The Management of Colorectal Cancer

5

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Learning Outcomes

- Consider the implications that a diagnosis of colorectal cancer may have for a person with an existing stoma. What support might they require?
- Try to identify specific points on the colorectal cancer pathway where intervention from a clinical nurse specialist may be needed.
- For a patient with advanced or metastatic colorectal cancer, many different specialities may be involved in their care. Can you identify some of them?

Introduction

Colorectal cancer refers to a malignancy that occurs in the colon or rectum. It is the fourth most common cancer in the UK accounting for around 43,000 cases per year, with incidence highest in people over the age of 50 [1, 2]. When diagnosed at the earliest stage, colorectal cancer can be successfully treated, with 92% of people surviving longer than 5 years [2]. However, symptoms often do not occur until an advanced stage. As a result, approximately 20% of patients diagnosed present with metastatic disease [3, 4]. Surgical resection remains the definitive treatment, providing the best possibility of a cure [3]. Depending upon the site of disease, this may involve stoma formation (see Chap. 6). A combination of interventions is often required in the management of colorectal cancer over time [5]. Support from a Clinical Nurse Specialist (CNS) is crucial for patients navigating complex pathways involving multiple specialities over extended periods [6, 7].

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Therefore knowledge surrounding the decision-making process involved in planning care and regarding available therapies and side effects is necessary for the CNS to provide accurate information and effective counselling to patients and families [5].

Development of Colorectal Cancer

The majority of colorectal cancers are adenocarcinomas which develop from normal bowel epithelium to adenomas or polyps through a process known as the adenoma—carcinoma sequence. [8, 9]. This is driven by gene mutations prompting changes within the adenoma from low grade dysplasia to high grade dysplasia and finally adenocarcinoma. [9]. See Fig. 5.1.

Adenocarcinoma can be further graded as well differentiated, moderately differentiated, and poorly differentiated, with poorly differentiated having the worst prognosis [11, 12].

The development of colorectal cancer can be classified as sporadic (occurring due to incidental mutations in cells in the bowel wall over time) or occur because of a genetic predisposition to develop a malignancy [13, 14]. Mismatch Repair genes (MMR) are responsible for correcting errors that have occurred during the DNA replication process [15]. Mutations in these genes can result in Microsatellite Instability (MSI) or an increased propensity for mutations to arise [15, 16]. Cancers where MMR genes are unaffected are referred to as proficient mismatch repair (pMMR) and as deficient mismatch repair (dMMR) where MMR genes are affected [17].

MSI is found in 10 to 15% of sporadic cancers [18]. This is commonly due to epigenetic changes in the MLH1 MMR repair gene [13]. However, in 2 to 3% of MSI tumours, germline mutations in MMR genes—MLH1, MSH2, MSH6 or PMS2 are responsible. This is the case with inherited conditions such as Lynch Syndrome,

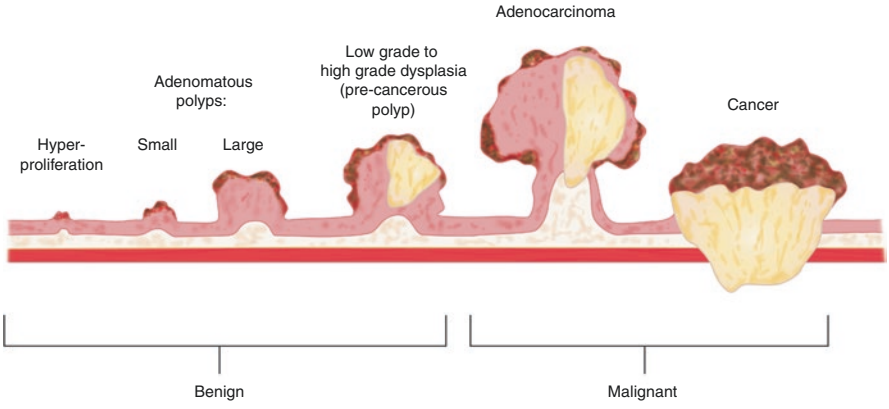

Fig. 5.1 Cancer progression from a polyp (copyright UHB NHS FT) [10]

increasing the likelihood of developing a colorectal cancer [13]. MSI high tumours are associated with a better prognosis than microsatellite stable tumours [19].

Mutations in the RAS and BRAF V600E genes in adenocarcinoma can also be predictive as to whether there will be a potential response to certain anti-cancer treatments. BRAF (V600E) mutation in metastatic disease is an overall poor prognostic factor [20]. NICE guidelines [21] recommend that all people with metastatic colorectal cancer be tested for RAS/BRAF mutations.

Testing on the molecular make-up of a tumour can now identify specific mutations which can provide prognostic information, guide treatment pathways, and suggest whether genetic screening of family members is advisable [21]. When looking at the histopathology of colorectal cancer multiple markers can be identified to individualise treatment [11].

Risk Factors

There is a strong association with colorectal cancer and age, with a steep rise in incidence over the age of 50 [1, 3]. Evidence that environmental factors such as smoking, high alcohol intake, a diet with limited fruit and vegetables and rich in processed foods, a sedentary lifestyle and obesity are all associated with colorectal cancer is well established [22, 23].

Pre-existing conditions can increase the probability of a cancer diagnosis. People who have a history of Crohn's disease or Ulcerative Colitis are known to be at a higher risk of developing colorectal cancer at a younger age and more advanced stage than on average [24, 25].

Another risk factor is a strong family history of colorectal cancer. People with three first degree relatives (e.g. parent, sibling or child) with colorectal cancer over one generation are categorised as high risk, and as moderate risk if they have either one first degree relative under the age of 50 or two first degree relatives of any age [26]. Recommendations are that people in the high-risk category have a colonoscopy every 5 years from the age of 40, and those in the moderate category have a colonoscopy at age 55 [26].

Certain inherited conditions can also greatly increase the incidence of a colorectal cancer diagnosis:

Lynch Syndrome (previously known as Hereditary Non-Polyposis Colorectal Cancer—HNPCC) is an inherited condition resulting from a germline mutation to one of four MMR genes and is responsible for approximately 3% of colorectal cancers [27, 28]. People diagnosed with Lynch syndrome have a 50 to 70% lifetime risk of developing colorectal cancer and are more likely to develop this at a young age, with an associated increased risk of developing other cancers [27, 29]. Colorectal cancers should now be routinely tested using PCR (polymerase chain reaction) or immunohistochemistry to identify MSI status or dMMR [26, 29]. Subsequent testing to confirm Lynch Syndrome can then take place and allow for regular surveillance for the individual and screening of their relatives [29]. The development of a cancer can be rapidly progressing in Lynch Syndrome as it does not always follow

the usual polypoidal pathway of colorectal cancer and can arise from seemingly normal bowel mucosa [27, 28]. Surveillance with colonoscopy is therefore recommended at two yearly intervals from the age of 25 or 35 depending on which MMR genes are affected [26]. Taking aspirin daily has also been found to reduce the risk of developing colorectal cancer in this group and is recommended by NICE [30]. When colorectal cancer does occur on a background of confirmed Lynch Syndrome, it should be considered that the chance of developing a further cancer is high, and therefore patients should be counselled regarding the risks and benefits of segmental resection vs sub-total colectomy [26, 27]. NHS England recommend that all Trusts nominate a surveillance lead for Lynch Syndrome to coordinate the pathway [31].

Familial Adenomatous Polyposis (FAP) is an inherited condition resulting in the development of numerous colorectal adenomas due to mutation in the APC (adenomatous polyposis coli tumour suppressor) gene [28]. If left untreated, development of colorectal cancer is inevitable [16, 27]. Testing of at-risk family members is recommended from age 12 with surveillance colonoscopy repeated every 1 to 3 years [26]. Prophylactic colonic resection is necessary to prevent the development of colorectal cancer. The timing of surgery will depend on colonoscopy findings. Surgical options include subtotal colectomy (STC) with ileo-rectal anastomosis or STC with an ileostomy. Further surgery with formation of an ileo-anal pouch may also be considered [26, 27]. Where the rectum is spared or an ileo-anal pouch formed, continued surveillance will be required [26, 27]. Preoperative counselling will be necessary to ensure that the patient is aware of the implications of the surgical procedures available to them (see Chaps. 6 and 11).

Referral Pathways

Early detection of colorectal cancer increases the potential for survival and cure [2, 21]. Routine screening programmes are well established in the UK and aim to identify disease in people who may not be exhibiting any symptoms. Currently, adults aged between 60 and 74 in England are offered a Faecal Immunochemical Test (FIT) every 2 years by the NHS Bowel Cancer Screening programme, with the aim to extend this to all adults over the age of 50 from 2021 [32]. Provision of screening varies across other countries in the UK. FIT can detect the presence of blood in the stool, and a positive test in people who are otherwise asymptomatic prompts a referral for endoscopy to exclude malignancy [5, 33].

There are some common symptoms associated with colorectal cancer—see Table 5.1 [5, 34]. Presentation in primary care with red flag symptoms should prompt an urgent "two week wait referral" for investigations [34]. A sigmoidoscopy or colonoscopy is then arranged, or a CT scan if there are concerns regarding fitness

Table 5.1 Red flag symptoms

Change in bowel habit
PR bleeding
Abdominal pain/bloating
Unintentional weight loss
Unexplained iron deficiency anaemia
Rectal/abdominal mass
Tenesmus

for endoscopy and bowel preparation (e.g., in cases of frailty or renal impairment) [5]. Should a likely malignancy be identified at endoscopy, biopsies will be obtained, and further investigations arranged in the form of a CT scan to look for distant metastases, and in the case of rectal cancer, an MRI to provide accurate radiological staging [9, 27]. A blood test for CEA levels, a tumour marker associated with colorectal cancer, may also be done at this stage [5]. All patients with a diagnosis of colorectal cancer will have their management plan discussed at a Multidisciplinary Team meeting (MDT) with core members including surgeons, radiologists, histopathologists, clinical and medical oncologists and Clinical Nurse Specialists, to formulate an individualised treatment plan based on the results of their biopsies, imaging, and overall health [9, 27]. In advanced disease, bowel obstruction may be the presenting complaint, potentially requiring emergency surgery [35]. However, post operatively, discussion will still take place at the MDT to decide on appropriate future management.

Further investigations may be recommended by the MDT before commencing treatment (e.g., MRI liver where liver metastases are identified on CT scan, or PET scan to further characterise features indeterminate on other imaging which are suspicious for metastasis) [36, 37].

The UK government has targets in place for Trusts to achieve when investigating and treating colorectal cancer. These are currently 28 days from referral to diagnosis, 31 days from agreement to treatment plan to starting treatment and 62 days from referral to starting treatment [32, 38, 39].

Staging of Colorectal Cancer

Colorectal cancer is staged using the TNM classification system, with T referring to tumour invasion through the bowel wall, N to lymph node involvement and M to distant metastasis (see Figs. 5.2 and 5.3). Staging can be radiological or histopathological following surgical resection.

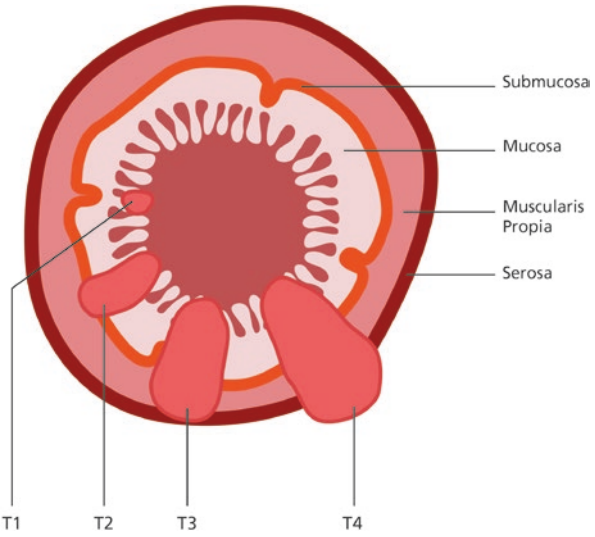

Fig. 5.2 Tumour invasion through the layers of the bowel (permission from UHB NHS Trust) see [40] for further information

STAGE	DESCRIPTION
TX	No tumour detectable
T0	No evidence of primary tumour
TIS	Tumour in situ, intramucosal carcinoma
T1	Tumour invades submucosa (through muscularis mucosa but not into muscularis propria
T2	Tumour invades muscularis propria
T3	Tumour invades through muscularis propria into pericolorectal tissues
T4A	Tumour invades through the visceral peritoneum
T4B	Tumour directly invades or adheres to other adjacant organs/structures

STAGE	DESCRIPTION
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1A	Metastasis in 1 regional lymph node
N1B	Metastasis in 2-3 regional lymph nodes
N1C	No regional lymph nodes but tumour deposits present
N2A	Metastasis in 4 to 6 regional lymph nodes
N2B	Metastasis in 7 or more regional lymph nodes

STAGE	DESCRIPTION
M0	No distant metastasis
M1A	Metastasis confined to one organ or site
M1B	Metastasis confined to 2 or more sites
M1C	Peritoneal metastasis alone or in combination with other sites

Fig. 5.3 T,N,M descriptors, unpublished table provided by author (see [40, 41] for further information)

In addition, evidence of blood vessel or extramural vascular invasion (EMVI), lymphovascular invasion and perineural invasion will be identified in the histology report. The surgical resection margin will be staged as R0 where there is a clear margin or R1/R2 where residual neoplastic tissue remains [9, 41, 42]. A prefix of p to TNM staging denotes pathological staging, and y identifies where preoperative chemotherapy or radiotherapy has been given [9, 41].

Treatments

Treatment for colorectal cancer depends on multiple factors including the site, stage, and molecular make-up of the cancer [4]. Pre-existing comorbidities and the overall health and fitness of the patient will be considered to assess the potential to tolerate interventions. This is commonly summarised using the WHO/ECOG Performance Status criteria (see Fig. 5.4).

Surgical procedures are discussed in Chap. 6. In this section, treatments that can be given in addition to surgery will be explored, either in a pre-operative (neoadjuvant), post-operative (adjuvant), or palliative setting. This is not an exhaustive list, and only options currently accessible through the NHS will be discussed.

Grade	Performance Status
0	Able to carry on all pre-disease performance without restriction, functions unlimited
1	Some limitations as restricted in physical strength but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all selfcare but limited ability to work; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of the time
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair; fully dependent
5	Dead

Fig. 5.4 Performance status descriptors—unpublished table provided by author based on WHO criteria (see [43] for further information)

Chemotherapy Agents

Fluorouracil forms the basis of systemic treatment for colorectal cancer and can be given as an infusion with folinic acid (5FU) or in tablet form as Capecitabine [44]. 5FU is given weekly via a cannula or via a PICC line in 2 weekly cycles. Capecitabine is given in 3 weekly cycles [45, 46]. The combination of other chemotherapy agents with Fluorouracil has been demonstrated to provide a potentially significant treatment benefit [14, 47].

Oxaliplatin is given as an infusion and can be combined with 5FU or Capecitabine (Folfox/Xelox) [14].

Irinotecan is also given as an infusion and can be combined with 5FU or Capecitabine to form Folfiri or Xeliri [48].

In some situations, all three chemotherapy agents will be given as a combination called Folfoxiri. This can provide a significant increase in response to treatment but also significantly increases the associated side effects, therefore a good performance status will be required. [14, 42, 49].

Lonsurf (trifluridine/tipiracil) is a tablet chemotherapy given in monthly cycles. It is only used in the palliative setting [50].

Chemotherapy affects both healthy and cancer cells, however healthy cells can regenerate after exposure while cancer cells cannot [51]. Cells with a high growth rate are more chemotherapy sensitive, therefore common side effects of chemotherapy involve the bone marrow with associated immunosuppression, damage to hair follicles causing hair loss and the GI tract resulting in mucositis, nausea, vomiting and bowel complications [51, 52]. Potential toxicity varies with each particular agent, e.g., hair loss is a common side effect of Irinotecan, but there may only be hair thinning or no hair loss at all with other chemotherapy agents given for colorectal cancer. In addition to general side effects there are side effects specific to chemotherapy drugs.

Dihydropyrimidine dehydrogenase (DPD) is an enzyme that breaks down Fluorouracil chemotherapy. A DPD deficiency can lead to severe toxicity, therefore a blood test will be taken prior to commencing 5FU/Capecitabine chemotherapy and if DPD deficiency is detected, doses will be adjusted accordingly [53].

Considerations for Ostomates

Common side effects of chemotherapy drugs given in colorectal cancer are diarrhoea or constipation. Capecitabine and Irinotecan, in particular, can cause severe diarrhoea. The combination of Capecitabine and Irinotecan, therefore, has the potential for severe toxicity [48]. People with an ileostomy are already at an increased risk of dehydration and Acute kidney Injury (AKI) [54]. Severe diarrhoea may result in hospitalisation, treatment delays, dose reductions or, in some cases, affect the ability to continue with treatment [55] (See Chap. 12 for management). Similarly, patients with a colostomy may experience diarrhoea necessitating change from their usual closed product to a drainable appliance to avoid multiple pouch changes [56, 57]. Constipation

in colostomates may be exacerbated by medication used to manage side effects of treatment or opioid analgesia and require management with dietary modifications and laxatives [35, 56].

A side effect specific to oxaliplatin is neurotoxicity, resulting in peripheral neuropathy to the hands and feet. This builds over time and can resolve after chemotherapy finishes but may be permanent [47]. When severe, fine motor skills can be affected, impacting on the patient's ability to fasten buttons, or hold a pen, and potentially to manage stoma care independently [35, 57]. Oxaliplatin may be avoided in patients who already have some pre-existing neuropathy, or used and side effects closely monitored [14].

Palmar-plantar erythrodysaesthesia (PPE) or hand-foot syndrome is a common side effect of fluorouracil-based chemotherapy causing soreness to hands and feet. When severe this may also affect dexterity [35].

EGFR Inhibitors

Epidermal growth factor receptor (EGFR) inhibitors or monoclonal antibodies are targeted therapies utilised in conjunction with chemotherapy agents. Cetuximab and Panitumumab are EGFR inhibitors currently in use for colorectal cancer treatment [58]. EGFR is a cell protein which promotes cell growth. EGFR inhibitors work by targeting and blocking EGFR, inhibiting growth of cancer cells [59]. Evidence has shown that tumours in the right side of the colon or that have mutations in the RAS/BRAF gene exhibit a poor response to EGFR inhibitors [58]. Therefore, only patients with left sided tumours who are RAS/BRAF wild type have the potential to benefit from this treatment [12, 60]. EGFR inhibitors have not been found to add benefit in the adjuvant setting and as a result they are only recommended for use in metastatic disease, either as a neoadjuvant or palliative treatment [61].

Considerations for Ostomates

Side effects of EGFR inhibitors include diarrhoea, hypomagnesemia and skin rashes [62, 63]. The severity of diarrhoea as a side effect of EGFR inhibitors is exacerbated when given in combination with chemotherapy [63]. Close monitoring is therefore required when used for patients with an ileostomy, due to their inherent risk of dehydration and low magnesium levels with a high output from their stoma (see Chap. 12).

Common skin complications include dry and itchy skin and a papulopustular rash most commonly on the face, but which can extend to the torso and abdomen. Management is with antibiotics and regular moisturising of the skin, however there are additional implications for ostomates when skin integrity is affected with the potential to affect pouch adhesion [57].

Radiotherapy

Radiotherapy is given for the treatment of rectal cancer. Each dose of radiotherapy is described as a fraction and the amount administered is measured in units known as Grays (Gy) targeted at a specific area [3, 64]. A planning CT scan takes place before treatment to ensure that the radiotherapy damages as little surrounding healthy tissue as possible [64].

Short term side effects from radiotherapy for rectal cancer include erythema or desquamation of the skin in the local area, cystitis, diarrhoea or constipation, fatigue, and pain [65, 66]. Symptoms are cumulative and may worsen after treatment has finished before they improve [66, 67]. Advice regarding skin care and appropriate wound dressings are provided by the radiotherapy department [65]. Long term side effects may include a permanent change in bowel and bladder function, rectal or stomal bleeding and haematuria, cosmetic changes in the treatment area, delayed wound healing to exposed tissue, pelvic bone thinning, lymphoedema, erectile dysfunction and vaginal stenosis [27, 65]. Pelvic radiotherapy causes infertility in both men and women. In women early menopause can be initiated [68]. Pre-treatment counselling regarding sexual dysfunction and fertility including referral for sperm/egg storage for those who have not completed their families is essential [69, 70, 71].

Considerations for Ostomates

Radiotherapy has potential temporary and long-term side effects with specific implications for ostomates. Stoma formation can have a profound impact on body image and sexuality (see Chap. 16). Side effects from radiotherapy such as erectile dysfunction and vaginal stenosis can compound these issues [72]. Awareness of the possibility of bleeding from the stoma or changes to bowel function can help with symptom management and reduce anxiety. Delayed wound healing is of particular importance for patients who have undergone pre-operative radiotherapy followed by APR surgery, as dehiscence of the perineal wound may occur and therefore requires close monitoring [27].

Neoadjuvant Treatment

Neoadjuvant treatment refers to treatment given prior to surgery, and in colorectal cancer varies depending on the site of the cancer and the stage of the disease [73].

Patients with advanced cancers may present with intermittent obstructing symptoms that, combined with the side effects of chemotherapy or chemoradiotherapy, can cause acute illness, affecting the ability to tolerate treatment. It may be necessary to consider a defunctioning stoma as part of neoadjuvant therapy to prevent complications and subsequent disruption to treatment [27, 74].

Rectal Cancer

Neoadjuvant treatment for rectal cancer is given either to downstage the tumour to give the best chance of attaining clear surgical resection margins or to reduce the risk of local recurrence [27, 73]. Treatment varies according to the staging of the disease and follows evidence- based recommendations made by NICE and the Association of Coloproctology of Great Britain and Ireland (ACPGBI). It can comprise of radiotherapy alone, or a combination of radiotherapy and chemotherapy.

Short course radiotherapy—recommended for rectal cancers with radiological high-risk features for local recurrence (e.g., stage T3c, mesorectal lymph node involvement or EMVI). Short course radiotherapy is administered as 5 fractions over 5 days. This is usually followed by surgery the following week. It is also an alternative in people who need, but cannot tolerate, long course chemoradiotherapy. In this scenario, the surgery is usually delayed by 6–12 weeks post radiotherapy. [27, 73].

Long course chemoradiotherapy—this is recommended for rectal cancers threatening or involving the mesorectal fascia to downstage the tumour and optimise the chance of a clear surgical resection margin. It is administered as 25 fractions of radiotherapy given over a 5-week period [27]. Chemotherapy is given throughout the treatment to increase the effectiveness of the radiotherapy [5]. This is given as a low dose capecitabine, taken daily, or intravenous 5-FU given in week 1 and 5 of the radiotherapy. Restaging CT and MRI scans should take place prior to surgery to assess response [73]. Surgery should be scheduled 8 to 12 weeks after completion of chemoradiotherapy [27].

RAPIDO Trial—this trial has demonstrated that rather than pre-operative long course chemoradiotherapy with or without adjuvant chemotherapy post-operatively, patients may benefit more from short course radiotherapy followed by neo-adjuvant chemotherapy [75]. This would be either 6 cycles of CAPOX or 9 cycles of FOLFOX (in total 18 weeks of chemotherapy). Surgery takes place after completion of neo-adjuvant chemotherapy with no adjuvant chemotherapy then required. This schedule has shown an increase in pathological complete response and decrease in development of distant metastases when compared to long course chemoradiotherapy with or without adjuvant chemotherapy post-operatively [75]. Suitability for this treatment depends on comorbidities and performance status.

Advanced Colorectal Cancer

Advanced colorectal cancers with lymphadenopathy or metastatic disease, downstaging chemotherapy is often given to control the cancer and reduce the disease volume, allowing the best chance of surgical resection [4, 6]. Treatment will usually involve combination chemotherapy with either Folfox/Capox or Folfoxiri depending on performance status [14, 42]. An EGFR inhibitor can be added if indicated by RAS testing [6]. Downstaging chemotherapy is usually given in 3-month treatment blocks followed by a restaging scan to assess response Should further downstaging be required then another treatment block may be recommended by MDT [4].

The FOxTROT randomised control trial concerned patients with resectable T3/T4 disease and compared the standard treatment of 24 weeks of adjuvant chemotherapy with 6 weeks of neo adjuvant Folfox chemotherapy followed by 18 weeks of adjuvant Folfox chemotherapy [76]. This was well tolerated, demonstrated histological regression, and resulted in a halving of incomplete resections [76]. The FOxTROT study is ongoing but based on initial findings NICE guidelines recommend that consideration is given to preoperative chemotherapy for patients with resectable T4 colonic cancer [21].

Adjuvant Treatment

The aim of adjuvant treatment is to reduce the risk of cancer recurrence, and in colorectal cancer is given after surgery as chemotherapy to treat microscopic disease [77]. The potential benefit from adjuvant treatment will depend on the histological staging post operatively. Poor prognostic features for cancer recurrence include pT4 tumour or tumour perforation, extramural vascular invasion, poor differentiation, involved resection margin, perineural invasion and poor lymph node harvest [9]. Evidence has shown that patients with dMMR and a low-grade cancer do not benefit from adjuvant treatment and therefore they would not be offered chemotherapy [28].

The recommendation about whether to refer for adjuvant treatment is made at the MDT, however that does not always guarantee that treatment will occur. Decisions about treatment are made on risk vs benefit ratio with potential benefits sometimes being statistically very low [78]. For patients with multiple comorbidities or the elderly, chemotherapy side effects can present a significant risk. Treatment is typically combination of 5FU/Capecitabine and oxaliplatin (Folfox or Capox) [21]. The potential long term neuropathic side effects and increased toxicity in those aged over 70 from oxaliplatin is well established [21, 78]. Except for patients with very high-risk features, reduction of the length of treatment from 6 to 3 months has been recommended by NICE [21] to help to mediate this risk. In those who are deemed too high risk for combination chemotherapy, single agent capecitabine may be offered. Decisions about adjuvant treatment are made following assessment of the individual and through detailed discussions regarding the risks and benefits of treatment [79].

Treatment for Metastatic Disease

Metastatic disease may be evident on presentation or develop over time as cancer recurrence [4, 80]. The most common sites of metastasis are the lymph nodes, liver and lung [6, 8]. Median survival without treatment is 6 months and traditionally patients diagnosed with metastatic colorectal cancer were deemed to have incurable disease [14]. However clinicians now have access to a combination of treatments that can prolong survival substantially with people remaining disease free for long periods [5, 6].

Surgery for Metastatic Disease

The potential for surgical resection in metastatic disease is multifactorial and the expertise of several MDTs will be required to plan care [42]. Surgical resection of metastases takes place at specialist centres, often requiring communication between Trusts [6]. Suitability for resection, site and number of metastatic deposits, the performance status of the patient and the speed of disease progression are all factors that will be considered, and neoadjuvant treatment may be required [4]. If resection is possible, combined surgical procedures may be offered (e.g., colonic and liver resection) however, where this is deemed too high risk, then separate major surgeries will be necessary [3, 6]. Radio frequency ablation (RFA) may be used to treat isolated deposits in the liver or lungs where surgery is not possible, or used in conjunction with surgical resection [3, 81].

Cytoreductive Surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

CRS and HIPEC can be used in some instances for the treatment of colorectal cancer which has spread to the peritoneum. There is a poor prognosis associated with colorectal peritoneal metastasis, with survival of less than 12 months without treatment, increasing to a median survival of 16 months with systemic treatment [82]. CRS and HIPEC offer 5-year survival rates of up to 52% [83]. Surgery involves stripping of the peritoneum, resection of affected organs and insertion of heated chemotherapy into the intraabdominal cavity, treating both macroscopic and microscopic disease simultaneously [84]. This intervention is a major undertaking and suitability will depend on performance status and the extent of the metastatic disease [84]. Patients will be referred to a specialist centre for MDT assessment for consideration. If surgical resection is not possible due to the volume of disease, then systemic treatment will be considered.

Immunotherapy

Immunotherapy treatments work by activating the body's immune system to attack cancer [85]. These have been shown to be very effective in other cancer sites such as melanoma and lung cancer [86]. However, in colorectal cancer, evidence has not demonstrated any significant benefit in pMMR/Microsatellite stable tumours, showing response only in dMMR/MSI high disease, which is in the minority [85]. Pembrolizumab is approved for first line treatment for metastatic colon cancer and has improved progression free survival and overall response compared with chemotherapy in this cohort of patients [4]. A combination of two immunotherapy drugs—Nivolumab and Ipilimumab is now also approved by NICE for second line treatment. [87]. Immunotherapy is better tolerated than long term chemotherapy [87]. However, when side effects do occur, they are in the form of an autoimmune response, resulting in symptoms such as colitis, arthritis and pneumonitis which can be severe [17].

Palliative Chemotherapy

Chemotherapy given in a palliative setting is usually discussed as first, second and third line treatment and has the aim of shrinking and controlling the disease [4]. Chemotherapy continues to be 5FU/Capecitabine based with options of either Oxaliplatin or Irinotecan, or both, being added [5]. For RAS/RAF wild type tumours, an EGFR inhibitor can also be added if appropriate [4]. Chemotherapy will typically be given in 3-month blocks, with CT scans to assess response to treatment [5]. The side effects of chemotherapy in a palliative setting will be closely monitored to ensure that quality of life is maintained. Adjustments to dosage and regime may be required when on treatment and treatment breaks can be added when the disease is well controlled to allow for recovery from symptoms [14, 42]. Cancer eventually develops resistance to chemotherapy resulting in disease progression [42, 88, 89]. When this occurs on first line treatment then Oxaliplatin can be switched to Irinotecan or vice versa for second line treatment [50]. When there is disease progression on second line treatment, then third line treatment would be considered with Lonsurf, however the benefit of this is small [50]. When chemotherapy options have been exhausted then the focus will shift to best supportive care and symptom control [89].

Colonic Stent

For left sided obstructing colonic tumours, endoscopic stent insertion can be considered as an alternative to surgery for patients with a poor performance status [21, 35]. Although this avoids the risks associated with emergency surgery, the cancer will continue to progress without further treatment and there remains a risk of colonic perforation or stent migration [42, 90].

Palliative Short Course Radiotherapy

For people with irresectable rectal cancers or for those who are not deemed fit for surgery, symptoms of pain, bleeding and discharge can be debilitating. Short course palliative radiotherapy can be given to slow disease progression and achieve improved symptom control [8, 91].

Anal Cancer

This is a rare cancer accounting for less than 1% of new cancer diagnosis in the UK [92]. Presentation is often with an anal mass with associated pain, itching and bleeding, which in many cases is initially mistaken for haemorrhoids [93]. When tumours are advanced, presentation may be with obstructive symptoms. Faecal incontinence can occur when the tumour involves the anal sphincter and there is also the potential

for fistulation [93, 94]. Anal cancers are primarily squamous cell carcinomas (SCC). Anal Intraepithelial Neoplasia (AIN) is caused by the Human Papillomavirus (HPV) and anal lesions containing AIN are precursors to anal SCC. The incidence of anal cancer is 30 to 40 times higher in people living with HIV [27, 95]. All patients with a new diagnosis of anal cancer should be referred to a specialist Anal Cancer MDT for management [27]. Treatment is similar to long course chemotherapy for rectal cancer, with the same associated side effects from treatment. However, skin toxicity is more common and often more severe due to the superficial nature of these cancers. 28 fractions of radiotherapy will be given over a five and a half week period. Concurrent chemotherapy with Mitomycin C intravenously at the start of treatment and Capecitabine is administered. 5-FU during week 1 and 5 of radiotherapy can be given as an alternative to Capecitabine [27]. Anal cancer responds well to a combination of chemotherapy and radiotherapy, with frequent complete responses seen [96]. Cancer Research UK report 5 and 10 year survival rates from anal cancer as 58% and 52% respectively [97].

A defunctioning stoma may be necessary prior to commencing treatment particularly if the tumour is bulky or the patient is particularly symptomatic. This may also reduce the risk of treatment-related complications and reduce treatment gaps during radiotherapy [27, 93]. Anal stenosis and sphincter damage is a common long term side effect of treatment, and therefore, even though technically reversible, the stoma is likely to be permanent [94, 98]. Definitive resection is only considered if there is an incomplete response to chemoradiotherapy, or local recurrence of the cancer. In this case APR surgery with a resulting permanent colostomy would be performed [98, 99].

The diagnosis of colorectal cancer has far-reaching implications for the individual and their family [100]. The Clinical Nurse Specialist is a vital resource for patients, providing expert advice, continuity, and support throughout the pathway [27, 101]. The psychological impact of surgery involving stoma formation is well documented [102]. For patients with an existing stoma, the side effects from treatments can compound these issues and affect stoma management [72, 103]. The Clinical Nurse Specialist is ideally placed to provide ostomates with the practical management advice, and psychological support that is essential to reduce anxiety when undergoing treatment for colorectal cancer [35, 102]. They are also key to coordination of care when multiple specialities are involved [7].

Conclusion

Greater understanding about colorectal cancer and increasing individualised management options have significantly improved prognosis over recent years. Treatment may take place over extended periods when presentation occurs at an advanced stage, or recurrent disease develops, involving multiple specialities and health care professionals. The clinical nurse specialist not only provides expert knowledge and support, but also continuity for patients and relatives. Knowledge of established treatment pathways and new therapies as they are developed, including

administration, side effects and implications for the individual receiving treatment, is essential for the clinical nurse specialist in order to practise effectively and to provide patient centred care.

References

1. Bowel Cancer UK. https://www.bowelcanceruk.org.uk/about-bowel-cancer/bowel-cancer/
2. Cancer Research. Bowel Cancer Statistics. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer
3. Peck J. Colorectal cancer: diagnosis and treatment. Nurs Pract. 2016. https://www.nursinginpractice.com/clinical/cancer/colorectal-cancer-diagnosis-and-treatment/
4. De Falco V, Napolitano S, Rosello S, Huerta M, Cervantes A, Ciardiello F, Troiani T. How we treat metastatic colorectal cancer. ESMO Open Cancer Horizons. 2020. https://doi.org/10.1136/esmoopen-2020-000813
5. Peck J. Presentation, diagnosis, and treatment of colorectal cancer. Nurs Stand. 2018. https://doi.org/10.7748/ns.2018.e11213
6. Sherwood L. Managing patients with resectable colorectal liver metastases. Cancer Nurs Pract. 2015;14(8):22–6. https://doi.org/10.7748/cnp.14.8.22.s21.
7. Henry R. The role of the cancer specialist nurse. Nurs Pract. 2015. https://www.nursinginpractice.com/clinical/cancer/the-role-of-the-cancer-specialist-nurse/
8. Tobias J, Hochhauser D. Cancer and it's management. 6th ed. Wiley-Blackwell; 2007.
9. Ilyas M. Pathology of colorectal cancer. In: Young A, Hobbs R, Kerr D, editors. ABC of Colorectal Cancer. 2nd ed. Wiley-Blackwell; 2011.
10. Davis D, Lahiri SS. Application of oncolytic viruses for cure of colorectal cancer. Cancer Res J. 2015;3(4):76–93. https://doi.org/10.11648/j.crj.20150304.13.
11. Fleming M, Ravula S, Tatischev SF, Wang H. Colorectal carcinoma: pathologic aspects. J Gastrointestinal Oncol. 2012;3(3):153–73. https://doi.org/10.3978/j.issn.2078-6891.2012.030.
12. Sagaert X, Vanstapel A, Verbeek S. Tumor heterogeneity in colorectal cancer: what do we know so far? Pathobiology. 2018;85:72–84. https://doi.org/10.1159/000486721.
13. Dellaire G, Berman JN, Arceci RJ. Cancer genomics. From Bench to personalized medicine. Elsevier; 2014.
14. Mead E, Dowling M. Management of metastatic colon cancer and its implications for patients and nurses. Cancer Nurs Pract. 2015;14(3):25–30. https://doi.org/10.7748/cnp.14.3.25.e1180.
15. De'Angelis GL, Bottarelli L, Azzoni C, De'Angelis N, Leandro G, Di Mario F, et al. Microsatellite instability in colorectal cancer. Acta Biomedica. 2018;89(9):97–101. https://doi.org/10.23750/abm.v89i9-S.7960.
16. Ong KR, Bowyer V, Cole T. Clinical genetics and the management of colon cancer. In Young A, Hobbs R, Kerr D, editors. ABC of colorectal cancer, 2nd ed. Wiley-Blackwell; 2011.
17. Ganesh K, Stadler ZK, Cercek A, Mendelsohn RB, Shia J, Segal NH, Diaz LA. Immunotherapy in colorectal cancer: rationale, challenges and potential. Nat Rev Gastroenterol Hepatol. 2019;16(6):361–75. https://doi.org/10.1038/s41575-019-0126-x
18. Kang S, Na Y, Joung S, Lee S, Oh SC, Min BW. The significance of microsatellite instability in colorectal cancer after controlling for clinicopathological factors. Medicine. 2018;97(9) https://doi.org/10.1097/MD.0000000000010019.
19. Vilar E, Grubar SB. Microsatellite instability in colorectal cancer – the stable evidence. Nat Rev Clin Oncol. 2010;7. 153–62. https://www.nature.com/articles/nrclinonc.2009.237
20. Wen-Long G, Miao-Zhen Q, Cai-Yun H, Li-Qiong Y, Ying J, Zhi-Qiang W, et al. Clinicopathologic features and prognosis of BRAF mutated colorectal cancer patients. Front Oncol. 2020; https://doi.org/10.3389/fonc.2020.563407.
21. NICE. Colorectal cancer (NG151). 2020. https://www.nice.org.uk/guidance/ng151/chapter/Recommendations

22. Islami F, Goding Sauer A, Miller KD, Siegel R, Fedewa SA, Jacobs EJ. et al. Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. Cancer J Clin. 2017. https://doi.org/10.3322/caac.21440
23. Whiteman DC, Webb PM, Green AC, Neale RE, Fritschi BCJ, Parkin DM, et al. Cancers in Australia in 2010 attributable to modifiable factors: summary and conclusions. Austral New Zealand J Public Health. 2015;39(5):477–84. https://doi.org/10.1111/1753-6405.12471.
24. Lakatos P, Lakatos I. Risk for colorectal cancer in ulcerative colitis: changes, causes and management strategies. World J Gastroenterol. 2008;14(25):3937–47. https://doi.org/10.3748/wjg.14.3937.
25. Maryńczak K, Włodarczyk J, Sabatowska Z, Dziki A, Dziki L, Włodarczyk M. Colitis-associated colorectal cancer in patients with inflammatory bowel diseases in a tertiary referral center: a propensity score matching analysis. J Clin Med. 2022;11(3):866. https://doi.org/10.3390/jcm11030866.
26. Monahan K. Bradshaw N, Dolwani S, Desouza B, Dunlop MG, East JE. et al Guidelines for the management of hereditary colorectal cancer from the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/United Kingdom Cancer Genetics Group (UKCGG) GUT.69:3. BMJ J. 2019. https://gut.bmj.com/content/69/3/411
27. ACPGBI (Association of Coloproctology of Great Britain and Ireland). 2017.Colorectal Disease. 19(1). Wiley Blackwell
28. Boland PB, Yurgelun MB, Boland CR. Recent progress in Lynch syndrome and other familial colorectal cancer syndromes. CA Cancer J Clin. 2018;68(3):217–31. https://doi.org/10.3322/caac.21448.
29. NICE. Molecular testing strategies for Lynch syndrome in people with colorectal cancer. DG27. 2017. https://www.nice.org.uk/guidance/dg27/chapter/2-Clinical-need-and-practice
30. NICE. NICE guideline NG151. 2020. https://www.nice.org.uk/guidance/ng151/evidence/a1-effectiveness-of-aspirin-in-the-prevention-of-colorectal-cancer-in-people-with-lynch-syndrome-pdf-7029391214
31. NHS England. PAR622. Implementing Lynch syndrome testing and surveillance pathways. A handbook to support local systems. 2021. https://www.england.nhs.uk/publication/implementing-lynch-syndrome-testing-and-surveillance-pathways/
32. NHS Long Term Plan. 2019. https://www.longtermplan.nhs.uk/wp-content/uploads/2019/08/nhs-long-term-plan-version-1.2.pdf
33. Bowel Cancer UK – Bowel cancer screening. https://www.bowelcanceruk.org.uk/about-bowel-cancer/screening/
34. NICE. Gastrointestinal tract (lower) cancers – recognition and referral. 2021. https://cks.nice.org.uk/topics/gastrointestinal-tract-lower-cancers-recognition-referral/
35. Henbrey R. Stoma formation as a palliative procedure: the role of the clinical nurse specialist in maintaining quality of life. Br J Nurs. 2021;30(6):4–8. https://doi.org/10.12968/bjon.2021.30.6.S4.
36. Yong D. PET/CT in Colorectal Cancer. Springer international Publishing AG. Ebook. 2017. https://ebookcentral.proquest.com/lib/heartnhs/search.action?eIsbn=9783319548371
37. Namasivayam S, Martin D, Saini S. Imaging of liver metastases. MRI Cancer Imaging. 2007;7(1):2–9. https://doi.org/10.1102/1470-7330.2007.0002.
38. NHS England. Rapid diagnostic and assessment pathways. Implementing a timed colorectal cancer diagnostic pathway. 2018. https://www.england.nhs.uk/publication/rapid-cancer-diagnostic-and-assessment-pathways/
39. Nuffield Trust. Cancer Waiting Times. 2021. https://www.nuffieldtrust.org.uk/resource/cancer-waiting-time-targets
40. Cancer Research UK. TNM Staging. https://www.cancerresearchuk.org/about-cancer/bowel-cancer/stages-types-and-grades/TNM-staging
41. Weisenberg E. Staging-carcinoma. PathologyOutlines.com website. 2022. https://www.pathologyoutlines.com/topic/colontumorstaging8ed.html

42. Costi R, Leonardi F, Zanoni D, Violi V, Roncoroni L. Palliative care and end-stage colorectal cancer management: the surgeon meets the oncologist. World J Gastroenterol. 2014;20(24):7602–21. https://doi.org/10.3748/wjg.v20.i24.7602.
43. ECOG Performance Status Scale. ECOG-ACRIN cancer research group. https://ecog-acrin.org/resources/ecog-performance-status/
44. Pfeiffer P, Qvortrup C. Introduction to oncology. In Baatrup G, editor. Multidisciplinary treatment of colorectal cancer. Staging, treatment, pathology and palliation. 2nd ed. Springer international Publications; 2020. E book. https://ebookcentral.proquest.com/lib/heartnhs/search.action?eIsbn=9783319061429
45. Cancer Research UK. Flourouracil (5FU) https://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/cancer-drugs/drugs/fluorouracil
46. Cancer Research UK. Capecitabine https://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/cancer-drugs/drugs/capecitabine
47. Han C, McKeage M. Neuropathies associated with oxaliplatin therapy. Asia-Pacific J Clin Oncol. 2012;8(2):107–10. https://doi.org/10.1111/j.1743-7563.2012.01547.x.
48. Iacovelli R, Pietrantonio F, Palazzo A, Maggi C, Ricchini F, de Braud F, et al. Incidence and relative risk of grade 3 and 4 diarrhoea in patients treated with capecitabine or 5-fluorouracil: a meta-analysis of published trials. Br J Clin Pharmacol. 2014;78(6):1228–37. https://doi.org/10.1111/bcp.12449.
49. Montagnani F, Chiriatti A, Turrisi G, Francini G, Fiorentini G. A systematic review of FOLFOXIRI chemotherapy for the first-line treatment of metastatic colorectal cancer: improved efficacy at the cost of increased toxicity. Colorectal Dis. 2011;13(8):846–52. https://doi.org/10.1111/j.1463-1318.2010.02206.x.
50. Tabernero J, Taieb J, Prager G.W, Ciardiello F, Fakih M, Leger C. et al (2020) Trifluridine/tipiracil plus bevacizumab for third-line management of metastatic colorectal cancer: SUNLIGHT study design. Fut Oncol 17(16) 1977–1985. doi: https://doi.org/10.2217/fon-2020-1238.
51. Gallimore E. Infusion-related risks associated with chemotherapy. Nurs Stand. 2015;30(25):51–60. https://doi.org/10.7748/ns.30.25.51.s48.
52. Coughlin M, Healey C. Nursing care, education and support for patients with neutropenia. Nurs Stand. 2008;22:46, 35–41. https://doi.org/10.7748/ns2008.07.22.46.35.c6598
53. European Medicines Agency. EMA recommendations on DPD testing prior to treatment with fluorouracil, capecitabine, tegafur and flucytosine; 2020. https://www.ema.europa.eu/en/news/ema-recommendations-dpd-testing-prior-treatment-fluorouracil-capecitabine-tegafur-flucytosine
54. Borucki JP, Schlaeger S, Crane J, Hernon JM, Stearns AT. Risk and consequences of dehydration following colorectal cancer resection with diverting ileostomy. A systematic review and meta-analysis. Colorectal Dis. 2021;23(7):1721–32. https://doi.org/10.1111/codi.15654?saml_referrer.
55. McQuade RM, Stojanovska V, Abalo R, Bornstein JC, Nurgali K. Chemotherapy-induced constipation and diarrhea: pathophysiolog, current and emerging treatments. Front Pharmacol. 2016;7:414. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5093116/
56. Burch J. Stoma related considerations in palliative patients. Br J Community Nurs. 2021;26(10). https://www.britishjournalofcommunitynursing.com/content/other/stoma-related-considerations-in-palliative-patients
57. Goodey A. The impact of chemotherapy on skin health in relation to stoma care. Gastrointestinal Nurs. 2021;9(6) https://doi.org/10.12968/gasn.2021.19.6.30.
58. Baran B, Ozupek NM, Tetik NY, Acar E, Bekcioglu O, Baskina Y. Difference between left-sided and right-sided colorectal cancer: a focused review of literature. Gastroenterol Res. 2018;11(4):264–73. https://doi.org/10.14740/gr1062w.
59. Chan DH, Segelov E, Wong RSH, Smith A, Herbertson RA, Li BT, et al. Epidermal growth factor receptor (EGFR) inhibitors for metastatic colorectal cancer. Cochrane Library; 2017. https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD007047.pub2/epdf/abstract

60. Shahib W, Mahajan R, El-Rayes B. Markers of resistance to anti-EGFR therapy in colorectal cancer. J Gastrointestinal Oncol. 2013;4(3):308–18. https://doi.org/10.3978/j.issn.2078-6891.2013.029.
61. Nelson VM, Benson AB. Status of targeted therapies in the adjuvant treatment of colon cancer. J Gastrointestinal Oncol. 2013;4(3):245–52. https://doi.org/10.3978/j.issn.2078-6891.2013.035.
62. Guggina L, Choi AW, Choi JN. EGFR inhibitors and cutaneous complications: a practical approach to management. Oncol Therapy. 2017;5:135–48. https://doi.org/10.1007/s40487-017-0050-6.
63. Fakih M, Vincent M. Adverse events associated with anti-EGFR therapies for the treatment of metastatic colorectal cancer. Curr Oncol. 2010;17(1). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2901793/
64. Cancer Research UK Radiotherapy. External Radiotherapy. https://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/radiotherapy/external/about#:~:text=Radiotherapy%20fractions,make%20up%20your%20radiotherapy%20course
65. Hollinworth H, Mann L. Managing acute skin reactions to radiotherapy treatment. Nurs Stand. 2010;24(24):53–64. https://doi.org/10.7748/ns2010.02.24.24.53.c7558.
66. O'Gorman C, Denieffe S, Gooney M. Literature review: preoperative radiotherapy and rectal cancer – impact on acute symptom presentation and quality of life. J Clin Nurs. 2014;23:3–4.333–351. https://doi.org/10.1111/jocn.12138
67. Robert RK, Collier M. Managing tissue viability issues in patients with cancer approaching the end of life. Nursing Standard. 2017;31(25):54–61. https://doi.org/10.7748/ns.2017.e10621.
68. Macmillan. Radiotherapy for Rectal Cancer. https://www.macmillan.org.uk/cancer-information-and-support/treatments-and-drugs/radiotherapy-for-rectal-cancer
69. Levine JM, Kelvin JF, Quinn GP, Gracia CR. Infertility in reproductive-age female cancer survivors. Cancer. 2015;121(10):1532–9.
70. Nice. (CG156) People with cancer who wish to preserve fertility. Recommendations | Fertility problems: assessment and treatment | Guidance | NICE. 2017.
71. Dames NB, Squire SE, Devin AB, Fish R, Bisset CN, Tozer P. 'Let's talk about sex': a patient-led survey on sexual function after colorectal and pelvic floor surgery. Colorectal Dis. 2021;23(6):1524–51. https://doi.org/10.1111/codi.15598.
72. Beck M, Justham D. Nurse's attitudes towards the sexuality of colorectal patients. Nurs Stand. 2009;23(31):44–8. https://doi.org/10.7748/ns.23.31.44.s48.
73. Feeney G, Seghal R, Sheehan M, Hogan A, Regan M, Joyce M, Kerin M. Neoadjuvant radiotherapy for rectal cancer management. World J Gastroenterol. 2019;25(33):4850–69. https://doi.org/10.3748/wjg.v25.i33.4850.
74. Mann CD, Norwood MG, Miller AS, Hemmingway D, Leicester Colorectal Specialist Interest Group. Nonresectional palliative abdominal surgery for patients with advanced colorectal cancer. Colorectal Dis. 2010;12(10):1039–43. https://doi.org/10.1111/j.1463-1318.2009.01926.x.
75. Bahadoer RR, Dijkstra EA, van Etten B, CAM M, Putter H, Meershoek-Klein Kranenbarg E, et al. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. Lancet Oncol. 2021;22(1):29–42. https://doi.org/10.1016/S1470-2045(20)30555-6.
76. Seymour M, Morton D. FOxTROT: an international randomised controlled trial in 1052 patients (pts) evaluating neoadjuvant chemotherapy (NAC) for colon cancer. J Clin Oncol. 2019;37(15). https://doi.org/10.1200/JCO.2019.37.15_suppl.3504.
77. Saridaki-Zoras Z, Kerr D. Adjuvant therapy. In: Young A, Hobbs R, Kerr D, editor. ABC of colorectal cancer. Wiley-Blackwell; 2011.
78. Staal S, Daily E, Allegra C. Controversies in adjuvant chemotherapy. In: Schofield JH, Eng C, editors. Colorectal cancer diagnosis and clinical management. Wiley. Ebook. 2014. https://ebookcentral.proquest.com/lib/heartnhs/search.action?eIsbn=9781118337912

79. Chan GHJ, Chee CE. Making sense of adjuvant chemotherapy in colorectal cancer. J Gastrointestinal Oncol. 2019;10(6):1183–92. https://doi.org/10.21037/jgo.2019.06.03.
80. Taylor I, Garcia-Aguilar J, Ward R. Fast facts. Colorectal cancer. 3rd ed. Health press LTD. Ebook; 2010. https://ebookcentral.proquest.com/lib/heartnhs/search.action?eIsbn=9781905832798
81. Mackay GJ, Dorrance HR, Molloy RG, O'Dwyer PJ. Colorectal Surgery. Oxford: Oxford University Press; 2010.
82. Polderdijk MCE, Brouwer M, Haverkamp L, Ziesemer KA, Tenhagen M, Boerma D, et al. Outcomes of combined peritoneal and local treatment for patients with peritoneal and limited liver metastases of colorectal origin: a systematic review and meta-analysis. Ann Surg Oncol. 2022;29:1952–62. https://doi.org/10.1245/s10434-021-10925-y.
83. Flood MP, Waters PS, Kelly ME, Shields C, Conneely J, Ramsay R, et al. Outcomes following synchronous liver resection, cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for colorectal liver and peritoneal metastases: a bi-institutional study. Surg Oncol. 2021;37 https://doi.org/10.1016/j.suronc.2021.101553.
84. Canaby E, Yonemura Y. Peritoneal surface malignancies: a curative approach. Springer International Publications AG; 2015. https://ebookcentral.proquest.com/lib/heartnhs/detail.action?docID=3567640&query=peritoneal+surface+malignancy
85. Arrichiello G, Poliero L, Borrelli C, Paragliola F, Nacca V, Napolitano S, et al. Immunotherapy in colorectal cancer: is the long-awaited revolution finally happening? Cancer Treatment Res Commun. 2021. https://doi.org/10.1016/j.ctarc.2021.100442.
86. Ciardiello D, Vitiello PP, Cardone C, Martini G, Troiani T, Martinelli E, Ciardiello F. Immunotherapy of colorectal cancer: Challenges for therapeutic efficacy. Cancer Treatment Rev. 2019;76:22–32. https://www.sciencedirect.com/science/article/pii/S0305737219300556
87. Cancer Research UK Immunotherapy. https://news.cancerresearchuk.org/2021/06/16/combination-immunotherapy-for-advanced-bowel-cancer-approved-for-nhs-in-england/
88. Briffa R, Langdon SP, Grech G, Harrison DJ. Acquired and intrinsic resistance to colorectal cancer treatment. In: Chen J, editor. Colorectal cancer. diagnosis, screening and management. Intech Open; 2018. https://www.intechopen.com/books/6177
89. Hammond WA, Swaika A, Mody K. Pharmacologic resistance in colorectal cancer: a review. Therapeutic Adv Med Oncol. 2016;8(1):57–84. https://doi.org/10.1177/1758834015614530.
90. Ferguson HJ, Ferguson CI, Speakman J, Ismail T. Management of intestinal obstruction in advanced malignancy. Ann Med Surg. 2015;4(3):264–70. https://doi.org/10.1016/j.amsu.2015.07.018.
91. Cameron MG, Kerston C, Vistad I, Fossa S, Guren M. Palliative pelvic radiotherapy of symptomatic incurable rectal cancer – a systematic review. Acta Oncologica. 2013;53:2. https://doi.org/10.3109/0284186X.2013.837582.
92. Cancer Research UK – Anal cancer incidence by sex and UK country. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/anal-cancer/incidence#heading-Zero
93. Coakes M, White M. Anal cancer: developments in treatment and patient management. Gastrointestinal Nurs. 2013;11(1) https://doi.org/10.12968/gasn.2013.11.1.32.
94. Cooper R, Mason M, Finan P, Byrne P, Sebag-Miontefiore D. Defunctioning stomas prior to chemoradiation for anal cancer are usually permanent. Colorectal Dis. 2012;14(1):87–91. https://doi.org/10.1111/j.1463-1318.2010.02529.x
95. Sadlier C, Lynam A, Kerr C, Sheils O, Bergin C. Anal cancer in people living with HIV: a case series. Int J STD AIDS. 2019. https://doi.org/10.1177/0956462419878039
96. Dee EC, Byrne JD, Wo JY. Evolution of the role of radiotherapy for anal cancer. Cancers. 2021;13(6) https://doi.org/10.3390/cancers13061208.
97. Cancer Research UK - Anal cancer survival statistics. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/anal-cancer/survival#heading-Zero

98. Poynter LR, Raman R, Wegstapel H, Summers J, Lawes DA. The prevalence and fate of the defunctioning stoma in patients with anal cancer: a regional experience following the ACT II trial. Colorectal Dis. 2017;19:12. https://doi.org/10.1111/codi.13855.
99. Ghosn M, Kourie HR, Abdayem P, Antoun J, Nasr D. Anal cancer treatment: current status and future perspectives. World J Gastroenterol. 2015;21(8):2294–302. https://doi.org/10.3748/wjg.v21.i8.2294.
100. McCulloch P, Young A. Supportive care for patients with colorectal cancer in young. In: Hobbs R, Kerr D, editor. ABC of colorectal cancer. 2nd edn. Wiley-Blackwell; 2011.
101. Cagayon H, Brady K, Donnelly L. Reviewing information provision for patients with colorectal cancer. Gastrointestinal Nurs. 2022;20(1):S16–8.
102. Black P, Notter J. Psychological issues affecting patients living with a stoma. Br J Nurs. 2021;30(6):S20–32.
103. Wallace A, Taylor C. Recognising how chemotherapy can affect stoma care. Cancer Nurs Pract. 2011;10(2):20–5. https://doi.org/10.7748/cnp2011.03.10.2.20.c8393.