some patients with stage III CRC may choose to receive capecitabine monotherapy rather than FOLFOX because of the relative convenience of oral chemotherapy.

MMR/MSI testing (desirable/ideal)

Currently, the most promising risk factor for colon cancer is MSI. Fluoropyrimidine-based chemotherapy is not effective or may be detrimental in MSI-positive patients as reported by one study. Tumour MMR status should be assessed in all patients who present with stage II CRC.MMR assessment should also be considered for patients fulfilling the Bethesda guidelines (see above). Currently MMR status can be assessed by the performance of immune-histochemistry (IHC) for the 4 major MMR genes, with loss of expression of one or more of the genes indicating deficient MMR (dMMR). Recent evidence has suggested that patients with dMMR and Dukes B tumours do not benefit from adjuvant 5-FU chemotherapy[36]. These results should be interpreted with consideration of the other factors mentioned above to determine which patients should receive 5-FU chemotherapy. The patient should be informed of the possibility that testing may identify a deficiency that could have a hereditary origin.

Besides MSI-high (MSI-H)/MMR, there is no validated molecular marker approved for use in adjuvant settings. Although *BRAF* mutation portends a poor survival in patients with stage II tumours without MSI-H status, it does not help in tailoring treatment. Similarly, the presence of *KRAS* mutation offers no additional prognostic or predictive value in adjuvant settings.

Age

Advanced age is not a contraindication for adjuvant therapy. Each patient should be assessed according to their general physical condition, on considering their wishes. However, the benefit of combination chemotherapy (oxaliplatin and fluoropyrimidines) in the elderly is less certain. On the basis of findings of subgroup analyses in trials from the MOSAIC trial and an analysis of data from the ACCENT database showing no improvement in overall survival with combination chemotherapy in patients aged 70 years, the panel recommends adjuvant fluoropyrimidine monotherapy (capecitabine unless contraindicated) in patients older than 70 years[34].

Gene expression profiling

Gene expression profiling is emerging as an important tool in decision making to aid clinicians and patients regarding adjuvant chemotherapy. For colon cancer, Oncotype DX and Coloprint are two such assays that are now available and may help in decision making.

Temporary stomas

Many patients have temporary stomas following resection of a primary tumour. In patients undergoing low resection, retaining the stoma during therapy can be helpful with regards to the control of chemotherapy-related diarrhoea. In some cases in which patients cope poorly, it may be beneficial to arrange for stoma reversal prior to commencement of adjuvant treatment. Adjuvant treatment can commence 2 weeks after uncomplicated stoma reversal.

Planned treatment should commence within 4–12 weeks (ideally, 6–8 weeks) following primary resection. There is no evidence of a benefit for adjuvant chemotherapy if it is started >12 weeks after surgery (Level 1A)[37].

Every treatment option including observation alone should be discussed with the patient. Adjuvant chemotherapy is indicated for patients with stage III (Duke C) tumours or high-risk patients with stage II tumours (Level IA).

High-risk: Patients with stage II tumours are at a high risk of recurrence if they present at least 1 of the following characteristics: number of lymph nodes sampled <12; poorly differentiated tumour; vascular, lymphatic perineural invasion; close, indeterminate, or positive margins; tumour presentation with obstruction or tumour perforation; and pT4 stage. (Level 2B)

Stage III tumours: Offer adjuvant chemotherapy (unless clinically contraindicated) with FOLFOX or CAPEOX (Level 1A).

Stage II tumours: The benefit of adjuvant chemotherapy for resected stage II CRC with no adverse features is small, at approximately 3.5 %[38]. Adjuvant treatment should be discussed with patients in the clinic. The relative need for adjuvant treatment should be guided by the treating consultant after an assessment of the case. The adverse features are extramural venous invasion, T4 stage, perforation, and poor lymph node yield (<12 retrieved). IHC for dMMR should be performed before adjuvant chemotherapy is offered, as patients with dMMR are usually advised against adjuvant 5-FU-based chemotherapy[36].

Capecitabine monotherapy is usually the most appropriate treatment for patients with high-risk stage II tumours (Level 2B)[34,39].

Patients who are referred for consideration of adjuvant therapy but who do not receive adjuvant treatment should continue follow up. Colonoscopic surveillance should be continued, at 1 year after surgery and every 3 years thereafter.

If polyps are observed, colonoscopy should be performed every 6–12 months until they disappear[40].

Adjuvant Therapy for Colon Cancer (M0)

Pathological stage	Management	Level
Tis; pT1N0, pT2N0	Observation	IA
pT3N0 (no high risk features)	Observation	IA
pT3N0 (high risk features)/pT4N0	5-FU/LV± oxaliplatin or capecitabine ± oxaliplatin orobservation	IA
pT1–3N1–2, pT4N1–2	FOLFOX, CAPEOX, 5-FU/LV, capecitabine (regimen details in Appendix D)	IA

B. RECTAL CANCER

General approach:

As with cancers of the colon, surgery is the primary treatment and may be curative in a number of patients. Unlike colon cancer, however, the ability to obtain wide radial (or circumferential) resection margins at surgery is frequently limited by the bony pelvis, and thus, local recurrence is a much greater problem in this disease. Efforts to reduce local recurrence have focused on improved surgical technique, radiotherapy, and combined chemo-radiotherapy (CTRT).

Endoscopic ultrasonography (EUS) and magnetic resonance imaging (MRI) of the pelvis are used to assess local spread, whereas CT is the main modality to assess systemic spread. CT is not useful for local staging of rectal cancer. In a meta-analysis involving 5000 patients, CT showed accuracy of 73% for T staging and of 22–73% for nodal staging[41].

Four prospective studies have compared EUS and MRI for the staging of rectal cancers. The data are difficult to interpret because of the different MRI and EUS equipment and protocols used. The findings of 3 of these studies suggest that EUS and MRI offer similar levels of accuracy for local staging of rectal tumours[25,42-44].

The main advantages of MRI compared with EUS are that it is not influenced by tumour stenosis and the mesorectal fascia/CRM can be identified. MRI of the rectum may be performed using either an endorectal coil or a phased-array surface coil. However, most centres perform rectal MRI using the phased array system, which provides a broader field of view and allows reliable identification of the mesorectal fascia, as confirmed in the multicentre European MERCURY study[45]. From a practical viewpoint, EUS is better than MRI for staging early cancers, whereas MRI shows better performance for large lesions where the CRM may be threatened (Level 2B).

Another advantage of EUS is the possibility of performing EUS-guided fine needle aspiration (FNA) of perirectal nodes, especially after neoadjuvant therapy. EUS is also useful for detecting local recurrence of rectal cancer, which is often extra-luminal and difficult to distinguish from inflammatory changes without tissue sampling[46].

Patients can be broadly classified into two groups:

1. Patients unlikely to benefit from a long course of NACTRT

In tumours with a low risk of positive or uninvolved CRM, surgery is the primary treatment modality. The aim should be to achieve a local recurrence rate of 10% or less[47]. The surgical technique that gives the best results in this respect is TME[48,49]. In select cases, the use of short-course preoperative radiotherapy (SCPRT) may be considered to reduce the risk of local recurrence[49]. SCPRT delivers a dose of 25 Gy in 5 daily fractions over a week. Surgery is usually performed soon after completion of radiotherapy. The short time interval between radiotherapy and surgery implies that SCPRT does not cause significant tumour shrinkage and as such is not considered for tumours with poor prognostic features. Patient factors such as frailty and co-morbidities are also taken into consideration.

2. Patients likely to benefit from a long course of NACTRT[50]

- Low tumours for which CTRT may facilitate sphincter-preserving surgery
- Tumours associated with poor prognosis with regard to local control with at-risk CRM as assessed by MRI:
    - ♦ Tumour within 2 mm of the mesorectal fascia

- Any T3 tumour at/below the levators
- T3c/d tumour at any other level,i.e.the tumour extends >5 mm into the perirectal fat
- T4 tumour
- Any T stage with 4 or more involved lymph nodes

T1/T2N0 lesions, some early T3 lesions,and the CRM is not threatened.

There is no role of neoadjuvant therapy.

Essential

Sphincter-preserving surgery:

Low anterior resection(LAR) is the gold standard operation for rectal cancer. Here, the tumour and rectum with its mesorectal package are resected, and the colon is mobilised and anastomosed to the rectal stump. The anastomosis lies below the peritoneal reflection.

Ultralow anterior resection (AR): The anastomosis lies on or below the pelvic floor.

Desirable

Sphincter-preserving surgery:

Local excision: Ideal for T1 lesions. The excision may or may not be full thickness.

Transanal endoscopic microsurgery (TEMS) excision:

This requires special expertise and equipment and should not be attempted without training. Tumours less than 4 cm in size, mobile, and involving less than a third of the circumference are amenable to TEMS. Excision is full thickness. Local nodal excision is possible. Local control is better than with local excision.

T3 lesions, some T4 lesions with only vaginal or peritoneal involvement, N+lesions, and the CRM is not threatened

Essential

SCPRT can be recommended followed by surgery, since this reduces local recurrence rates.(Level IA): 25 Gray (Gy), 5 Gy/fraction for 1 week followed by immediate surgery (<10 days from the first radiation fraction) is a convenient, simple, and low-toxic treatment (Level IA)[49].

T3/T4 lesions, N+lesions, and the CRM is threatened

Essential

Patients should be offered NACTRT (Level 1A). This is known to significantly decrease the local recurrence rate and improve disease-free survival when added to surgery. Preoperative CTRT has further advanced this progress by increasing sphincter preservation rates[51].

Treatment regimen: The radiation dosing guidelines are presented in Appendix E

- CTRT for 6 weeks
  - Pelvic radiotherapy (ISO DOC J-3-GIS-1-002) given in 2 phases:
  - Pelvis, 45 Gy in 25 fractions (5 weeks)
  - Boost, 5.4– 9 Gy, 1.8 Gy per fraction, 3–5 fractions (the lower dose is administered if the volume of small bowel included in the field is a concern)

- Capecitabine, 650–825 mg/m^2 twice a day for 6 weeks, continued during radiotherapy (Level 1)[52].

Standard preoperative CTRT refers to a dose of 46–50.4 Gy together with 5-FU given either as bolus injections with LV 6–10 times during radiation (Level 1A) or oral capecitabine, 825mg/m^2 per oral (PO) twice a day (BD) or prolonged continuous infusion of 5-FU (likely better than bolus 5-FU) (Level 2B).

There is no definite conclusion regarding the 5-FU regimen to be used for CTRT. An intergroup study revealed that bolus 5-FU is not inferior to bolus 5-FU/LV. Another phase III trial demonstrated equivalence between bolus 5-FU/LV and infusional 5-FU during CTRT. In contrast to the findings of the above study, a NCCTG study concluded that the infusional regimen was associated with a survival advantage. Capecitabine has been shown to be equivalent to infusional 5-FU[32]. The addition of oxaliplatin to the aforementioned regimens was found to be more toxic without any significant benefits with regard to sphincter preservation, surgical downstaging, or the rates of complete pathological response. Currently, the preferred regimen is the infusional 5-FU regimen or capecitabine for CTRT, and NACTRT is preferred over adjuvant CTRT[52]. The pathological complete remission rate post NACTRT ranges from 20% to30% in most studies and correlates with prolonged survival.

Adjuvant chemotherapy is recommended for stage II/III rectal cancer following neoadjuvant therapy, irrespective of the pathology results. In an EORTC study, adjuvant therapy after NACTRT did not decrease the local recurrence rates any further but increased the disease-free survival rates[53]. Most of the recommendations are extrapolated from the data available for colon cancer. The current recommendation is 6 months of perioperative treatment (Level 2A). The regimens recommended are the same as those used in colon cancer. In case no neoadjuvant therapy is given, adjuvant CTRT followed by adjuvant chemotherapy is recommended. The other option is to start with adjuvant chemotherapy, sandwich CTRT, and then complete the rest of the adjuvant chemotherapy regimen. Adjuvant therapy should be started as early as possible once the operative wound is healed, as every 4-week delay in treatment decreases survival rates by 14%[37].

A six-week break after completion of CTRT prior to surgery is recommended (Level 2A).

The need for adjuvant chemotherapy should be based on the initial radiological (MRI, if available) staging, and not on post-treatment pathological staging

Indications for adjuvant therapy are as follows: Adverse factors on histology, T3 disease or higher, N1 disease, lymphovascular or perineural invasion, and in general, receipt of neoadjuvant therapy. Patients with T2N0 disease have only a 5% benefit with chemotherapy[53].

Surgery (essential):

AR with stapled or hand-sewn anastomosis[54]. This operation should not be embarked upon without adequate expertise or equipment or if the CRM is unlikely to be clear. The mesorectum should be excised as part of the 'package', by dissecting in the 'holy plane' just external to the mesorectal fascia. The distal extent of the dissection should be at least 2 cm distal to the palpable lower edge of the tumour. For low rectal tumours, the dissection is performed down to the pelvic floor. Intestinal continuity is restored either by stapled anastomosis or by a hand-sewn coloanal anastomosis. When staplers cannot be used for some reason, intersphincteric dissection with hand-sewncoloanal anastomosis for low rectal tumours is recommended. Here, the inter-sphincteric plane is entered transanally and contact is made with the dissection planes achieved by the abdominal approach, preserving the puborectalis and levator ani for continence.

Ultralow AR: The anastomosis lies on or below the pelvic floor. This is facilitated by the use of staplers. Rectal transection on the pelvic floor and end-to-end anastomosis are reliably and quickly achieved using stapling devices.

Laparoscopic surgery (desirable):

Laparoscopic colorectal resection is recommended at centres with expertise in which the procedure is performed by oncologic laparoscopic surgeons, as laparoscopic colorectal resection has similar oncological outcomes with the added advantage of enhanced postoperative recovery.

The concerns regarding the higher rate of positive CRM in the laparoscopic arm and its impact on survival have been laid to rest with long-term data showing no difference between open and laparoscopic surgery[55].

Laparoscopic resection may be considered, if available, if there is no locally advanced disease and no acute obstruction or perforation. Patients at high risk for prohibitive abdominal adhesions should not be treated using the laparoscopic approach, and in patients who are found to have prohibitive adhesions during laparoscopic exploration, conversion to open procedure is recommended.

Robotic surgery for rectal cancer has theoretical advantages, but is not recommended at present. The ROLAAR trial will provide some evidence for or against robotic surgery.

The principles of surgery are as above. Curative surgery must not be embarked upon if R0 resection is not possible. This decision is based on preoperative imaging and MDT discussion.

Abdominoperineal excision: This is the operation of choice for rectal cancers within 5 cm of the anal verge. Patients with tumours proximal to this level should be given the option of LAR at a specialized centre. An attempt must be made to obtain a cylindrical specimen without 'waisting' at the pelvic floor[56].

Neoadjuvant and adjuvant therapy for rectal cancer (M0)

Pathological stage	Management	Level
Tis; pT1N0, pT2N0	Observation	IA
pT3–4N0, pT1–3N1–2, pT4N1–2	5-FU±LV or FOLFOX or capecitabine ± oxaliplatin followed by infusional 5-FU/radiotherapy (RT)or capecitabine + RT followed by 5-FU±LV OR FOLFOX or capecitabine ±oxaliplatin or infusional5-FU/RT OR capecitabine + RT followed by 5-FU±LV or FOLFOX or capecitabine ± oxaliplatin	IA
cT3N0, any TN1–2	Preoperative infusional 5-FU/RT or capecitabine + RT followed by surgery and then 5-FU±LV or FOLFOX or capecitabine ± oxaliplatin	IA
cT4 and/or locally unresectable	Infusional 5-FU/RT or capecitabine + RT followed by surgical resection if possible and then 5-FU±LV or FOLFOX or capecitabine ± oxaliplatin (regimen details in Appendix D)	IA

CHAPTER

5 MULTIDISCIPLINARY TREATMENT FOR ADVANCED DISEASE

Patients with metastatic disease can be classified into 4 groups:

1. Patients with resectable metastatic disease at presentation
2. Patients with unresectable disease at presentation that becomes potentially resectable after downstaging (conversion) with systemic therapy
3. Patients who have potentially resectable metastatic disease but who are not candidates for resective surgery
4. Patients with unresectable metastatic disease

1. Patients with resectable/potentially resectable metastatic liver disease at presentation:

In these patients, immediate surgical resection is usually recommended, provided the patients are medically fit. Neoadjuvant chemotherapy is an acceptable alternative approach[57]. Adjuvant (postoperative) chemotherapy is also usually recommended for these patients, in an attempt to reduce the rate of recurrence.

There have been difficulties in conducting randomized controlled trials investigating the benefit of adjuvant chemotherapy after liver resection, and therefore, high-level prospective evidence is relatively limited (small studies, inadequate power, slow accrual, and outdated regimens)[58]. However, given the strong rationale for this approach and on extrapolation of data from other adjuvant CRC trials, adjuvant chemotherapy after liver resection is usually recommended for patients who did not receive any preoperative treatment (Level 2A)[59]. The regimen to be used can be selected on the basis of the discussion with the patient. The options include FOLFOX, CAPEOX, or FOLFIRI or FOLFIRINOX. (Appendix D) with or without bevacizumab or cetuximab (for wild-type *RAS*) (Level 2B). Participation in clinical trials should be considered.

For patients with oligometastatic disease confined to the liver and lung, resection of liver and lung metastases is the standard of care. Studies have demonstrated that liver resection (when possible) can lead to 5-year survival rates of upto 40%, whereas without surgery, the 5-year survival rate in this patient group is close to zero[60,61]. More recently, it has been shown that, in select patients whose disease is deemed inoperable, the use of combination chemotherapy[62] and targeted therapy (such as cetuximab for wild-type *KRAS* metastatic CRC [mCRC][63] may downsize the disease bulk and allow for curative hepatic resection (Level 2A)[64].

Patients with metastatic disease should all undergo molecular testing of their tumour tissue for mutations in *RAS*[26,27,63]. Patients with potentially resectable mCRC comprise a heterogeneous patient group, and addressing all possible variations in disease presentation is beyond the scope of this document. All patients with metastatic disease isolated to a single organ site may be considered for resection, and occasionally, patients with small volume metastatic disease involving 2 sites may also be considered. Because of the morbidity associated with metastasectomy, it is crucial that care be taken to avoid treating

patients at high risk of early disease relapse. The use of high-resolution imaging such as CT, MRI, and PET and an MDT approach will help in this regard.

Data presented at ASCO 2013 from the New-EPOC study showed that, when patients with resectable CLM were randomised to receive chemotherapy versus chemotherapy plus cetuximab, progression-free survival was significantly better in the chemotherapy alone arm (21mo vs 14 mo P=0.03); however, we need to wait for the full publication before making any specific recommendations based on this finding.

♦ Liver metastases

General approach

Many patients present with metastatic disease isolated to the liver or develop isolated liver disease as recurrence after primary resection. The treatment plan for these patients is decided according to whether curative resection is thought possible at presentation or whether 'downstaging' chemotherapy would be required to allow for resection[57,64]. Where possible, these patients should also be enrolled in clinical trials.

The liver is divided into 8 anatomical segments. When the remnant liver is insufficient in size as assessed by cross-sectional imaging volumetrics, preoperative portal vein embolization of the involved liver can be performed to expand the FLR. In other cases, complete resection can be safely achieved via 2-stage liver resection.

- Liver biopsy is not routinely performed when patients are intended to eventually undergo liver metastasectomy, except for confirmation of the diagnosis when this is unclear.
- Imaging (confirmation of liver metastases with 2 imaging modalities is required to minimise the false positive rate):

Chest,abdomen,and pelvis CT: These procedures are required to exclude extrahepatic disease. Small or ill-placed hepatic metastases may be missed on CT, and distinction of benign liver pathology from malignant disease may be difficult.

PET: This procedure is used to detect hypermetabolic tissue. PET is useful in excluding extrahepatic disease. It should be used in conjunction with CT as false-negative and false-positive results do occur.

Once patients are identified for liver resection, they should be referred early to a specialist centre (essential)

Reasons to consider 'downstaging' chemotherapy instead of initial surgery:

- Large tumour size (>5cm)
- Difficult tumour location (near vessels)
- Multinodularity (≥4 lesions)

Perioperative systemic therapy (Details in Appendix D)

2. Patients with unresectable disease requiring downstaging

The aim is to convert unresectable liver metastatic disease to resectable disease. The use of neoadjuvant chemotherapy (NACT) allows for the assessment of tumour biology, which may facilitate the identification of patients with aggressive unresponsive tumours who are at high risk for early relapse post hepatic resection. The National Institute for Health and Care Excellence, United Kingdom, has recommended a

combination of cetuximab[64] plus FOLFOX (or cetuximab with FOLFIRI if oxaliplatin is not tolerated or contraindicated) for patients fit for surgery with disease isolated to the liver (and resected or potentially operable primary colorectal tumour) that is initially unresectable. Patients who relapse within 1 year of adjuvant chemotherapy may also be recommended to undergo further post-metastasectomy chemotherapy (Level 2B).

General approach

Curative resection will not be possible in many cases, and it is important that patients are aware of this fact. Following hepatic resection, if further hepatic recurrence develops, repeat resection may be considered.

Resectable lung metastases

Early referral to a specialist centre is recommended (essential).

Isolated resectable lung metastases should be treated using an approach similar to that for liver metastases.

Metastasectomy is the standard treatment provided the patient is medically fit, the patient has oligometastatic disease confined to the lung (with or without liver metastasis), the primary disease is controlled, and surgery is feasible. Because of the difficulty in confirming malignant disease by imaging studies alone (without biopsy), the findings should be confirmed using 2 complimentary imaging modalities. This minimises the false-positive rate. Contrast-enhanced CT and PET are used to define the metastases and resectability as well as to exclude the presence of widespread disease.

Adjuvant therapy: There are currently no randomised phase III data to aid the decision regarding whether adjuvant chemotherapy should be offered. However, given the rationale that these patients have a high risk of recurrence and that chemotherapy may reduce this recurrence risk, these patients are frequently offered adjuvant chemotherapy (similar to the approach used in the adjuvant disease setting after liver metastasectomy) if recommended by the treating consultant after a careful discussion with the patient.

Isolated lung and liver metastases

Some patients with limited lung and liver metastases may be selected for staged metastasectomy following protocol chemotherapy for advanced disease. These patients should be staged using contrast-enhanced CT, contrast-enhanced MRI of the liver, and PET. Adjuvant chemotherapy may also be advised in these highly selected cases.

3. Patients who have potentially resectable metastatic disease but who are not candidates for resective surgery

Some patients have potentially resectable liver or lung metastatic disease but are not suitable candidates for surgical resection because of co-morbidity or poor performance status (Appendix F). In these circumstances, non-surgical treatment strategies are available. These include the following:

- Radiofrequency ablation to the liver or lung after discussion with interventional radiologist: This should be considered when all measurable metastatic lesions can be treated[65].
- Stereotactic radiotherapy to the liver

4. Patients with unresectable metastatic disease Metastatic CRC (mCRC)

General approach:

Unfortunately, most patients will present with metastatic disease not amenable to resection. In these cases, curative treatment is not possible, but many patients will benefit in terms of both quality of life and survival from the use of systemic chemotherapy and supportive measures, with the median overall survival rate approaching 2 years in recent clinical trials. Evidence suggests that greater benefit is achieved if patients are treated early, before becoming symptomatic. The survival of patients with mCRC varies widely and is dependent on disease bulk, general clinical state, tumour biology, and response to treatment. Because of this, it is often better to avoid providing definite time periods when questioned about prognosis. Many patients, whether receiving chemotherapy or supportive care, will benefit from palliative care alone. Palliative care referrals should only be made at an appropriate time after discussion with the patient.

Two major clinical trials, CAIRO and FOCUS, have shown that a sequential approach to treat mCRC patients may be suitable for select patients through initial combination chemotherapy, which remains the backbone of mCRC therapy[66,67]. Despite the improved rates of tumour control, another phase III study failed to demonstrate a survival benefit from the addition of oxaliplatin to infused 5-FU and lend further support to the use of sequential monotherapy in some patients with this disease[68]. Hence, for patients not suited for resection of metastases, single-agent chemotherapy should be considered (Level 1B).

The COIN trial[69] addressed the issue of continuous versus intermittent chemotherapy in patients with mCRC. The trial did not meet its primary outcome objective, which was to demonstrate the non-inferiority of intermittent chemotherapy to continuous chemotherapy as first-line therapy in mCRC. However, it did show that intermittent chemotherapy is associated with improved quality of life, shortened time for chemotherapy, reduced number of hospital visits, and a minimum difference in overall survival. Hence, the panel recommends intermittent chemotherapy for patients with mCRC (Level 2B).

First-line treatment options for unresectable mCRC

- Clinical trials
- Capecitabine alone
- 5-FU/LV alone
- CAPEOX (with or without bevacizumab) (cetuximab is not given with CAPEOX because of the high incidence of diarrhoea and poor survival times)
- FOLFOX (with or without bevacizumab)
- FOLFIRI (with or without bevacizumab or cetuximab)
- CAPIRI (with or without bevacizumab)
- FOLFOX (with or without Panitumumab in ras-WT)

Second-line treatment options for mCRC

Treatment following progressive disease on or soon after the completion of first-line therapy:

- Clinical trials
- Single-agent irinotecan or FOLFIRI
- Oxaliplatin in combination with a fluoropyrimidine is usually given as second-line treatment if irinotecan-based chemotherapy was administered during first-line treatment

- Targeted therapeutic agents such as cetuximab, bevacizumab, and panitumumab
- Cetuximab or Panitumumab may be given with irinotecan in patients with wild-type RAS disease
- Bevacizumab may be given with fluoropyrimidine-based chemotherapy
- Aflibercept may be considered in some patients[70].

If progression occurs after a long disease-free interval (i.e. greater than 1 year), retreatment with the previous chemotherapy regimen may be considered.

Third-line treatment options for mCRC

Where possible, patients should be offered entry into appropriate clinical trials. In certain cases, particularly when patients are not eligible for trial entry, treatment may be offered 'off study'. Cetuximab and panitumumab have both been demonstrated to improve clinical outcomes in the third-line setting in cases of wild-type *RAS* disease. Referral for possible inclusion in phase I studies may also be considered.

- Clinical trials
- Cetuximab in combination with irinotecan or as monotherapy after failure of oxaliplatin-based and irinotecan-based therapy or intolerance to irinotecan
- In patients with liver predominant disease, liver intervention procedures can be considered, such as treatment with selective internal radiation therapy with yttrium-90 microspheres
- Off study chemotherapy treatment, such as retreatment with a previously successful regimen after a long disease-free interval or capecitabine/mitomycin C
- Referral to phase 1 trials if possible, provided the patient has good performance status and renal and hepatic function
- Regorafenib[71]
- Best supportive care alone

CHAPTER

6 SUPPORTIVE CARE

Supportive care refers to providing support at all stages of a person's experience with cancer. The primary aim of treatment is to bring about symptomatic benefit and improvement in the quality of life of patients with incurable malignancies and support patients while receiving chemotherapy. Common problems that may occur in patients with gastrointestinal malignancies include the following:

- Pain
- Nausea and vomiting
- Poor appetite
- Bowel obstruction
- Anxiety, emotional distress, or depression
- Chemotherapy-related toxicities

Optimal control of these symptoms often requires input from specialist teams, including palliative care providers, surgical teams, and psychological support experts. Where symptom control is problematic, many patients will benefit from early palliative care input.

Fertility

Chemotherapy (and radiotherapy) can potentially adversely affect fertility. The risk of infertility varies among chemotherapy drugs. An example of chemotherapy drugs used in the treatment of CRC that are associated with a risk of infertility is oxaliplatin.

Other commonly used chemotherapy agents may be associated with lesser risk, but all chemotherapy drugs should be considered to have the potential to negatively affect fertility. Pelvic irradiation is also gonadotoxic and places patients at risk of infertility. All men and premenopausal women undergoing treatment placing them at risk of infertility should have these risks discussed with them and should be offered the option to consider fertility-preserving strategies (e.g., sperm banking for men and in vitro fertilization/embryo freezing for women) before commencing chemotherapy, especially in the adjuvant chemotherapy setting. Men should be made aware that they need to be tested for hepatitis B, hepatitis C, and human immunodeficiency virus infection prior to sperm banking. For young women receiving pelvic radiotherapy for rectal cancers, ovarian transposition as an option should be discussed.

Bowel obstruction

Any intra-abdominal malignancy may cause bowel obstruction, especially in cases of peritoneal disease. This diagnosis must be borne in mind for any patient who presents with colicky abdominal pains, nausea, and vomiting. Patients who have protracted vomiting or whose pain is poorly controlled should be hospitalized. They should be kept nil by mouth, and intravenous (IV) fluid administration should be

commenced. Subcutaneous (SC) infusion of morphine (and cyclizine) can be effective for analgesia, and steroids can be given IV. These measures are often sufficient to improve symptoms, but if vomiting persists, it may be necessary to insert a nasogastric tube. In severe cases, octreotide can be considered, as this can be helpful in reducing gastrointestinal secretions. In select cases, the opinion of a surgeon should be taken for a single level of obstruction, which can be palliated with a stoma. Possible surgical interventions include palliative bypass procedures, defunctioning colostomy, and enteric or colonic stenting.

Algorithm for bowel obstruction:

Single: can be surgically resected to relieve obstruction

Multiple: surgery not an option, symptomatic medical management can be considered

- Sub-acute and potentially reversible: bowel sounds hyperactive

  Dexamethasone, 16mg/day SC/IV (rarely), to reduce tumour oedema
  Metoclopramide, 10–30mg q6h SC/IV, for vomiting
  Octreotide to reduce secretions
  Hyoscine butyl bromide, 20mg q6h SC, or dicyclomine, 10–20mg q6–8h SC, for colicky pain

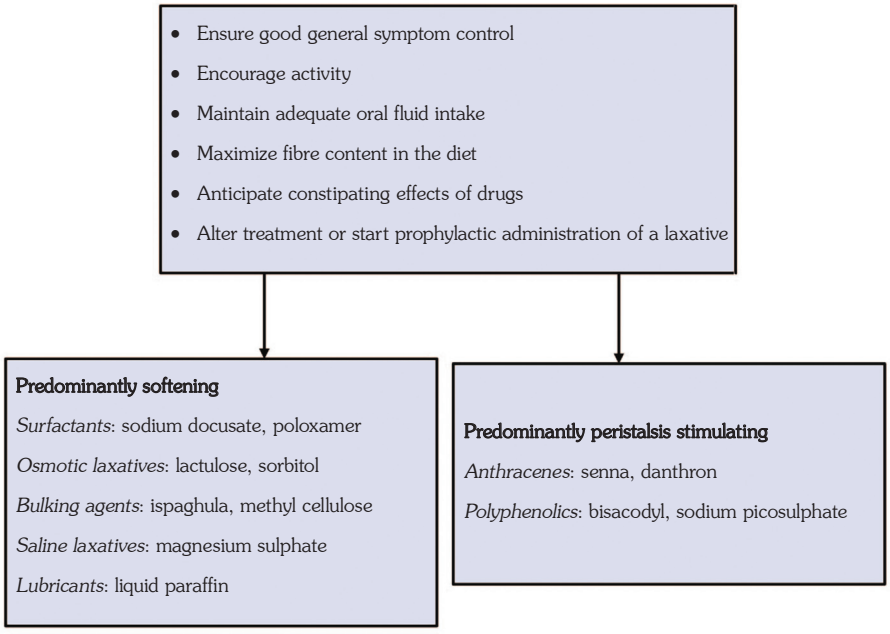
- Complete and irreversible: bowel sounds absent (terminal care)

  Morphine, 10mg q4h SC injection or rarely IV, to further relax the bowel
  Haloperidol, 1–2mg SC injection for 24h, to control vomiting
  Hyoscine butyl bromide, 20mg q6h SC, or octreotide to reduce secretions
  For high obstruction, venting gastrostomy can be considered

- Minimal hydration via the SC route, sips of fluid and ice or pineapple chunks

Constipation: This is commonly due to drugs, reduced oral intake, vomiting, or lack of exercise. Anti-emetic agents can also lead to constipation.

General measures



In general, combinations are found to be more effective,e.g., cremaffin plus (liquid paraffin + milk of magnesia + sodium picosulphate)

Liver pain

Patients with metastatic liver disease may describe sharp pain in the right hypochondrium, which may worsen on deep inspiration (referred shoulder tip pain may also be a feature). This pain is thought to be due to 'stretching' of the liver capsule by the tumour. A short reducing course of steroids (with proton pump inhibitor [PPI] cover) is usually an effective treatment for this pain, but long-term analgesia may also be necessary. Non-steroidal anti-inflammatory drugs with PPI cover can also be helpful.

Pain

World Health Organization (WHO) analgesic ladder

Step 1 Non-opioid ± adjuvant	**Step 2** "Mild opioid" for mild–moderate pain ± non-opioid ± adjuvant	**Step 3** "Strong opioid" for severe pain ± non-opioid ± adjuvant
General/neurosurgery/orthopaedic surgery Interventional anaesthetic techniques TENS/acupuncture/complementary therapy		
Disease-modifying treatment Chemotherapy/radiotherapy/radiopharmaceuticals/steroids/bisphosphonates		
Address psychological, emotional, spiritual, social, financial distress		

Mild opioid: Tramadol (100 mg 4 times a day [QDS] = 20 mg QDS of morphine), codeine, dihydrocodeine

Stronger opioid: morphine diamorphine, fentanyl, buprenorphine, oxycodone, hydromorphone

Paracentesis

a) The puncture site needs to be away from scars, tumour masses, distended bowels, the liver and bladder, and other organs; the right or left lower quadrant is usually safe.US should be arranged for the radiologist to mark a suitable site.

b) In patients who have undergone paracentesis multiple times, the ascites may become loculated. Ultrasonography is mandatory in these patients to locate the point of maximum fluid.

Surgery

Many patients present late with spurious diarrhoea due to obstructing lesions. These patients need to undergo faecal diversion before neoadjuvant therapy. Loop sigmoid colostomy has theoretical advantages in that it can be converted to end colostomy, should abdominoperineal excision be necessary, and can be used for anastomosis for ARs. Loop transverse colostomies provide adequate diversion and can be retained in situ if LAR is performed for continued diversion (Level 2B).

Diverting loop colostomy or ileostomy is often created at the time of LAR to mitigate septic complications of an anastomotic leak. Although the majority of surgeons perform loop transverse colostomy, the drawbacks are that the stoma is bulky; the effluent, odorous; and the stoma, prone to prolapse. The marginal artery could also theoretically get injured. Ileostomies, on the other hand, are smaller, less odorous, and easier to manage with appropriate appliances. Electrolyte and fluid imbalances are rare (Level 2A).

Stoma closure

There is no ideal time for closure of the diverting stoma often created at the time of LAR. Closure soon after confirming the absence of a leak in 7–10 days postoperatively, if uncomplicated, marks the end of surgical therapy, and the patient can carry on with adjuvant therapy. Closure during adjuvant chemotherapy is cumbersome, interrupts the schedule, and may be detrimental.

Closure after completion of adjuvant chemotherapy facilitates uninterrupted chemotherapy, but the patient has to live with a stoma for nearly a year. These options are to be discussed with the patient and a joint decision should be made in the best interest of the patient. Referral to a stoma clinic, when possible, should be made.

Rectal stent

High and mid rectal cancers can be stented prior to neoadjuvant therapy. Though expensive, stents provide effective relief of obstruction in the short term and avoid admission, anaesthesia, and surgery.

Symptomatic treatment of toxicities related to chemotherapy

Although chemotherapy agents each have individual toxicity profiles, the severity of side effects seen varies widely from patient to patient. The recording of treatment-related toxicity is standardised according to the National Cancer Institute Common Toxicity Criteria for Adverse Events. Two versions are in use, version 3.0 and 4.0 (applicable from 10.01.2009). Both versions are available on the intranet link 'NCIC common toxicity criteria' in the 'clinical' section or on the internet website http://ctep.cancer.gov/reporting/ctc.html. This terminology provides criteria to grade treatment-related toxicities on a scale of 1 to 5. Guidance on dose reduction (DR) required for patients receiving offstudy/trial treatment can be found in this handbook. A general guide:

Grade (general definitions)

0 = No adverse event or laboratory values within normal limits

1 = Mild adverse event

2 = Moderate adverse event

3 = Severe and undesirable adverse event

4 = Life-threatening or disabling adverse event

5 = Death related to adverse event

Diarrhoea

The cause of diarrhoea should be established so that the most appropriate treatment can be recommended. Rectal examination and plain radiography should enable the exclusion of overflow diarrhoea. Steatorrhoea should be considered in patients at risk of pancreatic insufficiency, and pancreatic supplements should be administered (Creon) if necessary (if patients have undergone colo-whipple for CRC). Recent antibiotic therapy may suggest *Clostridium difficile* diarrhoea and a stool sample should be sent for examination before commencing oral metronidazole. Loperamide should not be used in patients with proven *C. difficile* diarrhoea because of the risk of toxic megacolon. *In situ* rectal tumours may cause discharge, and palliative radiotherapy should be considered in these cases. Endoscopic laser ablation is an alternative if radiotherapy is not possible. Symptomatic relief may be achieved with loperamide and/or codeine phosphate.