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PRACTICE

CLINICAL UPDATES

Management of colorectal cancer

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What you need to know

- In patients with newly diagnosed colorectal cancer, order a test for serum carcinoembryonic antigen (CEA) level and computed tomography (CT) scan of the chest, abdomen, and pelvis for disease staging
- Laparoscopic surgery is the standard of care for colon cancer, but its role in rectal cancer is debated
- Patients with colorectal cancer are at high risk of malnutrition, particularly those undergoing chemoradiotherapy for rectal cancer
- Most patients undergoing sphincter preserving surgery (ie, without permanent colostomy) experience bowel dysfunction. Urinary and sexual dysfunction is common after rectal cancer surgery
- Following surgery, review serum CEA level at least every six months for three years and order at least two CT scans of the chest, abdomen, and pelvis in the first three years to detect recurrence

Colorectal cancer represents the third most commonly diagnosed cancer and is the fourth most common cause of cancer related mortality globally.[1] The highest incidence and mortality rates are seen in high income countries.[2]

Surgical resection is the mainstay of treatment. Systemic chemotherapy and local pelvic radiotherapy are important adjuvant treatment modalities. The primary care physician plays a critical role in coordinating increasingly complex multi-modal management strategies for patients with colorectal cancer. This article provides an overview of contemporary management of colorectal cancer for general practitioners and other non-specialists.

The presentation and diagnosis of colorectal cancers have been covered recently in another article in *The BMJ*.[3]

What investigations to order before surgery?

Endoscopic biopsy followed by histology of the specimen is essential to confirm a new diagnosis of colorectal cancer. Following this, several investigations are necessary for clinical staging. These inform prognosis and guide subsequent management. Some can be arranged by the primary care physician.

Primary care physicians

UK and Australian guidelines[4 5] advise obtaining a computed tomography (CT) scan of the chest, abdomen, and pelvis to assess the extent of local invasion, regional spread, and to identify distant metastatic deposits. Table 1 describes staging of the tumour based on extent of local tumour invasion (T stage), involvement of locoregional lymph nodes (N stage), and presence of distant metastases (M stage). When referring newly diagnosed patients to a specialist colorectal surgeon, provide any available previous imaging which can be reviewed and may avoid misdiagnosis of longstanding lesions as metastases. Review the patient's full blood count, electrolytes, and renal function. In addition, request a baseline serum carcinoembryonic antigen (CEA) test against which you can compare post-treatment levels as part of disease surveillance.

Specialist investigations

Further investigations may be arranged by specialist surgeons or oncologists. Magnetic resonance imaging (MRI) of the liver may be useful when intravenous contrast is contraindicated for CT imaging, to detect metastases or to further characterise potentially resectable hepatic metastases identified on CT imaging. In addition to staging CT, high resolution pelvic MRI is the initial staging investigation of choice for patients with rectal cancer. MRI allows highly accurate local staging –that is, assessment of the extent of local invasion of the tumour, particularly its relationship to the mesorectal fascia, as well as local lymph node involvement.[6]

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How can you prepare patients for surgery?

Many aspects of the preoperative assessment begin in primary care. Consider referral for further cardiopulmonary assessment and specialist review in patients with notable comorbidities. Further preoperative optimisation is generally coordinated by a colorectal cancer preadmission or preoperative assessment clinic, however this varies across different healthcare settings.

Enhanced recovery after surgery (ERAS)

ERAS programmes (box 1) are considered the standard of care in the perioperative management of patients undergoing colorectal surgery. They aim to reduce the impact of surgery on the patient and optimise postoperative recovery using a range of perioperative interventions.

Box 1: Enhanced recovery after surgery (ERAS) programmes for colorectal cancer

Principles of ERAS include

- preoperative education and counselling
- optimising preoperative nutritional status
- anaesthetic protocols
- early enteral feeding
- prevention of postoperative ileus
- optimal postoperative analgesia
- early mobilisation[7]

Institutions vary widely in their ERAS protocols and compliance. Use of ERAS protocols in patients undergoing colorectal surgery reduced length of hospital stay (mean difference 2.44 days, 95% confidence interval −3.06 to −1.83 days, P<0.00001) and overall complications (relative risk 0.71; 95% confidence interval 0.58 to 0.86, P=0.0006), as per a meta-analysis (13 randomised controlled trials, 1910 patients).[8]

Stomal therapy

Following colorectal surgery, some patients require a temporary or permanent stoma, which can impact their quality of life.[9] Patients will likely have concerns about life with a stoma, such as returning to their normal lifestyle, stoma leakages, odour, and fear of intimacy. Common physical complications of stoma include skin excoriation, parastomal herniation, retraction, or prolapse.[10] The decision to form a stoma is complex and depends on factors relating to the tumour (site, size, and staging), treatment (radiotherapy or not), patient (older, comorbidities, patient preferences, hereditary polyposis syndromes), and whether emergency surgery is required, such as in intestinal obstruction or ischaemia. In the elective setting, a permanent colostomy is usually required in patients with low rectal tumours or those involving the anal sphincter complex. Patients with mid to low rectal tumours may require a temporary ileostomy. Reversal can be considered after three months.

Schedule a preoperative consultation on stomal therapy in elective settings. This can take place on an outpatient basis and involves examination by the stomal therapist and selection of an appropriate site for the stoma. A systematic review noted that studies evaluating preoperative stoma education were heterogeneous, but identified two interventional studies that showed improvement in stoma-specific and overall quality of life (P=0.00001 and P=0.000-0.006).[11] One small randomised controlled trial (42 patients) showed a reduction in postoperative hospital stay after preoperative stomal education (8 days *v* 10 days, P=0.029).[12] A stomal consultation is often not feasible if surgery is performed in an emergency setting outside of working hours, in which case the stoma site is selected by a senior surgeon.

Bowel preparation

Mechanical bowel preparation involves use of oral (and/or rectal) osmotic laxative solutions and a clear fluid diet for 24 hours preoperatively to empty the bowel. Preparation in this way has traditionally been used routinely before colorectal cancer resections; however, multiple randomised controlled trials and subsequent meta-analyses, including a Cochrane review published in 2004,[13] failed to show a reduction in wound infections or anastomotic leaks.[14-16] Since then mechanical bowel preparation is less favoured among surgeons, particularly for colonic resections. However, it is being revisited after several American studies have shown reduction in postoperative infections after mechanical bowel preparation with oral antibiotics.[17-19] A nationwide analysis of 8442 patients undergoing colorectal surgery showed that mechanical bowel preparation with antibiotics was independently associated with lower rates of postoperative ileus (odds ratio 0.71, 95% confidence interval 0.56 to 0.90), surgical site infection (odds ratio 0.40, 95% confidence interval 0.31 to 0.53), and anastomotic leakage (odds ratio 0.57, 95% confidence interval 0.35 to 0.94) compared with patients without mechanical bowel preparation.[19] While uncertainty exists, current UK guidelines recommend against the routine use of mechanical bowel preparation before colorectal cancer resections, but state there may be benefit in patients undergoing restorative resection for rectal cancer.[20]

Nutritional interventions

Malnutrition is common among cancer patients as a result of chemotherapy, radiotherapy, and surgery, and the metabolic effect of malignancy. Patients with colorectal cancer are at higher risk of malnutrition compared with other cancer patients.[21] The highest rates are seen in patients with rectal cancer who undergo neoadjuvant chemoradiation.[22] Although nutritional assessment and support is routinely provided before colorectal surgery, there remains a paucity of data for its effectiveness.

Preoperative carbohydrate loading is often considered in patients undergoing elective surgery for colorectal cancer. A clear, oral carbohydrate solution is given before midnight on the day before surgery and again 2-3 hours before surgery. A small randomised controlled trial (36 patients) showed this reduced length of hospital stay (7.5 *v* 13 days, P=0.019).[23]

What are the surgical options for colorectal cancer?

Figure 1 depicts the prognosis for patients with colon and rectal cancer based on stage of disease, which will influence the decision on treatment. Survival can vary based on several prognostic factors. The specialist team would typically discuss this with the patient while informing them about the possible outcomes and complications of surgery and adjuvant treatments.

Open surgery

For malignant tumours of the colon and rectum, the segment of bowel containing the tumour and its supplying vascular pedicle is excised, keeping local margins free of malignancy. Radical resection of the mesentery, which contains the supplying vascular pedicle and lymphatic drainage, achieves regional lymphadenectomy. Figure 2 shows the various colorectal

resections performed depending on the anatomical location of the tumour. A detailed description of colorectal resection techniques and their variations is beyond the scope of this article.

Laparoscopic surgery

Laparoscopic colectomy is now well established as a safe alternative to open surgery for colon cancer, albeit with a longer operating time. Laparoscopic resection led to modest improvements in short term outcomes, including a reduction in perioperative mortality (odds ratio 0.33; P=0.005), blood loss (weighted mean difference 0.11 L; P<0.00001), wound related complications (odds ratio:0.65; P=0.01), and length of hospital stay (weighted mean difference 1.7 days; P<0.00001), and more rapid return of spontaneous bowel function (weighted mean difference 23.9 hours; P<0.00001) in an earlier meta-analysis (13 randomised controlled trials, 4013 operations).[24] Concerns surrounding the oncological and survival outcomes associated with laparoscopic resection remained until long term outcomes were available from large multicentre randomised controlled trials.[25-28] A subsequent meta-analysis of 12 randomised controlled trials showed no statistically significant difference between laparoscopic and open surgery in cancer related mortality for colon cancer (1575 patients, 14.6% versus 16.4%, 95% confidence interval 0.61 to 1.06, P=0.15) or rectal cancer (578 patients, 9.2% *v* 10.0%, 95% confidence interval 0.37 to 1.19, P=0.16).[29]

Debate is ongoing about the role of laparoscopic rectal resection, both in terms of oncological safety and functional outcomes,[30] such as continence and sexual function.[31] Two recent multicentre randomised controlled trials failed to show that laparoscopic rectal resection was not inferior to open surgery in terms of successful complete excision; 82% *v* 89% (risk difference −7.0%, 95% confidence interval -12.4% to ∞, P for non-inferiority=0.38) and 81.7 *v* 86.9% (−5.3%; 95% confidence interval −10.8% to ∞; P for non-inferiority=0.41).[32 33]

What are possible complications?

Immediate

Anastomotic leakage is a major complication specific to colorectal surgery and is a major source of morbidity and mortality.[34] Risk factors include tumour factors (large, advanced, or metastatic tumours, requiring low rectal anastomosis), patient factors (preoperative radiotherapy, smoking, vascular disease, pulmonary disease, diabetes, malnutrition, corticosteroids), and operative factors (technical failure, emergency surgery, blood loss, operative time, inotropes).[34] Other immediate complications are those with any major abdominal surgery and hospitalisation, including infection (particularly of the surgical site), haemorrhage, venous thromboembolism, and inadvertent injury to other anatomical structures.

Long term

Continence and sexual dysfunction are important long term complications following colorectal surgery. Primary care physicians and other care providers can play an important role in counselling and supporting patients in the long term.

More than 80% of patients who undergo sphincter preserving resection (that is, without permanent colostomy) will experience some degree of postoperative bowel dysfunction, more recently referred to as anterior resection syndrome. This may include increased frequency, incontinence, or obstructed defecation.[35] Risk factors include neoadjuvant therapy and anatomically low tumours.[36] Patients should be informed before surgery about the possibility of postoperative bowel related problems. A systematic review (14 non-randomised studies) showed no difference in quality of life outcomes between patients with sphincter-saving surgery and permanent colostomies, however a meta-analysis was not feasible because of study heterogeneity.[37 38]

Urinary incontinence and sexual dysfunction are also important problems in patients who undergo multimodal treatment of rectal cancer. These have been less well studied than bowel related quality of life,[39-41] but both dyspareunia in women and erectile dysfunction in men should be discussed preoperatively. Pretreatment sperm banking may be an option. It is now offered in certain situations in the UK via the NHS.

What is the role of adjuvant chemotherapy in colorectal cancer treatment?

Patients with resected stage III colorectal cancer and some patients with high risk stage II colorectal cancer may benefit from adjuvant chemotherapy, as per UK and Australian guidelines. It is intended to address unresected micrometastases which may lead to recurrent disease.[4 5 42] Between 15% and 50% of patients with stage III disease experience a recurrence.[43] Adjuvant chemotherapy containing fluorouracil has been shown to reduce the relative risk of recurrence by 40% with an associated statistically significant survival benefit.[44] A combination of oxaliplatin and fluorouracil increases this benefit and is the mainstay of adjuvant chemotherapy in these patients.[45] The absolute benefits range between 10 and 20% improvement in survival in patients with stage III disease. Adjuvant chemotherapy is typically given for six months. Newer drugs and combinations are being studied which may reduce the duration of chemotherapy.

Patients with stage II colorectal cancer have a lower risk of recurrence, and the benefits of adjuvant chemotherapy are therefore comparatively modest.[43] The treatment is reserved for patients who are at high risk of recurrence such as having poor tumour differentiation, lymphovascular invasion, fewer than 12 lymph nodes retrieved on resection, locally advanced disease (T4), and bowel obstruction or perforation.[4 5 46] In practice, decisions about adjuvant chemotherapy are made on a case-by-case basis by a multidisciplinary team considering the patient's age, fitness, and accessibility to oncology services (which varies between healthcare systems) and in consultation with the patient about their preferences for treatment.

Side effects and complications of specific chemotherapy regimens must be discussed with patients during their consultation with the oncologist. Common side effects of chemotherapy include fatigue, loss of appetite, nausea and vomiting, diarrhoea, bone marrow suppression, and peripheral neuropathy.

What is the role of neoadjuvant radiotherapy in rectal cancer treatment?

Neoadjuvant (preoperative) radiotherapy is recommended for advanced (at least T3 and/or at least N1) rectal tumours in the low and mid rectum. The primary aim is to reduce the risk of local recurrence, but it may also reduce tumour size to facilitate complete excision and lead to modest improvements in survival.[47] Radiotherapy may be delivered alone ("short course" radiotherapy delivered daily for five days) or combined with 5-flurouracil, most commonly as oral capecitabine ("long course" chemoradiotherapy over five weeks). Two large multicentre randomised controlled trials comparing short and

long course radiotherapy showed no difference in local recurrence (9.0% *v* 14.2%, P=0.170 and 7.5% *v* 4.4%, P=0.24) or overall survival (67.2% *v* 66.2% at 4 years, P=0.960 and 74% *v* 70% at 5 years, P=0.62).[48 49] Current UK, Australian, and European guidelines state either course is acceptable unless the tumour is T4 or there is concern about mesorectal fascial involvement, in which case long course chemoradiotherapy is recommended followed by surgery at 8-12 weeks to maximise reduction in tumour size.[4 5 42 50]

Inform patients of possible side effects, such as perianal skin excoriation, proctitis, incontinence, cystitis, and sexual dysfunction.

How should patients with colorectal cancer be followed up after surgery?

Most recurrent colorectal cancer will develop within two years of surgical resection. The median time from resection to recurrence is between 16 and 22 months.[51] Maintain a high index of suspicion in this period. Note any changes in bowel habit, weight loss, abdominal pain, or a palpable mass. Discuss with the treating surgeon and oncologist to arrange prompt imaging and/or endoscopic evaluation.

Current guidelines from the National Institute for Health and Care Excellence (NICE) recommend testing serum CEA level every six months and undertaking at least two CT scans of the chest, abdomen, and pelvis in the first three years after surgery.[4] A rising serum CEA level should raise suspicion of recurrence. A surveillance colonoscopy is offered one year after surgery.

How is metastatic and recurrent disease managed?

There are survival advantages associated with further surgery in patients with locally recurrent rectal cancer, limited liver and lung metastases, as well as small volume peritoneal disease. Refer these patients to centres with expertise in managing advanced and recurrent colorectal cancer.[3] A wide range of increasingly effective oncological interventions is available through specialist centres (which is beyond the scope of this article). However, most patients with advanced or metastatic colorectal cancer are not curable. Care for these patients requires coordination between the general practitioner, surgeon, oncologist, and palliative care physicians, with the individual patient's priorities in mind.

Box 2: Questions for future research

- What is the role of robotic surgery in the treatment of colorectal cancer?
- Can some patients with rectal cancer be treated curatively with chemoradiotherapy alone?
- In which patients can minimally invasive techniques be used?

Box 3: Additional educational resources

- Association of Coloproctology of Great Britain & Ireland guidelines for the management of cancer of the colon, rectum and anus: https://www.acpgbi.org.uk/resources/guidelines-management-cancer-colon-rectum-anus-2017/
- National Institute for Health and Care Excellence. Colorectal cancer: diagnosis and management (clinical guideline CG131). 2011. https://www.nice.org.uk/guidance/cg131
- American Joint Committee on Cancer. Colon and rectum cancer staging 7th Edition. https://cancerstaging.org/references-tools/quickreferences/documents/colonmedium.pdf

Box 4: Sources and selection criteria

We searched PubMed and Cochrane Database of Systematic Reviews databases using combinations of search terms relating to colorectal cancer (colon, rectum, colorectal, neoplasia, carcinoma, tumour, metastasis, malignancy), its treatment modalities (chemotherapy, radiotherapy, colorectal surgery, laparoscopic surgery, colectomy, anterior resection, enhanced recovery, stomal therapy), and outcomes (survival, recurrence, quality of life, sexual function, continence). Reference lists of identified manuscripts and recent review articles were also reviewed. We also reviewed articles in the authors' personal libraries. We considered clinical guidelines by the Australian National Health and Medical Research Council, National Institute for Health and Care Excellence, and Association of Coloproctology of Great Britain & Ireland for key practice recommendations

Education into practice

- How would you discuss bowel, bladder, and sexual function with patients who have had colorectal surgery for cancer?
- How often do you review your patients' stomas for skin excoriation, herniation, retraction, or prolapse?
- How many of your patients with colorectal cancer are at risk of malnutrition?

How patients were involved in the creation of this article

A patient kindly reviewed this article for *The BMJ*. He requested additional information on ERAS protocols and what this means for the patient. He also suggested providing information about the side effects of chemotherapy and radiotherapy. This information was subsequently included in the article. We thank the patient reviewer for their input.

Contributorship statements Kilian Brown—concept design and planning, literature search and reference identification, drafting manuscript, final approval. Michael Solomon—concept design and planning, reference identification, critical revision of manuscript, final approval. Sarah O'Shannassy—concept design and planning, reference identification, drafting manuscript, final approval. Kate Mahon—concept design and planning, reference identification, critical revision of manuscript, final approval. Guarantor: Michael Solomon.

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Table

Table 1| Colorectal cancer staging according to the American Joint Committee on Cancer (AJCC) (adapted from the American Cancer Society)

AJCC Stage	Stage grouping	Stage description
0	Tis N0 M0	The cancer is in its earliest stage, known as carcinoma in situ or intramucosal carcinoma (Tis). It has not grown beyond the inner layer (mucosa) of the colon or rectum
I	T1 or T2 N0 M0	The cancer has grown through the muscularis mucosa into the submucosa (T1), and it may also have grown into the muscularis propria (T2). It has not spread to nearby lymph nodes (N0) or to distant sites (M0)
IIA	T3 N0 M0	The cancer has grown into the outermost layers of the colon or rectum but has not gone through them (T3). It has not reached nearby organs. It has not spread to nearby lymph nodes (N0) or to distant sites (M0)
IIB	T4a N0 M0	The cancer has grown through the wall of the colon or rectum but has not grown into other nearby tissues or organs (T4a). It has not yet spread to nearby lymph nodes (N0) or to distant sites (M0)
IIC	T4b N0 M0	The cancer has grown through the wall of the colon or rectum and is attached to or has grown into other nearby tissues or organs (T4b). It has not yet spread to nearby lymph nodes (N0) or to distant sites (M0)
IIIA	T1 or T2 N1/N1c M0	The cancer has grown through the mucosa into the submucosa (T1), and it may also have grown into the muscularis propria (T2). It has spread to 1 to 3 nearby lymph nodes (N1) or into areas of fat near the lymph nodes but not the nodes themselves (N1c). It has not spread to distant sites (M0).
	T1 N2a M0	The cancer has grown through the mucosa into the submucosa (T1). It has spread to 4 to 6 nearby lymph nodes (N2a). It has not spread to distant sites (M0)
IIIB	T3 or T4a N1/N1c M0	The cancer has grown into the outermost layers of the colon or rectum (T3) or through the visceral peritoneum (T4a) but has not reached nearby organs. It has spread to 1 to 3 nearby lymph nodes (N1a or N1b) or into areas of fat near the lymph nodes but not the nodes themselves (N1c). It has not spread to distant sites (M0)
	T2 or T3 N2a M0	The cancer has grown into the muscularis propria (T2) or into the outermost layers of the colon or rectum (T3). It has spread to 4 to 6 nearby lymph nodes (N2a). It has not spread to distant sites (M0).
	T1 or T2 N2b M0	The cancer has grown through the mucosa into the submucosa (T1), and it may also have grown into the muscularis propria (T2). It has spread to 7 or more nearby lymph nodes (N2b). It has not spread to distant sites (M0)
IIIC	T4a N2a M0	The cancer has grown through the wall of the colon or rectum (including the visceral peritoneum) but has not reached nearby organs (T4a). It has spread to 4 to 6 nearby lymph nodes (N2a). It has not spread to distant sites (M0)
	T3 or T4a N2b M0	The cancer has grown into the outermost layers of the colon or rectum (T3) or through the visceral peritoneum (T4a) but has not reached nearby organs. It has spread to 7 or more nearby lymph nodes (N2b). It has not spread to distant sites (M0)
	T4b N1 or N2 M0	The cancer has grown through the wall of the colon or rectum and is attached to or has grown into other nearby tissues or organs (T4b). It has spread to at least one nearby lymph node or into areas of fat near the lymph nodes (N1 or N2). It has not spread to distant sites (M0)
IVA	Any T Any N M1a	The cancer may or may not have grown through the wall of the colon or rectum (Any T). It might or might not have spread to nearby lymph nodes (Any N). It has spread to 1 distant organ (such as the liver or lung) or distant set of lymph nodes, but not to distant parts of the peritoneum (the lining of the abdominal cavity) (M1a)
IVB	Any T Any N M1b	The cancer might or might not have grown through the wall of the colon or rectum (Any T). It might or might not have spread to nearby lymph nodes (Any N). It has spread to more than 1 distant organ (such as the liver or lung) or distant set of lymph nodes, but not to distant parts of the peritoneum (the lining of the abdominal cavity) (M1b)
IVC	Any T Any N M1c	The cancer might or might not have grown through the wall of the colon or rectum (Any T). It might or might not have spread to nearby lymph nodes (Any N). It has spread to distant parts of the peritoneum (the lining of the abdominal cavity), and may or may not have spread to distant organs or lymph nodes (M1c)

Figures

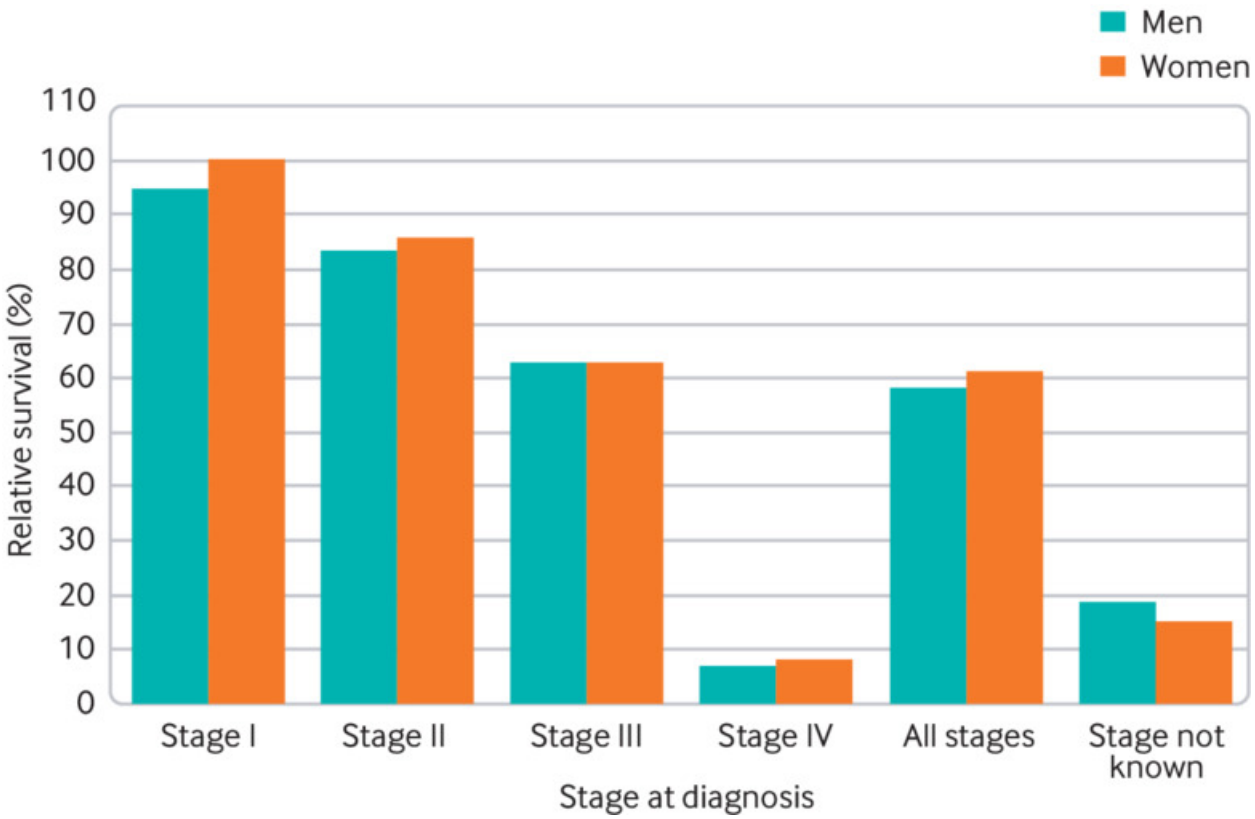

Fig 1 Five year relative survival by stage for patients with colon and rectal cancer (adapted from Cancer Research UK)

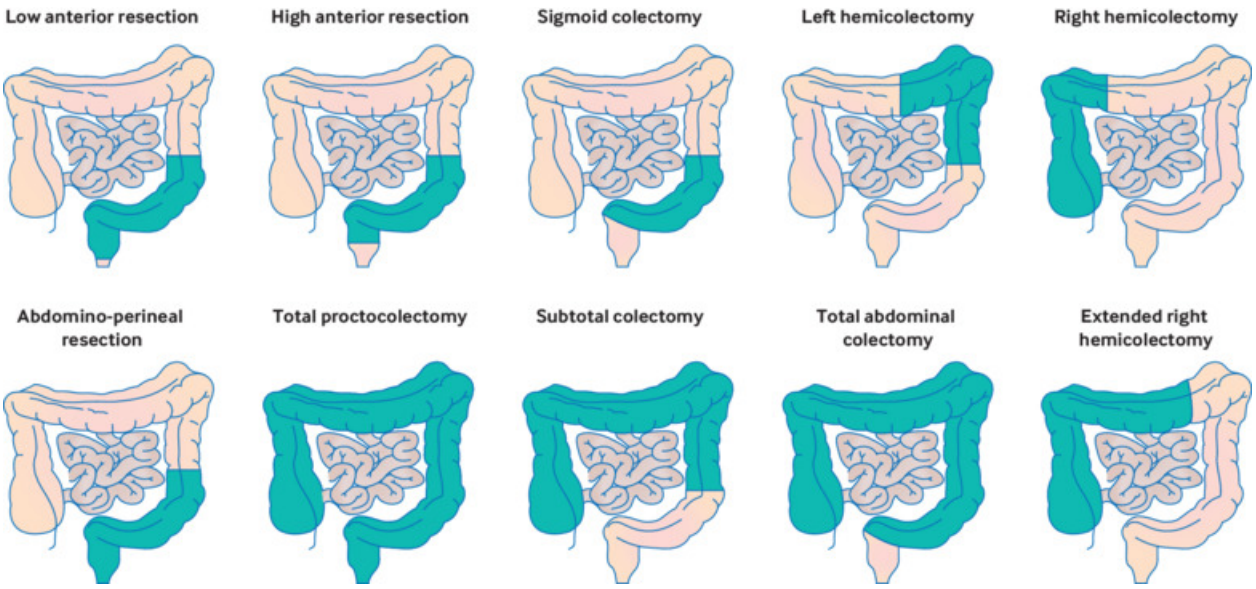

Fig 2 Diagram showing different colon and rectal resections performed depending on tumour location (Illustration by Scott Holmes, CMI, printed with permission from Baylor College of Medicine, https://www.bcm.edu/healthcare/care-centers/general-surgery/procedures/colon-resection)