# Management of Colorectal Cancer

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## Contents



Over recent decades there has been a marked improvement in survival outcomes of patients with CRC. A number of factors have contributed to this including earlier diagnosis through the utilisations of two-week rule referral pathways, the adoption of an MDT approach to management, refinements to the surgical management,

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improved staging including the utilising of MRI and PET in selected cases, developments in systemic chemotherapy and improved follow-up assessments.

## 3.1 Role of the Multidisciplinary Team (MDT)

The treatment plan for any individual patient is indicated by a number of factors, including:

- Primary site of disease (colon vs rectum)
- Stage of the tumour
- Patient factors including co-morbidities and performance status.

Localised colonic tumours are frequently managed with primary surgery. For rectal tumours neoadjuvant strategies utilising radiotherapy or chemoradiotherapy may be utilised to minimise the risk of subsequent local disease recurrence. A proportion of patients will present with oligometastatic disease (most commonly liver metastasis) that may be amenable to a curative approach. The multidisciplinary team input is key to achieving the optimal patient outcomes.

## 3.2 Management of Localised Disease

### 3.2.1 Surgery for Localised Disease

- Early T1 tumours: A small proportion of patients with early T1 tumours (with limited submucosal involvement) considered at low risk of nodal involvement may be amenable to removal by endoscopic mucosal resection.
- Localised colonic tumours are treated as follows:
  - Right hemicolectomy is performed for tumours of caecum, ascending colon and proximal transverse colon.
  - Tumours of descending and upper sigmoid colon are removed by left hemicolectomy.
  - Distal sigmoid and upper and mid rectal tumours are removed by anterior resection.
- It has been shown that there is no difference between open and laparoscopic approaches in experienced hands.
- It is important to achieve reasonable nodal clearance and a minimum of 8 and ideally at least >12 nodes is recommended for adequate staging. If lymph node clearance is not adequate, then there is a risk of under-staging.
- In patients presenting with complications, i.e. obstruction or perforation, emergency decompression and resection, can be performed as a one-stage or two-stage procedure with a stoma. Emergency surgery is associated with higher perioperative mortality due to poor nutritional status of patients, poor bowel preparation and locally advanced disease and higher rates of recurrence.

### 3.2.2 Rectal Tumours

- There have been significant improvements in local control rates with the adoption of total mesorectal excision (TME) surgery and the use of pre-op chemoradiotherapy or radiotherapy.
- In patients with rectal tumours, pelvic MRI is used to stage the local disease and nodes and relationship of tumour with mesorectal fascia. A distance of <2 mm between the primary tumour and the mesorectal fascia is predictive of potential involvement of circumferential resection margin (CRM) (<1 mm) following surgery. With the development of TME for rectal tumours, local recurrence rates have reduced from >20% to <10% [1, 2].
- Lower rectal tumours can be excised by abdomino-perineal resection with removal of the anal canal and a permanent stoma; more recently, however, there has been a shift towards low anastomosis without stoma.

## 3.3 Adjuvant Treatment in Localised Disease

### 3.3.1 Chemotherapy

- Adjuvant chemotherapy for 6 months with 5-fluorouracil or capecitabine with or without oxaliplatin has demonstrated benefit for patients with stage III disease [3, 4] (please see metastatic section for more details on chemotherapy).
- In patients with stage II disease, the benefit is more modest and adjuvant chemotherapy with single agent capecitabine is recommended in patients with the following high risk factors:
  - T4 tumours
  - Number of nodes examined not adequate
  - Poorly or undifferentiated tumours
  - Emergency presentation
  - Presence of extramural vascular invasion
- In patients with stage II disease with microsatellite instability (MSI), adjuvant chemotherapy is not recommended.

## 3.4 Radiotherapy

- Radiotherapy has an important role in patients with rectal tumours in the neoadjuvant and adjuvant setting, to either downsize locally advanced rectal tumours to render them resectable or to prevent local recurrence [5].
- Both short-course (25Gy in 5 fractions) and conventionally fractionated (45–50.4Gy in 1.8–2.0Gy/fraction) preoperative radiotherapy have demonstrated improved local control [6, 7]. Chemoradiotherapy has shown to be more effective than radiotherapy alone in resectable disease. In locally advanced rectal tumours, neoadjuvant concurrent chemoradiotherapy is the standard of care [8–10].

### 3.4.1 Follow-Up

Following adjuvant treatment patients are followed up every 3 months with tumour marker CEA (carcinoembryonic antigen) and annual CT scans up to 3 years to identify any early relapses especially oligo-metastatic disease which may be amenable to curative surgery.

## 3.5 Treatment of Metastatic Colorectal Cancer (mCRC)

- Around 30% of patients with mCRC present with stage IV or advanced disease and ~25% of patients treated with localised disease develop recurrent disease. PET/CT plays a key role in the delineation of the metastatic burden.
- Historically, median overall survival with best supportive care is less than 6 months.
- Treatment with systemic chemotherapy increases overall survival up to 20 months.
- Patients with metastatic disease need to undergo testing of the *RAS/RAF* status. Patients with mutations in *RAS/RAF* pathway do not respond to epidermal growth factor (EGFR)-targeted therapy. Recent data suggest that in patients with wild-type *RAS/RAF*, overall survival of up to 30 months can be achieved with the use of targeted agents. *BRAF* mutations are associated with poor prognosis and seen in 5–11% of patients with mCRC [11, 12].
- Surgery is used in the advanced setting for potentially resectable disease in the liver or lungs or for palliation of symptoms.

## 3.6 Systemic Therapy

### 3.6.1 Cytotoxics

#### 3.6.1.1 Fluropyrimidine-Based Therapy

- 5-FU is the backbone of the chemotherapeutic regimens used in advanced disease in first- and second-line settings. It works by inhibition of thymidylate synthase (TS), thereby inhibiting DNA synthesis. It is co-administered with folinic acid, which stabilises the interaction with TS. It can be administered as an infusion or bolus, with infusion having less marrow suppression.
- Capecitabine, an oral prodrug of 5-FU, has equal efficacy to 5-FU [13]. In meta-analyses, 5-FU-based regimens prolong median survival by 12 months. Side effects of infusional 5-FU include diarrhoea; capecitabine has comparatively much higher incidence of diarrhoea, mucositis and hand-foot syndrome. Coronary vasospasm is another side effect that limits use of 5-FU/capecitabine and raltitrexed is used in such patients.

#### 3.6.1.2 Doublet-Chemotherapy Regimens

5-FU or capecitabine is combined with oxaliplatin or irinotecan.

- Oxaliplatin is platinum-based chemotherapy that binds with DNA, forming intra- and interstrand adducts, which are cleared by DNA damage pathways. The main side effect with oxaliplatin is cumulative sensory neuropathy and is a dose-limiting toxicity. Combination of 5-FU with oxaliplatin (FOLFOX) improves progression-free survival but not overall survival; combining oxaliplatin with capecitabine showed equal efficacy and tolerability [13].
- Irinotecan causes DNA single-strand breaks by inhibiting topoisomerase 1 leading to apoptosis. Severe diarrhoea is a well-recognised side effect of irinotecan, and early initiation of anti-diarrhoeal therapy is recommended. Irinotecan in combination with infusional 5-FU (FOLFIRI) was reasonably well tolerated and improved response rates and overall survival in phase III trials [14]. Combining irinotecan with capecitabine, however, led to excessive diarrhoea and is not commonly used.

## 3.7 Targeted Agents

### 3.7.1 Bevacizumab

- Bevacizumab, a humanised monoclonal antibody against VEGF ligand, is an anti-angiogenic agent used in the first-line setting in combination with 5-FU/capecitabine and oxaliplatin [15].
- Hypertension and proteinuria are common side effects with the drug. Arterial thromboembolic events [16], haemorrhage, perforation and fistula formation are much rarer but serious side effects with bevacizumab. The risk of perforation is increased with recent surgery and peritoneal disease.

## 3.8 Cetuximab

- In patients with wild-type K-Ras, cetuximab, an anti-EGFR chimeric antibody, offers a small survival benefit over best supportive care in the third-line setting.
- In a select group of patients, it can be used in combination with chemotherapy in the first-line setting [17].
- An acneiform rash is a common side effect with cetuximab, and treatment with tetracycline-based antibiotics is now part of prophylaxis.

## 3.9 Aflibercept

Aflibercept, a VEGF trap antibody, has shown improved overall survival when used in combination with FOLFIRI in patients with mCRC after treatment with an oxaliplatin-based regimen, including bevacizumab-treated patients [18].

## 3.10 Regorafenib

Regorafenib is a small molecule multi-kinase inhibitor that has shown overall survival benefit in patients with mCRC who have progressed after standard lines of treatment [19].

## 3.11 Role of Surgery in Advanced Colorectal Cancer

- Metastatic disease is most commonly limited to the liver with a small percentage of patients presenting with lung metastases.
- Resection of liver-only metastases results in a 30% improved 5-year survival in patients with advanced disease. 10% of patients have liver metastases that is resectable at presentation and 10% of patients have metastases that can be downstaged by chemotherapy and then resected.
- In symptomatic patients with obstruction or bleeding, palliative surgery is performed as a semi-elective procedure or as an emergency. The use of colonic or rectal stents to relieve obstruction remains controversial and has been associated with high rates of perforation in few studies.

## 3.12 Other Modalities of Treatment

Radiofrequency ablation has a role in the treatment of liver metastases and lung metastases. Patients need to be selected carefully in a MDT setting for these treatments.

**Conclusion**

Patients with colorectal cancer have numerous treatment options, and personalising treatment care in a MDT setting achieves better survival outcomes. PET imaging plays an important role in the diagnostic pathway and management of these patients.

**Key Points**

- The treatment plan for any individual patient is indicated by a number of factors, including primary site of disease (colon vs rectum), stage of the tumour, patient factors including co-morbidities and performance status.
- Localised colonic tumours are frequently managed with primary surgery.
- Right hemicolectomy (tumours of caecum, ascending colon and proximal transverse colon).
- Left hemicolectomy (tumours of descending and upper sigmoid colon)

- Anterior resection (distal sigmoid and upper and mid rectal tumours)
- In patients with rectal tumours, neoadjuvant strategies utilising radiotherapy or chemoradiotherapy may be utilised to minimise the risk of subsequent local disease recurrence.
- Lower rectal tumours can be excised by abdomino-perineal resection with removal of the anal canal and a permanent stoma; more recently, however, there has been a shift towards low anastomosis without stoma:
  - Adjuvant chemotherapy for 6 months with 5-fluorouracil or capecitabine with or without oxaliplatin has demonstrated benefit for patients with stage III disease.
  - Radiotherapy has an important role in patients with rectal tumours in the neoadjuvant and adjuvant setting, to either downsize locally advanced rectal tumours to render them resectable or to prevent local recurrence.
- Around 30% of patients with mCRC present with stage IV or advanced disease, and ~25% of patients treated with localised disease develop recurrent disease. PET/CT plays a key role in the delineation of the metastatic burden.
- Metastatic disease is most commonly limited to the liver with a small percentage of patients presenting with lung metastases.
- Resection of liver-only metastases results in a 30% improved 5-year survival in patients with advanced disease.
- Radiofrequency ablation has a role in the treatment of liver metastases and lung metastases.

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