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CONSENSUS DOCUMENT FOR MANAGEMENT OF COLORECTAL CANCER

Prepared as an outcome of ICMR Subcommittee on Colorectal Cancer

Indian Council of Medical Research
2014

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Prepared as an outcome of ICMR Subcommittee on Colorectal Cancer

Coordinated by

Division of Non Communicable Diseases

Indian Council of Medical Research,

Ansari Nagar, New Delhi – 110029

2014

Disclaimer

This consensus document represents the current thinking of experts on the topic based on available evidence. This has been developed by national experts in the field and does not in any way bind a clinician to follow this guideline. One can use an alternate mode of therapy based on discussions with the patient and institution, national or international guidelines. The mention of pharmaceutical drugs for therapy does not constitute endorsement or recommendation for use but will act only as a guidance for clinicians in complex decision-making.

Dr. V.M. Katoch
Secretary,
Department of Health Research
and Director General, ICMR

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Foreword

I am glad to write this foreword for Consensus Document for Management of Colorectal Cancer. The ICMR had constituted sub-committee to prepare this document for management of various cancer sites. This document is the result of the hard work of various experts across the country working in the area of oncology.

This Consensus Document on Management of Colorectal Cancer summarizes the modalities of treatment including the site-specific anti-cancer therapies, supportive and palliative care and molecular markers and research questions. It also interweaves clinical, biochemical and epidemiological studies.

The various subcommittees constituted under Task Force project on Review of Cancer Management Guidelines worked tirelessly in drafting cancer site-specific guidelines. Each member of the subcommittee's contribution towards drafting of these guidelines deserves appreciation and acknowledgement for their dedicated research, experience and effort for successful completion. We hope that this document would provide guidance to practicing doctors and researchers for the management of colorectal cancer patients and also focusing their research efforts in Indian context.

It is understood that this document represents the current thinking of national experts on this topic based on available evidence and will have to be revised as we move. Mention of drugs and clinical tests for therapy do not imply endorsement or recommendation for their use, these are examples to guide clinicians in complex decision making. We are confident that this first edition of document will serve the desired purpose.

Dr. V.M. Katoch
Secretary, Department of Health Research
and Director General, ICMR

Message

I take this opportunity to thank Indian Council of Medical Research and all the expert members of the subcommittees for having faith in me and considering me as Chairperson of ICMR Task Force project on Guidelines for Management of Cancer.

The Task Force on Management of Cancers has been constituted to plan various research projects. Two sub-committees were constituted initially to review the literature on management practices. Subsequently, it was expanded to include more sub-committees to review the literature related to guidelines for management of various sites of cancers. The selected cancer sites are lung, breast, oesophagus, cervix, uterus, stomach, gall bladder, soft tissue sarcoma and osteo-sarcoma, tongue, acute myeloid leukaemia, acute lymphoblastic leukaemia, CLL, Non Hodgkin's Lymphoma-high grade, Non Hodgkin's Lymphoma-low grade, Hodgkin's Disease, Multiple Myeloma, Myelodysplastic Syndrome and paediatric lymphoma. All aspects related to management were considered including, specific anti-cancer treatment, supportive care, palliative care, molecular markers, epidemiological and clinical aspects. The published literature till December 2012 was reviewed while formulating consensus document and accordingly recommendations are made.

Now that I have spent over a quarter of a century devoting my career to the fight against cancer, I have witnessed how this disease drastically alters the lives of patients and their families. The theme behind the designing of the consensus document for management of cancers associated with various sites of body is to encourage all the eminent scientists and clinicians to actively participate in the diagnosis and treatment of cancers and provide educational information and support services to the patients and researchers. The assessment of the public-health importance of the disease has been hampered by the lack of common methods to investigate the overall; worldwide burden. The ICMR's National Cancer Registry Programme (NCRP) routinely collects data on cancer incidence, mortality and morbidity in India through its co-ordinating activities across the country since 1982 by the Population Based and Hospital Based Cancer Registries and witnessed the rise in cancer cases. Based upon NCRP's three year report of PBCR's (2009-2011) and Time trends on Cancer Incidence rates report, the burden of cancer in the country has increased many fold.

In summary, the Consensus Document for management of various cancer sites integrates diagnostic and prognostic criteria with supportive and palliative care that serve our three-part mission of clinical service, education and research. Widespread use of the consensus documents will further help us to improve the document in future and thus overall optimizing the outcome of patients. I, thank all the eminent faculties and scientists for the excellent work and urge all the practicing oncologists to use the document and give us valuable inputs.

(Dr. G.K. Rath)
Chairperson
ICMR Task Force Project

Preface

Colorectal cancer has the lowest incidence in India compared to the western world and other countries in South East Asia. However, it has seen a steady increase in numbers with the increasing urbanization of India. Amongst all digestive cancers, this cancer carries the best prognosis largely due to the multidisciplinary treatment options that have dramatically improved over the last decade.

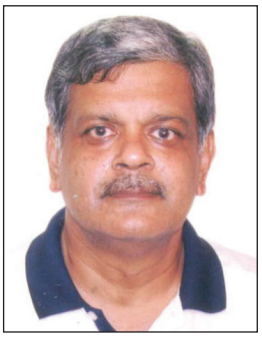
Given that colorectal cancer is an uncommon cancer in India, the busy clinician is often left confused with regard to definitive treatment algorithms in specific clinical situations. Hence the Indian Council for Medical Research (ICMR) set up a task force to come up with a consensus statement for management of Colorectal Cancers in India. The task of this renowned expert group from all corners of India was to analyse the available literature and develop practical and sound guidelines that can serve to both update the practising clinician and guide them in their day to day practice in the current Indian scenario. We apply the western data to treat our patients which may not be applicable not only because of increased toxicity as quite a few of our patients are malnourished, but there are no cost-effectiveness analyses relating to a developing country. The onus is on us to create the Indian data, hence the research questions generated by the group will help us to take this further.

I take this opportunity to thank each and every member of the group who took time out from their busy schedules and remained committed to their assigned tasks in a time bound manner. I would like to especially thank Dr Rath for inspiring us in this effort and Dr Tanvir Kaur for her continuous effort to make us stick to timelines.

These guidelines would be updated from time to time and I would look forward to your constructive feedback that would help us all in ultimately treat our patients better than ever before.

(Bhawna Sirohi)
Chairperson,
Subcommittee on Colorectal Cancer

Preface



Cancer is a leading cause of death worldwide. Globally cancer of various types effect millions of population and lead to loss of lives. According to the available data through our comprehensive nationwide registries on cancer incidence, prevalence and mortality in India among males; cancers of lung, mouth, oesophagus and stomach are leading sites of cancer and among females cancer of breast and cervix are leading sites. Literature on management and treatment of various cancers in west is widely available but data in Indian context is sparse. Cancer of gall bladder and oesophagus followed by cancer of breast marks as leading site in North-Eastern states. Therefore, cancer research and management practices become one of the crucial tasks of importance for effective management and clinical care for patient in any country. Hence, the need to develop a nationwide consensus for clinical management and treatment for various cancers was felt.

The consensus document is based on review of available evidence about effective management and treatment of cancers in Indian setting by an expert multidisciplinary team of oncologists whose endless efforts, comments, reviews and discussions helped in shaping this document to its current form. This document also represents as first leading step towards development of guidelines for various other cancer specific sites in future ahead. Development of these guidelines will ensure significant contribution in successful management and treatment of cancer and best care made available to patients.

I hope this document would help practicing doctors, clinicians, researchers and patients in complex decision making process in management of the disease. However, constant revision of the document forms another crucial task in future. With this, I would like to acknowledge the valuable contributions of all members of the Expert Committee in formulating, drafting and finalizing these national comprehensive guidelines which would bring uniformity in management and treatment of disease across the length and breadth of our country.

(Dr.D.K.Shukla)
Head, NCD Division

Acknowledgement

The Consensus Document on Management of Cancer is a concerted outcome of effort made by experts of varied disciplines of oncology across the nation. The Indian Council of Medical Research has constituted various sub committees to formulate the document for management of different cancer sites. The Task Force on Management of Cancers has been constituted to formulate the guidelines for management of cancer sites. The sub-committees were constituted to review the literature related to management and treatment practices being adopted nationally and internationally of different cancer sites. The selected cancer sites are that of lung, breast, oesophagus, cervix, uterus, stomach, gall bladder, soft tissue sarcoma and osteo-sarcoma, tongue, acute myeloid leukaemia, ALL, CLL, NHL-high grade, NHL-low grade, HD, MM, MDS, and paediatric lymphoma. All aspects related to treatment were considered including specific anti-cancer treatment, supportive care, palliative care, molecular markers, epidemiological and clinical aspects.

This document represents a joint effort of large number of individuals and it is my pleasure to acknowledge the dedication and determination of each member who worked tirelessly in completion of the document.

I would like to take this opportunity to thank Dr. GK Rath, chairperson, ICMR Task Force on Guidelines for Management of Cancer for his constant guidance and review in drafting the consensus document. The chairperson of subcommittee is specially acknowledged in getting the members together, organizing the meetings and drafting the document.

I would like to express gratitude to Dr. VM Katoch, Secretary, Department of Health Research and Director General, Indian Council of Medical Research, for taking his special interest and understanding the need of formulating the guidelines which are expected to help the cancer patients.

I would like to acknowledge here the initiative undertaken under the able guidance of Dr. Bela Shah. I would like to thank Dr. DK Shukla for his support and coordination in finalizing this document. I would also like to acknowledge the assistance provided by administrative staff. This document is the result of the deliberations by subcommittees constituted for this purpose. The guidelines were further ratified by circulation to extended group of researchers and practitioners drawn from all over the country. It is hoped that these guidelines will help the practicing doctors to treat cancer patients effectively and thus help them to lead a normal and healthy life.

The ICMR appreciatively acknowledges the valuable contribution of the members for extending their support in formulating these guidelines. The data inputs provided by National Cancer Registry Programme are gratefully acknowledged.

Tanvir Kaur

(Dr.Tanvir Kaur)
Programme Officer & Coordinator

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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

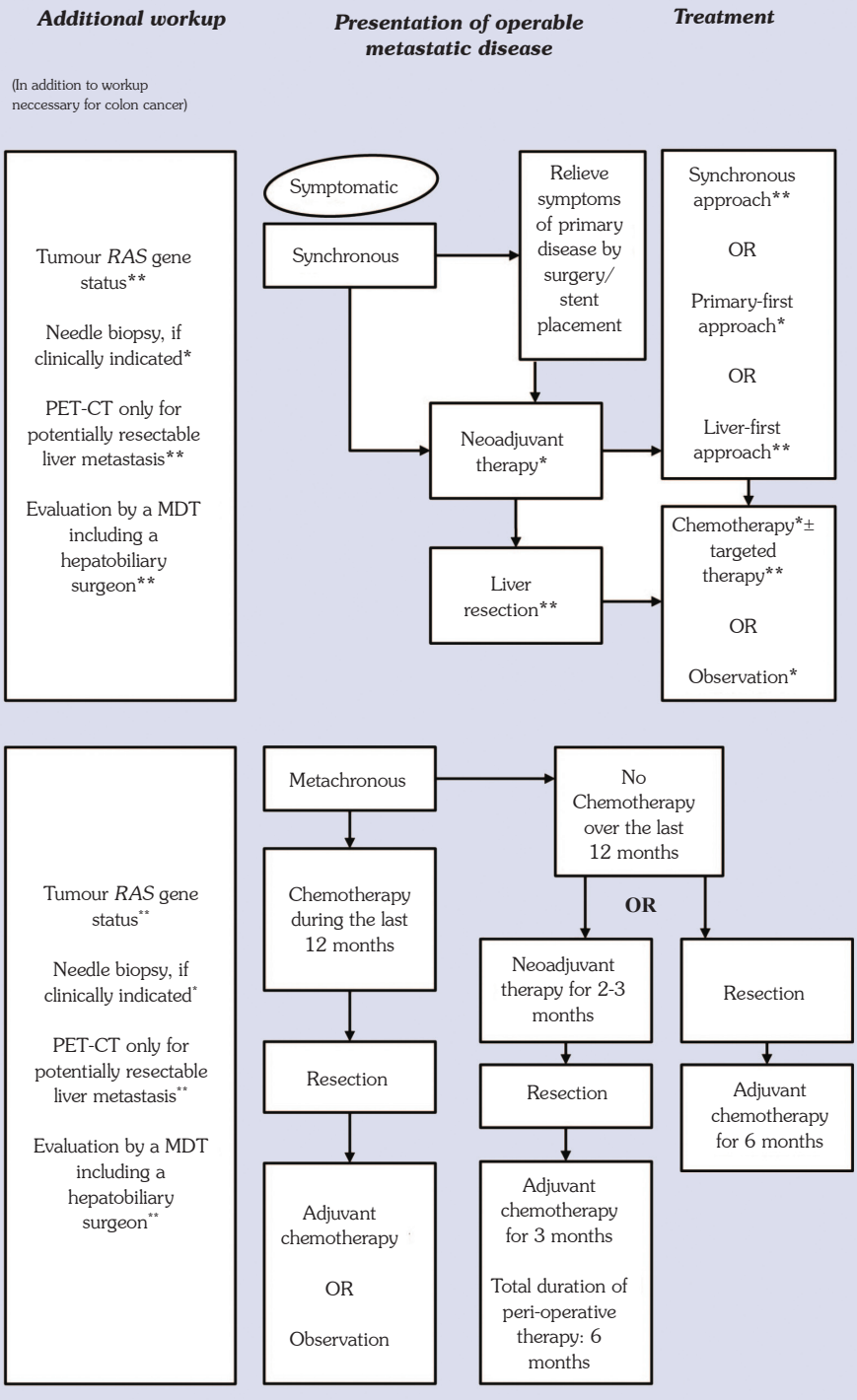
Tumour location	Radical surgery	Pedicles ligated at root
Caecum, ascending colon	Right hemicolectomy	Ileocolic, right colic, right branch of the middle colic
Hepatic flexure	Extended right hemicolectomy	As above and left branch of the middle colic
Transverse colon	Transverse colectomy/Extended right 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

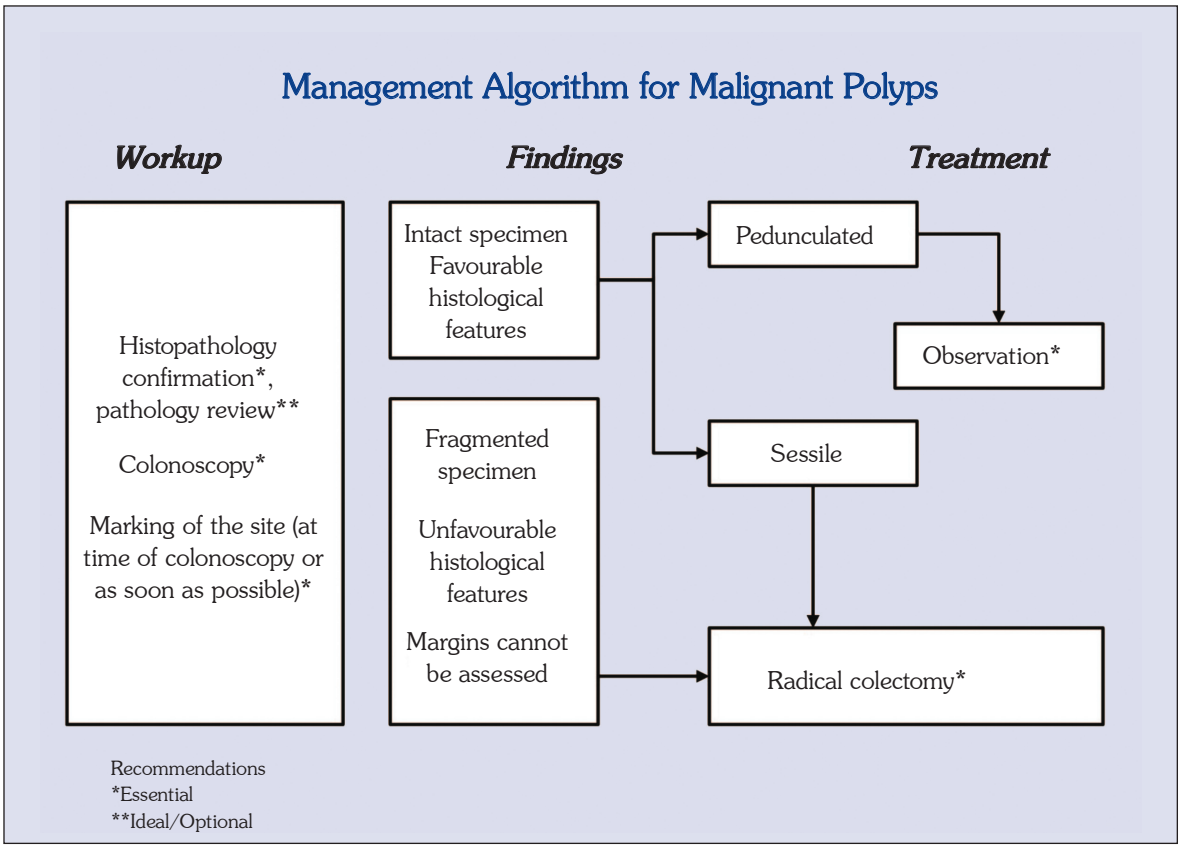
- Liver resection is the treatment of choice for resectable CLM.
- Preoperative assessment for resectability must be performed according to the location and extent of hepatic disease (segmental liver anatomy) as well as adequacy of future liver remnant (FLR).
- When the FLR is inadequate, portal venous 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,

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

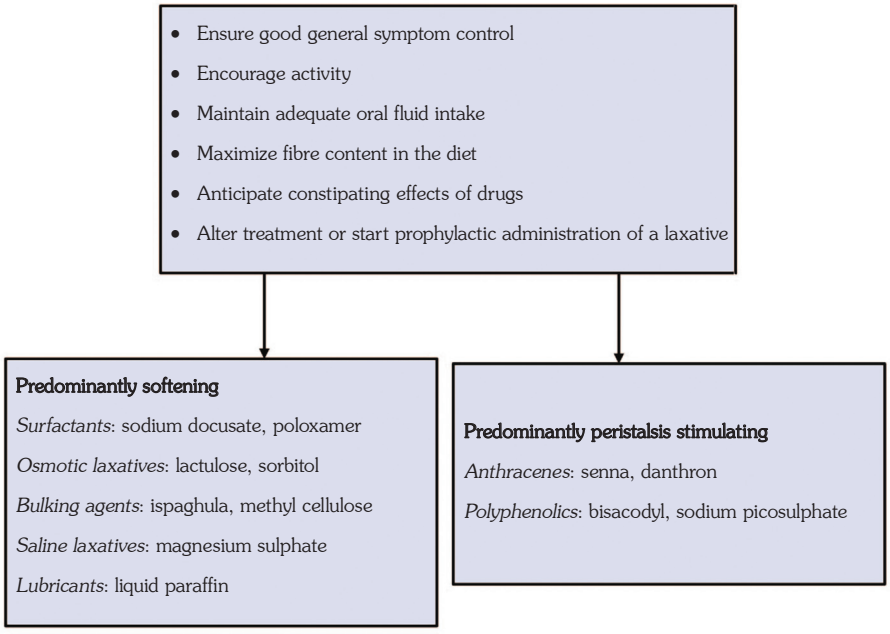
- Complete and irreversible: bowel sounds absent (terminal care)

  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.

For 5-FU-related diarrhoea,consider the following:

I. Evaluation

1. Onset and duration of diarrhoea: for a duration of >12 h,collect a stool sample
2. Number of stools and stool composition (watery, blood)
3. Assessment for fever, neutropenia, abdominal pain, dizziness, and weakness
4. Medication profile (diarrhoeatic e.g. bulk agents, softeners, and prokinetics) to be stopped

II. Management

1. Consider oral rehydration solution as part of fluid intake
2. Drink 8–10 large glasses of clear fluids per day (water, clear soup, non-carbonated soft drinks)
3. Consume frequent small meals as tolerated
4. Administer antibiotics as appropriate (fluoroquinolones)
5. Admit neutropenic patients with grade 3 diarrhoea or worse

III. Treatment

1. Initially, loperamide, 4mg followed by 2mg after every loose stool up to 16mg daily, or codeine phosphate 30–60mg QDS
2. Reassessment after 12 h

   After 12–24 h

Diarrhoea resolved

1. Stop loperamide administration after a 12-h diarrhoea-free interval
2. Check that the patient is eating small frequent meals

Persistent diarrhoea: grade 1–2

1. Continue with loperamide, 2mg every 2 h up to16mg for the first 24 h and then re-review.
2. Administer antibiotics as appropriate

Persistent diarrhoea: grade 3–4

1. Admit the patient
2. Budesonide, 9mg PO once a day (OD) until diarrhoea is resolved (all patients with a positive response to budesonide should receive prophylactic budesonide, 9mg PO OD, for 3–5 days, with subsequent courses)
3. IV fluids, antibiotics as appropriate
4. If diarrhoea is unresolved: octreotide 100–150mcg SC thrice a day (TDS) for 5 days, increased by 50mcg up to 200mcg TDS if necessary

Irinotecan-associated late-onset diarrhoea:

This may occur approximately 1 week after treatment (and may therefore coincide with neutropenia). There are specific instructions for patients to follow, which should be given on an information sheet to all patients receiving irinotecan.

These are as follows:

- Take loperamide, 4mg, once after the first liquid stool then 2mg every 2 h. Continue for 12 h after the last liquid stool (do not continue beyond 48h).
- If diarrhoea has not resolved within 24 h, start ciprofloxacin, 250mg PO BD, for 7 days.
- Patients should contact the hospital for advice as soon as diarrhoea is experienced.

If diarrhoea is severe, continues for more than 48 h, or is associated with nausea, vomiting or fever, the patient needs to be admitted to the hospital

- Examination on admission:
    - Stool culture, microscopy
    - Patients should be closely monitored: daily urea and electrolytes, abdominal radiography (as required), and urine output monitoring.
    - Ciprofloxacin should be continued for a total of 7 days, unless pyrexia develops, in which case, appropriate IV antibiotics should commence.
    - Loperamide should continue at 16 mg daily.
    - If diarrhoea persists, consider octreotide and other possible causes.

Chest pain whilst receiving fluoropyrimidines

Fluoropyrimidine agents (capecitabine/5-FU) are known to rarely cause a syndrome of angina-like chest pain, which is thought to relate to coronary artery spasm. If patients develop angina-like pain whilst receiving 5-FU or capecitabine, treatment should be discontinued immediately. Electrocardiography must be performed to exclude myocardial infarction and cardiac enzymes including troponin should be measured. Patients should be admitted overnight if significant pain has occurred within the previous 24 h. If electrocardiography or blood abnormalities are noted or the patient redevelops chest pain whilst off chemotherapy, referral for a cardiology opinion should be considered.

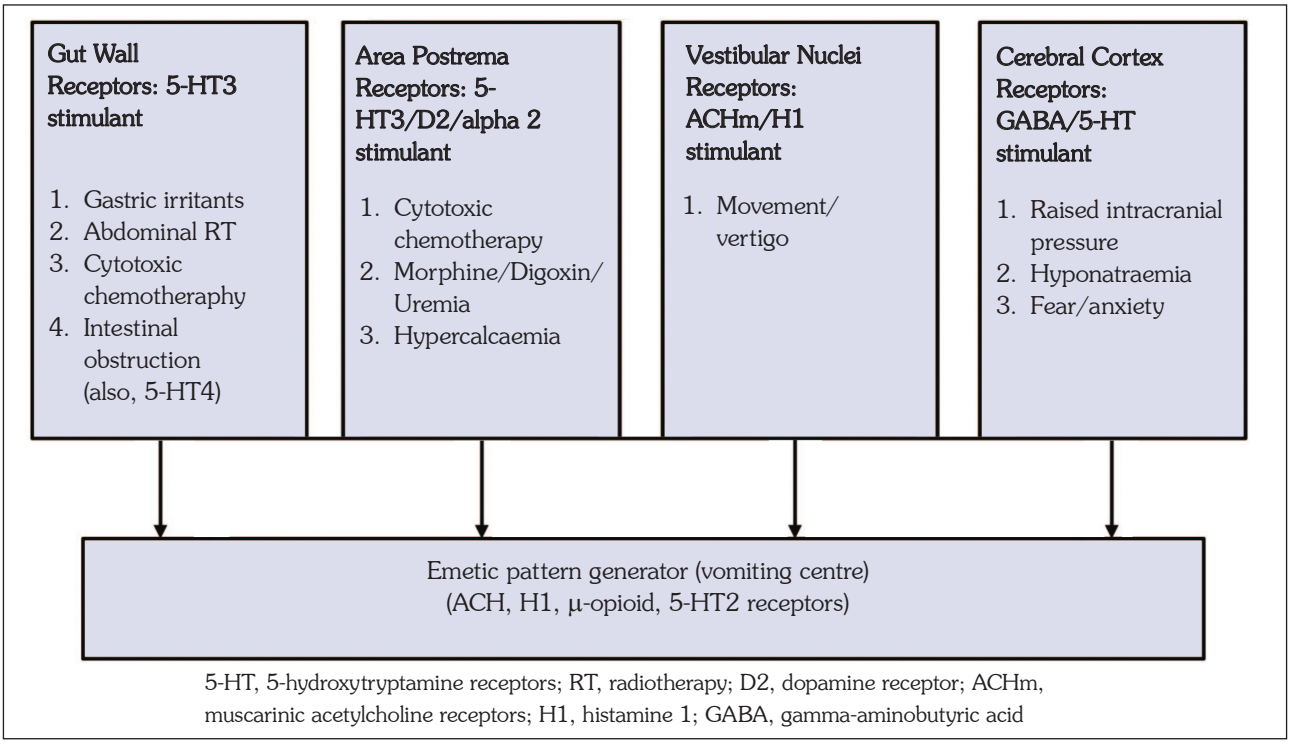
Patients should not recommence treatment, but their case should be discussed and alternative chemotherapy should be considered (oral tegafur-uracil). In some cases, in discussion with a cardiologist, fluoropyrimidines may be recommenced with anti-anginal cover (Ca^{++} channel antagonist and nitrate).

Nausea and vomiting

It is important to assess the cause of vomiting in order to be able to treat it appropriately.

- Comprehensive history and physical examination
- Minimum investigations
- Consider 'holistic' assessment

The receptors shown below are stimulated to induce vomiting. Drugs are chosen for specific receptors.



5-HT, 5-hydroxytryptamine receptors; RT, radiotherapy; D2, dopamine receptor; ACHm, muscarinic acetylcholine receptors; H1, histamine 1; GABA, gamma-aminobutyric acid

Commonly used drugs acting on specific receptors							
Drug	**Dosage**	**D2**	**H1**	**ACHm**	**5-HT2**	**5-HT3**	**5-HT4**
Metoclopramide	10–20 mg q4–6h PO/SC/IV	++	0	0	0	+	++
Domperidone	10–20 mg q4–8h PO	++	0	0	0	0	0
Haloperidol	0.5–2 mg q6–12h PO/SC/IV	+++	0	0	0	0	0
Ondansetron	4–8 mg q8–12	0	0	0	0	+++	0
Chlorpromazine	25–50 mg q6-8h PO/IV	++	++	+	0	0	0
Diphenhydramine	50–100 mg q4–6h PO/IV	0	++	++	0	0	0
Prochlorperazine	10–20 mg q6h PO/IV or 25 mg q6hPR	++	+	0	0	0	0
Olanzapine	1.25–2.5 mg PO OD	+	++	++	++	+	0
Dexamethasone	4–20mg qAM PO/IV/SC	0	0	0	0	?	0

Measures other than medication include consuming small tasty meals, a variety of foods, or cold food; a break from cooking; and home ventilation.

Before the administration of oxaliplatin, dexamethasone and ondansetron is recommended.

For the prevention of delayed nausea and vomiting, use corticosteroids and metoclopramide (and ondansetron, if required).

Hand-foot syndrome or palmar-plantar erythrodysesthesia

Capecitabine and 5-FU can both cause hand-foot syndrome or palmar-plantar erythrodysesthesia. This side effect can be prevented by advising patients as follows:

- Modify some of the normal daily activities to reduce friction and heat exposure to the hands and feet for a period of time following treatment (approximately 1 week after IV medication and as long as possible during the time tablets are being taken).

- Avoid prolonged exposure of hands and feet to hot water while, for example, washing dishes, taking a shower, or taking a tub bath.
- Take short showers in tepid water.
- Do not wear dishwashing gloves, as the rubber will hold heat against the palms.
- Avoid increased pressure on the soles of the feet or palms of the hands.
- Do not jog, do aerobics, perform power walking, or jump. Avoid long days of walking.
- Avoid using garden tools, household tools such as screwdrivers, and other tools that require squeezing the hand on a hard surface.
- Do not use knives to chop food as this may also cause excessive pressure and friction on the palms.
- Place the palms of the hands or soles of the feet on an ice pack or a bag of frozen peas (anything cold),as this may be very comforting. Alternate between placement on the cold surface and removal from the surface for 15–20 min at a time. Avoid rubbing lotion on the palms and soles during this period, although it is very important to keep these areas moist between treatments.
- Use emollients to provide excellent moisturizing to the hands and feet.
- Take paracetamol as this may be helpful in relieving the discomfort associated with hand-foot syndrome. Celecoxib also may be used for this purpose.
- Take vitamin B6 (pyridoxine), as this may be beneficial in preventing and treating hand-foot syndrome.

Skin rash associated with cetuximab

Management: the STEPP protocol[72]

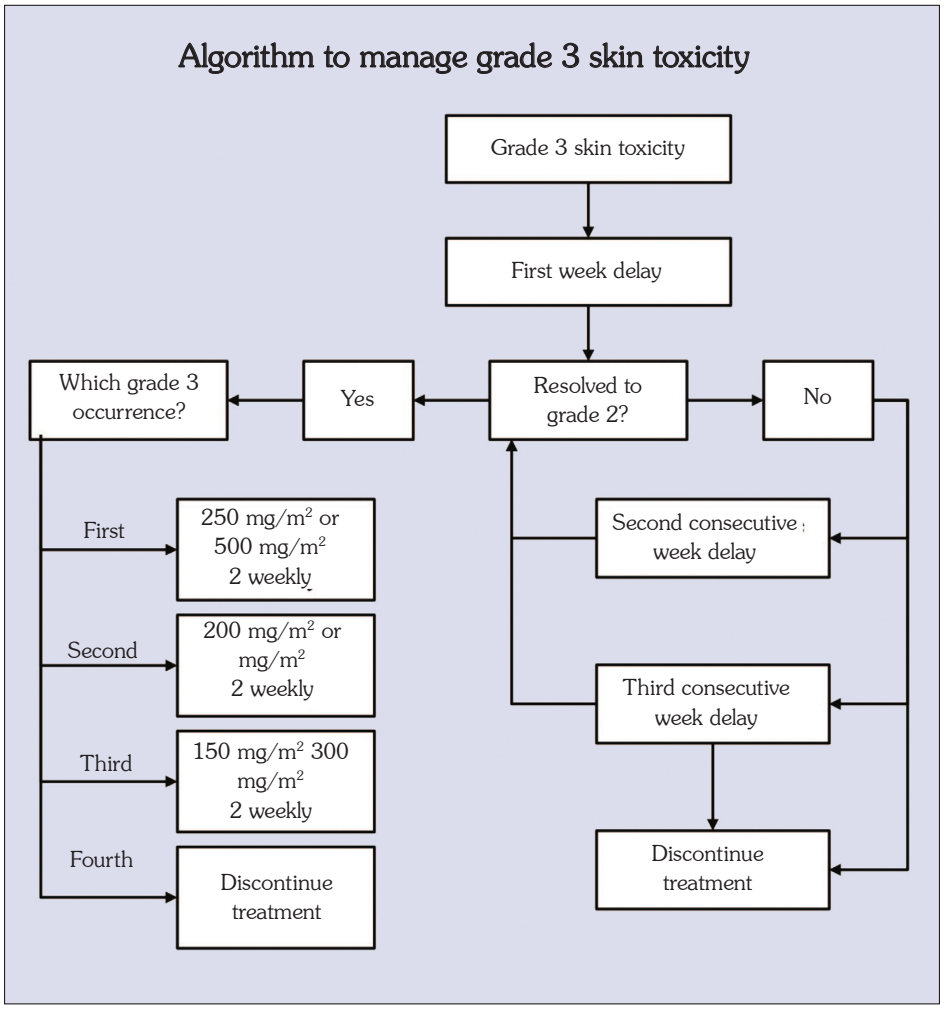
Prophylactic skincare reduces the number of skin reactions by 50% compared with reactive treatment.

All patients should receive the following:

- Emollient cream applied to the face, hands, feet, neck, back, and chest, once daily at bedtime
- Hydrocortisone 1% cream applied to the face, hands, feet, neck, back, and chest, at bedtime
- Lymecycline 408 mg OD
- Sunscreen, sun protection factor 15 or higher (with ultraviolet A and ultraviolet B protection), applied to exposed skin areas before going outdoors

In case of grade 3 skin toxicity, delay infusion.

Algorithm to manage grade 3 skin toxicity:



Vaccination during chemotherapy

Where possible, patients may receive vaccines such as the influenza vaccine before commencing chemotherapy. Immunization should be postponed if a patient is suffering from an acute illness. Minor infection, in the absence of fever or systemic symptoms, is not itself a contraindication to vaccination.

Live vaccines such as mumps and rubella, Bacillus Calmette–Guérin,and yellow fever should never be administered to immunocompromised patients, including those receiving chemotherapy, within 6 months after receiving chemotherapy.

Vaccines that are killed such as the influenza vaccine or protein subunits such as hepatitis B may be given, but the immunological response may be impaired by chemotherapy. These vaccines should be given at the end of the cycle when the degree of immunosuppression is at its lowest.

Vaccine	Live	Suitable for immunocompromised patients
Bacillus Calmette–Guérin Heaf Mantoux test	Yes No	No Yes
Hepatitis B	No	Yes

The decision to vaccinate should always be made on an individual patient basis.

CHAPTER 7

FOLLOW UP AND SURVIVORSHIP

Colerectal Cancer (CRC)

Follow-up after adjuvant chemotherapy or NACT

Year	Time from start of chemotherapy (months)	Clinical examination	Elevated tumour marker levels, CEA or CA19.9, at diagnosis	CT CAP	Discharge
0	0	✓	✓	✓	
1	3	✓	✓		
	6	✓	✓		
	9	✓	✓		
	12	✓	✓	✓	
2	18	✓	✓		
	24	✓	✓	✓	
3	30	✓	✓		
	36	✓	✓	✓	
4	48	✓	✓		
5	60	✓	✓		✓

Ensure that colonoscopic surveillance continues:

- Every 1 year after surgery and every 3 years thereafter
- If polyps are noted,every 6–12 months until polyp-free status is achieved

Follow-up after liver/lung resection

Year	Time after surgery (months)	Clinical examination	Elevated tumour marker levels, CEA or CA19.9	CT CAP	Discharge
0	0	✓	✓	✓	
1	3	✓	✓		
	6	✓	✓	✓	
	9	✓	✓		
	12	✓	✓	✓	
2	18	✓	✓	✓	
	24	✓	✓	✓	
3	30	✓	✓		
	36	✓	✓	✓	
4	48	✓	✓	✓	
5	60	✓	✓	✓	
6	72	✓	✓		
7	80	✓	✓		✓

Advanced disease

- Following completion of chemotherapy, review the case every 3 months (may be extended if the patient is stable).
- Measure CEA or CA19.9 levels (whichever was raised at diagnosis) at each clinic visit.
- Routine imaging is not indicated unless symptom driven.
- Consider CT if signs/symptoms suggest disease progression or if rising levels of tumour markers are noted.
- Ensure all patients have palliative care support if possible (desirable).
- If no further treatment can be offered following evidence of disease progression, the patient should be discharged from the clinic with adequate psychological/palliative support if possible.

CHAPTER

8 PALLIATIVE CARE

Palliative care is aimed at providing comfort to the patient in all possible scenarios. Patients should receive physical, psychological, spiritual, and social support, if feasible. Quality of life should be the main focus of care. Care should be offered for each suffering by a multidisciplinary professional team in the hospital, home, or hospice—the choice of the patient and family in concurrence with the treating physician.

Goals

- Relief from suffering
- Treatment of pain and other distressing symptoms
- Psychological and spiritual care
- Support system tohelp the patient live as actively as possible
- Support system to sustain and rehabilitate the patients' family

Aims

- Provide relief from pain, shortness of breath, nausea, and other distressing symptoms
- Affirm life and regard dying as a normal process
- Intend neither to hasten nor postpone death
- Integrate the psychological and spiritual aspects of patient care
- Offer a support system to help patients live as actively as possible
- Offer a support system to help the family cope
- Use a team approach to address the needs of patients and their families
- Improve quality of life
- Be applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy

Holistic Care

Patients should receive appropriate care for physical (e.g. pain, nausea and vomiting, constipation, dyspnoea, bowel obstruction, and fungating wounds), social (e.g. finance, education, job, and social environment), psychological (grief, helplessness, hopelessness, lack of self-worth, despair, and family collusion), and spiritual (e.g. address questions such as 'why me?', 'what is the meaning of disease', and 'what comes next?") suffering.

Psychological care

Psychological care and emotional support is an extremely essential part of palliative care. It offers a support system to help patients live as actively as possible until death and help the family cope during the patient's illness and in their own environment.

Principle guidelines for psychological care in the palliative care setting are as follows:

- At the time of initial consultation: assess psychological wellbeing, reactions to current losses, the support system and coping of patients and caregivers. Privacy and confidentiality should be maintained at all times.
- Assessment will include mood, feelings, concerns, family relationships, social support, and impact of illness on day-to-day life and work.
- Patients and caregivers both should be evaluated during assessment.
- All staff are directly responsible for patient care and should offer general emotional support based on skilled communication, effective information provision, genuineness, and respect.
- Psychological support should be provided through intimate care and positive communication skills during difficult situations
- Need based interventions should be planned, for example, from self-help to specialized psychological interventions for patients.
- Patients and caregivers with a significant level of psychological distress and premorbid psychiatric issues should be promptly referred to specialist psychiatric services.
- Psychological needs and problems of the staff caring for patients should be explicitly assessed and adequately met to improve the quality of care.

On-going psycho-social assessment is a fundamental need in palliation to assess the emotional, social, and economic status of patients and their families in order to help them be sustained during the advanced phase of cancer.

Interventions

- Facilitating respite care (if feasible): counselling, telephonic help, and material and emergency aid such as free medicines, monthly ration, education fees for dependents, fulfilling last wishes of children, and providing stay and food while the patient is on short-duration medical interventions like radiotherapy.
- Advocacy and referral networks: address economic and existential concerns of families when the patient is the primary source of income in his family and link families with local resources and various government schemes
- Empowering and educating families: help them combat fear of contagion, stigma, and isolation.
- Community outreach: create awareness amongst medical and paramedical health care professionals at the grass-root level.

CHAPTER 9

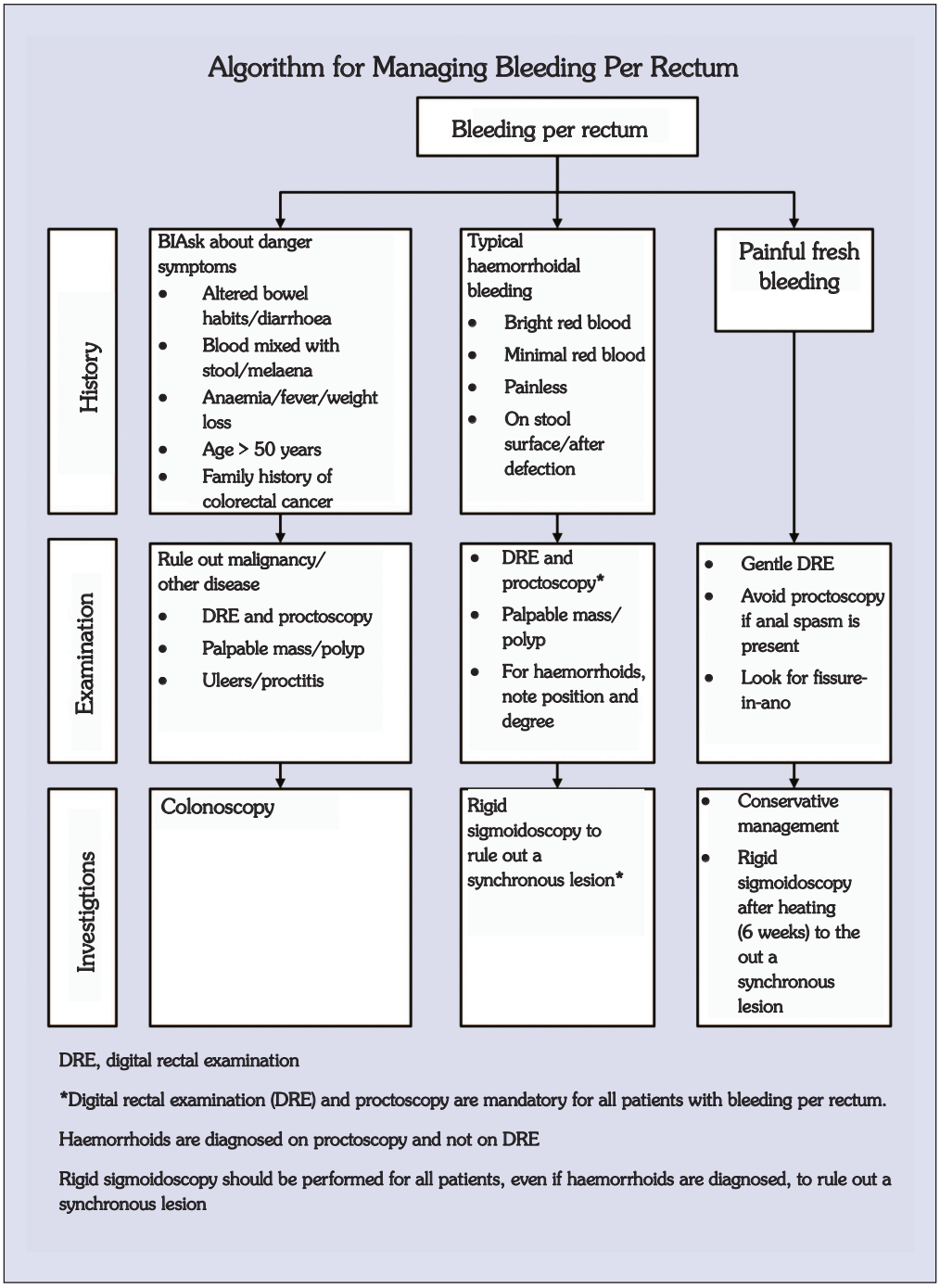
RESEARCH AVENUES

- Genetics, epidemiology, and lifestyle study of familial and non-familial CRC.
- Molecular diagnosis and characterisation including genomic sequencing
- Duration and role of chemotherapy in adjuvant setting
- Role of targeted therapies
- Role of radiotherapy in rectal cancers
- Role of surgery in colorectal liver metastases
- Training and credentialing of surgeons, pathologists, radiologists, medical oncologists and radiation oncologist in site-specific areas
- Role of new techniques for diagnosis and management – endoscopy, MRI and PET CT, IMRT, Radio gold nanospheres

CHAPTER

10 APPENDICES

Appendix A: Algorithm for Managing Bleeding Per Rectum



Appendix B: Radiology Reporting Template

Magnetic Resonance Imaging of the Pelvis: Rectal Cancer Staging Report Template

Primary tumour morphology

Polypoidal ☐ Annular ulcerating ☐ Annular non-ulcerating

Extramural spread

Present ☐ Absent ☐

Mucinous Tumour

Yes ☐ No ☐

Metastatic spread ☐

Nodes demonstrated, not suspicious

Yes ☐ No ☐

Nodes demonstrated, suspicious

Yes ☐ No ☐

Extramural venous invasion

Yes ☐ No ☐

Tumour deposits/satellites present

Yes ☐ No ☐

Local invasion

Submucosa (T1) ☐ Muscularis (T2) ☐

Beyond the muscularis < 1.00 mm (T3a) ☐

Beyond the muscularis 1.01–5.00 mm (T3b) ☐

Beyond the muscularis 5.01–15.00 mm (T3c) ☐

Beyond the muscularis > 15.01 mm (T3d) ☐

Into adjacent organs (T4a) ☐

Perforation of the visceral peritoneum (T4b) ☐

Margins

Distance to the mesorectal fascia < 1.00 mm ☐

Distance to the mesorectal fascia > 1.01 mm ☐

Low tumour (below the levator) > T2 ☐

Measurements

Maximum extramural spread of tumour ___ mm

Minimum distance to the mesorectal fascia/potential CRM from the outer edge of the tumour ___ mm

Distance to the CRM from

a. Main tumour ___ mm
b. Suspicious lymph nodes ___ mm
c. Extramural venous invasion ___ mm
d. Tumour satellite/deposits ___ mm

Distance to the sphincter (low tumours only) ___ mm

Summary: Overall stage: T[ ]N[ ]M[ ]

CRM, circumferential resection margin; Mel, tumour less than or equal to 1 mm of the mesorectal fascia; MeLev, tumour at or below the level of the levator ani muscle; Me0, tumour more than 1 mm from the mesorectal fascia

Computed Tomography of the Abdomen and Chest: Colon Cancer Staging Report Template

Primary tumour morphology: Annular/Ulcerating/Polypoidal/Villous/Mucinous

Border: Nodular/Smooth/Infiltrating

Site:Caecum/Ascending colon/Hepatic flexure/Transverse colon/Splenic flexure/Descending colon/ Sigmoid

Advancing edge of the tumour (border): Mesenteric/Peritoneal

The tumour is [confined to/extends through] the bowel wall

Peritoneal infiltration:No evidence/Evidence

Tumour extension:<5mm/>5mm

Tumour spread:___ mm

Tumour diameter: ___ mm

Tumour thickness:___ mm

Lymph nodes in colonic mesentery: Benign/Reactive/Malignant

There is [evidence/no evidence] of extramural venous invasion

There is [evidence/no evidence] of peritoneal dissemination

Retroperitoneal lymphadenopathy is [absent/present]

Incidental note is made of [intra-abdominal pathology/pelvic pathology]

There is [evidence/no evidence] of metastatic disease in liver:

Details: There is segmental sparing/There is no segmental sparing

Incidental note is made of [cysts/haemangiomas/equivocal low-density lesions]

[requires/does not require FNA]
[for follow-up]
[likely/unlikely to represent metastatic disease]

Pulmonary metastatic disease:No CT evidence/CT evidence

Details: Unilateral/Bilateral/Number/Lobes

Summary:Overall stage:T[ ]N[ ]M[ ]

Appendix C: Pathology Reporting of Colorectal Carcinoma and Staging

Surgical Anatomy of the Colorectum with Respect to the Visceral Peritoneum

A small part of the posterior surface of the caecum can be retroperitoneal. The ascending colon and descending colon are retroperitoneal posteriorly. The upper third of the rectum is invested by a peritoneal covering on its anterior and lateral aspects and is bare or non-peritonealised on its posterior aspect. The middle third is draped by the peritoneum only on its anterior aspect, leaving the lateral and posterior surfaces bare or non-peritonealised,whereas the lower third is completely devoid of peritoneal covering or is entirely non-peritonealised.

Clinical Relevance of the Anatomical Relationship of the Colorectum with the Visceral Peritoneum

In general, the prognosis of rectal tumours is poorer than that of tumours occurring in other parts of the colon. Within the rectum itself, tumours situated below the anterior peritoneal reflection have a poorer prognosis because of the high chances of local recurrence. This is especially true of the tumours located in the anterior and lateral quadrant of the rectum. The non-peritonealised surfaces (NPS) (previously referred to as the circumferential resection margin or CRM) of all parts of the colon as described above are dissected by the surgeon, and hence conceptually, they are surgical resection margins, or more precisely, surgical surfaces. The serosal surface on the other hand is not a surgical margin. It is the outer most barrier to the tumour formed by a layer of mesothelial cells and their basement membrane. When the serosa is invaded by the tumour, it gains unrestricted access to the peritoneal cavity. Thus, despite their close anatomic proximity, the serosa and NPS represent 2 conceptually different anatomic entities with entirely different connotations on the management of colorectal cancer (CRC).

Types of Surgical Specimens

1. Polypectomy: A polyp can be sessile or pedunculated
2. Right hemicolectomy, left hemicolectomy, transverse colectomy, descending colectomy, and sigmoid colectomy
3. Anterior resection (AR): AR is performed for high rectal tumours where preservation of the anal sphincter is easy.
4. Abdominoperineal resection (APR):APR involves en bloc resection of the rectosigmoid, the rectum, and the anus along with the surrounding sigmoid mesentery, mesorectum, and perianal soft tissues. APR is performed for low rectal and anal canal tumours where the anal sphincter cannot be saved.
5. Total proctocolectomy: Total proctocolectomy is usually performed in the setting of familial adenomatous polyposis syndrome.

Step-wise Technique and Principles of Grossing of Colorectal Oncology Surgical Specimens

1. Receipt of specimen: Receive the unopened specimen in formalin along with the proper clinical history. Check the specimen identification.Surgeons should refrain from opening the specimen because such practice could result in distorting important structures such as the serosa or NPS with respect to the tumour.
2. Note the nature of surgical procedure.
3. Record the length of the entire specimen. Record the length of the terminal ileum and appendix separately if present in the specimen.

4. Palpate the tumour from the outer aspect of the specimen. This will help re-enforce the ink on the bare area in relation to the tumour.
5. Assess the quality of total mesorectal excision (TME) before the application of ink or opening the APR and the AR specimens.

The concept of TME

The rectum is encased by a thick blanket of fatty tissue known as the mesorectum,which contains the blood vessels and lymph nodes that drain the rectum. The mesorectum is in turn enclosed by a fascia known as the endopelvic fascia. Removal of the mesorectum en bloc with the rectal tumour, referred to as TME, forms the current surgical 'gold standard' for rectal tumours. The goals of TME for rectal cancer resection are achieving adequate lymphadenectomy and a maximum lateral resection margin. TME of good quality reduces the possibility of locoregional relapse. Thus, the NPS is conceptually a surgical resection margin created to deliver the rectum together with its mesorectum. Involvement of the serosa by the tumour represents a pT4 stage, whereas involvement of the NPS (CRM/radial margin) implies pT3.

Pathological assessment of the quality of TME

TME of good quality improves local recurrence rates and corresponding survival by as much as 20%. The quality of mesorectal excision is assessed as follows:

A. Complete TME (grade 3):

The plane of surgery is the mesorectal fascial plane. The mesorectum is intact and bulky with a smooth surface. Only minor irregularities are noted on the mesorectal surface, with no surface defects greater than 5 mm in depth. Coning is not observed towards the distal margin of the specimen. The CRM is smooth on transverse slices.

B. Nearly complete TME (grade 2):

The plane of surgery is through the mesorectum. The bulk of the mesorectum is moderate.The mesorectal surface is irregular, with defects greater than 5 mm, but none extending to the muscularis propria. No areas of visibility of the muscularis propria except at the insertion site of the levator ani muscles. Moderate coning is seen towards the distal margin of the specimen. Moderate irregularity of the CRM is seen in transverse slices.

C. Incomplete TME (grade 1):

The plane of surgery is through the muscularis propria. The bulk of the mesorectum is slight. Defects in the mesorectum expose the muscularis propria.The circumferential margin in transverse sections appears very irregular. A very irregular CRM is seen in transverse slices. For AR specimens, only a single plane, i.e. the mesorectal plane, is evaluated. However, for an APR specimen, gross evaluation of the surgical plane of the anal canal is also evaluated. Surgical planes evaluated for the anal canal include the following:

a. The levator plane: the surgical plane lies outside the levators, which are removed en bloc in the APR specimens. The specimen is cylindrical.
b. The sphincteric plane: the surgical plane lies on the surface of the sphincter.
c. The intra-sphincteric plane: the surgical plane passes through the sphincter.

6. Photograph the specimen from both aspects for recording purposes.

7. Look for the presence of tumour site perforation before inking.

   Tumour site perforation is a poor prognostic factor, which results in high morbidity and mortality due to peritonitis and sepsis. Serosal perforation at the tumour site also gives tumour cells access to the peritoneal cavity. Therefore, when present, the tumour is classified as pT4 according to the TNM classification system. This is irrespective of the actual presence of tumour cells at the serosal surface on microscopy.

8. Paint the NPS with ink, with special reinforcement to the NPS associated with the tumour. The serosa is histologically identifiable by the presence of mesothelial cells and its basement membrane; hence, it should not be painted as the ink obscures the mesothelial cells.

9. Upon inking, open the specimen from the anterior aspect starting from either end of the tumour up to 1 cm above and below the tumour, thereby, keeping the segment containing the tumour intact. This ensures that the association of the tumour with the serosa is intact as is the NPS/CRM.

10. Note the distances of both longitudinal resection margins from the tumour. Record the distance from the pectinate line in the APR specimen. In APR specimens for rectal carcinoma, the distance from the pectinate line and from the anal verge will justify the surgical procedure,which results in permanent loss of the anal sphincter.

11. Record the location of the tumour in relation to the anterior peritoneal reflection in the rectosigmoid, AR, and APR specimens.

    Tumours located above the anterior peritoneal reflection are covered by peritoneum anteriorly and laterally while they are related to the NPS on the posterior aspect. Tumours at/astride the peritoneal reflection are covered by peritoneum only anteriorly while they are non-peritonealised on the lateral and posterior aspects. Tumours lying below the anterior peritoneal reflection are not at all related to the peritoneum and are entirely related to the NPS or the CRM.

12. Insert a cotton wick soaked in formalin into the lumen of the intact segment containing the tumour and fix the entire specimen in an appropriate volume of formalin overnight or for 48 h. Ideally, the colon should be pinned down onto a cork board and immersed in formalin.

13. Upon adequate fixation, sample longitudinal mucosal resection margins. If the tumour is less than 1 cm from the longitudinal mucosal resection margin, then sample the margin in a radial manner (perpendicular to the long axis of colon) after inking the resected end of the segment or anal verge. Otherwise, a 'shave' margin (parallel to long axis of colon) should suffice.

14. Document the size of the tumour in 2 dimensions. Tumour size has no prognostic relevance. However, it is important to correlate the actual size with imaging findings. It is especially important in patients who have received neoadjuvant chemotherapy and/or radiotherapy.

15. Sampling from the tumour

    Technique of tumour sampling

Cut serial slices,not more than 5mm in thickness, of the segment containing the tumour (which is kept intact and inked appropriately) in a transverse manner starting from 1 cm above and ending1cm below the limits of the tumour. Place the circular intact slices thus obtained sequentially, one below the other. Identify the deepest invasive parts of the tumour with respect to both serosa and the NPS/CRM (if applicable). Sample 4 to 5 sections of the deepest invasive parts of the tumour, each containing the most relevant anatomical surface (serosa and/or NPS/CRM). Document the distance between the tumour and NPS as well as the serosa.

16. Lymph node dissection in colorectal carcinoma

Adequate lymph node yield is extremely crucial for optimal staging. Patients with node positive disease are categorized as having T3 stage III disease, signifying a poor prognosis. Even a single positive node would warrant adjuvant chemotherapy in these patients. As per the current guidelines, a minimum of 12 lymph nodes should be examined to avoid tumour understaging (nodal yield less than 12 is considered inadequate and chemotherapy may be given to the patient under the presumption of understaging). Notably, lymph nodes, as small as 2 mm, may also be metastatic. Hence, every attempt should be made to recover as many nodes from each specimen as possible.

Method of lymph node dissection

Lymph nodes are not dissected from the specimen 'before' tumour sampling is completed to avoid disruption of the serosa and NPS. Lymph nodes present in the sections containing the tumour are included in situ without dissection. After tumour sampling is complete, each of the slices containing the tumour is dissected for lymph node retrieval. Then, the remaining proximal and distal parts of the colon are dissected for lymph nodes.

17. Examine the rest of the bowel segment for any abnormality such as synchronous carcinoma, features of inflammatory bowel disease, polyps, etc. Each of the synchronous carcinomas is sampled in a similar fashion. In a setting of familial adenomatous polyposis syndrome, samples from multiple polyps should be taken, especially large polyps. The total number of polyps hasto be recorded.
18. Sample mesorectum/pericolonic fat to confirm the presence or absence of extramural venous invasion. Presence of extramural venous emboli outside the bowel wall is an adverse prognostic feature in colorectal tumours.

Sections submitted

1. Four or five sections of the tumour
2. All lymph nodes dissected from the specimen and submitted according to the level of the tumour
3. Longitudinal mucosal resection margins
4. Adjacent mucosa
5. Sample from any other grossly abnormal area

Grossing of a colorectal polyp

Issues to be addressed in the pathology report of a colorectal polyp:

1. Type of polyp
2. Degree of dysplasia, if any
3. Completeness of excision

Ideally, the polyp is received intact, preferably with the base of excision marked by the surgeon. If a polyp has a stalk, then the base of the stalk should be inked and a 2-mm thick end should be sampled as the excision margin. In cases of broad-based, sessile polyps, the entire base should be inked. Serial parallel sections of the polyp should be obtained, each containing the inked base. Thus, the excision margin in a sessile polyp is sampled in a perpendicular manner. More than one section will be examined to assess the margin. It is important to reinforce the ink at the margin in both types of polyps because if an invasive

carcinoma is found in the polyp, the distance of carcinoma from the excision margin is to be measured in millimetres.

Microscopic reporting of colorectal resection specimens

Tumour type

World Health Organization classification of colorectal carcinoma should be followed:

1. Adenocarcinoma: Conventional adenocarcinoma consisting of a predominant glandular component. This is themost common tumour type of the colon.
2. Mucinous adenocarcinoma (area of extracellular mucin should be greater than 50%)
3. Signet-ring cell carcinoma (component of signet-ring cells should be more than 50%). It consists of discohesive, diffusely infiltrating tumour cells containing intracellular mucin. Areas of mucinous and signet-ring cell adenocarcinoma often co-exist. Both these tumour types are associated with poor prognosis.
4. Squamous cell carcinoma
5. Adenosquamous carcinoma
6. Medullary carcinoma:This is a distinctive histologic type showing a solid growth pattern. Presence of numerous tumour infiltrating lymphocytes is a conspicuous finding. This type of morphology is associated with hereditary non-polyposis colon carcinoma (HNPCC) syndrome.
7. Small cell carcinoma (high-grade neuroendocrine carcinoma)
8. Undifferentiated carcinoma
9. Other (specify)

Grading the tumour

Diagnosis of conventional colonic adenocarcinoma is further qualified with respect to the grade of the tumour. Colorectal adenocarcinomas are graded according to the predominant area of the tumour. Grading can be a 2- or 3-tier system. In the 3-tier system, tumours are graded as well, moderately,or poorly differentiated adenocarcinomas,whereas in the 2-tier system, well and moderately differentiated tumours are clubbed together as low-grade tumours. Poorly differentiated adenocarcinomas show complex, irregular arrangement of small, irregular glands or there can be an absence of tubular formation. Undifferentiated carcinomas are a different tumour type and should not be equated with poorly differentiated adenocarcinomas. By default, signet-ring cell carcinomas, small cell carcinomas, and undifferentiated carcinomas are considered high grade. Tumour budding at the advancing edge of the tumour should be documented. High tumour grade is an adverse prognostic factor.

Histological features indicative of microsatellite instability-high (MSI-H) status

1. Right-sided mucinous or signet-ring cell adenocarcinomas
2 Poorly differentiated or undifferentiated carcinomas
3. Increase in tumour-infiltrating lymphocytes.

Immunohistochemistry for mismatch repair (MMR) gene proteins should be performed if any of these histological features are seen, with a consideration of HNPCC.

Determination of TNM

1. Local invasion: the 'T' status

The maximum depth of local invasion into the bowel wall is recorded in order to determine the 'T' stage. The importance of appropriate grossing steps to address this parameter is mentioned in the above section. The tumour is defined as being of pT4 stage when there is invasion of the visceral serosa (pT4a) and tumour infiltration of an adjacent organ (pT4b).Involvement of the serosal (peritoneal) surface is defined as tumour breaching of the serosa with tumour cells either visible on the peritoneal surface or free in the peritoneal cavity.

Direct invasion of an adjacent organ through the serosa is always staged as pT4,whereas intramural extension into an adjacent part of the bowel (e.g. extension of a caecal tumour into the terminal ileum) does not affect the pT stage. Extramural extension of rectal cancer into theskeletal muscle of the external sphincter, levatorani, and/or puborectalis is classified as pT4b.

2. Lymph nodes: the 'N' status

All lymph nodes that have been retrieved from the specimen should be examinedhistologically as described above.

Extramural deposits of tumour that have no lymph node structure are regarded as lymph nodes.

3. Histologically confirmed distant metastases: the 'M' status

This biopsy specimen from a suspected metastatic site may be submitted separately by the surgeon. Otherwise, parameter 'M' is not a part of routine histopathology reporting of resected colorectal specimens.

Response to neoadjuvant therapy

Tumours showing complete or marked regression following neo-adjuvant therapy have a better prognosis than those without significant response. Several systems for assessing treatment response exist. The following 3-score system can be easily used:

Score 1: No residual tumour cells and/or mucus lakes only

Score 2: Minimal residual tumour, i.e. only occasional microscopic tumour foci are identified

Score 3: No marked regression

Resection margins

Margins

The longitudinal resection margins and/or doughnuts should be examined histologically for the presence or absence of tumour.

Non-peritonealised ('circumferential') resection margin: NPS or CRM

Involvement of the NPS in rectal cancer is predictive of local recurrenceand poor survival. It is an indication of neoadjuvant therapy. Evidence for its significance at other colonic sites such as the caecum and ascending colon isalso emerging. The circumferential margin is **regarded as involved if** the tumour is within or less than 1mm away. The 'tumour' may be directly infiltrating or could show vascular invasion or a lymph node deposit at the NPS.

Extramural venous invasion

This is recorded when the tumour is present within an extramural endothelium-lined space that is either surrounded by a rim of muscle or contains red blood cells. The prognostic significance of extramural venous invasion is well established. This feature has been demonstrated as an indicator of unfavourable outcome and increased risk of occurrence of hepatic metastasis.

Background abnormalities

The presence of any pathological abnormalities in the background bowel should be recorded.

1. Polyp(s): If multiple adenomas are detected, adequate sampling from the entire length of the affected segment(s) should be performed. The polyps are histologically classified primarily into adenomatous or non-adenomatous polyps. Adenomatous polyps are further qualified according to the grade of dysplasia. Recognition of high-grade dysplasia is important. Completeness of excision is assessed by the presence of normal colonic glands at the base of the polyp. Presence or absence of invasive carcinoma (malignancy in an adenoma is defined by presence of unequivocal invasion of the muscularis mucosa by malignant glandular epithelium) is recorded. If invasive adenocarcinoma is detected in an adenoma, revision surgery is undertaken if the invasive tumour is poorly differentiated,there is angioinvasion, or the tumour is located within 1 mm of the resection margin of the polyp.

Non-adenomatous polyps are classified microscopically. This category includes a spectrum of serrated polyps (inclusive of variants of hyperplastic polyps, sessile serrated adenomas, and traditional serrated adenomas), hamartomatous polyps, inflammatory polyps, lymphoid polyps, etc.

Perforation

Tumour perforation is an uncommon complication of CRC, but one that is associated with a poor outcome, including high in-hospital mortality and morbidity. Perforation of the uninvolved colon proximal to an obstructing tumour is also associated with high mortality because of generalized peritonitis and sepsis. Reported perforation rates range from 2.6% to 9%. Perforation is more likely to occur in older patients.

Mesorectal envelope

The quality of the surgical technique is a key factor in the success of surgical treatment for rectal cancer, both in the prevention of local recurrence and in long-term survival. Numerous studies have demonstrated that TME improves local recurrence rates and the corresponding survival by as much as 20%. This surgical technique entails precise sharp dissection within the areolar plane outside (lateral to) the visceral mesorectal fascia to remove the rectum. This plane encases the rectum, its mesentery, and all regional nodes and constitutes Waldeyer's fascia. TME of high quality reduces local recurrence rates from 20–30% to 8–10% or less and increases 5-year survival rates from 48% to 68%[51,56]. Adjuvant therapy together with TME of a high quality may further reduce local recurrence rates from 8% to 2.6%[56]. Pathologic evaluation of the resection specimen has been shown to be a sensitive means of assessing the quality of rectal surgery. It is superior to indirect measures of surgical quality assessment such as perioperative mortality, rates of complication, number of local recurrences, and 5-year survival. It has been shown that macroscopic pathologic assessment of the completeness of the mesorectum of the specimen, scored as complete, partially complete, or incomplete, accurately predicts both local recurrence and distant metastasis[56]. Microscopic parameters such as the status of the CRM, the distance between the tumour and nearest circumferential margin (i.e., 'surgical clearance'), and the distance between the tumour and the closest distal margin, are allimportant predictors of local recurrence and may be affected by the

surgical technique. There is strong evidence that the status of the CRM is a powerful predictor of local recurrence but is inconsistently evaluated and underreported.

The nonperitonealized surface of the fresh specimen is examined circumferentially, and the completeness of the mesorectum is scored as described.The entire specimen is scored according to the worst area.

PATHOLOGY REPORTING TEMPLATE FOR COLON CANCER

Gross Description

A specimen of total colectomy/right hemicolectomy/left hemicolectomy/sigmoid colectomy/total proctocolectomy measuring _____ cm in length was received. An ulceroproliferative/infiltrative tumour measuring _____ cm is seen in the _____. It is _____ cm from the proximal and _____ cm from the distal resection margins. It involves the bowel circumferentially/partly in the anterior quadrant/partly in the posterior quadrant. The tumour is seen to invade the _____ of the colon. Tumour site perforation is present (pT4)/absent. The rest of the colon shows no abnormality.

_____regional lymph nodes are dissected from the specimen at the level of the tumour, _____ lymph nodes are dissected above the level of the tumour, and _____ lymph nodes are dissected below the level of the tumour. Grossly, the lymph nodes are soft and grey/firm and white.

The terminal ileum measures _____ cm and shows no abnormality/_____

The appendix measures _____ cm and shows no abnormality/_____

SECTIONS

Histology

Total colectomy/right hemicolectomy/left hemicolectomy/sigmoid colectomy/total proctocolectomy (post chemotherapy and radiotherapy):

_____ differentiated adenocarcinoma of the _____ colon. Tumour invades the _____ _____ (pT).

Extramural vascular emboli are not seen/seen.

Histological features suggestive of MSI-H are not seen/seen in the form of _____ _____

The tumour regression grading system score post chemotherapy and radiotherapy is ___/5 since _____ _____ (Mandard scoring system)

Both longitudinal resection margins are free of/involved by the tumour.

The posterior NPS of the ascending colon/descending colon/sigmoid mesentery is free of the tumour/ involved by the tumour.

Doughnuts are free of the tumour/involved by the tumour.

Lymph nodes at the level of the tumour:_____

Lymph nodes above the level of the tumour: _____

Lymph nodes below the level of the tumour: _____

Apical nodes: _____

Satellite soft tissue deposits are seen/not seen.

Rest of the colonic segment shows _____

The terminal ileum and appendix _____

Immunohistochemistry results for mismatched repair (MMR) proteins to determine MSI status

MSH2: Tumour cell nuclei are positive/negative

MSH6: Tumour cell nuclei are positive/negative.

MLH1: Tumour cell nuclei are positive/negative.

PMS2: Tumour cell nuclei are positive/negative.

Thus, the tumour isMMR proficient (negative for MSI-H), showing intact expression of MMR proteins.

Thus, the tumour is considered to be MMR deficient (positive for MSI-H)

Comment: Immunohistochemistry stains are approximately 90–95% sensitive for the detection of MSI compared to polymerase chain reaction-based analysis. Loss of protein expression for any of the MMR genes indicates a genetic or epigenetic defect but does not differentiate somatic fromgermline mutations.

Impression

Total colectomy/right hemicolectomy/left hemicolectomy/sigmoid colectomy/total proctocolectomy (postoperative chemotherapy and radiotherapy)

_____adenocarcinoma

TNM (UICC seventh edition) pT pN/ypT ypN

Registrar: Consultant: Date:

PATHOLOGY REPORTING TEMPLATE FOR RECTAL CANCERS

Gross Description

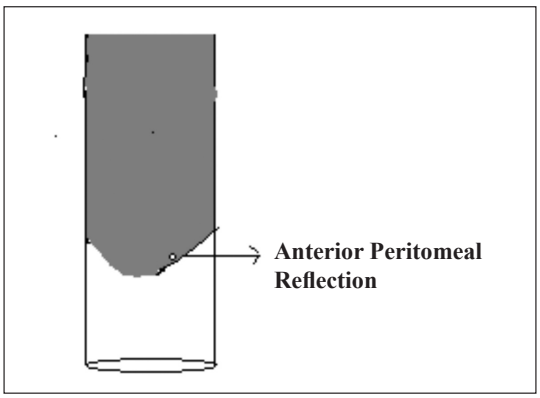
A specimen of rectosigmoid colectomy/low anterior resection/anterior resection/ultra-low anterior resection/abdominoperineal resection/total proctocolectomy measuring_____ cm in length was received(information regarding postoperative chemotherapy and radiotherapy is not available/post chemotherapy and radiotherapy.

An ulceroproliferative/infiltrative tumour measuring _____ cm is seen _____ cm from the proximal and _____ cm from the distal resection margins. The tumour is above/below/at the anterior peritoneal reflection. The distance of the tumour from the dentate line is _____ cm. The tumour involves the bowel circumferentially/partly in the anterior quadrant/partly in the posterior quadrant/in the lateral quadrant. The tumour invades into the _____ _____ of the colon/rectum. The non-peritonealised surface (circumferential resection margin[CRM]) is grossly free of tumour and is _____ cm from the tumour/involved by the tumour. Tumour site perforation is present (pT4)/absent. Perforation is present over the serosal surface/non-peritonealised surface.

Total mesorectal excision (TME) is through the mesorectal plane/intramesorectal plane/intramuscular plane. Hence,the quality of TME is assessed to be complete/nearly complete/incomplete.*

The rest of the colon is _____.

_____ regional lymph nodes are dissected from the specimen at the level of the tumour,_____ lymph nodes are dissected above the level of the tumour, and _____ lymph nodes are dissected below the level of the tumour. Grossly, the lymph nodes are soft and grey/firm and whitish. The apical node measures _____ cm and it is grossly_____.



Indicate tumour location with respect to the anterior peritoneal reflection.

SECTIONS

Histology

Recto-sigmoid colectomy/low anterior resection/anterior resection/ultra-low anterior resection/ abdominoperineal resection/total proctocolectomy(information regarding postoperative chemotherapy and radiotherapy not available/post chemotherapy and radiotherapy)

_____differentiated_____adenocarcinoma of the _____ colon/rectum. TRG score (after chemotherapy/radiotherapy) is _____/5, since _____ (Mandard scoring system)

The tumour invades _____ (pT).

Extramural vascular emboli are not seen/seen.

Histological features suggestive of MSI-H are not seen/seen.

The proximal and distal longitudinal resection margins are free of/involved by the tumour.

The non-peritonealised surface (circumferential resection margin [CRM]) is free of/involved by the tumour (includes the tumour within 1 mm of the CRM and a metastatic node lying within 1mm of the CRM).

Doughnuts are free of/involved by the tumour.

Lymph nodes at the level of the tumour: _____

Lymph nodes above the level of the tumour: _____

Lymph nodes below the level of the tumour: _____

Apical nodes: _____

Satellite deposits within mesorectal fat/subserosal fat are seen/not seen.

The rest of the colonic segment is unremarkable/shows_____

IMPRESSION: Recto-sigmoid colectomy/lowanterior resection/anterior resection/ultra-low anterior resection/abdominoperineal resection/total proctocolectomy (information regarding postoperative chemotherapy and radiotherapy is not available/post chemotherapy and radiotherapy)

Adenocarcinoma of _____

TNM (UICC TNM seventh edition) pT p N /ypT ypN

Registrar: Consultant: Date:

Appendix D: Chemotherapy Dosing and Modifications

Standard Adjuvant Chemotherapy Regimens for Colorectal Cancer

FOLFOX (2-weekly regimen)

Day 1	Oxaliplatin 85mg/m^2,infusion over 2h
	Folinic acid 350mg, infusion over 2 h
	5-FU 400mg/m^2, bolus
	5-FU 1200mg/m^2, continuous infusion over 24 h
Day 2	5-FU 1200mg/m^2, continuous infusion over 24 h

CAPOX (3-weekly regimen)

Day 1	Oxaliplatin 130mg/m^2, intravenous infusion over 2h
Days 1–14	Capecitabine 1700 mg/m^2 , oral in 2 divided doses

Age >75 years: reduced starting dose; oxaliplatin 100mg/m^2 and capecitabine 1300mg $m^{-2}day^{-1}$ for 14 days followed by a 7-day rest period

Capecitabine (3-weekly regimen)

Capecitabine: 2000mg/$m^{-2}day^{-1}$ in 2 divided doses for 14 days followed by a 1-week break.

Age >75 years:dose reduced to 1500mg/$m^{-2}day^{-1}$.

Age >80 years:dose reduced to 1000mg/$m^{-2}day^{-1}$.

Requirements:

Absolute neutrophil count >1.0 ×10^9/L, Platelets >75 ×10^9/L, Stable renal function (CrCl>30mL/min if on FOLFOX, CrCl>50mL/min if on Cape/CAPOX), Bilirubin < 1.4 mmol/L

Advanced Cancer Regimens

FOLFOX + cetuximab* (2-weekly regimen)

Day 1	Cetuximab 500mg/m^2,intravenous infusion over 2 h(subsequent doses over 1 h)
	Oxaliplatin 85mg/m^2, intravenous infusion over 2 h
	Folinic acid 350mg, intravenous infusion over 2 h
	5-FU 400mg/m^2, intravenous bolus
	5-FU 1200mg/m^2, continuous intravenous infusion over 24 h
Day 2	5-FU 1200mg/m^2 continuous intravenous infusion over 24 h

If oxaliplatin is not tolerated or contraindicated: **FOLFIRI + /- cetuximab* (2-weekly regimen)**

Day 1	Cetuximab 500mg/m^2, intravenous infusion over 2 h (subsequent doses over 1 h)
	Irinotecan 180mg/m^2, intravenous infusion over 1h

Folinic acid 350mg, intravenous infusion over 2 h

5-FU 400mg/m^2,intravenous bolus

5-FU 1200mg/m^2, continuous intravenous infusion over 24 h

Day 2 5-FU 1200mg/m^2 continuous intravenous infusion over 24 h

CAPOX/bevacizumab (3-weekly) regimen

Day 1 Bevacizumab 7.5mg/m^2, intravenous infusion over 15 min

Day 1 Oxaliplatin 130mg/m^2, intravenous infusion over 2–6 h

Days 1–14 Capecitabine 1700mg/m^{-2}, oral in 2 divided doses (followed by a 1-week break)

(Age ≥75 years, use starting dose oxaliplatin 100mg/m^2on day 1 and capecitabine 1300mg $m^{-2}day^{-1}$)

FOLFOX/bevacizumab (2-weekly regimen)

Day 1 Bevacizumab 5mg/kg,intravenous infusion over 10 min

Oxaliplatin 85mg/m^2,intravenous infusion over 2 h

Folinic acid 350mg,intravenous infusion over 2 h

5-FU 400mg/m^2, bolus

5-FU 1200mg/m^2, continuous infusion over 24 h

Day 2 5-FU 1200mg/m^2 continuous infusion over 24 h

FOLFIRI (2-weekly regimen)

Day 1 Irinotecan 180mg/m^2,intravenous infusion over 1 h

Folinic acid 350mg,intravenous infusion over 2 h

5-FU 400mg/m^2,intravenous bolus

5-FU 1200mg/m^2, continuous intravenous infusion over 24 h

Day 2 5-FU 1200mg/m^2, continuous intravenous infusion over 24 h

CAPIRI (3-weekly regimen)

Day 1 Irinotecan 200mg/m^2,intravenous infusion over 60 min

Days 1–14 Capecitabine 1700mg $m^{-2}day^{-1}$,oral in 2 divided doses followed by a 1-week break.

FOLFIRI/bevacizumab (2-weekly regimen)

Day 1 Bevacizumab 5mg/kg,intravenous infusion over 10 min

Irinotecan 180mg/m^2,intravenous infusion over 1 h

Folinic acid 350mg,intravenous infusion over 2 h

5-FU 400mg/m^2, intravenous bolus

5-FU 1200mg/m^2, continuous intravenous infusion over 24 h

Day 2 5-FU 1200mg/m^2, continuous infusion over 24 h

Irinotecan (3-weekly regimen)

Day 1 Irinotecan 350mg/m^2 (maximum,700mg),intravenous infusion over 1 h

Age >70 years, dose reduces to 250mg/m^2

Irinotecan/cetuximab (2-weekly regimen)

Day 1 Cetuximab 500mg/m^2, intravenous infusion over 2 h (subsequent infusions over 1 h)

Day 1 Irinotecan 180mg/m^2, intravenous infusion over 1 h

Cetuximab monotherapy (2-weekly regimen)

Day 1 Cetuximab 500mg/m^2, intravenous infusion over 2 h (subsequent infusions over 1 h)

Dose Modifications for FOLFOX

Toxicity NCI CTC grade	Therapeutic measures for toxicity	Initial doses (mg/m^2 course^{-1})		
		5-FU bolus 400	5-FU infusion 1200 × 2	Oxaliplatin 85
		Dose modifications (mg m^{-2}course^{-1})		
Neutrophils <1.0 (grade 3/4) (metastatic) See note below	Delay until > 1.0. Consider omitting bolus 5-FU	320 (consider omission)	960	65
Neutrophils<1.0 (grade 3/4) (adjuvant) See note below	Delay until > 1.0. Consider G-CSF for grade 4 neutropenia/febrile neutropenia	400	1200	85
Platelets 50–75 (grade 2)	Delay until grade 1 (≥75)	400	1200	85
Platelets <50 (grade 3/4) (see note below)	Delay until grade 1 (≥75) Consider omitting bolus 5-FU	320 (consider omission)	960	65
Stomatitis or Diarrhoea (grade 3)	Sucralfate, codeine,or loperamide, as indicated	320	960	85
Stomatitis or Diarrhoea recurrent (grade 3) or single (grade 4)	Sucralfate, codeine, or loperamide, as indicated	320	960	70
PPE (grade 3)	Emollients	320	960	None
Neuropathy		None	None	See below

In the metastatic setting, if severe toxicities recur despite dose modification,a second reduction can be made if clinically indicated. This is assessed on an individual basis.

In all cases, treatment should be delayed until recovery of toxicity to grade 2 (except thrombocytopenia, where recovery should be to grade 1 ≥75). Omission of the bolus of 5-FU can be considered in cases of neutropenia and thrombocytopenia.

In the adjuvant setting, if a patient develops grade 4 neutropenia, delay chemotherapy until recovery to grade 2 (neutrophils ≥1.0) and proceed with chemotherapy without any dose reductions (DRs) for subsequent cycles with granulocyte colony-stimulating factor support on days 7–11 post chemotherapy or pegylated granulocyte colony-stimulating factor(pegfilgrastim 6mg) 24 h following chemotherapy.

In cases of febrile neutropenia/neutropenic sepsis in patients on adjuvant treatment, subsequent cycles may require DR and/or the patient should be treated with prophylactic granulocyte colony-stimulating factor.

Mucositis or 'hand-foot'syndrome

In case of grade 3–4 toxicity, a reduction in dosage by 25% of both the 5-FU bolus and the continuous 5-FU infusion should be carried out for subsequent treatments.

Gastrointestinal toxicities

EVENTS	REDUCTION OF DOSE IN THE FOLLOWING CYCLE
Diarrhoea (grade 3/4) isolated or Diarrhoea + fever and/or neutropenia (grade 3/4)	First episode: reduce the irinotecan dose to 150 mg/m^2 and omit the bolus 5-FU dose on day 1 Second episode: in addition, reduce the oxaliplatin dose to 65 mg/m^2 and reduce the dose of continuous 5-FU by 25% Third episode: treatment discontinuation
Resistant diarrhoea ≥48 h despite high doses of loperamide	No reduction in the dose of irinotecan,oxaliplatin, or 5-FU after recovery,except in cases of diarrhoea grade 3/4, or diarrhoea + fever and/or neutropenia grade 3/4

EVENTS	REDUCTION OF DOSE TO FOLLOWING CYCLE
Febrile Neutropenia Neutropenia (grade 4) for more than 7 days Infection with concomitant neutropenia (grade 3/4)	First episode: reduce the irinotecan dose to 150 mg/m^2 and omit the bolus 5-FU dose on day 1 Second episode: in addition to the reduction in the irinotecan dose and omission of the bolus 5-FU dose, reduce the dose of oxaliplatin to 65 mg/m^2 Third episode: treatment discontinuation
Thrombocytopenia (grade 3/4)	First episode: reduce the oxaliplatin dose to 65 mg/m^2 and the continuous 5-FU dose by 25% Second episode: in addition, reduce the irinotecan dose to 150 mg/m^2 and the continuous 5-FU dose by an additional 25% Third episode: treatment discontinuation

Advise the administration of G-CSF for recurrent grade 3/4 neutropenia after a first-DR or after febrile neutropenia.

Haematological toxicities according to blood counts on day 15

NFS TO DAY 15	DELAY IN CYCLE	DOSE REDUCTION		
		Irinotecan	Oxaliplatin	LV/5-FU
Neutrophils ≥ 1.5 10^9/L and platelets ≥ 75 10^9/L	No delay in cycle	No DR		
Neutrophils < 1.5 10^9/L	Delay treatment until neutrophils ≥ 1.5 (until day 22 or day 29, if necessary). In case of non-recovery by day 29, stop treatment*	First episode: DR to 150 mg/m^2 Second episode: maintain the dose at 150 mg/m^2 Third episode: treatment discontinuation	First episode: no DR Second episode: DR to 60 mg/m^2 Third episode: treatment discontinuation	First episode: omit bolus 5-FU dose on day 1
Platelets < 75 10^9/L	Delay treatment until recovery (platelets ≥ 75 10^9/L). In case of non-recovery by day 29, stop treatment	First episode: no DR Second episode: DRto 150 mg/m^2 Third episode: treatment discontinuation	First episode: DR to 60 mg/m^2 Second episode: maintenance of the reduced dose Third episode: treatment discontinuation	First episode: DR of the bolus dose and of continuous infusion by 25%

Dose Modifications for FOLFIRI

Baseline/on treatment biochemistry assessments:

Renal function

CrCl >30mL/min: normal dose

CrCl 30mL/min: dose reduction of irinotecan by 50% and of 5-FU by 25%

Hepatic function:

Bilirubin 2.6 mg/dL: normal dose

Bilirubin 2.7–5.1 mg/dL: either withhold treatment or DR of irinotecan by 50%

Bilirubin >5.1 mg/dL: withhold treatment. Note that there is an increased risk of neutropenic sepsis in cases of abnormal liver function.

If patients have Gilbert's syndrome, DR of irinotecan by 25% should be considered.

Toxicity NCI CTC grade	Therapeutic measures for toxicity	Initial doses (mg/m^2/course)		
		5-FU bolus 400	5-FU infusion 1200 × 2	Irinotecan 180mg
		Dose modifications (mg m^{-2}course^{-1})		
Neutrophils (≥1.5)	Proceed	400	1200	180
Neutrophils 1.0–1.5	Delay until recovery to 1.5	400	1200	180
Neutrophils <1.0 (grade 3/4)	Delay until recovery to 1.5	320	960	135
Neutrophils <0.5 (grade 4) for >7 days, or second occurrence of neutropenia (grade 3/4) despite DR	Delay until recovery to 1.5	240 (consider omitting bolus)	720	90
Platelets ≥100	Proceed	400	1200	180
Platelets 50–100	Delay until recovery to 100	400	1200	180
Platelets 25–50 (grade 3), or second occurrence of 50–75 (grade 2)	Delay until recovery to 100	320 mg (consider omitting bolus)	960	135
Recurrent thrombocytopenia (grade 3/4)	Delay until recovery to 100	Omit bolus	720	90
Stomatitis or Diarrhoea (grade 3)	Sucralfate, codeine, or loperamide, as indicated	320	960	135
Stomatitis or Recurrent diarrhoea (grade 3)or first occurrence (grade 4)	Sucralfate, codeine, or loperamide, as indicated	320 (consider omitting bolus)	960	90
PPE (grade 3)	Emollient	320	960	None
Febrile neutropenia (grade 3/4)		320	960	135
If severe toxicities recur despite dose modifications,a second reduction can be made if clinically indicated, and this is assessed on an individual basis. If toxicity returns despite 2 DRs,FOLFIRI should be discontinued. In all cases, treatment should be delayed until recovery to grade 2 (except thrombocytopenia, where recovery should be to ≥100).				

Dose Modifications for Cetuximab

Allergic/hypersensitivity reaction

CTC Grade	Treatment
Grade 1 • Transient rash, drug-related fever <38 °C	• Decrease the cetuximab infusion rate by 50% and monitor closely for any worsening • The total infusion time for cetuximab at the weekly dose should not exceed 240 min
Grade 2 • Urticaria, drug-related fever of 38 °C and/ orasymptomatic bronchospasm	• Stop cetuximab infusion • Administer bronchodilators, oxygen, etc., as medically indicated • Resume infusion at 50% of the previous rate once the allergic/hypersensitivity reaction has resolved or decreased to grade 1 in severity and monitor closely for any worsening
Grade 3/4 • Grade 3: symptomatic bronchospasm requiring parenteral medication, with or without urticaria; hypersensitivity-related oedema, angioedema • Grade 4: anaphylaxis	• Stop cetuximab infusion immediately and disconnect infusion tubing from the patient • Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, IV fluids, vasopressor agents, oxygen, etc., as medically indicated • Treatment must be withdrawn and the patient must not receive any further cetuximab treatment

Dose Modifications for Bevacizumab

Dose reductions are not made for bevacizumab-related toxicities. Any patient who develops any one of the following toxicities attributable to bevacizumab should not receive further bevacizumab:

- gastrointestinal perforation
- arterial thromboembolic events
- grade 3/4 haemorrhagic events
- symptomatic grade 4 venous thromboembolic events
- grade 4 hypertension (hypertensive crisis)
- grade 4 proteinuria (nephrotic syndrome)
- cardiac toxicity, including left ventricular systolic or diastolic dysfunction of grade 2–4 severity or decreased of left ventricular ejection fraction by >20%, arrhythmias of grade 3/4 severity, and myocardial ischaemia/infarction.

Management of Bevacizumab-Induced Hypertension:

Patients should be monitored for the development or worsening of hypertension via frequent blood pressure measurement. Angiotensin-converting-enzyme inhibitors and calcium channel blockers tend to be the most effective agents, but diuretics, -blockers, and β-blockers can also be used.

Grade 1 Hypertension:

Asymptomatic, transient (<24 h) increase by >20 mmHg (diastolic) or to >150/100 mmHg if previously within normal limits

Intervention not indicated.

Grade 2 Hypertension:

Recurrent or persistent (>24 h) or symptomatic increase by 20 mmHg (diastolic) or to >150/100 mmHg if previously within normal limits

Anti-hypertensive monotherapy may be indicated.

Once controlled to <150/100 mmHg, patients may continue bevacizumab therapy.

Grade 3 hypertension:

Requiring more than one anti-hypertensive agent or more intensive therapy than previously administered

Bevacizumab should be withheld for persistent or symptomatic hypertension and should be permanently discontinued if hypertension is not controlled.

Grade 4 hypertension: Life-threatening consequence (e.g. hypertensive crisis)

Occurrence of grade 4 hypertension should lead to permanent discontinuation of bevacizumab

Dose Modifications for Capecitabine

Haematological toxicity:

This is likely due to oxaliplatin and not capecitabine, but omit capecitabine in the following situations: Neutrophils <1.0, Platelets <75, If febrile neutropenia is present or the neutrophil levelis <0.5 or platelet count is <50, omit capecitabine until the neutrophil level is ≥ 1.0 and the platelet count is ≥ 75. Re-start capecitabine at 75% dose.

Non-haematological toxicity:

Toxicity grading according to NCICTC	During a course of therapy	Dose adjustment for the next cycle (% of the starting dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2		
First appearance	Interrupt until resolved to grade 0–1	100%
Second appearance	Interrupt until resolved to grade 0–1	75%
Third appearance	Interrupt until resolved to grade 0–1	50%
Fourth appearance	Discontinue treatment permanently	
Grade 3		
First appearance	Interrupt until resolved to grade 0–1	75%
Second appearance	Interrupt until resolved to grade 0–1	50%
Third appearance	Discontinue treatment permanently	
Grade 4		
First appearance	Discontinue permanently or If the physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0–1	50%

All patients should be prescribed treatment for symptoms, such as loperamide, sucralfate, and emollients for diarrhoea, stomatitis, and hand-foot syndrome, respectively.

Renal function: For creatinine clearance 30–50mL/min the dose of capecitabine should be reduced by 25%.

Liver function: Capecitabine can cause an increase in bilirubin and liver transaminases. This is usually mild and of no clinical significance. However, if the bilirubin level increases to >3× normal or aspartate aminotransferase/alanine aminotransferase levels increase to >2.5× normal,capecitabine should be withheld until the bilirubin level is <2.5× upper normal limit and alanine aminotransferase is <2.5× upper normal limit, at which point treatment, can recommence without DR. If patients (with liver metastasis) have abnormally elevated liver transaminase levels prior to commencing capecitabine, only changes in the bilirubin level should be taken into account.

Appendix E: Radiotherapy Planning

(A) Patient positioning

The patient may be positioned supine with the hands on the chest or prone with the hands above the head. A belly board may be used in the prone position.

(B) Immobilization

The patient is immobilized using a customized thermoplastic immobilization device in the intended treatment position.

(C) CT simulation with fiducials (preoperative radiation): Three-dimensional conformal therapy

CT simulation for treatment planning is performed in the treatment position with the immobilization device in situ. The planning CT is a contrast-enhanced CT scan with orallyand intravenously administered contrast. The following steps are followed:

1. The patient is asked to void his/her bladder. Oral contrast (1 L water with 30 mL oral contrast)is administered over 30–45 min, 90 min before CT simulation. No bladder voiding is allowed after the oral contrast has been administered.
2. The patient is placed on the couch of the CT scanner
3. A 3-mm copper marker is placed at the anal verge and secured with a thin tape
4. The immobilization device is applied
5. Three copper fiducial markers are placed in a single plane at the level of a fixed bony landmark (e.g. 2 at the iliac crests on either side and 1 on the anterior abdomen) using the CT lasers
6. A scout film is taken
7. Contrast is injected intravenously (2 mL/kg body weight; 100 mL maximum) either manually or using an injector syringe. When manually injected, the scan is taken immediately after the entire contrast is injected from the cranial to caudal direction. When using the injector syringe, the rate of contrast flow is 2.7–3.2 mL/s depending on the IV cannula, with a scan delay of 15 s followed by scanning in the cranial to caudal direction.
8. The scan thickness is usually 3 mm throughout the scan

(D) CT simulation with fiducials (postoperative radiation): Three-dimensional conformal therapy

CT simulation for treatment planning is performed with the patient in the treatment position and the immobilization device in situ. The planning CT is a contrast enhanced CT scan with orallyand intravenously administered contrast. The following steps are followed:

1. The patient is asked to void his/her bladder. Oral contrast (1 L water with 30 mL oral contrast)is administered over 30–45 min, 90 min before CT simulation. No bladder voiding is allowed after oral contrastadministration.
2. The patient is placed on the couch of the CT scanner
3. A copper wire is taped to the APR scar or a 3-mm copper marker is placed at the anal verge and secured with a thin tape

4. The immobilization device is applied.
5. Three copper fiducial markers are placed in a single plane at the level of a fixed bony landmark (e.g. 2 at the iliac crests on either side and 1 on the anterior abdomen) using the CT lasers.
6. A scout film is taken
7. Contrast is injected intravenously (2 mL/kg body weight; 100 mL maximum) either manually or using an injector syringe. When manually injected, the scan is taken immediately after the entire contrast is injected from the cranial to caudal direction. When using the injector syringe, the rate of contrast flow is 2.7–3.2 mL/s depending on the IV cannula, with a scan delay of 15 s followed by scanning in the cranial to caudal direction.
8. The scan thickness is usually 3 mm throughout the scan

(E) Transfer to the treatment planning system:

The scans are exported through Digital Imaging and Communications in Medicineafter image reconstruction and imported into the planning system.

(F) Contouring guidelines (preoperative radiation): Clinical target volume delineation (CTV) (level 5)[73].

Three nodal CTVs are defined:

1. CTVA: internal iliac, pre-sacral,and perirectal nodal stations
2. CTVB: external iliac nodal stations
3. CTVC: inguinal nodal stations

For rectal cancer, in most cases, CTVA would be the only volume to receive elective radiation. However,for certain presentations (e.g. extension into genitourinary structures and extension to the perianal skin) one could consider adding the external iliac (CTVB) and even the inguinal regions (CTVC).

Three anatomical sites of the pelvis are considered for contouring:

Lower pelvis: The caudad extent of this elective target volume should be a minimum of 2 cm caudad to the gross disease, covering the entire mesorectum to the pelvic floor. Unless there is radiographic evidence of extension into the ischiorectal fossa, extension of the CTVA does not need to extend more than 5 mm beyond the levator muscles. For very advanced anal or rectal cancers extending through the mesorectum or the levators add a 1–2 cm margin up to the bone wherever the cancer extends beyond the usual compartments.

Mid pelvis: The posterior and lateral margins of CTVA should extend to the lateral pelvic sidewall musculature or, where absent, the bone. Anteriorly, CTVA should extend for 1 cm into the posterior bladder to account for day-to-day variation in bladder position. Include at least the posterior portion of the internal obturator vessels (which lie between the external and internal iliac crests in the mid pelvis) with CTVA.

Upper pelvis: The recommended superior extent of the perirectal component of CTVA is at the rectosigmoid junction or 2 cm proximal to the superior extent of macroscopic disease in the rectum/perirectal nodes, whichever is more cephalad. The most cephalad extent of CTVA will be higher than the perirectal component in order to properly cover the internal iliac and pre-sacral regions. The most cephalad aspect of CTVA should be at the bifurcation of the common iliac vessels into the external and internal iliac vessels (approximate bony landmark: sacral promontory).

For rectal carcinomas extending into gynaecologic or genitourinary structures, the external iliac region should be added.

Nodal contouring:

A 7–8 mm margin in soft tissue around the external iliac vessels should be considered, but one should consider a larger (>10 mm) margin anterolaterally, especially if small vessels or nodes are identified in this area.

The final CTV is created by fusing the various CTVs as described above.

Boost volume:

Boost clinical target volumes extend to the entire mesorectum and presacral region at involved levels, including 2 cm cephalad and caudad in the mesorectum and 2 cm on the gross tumour within the anorectal canal.

Planning target volume (PTV):

The CTV to PTV margin should be determined according to institutional preferences and experience (0.7–1.0 cm), depending on whether image-guided radiation therapy is being utilized.

Normal structures:

1. Bladder
2. Bilateral femoral heads
3. Male external genitalia
4. Small and large bowel 1cm above and below the PTV

Dose prescriptions:

45 Gy in 25 fractions over 5 weeks; 1 fraction daily prescribed to the PTV.

A 5.4 Gy boost in 3 fractions is optional for certain postoperative cases.

(G) Conventional two-dimensional radiotherapy planning on a simulator

Patient positioning and immobilization: please refer to (A) and (B) above.

Planning:

1. Mark the anal verge/APR scar using a copper wire
2. The source-to-axis distance technique is preferred for planning
3. A four-field box technique is used
4. The borders are as below:

Anteroposterior/posteroanteriorportal:

Upper border: L5–S1 junction

Lower border: Lower border of the obturator foramen

Lateral borders: 1.5 cm margin on the pelvic brim

Lateral portal:

Upper border: L5–S1 junction

Lower border: Lower border of the obturator foramen

Posterior border: Include the sacral hollow

Anterior border: Posterior border of the pubic symphysis

Corner shielding may be performed to save the bowel.

Dose prescription:

45 Gy in 25 fractions over 5 weeks; 1 fraction daily prescribed to the isocentre.

A 5.4 Gy boost in 3 fractions is optional for certain postoperative cases.

(H) Palliative radiation therapy planning for the pelvis:

Planning:

1. Mark the lower most extent of disease using a copper wire
2. The source-to-axis distance technique is preferred for planning
3. A two-field technique is used
4. The borders are as below:

Anteroposterior/posteroanteriorportal:

Upper border: L5–S1 junction

Lower border: Lower border of the obturator foramen

Lateral borders: 1.5-cm margin on the pelvic brim

Dose prescription:

20 Gy in 5 fractions or 30 Gy in 10 fractions; 1 fraction daily prescribed to the isocentre.

Support: Dr Vinay Gaikwad, Dr Santhosh Kumar D, Dr Mary Ann Muckaden, and Dr Rajiv Sarin from Tata Memorial Centre, Mumbai, and Rohin Mittal and Gigi Varghese from Christian Medical College, Vellore

Appendix F: Performance Status

This is an assessment of overall fitness. It can be a useful guide regarding the ability to tolerate chemotherapy. The most commonly used scale is the Eastern Cooperative Oncology Group performance status:

0. Able to carry out all normal activity without restriction
1. Restricted in physically strenuous activity but ambulatory and able to carry out light work
2. Ambulatory and capable of all self-care, but unable to carry out work; active for more than 50% of waking hours
3. Capable only of limited self-care; confined to the bed or chair for more than 50% of waking hours
4. Completely disabled; cannot carry out any self-care; completely confined to the bed or chair

Clinical trials will usually have their own performance status criteria for patient entry. Otherwise, chemotherapy should normally only be considered in those patients with performance status 0, 1, or 2.

CHAPTER

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CHAPTER

12 ABBREVIATIONS

5-HT	5-Hydroxytryptamine receptors
AAR	Annual incidence rate
ACHm	Muscarinic acetylcholine receptors
APC	Adenoma tous polyposis coli
APR	Abdominoperineal resection
AR	Anterior resection
ASA	American Society of Anaesthesiologists
ASCO	American Society of Clinical Oncology
BD	Twice a day
BRAF	Proto-oncogene encoding the protein B-raf
CA19.9	Carbohydrate antigen 19.9
CAP	Chest abdomen pelvis
CAPEOX	Capecitabine and oxaliplatin
CAPIRI	Capecitabine and irinotecan
CEA	Carcinoembryonic antigen
CLM	Colorectal liver metastasis
CT	Computed tomography
CECT	Contrast-enhanced computed tomography
CRC	Colorectal cancer
CRM	Circumferential resection margin
CTRT	Chemo-radiotherapy
CTV	Clinical target volume
D2	Dopamine receptor
DR	Dose reduction
dMMR	Deficient mismatch repair
DRE	Digital rectal examination
EUS	Endoscopic ultrasonography
5-FU	5-Fluorouracil
FA	Folinic acid
FAP	Familial adenomatous polyposis
FLR	Future liver remnant
FNA	Fine needle aspiration
FOLFOX	5-Fluourouracil, leucovorin, and oxaliplatin
FOLFIRI	5-Fluourouracil, leucovorin, and irinotecan
GABA	Gamma-aminobutyric acid receptor
Gy	Gray

H1	Histamine 1
HNPCC	Hereditary non-polyposis colon cancer
ICMR	Indian Council of Medical Research
IHC	Immunohistochemistry
IV	Intravenous
KRAS	Kirsten-ras oncogene homolog from mammalian ras gene family
LAR	Low anterior resection
LN	Lymph node
LV	Leucovorin
mCRC	Metastatic colorectal cancer
MDT	Multidisciplinary team
MLH1	MutL homolog1 gene
MMR	Mismatch repair
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
NACT	Neoadjuvant chemotherapy
NACTRT	Neoadjuvant chemo-radiotherapy
NCI CTC	National Cancer Institute Common Toxicity Criteria for Adverse Events
NPS	Non-peritonealised surface
OD	Once a day
PET	Positron emission tomography
PO	Per oral
PPI	Proton pump inhibitor
PR	Per rectum
PTV	Planning target volume
QDS	Four times a day
RFA	Radiofrequency ablation
RT	Radiotherapy
SC	Subcutaneous
SCPRT	Short-course preoperative radiotherapy
TDS	Thrice a day
TEMS	Transanal endoscopic microsurgery
TME	Total mesorectal excision
TRG	Tumour regression grade
US	Ultrasonography
WHO	World Health Organisation

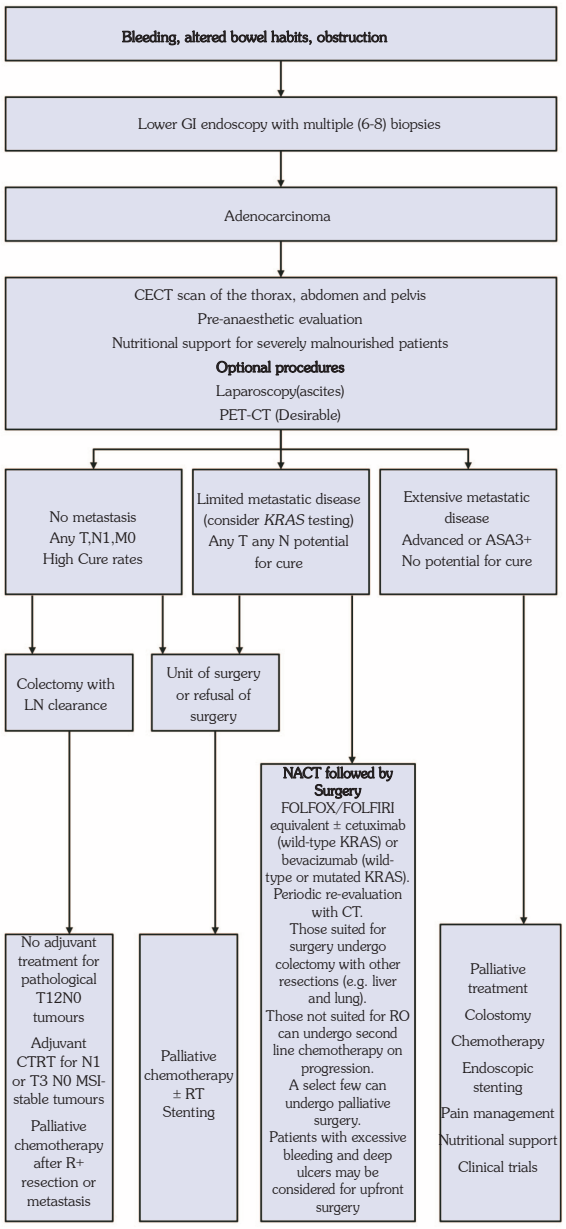
Desirable/Ideal: Tests and treatments that may not be available at all centres but the centres should aspire to have them in near future.

Essential: Bare minimum that should be offered to all the patients by all centres treating patients with cancer.

CHAPTER

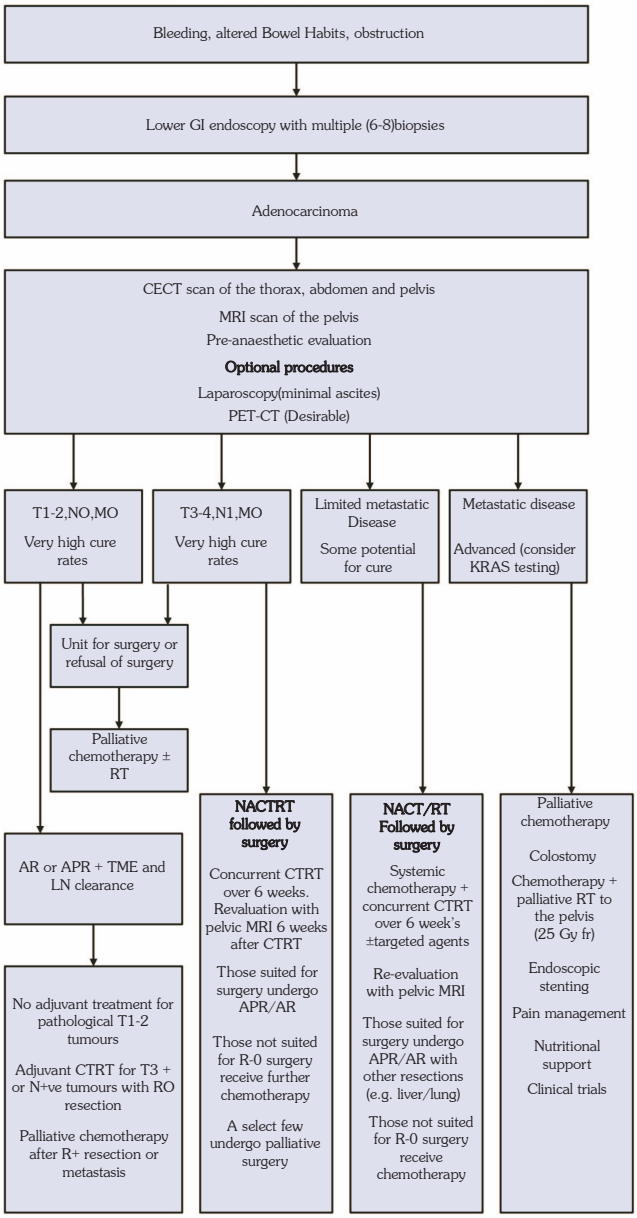
13 ALGORITHMS FOR COLON AND RECTAL CANCER

COLON CANCER



GI, gastrointestinal tract; CECT, contrast enhanced computed tomography; LN, Lymph node; CTRT, chemoradiotherapy; MSI, microsatellite instability RT, radiotherapy; KRAS, Kirsten ras -oncogene homolog from mammalian ras gene family NACT, neoadjuvant chemotherapy; FOLFOX, 5-fluorouracil leucovorin and oxaliplatin ; FOLFIRI, 5- fluorouracil leucovorin and irinotecan; CT-Computed tomography; ASA3, American society of Anesthesiologists 3

RECTAL CANCER



GI, gastrointestinal tract; CECT, contrast enhanced computed tomography; MRI, magnetic resonance imaging; AR, anterior resection; APR, abdominoperineal resection; TME, total mesorectal excision; LN, Lymph node; CTRT, chemoradiotherapy; RT, radiotherapy; NACTRT, neoadjuvant chemoradiotherapy; NACT neoadjuvant chemotherapy; KRAS, Kirsten ras -oncogene homolog from mammalian ras gene family

CHAPTER

14 SUMMARY

This consensus statement may be used as framework for more focused and planned research programmes to carry forward the process. The aim of the Indian Council of Medical Research Guidelines is to assist oncologists in making major clinical decisions encountered while managing their patients, while realizing the fact that some patients may require treatment strategies other than those suggested in these guidelines.

- Pattern of genomic alterations in colon and rectal tumours are similar, and hence, can be grouped together.
- Histological confirmation is mandatory prior to the commencement of definitive treatment.
- All patients should be staged according to the TNM staging system and risk should be assessed at diagnosis. A baseline contrast-enhanced computed tomography (CT) scan of the chest, abdomen, and pelvis should be considered.
- Select cases should be referred to genetics clinics as described.
- Patients should receive multidisciplinary care under the care of a surgical, medical, and radiation oncologist.
- Colon cancer (tumours lying above the peritoneal reflection):Primary surgery remains the standard of care. The need for adjuvant chemotherapy should be determined on an individual basis. The option of observation alone versus chemotherapy should be discussed with the patient.
- Rectal cancer: Neoadjuvant chemo-radiotherapy (NACTRT) should be strongly considered for locally advanced but resectable tumours for disease downstaging and organ preservation.
- *RAS* mutation testing may be performed for all patients with metastatic disease (desirable).
- Patients with liver-limited colorectal metastases should be referred early to a hepato-biliary surgeon to assess resectability.
- First-line chemotherapy for metastatic colorectal cancer (CRC):

5-Fluourouracil (5-FU), leucovorin (LV), and oxaliplatin (FOLFOX) as first-line treatment followed by single-agent irinotecan as second-line treatment

or

FOLFOX as first-line treatment followed by 5-FU, LV, and irinotecan (FOLFIRI) as second-line treatment or

Capecitabine and oxaliplatin (CAPEOX) as first-line treatment followed by FOLFIRI as second-line treatment

FOLFIRI or capecitabine and irinotecan (CAPIRI) may also be given as first-line therapy

- Targeted therapy (cetuximab and bevacizumab) may be considered in select patients.
- Patients should be offered regular surveillance after completion of curative resection or treatment of advanced disease.
- Participation in clinical trials should be encouraged.
- Referral for early palliative care should be made if indicated.