, cost-benefit analysis, cost analysis and cost. Articles were included if they were judged to be economic evaluations, that is, if they involved comparison of alternative interventions in terms of costs and consequences. Articles were classified into nine main areas:

- prevention
- population screening
- screening based on family history
- screening patients with symptoms
- diagnosis
- follow up
- treatment — surgery

- treatment — chemotherapy
- treatment — other (radiotherapy and radiofrequency ablation).

These groupings reflected the main areas in which economic evaluations of interventions have been undertaken.

Of the 121 articles included in these guidelines 49 investigated the effect of an intervention on outcomes such as life years saved (LYS) or gained (LYG), or quality of life on utility (QALY), and seven were cost-benefit or cost-minimisation studies. A further 26 were cost and consequence analyses investigating the costs and effects of an intervention using limited measures of clinical outcome such as cancers detected, deaths prevented, cured/surviving patient, curative resection, recurrence/cured recurrence, treating complications, and so on, or in some cases, output such as length of stay (LOS). The remainder consisted of 13 economic analyses that measured costs and outcomes/or outputs separately, four cost analyses measuring costs only, and 22 reviews or combined review/analyses.

The 49 articles measuring outcomes such as LYS and QALY were reviewed using the criteria recommended in *How to compare the costs and benefits: evaluation of the economic evidence (NHMRC).*[4]

Table 22.2 NHMRC's criteria: Assessing evidence using shadow prices

	Ranking of evidence on effects	
Ranking of evidence on costs	High	Low
Strong	Recommend if: < $70,000 per life year Do not recommend if > $100,000 per life year	Recommend if < $30,000 per life year Do not recommend if >$70,000 per life year
Weak	Recommend if < $30,000 per life year Do not recommend if > $70,000 per life year	Recommend if < $30,000 per life year Do not recommend if >$30,000 per life year

Source: *How to compare the costs and benefits: evaluation of the economic evidence* (NHMRC)[4] Table 6.1 pg 67.

The NHMRC provides comprehensive guidelines for evaluating the economic evidence for clinical practice guidelines. The evidence on both effectiveness and costs can be compared, providing a range of possibilities shown in the Table above. The threshold cost per life year should vary with the quality of evidence. The *lower* the ranking of the evidence, the more likely the decision will be to not recommend an option where the cost per life year falls between $30,000 and $100,000.

Table 22.2 shows that 'if highly ranked evidence is available on effects and there is strong evidence on costs, then options that cost less than $70,000 per life year saved are recommended and those that cost $100,000 are rejected. Those that cost between $70,000 and $100,000 should be considered.'

'If effectiveness evidence is ranked as low and the cost evidence as weak, options that cost more than $30,000 per life year saved are rejected.'

'If neither of the above cases applies [that is, where one of the criteria (costs or effects) is weak and the other is strong], then options of less than $30,000 are recommended and those greater than $70,000 are rejected. Those that are between $30,000 and $70,000 should be considered.'[4]

Health care alternatives require further consideration if they fall between $70,000-$100,000 per life year saved and rank highly for effects and costs, or if they fall between $30,000-$70,000 per life year saved and rank highly on one but not the other. Issues that enhance the attractiveness of a health care option and move the threshold towards a higher price include equity implications, prevention of adverse flow on effects to other sectors, rare diseases with no other health options, improvement of survival and quality of life and severe and preventable conditions.[4]

This methodology has not been applied in the development of these Guidelines. Rather, the economic information has been summarised and presented, but not graded. Hence they have not been assessed applying NHMRC's criteria and shadow prices framework.

However, assessment of overseas economic evaluations and even some Australian economic evaluations in these terms should be treated with caution. Whether these costs and outcomes would be realised if the intervention were adopted in the Australian context depends upon a number of factors, but particularly on whether the comparator for the study reflects current practice in Australia. This also applies where cost-effectiveness evaluations are made in terms of clinical comparators, as is the case in the majority of studies.

Cost-effectiveness results from studies are presented as reported in the relevant studies, but also, for comparative purposes, converted to 2004 Australian dollars. The conversion was undertaken using the OECD purchasing power parity estimates (<www.oecd.org/std/ppp/>) for the relevant year of the study to convert to Australian dollars, then using the Australian Bureau of Statistics Health Price Index (weighted average of eight capital cities)[5] to convert the relevant costs to 2004 Australian dollars. Results in terms of 2004 Australian dollars are reported in parentheses following the original results. However, in comparing across studies it should be noted that the results from different studies are not directly comparable. In particular, the scope of the studies may differ in terms of the range of costs and consequences considered, the perspective of the study, and the choice of comparator. In addition, particularly for earlier studies, there may be important changes in cost structures and technology that limit comparability. The indicative cost-effectiveness estimates in 2004 Australian dollars should be treated as providing a guide to the likely cost-effectiveness of the interventions in the Australian setting.

The findings of the literature review are summarised below. A summary table providing full terminology for all abbreviations used in the tables is presented in Appendix 4.

22.3 Prevention

A number of studies have investigated the cost-effectiveness of aspirin and non-steroidal anti-inflammatory drugs such as cyclo-oxygenase-2 specific inhibitors (COX-2) as chemoprevention agents. The results are summarised in Table 22.3. Neither COX-2 nor aspirin (ASA), as alternatives or adjuncts to screening with colonoscopy or combined flexible sigmoidoscopy (FSIG) and faecal occult blood testing (FOBT), have been found to be as effective or cost-effective. However, for persons already taking aspirin, the addition of screening may be potentially cost-effective. As there is only a limited number of studies evaluating each chemotherapy agent, and comparisons are not the same across studies, the results should be used as an indication only.

Table 22.3 Results of studies investigating the cost-effectiveness of COX-2 inhibitors and aspirin as chemoprevention agents

Study	Country	Study questions	Conclusion
Arguedas et al[6]	United States	Comparison of COX-2 vs COL for average risk post-polypectomy patients (secondary prevention)	COX-2 in average risk patients is not a cost-effective strategy compared to COL. ICERs/LYG (discounted) vs no surveillance for COL and COX-2 were $US27,970 and $US407,498 ($A49,225 and $A717161). Undiscounted and discounted ICER/LYG of COX-2 vs COL is $US1,613,333 and $US1,715,199 ($A2,839,324 and $A3,018,599). Sensitivity analysis confirms results are robust.
Ladabaum et al[7]	United States	Comparison of: *For average risk* COX-2 vs COL 10yrly vs FSIG 5yrly + FOBT yrly vs COX-2 + COL 10yrly vs COX-2 + FSIG 5yrly/FOBT yrly *For 1st- and 2nd-degree relatives* COX-2 vs COL 10yr vs COL 5yr vs COX-2 + COL 10yr vs COX-2 + COX-2 + COL 5yr	COX-2 is less effective and more costly than other strategies. For average risk persons, and for persons with two 1st-degree relatives, ICER/LYG vs no screening was $US233,000 and $US56,700 ($A410,059 and $A99,787) compared to $US20,200 ($A35,198) for COL 10yrly and $US16,800 ($A29,567) for SIG 5yrly + FOBT yrly; and $US1200 and $US2600 ($2112 and $A4576) for COL 10yrly and COL 5yrly. ICER of COX-2 as an adjunct to screening was $US828,000 ($A1,457,207) and $US404,700 ($A712,236). Results are highly sensitive to cost, and effect of COX-2on cancer risk.
Ladabaum et al[8]	United States	Comparison of no screening vs (ASA) vs FSIG/FOBT vs COL vs FSIG/FOBT + ASA vs COL + ASA	ASA should not be used for persons undergoing screening, or as a substitute for screening. ICERs/LYG vs no screening for ASA, FSIG/FOBT, COL were dominated, $US16,844 and $US20,172 ($A26,305 and $A31,502). ASA was dominated as an adjunct to FSIG/FOBT and had a high ICER/LYG as an adjunct to COL, of $US149,161 ($A239,940). In persons already taking ASA, screening with FSIG/FOBT or COL results in ICERs less than $US31,000/LYG ($A48,412).

Study	Country	Study questions	Conclusion
Suleiman et al[9]	United States	Comparison of no intervention vs COL (10yrly or 3yrly if polyps) vs ASA vs COL (10yrly or 3yrly if polyps) + ASA	Compared with COL 10yrly, use of ASA as a preventative measure saves fewer lives (5301 vs 7951–5166/1000) at higher costs. Compared to no screening, COL is more cost-effective than ASA or COL+ASA (ICER = $US10,983 [$A18,821] vs $US47,259 [$A80,987] vs $US41,929 [$A71854]). COL + ASA saves more lives but at a prohibitive cost (ICER/LYG vs COL = $US227,607 [$A390,048]).
Sonnenberg[10]	United States	Review of no intervention vs ASA vs ASA + COL	Chemo prevention with ASA is not cost-effective (ICER vs no intervention = $US47,249 [$A75,326])/LYG). If ASA is already being used, screening with COL10yrly results in ICER of $US34,800 ($A55,479)/LYG.
Inadomi[11]	United States	Review of no intervention vs ASA vs ASA + COL vs COL	The addition of ASA to COL is not cost-effective but if already using, ASA + COL may be cost-effective. ASA + COL vs ASA has ICER range of $US31,000–34,836 ($A45,801–51,468)/LYG.

22.4 Population screening

There have been numerous studies to investigate the effectiveness and cost-effectiveness of population screening. Methodologies used, and comparisons made, varied considerably across studies, with investigators comparing screening to no screening, different screening tests, different types of the same test, as well as different screening schedules or ages. There was also variation in terms of whether comparisons were made for single tests, combinations of tests, or both. The majority of the studies have been cost-effectiveness analyses, but there have also been several cost and consequences, economic and cost analyses, as well as numerous reviews. The results of studies conducting analyses are summarised in Table 22.4. Review studies are summarised in Table 22.5.

In the main, and across all studies, screening has been found to be cost-effective compared to no screening, and is therefore recommended. However, due to differences in the compared tests, screening intervals, methods and assumptions used, and results across studies, at present it is not possible to recommend any one screening test (single or combination) over another. Similarly, recommendations cannot be made about the best options for screening intervals or commencement age, except that commencement before 50 years of age appears to be less cost-effective than commencement after 50 years of age. At this stage, therefore, screening is recommended, but an optimal screening strategy cannot be identified and choice may best be determined based on local context and policy.

Between 2002 and 2004, a pilot study was conducted to determine the feasibility, acceptability and cost-effectiveness of Colorectal Cancer screening among the Australian population. The results will inform government decisions about whether to introduce a bowel cancer screening program and if so, how. As part of the evaluation of the pilot program, a cost-effectiveness study is being sponsored by the Medical Services Advisory Committee. However, at the time of writing, the results of the economic evaluation were not available.

Table 22.4 Results of studies investigating effectiveness, costs and cost-effectiveness of population screening

Study	Country	Comparator/ screening test	Conclusion
Stone et al[12]	Australia	FOBT vs no screening	There is support for a national program directed at 55–69yrs with extension to 70–74yrs if there are sufficient resources. Minimum or base program could avert 250 deaths per annum at a gross cost of $A55M (gross ICER = $A17,000/DALY gained). Sensitivity analysis indicates variation in parameters results in ICERs ranging from $A13,000 to $A52,000/DALY gained.
Whynes[13]	United Kingdom	FOBT vs no screening	FOBT screening is cost-effective with an ICER of £1584 ($A4007) LYG (with conservative assumptions). Results are sensitive to discount rates for survival benefits (6% increase results in 77.4% increase in ICER; if undiscounted, ICER falls 25.5%); survival estimates (if highest used, ICER falls 23.3%) and cost (if FOBT, investigation and treatment costs are doubled, ICER increases 59.6, 27.5 and 12.9%).
Whynes[14]	United Kingdom	FOBT vs no screening	FOBT is cost-effective with an ICER of £1400–5700 ($A3828–15,586)/QALY gained (depending on period of follow up). Results are sensitive to specificity (10% decrease doubles the ICER) and discount rate (3% rate raises ICER 50%).
Helm et al[15]	United States	FOBT vs no screening	Screening is considered cost-effective over a wide range of projected costs and irrespective of trial on which analysis is based (CERs range from $US2,500–20,500 [$A4,072–33,384]/LYG). FOBT still limited to ≤ 15% reduction in mortality. Results are sensitive to variation in procedure costs (up to 50% variation in ICER).
Whynes et al[16]	United Kingdom	FOBT vs no screening	Screening appears cost-effective with a cost/QALY gained range of £1371–5685 ($A3,381–14,019). Results are highly sensitive to a number of test parameters, in particular cost and test specificity, but ICERs remain acceptable.

Study	Country	Comparator/ screening test	Conclusion
Bouvier et al[17]	France	Assessment of 1st year treatment costs following implementation of screening programs (FOBT — Hemoccult)	There is no significant cost decrease in 1st year of treatment with advance of diagnosis. Mean costs for stages 1 to 6 were €1276, €17,579, €21,858, €31,110, €17,384 and €15,365 ($A2148, $A29,858, $A36,787, $A52,358, $A29,257 and $A 25,859) (total mean cost of €21,912 [$A36,877]). Only stage 1 (4.2% of the sample), treated by polypectomy, had significantly lower costs.
Yamamoto and Nakama,[18]	Japan	FOBT 1day vs, 2day vs 3day collection	Two-day method is suggested as it costs only slightly more than one day but has greater diagnostic accuracy. Sensitivity and specificity for 1, 2 and 3day tests were 58%, 96%; 89%, 96% and 100%, 94%. Cases detected were 13, 20.1 and 22.5 with costs/case detected of $US5924.06, $US6014.38 and $US7122.91 ($A10,629.68, $A10,719.74 and $A12,780.80).
Berchi et al[19]	France	20yrs biennial automated immunological test (magstream) vs guaiac stool test (Haemoccult)	Use of magstream leads to increased life expectancy of 0.0198yr with an ICER of €2980 ($A4568)/discounted LYG. Although results are sensitive to numerous variables, ICER is still below €10,000 ($A15,328)/undiscounted LYG, except when magstream sensitivity is 70% or 90% and cost of COL is €1000 ($A1533).
Gyrd-Hansen et al[20]	Denmark	Hydrated Hemoccult-II (HH-II), 55–74yrs vs HH-II, 50–74yrs vs hemeselect, 50–74yrs vs rehydrated H-II (RH-II), 50–74yr	The six most efficient H-II programs were 2yrly for 65–74yrs, 60–74yrs and 55–75yrs; 1.5yrly for 55–74yrs; and yrly for 55–74yrs and 50–74yrs. ICERs/LYG were DKK17,000, DKK18,896, DKK 23,012, DKK28,802, DKK35,471 and DKK42,500 ($A4197, $A4665, $A5682, $A7110, $A8757 and $A10,492). Results are robust, except if future unrelated health care costs not included and if no discounting.

Study	Country	Comparator/ screening test	Conclusion
Gyrd-Hansen[21]	Denmark	Unhydrated H-II, 55–74yrs 2yrly, vs hydrated H-II, 50–74yrs yrly vs hemeselect, 50–74yrs yrly, rehydrated H-II, 50–74yrs yrly	Unhydrated H-II test is cost-effective and preferable to other tests. Incremental cost/LYG with unhydrated H-II for 55–74yrs 2yrly is DKK17,500 ($A4320). Ave costs/LYG with unhydrated H-II, 55–74yrs yrly, 50-74yrs yrly, Hemeselect, 50–74yrs yrly, rehydrated H-II, 50–74yrs yrly were DKK30,000, DKK39,000, DKK71,300 and DKK138,000 ($A7,410, $A9,628, $A17,602 and $A34,068). Sensitivity analysis suggests cost-effectiveness is dependent on specificity >97% for yrly screening. For 2yrly intervals, <97% is allowable. Efficiency curve results suggest rehydrated H-II test is a viable option for beyond 55–74yrs, 2yrly.
Castiglione et al[22]	Italy	1day RPHA vs 3day RG Haemoccult	RPHA had higher efficacy. RPHA (+ and +/-) and RPHA (+ only) detected more cancers than RG Haemoccult. All Dukes A were detected by RPHA (+ and +/-). RPHA is also more cost saving. Hemoccult (-ve) had the highest cost/cancer or adenoma detected ($US12,900 [$A21,007]). RPHA (+) had the lowest cost per cancer detected ($US9,020 [$A14,689]) and RPHA (+ & +/-) had the lowest cost per person with adenoma ($US1780 [$A2899]).
Rae and Cleator 1994[23]	Canada	Two-tier FOBT (HO Sensa + hemeselect) vs hemoccult guaiac vs, HO Sensa guaiac vs hemeselect hemaglutination	The two-tier test is the most effective (specificity of 88.7% and 96.8% for high risk and asymptomatic/symptomatic, and a lower false negative rate). It is also the least expensive. For two tier vs the other tests, high-risk group costs/cancer detected and adenoma/polyp detected were $US1842 vs $US2261–3176 ($A3693 vs $A4533–6368) and $US972 vs $US1044–1444 ($1940 vs $A2093–2895). Asymptomatic/symptomatic group costs were $US10,825 vs $US20,948–27,165 ($A21,704 vs $A42,000–54,466). For asymptomatic alone, costs were $US5476 vs $US16,422–95,585 ($A10,979 vs $A32,926–191,647).
Whynes et al[24]	United Kingdom	Assessment of costs of FSIG screening in the UK	Total health service cost for screening plus subsequent management average approximately £91 ($A210)/person. Costs vary across centres.

Study	Country	Comparator/ screening test	Conclusion
Sonnenberg and Delco[25]	United States	Single COL (age 65yrs) vs repeated COL (from 50yrs) vs no screening	Compared to no screening, ICER/LYG for single and repeated COL is $US2981 and $US10,983 ($A5109 and $A18,821). Compared to single, ICER/LYG for repeated COL is $US14,878 ($A25,496). Sensitivity analysis shows single COL most effective if screening at 60yrs, most cost-effective after 70yrs. Depending on compliance, repeated COL is 2–3 times more effective than single COL. Repeated COL 10yrly is the best option. If high cost or low compliance renders this option not feasible, single COL at age 65yrs is a cost-effective alternative.
Sonnenberg et al[26]	United States	CT colonography vs COL vs no screening	COL is more cost-effective than CT colonography. ICER of CT colonography vs no screening, was $US11,484 ($A17,934)/LYG and ICER of COL vs CT colonography was $US10,408 ($A16,254)/LYG. Results are sensitive to cost and compliance. CT colonography cost <$US336 ($A525), or compliance rates 15–20% better than COL, would make it a cost-effective option.
Ladabaum et al[27]	United States	CTC 10yrly vs COL 10yrly	COL is the most cost-effective strategy with ICER/LYG of $US18,000 vs $US28,700 ($A26,594 vs $A42,403). Results are robust, except when cost of CTC ≤ 60% the cost of COL.
Norum[28]	Norway	FSIG + FOBT (followed by COL in selected risk groups) vs no screening	Screening with FSIG appears to be cost-effective vs no screening (ICER = £2889 ($A7541)/LYG). Sensitivity analysis suggests a linear correlation between compliance and cancer detected and/or prevented would result in cost/LYG remaining almost constant. If LYG is reduced from 2 to 1, cost per year doubles.
Flanagan et al[29]	Canada	FOBT + COL vs no screening	Biennial screening of 67% population aged 50–74yrs results in estimated 10yr mortality reduction of 16.7%, with an average life expectancy increase of 15 days. CER = $CAN11,907 ($A14,475)/LYG.

Study	Country	Comparator/ screening test	Conclusion
Salkeld et al 1996[30]	Australia	FOBT yrly + COL vs no screening	Screening is cost-effective compared to no screening, with an ICER/LYG = $A24,660, but further evidence is needed for screening efficacy as results are sensitive to this parameter (ICER range $A12,695–67,848) and to false +ve rate.
Banaszkiewicz et al[31]	Poland	Assessment of screening (FOBT + COL) and treatment costs	Overall cost is lower within screening (costs/patient = 9,261PLN vs 10,513PLN ($A6979 vs $A7915). Increased expense due to screening is offset by lower costs of adjuvant therapy.
Nakama et al[32]	Japan	FOBT + COL 1day vs 2day vs 3day collection	For 1, 2, and 3day collection, cases detected were 0.2, 0.4 and 0.5%. The 2day method is the least expensive. Average costs/case detected were $US3630.68, $US3350.65 and $US4136.36 ($A6222.17, $A5741.97 and $A7088.44).
Fric et al[33]	Czech Republic	Haemoccult + COL if +ve (7yr program for ages 45–60) vs no screening	The adapted program of screening 45–60yr olds is effective. A significantly higher proportion of Dukes A and B detected at no extra cost and GNP saving of approximately $US18,500 ($A53,849).
Nakama et al[34]	Japan	Immuno FOBT + COL at ages 40–49yrs, 50–59yrs, and 60+yrs)	Screening subjects under 50yrs is less effective and cost-effective than screening at over 50yrs. For ages 40–49yrs, 50–59yrs, and 60+yrs, detection rates are 0.3% vs 1.6% vs 1.7%, and average costs to detect are $US6023.64, vs $US1424 vs $US1410.47 ($A10,111.34 vs $A2,385.98 vs $A2,367.63).
Nakama et al[35]	Japan	1. FOBT + COL vs medical check up with COL if asymptomatic 2. 40–49yrs vs 50–59yrs vs 60+yrs	Screening efficiency and cost-effectiveness for subjects younger than 50yrs is less than for subjects over 50yrs. Detection rates and average detection costs at 40–49yrs, 50–59yrs and 60+yrs, for (i) population screening with FOBT + COL. and (ii) medical check up + COL if asymptomatic, are: 1. 0.09% vs 0.28% vs 0.29% and $US13,352.38 vs $US4554.59 vs $US4461.17 ($A7645.38 vs $A7488.57 vs $A10,886.43); 2. 0.3% vs 1.5% vs 1.7% and $US6850.89 vs $US1516.99 vs $US1391.44 ($A11,499.97 vs $A2546.43 vs $A2335.69).

Study	Country	Comparator/ screening test	Conclusion
O'Leary et al[36]	Australia	FSIG 10yrly vs FOBT yrly/ biennially vs COL 10yrly vs no screening	FSIG and COL are cost-effective strategies. Compared to no screening, ICERs/LYG for FSIG 10yrly, COL 10yrly, FOBT biennially and FOBT yrly were $A16,801, $A19,285, $A41,183 and $A46,910. Results are sensitive to several parameters, but order of effectiveness mostly remains unchanged.
McMahon et al[37]	United States	FSIG vs FOBT vs COL vs DCBE	Strategies including DCBE emerged as optimal. In average-risk persons, DCBE 3yrly, or 5yrly with FOBT yrly, had ICERs <$US55,000 ($A96,975)/LYG. However DCBE 3yrly + FOBT yrly was not cost-effective. More research is required.
Wong et al[38]	Singapore	FOBT, vs Immuno FOBT vs FSIG vs DCBE vs COL for ages 50–54yrs, 55–59yrs, 60–64yrs, 65–60yrs	All of the strategies increase life expectancy. Overall, FOBT is the most cost-effective method (cost/LYG = $SING162.11 vs $SING368.06 vs $SING340.36 vs $SING211.57 vs $SING402.24). Cost/LYS decreases with screening age. [a]
Leshno et al[39]	Israel	Single COL vs FOBT + SIG vs Annual FOBT vs COL 10yrly vs DNA vs no screening	Screening average risk individuals beyond age 50yrs is cost-effective, with COL and FOBT + SIG dominating the other strategies. ICER of FOBT + SIG vs COL was 1268 New Israeli Shekels (NIS) ($A487)/LYG. Results are robust across a large range of variables but compliance with follow up does affect the results (ICER/LYG = 5780NIS and 4980NIS [$A2272 and $A1914]) for 40% and 60% compliance.
McGrath et al[40]	Canada	FSIG vs FSIG + ACBE vs CTC vs COL	For 16.9% probability, advanced adenoma FSIG has lowest cost ($CAN1930 [$A$2725]/ detection vs $CAN2840, $CAN3681 and $CAN2290 [$A4010, $A5198 and $A3233] for FSIG + ACBE, CTC and COL). However, detection rate is only 69% vs 96% for COL. With ≥33.5%, probability of adenoma, COL is most cost saving ($CAN1235 [$A1744]/detection). Considering incremental costs to investigate 1000 patients, COL is most effective and cost-effective (ICER/advanced adenoma = $CAN29,902 [$A32,337]).

Study	Country	Comparator/ screening test	Conclusion
Glick et al[41]	United States	DCBE 5yrly vs DCBE 5yrly + FOBT yrly vs FOBT yrly vs COL 5yrly vs SIG 5yrly vs SIG 5yrly + FOBT	All programs are cost-effective in the order of SIG, DCBE, SIG + FOBT, FOBT, COL, DCBE + FOBT (for 5yr polyp dwell time) and DCBE, FOBT, SIG + FOBT, FOBT, COL, DCBE + FOBT (for 10yr dwell time). CERs/LYG for 5yr and 10yr dwell times, range from $US11,947–14,750 ($A18,657–23,035) and $US9435–12,815 ($A14,734–20,013). DCBE 5yrly was sensitive to changes in test sensitivity and specificity, but CERs remain acceptable.
Sorrentino et al[42]	Italy	FOBT vs SIG vs FOBT+ SIG vs COL vs FC50 vs no screening	Screening programs based on SIG or COL are more cost-effective than FOBT. FC50 at age 50yrs appears to be most cost-effective. The 10yr cost/death prevented for FOBT, SIG, FOBT+ SIG, COL vs FC50 are $US77,200, $US15,500, $US35,000, $US15,100 and $US14,000 ($A135,685, $A27,279, $A61,597, $A26,575, $A24,639).
Shimbo et al[43]	Japan	Combinations of BFOBT or IFOBT with COL, BE, or BE/SIG with variations in screening intervals	Programs using IFOBT are the most cost-effective, with IFOBT 2yrly followed by COL if test +ve the most cost-effective (ICER = $US13,100 [$A26,265]/LYG). Beginning screening at 45yrs has best CER ($US12,400 [$A24,862]/LYG). However, commencement at age 40yrs is still cost-effective with ICER vs 45yrs of $US16,800 ($A33,643)/LYG. However, if compliance drops 10, 15 and 20% after each screening, commencement at 40yrs is dominated by later screening.
Lieberman[44]	United States	FOBT yrly vs FSIG (5yrly repeat if -ve) vs FSIG 5yrly/FOBT yrly vs COL 10yrly vs BE (5yrly repeat if -ve) over 10 year period	COL has the greatest impact on mortality. FOBT alone is the most cost-effective at 100% compliance. Cost/death prevented for FOBT, FSIG, FOBT/FSIG, COL, BE ranged from $US225,000–280,000 ($A420,118–522,813). At 50% compliance, ranges were $US331,000–367,000 ($A618,040–685,258). (FOBT becomes comparable with FS/FOBT and COL). FOBT cost-effectiveness is sensitive to detection rate, cost of care, cost of COL, and compliance with evaluation of +ve results.

Study	Country	Comparator/ screening test	Conclusion
Song et al[45]	United States	FDNA vs FSIG 5yrly vs FOBT yrly vs COL 10yrly vs FSIG/FOBT (all beg at age 50yrs) vs no screening.	FDNA 5yrly appears to be effective and cost-effective vs no screening, but is inferior to other strategies, all of which increase life expectancy at reasonable cost. ICERs/LYG vs no screening for FDNA, FSIG, FOBT, COL and FS/FOBT were $US47,700, $US15,500, $US7200, $US17,010 and $US17,000 ($A70,474, $A22,162, $A10,638, $A25,131 and $A25,116). FDNA was dominated by the other strategies; FOBT dominated FSIG; COL had ICER/LYG of $US22,000 ($A32504) vs FSIG; FSIG/FOBT had ICER/LYG of $US22,100 ($A32,651) vs FSIG and $US16,300 ($A24,082) vs COL. Significant improvement in sensitivity/specificity and a cost of $US195 ($A288) is required for FDNA to become comparable to COL.
Sonnenberg[10]	United States	FOBT, FSIG 5yrly, COL, COL 10yrly, and FOBT/COL	For no intervention vs FOBT, FSIG, COL 10yrly and COL, ICERs/LYG were $US9705, $US36,509, $US10,983, and $US2981 ($A16,631, $A62,565, $A18,821 and $A4954). ICER of FOBT/COL vs no screening is $US11,400 ($A19,536). Single COL is the most cost-effective option. Sensitivity analysis suggests that overall, despite variations to parameters such as sensitivity/specificity, costs and compliance, COL remains the most cost-effective option.

Note [a]: Monetary values not converted to $A due to unavailability of OECD PPP estimates for Singapore.

Numerous reviews of cost-effectiveness evidence relating to Colorectal Cancer screening have been published. These range from small reviews of a few articles to large systematic reviews. The findings are summarised in Table 22.5 and confirm the findings of this current evaluation. As previously stated, screening is cost-effective compared to no screening, but optimal tests, strategies or commencement age cannot be determined or recommended based on current evidence.

Table 22.5 Summary of findings from reviews of cost-effectiveness of screening

Study	Country	Study questions	Conclusion
Deenadayalu and Rex[46]	United States	Review of cost-effectiveness evidence of FDNA vs various strategies	Initial assessments indicate FDNA is cost-effective (studies cite cost/QALY gained ranges for FDNA of $US674–9120 [$A940–12,721] and FDNA 5yrly/COL10yrly of $US14,528–17,095 [$A20,265–23,845]). One study indicated FDNA 4yrly is cost-effective vs COL10yrly if sensitivity to detect cancer and adenoma = 90% and 70% respectively.
Redaelli et al[47]	United States	Review of evidence for alternative screening strategies	Most screening strategies have ICERs of approx $US40,000 ($A59,098)/LYG. FOBT has shown best positive results in terms of both clinical and economic outcomes.
Inadomi[11]	United States	Review of cost-effectiveness of screening for colorectal neoplasia	Several strategies (FOBT, FOBT/FSIG, COL, DCBE, alone or in combination) are cost-effective. Costs/LYG range from $US8100–42,311 ($A11,967–62,512). Cost/cancer detected range from $US6851–13,352 ($A10,123–19,727). However, determining 'best' strategy is difficult given the differences in studies (e.g. strategies compared, screening intervals, assumptions, costing methods).
Pignone et al[48]	United States	Systematic review of evidence for FOBT yrly vs FSIG 5yrly vs FOBT yrly + FSIG 5yrly vs DCBE 5yrly vs COL 10yrly	Screening appears cost-effective vs no screening, but a single optimal strategy cannot be determined. Cost-effectiveness ratios range from $US5691–39,359 ($A9073–62,747)/LYG (most between $US10–20,000 [$A15,943–31,885/LYS). No one strategy was found to be consistently the most cost-effective or to have the best ICER. There is insufficient evidence to determine best starting and stopping age.
Pignone and Levin[49]	United States	Review of developments in screening with FOBT, BE, DCBE, COL, FSIG, DNA and CTC	Several methods are cost-effective vs no screening, but current evidence is not sufficient to determine most effective or cost-effective. ICERs range from $US10,000–25,000 ($A15,943–39,856)/LYG. DNA and CTC show early promise.

Study	Country	Study questions	Conclusion
Provenzale[50]	United States	Review of cost-effectiveness of screening for average-risk population	Screening is cost-effective with ICERs for the most effective strategies ranging from $US10,000–40,000 ($A15,943–63,769)/LYG. Variations in methods used, tests compared, screening intervals, etc. make it difficult to compare strategies.
Swaroop and Larson[51]	United States	Review of cost-effectiveness of screening (FOBT yrly, FSIG 3yrly and 10yrly, FOBT yrly + FSIG 3yrly, FOBT or FSIG 5yrly, COL 10yrly, FOBT + FSIG 5yrly (plus 21 other combinations or tests)	Screening strategies have shown ICERs ranging from $US9000–93,000 ($A14,348–148,263)/LYG. Several options appear to be cost-effective, but a single best option cannot be determined. Compliance plays an important role in the efficacy of COL screening. Due to the number of tests available, physicians and patients have choices. The important thing is that screening is conducted.
McMahon and Gazelle[52]	United States	Review of cost-effectiveness evidence for available screening tests	Screening for average-risk individuals is cost-effective, but studies recommend that a wide variety of strategies and comparisons are difficult due to differences in strategies compared, assumptions, and outcomes reported. At present the important thing is that screening is effective. Choice of test is less critical than choice to get screened.
Crott[53]	Belgium	Review of most current economic studies analysing choice of optimal screening strategies (FOBT, FSIG, COL, DCBE, CTC, DNA)	Given current data, either FSIG or DCBE 5yrly, or a mix of both, offer reasonable cost-effectiveness, but at a loss of efficacy compared to COL, (though better than FOBT). FOBT is generally less cost-effective due to yearly/biennial repeat testing and high false +ve rate. COL is most effective but has high cost and is more invasive. Ultimate choice depends on local context, and is a function of threshold levels for policy makers.
Bolin et al[54]	Australia	Review of cost-effectiveness of screening strategies (FOBT, FSIG, COL)	Current data suggests FOBT (yrly and 3yrly), COL and FSIG/FOBT are all cost-effective (ICERs under $A30,000/LYG).

Study	Country	Study questions	Conclusion
Gazelle et al[55]	United States	Review of current status and future outlook of screening and summary of cost-effectiveness literature	General consensus is that screening is cost-effective compared to no screening, but direct comparison of strategies is difficult. Costs/LYG range from $US2057–15,168 ($A3526–25,993) for FOBT (yrly or biennially) and $US9287–22,170 ($A15,915–37,992) for COL 10 yrly. There is evidence that cost-effectiveness of FOBT, and FSIG alone or in combination, is better than for BE or COL.
Frommer[56]	Australia	Review of effectiveness and cost-effectiveness of screening strategies (FOBT with Hemoccult II, FSIG, COL)	All strategies are cost-effective. However, estimations of cost-effectiveness are affected by so many factors (poorly quantified studies, different strategies compared, etc.), it is not possible to conclude any one is significantly superior to another.
Wagner[57]	United States	Review of cost-effectiveness evidence for screening	Screening is cost-effective compared to none. Ranking varies depending on studies. DCBE is relatively favourable across studies.

22.5 Screening based on family history

There have been relatively few papers investigating the cost-effectiveness of screening and genetic screening for persons at above average/moderate or high risk of cancer based on family history. The majority of papers were cost-effectiveness studies or cost minimisation studies.

22.5.1 Screening for above average / moderate risk persons

One study conducted in Taiwan by Wu et al[58] investigated the costs and clinical effectiveness of screening for persons at above average/moderate risk. They compared colonoscopy to flexible sigmoidoscopy (FSIG) plus air contrast barium enema (ACBE) and found that costs for the two strategies were similar (2108 vs 2171 New Taiwan [NT]). However, 42% of cancers would be beyond the reach of detection by FSIG and 36% would be missed by ACBE because they were smaller than 0.5 cm. The authors concluded that colonoscopy is a more appropriate alternative. Monetary values for this study have not been converted to Australian dollars due to the unavailability of OECD PPP estimates for Taiwan. Results from this study should be taken as an indication only.

22.5.2 Screening for high-risk persons

Five studies were identified that investigated cost-effectiveness of genetic screening for persons at high risk. The studies varied in terms of gene mutations and screening strategies investigated and comparisons made.

Three United States studies investigated the cost-effectiveness of strategies to identify HNPCC carriers. Ramsey et al[59] conducted a cost-effectiveness study comparing alternative strategies[1] to identify HNPCC carriers among newly diagnosed patients. The results showed that following strategy 1 (Bethesda guidelines) is the most cost-effective approach to screening for HNPCC. Compared to no screening, ICERs/LYG (for probands, for probands plus relatives) for strategies 1, 2, 3 and 4 were $US73,711, $US11,865 ($A117,512, $A18,915); $US213,290, $US35,617 ($A341,038, $A56,782); $US296,793, $US49,702 ($A473,156, $A79,236); $US1,625,787, $US267,548 ($A2,591,878, $A426,533). Results were sensitive to survival benefits from aggressive surveillance in mutation carriers without Colorectal Cancer, and to the prevalence of HNPCC in the population. The ordering of the two main parameters remains unchanged, but the relative influence of each parameter varied substantially from strategy to strategy.

In another study, Reyes et al[60] conducted an economic analysis comparing effectiveness and costs (separately) of alternative strategies.[2] The results indicated that limiting genetic testing to persons meeting the Amsterdam criteria is not effective (7.8 carriers detected for every thousand screened), but testing all patients, though effective (67.6/1000), may be prohibitively expensive (ICER per carrier detected of $US51,151 [$A85,863]). The mixed strategy was the most cost-effective approach (59.6/1000 detected and an ICER compared to the Amsterdam strategy of $US6441 ($A10,812)/carrier detected). Sensitivity analysis confirmed the robustness of the results.

The third United States study, a cost-effectiveness study by Ramsey et al[61] compared microsatellite instability (MSI) testing to no testing and found that screening patients with newly diagnosed cancer for HNPCC is cost-effective, especially if benefits to their immediate relatives are considered. Discounted ICERs/LYG for cancer patient, and for patient plus siblings and children, were $US42,210 and $US7556 ($A70,854 and $A12,684). Results were most sensitive to estimated survival gain from screening siblings and children, prevalence of HNPCC, and discount rate. Although these studies indicate that screening for HNPCC carriers is cost-effective, it is not possible to recommend any one particular strategy due to the variation in strategies evaluated.

Genetic screening can also be conducted for familial adenomatous polyposis (FAP). Only one study was identified that investigated this screening strategy. In Canada, Chikhaoui et al[62] conducted a cost-minimisation study comparing clinical screening with genetic testing for FAP.[3] The results showed that genetic testing is cost saving in comparison to clinical screening, and appears to be the optimal strategy. When FAP screening begins at puberty, costs for clinical screening compared to genetic testing were $CAN3181 compared to $CAN2259 ($A4244, $A3014). Cost savings continued up to a starting age of 36 years and the extent of savings was dependent on initial starting age ($CAN922) ($A1230) for starting age of 12 years) reduced to $CAN211.67 ($A282.40) for starting age of 30 years). The results were robust across a variety of assumptions.

The final study investigating genetic screening was a systematic review of the economic evidence for cancer genetic services conducted in the United Kingdom by Griffith et al in 2004.[63] Their findings stated that genetic testing has been shown to be cost saving and to prevent unnecessary invasive surveillance techniques with little or no loss of sensitivity in mutation detection. The extent of savings was dependent on the method used, with costs ranging from £653–5281 ($A1416–11,453) if genetic

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[1] **Strategy 1**: Bethesda guidelines (clinical/family history plus microsatellite instability testing and germline testing (MSI). Strategy 2: universal MSI. Strategy 3: germline test if meet clinical and family history criteria. Strategy 4: universal germline testing.

[2] **Modified:** tumour MSI if meet less stringent, modified, clinical criteria, and germline mutational if MSI-H tumour. **Test all**: tumour MSI for all, and germline mutational if MSI-H. **Mixed**: germline mutational testing if satisfy Amsterdam criteria and tumor MSI if meet less stringent criteria with substantial MSH2/MLH1 if MSI-H tumour. **Amsterdam**: germline MSH2 and MSH1 for high-risk persons meeting Amsterdam criteria.

[3] **Clinical screening**: FSIG yearly for 12-25yr, biennially for 26-35yr and triennially for 36-60yr. **Genetic testing**: proband tested for APC. If positive, at-risk relatives tested. Clinical surveillance for positive at-risk relative, no surveillance for negative at-risk relatives. If proband negative, all at-risk relatives have clinical surveillance.

testing was conducted first, to £2781–5667 ($A6031–12,291) for conventional screening. Population for testing for HNPCC mutation was found not to be cost-effective.

These studies provide some evidence for the cost-effectiveness of genetic screening, but due to the variations in strategies investigated and compared, the results should only be viewed as an indication of possible cost-effectiveness for particular screening options.

22.6 Screening patients with symptoms

A small number of studies were identified that investigated screening strategies for patients with symptoms. These consisted of only one cost-effectiveness study, three cost and consequences studies, one economic analysis and one review. The results are summarised in Table 22.6.

In general, the studies indicate that the strategies of FOBT, sigmoidoscopy (SIG), and rectosigmoidoscopy (RECT) plus immediate colonoscopy if polyps are found, are cost saving for the detection of cancer in symptomatic patients. For detection of both cancers and adenomas, FOBT plus endoscopy may be a cost-saving option. For patients with ulcerative colitis, colonoscopy every three years appears to provide cost-benefits. However, as these studies only evaluate costs and consequences, they provide, at best, an indication of possible cost savings.

The only cost-effectiveness study conducted indicated that flexible sigmoidoscopy (FSIG0 plus barium enema (BE) was cost-effective compared to FSIG for screening of patients with rectal bleeding. A definitive recommendation cannot be made on the basis of only one study. The results should be taken as an indication of possible cost-effectiveness with further research required.

Table 22.6 Results of studies investigating costs and outcomes of screening strategies for patients with symptoms

Study	Country	Study question	Conclusion
Ramsey et al[64]	United States	Comparison of screening vs evaluation of symptoms	Screening with FOBT can substantially reduce costs. Cancers detected by screening vs symptoms were 206 vs 717. Costs for the period 3mths pre-diagnosis to 12mths post-diagnosis were $US24,636 vs $US31,128 ($A39,275 vs $A49,625).
Sieg et al[65]	Germany	Evaluation of FOBT (faecal haemoglobin plus albumen) for symptomatic persons	Screening with FOBT is effective (99.5% specificity) and cost-effective. Cost/cancer detected = 8,667DM ($A13,465); savings from cancer prevented exceeded costs by approx 2.3 times.
Manus et al[66]	Germany	Comparison of FOBT (hemofec) + endoscopy vs SIG for symptomatic and asymptomatic persons	For cancer detection, SIG for persons over 50yrs is advisable. For detection of both cancer and adenomas, FOBT + endoscopy is acceptable and cost-effective. The cost of identifying one cancer bearer was $US1436 ($A4180) (study A) and $US271 ($A789) (study B). Cost of identifying one cancer patient was $US5435 ($A15,819).
Arrigoni et al[67]	Italy	Comparison of RECT + ImmCOL, vs RECT + COL at subsequent examination, vs ImmCOL	If polyps are found during RECT, extending examination to the entire colon to remove all lesions found is a justifiable compromise to ImmCOL, reducing overall costs. Costs/lesion detected and cancer prevented for RECT + ImmCOL vs RECT + COL at subsequent examination, vs ImmCOL, were $US898, $US6703 ($A1677, $A12,516) vs $US1243, $US8227 ($A2321, $A15,361), vs $US864, $US7082 ($A1613, $A13,223).
Lewis et al[68]	United States	Comparison of FSIG vs FSIG + BE vs BE vs COL vs ANO + FSIG (or FSIG + BE or FSIG + COL) for young patients with rectal bleeding	For persons mid 30yrs+, evaluation of the entire colon yields greatest life expectancy at incremental cost comparable to other widely used strategies. FSIG + BE yielded greatest life expectancy with an ICER of $US23,918 ($A37,352)/LYG vs FSIG alone. For persons mid 20yrs and under, ANO + FSIG may be most cost-effective, with an ICER of $US12,018 ($A18,768)/LYG.

Study	Country	Study question	Conclusion
Lashner[69]	United States	Review of COL (at various screening intervals) for persons with ulcerative colitis	COL is more effective and less costly than no screening. The most reasonable strategy appears to be COL 3yrly. For patients with low-grade dysplasia, prophylactic colectomy is recommended. Persons at very high risk should have COL yrly, but if this is a concern, prophylactic colectomy is an alternative.

22.7 Diagnosis

A small number of cost and consequences studies have investigated various diagnostic procedures for Colorectal Cancer. The results are summarised in Table 22.7. Three studies evaluated positron emission tomography (PET) and found that the use of PET results in cost savings. However, these studies are limited in that they rely on estimates of sensitivity and specificity of PET based on case series, and the results are dependent on the assumption that PET did or would have changed management of the patient. Results should therefore be used as an indication of possible cost savings only.

The other two studies investigated a range of diagnostic procedures including computerised tomography (CT), magnetic resonance imaging (MRI), digital rectal examination (DRE) and transrectal ultrasound (TRUS) or endoluminal ultrasound (EUS). However, as the studies did not compare the same strategies it is not possible to determine the most cost-effective option and the findings should be taken as indicative of potential cost savings for certain diagnostic options.

Table 22.7 Results of studies investigating costs and consequences of various diagnostic procedures

Study	Country	Study question	Conclusion
Miles[70]	Australia	Evaluation of FDG–PET costs for preoperative evaluation of recurrent cancer and comparison of decision-tree analysis results with actual experience	Studies using decision-tree analysis suggest a cost saving of $A2301.27/patient, with sensitivity analysis indicating the results are robust. Studies based on actual experience suggest a smaller saving of $A230.75. The discrepancy suggests decision-tree models may not reflect actual practice.
Valk et al[71]	United States	Evaluation of effectiveness, impact and costs of PET for patients with of recurrent cancer	PET shows more sensitivity (93% vs 69%) and specificity (98% vs 96%) than CT. PET may avoid unnecessary surgery, thereby reducing costs. Total PET costs were $US140,400 ($A247,092). Savings from surgery avoided would be $US3003 ($A5285)/patient.
Valk et al[72]	United States	Assessment of impact and costs of PET for patients with recurrent cancer	PET suggested change in surgical management in 35% patients. Costs for procedures that would have been avoided and PET were $US300,000 ($A601,497) and $US112,000 ($A224,559), a savings/cost ratio of 2:5. If PET replaced CT, the net cost would be $US68,000 ($A136,339), a savings/cost ratio of 4:4.
Harewood and Wiersema[73]	United States	Comparison of abdominal and pelvic CT vs abdominal CT + EUS vs abdominal CT + pelvic MRI	Abdominal CT+ EUS is the most cost-effective approach (recurrence-free rate of 87%, CER = $US24,668 ($A39,326)/yr). It dominated the other two strategies. Results are sensitive to sensitivity and specificity of EUS and pelvic MRI but remained mostly cost-effective if the sensitivity of EUS >66% and pelvic MRI <90%, and the specificity of EUS >78% and pelvic MRI <90%.
Brown et al[74]	United Kingdom	Comparison of MRI vs DRE vs EUS in staging CRC	MRI shows clinical and cost benefits over DRE and EUS. Agreement between staging and histological assessment was 94% vs 65% vs 69%. Cost per additional successful and accurately staged patient was £67,164 ($A145,666) for MRI vs DRE, and £92,244 ($A200,060) for MRI vs EUS. Sensitivity analysis suggests an MRI cost of £1079 ($A2340) is required for MRI to equate with EUS. Ignoring resource implications of incorrect staging would result in cost per additional successful and accurately staged patient of £151 ($A327) for MRI vs EUS and £288 ($A625) vs DRE.

22.8 Follow up

Several cost-effectiveness/utility studies and cost and consequences studies were identified that investigated the effectiveness and costs of follow up. In addition, one review was found. Two studies compared follow up with no follow up, three investigated various follow-up tests, and another five compared different schedules. The studies comparing follow-up schedules were predominately cost-effectiveness/cost-utility studies. The results are summarised in Table 22.8.

Findings suggest that follow up is expensive, but effective. In general, carcinoembryonic antigen testing (CEA) has been identified as the most cost-effective individual follow-up test. Results regarding scheduling of follow up differ across studies, with intensive follow up identified as cost-effective in some studies but not in others. Risk-adapted follow up has been identified as a cost-effective alternative.

The studies provide some evidence that follow-up costs are justified and that CEA is potentially cost-effective. However, in relation to follow-up scheduling, as the studies evaluate different schedules, not only in terms of comparisons but also in, for example, what intensive or standard follow up involves, at this stage it is not possible to recommend any one follow-up schedule over another. Results should be used as an indication only.

Table 22.8 Results of studies investigating costs, effectiveness and cost-effectiveness of follow-up strategies

Study	Country	Study question	Conclusion
Ketteniss et al[75]	Germany	Comparison of follow up following resection vs no follow up (focus on patients with liver metastases)	Costs are high, but justified by good outcome in patients for whom early diagnosis is made (26.7% of patients with liver metastases are detected at early stage, when resection can be performed). Cost/LYG is 28,258DM ($A47,945).
Audisio et al[76]	Italy	Comparison of follow up vs none following curative surgery	Postoperative follow up is expensive (cost/patient cured = $US106,383 [$A190,885]), but potentially effective (25% of detected recurrences are suitable for potentially curative second surgery). However, follow up should be tailored according to stage/site of the primary to reduce costs.
Matasar et al[77]	United States	Review of CEA, chest x-ray, COL, physical examination, standard follow up, and intensive/aggressive follow up for elderly patients	CEA appears most cost-effective and intensive follow up has also been identified as a cost-effective option. However more research is needed.
Bleeker et al[78]	The Netherlands	Assessment of costs and outcomes for symptoms vs CEA vs chest x-ray vs COL vs CT/ultrasound vs combination, vs physical examination as follow up for Dukes C patients	Mean cost of diagnostic procedure/ curative resection is $US9011 ($A15,126). Ultrasound/CT and COL identified 22 recurrences at a cost of $US11,970 ($A20,093) per patient, while CEA, x-ray and physical examination identified a further six at a cost of $US19,850 ($A19,892) per patient.
Graham et al[79]	United States	Comparison of CEA vs chest x-ray vs COL vs physician examination for detecting recurrent disease	CEA is the most cost-effective surveillance procedure for curable and potentially curable patients. Costs per recurrence for CEA, chest x-ray, COL, physical examination were $US5696, $US10,078, $US45,810, no benefit ($A10,636, $A18,818, $A85,536, no benefit).

Study	Country	Study question	Conclusion
Michel et al[80]	France	Comparison of seven postoperative management strategies[a] for patients with stage II or III resected cancer	Current standard strategy may not be the most cost-effective strategy. Cost per surviving patient for strategies 1–7 were $US10,788, $US9118, $US7373, $US6781, $US12,421, $US9308 and $US8954 ($A18,986, $A16,947, $A12,976, $A11,934, $A21,860, $A16,381 and $A15,758).
Worthington et al[81]	Australia	Review of evidence for intensive vs conventional follow up	Available data indicate intensive follow up using CEA would be of benefit in terms of lives saved (studies suggest CEA would be 1st indicator of recurrent disease in 38% and 89% of patients), and cost-effectiveness. Application of Australian values to results in overseas studies suggest CER is $A23,812/LYG.
Renehan et al[82]	United Kingdom	Comparison of intensive vs conventional follow up	Intensive follow up is economically justified with an ICERs for the 5yr and 4yr trials of £3402 ($A7378)/LYG and £3077 ($A6673)/LYG. Sensitivity analysis confirmed the results are robust.
Staib et al[83]	Germany	Comparison of minimal vs intensive vs proposed risk-adapted follow up	Intensive follow up has low efficacy — 2% (current study), 10–15% (literature) — and is cost intensive. Costs per cured recurrent patient (current study and literature) were €6015 ($A10,371) and €1683–5049 ($A2902–8705) compared to minimal follow up €616–2624 ($A1062–4524). Costs for proposed or risk-adapted follow up range from (low to high risk) €610–5910 ($A1052–10,190).
Borie et al[84]	France	Comparison of simplified vs standard (includes CEA) follow up after curative resection (standard = 1998 French Consensus Conference)	For Dukes A, B and C, CERs were €4693, €10,068 and €1058 ($A7898, $A16,944, $A1781) per QALY gained in favour of standard follow up. However, high variability (±€44,830 [$A75,449], ± €180,195 [$A303,268] and ±€2746 [$A4622]) suggests no difference for the strategies. Sensitivity analysis indicates the results are robust.

[a] Strategies compared in Michele, Merle, et al[79] are as follows. Strategies (S) 1–4 comprised adjuvant chemotherapy following curative resection of Stage III, plus: S1 – follow up for stage II/III patients; S2 – follow up for stage II/III younger than 75yrs; S3 – follow up for stage II/III younger than 75yrs, and for stage III patients with CEA >5 ng/ml; S4 – no follow up. Strategies 5–7 comprised adjuvant chemotherapy following curative resection of stage II/III, plus; S5 – follow up for patients stage II/III patients; S6 – follow up for stage II/III younger than 75yrs, and stage III with CEA >5 ng/ml; S7 – no follow up

22.9 Treatments

22.9.1 Surgery

Several studies investigating various surgical techniques and treatments were identified. The studies are varied in relation to disease stage investigated, techniques evaluated and comparisons made. The majority were economic analyses evaluating costs and effectiveness separately (5), or cost and consequences studies (2). Only two were cost-effectiveness/utility studies. The results are summarised in Table 22.9.

In general, the studies indicate that stenting is an effective and cost-saving procedure and that surgical resection is potentially more cost-effective than palliative chemotherapy. Findings for laparoscopic techniques vary across studies, with some indicating cost savings but others finding no cost-benefit.

Due to the variation in disease stage, techniques and treatments evaluated, comparisons made, results reported, and the studies being predominately economic analyses and cost and consequences analyses, it is not possible to recommend any one technique or treatment over another on the basis of cost-effectiveness. The studies at best provide an indication of possible cost savings for particular techniques or treatments.

Table 22.9 Results of studies investigating effectiveness, costs and cost-effectiveness of various surgical techniques and treatments

Study	Country	Study questions	Conclusion
Bouvet et al[85]	United States	Assessment of cost and outcomes for laparoscopic colon resection (LCR) vs laparoscopy converted to open colon resection (CCR) vs planned open colon resection (OCR)	LCR is an effective procedure, with costs similar to OCR but significantly less than CCR. Morbidity and mortality rates for LCR, CCR and OCR are similar, with two-year actuarial disease-free and disease-specific survival of 93%, 88%; 87%, 84%; and 88%, 84%. Costs ($x10^3$) were $US12, $US15 and $US11 ($A18.7, $A23.4 and $A17).
Janson et al[86]	Sweden	Assessment of costs to society and the health care system, of LCR compared to OCR	Within 12 weeks of surgery there is no significant difference in total cost to society (mean difference of €1846 [$A3193]. However LCR is significantly more costly to the health care system (mean difference of €1556 [$A2750]).
Vardulaki et al[87]	United Kingdom	Comparison of open vs laparoscopic surgery (LS)	LS costs more but the difference is relatively small (£227 [$A607]). Short-term outcomes indicate a benefit for LS (overall conversion rate of 13% across studies, but 8% for studies with only Colorectal Cancer patients; reduction in complication rates but not significant). There was no significant difference in long-term outcomes.
Philipson et al[88]	Australia	Assessment of costs for open right hemicolectomy (ORHC) vs laparoscopically-assisted right hemicolectomy (LARHC)	LARHC results in no cost benefit. Total costs for ORHC vs LARHC were $A7881 vs $A9064. LAHRC is significantly more expensive.
Targarona et al[89]	Spain	Assessment of cost and outcomes of hand-assisted laparoscopic colectomy (HALS) compared to LS	HALS simplifies difficult intra-operative situations and is as effective as LS (no significant difference in clinical outcomes), with similar costs ($US1782 vs $US1710 [$A2841 vs $A2726]). HALS should be considered as a useful adjunct.

Study	Country	Study questions	Conclusion
Koperna[90]	Austria	Comparison of low anterior resections (LAR) with or without defunctioning stomas	Rate of defunctioning stomas should be reduced due to effect on overall costs, especially in patients with low leakage rates. Patients (without stoma) with anastomotic leakage need significantly longer hospital stay (45.3 vs 17.5 and 18 days for no stoma and stoma). Costs for LAR without stoma/no leakage, with stoma, and with leakage were €8400, €13,985 and €42,450 ($A15,549, $A25,888 and $A78,580). ICER for with stoma is €158,705 ($A293,780) and €60,915 ($A112,760)/leakage avoided (leakage rates <3% and 6%). A 16.5% leakage rate is required to balance costs. Only duration and costs of ICU might influence the results.
Osman et al[91]	United Kingdom	Assessment of costs and outcomes for stenting vs surgical decompression	Stenting is successful and cost saving. Procedure success rates, 30-day mortality and mean hospital days for stenting and surgical decompression were 94% and 100%; 0 and 1; 2.5 and 13.5. Costs/day were £1445 ($A3866) vs £3205 ($A8574) (mean saving of £1760 [$A4708]/day for stenting, and at 15 procedures per year, an annual saving of £26,400 [$A70,624]). Costs for stented proceeding to elective anterior resection vs decompression proceeding to reversal were £5035 vs £5720 ($A13,469 vs $A15,302 (saving of £685 [$A1833]).
Xinopoulos et al[92]	Greece	Assessment of cost and outcomes for self-expanding metallic stents vs stoma for patients with inoperable malignant obstructions	Stenting is a suitable alternative, with similar costs to stoma. LOSfor stenting vs stoma was 28 days vs 60 days. There was no significant difference in survival (21.4wks vs 20.9wks). Total costs were €2224 vs €2092 ($A4265 vs $A4011) (6.9% difference).
Binkert et al[93]	Switzerland	Assessment of cost and outcomes for self-expanding metallic stents as either a preoperative procedure or palliation	Metallic stent placement is a minimally invasive and less costly procedure. Average costs for stent vs no stent were 4362.11FR ($A3211.08) vs 5538.46FR ($A4077.03). Lower costs were due to shorter LOS, fewer surgical procedures and fewer days in ICU.

Study	Country	Study questions	Conclusion
Bissett et al[94]	New Zealand	Comparison of extrafascial excision (EFE) vs conventional surgery	EFE reduces local recurrence and appears to be associated with improved survival at costs similar to conventional surgery. For conventional vs EFE, rates for local recurrence were 21% vs 6%, 5yr actuarial local recurrence were 30% vs 10%, cancer-free survival were 63% vs 74%, and 5yr overall survival were 54% vs 60%). Average cost per local recurrence was an additional $NZ10,471 ($A12,468).
Beard et al[95]	United Kingdom	Comparison of hepatic liver resection vs standard non-surgical cytotoxic treatment (palliative)	Hepatic resection is cost-effective compared with non-surgical treatment. At 5yr survival, marginal benefit is 1.6LYG (undiscounted) at a marginal cost of £6742 ($A18,435). If 17% have only palliative resections, cost is £5236 ($A14,317)/LYG (£5985 ($A16,365) discounted). For 20yr survival, approximate costs are £1821 ($A4979) (£2793 ($A7637) discounted). Sensitivity analysis shows costs/LYG are consistently less than £15,000 ($A41,076).
Miller et al[96]	United States	Comparison of surgical resection vs diagnostic/ palliative surgery vs non-operative treatment	Diagnostic/palliative surgery is expensive and affects QALY survival adversely (1.92yr). Surgical resection may be cost-effective, particularly if calculated using patient preferences. ICER/QALY gained using health care professional preferences, and patient preferences were $US109,777 and $US56,698 ($A188,124 and $A97,163).

22.9.2 Chemotherapy

Numerous studies have investigated the effectiveness and cost-effectiveness of various chemotherapy regimes or agents, methods of delivery, timing and setting. Methodologies used and comparisons made varied considerably across studies. The majority of the studies have conducted cost-effectiveness, cost-utility, cost-benefit or cost-minimisation analyses. There have also been several cost and consequences, economic, and cost analyses, as well as a few reviews. The results of studies conducting analyses are summarised in Table 22.10. Reviews are summarised in Table 22.11.

Although these studies indicate some regimes or agents, delivery methods, timing or setting appear to be relatively more cost-effective or cost saving than others, there is insufficient evidence at this stage to recommend one over others on the basis of cost-effectiveness. It should also be noted that extrapolating these results to the Australian context is not appropriate, as relative cost-effectiveness is largely driven by the costs of the different chemotherapy regimes and modes of delivery, which can very internationally. The studies at best provide an indication of possible cost-effectiveness or cost savings for particular regimes or agents, delivery methods, timing or setting.

Table 22.10 Results of studies investigating effectiveness, costs and cost-effectiveness of alternative chemotherapy regimes

Study	Country	Study questions	Conclusion
Durand-Zaleski et al[97]	France/United States	Comparison of HAI vs intravenous chemotherapy vs symptom palliation	Cost-effectiveness of HAI is within the range of accepted treatment for serious conditions, but may be borderline in some countries. Mean discounted survival HAI vs intravenous chemotherapy was 16.3mths vs13.1mth). ICERs/LYG for Paris and Canada were $US73,635 and $US72,300 ($A137,491 and $A134,998). Sensitivity analysis indicates variations in survival and costs result in ICER ranges of $US63,717–73,680 ($A118,972–137,574) (Paris) and $US65,867–87,012 ($A122,986–162,468) (Canada).
Vidal-Jove et al[98]	Spain	Comparison of intra-arterial chemotherapy vs IV chemotherapy for advanced malignancies	Intra-arterial chemotherapy results in improved median survival (13mths vs 6mths) and overall response rates (80% vs 20%) and is cost-effective compared to IV chemotherapy (cost per response-for each month of survival month of $US919 vs $US662 [$A1843 vs $A1327]).
Tampellini et al[99]	Italy	Assessment of cost of chronochemotherapy vs FOLFOX (de Gramont)	Direct costs for a single cycle of chronochemotherapy appear to be comparable to single course FOLFOX (€337 ($A543) or €356 ($A574) (rented pump) vs €346 ($A558). Major material cost is balanced out by lower toxicity costs (€144 vs €288 [$A232 vs $A464]).
Messori et al[100]	Italy	Comparison of adjuvant intraportal chemotherapy vs none	Adjuvant intraportal chemotherapy is cost-effective with an ICER/ LYG of $US1210 ($A2171)/discounted ($US494 ($A888) undiscounted). Sensitivity analysis shows results are robust for drug costs and still cost-effective for variation in LOS and survival.
Jansman et al[101]	Netherlands	Analysis of the cost benefit of capecitabine vs 5-FU+LV	Treatment with oral capecitabine is cost-saving compared to 5-FU+LV. Baseline savings for palliative and adjuvant treatment estimated at €1610 ($A2946) and €934 ($A1709). Sensitivity analysis shows results are robust.

Study	Country	Study questions	Conclusion
Hieke et al[102]	Germany	Assessment of costs for 5-FU regimens (Mayo, AIO/ Ardalan) vs oral capecitabine as inpatient vs outpatient/day clinic vs office-based oncologist treatment	Most expensive treatments were AIO/Ardalan for office-based, and Mayo for hospital setting. The least costly in office-based was capecitabine. Overall, the least expensive option was AIO/Ardalan in municipal hospital settings. Hospitals are unlikely to cover costs in this situation. Substantial cost savings (without incurring loss to the provider) possible with office-based capecitabine treatment.
Iveson et al[103]	United Kingdom	Comparison of irinotecan vs infusional 5-FU	Irinotecan is cost-effective compared to 5-FU, with an ICER/LYG of £7696 ($A20,089) (de Gramont) and £11,947 ($A31,185) (Lokich). Sensitivity analysis shows that using lifetime estimates instead of median survival changes ICERs to £10,104 and £14, 942 ($A26,583 and $A39,003).
Levy-Piedbois et al[104]	France	Comparison of irinotecan vs intrafusional 5-FU (Lokich) vs intrafusional 5-FU (AIO) vs intrafusional 5-FU (de Gramont [LV5-FU2]) for 2nd-line treatment	Least expensive treatment is 5-FU, but the additional cost of irinotecan is balanced by additional survival (2.3 mths). ICERs range from $US9344 to $US10,137 ($A16,445–17,840)/LYG. Sensitivity analysis shows that with variation in survival, ICERs range from $US3000–45,000 ($A5280–79,196), and adding irinotecan to intrafusional 5-FU (de Gramont [LV5-FU2] results in an ICER of $US29,373 ($A42,190)/LYG.
Norum et al[105]	Norway	Assessment of cost and outcomes for raltitrexed vs Nordic-FLv in metastatic cancer	No difference in overall survival (median survival of 14.7mths vs 15.4 mths) and costs (€6800 vs €6881 [$A1235 vs $A1249]). Raltitrexed is the most toxic in terms of diarrhoea, nausea/vomiting, appetite loss, but more patients receiving raltitrexed preferred the treatment schedule and frequency of hospital visits (87% and 75%) than did those having Nordic Fly (55% and 45%).
Groener et al[106]	Netherlands	Comparison of 5-FU+LV vs raltitrexed	There was no significant difference in survival benefits, but raltitrexed resulted in fewer side effects (rate of 57.07% vs 72.97%). The ICERs/additional survivor post 6mths and 12mths of raltitrexed were $US16,086 and $US154,611 ($A29, 894 and $A272,102). ICER/additional side-effect-free patient was $US3936 ($A6927).

Study	Country	Study questions	Conclusion
Kerr and O'Connor[107]	United Kingdom	Assessment of cost and outcomes for raltitrexed vs 5-FU (Mayo regimen)	There is no difference in response rate and survival, but raltitrexed reduces demand on clinic and pharmacy resources (reduced toxicity (12.4 vs 16.7) and administration (6 vs 22 days) without increasing cost of monthly treatment (£781 [$A2039] [raltitrexed] vs £834 [$A2177] [5-FU]).
Maroun et al [108]	Canada	Comparison of UFT/FA vs parenteral FU/FA	Cost of treatment per patient and per cycle using UFT/FA is less than using FU/FA. Total cost savings per patient per cycle and per treatment were $CAN826 and $CAN3221 ($A1217 and $A4745).
Ward et al[109]	United Kingdom	Assessment of cost and outcomes for capecitabine vs UFT/LV vs three 5-FU regimens — (Mayo, modified de Gramont and inpatient de Gramont), as 1st-line treatment	Oral therapies are associated with cost-benefits but have no proven survival benefit. There is no proven survival difference for the 5-FU regimens. Cost savings for capecitabine and UFT/LV vs Mayo, modified de Gramont and de Gramont were £1461, £1353 and £4123; £209, £101 and £2870 ($A3696, $A3422, $A10,429, $A529, $A255 and $A7260). Sensitivity analysis indicates savings for capecitabine could range from £483 ($A1222) vs modified de Gramont to £4123 ($A10,429) vs de Gramont; Results for UFT/LV could range from saving of £101 ($A255) vs modified de Gramont to an additional cost of £445 ($A1126) vs Mayo.
Smith et al[110]	Australia	Comparison of 5-FU + levamisole vs no chemotherapy after full resection for Dukes C patients	Inclusion of 5-FU results in incremental cost of $A7000 with ICER of $A2916/LYG and $A17,500/QALY gained. Sensitivity analysis shows results may vary from $A12,000–$A31,900.
Glimelius et al[111]	Sweden	Comparison of 5-FU+LV (palliative chemotherapy) + best supportive care vs best supportive care	Palliative chemotherapy is cost-effective with an ICER/LYG of 102,000–204,000SEK ($A25,166–50,332). Results are sensitive to changes in survival differences.
Bonistalli et al[112]	Italy	Comparison of adjuvant FU+ levamisole vs no chemotherapy for stage III cancer	Adjuvant therapy with FU + levamisole has favourable economic benefits (ICERs = $US1422 ($A3239)/LYG, $US1501 ($A3419)/QALY gained. Sensitivity analysis confirms the results robust.

Study	Country	Study questions	Conclusion
Cunningham et al[113]	United Kingdom	Comparison of irinotecan + 5-FU+ FA vs 5-FU+FA alone as 1st-line treatment	Irinotecan + 5-FU/FA is cost-effective compared to FU/FA alone, with ICER = £14,794 ($A40,452)/LYG. Sensitivity analysis confirms the results are robust.
Poston et al[114]	United Kingdom	Comparison of oxaliplatin + 5-FUFA vs 5-FU/FA alone	Oxaliplatin + 5-FU/FA increases resection rates compared to 5-FU/FA at an acceptable cost (ICER = £11,985 [$A31,182]/LYG). Sensitivity analysis indicates an ICER range of £5489–15,624 ($A14,560–41,471), with variations to resection rates, survival rates and discounting.
Koperna and Semmler[115]	Austria	Comparison of oxaliplatin + FU/LV vs FU/LV alone for stage III patients	Oxaliplatin + FU/LV is cost-effective for stage III patients. Even under the most conservative scenario, (20% increase in mortality and recurrence reduction rates), compared to best supportive care, LYG (undiscounted and discounted) for FU/LV and for oxaliplatin + FU/LV was 51 vs 62; 41.8 vs 50.8. Undiscounted and discounted ICERs/LYG were $US5352, $US6503 ($A7907, $A9608); $US7425, $US8865 ($A10,970, $A13,098); $US9920, $US10,956 ($A14,656, $A16,187); and $US10,609, $US12,485 ($A15,674 $A18,446).
Focan[116]	Belgium	Comparison of 5-FU/FA + oxaliplatin administered either as standard (flat arm A) or chronomodulated (arm B) drug infusions	Costs are basically equivalent. Higher treatment costs for chronomodulated drug infusion are counterbalanced by fewer complications and shorter LOS. Costs are also less for melodie pump. For flat arm A and arm B (intellijject and melodie pump), costs/course were 131,340BEF, 107,176 BEF, 134,668 BEF and 110,592 BEF ($A246,129, $A200,846, $A252,366, A207,248).

Study	Country	Study questions	Conclusion
Murad et al[117]	Brazil	Assessment of costs of UFT/LV compared to 5-FU	UFT/LV has an economic advantage over 5-FU and is therefore a useful and economic alternative. Costs for UFT/LV vs 5-FU (Brazil; Argentina) as adjuvant therapy were $US9624 vs $US9654 ($A15,672 vs $A15,721); $US12,295 vs $US13,077 ($A20,022 vs $A21,296). For treatment of metastatic disease, costs were $US10,178 vs $US10,491 ($A16,575 vs $A17,084); $US12,369 vs $US13,558 ($A20,143 vs $A22,079). Sensitivity analysis indicates the results are robust.
Monz et al[118]	Germany	Comparison of FU/FA + levamisole vs FU + levamisole alone	Adding FA results in clinical benefits and costs that may be acceptable to decision makers in the long term. The 5yr trial mean overall and disease-free survival (5% discounted) for FA vs none was 3.72yrs, 3.27yrs vs 3.52yrs vs 2.90yrs. Survival for beyond the trial was 9.38yrs, 8.11yrs vs 8.13yrs, 7.06yrs. For the trial, ICERs/LYG and disease free LYG (5% discounted) were €51,225 and €33,008 ($A88,324 and $A56,913). Beyond the trial, ICERs were €11,020 and €11,176 ($A19,001 and $A19,270). Sensitivity analysis confirmed the results are robust.
Nicholls et al[119]	United Kingdom	Comparison of 5-FU/FA + oxaliplatin vs 5-FU/FA + irinotecan vs 5-FU/FA alone	Both combinations offer comparable benefits in terms of effectiveness and cost-effectiveness over 5-FU/FA alone. The addition of oxaliplatin is more cost-effective than the addition of irinotecan. Compared to 5-FU/FA, the ICERs per progression-free year were £26,665 and £30,171 ($A70,877 and $A80,102). Sensitivity analysis indicated ICERs could range from £21,421–31,909 ($A56,863–84696) and £23,692–36,651 ($A62,886–97,284).

Study	Country	Study questions	Conclusion
Lloyd Jones et al[120]	United Kingdom	Comparison of irinotecan vs oxaliplatin vs raltitrexed vs (all either alone or in combination with 5-FU/FA) vs 5-FU/FA in 1st- and 2nd-line treatment for advanced patients	For 1st-line treatment, a combination of either irinotecan or oxaliplatin with infusional FU/FA appears to extend progression-free survival by 2–3mths compared to 5-FU/FA alone. Marginal costs per progression-free survival year for oxaliplatin and irinotecan are £23,000 and £58,400 ($A61,049 and $A155,012). If it is assumed all treatment is conducted as outpatients, ICER per progression-free year is unchanged for oxaliplatin, £49,000 ($A130,061) for irinotecan, and £26,400 ($A70,074) for 2nd irinotecan. For 2nd-line treatment ICER/LYG for irinotecan vs outpatient 5-FU/FA and best supportive care are £11,180 and £17,700–28,200 ($A29,675 and $A46,981–74,852).
Hale et al[121]	United Kingdom	Assessment of costs and outcomes of de Gramont regimen vs Lokich regimen vs raltitrexed	Lokich, with comparable clinical benefit at only ½ the cost of de Gramont, offers best value for money. Total societal costs for de Gramont, Lokich and raltitrexed were £5050 vs £2616 vs £2435 ($A13,807 vs $A7,153 vs $A6,658). From the hospital perspective, Lokich was the least costly (£1699 vs £666 vs £814 ($A4646 vs $A1821 vs $A2226). Although cost differences for treatment of side effects and serious adverse events were not significant, raltitrexed resulted in higher toxicity and impaired QoL vs de Gramont and Lokich. Sensitivity analysis confirmed the results are robust.
Rowe et al[122]	United Kingdom	Assessment of outpatient de Gramont (using elastoneric infusional device) vs inpatient treatment	Outpatient administration is acceptable to patients who chose it, shows better QoL scores (improved overall health and QoL scores), and results in considerable cost saving (£3800 vs £1735 [$A9612 vs $A4389]).

Only a few reviews have been published, predominately concerning evidence about the cost-effectiveness of newer agents such as capecitabine, raltitrexed, irinotecan, oxaliplatin and oral tegafur compared to 5-FU-based regimens. The findings, summarised in Table 22.11, suggest that the newer agents may be more cost-effective than the 5-FU-based regimens, but further research is required and an optimal agent is difficult to determine. The reviews confirm the findings of this current evaluation. There is insufficient evidence at this stage to recommend one chemotherapy regime or agent over others on the basis of cost-effectiveness. The studies at best provide an indication of possible cost-effectiveness or cost savings for particular regimes or agents.

Table 22.11 Summary of findings from reviews of cost-effectiveness of chemotherapy agents and regimes

Study	Country	Study questions	Conclusion
Redaelli et al[47]	United States	Review cost-effectiveness evidence for alternative chemotherapy regimens	New treatments (particularly oral tegafur) appear to be more cost-effective than 5-FU-based therapies for advanced and metastatic cancer. Depending on country, setting (1st-line, 2nd-line or rescue therapy) and comparative treatments, ICERs of irinotecan and raltitrexed are generally within the threshold of $US30–50,000 ($A44,323–73,872)/LYG. Both have significant and consistent economic advantage over 5-FU. There is a limited evidence for adjuvant therapy. It appears FU + levamisole or FA are cost-effective (if 5% improvement in 5yr survival rate), with possible ICERs of $US2094–6500 ($A3094–9,603)/LYG. More research is needed.
Scott and Twelves[123]	United Kingdom	Review cost-effectiveness of new chemotherapy drugs vs FU (concentrating on drug costs)	Capecitabine, raltitrexed, irinotecan and oxaliplatin alone, or in combination with 5-FU or FU/FA, are cost-effective compared to FU or FU/FA alone. Cost savings range from $US626–5000 ($A925–7387) per patient, ICERs/LYG range from $US21,591–59,403 ($A31,899–87,764) (1st-line treatment) and $US9344–10,137 ($A13,805–14,977) (2nd-line treatment). Comparisons between newer agents is difficult due to non standardised methods, and judgments may differ between countries, tumour type, available treatments, etc.
Matasar et al[77]	United States	Review cost-effectiveness of chemo regimens in elderly patients	ICER of fluorouracil-based regimens, depending on delivery strategy, use of model agents and stage of cancer, vary from $US2000–20,000 ($A2790–27,897) per QALY gained. Reported ICER of $US10,000 ($A13,949) per QALY gained for irinotecan is likely to be an underestimate and requires further research. Raltitrexed, capecitabine and oxaliplatin also require further research. UFT appears to be potentially cost saving. HAL cannot be recommended for elderly patients

22.9.3 Other

A small number of studies have investigated other treatment alternatives such as preoperative radiotherapy and radiofrequency ablation.

In the Netherlands, van den Brink et al[124] evaluated the cost utility of preoperative radiotherapy (PRT) and found that, in the short term, PRT is effective and cost-effective, with a cost/QALY gained of $US25,100 ($A40,015). Sensitivity analysis confirmed the results are robust. In a Swedish study, Dahlberg et al[125] investigated the cost-effectiveness of PRT in the primary treatment of resectable rectal cancer and found it to be cost-effective with a cost/LYG of $US3654 ($A6134). Even in the most pessimistic scenario, the cost/LYG was US15,228 ($A25,562). These studies provide some evidence that PRT is cost-effective, but additional evidence from further research is needed before a definitive recommendation can be made.

Radiofrequency (RF) ablation for the treatment of liver metastases was evaluated in a cost-effectiveness study by Shetty et al.[126] Results of the study indicate RF ablation is a cost-effective strategy compared to palliative care. Incremental cost-effectiveness ratios per life year gained at six months, one-, two-, three- and five-year median survival were $US20,424, $US11,407, $US6731, $US5034 and $US3492 ($A31,895, $A17,814, $A10,512, $A7861 and $A5453). Sensitivity analysis shows that the results, though sensitive to observation hours, number of lifetime treatments, frequency of follow up, and cost of abdominal CT and outpatient treatment, remain cost-effective. While these results suggest that RF is cost-effective, recommendations cannot be based on the findings of only one study. These results indicate that RF is potentially cost-effective with further research required.

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CHAPTER 23 SOCIO-ECONOMIC ASPECTS IN COLORECTAL CANCER

23.1 Socio-economics

Socio-economics are now being considered more widely in guideline development as they play a significant role in health care. Even in an affluent setting, ignorance can produce inequalities that need to be addressed.

The overall effect of socio-economics research is that deprivation has been well documented in Australia and is recognised as a factor in developing clinical practice guidelines.[1]

In Colorectal Cancer, there is a paucity of randomised clinical trials involving socio-economic background. They relate largely to screening factors, compliance with treatment, and the outcomes of treatment.

Pilot screening programs using faecal occult blood testing (FOBT) have been carried out in Australia (see Chapter 3) and it is planned to extend them. While such programs should allow greater access to screening for all levels of the population, they will not reduce the need to maintain education and persuasive advertising to participate in screening.

Whynes et al[2] aimed to determine the effects and extent of socioeconomic deprivation, analysing clinical data from a large randomised control trial augmented by geographically-based indices of deprivation. While deprivation had no significant effect on prevalence of Colorectal Cancer, it had a significant effect on participation in screening. People from more economically deprived areas have less interest than economically replete people in accepting an invitation to be screened. A similar observation has been made in other trials. In Glasgow,[3] a randomised controlled trial in people aged 55–65 years noted that lower socio-economic or deprived groups expressed lower levels of interest in screening tests. In a study in France[4] on the offering of FOBT, 1129 persons were circularised with a questionnaire and 645 (57.1%) returned it. However, review revealed that actually undertaking the test cannot be assumed from intention to do so. The authors suggest that this type of study based on questionnaires should be avoided in determining underlying behaviour towards secondary prevention.

In aiming to increase FOBT in the USA, a national priority is to increase participation by African Americans.[5,6] Fatalism is believed to be a barrier to FOBT screening in this population. In this study of elderly white and African Americans, the latter were the larger number but even when factors such as age, poverty and education were controlled, fatalism remained the only significant barrier to FOBT. Fatalism deserves significant attention in some ethnic groups, to derive interventions to reduce its effectiveness.

A cohort study of white and African Americans with advanced lung and colon cancer and who had not had previous chemotherapy, had their socioeconomic and biological data collected prospectively in twelve medical centres in the U.S. Veterans Administration System (May 1981–May 1986).[7] The essential findings of the study were that lung and colon cancer outcomes ‘may be similar among black and white patients who have equal access to comparable medical care in spite of socioeconomic differences’. This study puts equal access to care as a necessary accompaniment to good clinical care.

Based on a randomised study after mailing FOBT kits, Myers et al[8] recommended that health professionals raise awareness of risk factors and curability of Colorectal Cancer to encourage potential screenees to commit to recommended behaviour patterns. They also recommended that messages be tailored to keep past testers in the screening loop.

The approaches outlined are designed to maintain the educational thrust and to bring readers’ attention to advocacy for equal access as an aid for those with socio-economic deprivation.

References

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Appendices

APPENDIX 1 THE PRINCIPLES OF MULTIDISCIPLINARY CARE

Multidisciplinary care (MDC) has been the focus of increasing attention in recent years, with efforts to promote its broad implementation increasing as evidence of its benefits become apparent. Work by Paul Mitchell and Craig White has explored the introduction of a clinical implementation group for Colorectal Cancer[1] which involves interaction of consumers and clinicians, but to date much of the work conducted to explore models of MDC in Australia has used breast cancer as an example.

A flexible approach to MDC models has been advocated in Australia, as one model will not fit all circumstances. Approaches need to be sufficiently flexible to take account of Australia's diverse geography, the mix of public and private service provision and significant regional differences in population, resource availability and access.

A number of models for the implementation of MDC exist. A central component of all models is treatment planning meetings (either face-to-face or via tele-/videoconference) involving a broad range of personnel with input from both specialist clinicians and nursing/allied health professions, and incorporating patient preferences. A key issue for consumers is the need for them to know that multidisciplinary discussion has occurred but with confident knowledge of who is driving their care.

The Working Party was of the opinion that the *Principles of Multidisciplinary Care* outlined by Zorbas et al [2] should underpin the implementation of MDC. The *Principles* identify the need for a team-based, equitable, evidence-driven, patient-centred approach to cancer care. While the *Principles* were developed with a focus on breast cancer, they clearly have broader application to other types of malignancy and chronic disease. The *Principles of Multidisciplinary Care* provide a good foundation for the implementation of MDC, and with adequate resourcing and support, MDC can become incorporated standard practice using a range of models for cancer care and probably chronic disease care in Australia.

References

1. Mitchell P, White C, Austin. Bowel Cancer Consortium: changing culture in bowel care. Principles of multidisciplinary care (National Multidisciplinary Care Demonstration Project) MJA 2004: 180 (10) 579-82

2. Zorbas H, Barraclough B, Rainbird K, Luxford K, Redman S. Multidisciplinary care for women with early breast cancer in the Australian context: what does it mean? MJA 17 Nov 2003; 179:528-31.

Principles of multidisciplinary care (National Multidisciplinary Care Demonstration Project)

Principle of care	Outcome
Team	
The disciplines represented by the "core" team should minimally include surgery, oncology (radiation and medical oncology), pathology, radiology and supportive care. The individual woman's general practitioner will be part of her team.	The "breast cancer care team" is established and known.
In order to ensure that the woman has access to the full range of therapeutic options, the "core team" may be expanded or contracted to include services (which may be off site) such as genetics, psychiatry, physiotherapy and nuclear medicine.	Referral networks established for non-core team specialist services.
Communication	
A communications framework should be established which supports and ensures interactive participation from all relevant team members at regular and dedicated case-conference meetings.	Communication mechanisms are established to facilitate case discussion by all team members.
Multidisciplinary input should be considered for all women with breast cancer; however, not all cases may ultimately necessitate team discussion.	A local protocol is established for deciding which cases may not require team discussion.
Full therapeutic range	
Geographical remoteness and/or small size of the institution delivering care should not be impediments to the delivery of multidisciplinary care for women with breast cancer.	Systems are established for ensuring that all women have access to all relevant services.
The members of the team should support the multidisciplinary approach to care by establishing collaborative working links.	Systems are established to support collaborative working links between team members.
Standards of care	
All clinicians involved in the management of women with breast cancer should practice in accord with guideline recommendations.	Local clinician data are consistent with national benchmarks.
The treatment plan for a woman should consider individual patient circumstances and wishes.	The final treatment plan should be acceptable to the woman.
Discussion and decisions about treatment options should only be considered when all relevant patient results and information are available.	Final reports are available to all core team members before treatment planning.
In areas where the number of new cancers is small, formal collaborative links with larger units/centres should give support and foster expertise in the smaller unit.	Systems are established for the exchange of knowledge and expertise between larger and smaller caseload centres.
Maintenance of standards of best practice is supported by a number of activities which promote professional development.	Systems are established for the support of professional education activities.
Involvement of the woman	
Women with breast cancer should be encouraged to participate as a member of the multidisciplinary team in treatment planning.	Women are supported to have as much input into their treatment plan as they wish.
The woman diagnosed with breast cancer should be fully informed of her treatment options as well as the benefits, risks and possible complications of treatments offered. Appropriate literature should be offered to assist her in decision-making. This information should be made available to the woman in a form that is appropriate to her educational level, language and culture.	All women should be fully informed about all aspects of their treatment choices.
Supportive care is an integral part of multidisciplinary care. Clinicians who treat women with breast cancer should inform them of how to access appropriate support services.	All clinicians involved in the management of women with breast cancer should ensure that women have information about and access to support services.
The woman with breast cancer should be aware of the ongoing collaboration and communication between members of the multidisciplinary team about her treatment.	Women with breast cancer feel that their care is coordinated and not fragmented.

"Zorbas et al [2] **Multidisciplinary care for women with early breast cancer in the Australian context: what does it mean?** MJA 2003; 179: 528-531 © Copyright 2003. *The Medical Journal of Australia* – reproduced with permission"

APPENDIX 2 GUIDELINE DEVELOPMENT PROCESS

Introduction

This manuscript is a current revision and update of the 'Guidelines for the prevention, early detection and management of Colorectal Cancer (CRC)' endorsed by the NHMRC in 1999.[1] The guidelines were produced by the Australian Cancer Network (ACN), a subsidiary of The Cancer Council Australia, and The Clinical Oncological Society of Australia, and resourced by them.

Active professional bodies have been invaluable in guideline development and are promoting prevention, early diagnosis and the embracing of the best available evidence of therapeutic treatment options.

Colorectal Cancer is the most common cancer in Australia, apart from skin cancer. It is responsible for 13% of cancer deaths. Clinicians, government and consumers have requested an update of the 1999 document to provide contemporary and easy-to-follow guidelines based on the best current evidence for aspects of CRC prevention, detection and management.

The 1999 document has been widely used by clinicians and evaluated by questionnaire,[2] report[3] and publication.[4] These studies and frequent phone requests to the ACN secretariat are an additional reason for revision.

The National Colorectal Cancer Care Survey (NCCS)[2,3] was initiated at the time the 1999 guidelines were disseminated. All new cases of Colorectal Cancer registered at each cancer registry in Australia from 1 February to 30 April 2000 were included in the survey. The responses were recorded in the survey evaluation of 18 of the 86 guidelines. They covered a wide range of surgical management. A survey of 172 surgeons in 2001 noted changed views in regard to screening by faecal occult blood testing (FOBT), so revealing some impact of the guidelines.[4] On the other hand, it is clear that significant effort is required to ensure that patients with CRC detected through screening receive evidence-based management.[5] This should be achievable as surgeons have been shown to be receptive to clinical practice guidelines.[6,7,8]

The concordance between clinical care and the majority of the guidelines studied was clear at the time of the NCCS.[2] However, there is still a gap that needs to be filled before all management complies with the guidelines.

Structure and function of the Working Party

The work program was carried out under a principal committee of nine members, with joint chairmanship. The committee was composed of three colorectal surgeons, two gastroenterologists, a surgical oncologist, a medical oncologist, a consumer and a surgeon convenor.

Each chapter of the guidelines had a 'writing' subcommittee that developed the content under the guidance of a chair. The principal committee and the chairs of the developmental committees comprised the working party, which was chaired by the joint chairs. The membership of the Working Party was multidisciplinary and comprised four colorectal surgeons, one surgical oncologist, three medical oncologists, two gastroenterologists, one radiation oncologist, one pathologist-molecular biologist, one psychosocial expert, one consumer and a convenor. The Working Party was the final arbiter on strengths of recommendations.

Draft documents on surgically-related matters were developed by the subcommittees. When completed, the manuscripts were submitted to the ACN secretariat then distributed to members of the principal committee, which held several face-to-face meetings to consider the submissions for each chapter. A similar process was carried out by the authors of the medical and radiation oncology chapters. The gastroenterologists also followed the same pattern, but worked in close association with

a pathologist-molecular biologist on Chapter 9. The chapter authors, all clinicians practising in their specialty, consulted widely during the development process. Apart from their clinical expertise, virtually all had published in peer-reviewed journals and been involved in state, national, and some in international meetings involved in Colorectal Cancer. Most had significant input into writing the document and all had a role in its review. There was considerable crossover of personnel and cross fertilisation between groups. Geographic spread was observed in accruing Working Party membership. All personnel involved are listed in Appendix 3.

All chapter authors were made aware of the importance of ensuring readability of the manuscript and of noting matters that are suitable for research or would affect implementation.

Time schedule of development of the guidelines

Date	Composition of meetings	Location
May 2002	Telephone call to Professor Robert Thomas, Professor John Zalcberg, Professor Michael Solomon and Russell Stitz	ACN Office, Camperdown
2 December 2002	Full committee meeting	Qantas Club Business Centre, Melbourne Airport
11 March 2003	Professor Michael Solomon	ACN Office, Camperdown
25 March 2003	Professor Michael Solomon	ACN Office, Camperdown
3 June 2003	Executive teleconference	ACN Office, Camperdown
3 July 2003	Professor Michael Solomon	ACN Office, Camperdown
8 July 2003	CRC meeting	ACN Office, Camperdown
26 August 2003	Executive meeting	Qantas Club Business Centre, Sydney Airport
2 December 2003	Executive meeting	Qantas Club Business Centre, Melbourne Airport
2 February 2004	Professor Michael Solomon	ACN Office, Camperdown
23 March 2004,	Editorial Group Meeting	ACN Office, Camperdown
20 July 2004	Meeting with Dr Mike Liem and Professor Michael Solomon	ACN Office, Camperdown
10 August 2004	Executive meeting	Qantas Club Business Centre, Melbourne Airport
9 September 2004	Dr Mike Liem	ACN Office, Camperdown
14 September 2004	Meeting with Dr Mike Liem and Professor Michael Solomon	ACN Office, Camperdown
21 September 2004	Dr Mike Liem	ACN Office, Camperdown
12 October 2004	Dr Mike Liem	ACN Office, Camperdown
28 January 2005	Professor Michael Solomon	ACN Office, Camperdown

The Working Party designated an Executive (Appendix 3) and met by phone on several occasions to develop the next steps in the review structure. A writing and review structure was proffered by Professor Michael Solomon.

Professional and Public Consultation

The draft guidelines were sent to interested and relevant experts, representatives of professional colleges and consumer organisations. The guidelines were also advertised in the national press as being available for comment.

Thirty two notifications and thirty one submissions were received. Individual chapter leaders and their teams reviewed comments.

A special committee was also established under the chairmanship of Professor Bruce Barraclough (Appendix 4), it met on June 9 2005 and deferred some matters to July 4 for final consideration. A special meeting was also held on July 23, 2005 to discuss some Oncological questions (Attendances noted in Appendix 4).

These meetings carefully reviewed responses to public and professional submissions to ensure that the final product reflected best practice and the best available evidence. When full revision was achieved the document was approved by the Executive of the Working Party and forwarded to NHMRC for further review.

Dissemination

Dissemination of the guidelines will follow previous patterns. The guidelines will be advertised in the national press for public review, and placed on our website. All interest groups (68) involved in ACN will be alerted to the availability of draft-for-comment copies and there will be a notice in the ACN newsletter 'Wongi Yabber', which has 950 recipients. All submissions will be carefully reviewed before submission to the Health Advisory Committee.

When the draft document receives approval, the approved document will replace the draft on the ACN website. The process of alerting interest groups and newsletter readers will be repeated. These announcements are usually carried in the publications of the State Cancer Council Oncology Groups.

Copies of guidelines will be available from the ACN secretariat.

Implementation

ACN has a multidisciplinary, broadly-based working party developing implementation strategies under the chair of Professor Bruce Barraclough.

A preliminary matrix has been drafted and is being developed. It is planned to interlock implementation with work being done by accreditation and credentialing working parties to encourage the introduction and maintenance of evidence-based activity in clinical practice. Where possible, surgical groups will be encouraged to adopt and adapt guidelines to their local practice and to enter into multidisciplinary arrangements with radiation and medical oncologists, stomal therapists and special nursing staff where possible. Academic detailing of guidelines is also being considered.[6,7]Appropriate resourcing and process is being addressed to increase the effectiveness of implementation. This is imperative if the document is to be widely integrated into clinical care.

Revision

It is expected that the guidelines will be revised in 3 to 5 years. The format is to be decided closer to the time.

References

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8. Cooney A, Gattellari M, Donnelly N, Ward J. Impact of national guidelines about the management of colorectal cancer on Australian surgeons' awareness of evidence: a pre/post survey. Colorectal Dis 2004; 6: 418–27.

APPENDIX 3 LITERATURE REVIEW

Methods

Each chapter author used the specific expertise of the writing and review group and retrieved quoted articles from the 1999 document relevant to the chapter. Hand searches of important international and national journals were used in addition to standard reference sources such as PubMed and Cochrane Library. Each guideline in the 1999 document served as a template and was challenged in the light of updated data. As a result, a number of guidelines from 1999 were modified or replaced. A major concern of each group was to ensure the credibility, readability and the highest level of clinical relevance and application in the document.

Questions to be answered

The approach was to ask clinically relevant questions encountered in everyday practise and use the 1999 document as a template.

The chapters and sections have been developed in a sequence of clinical situations based on clinical questions developed using the PICO criteria (population, intervention, control and outcomes). Questions were developed by the subcommittee for each chapter and discussed when the Working Party met on 2 December 2003. There have been face-to-face and phone discussions since then.

Search methodology

The literature searched for each chapter is outlined below. The initial approach in each chapter was to review the references from the previous publication and update as appropriate. As a result of delays, a further review of Cochrane databases, PubMed, Ovid EBMR, Clinical Evidence and MD Consult were done as outlined between January 1998 and June 2004. Randomised control trials references were sent to writing groups except where otherwise specified. Hand searches have also been used.

Where a sound meta-analysis or a Cochrane review of relevant literature was available at the time of the search, it was cited in preference to quoting individual papers.

In 2004 (June), an updated review was done of the database outlined above. A hard copy of this standardised search including all references and, where available, abstracts were sent to chapter editors with a request that they critically evaluate each reference for relevance. If the reference was judged relevant and suitable, and not already incorporated, it was added to the references in the chapter and incorporated into the chapter text.

Some chapter authors were not sent this standardised search because they considered that the search they had already conducted was complete. In these cases the revision was made by the chapter chairs. Additional details of the methods followed for each individual chapter are outlined below.

If an author deviated from using the search, this is explained in the comprehensive explanation of the search strategy used for each chapter.

Chapter 1 — Setting the scene

This chapter provides a broad analysis of Colorectal Cancer in Australia and matters affecting clinical personnel, patients and carers. The literature quoted is eclectic, and chosen to highlight special patients to be addressed in the document.

Chapter 2 — Primary prevention and Chapter 3 — Population screening

Search strategy

A variety of sources were used:

- INGENTA reports from the Ingenta website, an online collection of academic journals and publications, were reviewed each week. These cover primary prevention of Colorectal Cancer, including chemoprevention and population screening
- daily reports on new publications produced by the Cancer Information Service at the Cancer Council of Victoria
- weekly reviews of new journals received by National Cancer Control Initiative (NCCI) and the Biomedical Sciences Library at the Royal Melbourne Hospital
- the Cochrane Library — visited regularly
- the literature database at the NCCI — the project officer in charge retrieved relevant literature

Selection of articles for consideration for the chapters depends on judgements about their reliability and contribution to the area. All articles about primary prevention using cancer or adenoma as an endpoint were considered for Chapter 2, as stated at the beginning of the chapter, with special emphasis on new approaches and results from large continuing studies. We have used articles published well into 2004.

Dates

Updated 1999 document to April 2004.

Search terms

Publications about primary prevention using cancer or adenoma as an endpoint.

Inclusion/exclusion criteria

Care was taken to include important reviews, for example, the *Handbook of cancer prevention* published by the International Agency for Research on Cancer (World Health Organization) in 2002, which reviewed weight control and physical activity; the Cochrane review on calcium supplementation; and the pooled analysis of eight cohort studies on alcohol intake and Colorectal Cancer, published in *Annals of Internal Medicine*, 20 April 2004.

Criteria for inclusion in the chapters were the timing of the publication (giving credit to original observations rather than confirmation, although several publications were often used to support individual statements), soundness of design, quality of the studies and relevance to the content of the chapters.

Results

Seventy-three new references were identified, increasing citations to 131, and 19 references were deleted from Chapter 2 of the 1999 document.

Comments

Special emphasis was placed on new approaches and on results from large ongoing studies. Many of the publications were focused too narrowly to warrant inclusion in the chapters.

Chapter 4 — Communication with the patient

Search strategy

Cochrane Library, PubMed/Medline, hand searches

Dates/limits

Updated 1999 document to June 2004

Search terms

Patient communications, cancer, surgery

Results

No Cochrane reviews were located.

PubMed and Medline databases revealed 819 articles, one meta-analysis and 16 randomised controlled trials.

Inclusion/exclusion criteria

Relevance to patient needs was the guiding factor.

Comments

The one meta-analysis and the great majority of retrieved articles were of little relevance as they were directed towards other cancers. New data were added from hand searching.

Chapter 5 — The patient with symptoms

Search strategy

Cochrane Library, PubMed/Medline

Dates

Updated 1999 document to September 2004.

Search terms

Rectal bleeding, Colorectal Cancer symptoms, colonoscopy, iron deficiency anaemia

Results

PubMed:

- meta-analyses for colonoscopy — 13
- RCTs for colonoscopy — 553
- RCTs for Colorectal Cancer symptoms — 507
- RCTs for iron deficiency anaemia — 74

Cochrane Library:

- systematic reviews Colorectal Cancer symptoms — 3
- RCTs for Colorectal Cancer symptoms — 6

Three Cochrane systematic reviews were not relevant to the chapter. Six Cochrane randomised controlled trials (RCTs) were evaluated, and one included.

Inclusion/exclusion criteria

Most publications were directed at screening, faecal occult blood testing, treatment regimes, anaesthesia, or diseases other than cancer. Those directed to non-procedural colonoscopy were carefully reviewed.

Comments

This chapter has been inserted to ensure that clinical notice is taken of risk factors for Colorectal Cancer and to ensure proper investigation of rectal bleeding.

Chapter 6 — Screening and family history and Chapter 7 — High-risk familial cancer syndromes

Search strategy/dates

The same process was followed as for Chapters 2 and 3. The original search was reviewed and updated by further search to June 2004.

Dates

Updated 1999 document to June 2004

Search terms

Chapter subsection headings

Inclusion/exclusion criteria

Official hereditary bowel cancer registers in Australia and New Zealand are annotated at the end of the chapter.

Authors used timing of publication, giving credit to original observations rather than papers confirming original observation. Several publications were often used to support individual statements. Other criteria were soundness of design, quality of the studies, and relevance to content of the chapter.

Results

Many of the publications focused on too narrow an area to warrant inclusion in the chapters.

Comments

As part of its development, Chapter 7 was reviewed by The Cancer Council Victoria Hereditary Bowel Group in July 2004.

Chapter 8 — Diagnostic tests and preoperative assessment

Search strategy

PubMed, Medline, English language publications

Dates

Updated 1999 document with search from 1998 to June 2004.

Search terms

Subsection titles from the 1999 chapter were used as search terms.

Inclusion/exclusion criteria

Relevance to diagnostic tests and preoperative assessments

Results

Four PubMed general papers. Remainder were on individual subjects.

Colonography (virtual colonoscopy) appeared as the most important update. *Section 8.1.5 Virtual colonoscopy* has been added.

Comments

Each article was discussed by the writing groups and, if relevant, included in the chapter.

A further meeting was held to review the current recommendations and decide whether change was necessary in view of the more recently published literature.

In general, there was very little change to the chapter, apart from the increasing role of colonography.

Chapter 9 — Management of epithelial polyps

Search strategy

Cochrane Library, PubMed

Dates

Updated 1999 document to September 2004

Search terms

Colorectal epithelial polyps, hyperplastic polyps, management, headings of sections in chapter

Inclusion/exclusion criteria

Citations required to address search terms, or be rejected

Results

Cochrane Library: seven references, one systematic review not relevant, three RCTs, two EBM, one clinical evidence

PubMed: seven RCTs — one included

Hyperplastic polyps: PubMed — 59 papers, no RCTs; Cochrane Library — no references; hand searching

Comments

Professor Finlay Macrae and Professor Jeremy Jass have a cutting-edge, running literature update and continuous engagement with the literature on this topic, active research insights, and Biennial Medline Reviews until September 2004.

Additions to the chapter are *Section 9.4.2 Other polyposis conditions* and *Section 9.5 Hyperplastic polyps and polyposis*.

Chapter 10 — Preparation for surgery

Search strategy

PubMed and Cochrane Library

Dates

1 January 1998 to June 2004

Search terms

Terms searched as per subheading titles of chapters with key words: stoma education and preparation (Section 10.2), bowel preparation (Section 10.3), blood transfusion and colorectal surgery (Section 10.4), thromboembolism prophylaxis and colorectal surgery (Section 10.5), antibiotic prophylaxis and colorectal surgery (Section 10.6).

Inclusion/exclusion criteria

Articles were excluded if they were not published in English; if found not to be relevant to the subject; if not relevant to Australian practices, for example, medication such as antibiotics not in routine use in Australia; if the full publication was not readily available either online or through library resources.

Results

Antibiotic prophylaxis and colorectal surgery (retrieved 29 articles — used one); thromboembolism prophylaxis and colorectal surgery (retrieved four articles — used 2); blood transfusion and colorectal surgery (retrieved 11 articles — used one); stomal related (116 RCTs, used one); bowel preparation (retrieved 175, used ten); body temperature (retrieved 22, used one); most studies applied to colonoscopy.

Comments

If a well conducted meta-analyses or Cochrane review of all relevant literature was available at time of search it was cited in preference to citing all the individual publications. A recent published meta-analysis was available and used to justify the changed guideline.

Chapter 11 — Elective surgery for colon cancer

Search strategy

English publications in PubMed and Cochrane Library

Dates

Update of 1999 document from 1998–2001, subsequently updated to June 2004.

Search terms

Colon cancer, surgery, key words from subsection of chapters

Inclusion/exclusion criteria

Clinical importance, shift in surgical thinking

Results

There are 42 references in Chapter 11. Of these, 17 were included in the original guidelines, and 19 new references and one personal communication were identified in the initial search as follows:

- one meta-analyses (ref 8)
- seven randomised trials (25, 26, 27, 29, 30, 31 and 32)
- three represented a shift in surgical thinking (6, 21, 24)

- seven were papers on new subjects: refs 9, 10, 11 on omental wrapping of anastomoses; refs 34, 35, 36, 37 on metal stents for obstructing cancer
- one paper — the most up to date Australian paper on a subject where no local paper has been published (ref 28)
- one personal communication from the coordinator of the Australian randomised trial comparing open and laparoscopic colectomy — the work is unpublished as the trial is not complete.

In a further literature review in June 2004, a review of the Cochrane Library revealed eight randomised controlled studies. These were considered, but did not add substantially to the manuscript as five included chemotherapeutic approaches (Chapter 15), one referred to antibiotic and chemoprevention of wound infection (Chapter 10), and one to surgical volume and outcome (Chapter 12). References 33, 34 and 35 were added to Section 11.11, stressing the current status of laparoscopic colectomy.

Chapter 12 — Elective surgery for rectal cancer

Search strategy

PubMed, Ovid and Cochrane Library

Dates

Updated 1999 document from 1980 to 2002, and further updated to June 2004

Search terms

Rectal, rectal cancer, surgery

Inclusion/exclusion criteria

Clinical importance, rigour of methods and statistical analyses, strength of trial

Results

Following revision to 2002, a subsequent review of Cochrane Library, PubMed and EBMR was carried out on publications to June 2004. Of the 113 articles retrieved, five RCTs were included in the chapter. The others were not relevant to Chapter 12 and were considered in Chapters 15, 16 and 19.

Comments

The original document was reviewed, the references checked and updated to current practice.

The references used in the articles were further examined for other related articles that may have been missed in the initial search. This review was extensive and thorough and carefully considered. Data that were flawed in a material way on the basis of methodology, exclusions, analysis, etc. were not used.

A large amount of the reference material was not directed at surgery in a ‘pure’ sense; it was also directed at chemotherapy and radiotherapy and so was not relevant in the context of this chapter as these data are covered in Chapters 16 and 19.

Chapter 13 — Emergency surgery

Search strategy

Cochrane databases, PubMed

Dates

Update of 1999 document from 1 January 1993 – 1 June 2004

Search terms

Colon cancer, rectal cancer, surgery, emergency

Inclusion/exclusion criteria

Excluded five foreign language papers and non-RCTs. There is no RCT of treatment versus no treatment.

Results

Search titles: PubMed — ten non-RCT citations, two RCTs (refs 22 and 15); the bona-fides of 15 RCTs are questioned in a Cochrane review by De Salvo et al (ref 16) that refers only to left-sided Colorectal Cancer.

Primary resection is standard practice for right colon obstruction; there are no RCTs.

Surgeons in Australia prefer primary resection for obstruction of both right colon and left colon. Current practice does not change on basis of no RCTs. There is no recommendation when there are no trials, merely advice to consider an approach based on observation. Cochrane review considers that this treatment 'has not yet been established as being more effective than a two stage procedure in patients with obstruction from primary left colon carcinoma'.[1] The lack of RCTs or favoured RCTs should not stop good things being done. Expert opinion is based on evidence level and strength of recommendation.

Comments

This chapter addresses clinical problems of patients with Colorectal Cancer who are in acute difficulty. The area addressed is quite deficient on randomised clinical trials. It is considered in Cochrane review that the variables involved in clinical circumstances render an RCT approach very difficult.

Cross-referencing to Chapter 10 is extensive

Chapter 14 — Clinicopathological staging and reporting

Search strategy

Cochrane Library, EBMR, Ovid, MD Consult, BMJ Clinical Evidence, PubMed.

Dates

Update of 1999 document. January 1998 – June 2004

Search terms

Clinicopathological staging, colon cancer, Colorectal Cancer, rectal cancer

Inclusion/exclusion criteria

Reference to the parameters of clinicopathological correlation with prognosis

Results

Two Cochrane systematic reviews and nine RCTs. One RCT not relevant. Hand searching, no further yield.

Clinicopathological staging, rectal cancer

PubMed — one RCT

Colorectal Cancer staging

Cochrane Library — three systematic reviews, nine RCTs

Clinical evidence — three

Ovid — 1one review

MD Consult — three

PubMed — nine meta-analyses

PubMed — 85 RCTs

Comments

Clinicopathological staging and reporting involving use of minimum data set. The clinical and histological findings are outlined in Sections 14.1 and 14.2, including Tables 14.1, 14.2 and 14.3.

This chapter is essentially unchanged. It relates to 'the classification of the tumour according to the extent of spread in a manner that has a clinically useful correlation with prognosis'.

References to specific imaging techniques such as MRI, PET and CT scanning do not relate to staging in its true sense; rather, they represent modalities of investigation for assessing the extent of the tumour spread at the time of diagnosis (see Chapter 8). Staging requires surgical and histopathological input as outlined in the guidelines to confer a stage on the tumour. Imaging modalities do not relate to prognosis in a statistically reproducible fashion and therefore, strictly speaking, they make no contribution to staging in the pure sense of the word.

There is no known, reliable preoperative staging system that correlates accurately with patient survival.

Chapter 15 and 16 — Adjuvant therapy for colon cancer and adjuvant therapy for rectal cancer

Search strategy

A systematic literature search was performed of the Medline database (January 1996 – January 2003). The Cochrane Library 2002 Issue 4 was also searched using the search phrases 'colorectal', 'colon', 'rectal' and 'cancer'. A title alert was set up on Zetoc, the British Library Electronic Table of Contents service, using the terms 'colon' and 'adjuvant' (July 2002 – July 2003) to identify new articles as they were published. Hand searches were conducted of Conference Proceedings of the American Society of Clinical Oncology (1996–2003), the European Cancer Conference (1999, 2001, 2002), European Society of Therapeutic Radiation Oncology (2002) and the American Society for Therapeutic Radiation and Oncology (2001–2003).

Further searches of the Cochrane Database of Systematic Reviews, BMJ Clinical Evidence, Ovid, EBMR and PubMed to June 2004, using search terms 'surgery' and 'rectal cancer' revealed the following results.

Dates

Update of 1999 document from 1996 to 2004

Search terms

MeSH terms were ‘colorectal neoplasms’, ‘colonic neoplasms’, ‘rectal neoplasms’, ‘randomised controlled trials’ and ‘chemotherapy adjuvant’. Additional keywords used included ‘adjuvant’, ‘Colorectal Cancer’, publication type and ‘reviews’.

Inclusion/exclusion criteria

Relevance of reference. Quality of trials, and shortcomings where present, are discussed in text. All identified randomised trials not included in meta-analyses 4, 32, 44, 45 in Chapter 15 and 26, 27, 28 and 29 in Chapter 16 were included in references for the chapters.

Results

One hundred and thirteen (113) randomised trials were retrieved from PubMed 1 January 1998 to June 2004 and reviewed by the authors of Chapters 12, 15, 16 and 19. Most were not relevant to Chapters 15 and 16; however, seven trials were appropriate and incorporated into Chapters 15 and 16.

Comments

Recent review articles, meta-analyses and clinical guidelines were identified. The trials listed in these were crosschecked with references that were found by the searches above. The writing committee consisted of two authors who reviewed the trials. The chapters from the first edition of the guidelines were rewritten incorporating updates of trials and reviews in the original chapters, as well as the new trials identified. Formal meta-analysis was not carried out. The drafts were then circulated for external review by five medical oncologists, three radiation oncologists and three colorectal surgeons. Suggestions and feedback were incorporated in the drafts before they were considered by the main Working Party for these guidelines.

Chapter 17 — Follow up after curative resection for Colorectal Cancer

Search strategy

PubMed, Cochrane Library

Dates

Update of 1999 document from 1 January 1998 – 1 June 2004 (date limits extended if relevant article not previously cited)

Search terms

Follow up, curative resection, Colorectal Cancer

Inclusion/exclusion criteria

Headings of subsections in chapter served as search terms. Relevance to chapter subheadings if reference to be included.

Articles were excluded if they were not published in English; if they were not found to be relevant to the subject; if they were not relevant to Australian practices, for example, medication such as antibiotics not in routine use in Australia; or if the full publication was not readily available either online or through library resources.

Results

Two recent meta-analyses relating to intensive follow up and cost-effectiveness were identified and incorporated in the text. No other relevant studies were identified — most related to specific chemotherapeutic follow-up approaches.

Chapter 18 — Psychosocial care

Search strategy

Cochrane Library, PubMed

Dates

Update of 1999 document with search from 1 January 1998 to 1 June 2004

Search terms

Psychosocial care, cancer

Inclusion/exclusion criteria

Relevance to Colorectal Cancer

Results

A search of the Cochrane databases with the search terms 'psychosocial care' and 'cancer' yielded three systematic reviews that were not specific to Colorectal Cancer.

The register of controlled trials contained no trials relevant to Colorectal Cancer.

PubMed yielded 16 papers but their content was either not relevant to the chapter or was covered by the spectra of references.

Ovid, EBMR search and MD Consult Guidelines Research did not yield further information.

Comments

Clinical practice guidelines for the psychosocial care of adults with cancer (NBCC and NCCI 2003) was a significant source of tested reference material.

Chapter 19 — Recurrent and advanced Colorectal Cancer: general approach and local management (see Chapter 16)

Search strategy

As for Chapters 15 and 16

Dates

Updated 1999 document with search from January 1998 to June 2004

Search terms

Colon cancer, subsection headings

Results

This chapter was developed in consultation with the authors of Chapters 15 and 16.

Comments

The references from 1999 were reviewed and updated to June 2004.

Literature searches of PubMed and Cochrane reviews until June 2004 reveal scant good-quality clinical trials in which the treatment alternatives of surgery, medical oncology and radiation oncology have been compared. This situation often made the decision about the appropriate option both complex and difficult.

Chapter 20 — The role of systemic chemotherapy in metastatic disease and Chapter 21 — Management of liver and other distant metastases

Search strategy

Medline (1996 –January 2003), The Cochrane Library 2002 Issue 4

A title alert was set up on Zetoc, the British Library Electronic Table of Contents service, using the terms 'colon' and 'adjuvant' (July 2002 – July 2003) to identify new articles as they were published. Hand searching of Conference Proceedings of the American Society of Clinical Oncology (1996–2003), the European Cancer Conference (1999, 2001, 2002), European Society of Therapeutic Radiation Oncology (2002) and the American Society for Therapeutic Radiation and Oncology (2001–2003).

Recent review articles, meta-analyses and clinical guidelines were identified and the trials listed in them were crosschecked with references were found by the searches listed above.

Dates

Update of 1999 document from 1996 to 2004

Search terms

As above, and including 'radiotherapy', 'radiation oncology', 'peritoneal cytoreduction surgery'

PubMed: MeSH terms were 'colorectal neoplasms', 'rectal neoplasms', 'randomised controlled trials' and 'chemotherapy metastatic'. Additional keywords used included 'metastatic', 'Colorectal Cancer', publication type and 'reviews'.

Cochrane Library: 'colorectal', 'colon', 'rectal', 'cancer'

Inclusion/exclusion criteria

Results

Extensions of review to 2004 with inclusion of Cochrane review comparing therapy as against no therapy. Inclusion of Cochrane review on adjuvant chemotherapy post liver resection. (Chapter 21). Peritoneal cytoreductive surgery was reviewed. PubMed 4 meta-analyses — all related to ovarian cancer and 45 RCTs, 2 relating to colorectal surgery. 3 Cochrane Systematic Reviews for cytoreductive surgery relate to glioma. This section was added to further address completeness in the current practice environment.

Comments

The writing committee consisted of two authors who reviewed the trials to ensure that the relevant studies that were used in treatment recommendations were randomised controlled trials. The chapters from the first edition of the Guidelines were rewritten incorporating updates of trials and reviews in the original chapters, as well as the new trials identified. Formal meta-analysis was not carried out. The drafts were then circulated for external review by two medical oncologists. Suggestions and feedback were incorporated in the drafts before consideration by the main Working Party for these Guidelines.

Chapter 22 —cost-effectiveness

Search strategy

A search was conducted using the databases Pre-Medline, Medline and Embase. Identified abstracts were scanned and all possible inclusions identified and obtained. The obtained articles were reviewed

and assessed based on the inclusion/exclusion criteria, and non-relevant articles were excluded. All remaining articles were thoroughly reviewed and summarised for inclusion in the guidelines.

Dates

January 1994 to December 2004

Search terms

Colorectal Cancer, colon cancer, rectal cancer, economic evaluation, cost-effectiveness analysis, cost benefit analysis, cost analysis and cost.

Inclusion/exclusion criteria

Articles were included if they were in English, judged to be economic evaluations, that is, if they involved comparison of alternative interventions in terms of costs and consequences, or if they were reviews of economic evaluations.

Results

Possible inclusions originally identified: 164

Exclusions after review of articles: 43

Articles included in guidelines chapter: 121

Reasons for exclusion were as follows

1 = not English

29 = not relevant (not economic evaluation or predominately Colorectal Cancer)

4 = double (e.g. same study in different journals or original article and summary of same article)

9 = comprehensively reviewed in a systematic review already included

Comments

Of the 121 articles included in these guidelines, 49 investigated the effect of an intervention on outcomes such as lifeyears saved or gained or quality of life on utility, and seven were cost-benefit or cost-minimisation studies. A further 26 were cost and consequence analyses investigating the costs and effects of an intervention using limited measures of clinical outcome such as cancers detected, deaths prevented, cured or surviving patient, curative resection, recurrence/cured recurrence, and/or treating complications, or in some cases, output such as length of stay. The remainder consisted of 13 economic analyses that measured costs and outcomes/or outputs separately, four cost analyses measuring costs only, and 22 reviews or combined review/analyses.

The chapter also included four journals relating to the economic burden of cancer and the role of economic evidence in the development of guidelines of Colorectal Cancer.

Chapter 23 — Socioeconomic aspects in Colorectal Cancer

Search strategy

PubMed, Cochrane database

Dates

1990–2003

Search terms

Colorectal Cancer, socioeconomic, screening

Inclusion/exclusion criteria

RCT — relevance

Results

Eight RCTs — six used

Comments

Centred on compliance and avoided diet and medication implications

Assessment of evidence

General critical appraisal of literature followed the pattern listed below[8]:

1. Were the treatments randomised?

2. Were there adequate controls?

3. Were sample sizes adequate?

4. Were exclusions specified and appropriate?

5. Were methods reproducible?

6. Were outcomes measured objectively?

7. Were results analysed statistically?

8. Was follow up complete?

9. Do results justify conclusions?

The guidelines are based on evidence that has been rated as level I, II, III-1, III-2, III-3 or IV according to the National Health and Medical Research Council (NHMRC) scale published in *A guide for the development, implementation and evaluation of clinical practice guidelines* (NHMRC 1999).[2]This scale does not include 'expert opinion', as did a former NHMRC scale used before publication of the 1999 guidelines. Accordingly, there are no formal guidelines based on expert opinion alone. Further research is required to provide evidence in these areas.

In accordance with the NHMRC handbook *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000), each recommendation has been further evaluated according to the level, quality and statistical precision of the included studies (strength of evidence), and the overall size and clinical importance of the effect. These detailed summations and other considerations, are included in each chapter.

A clinical recommendation has been added alongside the level of evidence for each guideline to reproducibly interpret the expert panel's view of the overall strength of the recommendation. The background and clinical importance 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 general practitioner and consumer.

Levels of evidence[2]

I Evidence obtained from a systematic review of all relevant randomised controlled trials

II Evidence obtained from at least one properly designed randomised controlled trial III-I Evidence obtained from well-designed pseudo randomised controlled trials (alternate allocation or some other method)

III-2 Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group

III-3 Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group

IV Evidence obtained from case series, either post-test or pre-test/post-test

Strength of recommendations[3,4]

The strength of recommendations is determined by the expert advisory panel and ranges from strongly recommended to strongly not recommended. These levels of recommendation are modified from The Canadian Task Force on the Periodic Health Examination.

Strongly recommended	Recommended	Equivocal (as evidence is inconclusive)	Not recommended	Strongly not recommended

To assign a level of recommendation, it was important for the clinical question to be clearly defined, for example:

> 'Should prophylactic antibiotics be given for surgery for Colorectal Cancer' (Section 10:6).

The evidence was then considered on a case-by-case basis taking into account the level of evidence, quality of studies, size of effect, and clinical importance for all the included studies. The following list shows examples of how the hierarchy of recommendations were applied:

Strongly recommended Clinically significant level I in favour of clinical question — strongly recommended in favour.

Recommended Clinically significant lower levels (e.g. II, III-1, III-2) in favour of clinical question — less strongly recommended in favour.

Equivocal Lack of higher levels of evidence (e.g. III-3 or IV) OR equivocal level I or II evidence for and against clinical question — no recommendation for or against, as evidence is inconclusive — recommend further research.

Not recommended Clinically significant lower levels (e.g. II, III-1, III-2) against the clinical question — weak recommendation against.

Strongly not recommended Clinically significant level I against the clinical question — strong recommendation against.

However, in some cases it was also necessary to take into account the best study types for particular clinical questions, such as cohort studies (level III-2) for questions of aetiology (risk) or prognosis. Therefore, for questions of aetiology and prognosis, a large body of good quality, clinically significant, level III-2 evidence was categorised "strongly recommended". In other recommendations where there is a paucity of RCTs, the recommendation remains based on the accepted current practice, particularly where it is unlikely that there will be any RCTs conducted in the future.

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- Chapters 8, 11 and 13 — Dr Lincoln Israel is a Colorectal Fellow at the Royal Melbourne Hospital
- Professor Peter Russell — Chapter 11 – Professor of Pathology, The University of Sydney and at Royal Prince Alfred Hospital
- Dr Alison Evans — Appendix 1 – Project Officer, National Breast Cancer Centre

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Individual chapter chairs answered specific questions arising from review.

APPENDIX 5 ABBREVIATIONS AND GLOSSARY

ABBREVIATIONS

5-FU	5-fluourocil
ACBE	air contrast barium enema
ACN	Australian Cancer Network
ACPS	Australian clinicopathological stage
AHTAC	Australian Health Technology Advisory Committee
AJCC	American Joint Committee on Cancer
ALCCaS	Australian multicentre prospective clinical study, comparing laparoscopic and conventional open surgical treatment of colon cancer in adults
ANO	anoscopy
APC	adenomatous polyposis coli
APR	abdominoperineal resection
ASA	aspirin
ASCO	American College of Clinical Oncology
BE	barium enema
BFOBT	biochemical faecal occult blood testing
CCOPGI	Cancer Care Ontario Practice Guidelines Initiative
CCR	(laparoscopy) converted (to open) colon resection
CEA	carcinoembryonic antigen
CER	Cost-Effectiveness Ratio
CHRPE	congenital hypertrophy of retinal pigmented epithelium
CI	confidence interval
CMT	combined modality therapy (comprising both radiotherapy and chemotherapy)
COL	colonoscopy
COX-2	cyclo-oxynegase-2 specific inhibitor
CRC	Colorectal Cancer
CT	computerised tomography
CTAP	computerised tomography arterial portography
CTC	computerised tomography colonoscopy (virtual colonoscopy)
DALY	Disability Adjusted Life Year
DCBE	double contrast barium enema
DFMO	difluoromethylornithine
DFS	disease free survival
DRE	digital rectal examination

DVT	deep venous thrombosis
ECOG	European Cooperative Oncology Group
EFE	extrafascial excision
EORTC	European Organisation for Research and Treatment of Cancer
EPIC	European Prospective Investigation into Cancer and Nutrition
ERUS	endorectal ultrasound
EUS	endoluminal ultrasound
FA	folinic acid
FAP	familial adenomatous polyposis
FC50	filter colonoscopy
FDG-PET	fluorodeoxyglucose-positron emission tomography
FNDA	fecal DNA
FOBT	faecal occult blood testing
FOLFIRI	5-FU plus irinotecan
FOLFOX	5-FU plus oxaliplatin
FSIG	flexible sigmoidoscopy
FUDR	5-fluoro-2'-deoxyuridine
H – II	Hemoccult II
HAI	hepatic arterial infusion
HAL	hand assisted laparoscopy
HDLV	high-dose leucovorin
HNPCC	hereditary nonpolyposis Colorectal Cancer
HRT	hormone replacement therapy
ICER	Incremental cost effectiveness ratio
IFL	bolus 5-FU plus irinotecan
IFOBT	immunological faecal occult blood testing
IHC	immunohistochemical staining
ImmCOL	immediate total colonoscopy
LAR	low anterior resections
LARHC	laparoscopically assisted right hemicolectomy
LCR	laparoscopic colon resection
LDLV	low-dose leucovorin
LS	laparoscopic surgery
LV	Leucovorin
MAC	Modified Astler-Coller

MACRONUTRIENTS	An essential nutrient required in a relatively large amount, including carbohydrates, fats, proteins, water and some minerals.
MAP	MYH-associated polyposis
MICRONUTRIENTS	An essential dietary element required only in small quantities such as trace minerals
MMR	mismatch repair genes
MRC	magnetic resonance colonography
MRI	magnetic resonance imaging
MSI	microsatellite instability
MSI-H	microsatellite instability — high
MSI-L	microsatellite instability — low
MSS	microsatellite stable
MTHFR	methylenetetrahydrofolate reductase
MYH	mutY homologue
NACCP	Netherlands Adjuvant Colorectal Cancer Project
NCCTG	Northern Central Cancer Treatment Group
NHMRC	National Health and Medical Research Council
NSABP	National Surgical Adjuvant Breast Project
NSAID	nonsteroidal anti-inflammatory drug
OCR	planned open colon resection
ORHC	open right hemicolectomy
PET	positron emission tomography
PLCO	Prostate, Lung, Colorectal and Ovarian (Cancer Screening Trial)
PVI	protracted venous infusional
QALY	quality adjusted life-year
QPL	Question Prompt List
QUASAR	quick and simple and reliable
RCT	randomised controlled trial
RECT	rectosigmoidoscopy
RFA	radiofrequency ablation
RFTA	radiofrequency thermal ablation
RG	rehydrated guaiac
RPHA	reversed passive hemmagglutination
SEER	surveillance, epidemiology and end results (data collection program of the National Cancer institute in the United States)
SWOG	South Western Oncology Group
TEMS	transanal endoscopic microsurgery
TME	total mesorectal excision

TNM	tumour, node, metastasis staging system
TRUS	Transrectal ultrasound
TVUS	transvaginal ultrasound
UFT	tegafur + uracil
pTNM	pathological staging
VCOG	Victorian Cooperative Oncology Group
WHO	World Health Organization

GLOSSARY

Abdomen	The part of the body between the chest and hips, which contains the stomach, liver, intestines, bladder and kidneys.
Adjuvant chemotherapy	Chemotherapy that is used in a supplementary but not dominant therapy.
Advanced cancer	Cancer that has metastasised and/or is unlikely to be cured
Aetiology	Cause or causality
Age-standardised rate	A procedure for adjusting rates eg death rates, designed to minimise the effects of differences in age composition when comparing rates for different populations.
Aggressive	A word for a fast-growing cancer.
Allogeneic	Tissue from a donor.
Alpha interferon	A glycoprotein used in the treatment of cancer. One of its effects is to inhibit cell growth.
Alternative therapies	A term used to loosely describe any type of therapy outside the orthodox circle of surgery, radiation or chemotherapy. Alternative therapies include things such as diet therapy, vitamins and herbs. *(See also Complementary therapies)*
Antibody	A protein that is made in lymph tissue to destroy infections and other potentially harmful 'invaders' in the body.
Anticoagulant	A substance that prevents blood clotting.
Anxiety	A diffuse highly unpleasant, often vague feeling of apprehension, accompanied by bodily sensations such as pounding heart or sweating. There is an associated anticipation of future misfortune or danger, external or internal.
Apoptosis	Process of cell death.
Autologous	Tissue graft, blood transfusion etc arising from the recipient.
Benign	Not cancerous. Benign cells are not able to spread like cancer cells.
Biopsy	The removal of a small sample of tissue from the body, for examination under a microscope, to help diagnose a disease
Cancer registry	A centre in each state and territory where details of cancers are collected to monitor trends.
Case control study	A study that starts with the identification of people with the disease of interest and uses a suitable group without the disease for comparison to assess possible factors involved in the development of the disease. Such studies are often called retrospective as they look back from the outcome to its causes.
Cells	The 'building blocks' of the body. A human is made of millions of cells, which are adapted for different functions. Cells are able to reproduce themselves exactly, unless they are abnormal or damaged, as are cancer cells.

Chemotherapy	The use of drugs (which are cytotoxic) or a combination of drugs to kill cancer cells or prevent or slow their growth
Chest cavity	The area enclosed by the ribs, above the diaphragm.
Chemo-responsiveness	The measure of how a tumour reacts when an anti-tumour drug is administered
Chlorambucil	A cytotoxic agent or drug used during chemotherapy to kill cancer or lymphoma cells.
Clinical practice guidelines	The bringing together by a central authority of the best available evidence to support recommendations for the prevention, diagnosis and treatment of cancer.
Colonoscopy	Examination of the whole Colon by means of an appropriately lighted flexible, elongated tube.
Complementary therapies	A term used to refer to therapies, such as meditation and relaxation therapy, that can work alongside conventional therapy.
Counselling	Refers generically to a form of supportive care delivered by all health professionals. There are differing levels of sophistication depending on the training and experiences of the practitioner involved.
CT scanning	Computerised tomography is a technique for constructing pictures from cross sections of the body, by x-raying from many different angles the part of the body to be examined.
Cyclophosphamide	A cytotoxic agent used during chemotherapy to kill cancer or lymphoma cells.
Cytology	The study of the origin, structure, function and pathology of cells.
Depression	A pervasive or sustained lowering of mood or the loss of interest in nearly all activities. When used clinically, it is a cluster of symptoms or a syndrome, whose other features may include: changes in appetite or weight, sleep or psychomotor activity; decreased energy; feelings of worthlessness or guilt; difficulty thinking, concentrating or making decisions; or recurrent thoughts of death or suicide ideation, plans or attempts.
Diagnosis	The process of identifying a person's illness.
Diaphragm	A muscle below the lungs and heart. It separates the chest cavity from the abdominal cavity.
Doxorubicin/liposomal doxorubicin	Agent used in chemotherapy.
Efficacy	The ability of a drug or intervention to produce the desired beneficial effect under ideal conditions.
Epidemiology	The study of the distribution and determinants of health-related states or events in specified populations and the application of this study to the control of health problems.
FDG	Fluoro-deoxy glucose (see PET scanning)
First line therapy	The first administration of therapy such as chemotherapy following surgical removal of the tumour.

FAP	Familial adenomalous Polyposis
FNA	Fine needle aspiration is a procedure in which a fine needle is used to suck up a few cells from a tumour, for biopsy
Frozen section	A specimen of tissue that has been quick frozen, cut and stained immediately for rapid histological diagnosis of malignant tissue
Gene	One of the biologic units of heredity which are situated in specific locations on particular chromosomes in the body. Genes make up the DNA molecules that control cell reproduction and function.
Genome	A complete set of hereditary factors in the chromosomes
Growth factor	A substance that stimulates cells to reproduce and rapidly multiply.
H&E sections	Use of a stain -Hematoxylin-eosin - for routine examination of tissue under a microscope. Cell nuclei are stained deep blue and the surrounds (cytoplasm) pink.
Histology	The study of the minute structure, composition and function of tissues.
HNPC	Hereditary non-polyposis Colorectal Cancer.
Immune system	The body's natural defence system. It protects against anything it recognises as an "invader", for example, bacteria, viruses, transplanted organs and tissues, tumour cells and parasites.
Immunotherapy	Treatment with immunopotentials and immunosuppressnats.
Incidence	The number of new cases of illness or disease during a given period in a specified population.
Indolent	A word for a slow-growing cancer.
Interferon	A substance made by the body in response to viral infection. It inhibits virus multiplication and has shown some activity against a few uncommon cancers.
Infusion	Introduction of a fluid such as a saline solution into the blood by gravity flow.
Intravenous chemotherapy	Administration of a chemotherapy using the veins
Laparoscopy	Examination of a body cavity by means of a laparoscope.
Laparotomy	Surgery where an incision is made through the abdominal wall to expose abdominal contents.
Lymph nodes	Also called lymph glands. Small, bean-shaped structures which form part of the lymphatic system. Lymph is the fluid that flows through this system and carries cells that help to fight disease and infection. The lymph nodes filter the lymph to remove bacteria and other harmful agents, such as cancer cells.
Lymphatic system	The lymphatic system is part of the immune system, which protects the body against 'invaders', like bacteria and parasites. The lymphatic system is a network of small lymph nodes connected by very thin lymph vessels, which branch into every part of the body.

Malignant Cancerous	Malignant cells can spread (metastasise) and can eventually cause death if they cannot be treated.
Meta-analysis	A statistical method used to combine the results of different studies on the same topic. Used to pool results from a number of small randomised controlled trials to provide an aggregate that will allow for demonstration of statistically significant results.
Metastasis	Also known as a secondary tumour. A tumour that develops when cancer cells become detached from the original (or primary) tumour and are carried by the lymph and blood systems to other parts of the body.
Micronutrients	An essential dietary element required only in small quantities as trace elements.
Mitosis	The process of cell division where new cells are formed. Used by the body to replace dead cells.
Monoclonal antibody	An antibody derived from a single cell, relating to a single clone.
Morbidity	Term used to report on illness. Can also be used to show persons who were ill, the period of illness and the duration of the illness.
Mortality	Death rate due to a particular cause or disease.
MRI	A special imaging technique used to image internal structures of the body. It uses the influence of a large magnet to polarize hydrogen atoms in the tissues and then monitors the summation of the spinning energies within living cells. Images are very clear and are particularly good for soft tissue, brain and spinal cord, joints and abdomen. These scans may be used for detecting some cancers or for following their progress.
Multidisciplinary care	Multidisciplinary care is the co-ordinated approach using a collaborative group of health professionals and a range of treatment modalities. The team as a whole is responsible for the diagnosis, continuing management and palliative care of the woman with ovarian cancer.
Multidisciplinary team	A group of clinicians and health professionals, from a number of disciplines, working together to manage the care of a patient. The members of the team may include: a surgical oncologist, pathologist, medical oncologist, radiation oncologist, radiologist with a special interest in diagnosis of malignancy, general practitioners, specialist nurses, physiotherapists, pharmacists, psychologists, social workers, genetic counsellors, geneticists, and palliative care specialists.
Mutation	A permanent and transmissible change in genetic material.
Myelosuppression	Suppression of bone marrow activity resulting in a decrease in the number of platelets, red cells and white cells.
Neo-adjuvant	Chemotherapy that is administered before the dominant therapy, for example, radiotherapy/surgery
Oral alkylating agent therapy	An anti-cancer or cytotoxic agent eg a platinum compound. An alkylating agent is one which substitutes an alkayl group for an active hydrogen in an organic compound.

Palliative care	The active total care of patients whose disease is not responsive to curative treatment. It encompasses the provision of co-ordinated medical, nursing and allied services to help relieve physical symptoms and to provide psychological, emotional and spiritual support.
Pathology	The study of diseases, especially their causes and nature.
Pathogenesis	The development of a disease, specifically the cellular events, reactions and other pathologic mechanisms that occur.
Peritoneum	The lining of the abdomen.
PET scan	Positron emission tomography. A technique that is used to build up clear and detailed cross-section pictures of the body. The person is injected with a glucose solution containing a small amount of radioactive material. The PET scanner can 'see' the radioactive substance. Damaged or cancerous cells show up as areas where the glucose solution is being used.
Phase I, II, III trial	The different stages of a clinical trial. Phase I is designed to evaluate the relationship between dose and toxicity. In Phase II new treatments are screened for their anti-tumour effect, to see which are worthy of further evaluation and in Phase III patients are randomly allocated to receive the new treatment or the best available standard treatment.
Ploidy studies	Identification of the number of genomes (complete set of chromosomes) it contains
Pooled data	Data from a number of studies combined for analysis to look for an effect/result
Prognosis	A forecast as to the probable outcome of a disease and the prospect of recovery based on the nature of the case.
Proliferating	Growth by reproduction of similar cells
Quality of life	A person's view of their situation and well-being. It encompasses symptoms of disease, side effects of treatment, relationships, occupational and social functioning and a subjective evaluation of adjustment to daily life.
Radiotherapy	The use of radiation, usually x-rays or gamma rays, to kill cancer cells or injure them so they cannot grow and multiply. Radiotherapy treatment can also harm normal cells, but they are able to repair themselves.
Randomised controlled trial (RCT)	A study or experiment where subjects are allocated at random to receive or not receive the treatment, procedure or intervention. The results for each group are compared. Generally held to be the most scientifically rigorous method of testing an hypothesis.
Relapse	The return of a disease after a period of improvement or remission.
Relative risk	The risk (of a disease or death) among those exposed to the risk compared to those who are not exposed to the risk.
Relative survival	Relative survival analysis aims to quantify how long someone

	with a specific disease might survive when compared to the "general population". The general population are matched to the "disease" cases by age, sex and year of diagnosis. Relative survival is thus the ratio of the proportion of survivors in the disease group to the proportion of survivors in a similar group of people without the disease. A relative survival of 100% would indicate that persons with disease do not die any more rapidly as they age than people without the disease whereas a result of less than 100% indicates that the disease is resulting in premature death, even when other causes of death have been accounted for.
Remission	The decrease or disappearance of the symptoms of a disease. A person is said to be in complete remission when there is no evidence of active disease.
Resection	Surgical removal of part of all of an organ or tissue.
Risk factor	Things that cause people to have a greater chance of developing an illness. Risk factors for cancer include exposure to harmful substances (such as asbestos, some viruses and cigarette smoke) and inheriting a predisposition to a cancer.
Sigmoidoscopy	Inspection of sigmoid colon through either a rigid of flexible hollow tube appropriately lighted to view the lumen of the sigmoid.
Spleen	An organ in the upper part of the abdomen on the left side, below and behind the stomach. The spleen produces lymphocytes, filters blood, stores blood and destroys cells that are ageing. It can mount an immune response to infections in the blood system.
Staging	Investigations to find out how far a cancer has progressed. This is important in planning the best treatment.
Stage/staging/stage distribution	The classification of a tumour according to its extent.
Tissue	A collection of cells
Tissue biopsy	Examination of tissue, which has been removed from the body, under a microscope so that any abnormalities in the cells can be seen.
Toxicity	The quality of being poisonous
Tumour	Also called neoplasm. A new growth of tissue in which cell multiplication is uncontrolled and progressive. Tumours are classified in a number of ways the simplest being their origin and whether they are malignant or benign.
Tumour/tumourgenesis	The production of tumours
Tumour marker	A substance found in the body that suggests the presence of a tumour.
Ultrasound	'Ultrasound' is sound waves of a very high frequency (higher than the human ear can hear). If ultrasound is directed at the body, it is reflected back differently by different types of tissue. In an ultrasound scan, these differences are measured and used to build

	up pictures of structures in the body. Ultrasound pictures are usually taken by an ultrasound technician, who guides the scanning by watching the images on a screen like a television.
Vinblastine	A cytotoxic agent or drug used during chemotherapy to kill cancer or lymphoma cells.
Vincristine	A cytotoxic agent or drug used during chemotherapy to kill cancer or lymphoma cells.
Virtual colonoscopy	Visualisation of the large bowel by computer tomography.
White blood cells	Also known as leucocytes. One of the two main types of cells present in blood. They play a major role in fighting infection.

Partly adopted from The Cancer Council Victoria handbook titled: 'Lymphoma, a guide for people with cancer, their families and friends'.