every 24 hours, of which only approximately 200 mL is excreted in faeces. Sodium absorption is efficiently accomplished by an active transport system, while chloride and water are absorbed passively. Fermentation of dietary fibre in the colon by the normal colonic microflora leads to the generation of short chain fatty acids, which are an important metabolic substrate for colonic mucosa. Diversion of the faecal stream, denying the mucosa of this nutrition, may lead to inflammatory changes in the colon downstream (diversion colitis). Absorption of nutrients, including glucose, fatty acids, amino acids and vitamins, can also take place in the colon.

Colonic motility is variable. In general, faecal residue reaches the caecum 4 hours after a meal and the rectum after 24 hours. Passage of stool is not orderly because of mixing within the colon (see ***Chapter 73***).

TUMOURS OF THE LARGE INTESTINE

Benign

The term 'polyp' is a clinical description of any protrusion of the mucosa. It encompasses a variety of histologically different tumours (***Table 77.1***). Polyps can occur singly, synchronously in small numbers or as part of a polyposis syndrome.

Metaplastic polyps

Metaplastic or hyperplastic polyps are common and are generally considered benign. Recently certain subtypes have been recognised to have malignant potential. Sessile serrated lesions and hyperplastic polyps ≥10 mm in diameter are associated with *KRAS*/*BRAF* mutation that may lead to methylation of tumour-suppressing genes, dysplasia and malignancy along what is termed the 'serrated pathway'. Such polyps should be removed and follow-up colonoscopy arranged (***Figure 77.1***).

TABLE 77.1 Classification of intestinal polyps.

Inflammatory	Inflammatory polyps (pseudopolyps in ulcerative colitis) (see ***Chapter 75***)
Hamartomatous	Peutz–Jeghers polyp
	Juvenile polyp
Serrated polyps (serrated lesions)	Hyperplastic polyp
	Sessile serrated lesion
	Sessile serrated lesion with dysplasia
	Traditional serrated adenomas
	Mixed polyp
Adenoma	Tubular
	Tubulovillous
	Villous
Malignant polyp	Adenocarcinoma

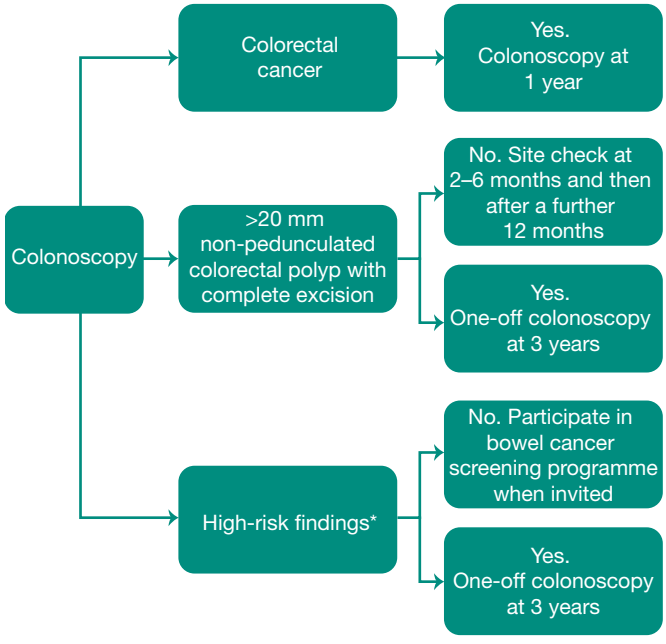

Figure 77.1 Recommendations for polyp follow-up. *Two or more premalignant polyps including at least one advanced polyp (serrated polyp >10 mm or with dysplasia, adenoma more than 10 mm in size or with high-grade dysplasia); or five or more premalignant polyps. (Adapted from Rutter MD, East J, Rees CJ *et al*. British Society of Gastroenterology/Association of Coloproctology of Great Britain and Ireland/Public Health England post-polypectomy and post-colorectal cancer resection surveillance guidelines. *Gut* 2020; **69**: 201–23.)

Adenomatous polyps

Adenomatous polyps are the most common polyps with malignant potential. The risk of malignancy is dependent on histology, morphology and size. Tubular adenomas have the lowest risk, with increasing risk as villous features predominate. Sessile and particularly depressed lesions have more malignant potential than pedunculated lesions (***Figure 77.2***). The risk of malignant change increases with size, almost one-third of large (>3 cm) colonic adenomas will have an area of invasive malignancy. Size is easily assessed endoscopically, which, alongside pit pattern and morphological classification, aids management. If felt appropriate and safe to resect endoscopically, various techniques are available, including hot or cold snare polypectomy for the most common smaller pedunculated lesions. Larger or flatter polyps may require infiltration of a solution to 'raise' the polyp before snare resection. The area of the polyp should be tattooed to facilitate later endoscopic or laparoscopic localisation of the site of the polyp. Failure of submucosal injection to elevate a polyp is suggestive of malignancy. In these circumstances, the site should be tattooed. A biopsy should not be taken if referral for endoscopic mucosal resection or endoscopic submucosal dissection is being considered. Such techniques carry a risk of colonic perforation and should only

John Law Augustine Peutz, 1886–1968, Chief Specialist for Internal Medicine, St John's Hospital, The Hague, The Netherlands.
Harold Joseph Jeghers, 1904–1990, Professor of Internal Medicine, New Jersey College of Medicine and Dentistry, Jersey City, NJ, USA.

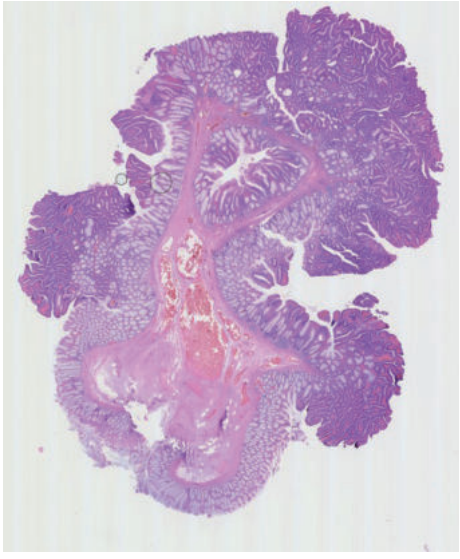

Figure 77.2 Pedunculated polyp of the large intestine showing tubulovillous changes at the apex and normal colonic mucosa at the base (courtesy of Dr Philip Kaye, Nottingham University Hospitals, Nottingham, UK).

be performed by an experienced endoscopist. Rectal adenomas may also be treated by endoscopic or transanal resection (see ***Chapter 79***).

Polyp surveillance

After successful endoscopic removal of polyps, there is a risk of further polyp development; however, the risk of subsequent development of colorectal cancer is low. The need for and frequency of follow-up surveillance endoscopy is dependent on polyp morphology, number and size, age and comorbidity of the patient, presence of a family history and accuracy and completeness of the index test. These factors allow polyps to be divided into low, intermediate and high risk. Recent guidelines (***Figure 77.1***) published by the British Society of Gastroenterology have identified patients at high risk needing follow-up colonoscopy as those with either:

- two or more premalignant polyps, including at least one advanced colorectal polyp (defined as a serrated polyp ≥10 mm in size or containing any grade of dysplasia or as an adenoma ≥10 mm in size or containing high-grade dysplasia); or
- five or more premalignant polyps.

Polyposis syndromes

Polyposis syndromes can be divided into familial adenomatous polyposis (FAP), attenuated familial adenomatous polyposis (AFAP), *MUTYH*-associated polyposis (MAP) and *NTHL1*-associated polyposis (NAP).

Familial adenomatous polyposis

FAP is defined clinically by the presence of more than 100 colorectal adenomas but is also characterised by duodenal adenomas and multiple extraintestinal manifestations (***Summary boxes 77.1 and 77.2***). Over 80% of cases come from those with a positive family history. The remainder arise as a result of new mutations in the adenomatous polyposis coli (*APC*) gene on the long arm of chromosome 5. FAP is inherited as an autosomal dominant condition and is consequently equally likely in men and women. The lifetime risk of colorectal cancer is up to 100% in those with an *APC* gene mutation. FAP can also be associated with benign mesodermal tumours such as desmoid tumours and osteomas. Epidermoid cysts can also occur (Gardner's syndrome); desmoid tumours in the abdomen spread locally to involve the intestinal mesentery and, although non-metastasising, they may become unresectable. Up to 50% of people with FAP have congenital hypertrophy of the retinal pigment epithelium (CHRPE), which can be used to screen affected families if genetic testing is unavailable.

Clinical features

Polyps are usually visible on sigmoidoscopy by the age of 15 years and will almost always be visible by the age of 30 years. Regular endoscopic surveillance in a suspected family member should therefore commence at the age of 12–14 years, even if a genetic mutation has not been identified. Patients with mutations located between codons 1286 and 1513 of the *APC* gene generally have a worse prognosis with earlier disease onset than those with mutations outside this region. Germline mutations at codon 1309 are associated with the most severe disease. AFAP, also associated with *APC* gene mutation, is associated with fewer than 100 polyps and may not present until the fourth decade.

If the diagnosis is made during adolescence, surgery is usually deferred to the age of 17 or 18 years unless symptoms develop. Malignant change is unusual before the age of 20 years. Examination of blood relatives, including cousins, nephews and nieces, is essential; a family tree should be constructed, and a register of affected families maintained. Referral to a medical geneticist is essential. If over 100 adenomas are present at colonoscopy, the diagnosis can be made confidently (***Figure 77.3***).

Summary box 77.1

Features of FAP

- Autosomal dominant inherited disease due to mutations of the *APC* gene
- More than 100 colonic adenomas are diagnostic
- Prophylactic surgery is indicated to prevent colorectal cancer
- Polyps and malignant tumours can develop particularly around the duodenal ampulla

Eldon John Gardner, 1909–1989, geneticist, The University of Utah, Salt Lake City, UT, USA, described this syndrome in 1950.

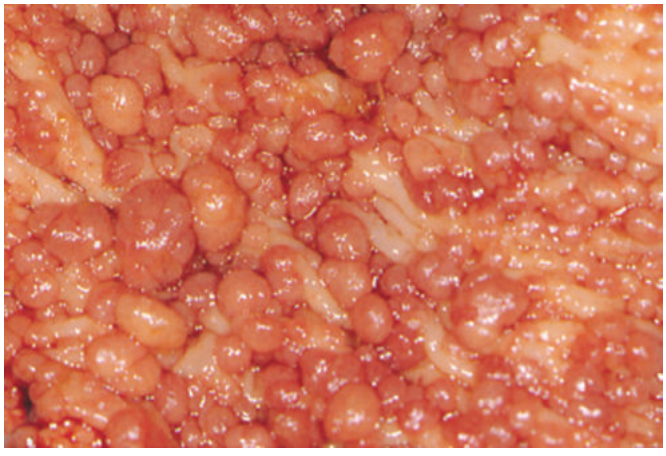

Figure 77.3 Familial adenomatous polyposis showing hundreds of adenomatous polyps.

Summary box 77.2

Extracolonic manifestations of FAP

- Endodermal derivatives
  - Adenomas and carcinomas, particularly around the duodenal ampulla but also stomach, small intestine, thyroid and biliary tree
  - Gastric fundic gland polyps
  - Hepatoblastoma
- Ectodermal derivatives
  - Epidermoid cysts
  - Pilomatrixoma
  - Congenital hypertrophy of the retinal pigment epithelium (CHRPE)
  - Brain tumours
- Mesodermal derivatives
  - Desmoid tumours
  - Osteomas
  - Dental problems

Treatment

The aim of surgery in FAP is to prevent the development of colorectal cancer. The surgical options are:

1. restorative proctocolectomy with an ileal pouch–anal anastomosis;
2. colectomy with ileorectal anastomosis (IRA);
3. total proctocolectomy and end-ileostomy.

As patients are often young, most prefer to avoid a stoma, restorative proctocolectomy with ileal pouch–anal anastomosis has the advantage of removing the whole colon and rectum without the need for a permanent stoma (see ***Chapter 75***). However, there is a pouch failure rate of approximately 10%. In addition, and particularly when a stapled anastomosis has been created, endoscopic surveillance is still required as malignant change can occur in the 'rectal cuff' (the small strip of rectal mucosa between the pouch and the dentate line). Some advocate complete mucosectomy of this residual cuff and a transanal anastomosis, although this may result in worse function. In experienced hands, a laparoscopic approach is associated with swifter recovery, improved cosmesis and perhaps increased fecundity in women.

For patients with relative rectal sparing (<20 polyps), total colectomy and IRA is an option to be considered, particularly as it is associated with less risk of sexual dysfunction in males and less infertility in females. However, the rectum requires regular endoscopic surveillance as up to 10% of patients will develop invasive malignancy in the rectum. In AFAP, patients may consider rectal preservation surgery on the understanding that their cancer risk is lower (around 2%) but still present.

Proctocolectomy and ileostomy is the recommended option for patients with poor anal sphincter function, those who have already developed a rectal cancer or those who wish to have a definitive single-stage procedure.

Postoperative surveillance

Because of the ongoing cancer risk, regular lifelong endoscopic surveillance of the rectum/pouch is important with biopsy of the rectal cuff unless mucosal proctectomy has been performed. Endoscopy is also carried out to detect upper gastrointestinal tumours, particularly around the duodenal ampulla (see ***Chapter 67***). A side-viewing duodenoscope is required. Despite surveillance, life expectancy is reduced because of extracolonic cancers and complications of desmoid tumours.

MUTYH-associated polyposis

The appearances of MAP can be similar to FAP but it is inherited as an autosomal recessive phenotype and predisposes individuals to multiple colonic polyps. If an *APC* pathogenic variant is not identified in an individual with colonic polyposis, molecular genetic testing of *MUTYH* should be considered. There is an increased risk of colorectal cancer of between three- and sixfold depending on the particular *MUTYH* mutation. Colonoscopy should be performed every 2 years. Colectomy is required when the number and/or characteristics of the polyps do not allow complete endoscopic resection or malignancy is diagnosed. Surveillance for duodenal adenomas is recommended.

NTHL1 tumour syndrome

NTHL1 tumour syndrome is a rare autosomal recessive cause of colorectal polyposis and increased lifetime risk for colorectal cancer. Colorectal polyps can be adenomatous, hyperplastic or sessile serrated. Management is similar to MAP.

Peutz–Jeghers and juvenile polyposis syndrome

Peutz–Jeghers syndrome (PJS) is an autosomal dominant genetic disorder characterised by the development of benign hamartomas in the gastrointestinal tract along with hyperpigmented lesions on the lips and oral mucosa. The main clinical risks are small bowel intussusception in children and increased incidence of gastrointestinal malignancy in adult life (see ***Chapter 74***).

Juvenile polyposis (JPS) is an autosomal dominant inherited condition that presents with hamartomatous polyps due to

mutations in the *BMPR1A*, *SMAD4* or *ENG* genes. Pigmentation characteristic of PJS is not present.

Lynch syndrome (hereditary non-polyposis colorectal cancer)

Lynch syndrome, previously known as hereditary non-polyposis colorectal cancer (HNPCC), is characterised by an increased risk of colorectal cancer and also cancers of the endometrium, ovary, stomach and small intestine, urinary tract, pancreas, prostate and kidney. It is an autosomal dominant condition caused by a mutation in one of four DNA mismatch repair genes (*MLH1*, *MSH2*, *MSH6* and *PMS2*). These genes, when functioning normally, code for mismatch repair (MMR) proteins, which repair sporadic mutations that occur in other genes. If faulty, mutations accumulate in other key genes, leading to characteristic repeat sequences of DNA, termed microsatellite instability (MSI), and acceleration of the adenoma–carcinoma sequence. Thus individuals with an MMR gene mutation tend to develop colorectal polyps at an early age (before the age of 50 years) that quickly become cancerous. Not everyone with a mutation develops cancer; the lifetime risk is 80%. Most cancers develop in the proximal colon. Females have a 30–50% lifetime risk of developing endometrial cancer.

Diagnosis

Lynch syndrome was historically diagnosed based on a family history of cancer and the clinical parameters set out in the Amsterdam (***Summary box 77.3***) and Bethesda criteria. Recent advances in immunohistochemistry allow for MMR proteins or MSI to be accurately identified in all colorectal tumours with subsequent genetic testing in patients and families of those proven positive.

Summary box 77.3

Amsterdam II criteria

- Three or more family members with a Lynch syndrome-related cancer (colorectal, endometrial, small bowel, ureter, renal pelvis), one of whom is a first-degree relative of the other two
- Two or more successive affected generations
- At least one tumour diagnosed before the age of 50 years
- FAP excluded
- Tumours verified by pathological examination

Because of the accelerated pathway from adenoma to cancer in Lynch syndrome those with a gene mutation should be offered 2-yearly endoscopic surveillance from age 25 years (*MLH1* and *MSH2* carriers) or 35 years (*MSH6* carriers). *PMS2* carriers should be offered 5-yearly screening beginning at age 35 years (see ***Further reading***). For patients with polyps that cannot be managed with endoscopic polypectomy or those who develop a cancer, an extended colectomy (*MLH1* and *MSH2* carriers) should be considered. The benefit of screening other areas of the gastrointestinal tract is unclear but gynaecological screening is recommended in accordance with the 2019 Manchester Consensus (see ***Further reading***).

Malignant: colorectal carcinoma

Epidemiology

In the UK, colorectal cancer is the second most common cause of cancer death. Approximately 42 000 patients are diagnosed with colorectal cancer every year in the UK. Approximately one-third of these tumours are in the rectum and two-thirds in the colon. The burden of disease is greater in men than in women (56% versus 44%). Colorectal cancer occurs less frequently in resource-poor than in resource-rich countries.

Aetiology

Most colorectal cancers are thought to develop from adenomatous polyps through a sequence of genetic mutations influenced by environmental factors. This adenoma–carcinoma sequence is based on strong observational evidence (***Summary box 77.4***). The adenoma–carcinoma sequence is not a simple stepwise progression of mutations but a complicated array of multiple genetic alterations, ultimately resulting in an invasive tumour. Mutations of the *APC* gene occur in two-thirds of colonic adenomas and are thought to develop early in the carcinogenesis pathway. *K-ras* mutations result in activation of cell signalling pathways and are more common in larger lesions, suggesting that that they are later events in mutagenesis. The *p53* gene is frequently mutated in carcinomas but not in adenomas and therefore thought to be a marker of invasion. A recent international consortium has identified four consensus molecular subtypes (CMSs) of colorectal cancer based on bioinformatic analysis of gene expression in more than 4000 patients. MSI, a feature of Lynch syndrome, may occur sporadically, particularly in right-sided tumours (CMS1), while others show *WNT* and *MYC* signalling activation (CMS2), metabolic dysregulation (CMS3) and transforming growth factor beta activation (CMS4). The value of this classification in interpreting tumour aetiology, biology and targeted treatment remains to be determined.

Summary box 77.4

Evidence for adenoma–carcinoma sequence

- The distribution of adenomas is similar to that of cancers (70% left sided)
- Larger adenomas are more likely to be dysplastic than small adenomas
- The majority of early cancers have adjacent adenomatous tissue
- Adenomas are found in one-third of specimens resected for colorectal cancer
- Incidence of colorectal cancer decreases within a screening programme that involves colonoscopy and polypectomy

Henry Thompson Lynch, 1928–2019, physician and geneticist, Omaha, NE, USA, first presented his findings of a family with a strong history of colorectal cancer without polyposis in 1964.

Worldwide, the prevalence of colorectal cancer is closely associated with intake of red meat and particularly processed meat products (haem and *N*-nitroso compounds). A protective effect of dietary fibre is also suggested by epidemiological studies. A long-held hypothesis is that increased roughage is associated with reduced colonic transit times that in turn reduce exposure of the mucosa to dietary carcinogens. However, there is increasing evidence associating the colonic microbiota with inflammation, gene methylation and dysplastic changes. Increased risks for colorectal cancer have also been associated with smoking and alcohol. Conversely, high magnesium and calcium intake may be protective. A protective potential for antioxidants such as vitamin E and selenium is as yet unproven.

The epidemiological evidence supporting prostaglandin inhibitors, particularly aspirin, in preventing colorectal cancer is substantial. Given the potential hazards of taking long-term aspirin, the challenge is to identify individuals for whom the protective benefits outweigh the harm. Other factors that increase the risk of developing colorectal cancer include inflammatory bowel disease (IBD) (see ***Chapter 75***). Cholecystectomy may marginally increase the risk of right-sided colon cancer.

Pathology

Macroscopically, the tumour may take one of several forms: annular cancers tend to give rise to obstructive symptoms whereas ulcerating cancers tend to present with bleeding. Most large bowel cancers (***Figure 77.4***) arise from the left colon, notably the rectum (38%), sigmoid (21%) and descending colon (4%). Cancer of the caecum (12%) and ascending colon (5%) is less common but may be gradually increasing in incidence. Cancer of the transverse colon (5.5%), flexures (2–3%) and appendix (0.5%) are relatively uncommon. Microscopically, the neoplasm is a columnar cell adenocarcinoma.

Spread

Colonic cancer can spread locally, via the lymphatics, bloodstream (haematogenous) or across the peritoneal cavity (transcoelomic spread). Direct spread may be longitudinal or radial. Radial spread may be retroperitoneal into the ureter, duodenum and posterior abdominal wall muscles or intraperitoneal into adjacent organs or the anterior abdominal wall.

In general, involvement of the lymph nodes by tumour progresses from those closest to the bowel along the course of lymphatics to central nodes. However, this orderly process does not always occur. Haematogenous spread is most commonly to the liver via the portal vein. One-third of patients will have liver metastases at the time of diagnosis and 50% will develop metastases at some point, accounting for the majority of deaths. The lung is the next most common site of metastatic disease whereas spread to the ovaries, brain, kidney and bone is less common. Colorectal cancer can spread from the serosa of the bowel or via subperitoneal lymphatics to other structures within the peritoneal cavity, including peritoneum, ovary and omentum.

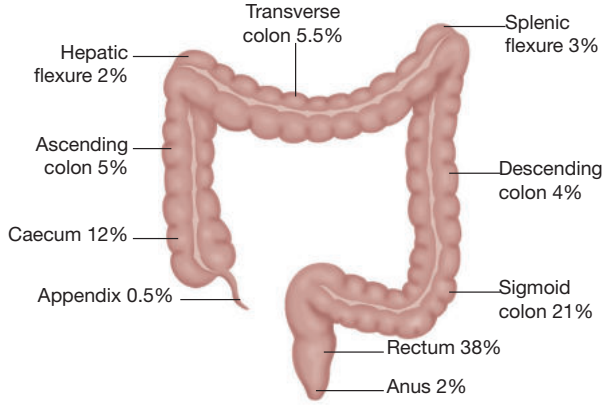

Figure 77.4 Distribution of colorectal cancer by site.

Staging colon cancer

Preoperative staging is important to decide whether patients can be managed with curative intent and whether they should have neoadjuvant therapy, undergo palliative interventions including colonic stenting or have symptomatic treatment. Additional interventions include ureteric stenting, en bloc resection for locally advanced disease, intraoperative chemotherapy (hyperthermic intraperitoneal chemotherapy [HIPEC]) for peritoneal disease or synchronous organ resection (e.g. liver, ovaries [Krukenberg tumour]). Information is collated, including patient characteristics (age, frailty, symptoms and comorbidities), endoscopic assessment, histological analysis of biopsies and imaging studies. These factors should be discussed in a dedicated preoperative multidisciplinary meeting. Postoperative pathological staging should also be discussed in the same forum, allowing for decisions about adjuvant therapy.

A variety of staging systems are described for colorectal cancer. Dukes' classification was originally described for rectal tumours but has been adopted for histopathological reporting of colon cancer. Although it is simple and widely recognised (***Summary box 77.5***) the more detailed TNM system is regarded as the international standard (***Summary box 77.6***).

Summary box 77.5

Dukes' staging for colorectal cancer

- A: Invasion of but not breaching the muscularis propria
- B: Breaching the muscularis propria but not involving lymph nodes
- C: Lymph nodes involved

Dukes himself never described a stage D, but this is often used to describe metastatic disease

Friedrich Ernst Krukenberg, 1871–1946, Professor of Gynaecology, Bonn, Germany
Cuthbert Esquire Dukes, 1890–1977, pathologist, St Mark's Hospital, London, UK. The original Dukes' classification in 1932 gave three stages, A–C.

Summary box 77.6

TNM classification for colonic cancer

(note the prefix y refers to neoadjuvant radio- or chemotherapy, p refers to pathological confirmation of stage; Union for International Cancer Control, 8th edn)

- T Tumour stage
  - T1 Tumour invades into submucosa
  - T2 Tumour invades into muscularis propria
  - T3 Tumour invades into non-peritonealised pericolic tissues or subserosa
  - T4a Tumour breaches visceral peritoneum
  - T4b Tumour directly invades another organ/structure
- N Nodal stage
  - N0 No nodes involved
  - N1 1–3 nodes involved (N1a, 1 regional lymph node involved; N1b, 2 or 3 regional lymph nodes involved; N1c, satellite extranodal tumour deposits)
  - N2 4 or more nodes involved (N2a, 4–6 regional lymph nodes involved; N2b, 7 or more regional lymph nodes involved)
- M Metastases
  - M0 No metastases
  - M1 Metastases (M1a, metastasis confined to 1 organ; M1b, metastasis to more than 1 organ; M1c, metastasis to the peritoneum)

Clinical features

Carcinoma of the colon typically occurs in patients over 50 years of age and is most common in the eighth decade of life. Emergency presentation occurs in 20% of cases and is associated with a considerably worse prognosis, even when matched for disease stage. A careful family history should be taken. A first-degree relative who has developed colorectal cancer before the age of 50 years may indicate one of the colorectal cancer familial syndromes. Tumours of the left side of the colon usually present with a change in bowel habit or rectal bleeding, while proximal lesions typically present with iron deficiency anaemia or a mass (***Figure 77.5***). Patients may present with metastatic disease.

Investigation of colon cancer

Screening

Colon cancer is suited to screening as the prognosis is better the earlier stage the disease is diagnosed and polypectomy allows the prevention of cancer development. In the UK screening is offered every 2 years to men and women aged 60–74 years, followed by colonoscopy in those who test positive. Originally a guaiac-based test was used, which detects peroxidase-like activity of faecal haematin. Studies suggested a 15–20% reduction in colorectal cancer-specific mortality in the screened population. More recently the faecal immunochemical test (FIT) has been introduced. This test is more accurate and easier to complete than the old faecal occult blood test. A one-off flexible sigmoidoscopy for people aged 55 was offered as a screening tool in the UK. It was shown to reduce colorectal cancer-specific mortality but is now being replaced with FIT screening.

Endoscopy

For symptomatic patients with rectal bleeding, direct referral from primary care for a flexible sigmoidoscopy is increasingly used. The patient is prepared with an enema and sedation is not usually necessary. The bowel can be assessed as far as the splenic flexure, allowing detection of up to 70% of cancers and almost all that cause fresh rectal bleeding. Finding left-sided colonic polyps or cancer mandates subsequent completion colonoscopy.

Colonoscopy is the investigation of choice if colorectal cancer is suspected (***Figure 77.5***). It has the advantage of not only securing histological diagnosis of a primary cancer but also detecting synchronous polyps or carcinomas, which occur in 3–5% of cases. There is a small risk of perforation (1:1000).

Radiology

Double-contrast barium enema has now been largely replaced by computed tomography (CT) colonography, which is extremely sensitive in picking up polyps to a size of 6 mm (***Figure 77.6***). It has the advantage of being less invasive than colonoscopy but, if a biopsy is required, an endoscopy will still be needed. CT is used as a diagnostic tool in patients with a palpable abdominal mass. CT of the thorax, abdomen and pelvis now represents the standard means of staging colorectal cancer; patients with rectal cancer require magnetic resonance imaging (MRI) for local staging (see ***Chapter 79***).

Surgical treatment

Preoperative preparation

With the advent of perioperative enhanced recovery after surgery (ERAS) protocols, mechanical bowel preparation fell out of favour. However, there is evidence that preoperative mechanical bowel preparation in combination with preoperative oral antibiotics not only reduces surgical site infection rates but also rates of anastomotic leak, postoperative ileus, reoperation and even mortality. Further research is required

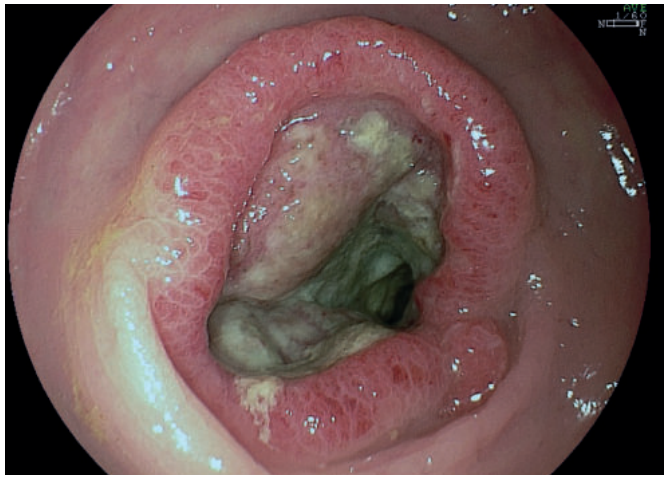

Figure 77.5 Colon cancer seen at colonoscopy (courtesy of Dr Adolfo Parra-Blanco, Nottingham University Hospitals, Nottingham, UK).

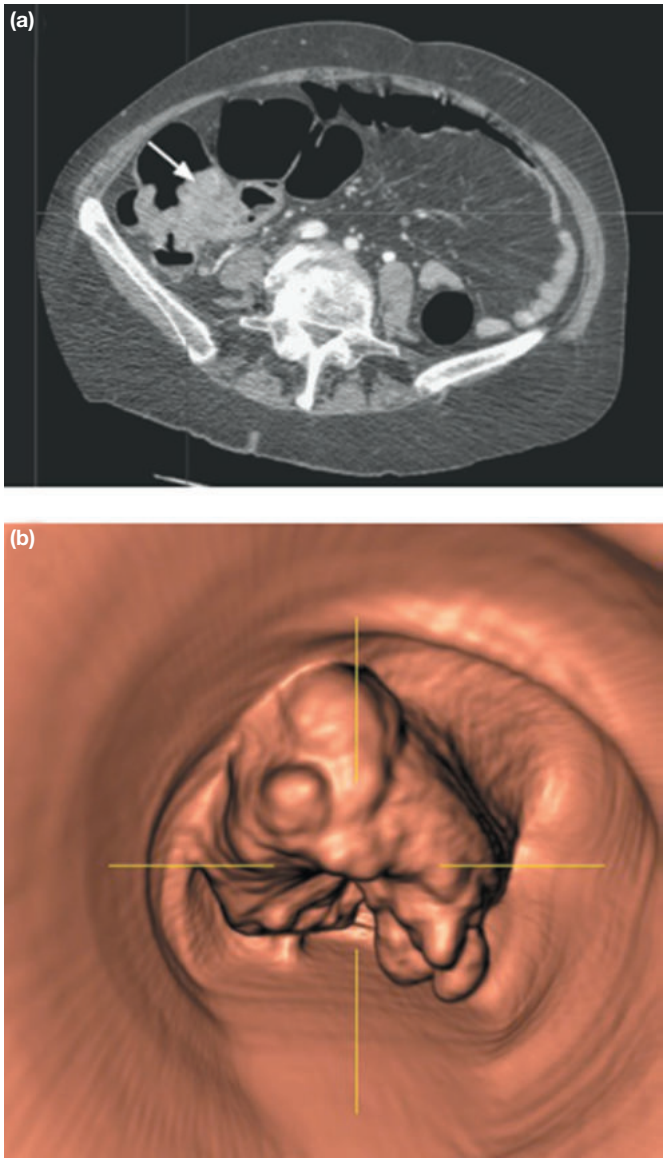

Figure 77.6 Virtual colonoscopy of the right colon. **(a)** Computed tomography scan of the abdomen showing a caecal tumour (arrow). **(b)** Formatted 'virtual' image of the same lesion as in **(a)** (courtesy of Dr A Slater, John Radcliffe Hospital, Oxford, UK).

but mechanical bowel preparation with oral antibiotics appears safe and could reasonably be used in combination with a surgical site infection bundle. This bundle should contain common and variable components such as preoperative bathing, intravenous prophylactic antibiotics given before surgical incision, maintenance of normoglycaemia and normothermia and use of wound protection devices. Antithrombotic stockings should be fitted, and the patient started on prophylactic subcutaneous low-molecular-weight heparin. Manual compression boots may be used perioperatively. In all cases where a stoma is anticipated, careful preoperative counselling and marking of an appropriate site by an enterostomal therapist is essential. ERAS programmes are widely used to reduce the physiological insult of surgery and improve postoperative outcomes (***Summary box 77.7***).

Summary box 77.7

Key elements of an ERAS programme

- Preadmission counselling
- Preoperative carbohydrate loading
- Avoidance of preoperative dehydration
- Avoidance of nasogastric tubes
- Short, transverse incisions (or laparoscopic procedure)
- Short-acting anaesthetic drugs
- Avoidance of perioperative fluid/salt overload
- Avoidance of opiate analgesia
- Maintenance of perioperative temperature
- Prevention of postoperative nausea and vomiting
- Early mobilisation
- Early introduction of oral fluids/diets/supplements
- Early removal of urinary catheters
- Continual audit of outcomes

Operations

The operations described are designed to remove the primary tumour and its draining locoregional lymph nodes. It is unusual to find unsuspected metastases at laparotomy (or laparoscopy) after CT staging, but the presence of peritoneal metastases may predicate a palliative strategy with a segmental resection and less aggressive lymphadenectomy. Similarly, a complete preoperative colonoscopy or CT colonography will have excluded synchronous bowel lesions. The use of stapling and hand-suturing techniques for colonic anastomoses have been compared, and there is probably little difference in leak rate. It is more important that healthy bowel, free of tension or distal obstruction, is used to construct an anastomosis and that patients are adequately nourished and free from active infection if anastomotic leakage is to be avoided.

Right hemicolectomy Carcinoma of the caecum or ascending colon (***Figure 77.7***) is treated by right hemicolectomy (***Figure 77.8***). At open surgery the peritoneum lateral to the ascending colon is incised, and the incision is continued

Figure 77.7 Right hemicolectomy specimen showing an ascending colon cancer (courtesy of Dr Philip Kaye, Nottingham University Hospitals, Nottingham, UK).

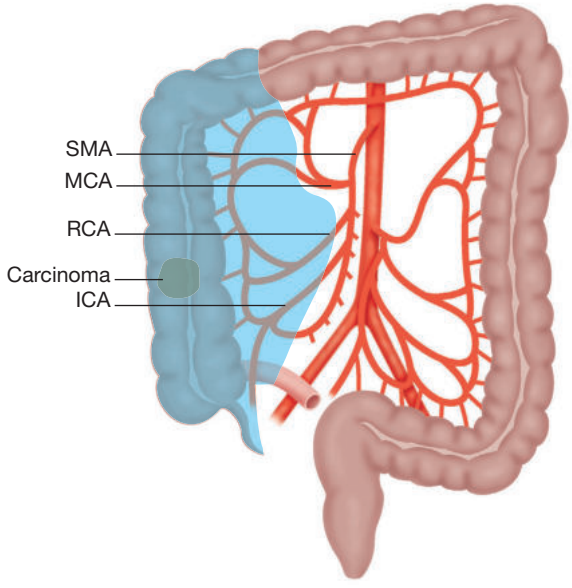

Figure 77.8 Schematic showing right hemicolectomy. This shows the basic plane of dissection for a complete mesocolic excision. ICA, ileocolic artery; MCA, middle colic artery; RCA, right colic artery; SMA, superior mesenteric artery.

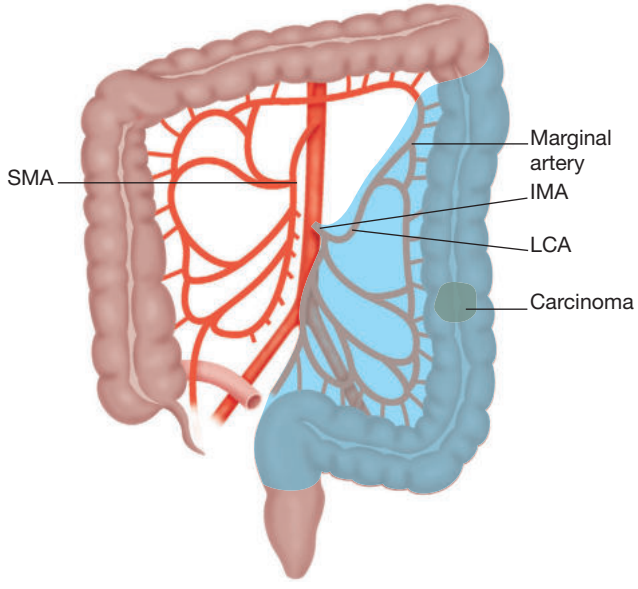

Figure 77.9 Schematic showing left hemicolectomy. This shows the basic plane of dissection for a complete mesocolic excision. IMA, inferior mesenteric artery; LCA, left colic artery; SMA, superior mesenteric artery.

around the hepatic flexure. The right colon and mesentery are elevated, taking care not to injure the ureter, gonadal vessels or the duodenum. The ileocolic artery is ligated close to its origin from the superior mesenteric artery ('high-tie') and divided. Complete mesocolic excision with dissection along embryological planes (see ***Chapter 65***) and removal of the lymphovascular supply of the resected colon with flush ligation of the ileocolic and right colic vessels at their origin from the superior mesenteric artery may improve survival in node-positive disease (Hohenburger). The mesentery of the distal 10 cm of the ileum and the mesocolon as far as the proximal third of the transverse colon is divided. The greater omentum is divided up to the point of intended division of the transverse colon. When it is clear that there is an adequate blood supply at the resection margins, the right colon is resected and an anastomosis is fashioned between the ileum and the transverse colon. If the tumour is at the hepatic flexure the resection must be extended further along the transverse colon and will involve dividing the right branch of the middle colic artery.

Extended right hemicolectomy Carcinomas of the transverse colon and splenic flexure are most commonly treated by an extended right hemicolectomy. The mobilisation is as for a right hemicolectomy but dissection continues to include the tumour, this may include taking down the splenic flexure and excising the whole transverse mesocolon. Some surgeons prefer to perform a left hemicolectomy for a splenic flexure cancer.

Left hemicolectomy This is the operation of choice for descending colon and sigmoid cancers (***Figure 77.9***). The left half of the colon is mobilised completely along the 'white line' that marks the lateral attachment of the mesocolon (see ***Chapter 65***). As the sigmoid mesentery is mobilised, the left ureter and gonadal vessels must be identified and protected. The splenic flexure may be mobilised by extending the lateral dissection from below and completed by entering the lesser sac. The inferior mesenteric artery below its left colic branch, together with the related paracolic lymph nodes, is included in the resection by ligating the inferior mesenteric artery close to its origin ('high-tie'). For full mobility the inferior mesenteric vein is also ligated and divided at the lower border of the pancreas. The bowel and mesentery can then be resected to allow a tension-free anastomosis. A temporary diverting stoma may be fashioned proximally, usually by formation of a loop ileostomy. This is usually undertaken if the anastomosis is below the peritoneal reflection of the rectum, because of the greater risk of anastomotic leakage.

Laparoscopic surgery

Laparoscopic surgery for colon cancer has been shown to have equivalent overall and cancer-related outcomes to open surgery. Lymph node harvests are equivalent to open surgery and initial concerns about reports of port-site recurrence have been dispelled as world experience has grown. In the UK, the National Institute for Health and Care Excellence (NICE) has stated that laparoscopic colorectal surgery should be offered to suitable patients. Operation times are longer but wound infection rates, blood loss and postoperative pain scores are lower than for open surgery. The costs of laparoscopic surgery are, however, generally higher and this may be particularly relevant where funds are limited.

Werner Hohenburger, contemporary, surgeon, Erlangen, Germany.

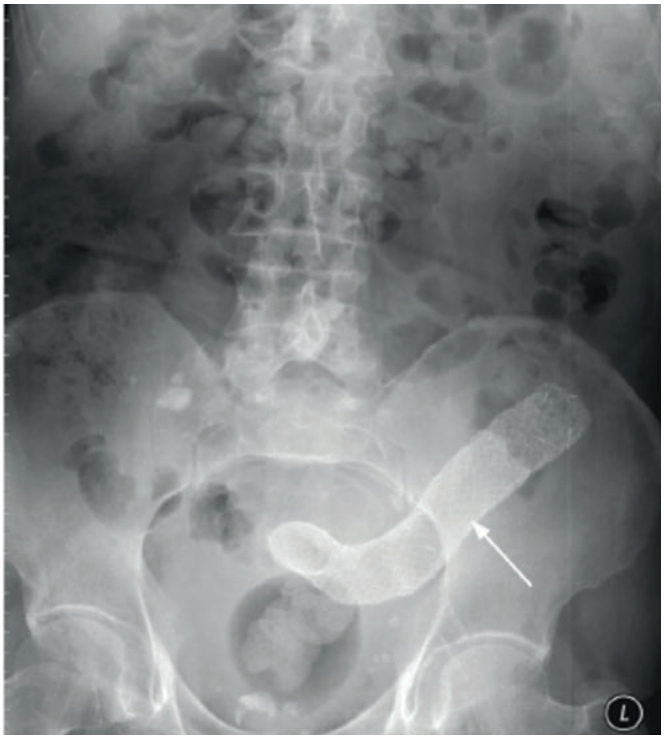

Figure 77.10 Abdominal radiograph demonstrating a colonic stent in position (arrow) (courtesy of Dr D Kasir, Hope Hospital, Salford, UK).

If laparoscopic surgery is planned it is useful to tattoo the lesion at prior colonoscopy as it not possible to locate lesions by palpation. The laparoscopic operation has particular advantages if performed in a medial to lateral manner, i.e. starting the dissection by controlling and dividing the major vascular pedicles and only taking the lateral peritoneal reflection once the mesocolon is completely free. Specimen retrieval and bowel anastomosis can then be performed via a small incision. Dedicated training in laparoscopic colorectal surgery is important as there is a relatively long learning curve.

Emergency surgery

In the UK, 20% of patients with colonic cancer will present as an emergency, the majority with obstruction, but occasionally with haemorrhage or perforation. If the lesion is right sided, it is usually possible to perform a right hemicolectomy and anastomosis in the usual manner. If there has been perforation with substantial contamination or if the patient is unstable, it may be advisable to bring out an ileocolostomy following resection of the lesion rather than forming an anastomosis. For a left-sided lesion the decision lies between a Hartmann's procedure and a resection and anastomosis. An on-table washout may be necessary to remove residual faecal content in the proximally obstructed bowel. Alternatively, removal of the whole proximal bowel may be required if the colon is markedly distended or if there is concern regarding its viability. Where endoscopic and radiological facilities are present an obstructing left-sided lesion can often be treated initially with an expanding metal stent (***Figure 77.10***). This allows decompression of the obstructed bowel and may allow conversion of an emergency operation with a high chance of a stoma to a situation that can be managed semielectively by resection and anastomosis. Although early studies cast doubt on the benefits of colorectal stenting, more recently evidence has emerged that stenting leads to a reduction in stoma rates.

Postoperative care

Patients should be closely monitored after colonic resection as there is a small incidence of postoperative bleeding. Antithrombosis measures should be continued and as currently recommended for 28 days postoperatively. There is no advantage to placing intra-abdominal drains after colonic surgery. Wound infections are relatively common after colonic surgery and may well be more frequent than the 10% usually quoted. Anastomotic leaks occur in 4–8% of ileocolic or colocolic anastomoses. The possibility should be borne in mind in any patient not progressing as expected or with unexplained cardiac abnormalities, fever or worsening abdominal pain. Early investigation with contrast-enhanced CT scan is appropriate. In the presence of sepsis or peritonitis, early return to theatre and taking down the leaking anastomosis with the formation of stomas is usually advised.

Prolonged nasogastric drainage, intravenous fluid therapy and cautious introduction of oral fluid and diet represented traditional postoperative practice. ERAS programmes that include preoperative, intraoperative and postoperative components have been shown to reduce length of hospital stay from 10–14 days to as little as 3–5 days by modulating the surgical stress response and reducing postoperative ileus (***Summary box 77.7***). It is important to appreciate that these programmes require multiple interventions and considerable time, effort and education from the surgical, anaesthetic and ward teams.

Adjuvant therapy

In most patients with colon cancer preoperative chemotherapy is not required; however, a recent research study (FOxTROT) has shown that it is safe and further work on case selection has been recommended. Adjuvant chemotherapy improves survival after surgery in patients with node-positive colon cancer (stage III/Dukes' C). Fluoropyrimidine regimes are often used, with the addition of oxaliplatin in patients who are otherwise fit and have high-risk stage III disease. Patients with stage II disease show less benefit in overall survival with adjuvant chemotherapy, thus it is reserved for those with high-risk stage II disease. Presence of MSI (in the tumour histology) also affects tumour recurrence and is taken into account when making decisions with patients about chemotherapy (see ***Chapter 12***).

Metastatic disease

Hepatic and pulmonary metastases can be resected and series have demonstrated 5-year survival of around 40% in resectable disease. CT, MRI and positron emission tomography (PET) scanning are all used to identify colorectal metastases and assess patients' suitability for further resection (***Figure 77.11***).

Henri Albert Antoine Hartmann, 1860–1952, Professor of Clinical Surgery in the Faculty of Medicine, University of Paris, Paris, France.

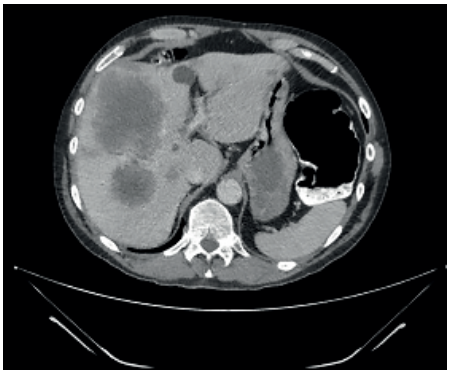

Figure 77.11 Computed tomography scan of the liver showing multiple metastases from carcinoma of the colon (courtesy of Dr Rajpal Dhingsa, Nottingham University Hospitals, Nottingham, UK).

The role of chemotherapy and the timing of colonic and hepatic surgery in synchronous metastases is still a matter of debate and such cases should be carefully discussed by a multidisciplinary team. Many centres offer adjuvant chemotherapy as standard and neoadjuvant therapy also in those with high-risk disease.

Isolated lung metastases may be suitable for resection or stereotactic radiofrequency ablation, but they are more commonly accompanied by metastases elsewhere. In patients with widespread disease, palliative chemotherapy is offered alongside symptomatic treatment and support by a palliative care team.

Prognosis

Overall 5-year survival for colorectal cancer is approximately 58%. While there are numerous factors that may predict prognosis (***Summary box 77.8***) the most important determinant is tumour stage and, in particular, lymph node status. Patients with disease confined to the bowel wall (TNM stage 1, Dukes' stage A) will usually have cure by surgical resection alone and around 95% will have disease-free survival at 5 years. Spread beyond the bowel wall (TNM stage 2, Dukes' B) reduces 5-year disease-free survival to approximately 85% with surgery alone. Patients with lymph node metastases (TNM stage 3, Dukes' C) have a 5-year disease-free survival of around 45–50% with surgery alone.

Adjuvant chemotherapy based on 5-fluorouracil (5-FU) and folinic acid (leucovorin) usually in combination with oxaliplatin (FolFox) is used on an individual basis for those with stage II disease (Dukes' stage B), although the benefit is uncertain. In those with stage III disease adjuvant chemotherapy increases the chance of 5-year disease-free survival by approximately 20% to 67–70%. Those presenting with unresectable metastatic disease at diagnosis have a 5-year survival of approximately 10%.

In metastatic disease chemotherapy based on 5-FU and folinic acid in combination with irinotecan (FolFiri) is often used as first-line treatment. Second-line therapy may include introduction of a monoclonal antibody such as a vascular endothelial growth factor (VEGF) inhibitor (bevacizumab) or an epidermal growth factor receptor (EGFR) inhibitor in *KRAS* wild-type tumours (cetuximab, panitumumab). Recently immunotherapy (pembrolizumab) has been shown to have a role in MSI tumours. Tumours exhibiting the *BRAF* V660E mutation (approximately 10%) have a poor prognosis but may respond to treatment with combined BRAF (encorafenib) and MAP kinase (binimetinib) inhibitors.

Summary box 77.8

Histopathological factors that influence prognosis

- Tumour stage
- Histological grade
- Degree of mucin secretin
- Presence of signet cells
- Venous invasion
- Perineural invasion
- Pushing versus infiltrative margin
- Tumour infiltrating lymphocytes
- Presence of MSI

Colorectal cancer follow-up

Since the advent of safe liver resection for metastases the outcome benefit of follow-up has been clearly demonstrated. Follow-up aims to identify synchronous bowel tumours (present in 3%) that were not identified at the time of original diagnosis. Similarly, 3% of patients will develop a metachronous (at a different time) colonic cancer. Up to a half of all patients with colorectal cancer will develop liver metastases at some point. Regular imaging of the liver (CT scan) and measurement of carcinoembryonic antigen (CEA) is designed to diagnose this early, in order to allow curative metastectomy. Optimum follow-up pathways continue to be developed. NICE guidelines recommend CT scans of the abdomen, pelvis and thorax as well as CEA measurements during the first 3 years after treatment of colon cancer with curative intent but identified no clinically important difference in colorectal cancer-specific survival with a more intensive follow-up schedule compared with a less intensive follow-up.

Palliative care

About 20% of patients present with metastatic disease and about one-fifth of these patients are suitable for potentially curative management. For the rest, quality of residual life is the main outcome but it should be borne in mind that with the combination of interventions including chemotherapy, metastectomy, cytoreductive surgery and intraperitoneal chemotherapy some colonic disease may 'convert to resectable'. For those whose disease remains incurable colonic surgery may still be offered, particularly if symptomatic. This may be non-resectional (defunctioning stoma or internal bypass) or resectional (procedures detailed earlier but with a smaller segmental resection and less aggressive lymphadenectomy). Non-surgical techniques include palliative chemotherapy, stenting for obstruction, intraluminal laser, argon plasma coagulation and radiotherapy for bleeding and pain (especially in rectal cancers).

Malignant: miscellaneous cancers

Gastrointestinal stromal tumours

Gastrointestinal stromal tumours (GISTs) are extremely rare, constituting less than 0.1% of all colorectal tumours. They appear to arise from the interstitial cells of Cajal and are mainly due to a mutation in a specific gene called *c-kit*. This allows a specific marker to be used to diagnose most tumours as well as targeted chemotherapy with imatinib. Thirty per cent are malignant with mitotic rate, Ki-67 (>10%), size (>5 cm), local invasion and cellularity the best indicators of malignant potential. Diagnosis is by CT or MRI and endoscopic biopsy. Surgical resection is the mainstay of treatment with imatinib for those tumours that are unresectable, have metastasised or recurred. Adjuvant imatinib may be used for tumours felt to be at high risk of recurrence.

Carcinoid

'Carcinoids' are well-differentiated neuroendocrine tumours of the colon and are part of a spectrum of disease with poorly differentiated neuroendocrine carcinomas at the most aggressive end of this spectrum.

They constitute around 50% of all neuroendocrine tumours of the gut and about 5% of all colonic tumours. Fewer than 10% of colonic carcinoid tumours present with carcinoid syndrome (skin erythema, diarrhoea, cardiorespiratory symptoms) owing to release of hormones. Surgery remains the only potentially curative treatment and, since the possibility of metastatic disease is directly related to the size of the primary tumour, the extent of resection should be determined accordingly. Tumours greater than 2 cm require en bloc resection of adjacent mesenteric lymph nodes. In the midgut (the area receiving its blood supply from the superior mesenteric artery) even lesions less than 1 cm have been shown to metastasise and radical resection is also indicated. Small (<1 cm) hindgut tumours (the area receiving its blood supply from the inferior mesenteric artery) can be safely locally excised (see ***Chapters 74 and 76***).

Lymphoma

Primary lymphoma of the colon is rare, accounting for less than 1% of all colonic malignancies. The caecum is the most common site of occurrence, usually with non-Hodgkin's type lymphoma (NHL). Patients present with abdominal pain, a mass, change in bowel habit, per rectal bleeding, obstruction or intussusception. These tumours may occasionally perforate. The lack of specific complaints and rarity of intestinal obstruction probably accounts for the often delayed diagnosis. CT and colonoscopy with submucosal biopsy are required for diagnosis. Treatment is combination surgery with systemic chemotherapy, although surgery alone may be considered adequate treatment for low-grade NHL disease that does not infiltrate beyond the submucosa.

Metastatic disease to colon

Metastatic disease to the colon from other primary sites constitutes about 1% of all colorectal cancers. There is often a known primary, usually lung, ovary, breast, kidney, skin, stomach or hepatobiliary system tumours. In most cases multiple lesions are seen and one-third may be asymptomatic. The most common pathway of spread is through peritoneal seeding (typical of ovarian cancer), although haematological and lymphatic dissemination is described in breast and lung cancer and melanoma. Patients may present with obstruction, per rectal bleeding (especially melanoma), anaemia and weight loss. CT and colonoscopic biopsy are required for diagnosis and treatment should be individualised to patient symptoms and prognosis.

COLITIS

There are two types of colitides: IBD (discussed in ***Chapter 75***) and non-IBD. The non-IBD causes can be grouped into infective and non-infective causes, with infective being by far the most common. The majority of non-IBD colitides present acutely with severity ranging from a self-limiting illness to severe disease necessitating emergency colectomy.

A careful history of acute onset and potential predisposing factors, including the use of antibiotics, is often key. Investigations include stool culture, serology and inflammatory markers. Supine abdominal radiographs may demonstrate bowel oedema, colonic distension or, in severe cases, gas in the bowel wall. CT may determine the extent of disease, presence of alternative pathology or resultant complications. In a deteriorating patient awaiting cultures, endoscopic biopsies may also be helpful.

Infective colitides

Infective causes may be classified as bacterial, protozoal, viral and fungal. Common infections include the following.

Escherichia coli

E. coli is a Gram-negative bacillus transmitted via the faecooral route from contaminated food or water. Symptoms vary according to strain, with the most common form – enterotoxigenic *E. coli* – causing 'traveller's' diarrhoea (diarrhoea, vomiting and colicky pain). In adults, infection is usually brief and self-limiting. A more severe form – enteroinvasive *E. coli* – causes a more systemic illness and haematochezia. A very severe form – enterohaemorrhagic *E. coli* – results in colonic oedema, ulceration and haemorrhage with the very ill requiring colectomy.

Campylobacter

Infection with *Campylobacter jejuni* (a Gram-negative rod with a distinctive spiral shape) is the most common form of gastroenteritis in resource-rich countries, typically acquired from eating infected poultry. It causes diarrhoea and abdominal pain. Severe cases may resemble ulcerative colitis. The organism

Santiago Ramon y Cajal, 1852–1934, Spanish neuroscientist, pathologist and Nobel prize winner (1906) for studies of cellular anatomy of the nervous system.
Thomas Hodgkin, 1798–1866, pathologist, Guy's Hospital, London, UK, described 'Morbid appearances of the absorbent glands and spleen' in 1832.