CONSENSUS DOCUMENT FOR MANAGEMENT OF COLORECTAL CANCER

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CHAPTER

1 INTRODUCTION

Colorectal cancer (CRC) is a formidable health problem worldwide. It is the third most common cancer in men (663000 cases, 10.0% of all cancer cases) and the second most common in women (571000 cases, 9.4% of all cancer cases)[1]. Almost 60% of cases are encountered in developed countries. The number of CRC-related deaths is estimated to be approximately 608000 worldwide, accounting for 8% of all cancer deaths and making CRC the fourth most common cause of death due to cancer. In India, the annual incidence rates (AARs) for colon cancer and rectal cancer in men are 4.4 and 4.1 per 100000, respectively. The AAR for colon cancer in women is 3.9 per 100000. Colon cancer ranks 8th and rectal cancer ranks 9th among men. For women, rectal cancer does not figure in the top 10 cancers, whereas colon cancer ranks 9th [2].

In the 2013 report, the highest AAR in men for CRCs was recorded in Thiruvananthapuram (4.1) followed by Banglore (3.9) and Mumbai (3.7) . The highest AAR in women for CRCs was recorded in Nagaland (5.2) followed by Aizwal (4.5)[2].

In a recently conducted study of 224 colorectal tumours by the Cancer Genome Atlas Network, the pattern of genomic alterations in colon and rectal tissues was found to be similar, regardless of the anatomic location and origin. The researchers concluded that tumours of the colon and rectum can be grouped together. The study identified a set of 24 genes mutated in a significant number of cases. In addition to genes found through prior research (e.g.APC, ARIDIA, TP53, KRAS, and PIK3CA), the researchers identified new genes such as SOX9, FAM123B/WTX, ERBB2, and IGF2. These genes were involved in regulating cell proliferation and can therefore serve as potential therapeutic drug targets[3].

Several international consensus guidelines are available for the management of CRC but we don't have something specific for India, hence the need for this consensus document.

Risk factors for CRC can be broadly divided into genetic and environmental or lifestyle-related factors. Most CRCs are sporadic, although genetic factors increase the risk considerably.

A. GENETIC FACTORS INCLUDING HEREDITARY CRC SYNDROMES

These can be classified as those associated with colonic polyposis and those not associated with colonic polyposis.

Among the colonic polyposis syndromes, familial adenomatous polyposis(FAP)and its variants (Turcot, Gardner, and attenuated FAP) and MYH-associated polyposis are the most common. Hereditary non-polyposis colon cancer(HNPCC) or Lynch syndrome comprises the non-colonic polyposis category.

- FAP is characterized by multiple colonic adenomatous polyps appearing in childhood with subsequent transformation to malignancy at an average age of 45 years and is caused by a germline mutation in the *APC* gene on chromosome 5[4].

- Turcot syndrome (glioma-polyposis) is a variant of FAP in which there exists an association between multiple colorectal adenomas and primary neuroepithelial brain tumours as a result of a germline *APC* mutation or mutations in mismatch repair (MMR) genes (*MLH1* and *PMS2*).
- Gardner syndrome includes mandibulomaxillary osteomas and multiple epidermoid cysts along with multiple colonic polyps.
- Attenuated FAP is associated with the same genetic mutation as FAP but is characterized by fewer adenomas and a later average age at CRC presentation.
- MYH-associated polyposis is inherited in an autosomal recessive pattern, with mutations in the base excision repair gene *mutY* homologue[5].
- Lynch syndrome(HNPCC) is an autosomal dominant condition and is caused by a defect in one of the MMR genes, namely*MLH1*, *MSH2*, *hMSH6*, or *PMS2*. The peculiarity of Lynch syndrome is the early average age of onset of colorectal malignancy and the predominance of right-sided colonic lesions. Breast, thyroid, and gynaecological cancers can co-exist[6,7].

B. ENVIRONMENTAL FACTORS

- Age and gender: Older men are at a high risk (25% higher in men than in women)[8].
- Ulcerative colitis:The extent, duration, and activity of disease are primary determinants[9].
- Ethnicity: The African American populationis at an increased risk.
- Long-term immunosuppression following organ transplantation, especially renal transplantation: The relative risk is the same as that of the normal population, but aged 20–30 years older[10].
- Diabetes mellitus associated with insulin resistance: This linked to the long-term effects of insulin-like growth factors[11,12].
- Alcohol consumption: Reduction in alcohol consumption may decrease the incidence of colorectal malignancy, especially among those with a positive family history[13].
- Consumption of fresh red meat and processed meat is associatedwith increased risk[14-16].
- Obesity[17].
- Cigarette smoking[18].
- Use of androgen deprivation therapy, e.g.orchidectomy and gonadotropin-releasing hormone analogues.
- Acromegaly[19].
- History of cholecystectomy[20].
- Ureterocolic anastomosis.

- Several associations show conflicting evidence in the current literature. The following are some of major associations with CRC[19].
    1. Presence of coronary heart disease
    2. Decreased dietary fibre and fruit intake
    3. History of radiation therapy for prostate cancer
    4. Human immunodeficiency virus infection/acquired immunodeficiency syndrome
    5. Prior treatment of Hodgkin lymphoma
    6. Decreased physical activity

CHAPTER

2 DIAGNOSIS CRITERIA AND INITIAL WORKUP

- **History**

All patients with colon cancer should be counselled regarding family history and risk assessment. Significant family history includes FAP and HNPCC. An algorithm on how to manage bleeding per rectum is shown in Appendix A.

- **Physical Examination**

Digital rectal examination has a high positive predictive value for the presence of rectal tumours. However, a negative examination does not rule out CRC, as more than 60% of lesions are out of reach of the palpating finger.

- **Blood Tests**

These tests include complete blood counts, liver and kidney function tests, carcinoembryonic antigen (CEA) tests, and carbohydrate antigen 19.9 (CA19.9). Preoperative CEA levels predict recurrence in patients with stage C (stage III) disease and in those with stage B (stage II) disease as well. In a study of patients with stage B disease, the recurrence rate was 10% for CEA levels of <2.5 ng/mL and 30% for CEA levels of >10 ng/mL. In patients with stage C disease, a preoperative CEA level of >2.5ng/mL was associated with a 1.8-fold higher risk of recurrence[21]. Both CEA and CA19.9 (whichever is high at diagnosis) can be useful markers for patient follow up. An increasing tumour marker level can be an indication for early imaging studies for staging in order to detect recurrence.

- **Colonoscopy**

Rigid sigmoidoscopy instruments limit evaluation to the distal 25 cm of the colon, whereas flexible sigmoidoscopy permits evaluation of the distal 55–60 cm of the colon. However, with this technique, the proximal half of the large bowel is still left unscreened. Any significant finding on sigmoidoscopy is likely followed by complete colonoscopy. In addition, in older patients, the proportion of proximal colonic cancers increases.

Complete colonoscopy (essential) should be attempted in all patients before or after surgery (within a 3-month period if index colonoscopy has not been completed). This is essential to exclude synchronous lesions or polyps. Although CT colography can be relatively sensitive and specific in research settings (85% to 90%), recent reports have suggested lower accuracy when performed by less experienced examiners. Lesions in the rectosigmoid colon may be missed on CT colography because of the difficulty in achieving adequate luminal distention in this segment[22].

- **Histopathology**

Histological confirmation of primary neoplasms is preferable, but if this is not feasible, histological confirmation of the metastatic lesion is mandatory before definitive therapy.

• Radiology

A synoptic reporting template for radiology is shown in Appendix B.

	Essential	Desirable/Ideal
Colon cancer	• Chest radiography • Abdominal ultrasonography (US) • Abdominal CT (triple phase for the liver) if liver surgery is planned	• CECT scan of the chest, abdomen, and pelvis. • A separate section on PET-CT scanning has been added. This is not routinely indicated.
Rectal cancer	Same as for colon cancer CECT scan of the pelvis	• MRI of the pelvis (preferably with an endorectal coil) • EUS • Chest CT • Abdominal CT (triple phase for the liver) • PET-CT scan if patients with mCRC are being treated with curative intent

Indications for PET-CT (desirable)

Suspected recurrence on the basis of increasing tumour marker levels or clinical symptoms: Level 1[23,24].

Diagnosis and staging: Level 2[25,26].

Before curative resection of metastatic disease[24].

CHAPTER

3 STAGING AND PROGNOSTIC CRITERIA

Tumours are staged according to the Union for International Cancer Control (UICC) TNM staging system (Appendix C). In this consensus statement, Dukes classification is used to report on evidence derived on the basis of this system. For all intent and purposes, the TNM staging system should be used for staging CRC (Level 1A).

• Stage Groupings

Stage	T	N	M	Dukes*	MAC**
0	Tis	N0	M0	–	–
I	T1	N0	M0	A	A
	T2	N0	M0	A	B1
IIA	T3	N0	M0	B	B2
IIB	T4a	N0	M0	B	B2
IIC	T4b	N0	M0	B	B3
IIIA	T1–T2	N1/N1c	M0	C	C1
	T1	N2a	M0	C	C1
IIIB	T3–T4a	N1/N1c	M0	C	C2
	T2–T3	N2a	M0	C	C1/C2
	T1–T2	N2b	M0	C	C1
IIIC	T4a	N2a	M0	C	C2
	T3–T4a	N2b	M0	C	C2
	T4b	N1–N2	M0	C	C3
IVA	Any T	Any N	M1a	–	–
IVB	Any T	Any N	M1b	–	–

NOTE:
*Dukes B is a composite of relatively good (T3N0M0) and poor (T4N0M0) prognostic groups, as is Dukes C (any TN1M0 and any TN2M0).
**MAC,modified Astler-Coller classification

• Pathological Examination

Pathologic examination should include (essential) determination of the following, as each of these factors are known to be associated with patient prognosis:

Pathologic reporting for gross and microscopic examination is shown in Appendix C.

- Tumour grade
- Depth of penetration
- Number of positive lymph nodes and number of lymph nodes evaluated (a minimum of 12 lymph nodes should be evaluated).

- Lymphovascular invasion
- Perineural invasion
- Extranodal tumour deposits
- Status of proximal, distal, and radial (circumferential) margins

For rectal cancers: circumferential resection margin (CRM) and neoadjuvant therapy effect (tumour regression grade [TRG] score). A positive CRM is defined as within 1mm. A positive CRM is a more powerful predictor of local recurrence in patients treated with neoadjuvant therapy[25].

RAS mutation testing is recommended for patients with metastatic disease: Level 1B[26a-29].

Mutations in *RAS* gene predict a lack of response to therapy with cetuximab and panitumumab.

BRAF mutation testing is not currently recommended.

CHAPTER

4 MULTIDISCIPLINARY TREATMENT FOR EARLY DISEASE

Multidisciplinary care remains at the core of treating CRCs. It relies upon an effective multidisciplinary network of surgical, medical, and radiation oncologists; gastroenterologists; pathologists; radiologists (including interventional and nuclear medicine radiologists); nurse specialists including stoma nurses; and palliative care physicians.

A. COLON CANCER

All new cases should be discussed at the tumour board or at multidisciplinary team (MDT) meetings and the treatment strategy should be confirmed. In a majority of patients with localised disease, resection will be the treatment of choice, with consideration given to adjuvant chemotherapy following resection. Occasionally, patients will present with local disease that has infiltrated adjacent structures; in these cases, the use of preoperative chemotherapy should be considered. Most patients with metastatic disease will be considered for palliative chemotherapy. A small proportion of these patients may be curable.

Treatment options

Operable disease: Primary surgery with or without adjuvant chemotherapy

Locally advanced disease, primary curative resection unlikely: Consider preoperative chemotherapy

Isolated metastatic disease: Consider resection of primary disease followed by metastasectomy with or without neoadjuvant and/or adjuvant chemotherapy

Widespread metastatic disease: Palliative chemotherapy, supportive care

Hereditary CRC

Approximately 5% of all CRCs can be attributed to a hereditary genetic predisposition, including Lynch syndrome (HNPCC) and FAP among others.

As the identification of a hereditary genetic predisposition can have implications for management of the patient and their relatives (in terms of frequency of screening colonoscopies and adjuvant chemotherapy for Dukes B disease), referral for genetic testing should be discussed with the individual patient and considered for all patients at risk.

The Revised Bethesda Guidelines and Amsterdam II criteria have been developed to identify those in whom further testing may be warranted[30]:

Amsterdam Criteria II
At least 3 relatives with CRC or Lynch syndrome-associated cancer: cancer of the endometrium, small bowel, ureter, or renal pelvis
One relative should be a first-degree relative of the other 2
At least 2 successive generations should be affected
At least 1 tumour should be diagnosed before the age of 50
FAP should be excluded in the CRC case if any present
Tumours should be verified by histopathological examination
Revised Bethesda guidelines
1. CRC diagnosed in a patient aged <50 years
2. Presence of synchronous, metachronous colorectal, or other Lynch syndrome-related* tumour, regardless of age
3. CRC with a MSI-H phenotype diagnosed in a patient aged <60 years
4. Patient with CRC and a first-degree relative with a Lynch syndrome-related tumour, with one of the cancers diagnosed at the age of <50 years
5. Patient with CRC with 2 or more first-degree or second-degree relatives with a Lynch syndrome-related tumour, regardless of age
*Lynch syndrome-related tumours include colorectal, endometrial, stomach, ovarian, pancreas, ureter, renal pelvis, biliary tract, and brain tumours; sebaceous gland adenomas and keratoacanthomas; and carcinoma of the small bowel

Genetic risk assessment for hereditary CRC (HNPCC or FAP) and referral for genetics evaluation should be considered in the following cases:

- Personal history of any CRC or gastrointestinal cancer before the age of 40 years
- Personal history of uterine cancer before the age of 45 years
- Personal history of multiple gastrointestinal polyposis
- Personal history of 2 separate primary gastrointestinal cancers or CRC
- Personal history of any cancer along with gastrointestinal hamartomas or any dysmorphology, including short stature, skeletal, neurological, and ocular and skin anomalies
- Personal history of 2 or more of the following primary cancers:
  - Colorectal
  - Endometrial
  - Gastric (stomach)
  - Ovarian
  - Urinary tract (kidneys, ureters, bladder, or urethra)
  - Hepatobiliary (liver, bile ducts, or gallbladder)
  - Small bowel (small intestine)
  - Skin
  - Brain

- Family history of colorectal or uterine cancer and a first-degree relative with any of the cancers listed above
- Individuals who fulfil the Amsterdam criteria (all 3 must be met)
- A first-degree relative has a clinical diagnosis of a polyposis syndrome such as FAP.
- A known genetic mutation in the *APC*, *MYH*, *MLH1*, *MSH2*, *MSH6*, or *PMS2* gene in a family member

While hereditary CRC (HNPCC or FAP) syndromes are most commonly seen, approximately 20 cancer predisposition syndromes, some rare, with gastro-intestinal manifestations are also noted. These cases should be referred to a geneticstesting service for complete syndromic evaluation.

Surgery for Primary CRC

Principles of Surgery

- For colon cancer: The affected part of the colon and at least a 5-cm segment on either side together with the draining lymph nodes along the feeding vessels should be resected.
- For rectal cancer: A distal margin of 1–2 cm may be acceptable (confirmed by frozen section) for low rectal cancers. Total mesorectal excision (TME) extending 4–5 cm below the distal edge of the tumour/complete TME should be performed.
- Transanal excision may be considered for mobile T1 tumours, <3 cm in size, within 8cm from the anal verge, involving <30% of the circumference, well or moderately differentiated adenocarcinoma with no angiolymphatic invasion, and with no clinically apparent nodal disease.
- Surgery should be performed 5–10 weeks after completion of a long course of NACTRT (Level 2A).
- A minimum lymph node yield of 12 is required for adequate staging (Level 1A)[31].
- Laparoscopy-assisted/Laparoscopic resection may be considered by experienced laparoscopic surgeons for uncomplicated early disease.
- Hand-sewn and stapler anastomotic techniques afford equivalent surgical outcomes. (Level 2A)
- Primary anastomosis may be deferred for long-standing obstruction leading to bowel oedema, poor nutritional status, peritonitis, and co-morbidities.
- There is no convincing evidence that mechanical bowel preparation results in a decrease in anastomotic leakage rates, and this might even be detrimental.
- R0 re-resection (salvage surgery) for recurrent disease has a role in improving long-term survival. (Level 2B)
- Resection is considered curative only if complete resection is carried out in conformation with the above principles.
- A MDT approach should be exercised in decision making.

Extent of Radical Surgery According to the Location of the Tumour

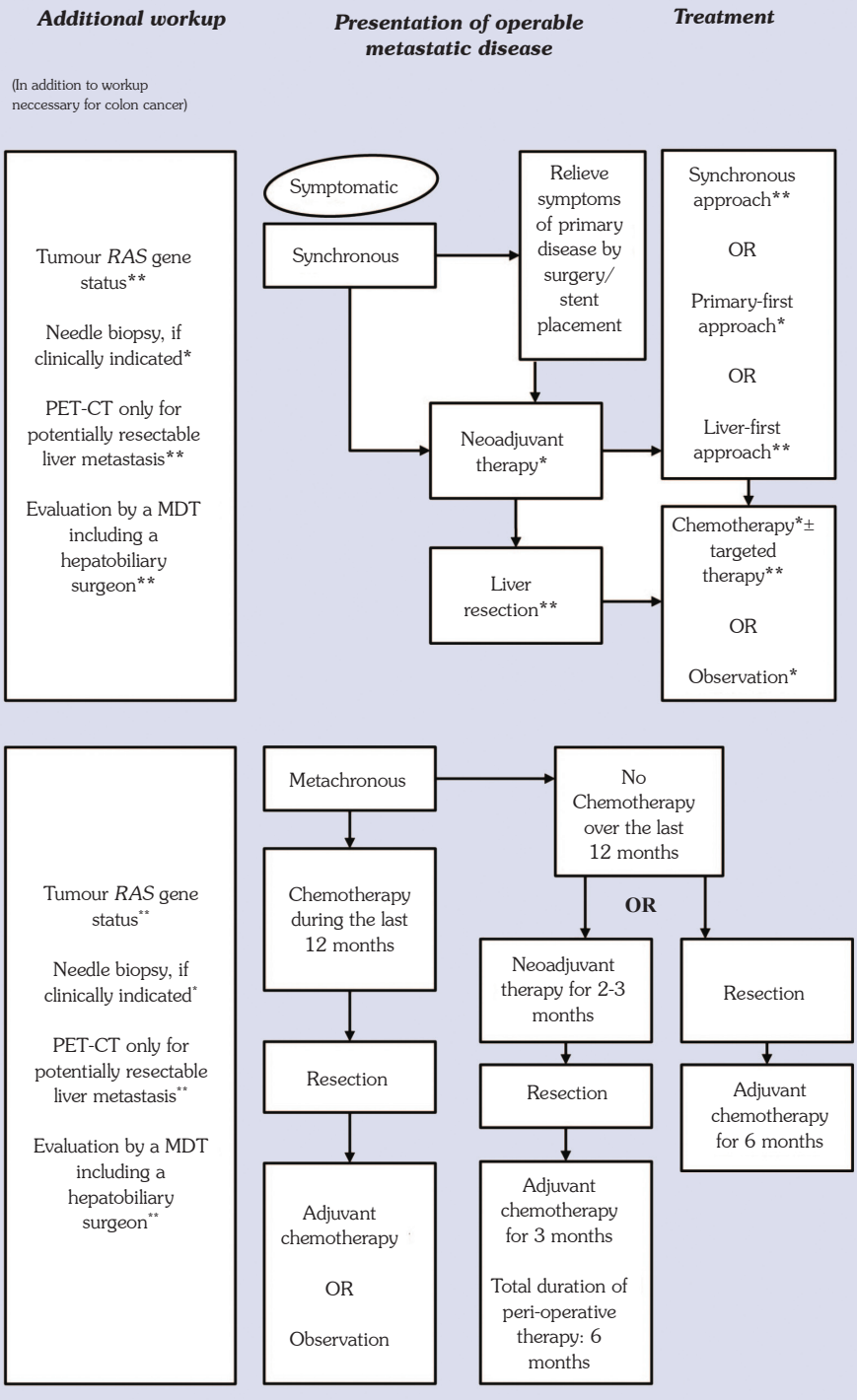
Tumour location	Radical surgery	Pedicles ligated at root
Caecum, ascending colon	Right hemicolectomy	Ileocolic, right colic, right branch of the middle colic
Hepatic flexure	Extended right hemicolectomy	As above and left branch of the middle colic
Transverse colon	Transverse colectomy/Extended right or extended left hemicolectomy	As required depending on the extent of resection
Splenic flexure	Extended left hemicolectomy	Left colic, left and right branch of the middle colic
Descending colon	Left hemicolectomy	Left colic, left branch of the middle colic
Sigmoid colon	Sigmoid colectomy	Sigmoid
Upper/mid rectum	Recto-sigmoidectomy/Low anterior resection	Inferior mesenteric vessels ligated, sparing sigmoid branches
Low rectal/Anal canal	Ultra-low anterior resection/ Inter-sphincteric resection/ Abdominoperineal excision	Inferior mesenteric vessels ligated, sparing sigmoid branches

Surgery for Colorectal Liver Metastasis (CLM)

Principles of Surgery

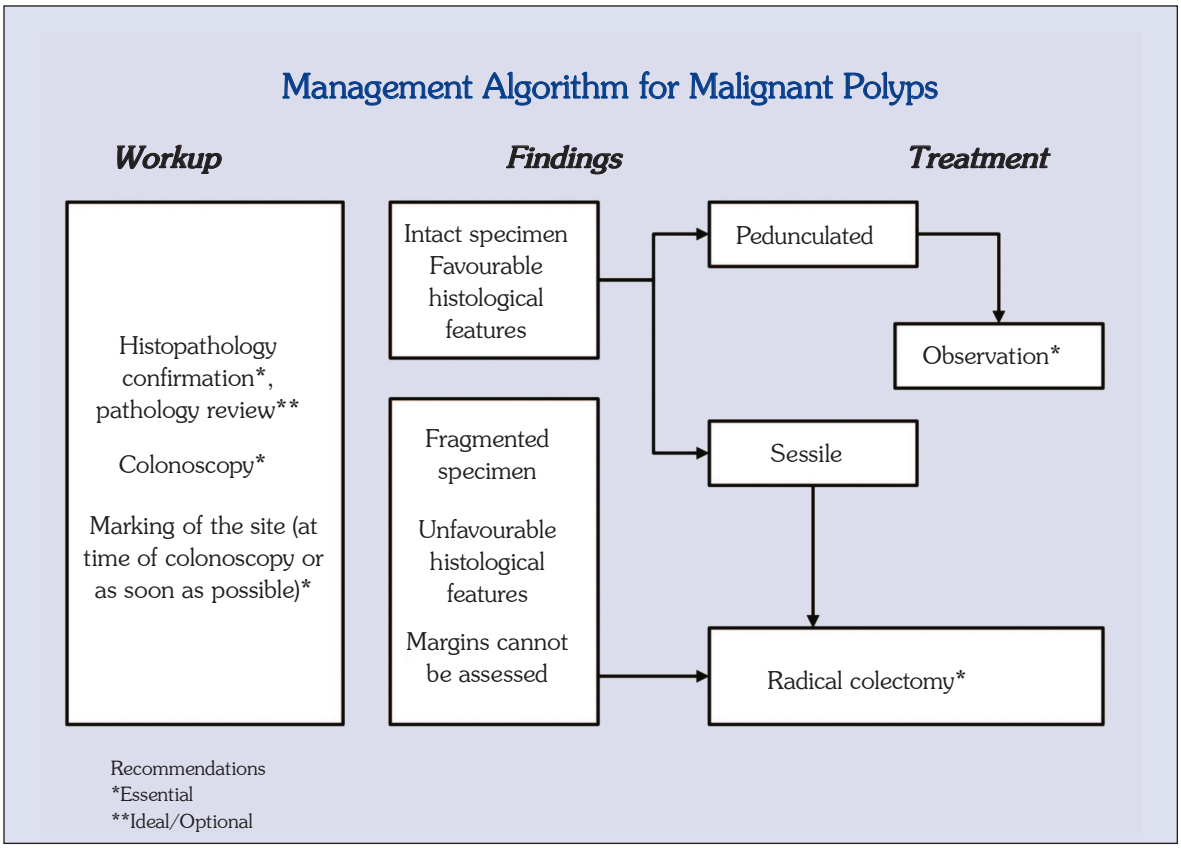
- Liver resection is the treatment of choice for resectable CLM.
- Preoperative assessment for resectability must be performed according to the location and extent of hepatic disease (segmental liver anatomy) as well as adequacy of future liver remnant (FLR).
- When the FLR is inadequate, portal venous embolization or staged liver resection can be considered.
- The primary tumour must be resectable/completely resected (R0)
- Extrahepatic disease, if present, must also be resectable.
- 'Debulking' surgery plays no role.
- For synchronous liver metastasis, simultaneous resection or a staged approach can be adopted depending on the anticipated complexity of surgery of the primary tumour and of the liver disease, available surgical expertise, and co-morbidities.
- There is an extremely low level of evidence for a 'liver first' approach.
- Liver-directed therapies can be considered alone or in conjunction with resection.
- Highly selected patients can be considered for re-resection (no extrahepatic disease, tumour<5cm, and stable serum CEA levels prior to the first hepatectomy).
- Re-evaluation for conversion to resectable disease should be considered every 2 months after preoperative chemotherapy, provided all original sites are amenable to resection.

Management Algorithm for CLM



Recommendations
*Essential
**Ideal/Optional

RAS, ras oncogene homolog from mammalian ras gene family; PET, positron emission tomography; CT, computed tomography; MDT, multidisciplinary team



Development of CRC against a Background of Polyposis

Principles of Pathology Reporting for Endoscopically Removed Malignant Polyps

- The tumour must invade the submucosa (pT1) to be defined as a malignant polyp.
- Favourable histological features include grade 1 or 2, no angiolymphatic invasion, and negative margins.
- There is no consensus on the definition of a positive margin (tumour at margin/<1mm/<2mm).
- There is no consensus on whether sessile polyps can be successfully treated by endoscopic removal.

Adjuvant Therapy for Colon Cancer

(Details of regimens with dose modification are presented in Appendix D)

General Considerations:

Five-year survival rates without adjuvant chemotherapy:

Stage I: >90%

Stage II: 70–80%

Stage III: 50–60%

These consensus statements apply to patients who have undergone potentially curative resection with no residual disease (margin-negative resection). Patients who have undergone margin-positive resection can be considered for radiotherapy.

Over the past decade, a number of clinical trials have shown a significant survival benefit for adjuvant chemotherapy with 5-fluorouracil (5-FU), capecitabine, and FOLFOX chemotherapy after resection of stage III colorectal tumours. Capecitabine has been demonstrated to be at least as effective as bolus 5-FU/folinic acid (FA) in the adjuvant setting (X-ACT trial)[32]. The MOSAIC trial demonstrated that adjuvant chemotherapy increases the 5-year survival rate to 73% for stage III/Dukes C tumours treated with adjuvant FOLFOX compared to approximately 69% for tumours treated with 5-FU/FA[33]. The benefit of adjuvant chemotherapy for stage II/Dukes B tumours is controversial, as trials have not consistently demonstrated significant advantages with regard to overall survival and disease-free survival[33]. The absolute improvement in overall survival at 5 years with adjuvant 5-FU-based chemotherapy is approximately 3–4%, although the benefit may be higher in those with high-risk features. The risks and benefits of adjuvant capecitabine monotherapy should be discussed with patients with high-risk stage II CRC. Exploratory post hoc analyses of the MOSAIC trial did not reveal survival benefits with the addition of oxaliplatin to 5-FU/LV in subgroups of patients with stage II disease (including high-risk) or patients aged 70–75 years receiving adjuvant chemotherapy[34].

Adjuvant chemotherapy, for the most part, is well tolerated, but can potentially cause significant morbidity. Selection of patients likely to gain most benefit from adjuvant treatment is important to avoid the treatment of patients with an adverse risk–benefit ratio. When assessing a patient with Dukes B CRC, the following high-risk features should be considered:

Number of nodes examined for spread (essential)

Knowledge of the number of lymph nodes examined for evidence of spread (in stage II tumours) is important when assessing an individual's risk for disease recurrence. To be considered adequately staged, a minimum of 8 nodes and ideally >12 lymph nodes should have been examined for metastatic spread. The lower the number of nodes resected, the greater the risk of understaging for stage III tumours[31,35].

Poorly/undifferentiated differentiated tumours (essential)

These tumour types indicate aggressive tumour biology and a relatively high risk of recurrence.

Emergency presentation (essential)

Presentation with bowel perforation increases the risk of recurrence.

Presence of extramural vascular invasion or perineural invasion (essential)

Extramural vascular invasion or perineural invasion, if present, is associated with a relatively high risk of tumour recurrence.

T4 classification (essential)

T4 tumours are associated with a relatively high risk of tumour recurrence.

Other factors for consideration in adjuvant treatment:

Co-morbidities

Patients with a poor performance status or co-morbidities are likely to be at greater risk of toxicity due to adjuvant therapy.

Patient choice

Not all patients who receive adjuvant therapy benefit from it. Some patients with stage II or stage III CRC may choose not to undergo adjuvant treatment and feel that surgery alone is adequate. Similarly,