Guidelines for Colorectal Cancers

Vol X

Part C

Editor

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Dedicated to
all our patients at
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Preface

The Centre for Evidence Based Medicine (EBM) defines EBM as "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients". EBM has percolated into all fields and levels of medical practice and this has been particularly exemplified in current oncology practice. There is an increasing need to update our knowledge and be guided by EBM, especially in an era where there have been rapid developments and innovations in oncology.

Important innovations have been made in diagnostic methods and surgical management of colorectal cancers. Minimally invasive surgery and robotic surgery have been adopted by gastrointestinal surgeons the world over and have had preliminary validation in randomized trials. Major progress has also been made in the treatment paradigms of colorectal cancers. The role of neoadjuvant and adjuvant treatment for localized disease as well as palliative treatment for advanced disease continues is established. Targeted therapy has revolutionized the way we treat several solid cancers and inroads have been made in colorectal cancers too with anti VEGF drugs.

In the internet era, information overload can be as much of a problem as paucity of information. The busy clinican

is frequently unable to separate real data from mere hype; the Ninth annual EBM meeting and the guidelines book on colorectal is planned to do precisely this. As always, in addition to collating the best available evidence, the meeting and book also highlight areas where strong evidence is lacking. Exciting new research in areas of multidisciplinary management of colorectal cancers and targeted therapy is ongoing. Controversies in management can only be resolved with large multi centric studies. I hope that in addition to updating practicing oncologists, this book and meeting serves as a stimulus for investigators to actively participate in clinical research and further improve treatment outcomes.

C S Pramesh
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CHAPTER-1

Overview

i) Purpose

The colorectal cancer (CRC) treatment goals are: to improve long term survival, control symptoms of local disease and maintain an acceptable quality of life while preserving the body functions. Achiveing these goals require a multimodal approach where different surgical procedures are combined with adjuvant and neoadjuvant chemotherapy and radiation therapy. The best practises requires an individualized approach guided by several factors as disease stage, nodal involvement, the presence of metastatic disease or other comorbidities, family history, and the age of the patient.

Colorectal cancer (CRC) is one of the leading causes of cancer deaths in the world. While the incidence rates of CRC is much lower in India, the survival rates for CRC are disproportianately lower. This is in part due to more advanced stage at diagnosis and in part due to inadequate treatments given to the CRC patients in India.

Several new diagnostic procedures and therapies that have emerged in the past decade. Indiscrimnate use of all these

expensive modalities for all patients could result in net harm. The EBM guidelines are meant to improve the management of CRC in India in a cost-efficient way. It is hoped that these guidelines would also be accepted as the standard of care for reimbursement purposes in India.

ii) Development of guidelines

The topics having direct impact on patient care in India were identified and distributed to various members of the DMG. All the contributors reviewed the published literature and summarized the evidence covering their areas of expertise. After compiling all the chapters, it was subjected to a centralized editing. Modifications following the EBM conference will be placed as an addendum on the TMH website.

iii) Grading of Recommendations:

Recommendations have been classified as:

A: Recommendation based on levels Ia, Ib evidence.

B: Recommendations based on levels IIa, IIb, and III evidence.

C: Recommendations based on level IV evidence.

iv) Grading of Evidence

All the evidence complied in this report is classified as follows.

1a: Evidence from meta-analysis of several randomized controlled trials

1b: Evidence from at least one large randomized controlled trial

2a: Evidence from at least one large controlled study without randomization

2b: Evidence from at least one large quasi-experimental study

3: Evidence from large non-randomized descriptive or correlation studies and case series.

4: Opinions of expert committees and opinion leaders managing CRC in India.

v) Applicability of evidence:

Ability to use the recommendations at TMH is graded as:

A: Applicable to all patients without any modifications.

B: Applicable to all with some modifications of standards of practice.

C: Applicable only after extensive modification of current standards of care at TMH.

vi) External validity

Most of the guideline statements in this book are extrapolated from the results of trials done in Europe and North America. Individual contributers have used their own Indian experience to increase the validity of the statements. Because of these reasons the exact duplication of the results at TMH and in other parts of India will have some limitations.

vii) Review of Guidelines:

it is proposed to incprporate any changes suggested during the EBM meeting by 31st march 2011. An annual review of all the new studies reported would be done and appropriate changes are made in the EBM guidelines in January 2012.

CHAPTER-2

Summary Points

General

1. All new CRC patients must be discussed in the DMG at presentation for adequate work up within 2 days, and after the work up is completed for making a treatment plan. All cancer treatments including surgery, radiotherapy and chemotherapy in a primary, neoadjuvant or adjuvant settings should started only after discussion at the DMG meeting.
2. All discussions in the DMG with the treatment plans agreed to must be recorded and dated in the case record files or EMR.
3. Treatment should begin within two weeks from the date of final treatment planning in the DMG. Treatments of patients with a chance for cure (primary surgery and adjuvant therapy) must not be delayed and their treatment should be fast-tracked with earlier appointments.
   Recommendation grade-A
4. Informed consent should be obtained from all patients undergoing surgery, radiotherapy or chemotherapy. Information on likely benefits and

risks of the proposed treatment and alternative therapies should be provided to all patients. Informed consent should be obtained by a senior member of the DMG where possible. Patients who are likely to get either a temporary or permanent colostomy must be counseled for stoma care by trained personal several days before the planned surgery.

5. Any cancer with distal margin at or less than 15 cm from the anal verge during flexible endoscopy should be termed as rectal cancer and managed as rectal cancer. The primary treatment for rectal cancer is different from colon cancer and includes the use of perioperative chemo-radiotherapy for locally advanced disease. However the follow up and treatment of recurrent cancer and metastatic cancer are largely similar for cancers of the rectum and colon.
6. Patients should be encouraged to participate in various trials and follow up regularly.
7. Pathological examinations of the CRC specimens should be carried out in laboratories which perform to high technical standards such as those required for Clinical Pathology Accreditation. Pathology laboratories should store stained histology slides for a minimum of 10 years, and tissue blocks from specimens indefinitely, in order to facilitate future case review, clinical audit, and research.

Pre treatment work up

8. All patients must be evaluated with careful attention to family history and co morbidity. Patients with probable family history for inherited CRC such as polyposis or HNPCC syndromes, etc should be referred to the cancer genetics clinics for further work

up and counseling. The surgical procedures for FAP and HNPCC associated CRC are different.

9. All patients with CRC should be investigated with a full colonoscopy with adequate biopsy sampling before starting any therapy. The only exception being emergency surgery. Colonoscopy is done to exclude synchronous polyps and cancers. Patients who have not had a full colonoscopy before should have one within 6 months of surgery.
10. Pre-operative histology must be made for all tumors. Tumor blocks should be obtained for all those who have undergone biopsies elsewhere. The paraffin tumor blocks should be preserved for future biomarker studies.
11. All patients with colon or rectal cancer with the exception of those undergoing emergency surgery, should have adequate pre-operative staging with a MD-CECT scan of the chest abdomen and pelvis to determine the base line extent of the disease and the presence of lung or liver metastases. Patients with low rectal cancer and those with borderline resectability should have MRI scans of the pelvis or EUS of the rectum when sphincter saving surgery is being considered.
12. Routine PET-CT scan has little role in the primary staging of CRC. The PET-CT scan is recommended to exclude other metastasis when more invasive surgical treatments such as liver and lung resections are proposed.
13. Routine blood transfusions to raise hemoglobin up to 10 G/dl or more can be detrimental and is discouraged. The transfusion threshold of 7.0G/dl is recommended for patients without any co-existing ischemic heart disease.

Enhancing recovery after surgery

14. Quick recovery after surgery helps to start adjuvant treatments on time and saves costs. There is good scientific evidence for an enhanced recovery after surgery (ERAS) program during CRC surgery. **Recommendation grade-A**
15. Vigorous bowel preparation using methods that are known to cause starvation, dehydration and electrolyte disturbances in the patient during surgery should be avoided before CRC surgery. The ultimate decision on the need for bowel preparation should be made by the operating surgeon and this should be recorded in the EMR.
16. All patients should be given thrombo-prophylaxis before colorectal surgery unless contraindicated.
17. All patients should have antibiotic prophylaxis before surgery. A single large dose of appropriate intravenous antibiotic (second generation cephalosporins) is half hour before surgery is recommended for surgeries lasting up to 4 hours. For longer lasting surgeries a second dose may be repeated after 4 hours.
18. All patients are advised a nutritional counseling before surgery, chemotherapy or radiation. Patients should not be starved for more than 6 hours. Carbohydrate rich drink may be administered to obstructed patients up to 4 hours before general anesthesia. Patients having severe malnutrition should receive intensive nutrition support for 10-14 days before undertaking elective surgery.
19. All patients should receive adequate analgesia before during and after surgery. The use of perioperative epidural analgesia is to be encouraged as part of the ERAS.

Primary surgical treatment

20. All surgeries should be planned to achieve a R0 resection by resecting with wide margins, but this will finally depend in part on the stage at which the CRC is diagnosed. The term curative resection (R-0) should be based on operative notes and the final histological findings.
21. The use of a check list before surgery has been shown to reduce morbidity and mortality.
22. All care and precautions should be exercised to preserve the pelvic nerves in order to minimize bladder, bowel and sexual dysfunction following surgery.
23. Tumors should be handled carefully with early venous ligation. Rupture of the tumour during an operation should be avoided at all costs.
24. Adequate excision of lymph nodes should be performed so as to obtain a minimum of 12 nodes for pathological staging.
25. All patients with cancer in the lower two-third of rectum should get a total mesorectal excision as part of a low anterior resection (AR) or abdomino-perineal resection (APR). In patients with cancers of the upper rectum, the mesorectum should be divided no less than 5 cm below the lower margin of the tumour.
26. Judicious use of prophylactic colostomy may be used for ultra-low pelvic anastomoses for sphincter saving ultra low anastamoses as they are associated with a higher leak rate.
27. Local transanal or endoscopic excision of rectal cancer with curative intention should be restricted to small T1 cancers that are less than 3cm in diameter with good or moderate differentiation. Subsequent

histopathology examination of the resected cancer is needed to identify a proportion which requires more radical surgery.

28. All laparoscopic colorectal operations should be performed by surgeons properly trained in colorectal surgery. These surgeons should also have undergone laparoscopic training under supervision, particularly in rectal procedures. Their results should be carefully audited by the DMG.
29. Emergency surgery can be more difficult and prone for more complications, should be carried out during the routine hours as far as possible with the direct supervision by experienced surgeon and anesthetist.
30. Patients presenting with intestinal obstruction should preferably get a MDCT scan before surgery to exclude pseudo-obstruction and cancer stage before surgery.
31. In patients with acute large bowel obstruction, the placement of an expandable stent is a treatment option as a bridge to planned surgery. Stenting may also be used for palliation of obstruction in disseminated CRC.
32. The overall post operative mortality at 4 weeks should be below 5%. Efforts should be made to keep the operative mortality less than 3% for elective surgery. A leak rate below 8% for anterior resections and below 4% for other types of resection should be achieved.
33. All resected tissues including polyps, tumors, piles, etc should be submitted in enbloc for histopathology examination.
34. Pathology reports should contain information on all the data items contained in the Minimum Data Set for CRC (See Appendix).

35. Operative notes should be recorded soon after the surgery. A template should be used to construct an operation record so that all the relevant data points are captured. It should not be left to in experienced resident or filled out after another surgery by the same team. For emergency surgeries notes be recorded on the paper CRF and transferred to the EMR the next working day.

Adjuvant and neoadjuvant treatments

36. Appropriate adjuvant and neoadjuvant treatments improve outcomes for patients with high risk CRC including those over 70 years of age. **Recommendation grade-A**
37. After an R0 resection is achieved, all high risk patients with colon cancer should be offered adjuvant therapy. Oxaliplatin in combination with 5-FU and leucovorine or capecitabine or Capecitabine monotherapy or 5-fluorouracil and folinic acid should be considered as options for the adjuvant treatment
38. Patients with high-risk node-negative colon cancer should be individually counseled by an oncologist with regard to their level of risk and the possible benefits of fluoropyrimidine-based chemotherapy. The use of MSI testing is recommended in such a setting.
39. If the addition of radiotherapy to surgery is deemed necessary for rectal cancer, it should ideally be given pre-operatively. Patients with resectable rectal cancer can be considered for short-course preoperative radiotherapy (25Gy in 5 fractions in 1 week) when surgery can be performed within one week of completion of radiation. Neoadjuvant chemo-radiotherapy of longer duration is recommended for all other patients with high risk rectal cancer.

40. When the DMG decides that chemo-radiotherapy would be appropriate to downstage the tumour, a radiation dose of 45Gy in 25 fractions over 5 weeks, with or without a reduced volume boost dose of 5.4-9Gy in 3-5 fractions, is recommended.

41. Post operative adjuvant chemo-radiotherapy should be given to patients with well established predictive factors for local recurrence (e.g. evidence of tumour at the circumferential resection margin, mesorectal lymph node involvement and extramural vascular invasion), if they had not received pre-operative radiotherapy. A dose of 45Gy in 25 fractions over 5 weeks with a planned boost dose of 5.4-9Gy in 3-5 fractions is recommended.

42. Patients with inoperable but non-metastatic rectal carcinoma should be offered primary chemo-radiation. When the course is completed, the tumour should be re-staged after 6 weeks and considered for resection if appropriate.

43. A CT based radiotherapy planning using multiple fields are recommended for planning radiotherapy for rectal cancers, as this approach lowers the morbidity and mortality.

44. Capecitabine monotherapy or combination of 5-fluorouracil and folinic acid should be considered as options for concurrent treatment during preoperative or post operative adjuvant chemoradiation of rectal cancer. Oxaliplatin should not be used during radiotherapy.

Management of limited metastasis

45. Patients with operable liver or lung metastases should be reviewed in the DMG with a PET scan in the presence of a hepatobiliary (or thoracic) surgeon and

colorectal oncologist, to evaluate operability and to decide on a combined plan of management to optimize the chance of successful R-0 resection of all metastatic disease.

46. Patients with potentially operable liver or lung metastases should be offered the best combination chemotherapy including a targeted agent known to down stage and review periodically until sufficient down staging has been achieved. A hepatobiliary or thoracic surgeon and colorectal oncologist, should evaluate the patient periodically for operability to optimize the chance of successful R-0 resection of all metastatic disease.
47. After an R0 resection is achieved, all patients should be offered continuation of the chemotherapy for up to 6 months. Oxaliplatin in combination with 5-FU and leucovorine or capecitabine or Capecitabine monotherapy or 5-fluorouracil and folinic acid should be considered as options for such adjuvant treatment.

Palliative treatments

48. The treatments plans for patients who are found to have recurrence during follow up after initial treatment should be made by the DMG.
49. Patients with more widespread or unresectable metastatic disease should be referred to a medical oncologist for consideration of palliative chemotherapy. These patients should be counseled for a continuum of care with multiple chemotherapy interventions.
50. Palliative treatment using fluoropyrimidine alone, or 5FU in combination with Oxaliplatin or Irinotecan, has been approved in India for the treatment of

metastatic CRC. The continuum of care usually comprises of FOLFOX/CAPEOX followed by FOLFIRI/ CAPEIRI as shown in the appendix.

51. There is good evidence that targeted monoclonal antibodies such as cetuximab (in tumors that are KRAS wild type) and bevazucimab improves progression free survival and overall survival when added to standard first and second line chemotherapies listed in appendix.. We recommend testing of tumor blocks for mutation of the KRAS gene and restrict the use of cetuximab in patients with wild type of KRAS gene.
52. All patients should be given adequate supportive treatments including pain relief, nutritional support, etc throughout their treatment.

Follow up after primary treatments

53. Regular follow up are recommended at 3 monthly intervals for 2 years and six monthly intervals for 3 more years to detect potentially curable recurrence.
54. A base line CT scan of the thorax, abdomen and pelvis should be done in all patients after completion of curative therapy. Thereafter it should be repeated every 6 monthly in the first two post-operative years for detecting resectable metastatic recurrence.
55. Follow up colonoscopy should be done every 5years in average risk patients. It should be done more frequently in familial CRC and when interval recurrence is suspected.
56. Tumor marker CEA should be done during follow up visits in patients having elevated CEA before resection.
57. Periodic audits using structured forms are needed to determine the end results such as post-operative

mortality, anastomotic leak rates, colostomy rates and 5-year survival. Audit should include information on variables such as the socio-economic status of patients, which can lead to variation in outcomes from different centres.

Screening

58. There is no evidence to support routine screening of asymptomatic general public for CRC in India.
59. Surveillance of high risk individuals for polyps and CRC must be done on a case to case basis. All middle aged and elderly patients presenting with altered bowel habits, rectal bleeding and iron deficiency anemia should be evaluated for presence of colorectal disease including CRC.

Anal cancer management

1. Squamous cell carcinoma (SCC) of anal cancer is not uncommon in India and can present in different ways. It is often passed off or treated as piles. All suspicious lesion/ ulcer in the anal canal should be biopsied adequately.
2. All patients with SCC of anal canal should be discussed at the DMG. They are treated differently from CRC.
3. All patients with anal canal cancer must be staged using clinical examination and MDCT scan to determine the sphincter tone, local lymph node metastasis and the presence of distant metastases.
4. Small well differentiated anal cancers (less than 2cm) can be locally excised with wide clear margins.
5. Anal canal cancer is usually treated with concurrent chemo-radiotherapy and not by surgery. Chemotherapeutic drugs 5FU and Mitomycin-C are to be used concurrently with external radiation.

CAHPTER-3

Clinical Presentation and Work up

Clinical History

As common experience tells us, colorectal malignancies may present in two different ways: in the routine OPD with long standing chronic symptoms as detailed below, or in the emergency setting either with an acute obstruction or as a perforation. Reports by various workers put the figures as chronic symptoms to be about 77% to 92%, acute obstruction about 4% to 8% and perforations to be about 2% to 4%. [1, 2, 3]

The primary symptoms of CRC will depend on the site of the lesion. Bleeding per rectum is probably the most common symptom which the patient presents with. In case of rectal growths, it may be frank blood while it may be altered in colour in growths higher up in the colon. Right colonic cancers tend to be of polypoidal nature and keep on bleeding in small amounts, resulting in anemia. Though hemorrhoids is the most common cause of bleeding per rectum, Beart et al. (4) found that CRCs accounted for about 6% of patients having rectal bleeding and diagnosed with hemorrhoids. It is fair to say that, any

case of bleeding per rectum must be evaluated adequately, to rule out an underlying malignancy.

Alteration of bowel habits is the other common symptom which many patients present with. By definition, alteration of bowel habit would imply any persistent deviation from the routine. This is much more common in left colonic cancers, where the growth tends to be annular and stricturous and stools reaching up to the left colon tend to be fairly formed. Progressively increasing constipation can occur.

Pain is almost always related to partially obstructing lesion of the colon. Pain is usually poorly localized and may be colicky in nature. Rest pain is never a feature of colorectal carcinomas till the lesion is very advanced so as to involve the nerve roots.

Rectal growth may lead to a variety of symptoms in addition. Patients may have a feeling of incomplete evacuation due to the growth occupying the rectal ampulla. They may have a 'spurious' diarrhea, which is due to mucus secretion from the lesion in the rectum. Though the growth may be obstructing the lumen, patient may have the feeling of repeated urge to pass and all that he passes is some mucus. This symptom can be rather troublesome especially if the cancer is advanced. Advanced rectal cancers may infiltrate the nerve roots and may produce a severe pain, not responding to routine analgesics.

Other common symptoms may include loss of weight and appetite, though they are not very commonly seen with lower GI cancers as compared to upper GI cancers. An iron deficiency anemia may occur due to chronic low volume blood loss in the stools, usually in right colonic

cancers and rarely, patient may present with symptoms of anemia and on work up is diagnosed to have an underlying colonic cancer.

Important to mention here, is family history of CRCs and other disorders like ulcerative colitis, FAP, HNPCC etc, since they have a bearing on treatment planning, follow up and influence the outcomes.

As far as clinical examination goes, colonic cancers may occasionally be palpable as mass in the abdomen, else there is no other physical finding. In rectal cancers, a per rectal examination will give valuable information as to the location of lesion with respect to distance from anal verge, luminal compromise, mobility with surrounding structures etc. It is essential to look for inguinal nodes as well as left supraclavicular nodes.

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Diagnosis and Investigation

When a CRC is suspected, it is important that the investigations are carried out promptly. There is evidence

that treatment delays increases the costs and decreases the survival. Furthermore, delays causes considerable psychological morbidity which makes it harder for patients and their families to cope with their disease, especially if it is incurable.

It is important to develop management strategies which ensure that time lags before referral, diagnosis and treatment are kept to a minimum. Some delays are unavoidable. The reasons could be the following: the diagnostic process, which incorporates 'treat, watch-and wait' strategies by both patients and GPs, the time taken for appointments to be arranged, the time for diagnostic investigations and staging of the cancer, optimising the patient's general health for surgery, and the time required to arrange for admission and operation, ensuring that adequate facilities (such as high dependency or intensive care beds) are available when necessary. It should be possible to minimise delays after referral to hospital, but reducing delays before this may be difficult. Public awareness campaigns and referral guidelines over many years have not achieved earlier referral.

Clinical Examination

Clinical examination remains important, and can lead to appropriate timely referrals. There is a palpable rectal mass in 40-80% of patients with rectal cancer[1,2]. A study has shown that 82% of palpable rectal cancers may be detected by Primary care Physicians[3]. A Digital Rectal Examination (DRE) should be an essential part of the examination of any patient presenting with lower GI symptoms above the age of 40 years, and of anybody below this age with persistent symptoms[4]. A small cancer at the anorectal junction which may be missed by

endoscopy can often be detected by rectal examination[4]. Vaginal examination should be part of the assessment of suspected rectal cancer in women. A right-sided abdominal mass could be of greater diagnostic value than a left-sided mass, in view of a higher prevalence of a palpable sigmoid colon[4]. When there is uncertainty about the cause of an abdominal mass, the patient should be treated with laxatives and re-examined to establish whether the mass is persistent before referral[4].

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Radiology and imaging

Accurate prediction of achieving a curative resection and warning the DMG team about a possibility of R+ resection is critical in selection of patients for pre-operative chemotherapy in rectal malignancies. Computed tomography is the gold standard for pre-operative evaluation and local staging of rectal tumors. There is increasing evidence in favor of Magnetic Resonance Imaging from results of systematic observational studies.

One of the most promising results was generated from the MERCURY trial (BMJ 2005) which proposed MRI as the most reproducible method of assessing the relation of the rectal cancer to the potential circumferential resection margin which is the mesorectal fascia. The group noted that the technique could identify most patients with potentially affected margins at presentation, thus preventing incomplete resection of the tumor and local recurrence. Staging with magnetic resonance imaging provided an accurate assessment of tumor spread before preoperative treatment, allowing for standardization of inclusion into clinical trials.

No large randomized trial has however till date been undertaken in this regards, this may be the reason for most high volume centers (including TMH) continue to use CT scan for the purpose. New MRI sequences including Diffusion Weighted Imaging (DWI) can help differentiate subtle muscle invasion and response of tumor to chemotherapy. Improvement in hardware and homogeneity & field strength of magnets has led to generation high resolution volumetric 3-D imaging, which can be post-processed in any plane without losing vital information due to the isotropic nature of such data. This would extrapolate to a better pre-operative understanding of surgical anatomy and variations in complex closed compartments, ano-rectal region being one of them. The available evidences in favor of the above notion range from Level I (the MERCURY trial) to Level V. Most of the studies are an assortment of non-consecutive patients presenting to routine clinical facilities. With experience (unpublished data) of a series of consecutive preoperative rectal malignancy evaluation by MRI in the recent past, we however observe the modality to be more informative than CT scan for the purpose.

PET Scan

Accurate pre-operative staging is important for optimal therapeutic planning. Early detection of recurrence can lead to better survival if the sites of recurrence are localized and amenable to surgical excision. The role of PET scan is limited in the primary staging of newly diagnosed CRC, due to the low sensitivity of FDG PET for small lesions (less than 1 cm) and the chance of false positives in inflammatory bowel lesions. There is lack of evidence to use FDG PET as part of routine screening or initial staging of CRC patients. However there are reports of FDG PET imaging leading to a management change in 2-36% patients of CRC undergoing initial staging. The body of evidence to support this weak. A lack of cost –benefit analysis has not led to an impact on general clinical practice particularly in nations where resources are limited. The primary staging of rectal cancers is one specific indication where FDG PET-CT is likely to make an impact on management decisions. Though MRI has an established role in rectal tumor staging by facilitating accurate assessment of local tumor extension, addition of PET can provide more accurate assessment of nodal & metastatic disease.

For evaluation of disease recurrence PET has an established role in the standard of care of patients with suspected recurrence either due to clinical symptoms or rising tumor marker levels. A meta-analysis by Huebner et al found that FDG PET has a sensitivity and specificity of 97% and 76% in the detection of recurrent CRC which led to management change in 29% patients. This number is similar to the 32% management change demonstrated by Gambhir et al. A prospective blinded comparison by Valk et al between FDG PET and CT has shown a sensitivity

and specificity of 93% and 98% for FDG PET and 96% and 69% for CT. FDG PET can be particularly useful in detecting subtle peritoneal and omental disease which can be difficult on CT scan alone. It is very useful in proper selection of patients who are suitable for surgery for recurrent disease. One of the most compelling indication of FDG PET in CRC is to look for occult extrahepatic disease before planning a metastatectomy. Two meta analyses have shown a pooled sensitivity and specificity of 91.5 % and 95.5% versus 61 % and 91% for CT in this setting.

FDG PET has been used in assessing response at the completion of radiotherapy, chemoradiation or local ablative therapy. When performed at an appropriate time interval after treatment it can provide information on presence of viable tumor, differentiate disease from fibrosis/scar and also helps predict survival. There are a few prospective studies in literature which have looked at the role of FDG PET after radiation therapy in the prognostic stratification in patients with locally advanced rectal cancer. They concluded that a significant survival benefit was observed in patients with low FDG uptake after pre-operative radiotherapy in locally advanced tumors of the rectum.

Timing of the PET/CT	**Hierarchy of Diagnostic Efficacy**	**Relevance of test**	**Level of evidence**
Diagnosis	Level 2	Potentially appropriate	Level II
Staging	Level 5	appropriate	Level II
Response evaluation and restaging	Level 5	Appropriate	Level I
Restaging suspected recurrence	Level 5	Appropriate	Level I
Follow up	Level 4	Probably appropriate	Level I
RT planning	Level 4	Potentially appropriate	Level II

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CHAPTER-4

Histopathology and Staging

A thorough gross and microscopic examination of the specimen removed as a part of curative surgery, is essential for prognostication and planning adjuvant treatments. It also helps in patient stratification for clinical trials, audit of pathology services, audit of the colorectal surgeries with resultant improvement in the surgical skills. It also is a strong tool in planning service delivery and cancer epidemiology.

A) Specimen Handling And Dissection

The specimen is received in the laboratory in the fresh state. The length of the specimen should be measured, and it is opened along the anterior wall. It should be adequately fixed for 24-48 hours in 10% formalin, preferably on a flat board. Photographs can be taken before or after fixation. The area of tumor involving the peri colorectal fat can be left unopened for subsequent transverse slicing. Grading of the surgical plane of resection in rectal cancer specimens. Evidence from two large prospective randomized trials have demonstrated that grading of the surgical plane of resection in CRCs predicts

local recurrence and survival. Its continual feedback to multidisciplinary teams may lead to improved quality of surgery. (10, 11)

B) Macroscopic Assessment (12,13)

1) Site of tumor- This should be evident from the clinical information and the gross examination of the specimen. Gross involvement of the serosa in sigmoid colon, anterior ascending or descending colon is to be recorded.
2) Maximum tumor diameter- measured from the luminal aspect of the tumor. The tumor thickness is ignored for this measurement.
3) Distance of the tumor to nearest margin- longitudinal distance (distance to cut end) is measured. If the distance is more than 3 cm, the histological examination need not be carried out (presumed negative), except if the tumor is widely invasive in the tissue and is showing extensive lymph vascular emboli, the tumor is a signet ring cell carcinoma, small cell carcinoma or undifferentiated carcinoma
4) Presence of tumor perforation- Grossly if there is presence of tumor perforation, then it is to be regarded as a TNM stage T4.
5) Recording of distance to the peritoneal reflection in rectal tumors- Interiorly, the rectum is partly covered by the peritoneal reflection and the site of the tumor above, at or below the peritoneal reflection is recorded.
6) Involvement of the circumferential resection margin (CRM) in rectum-

Accurate assessment of the CRM is crucial as it will dictate the future adjuvant therapy. CRM negative patients show

significant improvement in survival compared to CRM positive patients. It represents the involvement of the surgical margin of the connective tissue around the rectum where there is no peritoneal covering (non peritonealised surface). Anteriorly, the rectum is covered by peritoneum to a large extent; whereas posteriorly it is high up. The bare area anteriorly below the peritoneal reflection, and posteriorly the bare area (triangular shaped bare area running up to the start of the sigmoid mesocolon) are to be assessed.

It is recommended that that whole of this mesorectal margin is painted with ink and sliced at 3-4 mm interval to select block from the area closest macroscopically to the CRM. The minimum distance between the tumor and the CRM is measured in mm from the histological slide. If this distance is less than or equal to1 mm, then the CRM is considered involved. Such involvement may be because of the direct continuity of the tumor OR also because of tumor in lymphatic, blood vessel or a lymph node situated less than or equal to 1mm from the CRM (figure 1,2)

It is also to be understood that ascending colon, descending colon is partly covered by peritoneal covering (anteriorly) and the posterior surface of which is bear area and also constitutes CRM(14)

7) Lymph nodes

The minimum number of Lymph nodes needed for accurate staging has been a subject of controversy. Dissecting lymph nodes is a laborious and time consuming procedure. The task becomes even more difficult when the nodes are small. Several factors influence the number of lymph nodes dissected out from the surgical specimen. The quality of surgery and grossing techniques are undoubtedly two major factors affecting the yield of the

lymph nodes. College of American Pathologists consensus meeting publications recommend examination of at least 12 LN for accurate identification of regional lymph node (15) However, in spite of these recommendations, it has been shown by several studies including that of Goldstein's (16) that greater the number of lymph nodes dissected out from the pericolic fat, greater the chances of finding a positive node. (17)metastasis.

C) MICROSCOPIC ASSESSMENT

1) Virtually all the carcinomas in colorecum are adenocarcinomas. Other special types of carcinomas which could be mentioned are adenosquamous carcinomas, pure squamous carcinomas, small cell carcinomas, and undifferentiated carcinomas. Signet ring cell carcinomas are recorded as adenocarcinomas.

2) Differentiation-- The tumor differentiation is given based on the differentiation of the predominant area of the tumor. Our practice is to grade it into well, moderate or poorly differentiated adenocarcinomas.

   Due to the possibility of interobserver variability in grading, it is proposed that a two grade system be used as Low grade and High grade adenocarcinoma e.g.

   Low-grade: Well-differentiated and moderately differentiated (Greater than or equal to 50% gland formation)

   High-grade: Poorly differentiated and undifferentiated (Less than 50% gland formation) (18)

3) Local invasion- Maximum invasion in the bowel wall is recorded. The peritoneal involvement is defined as presence of tumor on the peritoneal surface. Thus

tumor cell penetration of the serosa or serosal ulceration is to be seen. Peritoneal involvement DOES NOT constitute involvement of the CRM

4) Involvement of the serosa also DOES NOT make a resection R1

Involvement of the peritoneal surface can be seen in up to 25% cases and has adverse prognostic influence.(19) Subdivision of T4 into T4a and T4b. Serosal involvement by tumor cells (pT4a) has been demonstrated by multivariate analysis to have a negative impact on prognosis,32 as does direct invasion of adjacent organs (pT4b). Visceral peritoneal involvement can be missed without thorough sampling and/or sectioning, and malignant cells have been identified in serosal scrapings in as many as 26% of specimens categorized as pT3 by histological examination alone. Although the absence of standard guidelines for assessing peritoneal involvement may contribute to underdiagnosis, the following findings are considered to represent serosal involvement by tumor:

1. Tumor present at the serosal surface with inflammatory reaction, mesothelial hyperplasia, and/or erosion/ulceration
2. Free tumor cells on the serosal surface (in the peritoneum) with underlying ulceration of the visceral peritoneum

Both types of peritoneal involvement are associated with decreased survival.(19)

5) Metastatic spread

a) All the number of lymph nodes harvested from the specimen are to counted and metastatic lymph nodes are to be recorded

b) extramural tumor deposits equal to or more than 3 mm size are to counted as involved nodes, even if residual lymph node architecture is not visible. Smaller deposits are taken as discontinuous extramural tumor deposits.

c) For Dukes' staging, the apical node status is mentioned. This is the highest node found at the tie.

d) All grossly negative or equivocal lymph nodes are to be submitted entirely. Grossly positive lymph nodes may be partially submitted for microscopic confirmation of metastasis.

e) A tumor nodule in the pericolonic/perirectal fat without histological evidence of residual lymph node tissue is classified as a tumor deposit (peritumoral deposit or satellite nodule) and is not considered a positive lymph node. Such tumor deposits may represent discontinuous spread, lymph-vascular spread with extravascular extension, or totally replaced lymph nodes. In the absence of unequivocal lymph node metastases, tumor deposits are recorded as N1c

6) Histopathologic Features Suggestive of Microsatellite Instability

Identification of MSI-H colorectal tumors is important, as mismatch repair deficiency may serve as a prognostic marker of patient outcome, a predictive marker of response to chemotherapy, and as a screening tool for hereditary nonpolyposis colon cancer (HNPCC) (Lynch syndrome). Revised Bethesda guidelines for HNPCC detection recommend testing colorectal tumors for microsatellite instability under the following circumstances

I) CRC diagnosed in a patient who is younger than 50 years.

ii) Presence of synchronous, metachronous, or other HNPCC-associated tumors (endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, small bowel, and brain tumors and sebaceous adenomas and keratoacanthomas), regardless of age.

iii) CRC with MSI-H histology in a patient who is younger than 60 years.

iv) CRC in 1 or more first-degree relatives with an HNPCC-related tumor, with 1 of the cancers being diagnosed in a person younger than 50 years.

v) CRC diagnosed in 2 or more first- or second-degree relatives with HNPCC-related tumors, regardless of age.

MSI-H histologic features are defined as presence of tumor-infiltrating lymphocytes, Crohn-like lymphocytic reaction, mucinous/signet-ring cell differentiation, or medullary growth pattern. The neuroendocrine markers on immunohistochemistry are negative (20,21,22)

7) Assessment of the specimen after neoadjuvant therapy (CTRT)

There is preliminary evidence that completely excised rectal carcinomas that have received pre-operative neoadjuvant chemoradiotherapy that has resulted in complete or marked regression has a better prognosis than those without significant regression.(23) For staging, a prefix 'y' is applied. The tumor may show a complete or a partial response. The response is graded on a 3 or a 5 grade system and a Tumor Regression Grade is given (TRG)

The tumor response is graded on a 5 grade system.

Tumor regression should be assessed only in the primary tumor; lymph node metastases should not be included in

the assessment. Acellular pools of mucin in specimens from patient receiving neoadjuvant therapy are considered to represent completely eradicated tumor and are not used to assign pT stage or counted as positive lymph nodes.(24)

D) TNM staging-

We routinely use only TNM staging in our histopathology proformas (Appendix 1-4)

Molecular pathology of colorectal carcinoma:

Molecular pathology of colorectal carcinoma (CRC) is a continuously evolving field which is proving its great impact on not only understanding the pathogenesis of this disease but also on newer classification and treatment. Thus, molecular pathology of CRC should be viewed from three distinct perspectives.

1. Understanding pathogenesis and heterogeneity of CRC:

   Different molecular events involved in causation and progression of CRC are being recognised.[1] Recognition of these different mechanisms implicated in CRCs has resulted in a paradigm change in understanding of clinical, therapeutic and epidemiological aspects of CRC. It is clearly emerging that CRC is not a single disease entity but a heterogeneous group with specific clinical implications. A new classification of CRC has been proposed based on molecular characteristics.

2. Understanding hereditary CRC: Molecular pathology is the tool that has led to recognition of hereditary CRC such as Lynch syndrome .Molecular basis of familial adenomatous polyposis syndrome is also well understood. Molecular testing is a part of management of Lynch syndrome.

3. Basis of ' targeted' treatment of colorectal carcinoma:

Recent medical and surgical advances have widened therapeutic options available for CRC. Understanding of molecular basis of CRC has undoubtedly revealed heterogeneity within this group of tumours.[2] The implications of this heterogeneity has far reaching impact on predicting response to treatment.

Pathogenesis and heterogeneity of CRC based on molecular characteristics:

The Vogelstein model of adenoma – carcinoma sequence in colon is well understood.[3] This sequence involves the suppressor pathway initiated with mutation of tumour suppressor gene APC found in the smallest of the adenomatous lesions. The progression of adenoma to carcinoma is believed to occur over years by means of a slow process driven by a linear and stepwise series of genetic alterations in genes such as APC, KRAS and TP53. This concept has formed the basis of screening for CRC and has helped define the interval of sequencial screening by coloscopy if an adenoma has been detected in the colorectum.

However, it has become evident now that not all colorectal carcinomas bear a 'classic' molecular signature and in fact only 60% of total CRCs develop along the suressor pathway. Thus CRC is now considered a heterogeneous disease group based on molecular characterization which in turn has impact on clinical presentations, gross and microscopic appearances, prognosis, treatment and screening protocols.

Most of the remaining 40% of CRC occur via recently described **'serrated pathway'.**[4] The initiating event in

serrated pathway is not APC mutation but activating mutation of the BRAF gene. BRAF gene is a effecter gene of KRAS. BRAF gene mutation leads to inhibition of apoptosis of colonic epithelial cells. It leads to development of lesions such as serrated microvesicular hyperplastic polyps or sessile serrated adenomas/ polyps. These early serrated lesions are prone to methylation of CpG island promoter gene called as CIMP (CpG island methylator phenotype). Methylation of CpG island leads to epigenetic silencing of a number of genes, hMLH-1 being most relevant to development of CRC. Since hMLH1 is one of the mismatch repair genes, its silencing renders the genome of cells in serrated lesion microsatellite unstable (MSI-H). MSI-H lesions are prone to accumulation of additional mutations at a rapid rate resulting in development of carcinoma.[5] The tumours developing via the above mentioned pathway thus are called 'CIMP+ MSI' carcinoma as against CIMP-MSS (microsatellite stable) carcinomas developing through the suppressor pathway.

Recognizing the serrated pathway of CRC development has an impact on the screening strategies.[6] It is increasingly becoming apparent that most 'interval cancers' occurring in screening population belong to the group of tumours developing via serrated pathway. This is because once the preexisting serrated lesion acquires hMLH1 gene silencing; it rapidly progresses to invasive carcinoma. The rate of development of invasive carcinoma is much more than conventional APC / suppressor pathway. Moreover, the serrated lesion most commonly implicated as precursor lesions of carcinoma, the sessile serrated adenoma/polyp (SSA/P) is a very subtle lesion and is difficult to identify on endoscopy. Thus the reasoning behind the occurrence of interval cancers and their high propensity of being MSI-H is proposed to be related to serrated lesions either turning

malignant rapidly with their lifespan fitting in 5 to 10 years between screening examinations or SSA/P being missed on endoscopy.[7] Thus, it could also be presumed that existing screening strategies are targetted to prevent only 60% of total colorectal carcinomas. Serrated pathway cancers would require shorter intervals in screening.

The serrated pathway itself is complex and heterogeneous. Not all serrated lesions are related to BRAF gene mutation. KRAS gene mutation is implicated in goblet cell rich hyperplastic polyp.

Different molecular characteristics have highlighted heterogeneity resulting in complex groupings within CRC. Several investigators are proposing a new classification of CRC either based on molecular features along with clinical and histomorphological criterion.[8]

Hereditary colorectal carcinoma

1) Familial adenomatous polyposis (FAP) characterized by multiple colonic and also extra colonic adenomas with a 100% potential to develop into invasive carcinoma by age of 50 years. Germline mutation of APC gene is the genetic basis of this syndrome.
2) Lynch syndrome (Hereditary non- polyposis colorectal carcinoma HNPCC). Lynch syndrome is defined by Bethesda criterion. Germline mutation of mismatch repair (MMR) genes is the genetic basis of his syndrome. It has an autosomal dominant inheritance pattern with 60 to 80 % penetrance.

   Recognition of both the above hereditary syndromes is important for prophylactic treatment in FAP and identifying other family members at risk with subsequent counseling in a setting of HNPCC respectively.

Molecular basis of development of adenomas and their progression to carcinoma in FAP syndrome is **APC gene mutation** (suppressor pathway). It is similar to adenoma-carcinoma sequence in sporadic CRC; the difference being that the mutation in FAP is germline versus somatic in sporadic carcinoma. The patient FAP syndrome is born with mutation of APC gene at one of the two alleles. Second mutation is acquired in life which then leads to development of numerous adenomas much earlier in life than sporadic adenoma with 100% potential to progress to carcinoma. This process is much slower in sporadic carcinomas since mutations at both alleles of APC gene are acquired.

Mutations of DNA mismatch repair (MMR) genes are implicated in CRC (CRC) development in Lynch syndrome. MMR gene mutation leads to loss of function of the MMR pathway. Failure to repair replication-associated errors due to a defective MMR system allows persistence of mismatch mutations all over the genome, but especially in regions of repetitive DNA known as microsatellites, giving rise to the phenomenon of microsatellite instability (MSI). A high frequency of instability at microsatellites (MSI-H) is the hallmark of the most common form of hereditary susceptibility to CRC, known as Lynch syndrome (LS) (also known as hereditary non-polyposis CRC syndrome), but is also observed in approximately 15-20% of sporadic colonic cancers (and rarely in rectal cancers). Tumour analysis by both MMR protein immunohistochemistry and DNA testing for MSI is necessary to provide a comprehensive picture of molecular abnormality, for use in conjunction with family history data and other clinicopathological features, in order to distinguish LS from sporadic MMR-deficient CRC.

The four most commonly mutated DNA mismatch repair genes are *MLH1*, *MSH2*, *MSH6*, or *PMS2.* Approximately 70% of mutations are found in *MLH1* and *MSH2*. The *MSH6* and *PMS2* genes are less commonly involved, and mutations in *MSH6* and *PMS2* each account for 15% of all known mutations. Conventionally, testing for MSI (thus classifying microsatellite stable, MSI–H and MSI–L) is done by molecular testing of at least five loci recommended by NCI. An adjunctive approach to MSI testing is immunohistochemical staining for MMR proteins .Around 1996, monoclonal antibodies against MMR proteins started to become available; first came antibodies to MSH2 and then to others. Such antibodies rendered IHC detection of MMR protein possible, providing an alterative methodology for detecting MMR deficiency.[9] Specific staining is performed on tumor tissue for each of the 4 mismatch repair proteins. Mutations in MMR genes typically lead to truncated nonfunctional proteins that do not stain by IHC. If a tumor exhibits MSI or abnormal IHC staining, genetic testing using peripheral blood DNA is the next step. An abnormal immunostain can guide the choice of genes analyzed. Both IHC and MSI tests are somewhat complementary and can be integrated into a genetic testing algorithm. Up to 15% of sporadic colon cancers are also associated with microsatellite instability, usually due to somatic hypermethylation of the *MLH1* promoter. These cases can be distinguished from Lynch syndrome by the presence of mutations in the *BRAF* gene in the tumor.

Role of pathology in Targeted treatment

Surgery has remained the mainstay of treatment for CRC over years. Systemic chemotherapy acts as an adjunct to surgery to improve survival in patients with stage III CRC.

The conventional cytotoxic drugs including their modulators have significantly contributed to prolonging survival. Undesirable side effects, however accompany their usage. Therefore, development of drugs which target a particular molecule or designing and synthesizing an antibody against a small molecule crucial in carcinogenesis has taken centre stage. Molecular testing remains the basis of on going research in this field.

In spite of the hope that these targeted treatment had less side effects, this has not been the case. Moreover, not all patients respond uniformly, thus selection of patients based on biomarkers is the current challenge facing clinicians.

Currently, drugs targeting vascular endothelial growth factor (VGEF) and molecules involved in EGFR mediated pathway are being used in colorectal carcinoma.

1. Targeting VGEF: Bevacizumab is a monoclonal antibody against human VGEF. In addition to being anti-angiogenic, it also alters the tumour vasculature, thus facilitating delivery of classic chemotherapeutic agents. Currently, bevacizumab has been approved for usage in combination with conventional chemotherapy in first and second line treatment for metastatic CRC.
2. Targeting EGFR pathway: This includes targeting the receptor itself as well as the downstream proteins in the EGFR signaling pathway. The epidermal growth factor receptor is a transmembrane tyrosine kinase receptor that plays important role in cell proliferation. Since EGFR axis is involved in CRC tumourigenesis and progression, this receptor has been selected as target for anticancer therapy. EGFR signaling can be targeted by using monoclonal antibodies that

compete with natural ligands to the receptors and small-molecule tyrosine kinase inhibitors. Currently monoclonal antibodies cetuximab and panitumumab as single agent or in combination with conventional chemotherapy are being widely studied in phase III trials for treatment of stage III CRC.

Predictive biomarkers for success of EGFR- targeted treatment-

1. EGFR protein overexpression :

Upon understanding the EGFR structure, function and the various downstream pathways involved in carcinogenesis, it was presumed that EGFR protein overexpression would act as a predictive marker in order to select patients for anti-EGFR therapy. This notion was supported by prior experience with HER2/neu expression in breast cancer and its correlation with Trastuzumab treatment. However, several studies have shown that unlike breast cancer, EGFR protein expression (tested by IHC, western blot, fluorescence in situ hybridization (FISH) and enzyme linked immunoadsorption assays) does not correlate with response of tumours to cetuximab, panitumumab or Geftinib therapy.

There are various reasons behind this fact are biologic, technical and analytical. This includes differences in affinities of EGF binding sites and significant role of downstream regulating molecules irrespective of function of the receptor.

2. EGFR gene mutations: EGFR gene mutations are found infrequently in CRCs and thus do not have predictive impact as against non-small cell carcinoma of lung where mutations in catalytic domain of EGFR is predictive of geftinib treatment.

3. EGFR gene copy number (CGN):

Various studies have demonstrated that an increased EGFR gene copy numbering CRC as detected by FISH is associated with a better response to anti-EGFR therapies. However, currently this parameter is not used to make clinical decisions since many other studies including a phase II trial have shown no correlation of increased EGFR gene copy number and response to cetuximab therapy. In spite of this contradictory evidence, it is suggested that the non-increased rather than the increased EGFR gene copy number status is the most accurate predictive element for clinical outcome. CRC with low EGFR CGN are unlikely to respond to treatment .

Thus to conclude, EGFR protein expression has no predictive value for the efficacy of anti-EGFR therapy. Other proposed EGFR related bio-markers like expression of EGFR ligands and activated EGFR are still under investigation.

Hence there is a need to study downstream proteins in order to recognize more reliable biomarkers that would help select patients for targeted therapy.

Downstream proteins in EGFR signaling pathway:

KRAS oncogene:

KRAS is a downstream protein in EGFR mediated pathway. It is involved in cell proliferation. More than 30% of CRCs show mutation of KRAS oncogene. These are somatic missense mutations leading to single amino acid substitution and occur independent of EGFR status. The most frequent mutations are detected in codon 12 and 13 in exon 2 of KRAS gene. The mutant protein leads to constant activation of signaling pathway resulting in uncontrolled cell proliferation which is independent of

EGFR signaling. Hence in tumours carrying KRAS mutations, blocking EGF signaling at the receptor level will not block the transmission of a signal in downstream pathway. KRAS mutation in CRC thus has a large impact on therapeutic decisions. Several studies till date have shown that KRAS mutations in codon 12 and 13 are associated with poor response to therapy, reduced progression free survival and shorter over all survival of patients who are treated with ant-EGFR therapy either alone or in combination.[10]

In spite of the above clinical evidence, not all patients with CRCs showing wild type KRAS respond to anti-EGFR therapy and search for additional bio-markers is on going. Significance of BRAF (which is a principle effector of KRAS) mutation is also under investigation.

KRAS testing can be performed either by real-time PCR using fluorescent probes or direct sequencing analysis.

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CHAPTER-5

Primary Treatment

Surgical Specialization

There is considerable variability between outcomes achieved by individual surgeons. A prospective study found wide variations between surgeons in rates of curative resection, operative mortality, anastomotic leak, local recurrence and survival, even when hazard rate ratios were adjusted for patient-related risk factors[1]. Three UK major population audits, Trent/Wales, Wessex, and Lothian; all give similar figures for operative mortality, but more recent data from NORCCAG show an improving operative mortality rate; this probably reflects the trend to sub-specialisation and changes in surgical training[2].

There is now a substantial body of research assessing the effects of surgical specialisation and patient throughput (both the number of cases treated per surgeon and per hospital) on outcomes in CRC – 6 systematic reviews and 28 other studies[3]. Considered as a whole, this evidence shows that surgical specialisation is associated with better outcomes, particularly in rectal cancer.

As a general rule, the more complex the operation, the greater the surgical skill required; such skill is acquired

and developed through specialised training and experience and maintained by regular practice. A surgical training programme for rectal cancer in Stockholm reduced the permanent stoma rate and local recurrence rates, and 5 year cancer-specific survival rates increased as a result of the total mesorectal excision project[4]. It is not, therefore, surprising that in surgical oncology as a whole, the benefits of higher volume practice and greater specialisation would be particularly apparent in outcomes for types of cancer for which surgery is more challenging; and this is indeed the pattern with CRC.

Surgery for rectal cancer, which is more difficult to do well, shows volume and specialisation effects much more clearly than surgery for colon cancer. A study of 3200 patients in Scotland who underwent resection for CRC between 1991 and 1994 reported that differences in outcome following apparently curative resection for CRC among surgeons appeared to reflect the degree of specialisation rather than case volume, and concluded that it was likely that increasing specialisation would lead to further improvements in survival[5].

A survey in Australia of all new cases of CRC registered at each Australian State Cancer Registry reported that patients seen by low volume surgeons were most likely to be given a permanent stoma and that patients with rectal cancer who were operated on by high volume surgeons were significantly more likely to receive a colonic pouch[6]. Similar results were reported from California, where a study of 7257 patients with rectal cancer treated between January 1994 and December 1997 showed that patients with rectal cancer who underwent surgery at high volume hospitals were less likely to have permanent colostomy and had better survival rates than those who were treated at low volume hospitals[7].

In rectal cancer, 11 of 13 studies assessing surgical specialisation reported that more specialised surgeons achieved better outcomes. Greater specialisation tends to be associated with higher patient throughput, so it is difficult to separate these issues. Six out of eight good quality studies of specialisation in rectal cancer showed significant effects on one or more of the following measures of outcome; survival rates (up to five years); quality of surgery (assessed by complication rates or tumour-free excision margins); and local recurrence rates. Greater specialisation is also associated with shorter in-patient stay and less frequent use of stomas[3].

There is less evidence for colon cancer: only two studies looked at colon cancer alone[3]. Eight publications reported on patients with CRC, the majority of whom would have had cancer of the colon. These show little evidence of any effect of patient throughput. However, two studies found that surgery by specialists was reflected in higher survival rates. One study examined liver resection for metastatic CRC. This found a highly significant association between higher hospital throughput and 30-day survival rates[3].

Surgery for CRC should only be carried out by surgeons with appropriate training and experience, working as part of a multidisciplinary team. Recommendation grade B

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Informed consent

Valid consent to treatment for CRC is essential and reflects our patients' fundamental legal and ethical right to determine what happens to their own body.

Valid consent requires that the patient must be competent to take decisions about treatment options, must have received sufficient information in an understandable form to make this decision, and must not be acting under duress.

Informed consent is therefore a process of discussing options and coming to a joint decision with the patient by providing information about:

- Benefits and risks of the proposed treatment
- What the treatment will involve

- What the implications of not having the treatment are
- What alternatives may be available
- What the practical effect on their life of having, or not having, the treatment will be

The information will be gathered from a number of sources including the responsible Consultant, , Stoma Therapist, Patient Support Groups and other information sources (eg. Internet). This process would allow a patient time to reflect on the options and agree treatment with the responsible clinician.

The health professionals carrying out a procedure are ultimately responsible for ensuring that the patient is genuinely consenting to what is being done as it is they who would be held responsible in law if this were challenged later. In most circumstances, the surgeon who is undertaking an operative procedure will signal completion of the consent process by completing a written consent form with the patient.

The risks attached to operative treatment should be discussed and documented, in particular, the risk of bleeding, infection, DVT, PE, anastomotic leak, the risk of an unplanned stoma and, in pelvic surgery, urinary and sexual dysfunction.

Functional outcome should form part of the general discussion about the outcomes of treatment. It may be appropriate to discuss mortality risk and, increasingly, risk models are available to offer validated predictions to patients requiring this level of information.

Adult patients are always assumed to be competent to give consent unless demonstrated otherwise. Competent adult patients are entitled to refuse treatment. Practitioners

should be aware that no one can give consent on behalf of an incompetent adult, who should be treated in their "best interest". "Best interests" go wider than "best medical interests", to include factors such as the wishes and beliefs of the patient when competent, their current wishes, their general well being and their spiritual and religious welfare.

People close to the patient may be able to give information on some of these factors. Where the patient has never been competent, relatives, carers and friends may be best placed to advise on the patient's needs and preferences.

Clinicians are wise to document carefully the reasons for their decision in delivering a particular treatment when acting on behalf of a patient without written consent.

Separate consent is required for the lawful retention and use of body parts, organs and tissues from the living or the deceased for specific health related purposes and public display.

Clinicians are referred to information available from the Indian Council of Medical Research (ICMR) website for further guidance (http://icmr.nic.in).

It is important that patients with CRC are offered the opportunity to ask questions and to have important information repeated. Provision of information should be an essential part of every consultation. **Recommendation grade B**

All patients undergoing surgery for CRC should give informed consent. Informed consent implies being given information about the likely benefits and risks of the proposed treatment and details of any alternatives. Informed consent should be obtained by the operating surgeon where possible. **Recommendation grade C**

References:

Guidelines for the Management of CRC 3rd edition (2007). Issued by The Association of Coloproctology of Great Britain and Ireland

Preparation for stoma formation

If a patient may require a stoma, the nature and consequences of this should be carefully explained. Additionally, the site of the stoma should be marked prior to surgery to ensure optimum fitting of the appliance[1], and the patient should be seen by a stoma nurse prior to surgery[2] . This referral should be made at the earliest opportunity to allow adequate time for preparation[3]. This may not be possible in some emergency situations and in this situation the stoma site should be marked by an experienced surgeon. **Recommendation grade C**

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Thrombo-embolism Prophylaxis

Patients undergoing surgery for CRC are at risk of deep vein thrombosis (DVT) and pulmonary embolism (PE)[1]. The most widely studied prophylactic measure against these complications is the use of subcutaneous heparin. Increasingly, Low molecular weight heparin (LMWH) has been used, and although a large randomised trial in

patients undergoing abdominal surgery has shown it to be of similar efficacy to standard heparin, bleeding related complications were less common[2]. Although there have been no studies confined to patients with CRC, a meta-analysis of appropriate trials has indicated that the rates of DVT, PE and death from PE can all be significantly reduced in general surgical patients with heparin[3,4].

Other measures which can be taken are intravenous dextran, the use of intermittent pneumatic compression devices and the use of graduated compression stockings. Dextran does not appear to be as effective as heparin[1], but there has been one trial indicating that intermittent compression is equivalent to heparin in reducing the incidence of DVT at least[5]. Graduated stockings alone are less effective than other measures[5]. Patients undergoing pelvic surgery for malignancy may be considered "high risk" for thromboembolic disease, particularly after pre-operative adjuvant therapy. In these "high risk" cases the use of self administered LMWH for 2-3 weeks following surgery is recommended by the Cochrane review.

A combination of graduated compression stockings and heparin should be used for thrombo-prophylaxis for patients undergoing colorectal surgery. **Recommendation grade A**

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Enhanced Recovery

The aim of the Enhanced Recovery After Surgery (ERAS) pathway is to attenuate the stress response to surgery and enable rapid recovery. ERAS programs have reported improvement of patient care, while reducing complication rates and shortening hospital stay following colorectal surgery. Metaanalysis of six randomized controlled trials with 452 patients were included. The number of individual ERAS elements used ranged from 4 to 12, with a mean of 9. The length of hospital stay [weighted mean difference (95% confidence interval): -2.55 (-3.24, -1.85)] and complication rates [relative risk (95% confidence interval): 0.53 (0.44, 0.64)] were significantly reduced in the enhanced recovery group. There was no statistically significant difference in readmission and mortality rates. ERAS pathways appear to reduce the length of stay and complication rates after major elective open colorectal surgery without compromising patient safety.

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Laparoscopic Surgery

Case Selection

Laparoscopic (including laparoscopically assisted) resection is increasingly being adopted as an alternative to open resection for individuals with CRC in whom both laparoscopic and open surgery are considered suitable. Laparoscopic surgery offers a range of potential benefits for patients. As with all new surgical techniques, extensive practice is required to develop the necessary skills. The decision about which of the procedures (open or laparoscopic) is undertaken should be made after informed discussion between the patient and the surgeon. In particular, they should consider:

- the suitability of the lesion for laparoscopic resection
- the risks and benefits of the two procedures
- the experience of the surgeon in both procedures.

Recommendation grade C

Preparation for laparoscopic surgery

Laparoscopic colorectal surgery should be performed only by surgeons who have completed appropriate training in the technique and who perform this procedure often enough to maintain competence. The exact criteria to be used should be determined by the relevant national professional bodies like ACRSI, AMASI & IAGES.

Cancer networks and constituent Organizations should ensure that any local laparoscopic colorectal surgical practice meets these criteria as part of their clinical governance arrangements. All laparoscopic colorectal operations should be performed by properly trained surgeons in colorectal surgery. These surgeons should have undergone preceptorship laparoscopic training, particularly in rectal procedures. Their results should be carefully audited. Recommendation grade C

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Laparoscopic techniques and results

Early reports of laparoscopic CRC surgery led to concern about port-site metastases. Subsequent studies have demonstrated that these were due to poor techniques rather than inherent problems with laparoscopic cancer surgery, and that the incidence is less than 1% - similar to open surgery[1] (Silecchia et al 2002 III). Laparoscopic colorectal resection takes longer to perform than open procedure, but operative duration falls with increasing

experience. Blood loss and blood transfusion requirements are less in patients undergoing laparoscopic colorectal surgery[2] (Schwenk et al 2005 IV).

Short term complications, particularly wound infections, are reduced in laparoscopic surgery, whilst anastomotic leakage and mortality rates are similar to those for open procedures. There is also a tendency for less long term morbidities, especially in the rates of incisional herniation and small bowel obstruction[3] (Duepree et al 2003 III). Hospital stay is 20% shorter for laparoscopic surgery[4] (Abraham et al 2004 Ia). Laparoscopic colorectal resection results in less postoperative pain and in less need for analgesia compared with open surgery, as well as short term improvements in quality of life2 (Schwenk et al 2005 IV).

Several recent randomised studies have compared short and long term results of laparoscopic CRC surgery with open surgery. Three trials involving 750 patients undergoing laparoscopic surgery showed that there was no difference in the rates of overall survival, disease-free survival and tumour recurrence compared with open resection[5-7] (Lacey et al 2002 Ib, COST study group 2004 III, Leung et al 2004 Ib).

Furthermore, the study from Barcelona suggested that survival for stage III disease may be better after laparoscopic surgery[5] (Lacey et al 2002 Ib) but long term results from the MRC-CLASSIC[8] (Guillou et al 2005 Ib) and the European COLOR[9] (Veldkamp et al 2005 Ib) studies may yield more information. One meta-analysis[4] (Abraham et al 2004 Ia) and other randomised studies[5-9] (Lacey et al 2002 Ib, COST study group 2004 III, Leung et al 2004 Ib, Guillou e al 2005 Ib, Veldkamp et al 2005 Ib) have demonstrated that lymph node harvest is no different between laparoscopic and open surgery.

Completeness of resection margins is also similar, and although circumferential margin positivity in the MRC-CLASSIC study was greater in laparoscopic than in open anterior resection (12% vs 6% respectively), this was not statistically significant[8] (Guillou et al 2005 Ib). However, there may be a tendency towards male sexual dysfunction after laparoscopic rectal excisions[10] (Jayne et al 2005 Ib).

Some patients who were originally randomised to undergo laparoscopic surgery were converted intra-operatively to open resection. Eleven RCTs reported conversion rates: the mean overall rate was 20%. Three RCTs recorded separate outcome data for converted patients who appeared to have higher blood loss, require a longer hospital stay and have a greater risk of tumour recurrence than patients who underwent the laparoscopic or open procedure as planned[11].

Anastomotic leakage was the only outcome for which there were sufficient data to conduct a stratified meta-analysis by location of cancer (that is, to establish differences in clinical effectiveness for cancers of the colon and rectum). The increased risk of anastomotic leakage with laparoscopic resection compared with open resection was similar for colon and rectal cancers (pooled RR for colon cancer 1.27, 95% CI 0.70 to 2.31, four studies; pooled RR for rectal cancer 1.25, 95% CI 0.63 to 2.46, two studies)[11].

Only two RCTs reported subgroup analyses by stage of cancer for overall survival. Both reported that there was no statistically significant difference in overall survival between patients undergoing laparoscopic surgery and those undergoing open surgery for cancer stages I, II or III.

Submissions from manufacturer and professional consultees contended that long-term clinical outcomes between open and laparoscopic colorectal surgery are equivalent, while short-term clinical outcomes favour the laparoscopic approach[11].

Although laparoscopic colorectal surgery is more costly to the healthcare providers, the overall cost to society is the same[12] (Janson et al 2004 Ib). The addition of an enhanced recovery programme with laparoscopic CRC surgery may further improve short term recovery and reduce hospital stay[13] (King et al 2006 Ib).

The 5-year results from the CLASICC study has found no differences between laparoscopically assisted and open surgery in terms of overall survival, disease-free survival, and local and distant recurrence. This strongly supports the oncological safety of laparoscopic surgery for both colonic and rectal cancers[14] **Recommendation grade A**

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Surgical Technique for Rectum

Definition of Rectal Tumour

In 1999, representatives of the American Society of Colon and Rectal Surgeons and the Association of Coloproctology met with the Australian Societies to define the rectum and the procedures used to treat cancer of the rectum. As the treatment of rectal cancer differs from the treatment of colonic cancer in some important respects, particularly in the areas of surgery and radiotherapy, it is important to have a clear anatomical definition of the rectum. Strictly, the rectum is that part

of the large bowel distal to the sigmoid colon and its upper limit is indicated by the end of the sigmoid mesocolon. Standard anatomical texts put this at the level of the third sacral vertebra[1], but it is generally agreed by surgeons that the rectum starts at the sacral promontory[2].

It has been agreed by the Expert Advisory Committee constituted by the Association of Coloproctology of Great Britain and Ireland to set up Guidelines for the Management of CRC 3rd edition (2007) that **any tumour whose distal margin is seen at 15cm or less from the anal verge using a rigid sigmoidoscope should be classified as rectal**[3].

Rectal resection

Surgical resection of the rectum for invasive rectal cancer should include total excision of the mesorectum (TME) with adequate circumferential and distal margins, and inferior mesenteric lymphadenectomy. TME is associated with a reduced risk of local recurrence whether or not combined with preoperative radiotherapy or chemo radiotherapy[4-6].

Intermediate stage (stages II–III resectable)

Intermediate tumours are defined as neoplasms extending beyond the rectal wall but without unresectable infiltration to surrounding organs (c/p T3–4 or N1–2 M0). The role of TME Total Mesorectal Excision (TME) has changed dramatically locoregional tumour control in rectal cancer surgery. Local relapses after TME alone for pT3–4 N1–2 of the mediumor low-rectal cancer still range between 15% and 21% in randomized trials[7,8].

Population-based registries show that improvements in outcome after TME occur mainly in younger patients.

Furthermore, 6-month postoperative mortality is significantly increased in elderly patients (> or =75 years of age) compared with younger patients (<75 years of age).

For elderly patients who have good physical and mental status, the same treatment that is given to younger patients is appropriate. In contrast, for those with diminished physiological reserves and co-morbid conditions, alternative treatments that keep surgical trauma to a minimum and optimize the use of radiotherapy might be more suitable[9,10].

By using anterior resection with TME radical surgery can be achieved also in distal rectal cancer since rectal cancer rarely grows more than a few millimeters distally from the macroscopic margin in the bowel wall, indicating that a distal margin of 1 cm will probably be sufficient for local cure in terms of intramural spread. If such an approach is considered, frozen section (during surgical intervention) is mandatory. In patients with tumours in the middle or distal third of the rectum, lymph nodes or other tumour deposits can be found in the mesorectum up to 4 cm distally from the tumour. Complete removal of mesorectum distally is always indicated in these tumours locations[11,12]. In tumours located in the upper rectum a Partial Mesorectal Excision (PME) extending 5 cm below lower tumour margin and sparing the distal part of the mesorectum is feasible. However, definitive evidence for this is not available.

The APR planes

Pathological studies of the CRM at the level of the anorectal junction and anal sphincters show high risk of tumour involvement[13]. The quality of surgery in the levator/anal canal area below the mesorectum varies between surgeons

who may operate in different surgical planes: intrasphincteric/submucosal plane, sphincteric plane and levator plane[14-16]. With an APR there are two planes: one for the mesorectum and one for the anal canal. It is crucial to have the correct strategy when an APR is performed. The dissection from above has to be stopped before entering the levator plane. The next step is to dissect from below outside the sphincteric plane and by doing so finally divide the levators from below. With this technique a waist in the specimen, or an ''apple core" just at the place of the tumour, can be avoided and can prevent the specimen from having positive CRM[11,16-18].

The value of sphincter/organ-saving surgery Sphincter preservation is usually considered when tumour is located in the lower third of the rectum. Since the mesorectum decreases in size close to the top of the anal canal, tumours arising in this area can easily invade surrounding structures, such as the levator muscles or the internal and external sphincters. Consequently, it is crucial to ensure that the pelvic floor is free from tumour if a loco-regional curative procedure, with the sphincters intact, is to be performed in very low T2 or greater rectal cancers[19]. From both single-institution series, randomized trials, and national registers the number of patients with preserved sphincters has increased from 25% up to 50–75% in the past 30 years. Moreover, there are centers of excellence, where the number of patients with preserved sphincters is as high as 90%, although it is always difficult to interpret these data due to selection bias and case mix. Based upon prospective population-based registration the proportion of patients in the total population having a sphincter preserving procedure is approximately 65%. Sphincter-saving surgery is feasible in most patients with mid and low rectal cancers if the distal margin is 1 cm or more.

Intestinal continuity can be restored with colorectal or coloanal anastomosis according to the level of the tumour. For very low tumours, TME can be combined with resection of the internal sphincter of the anus without increasing the rate of local recurrence[20,21]

Functional results after TME are associated with the level of the anastomosis. Risk of faecal incontinence is increased in patients with very low coloanal anastomosis, particularly after preoperative radiation[22,23]. Important progress has been made in the treatment of this disease with use of multimodality and multidisciplinary methods. Modern neoadjuvant radiotherapy in a setting has further changed surgical philosophy, since many surgeons claim that more sphincters can be preserved, provided that preoperative chemoradiotherapy is used[19].

Unfortunately, the randomized trials nor meta-analyses of the trials support this idea although a subgroup analysis of one of the large trials reported increased sphincter preservation [59]. When comparing recent data with historical controls, one has to take into account the main changes in rectal cancer surgery during the past 10–15 years. It seems that the change in surgical attitude may be more important than the effects of any preceding radio(chemo)therapy. As the Swedish Council of Technology Assessment in Health Care (SBU) pointed out, at this moment the literature is inconclusive in evaluating the role of preoperative radiotherapy alone or with concurrent chemotherapy in promoting sphincter-saving surgery in low-lying tumours[24,2]

Sphincter preservation without good function is of questionable benefit. Based upon reports, most patients are considered to have an acceptable to good function but as many as 20% will be more or less incontinent, not

only for flatus or loose stool but also for solid stool. For some elderly and immobile patients a stoma can even be preferable to a preserved but moderately functioning sphincter. Based upon questionnaire studies stoma patients, as a group, do not have a worse quality of life than patients treated with sphincter preservation. Cultural differences are significant. For example a stoma may be more or less disastrous for the patient than a local failure in some parts of our country as compared to the western world. Therefore, many patients from our country may accept poor bowel function in preference to a stoma[19].

Rates of curative resection

Curative resection can be defined as removal of all macroscopic disease at the time of operation, backed up by histological evidence that the resection margins of the specimen submitted to the pathologist are clear of tumour[26]. If the surgeon is in doubt as to whether this has been achieved, this should be stated. If residual tumour is thought to remain, it should be biopsied where it is safe to do so[2].

The rate of curative resection achieved by an individual surgeon will, to some extent, depend on the stage of the tumours seen in his or her practice. The Trent/Wales and Wessex audits have shown that this varies across districts, with the percentage of tumours presenting at Dukes' stage A varying from 6 to 18% and the percentage with distant metastases varying from 19 to 39%[3]. The rate of curative resection varied from 31% to 72%, and was inversely correlated with the percentages of cases with distant metastases.

The ACPGBI audit report based on data from 10194 patients between April 2002 and March 2003 showed

that overall, approximately 30% of patients have incurable disease at presentation. This total was made up of 14% who had no operation (advanced cancer, co-morbid disease or patient choice), 4% who had an operative procedure that did not include cancer resection and a minimum of 12% who had metastatic disease at surgery[3].

Curative resection also depends on good surgical technique, especially for rectal cancers. As this is a subjective intra-operative assessment, surgeons vary as to the proportion of their operations which are classified as curative[27]. In the Trent/Wales audit, the overall rate of curative resection was 60% and in Wessex it was 53%, figures very similar to those reported by two large prospective studies involving around 150 surgeons in the UK[26,27]. Better results are described in the literature, however; an overall curative resection rate for low rectal tumours of 77% has been reported[28], and other specialist centres describe similar results[29-33]. Although it is tempting to ascribe this finding purely to the skill and experience of specialist surgeons, particularly good results such as these may be the result of selective referral patterns to specialist units.

The term curative resection should be based on surgical and histological confirmation of complete excision. Surgeons should expect to achieve an overall curative resection rate of 60%, but it is appreciated that this will depend at least in part on the stage at which patients present. In summary, it is recommended that total mesorectal excision should be performed for tumours in the lower two-thirds of the rectum, either as part of a low anterior resection or an APER. In tumours of the upper rectum the mesorectum should be divided no less than 5cm below the lower margin of the tumour. Care should

be taken to preserve the pelvic autonomic nerves and plexuses, and perforation of the tumour during operation should be avoided. **Recommendation grade B**

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Anastomosis

Anastomotic dehiscence remains a major source of operative morbidity and mortality after resection for CRC. Its rate varies greatly from one surgeon to another and is more common after anterior resection of the rectum than after colonic resection[1,2]. In the Trent/Wales audit, the overall leak rate was 4.9%, and the associated mortality was 20%. For anterior resection, however, the leak rate was 7.4%, compared with 3.7% for other types of resection[3]. The Wessex audit revealed very similar figures, with an overall leak rate of 3.4% (6.9% for anterior resection, 2.6% for others), and an associated mortality of 23.2%. The NORCCAG study similarly showed a colonic leak rate of 4.1% and a leak rate of 6% for anterior resection[3].

Things have moved on since the 13% leak rate seen in the Large Bowel Cancer project in 1980. Review of the literature indicates that even better results can be achieved by individual surgeons, some of whom report rates below 5%[4-6]. It is not possible to be dogmatic as regards method of anastomosis. Although the best published results involved the use of a single layer interrupted serosubmucosal technique[4,7], this may have been due to the skill of the surgeon and/or case selection rather than the technique itself.

A Cochrane review has not shown any advantage of stapled over hand-sewn anastomosis[8], but a Scandinavian study did report a significant difference in leak rates between two types of stapling device[9]. Stapling has, however, made the performance of the ultra-low anastomosis after anterior resection much more feasible. As it is known that distal intramural spread rarely extends more than 1cm beyond the palpable edge of the tumour[10],

the ability to obtain distal clearance of 1cm or more should therefore allow an anterior resection which is oncologically sound so long as it is combined with total mesorectal excision.

Unfortunately, such anastomoses are associated with a high leakage rate, even when the same surgeon has very acceptable leakage rates from other types of resection[11]. This desire for more distal anastomoses is based on the perception that quality of life is better with a low anastomosis than with a permanent colostomy. This is not, however, supported by a review of 11 trials including 1412 patients, which identified no differences in quality of life differences between the two treatment modalities[12]. Cochrane reviews have shown no difference in leak rates in patients where bowel preparation has been omitted and whose anastomoses have not been drained[13, 14].

There is evidence that a defunctioning stoma can ameliorate the consequences of leakage, decreasing the risk of death and need for a permanent stoma[11]. A number of trials have compared a defunctioning ileostomy with defunctioning colostomy with mixed outcomes. There are advantages and disadvantages for each type of stoma. The balance of evidence slightly favours a defunctioning ileostomy over transverse colostomy[15,16].

Other problems associated with the low anastomosis are functional; many patients have urgency and increased frequency of bowel action[17] after low anterior resection, and this has been attributed to loss of the reservoir function of the rectum. Formation of a colonic J-pouch may overcome this difficulty (pouch limbs should be no more than 5-6cm long), and several studies now attest the efficacy of this procedure[18,19].

Finally, as large numbers of viable tumour cells can be demonstrated in the lumen of the colon at the time of operation[20], the use of a cytocidal washout prior to anastomosis is generally accepted as a sensible precaution to reduce the risk of anastomotic recurrence. Although no definite recommendations can be made regarding anastomotic technique, the interrupted serosubmucosal method has the lowest reported leak rate and stapling facilitates ultra-low pelvic anastomoses.

- Cytocidal washout of the rectal stump should be used prior to anastomosis.
- Surgeons should carefully audit their leak rate for colorectal surgery, and should expect to achieve an overall rate below 8% for anterior resections and below 4% for other types of resection.
- Surgeons should expect to achieve an operative mortality of less than 20% for emergency surgery and less than 7% for elective surgery for CRC.
- After anterior resection and total mesorectal excision, the judicious use of a temporary defunctioning stoma is recommended, and the formation of a colonic pouch should be considered.

Recommendation grade B

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Rates of Permanent Stoma Formation

There has been a general reduction in the proportion of rectal cancer treated by APR with the passage of time, but there is still marked individual variation. Case mix and an increasingly elderly population may explain some of this variation. Distal intramural spread rarely extends more than 1cm beyond the palpable edge of the tumour[1], and it is possible that failure to recognize this finding results in an inappropriate number of APRs being performed by non-specialist surgeons.

In low rectal cancers, a surgeon may be unsure of the feasibility of anterior resection. In such a case, it is strongly recommended that a second opinion from an experienced rectal surgeon is obtained. The rate of permanent stoma formation for rectal cancer in specialist centres remain under 10%, and these centres routinely employ a stapled anastomotic technique for low anterior resection[2,3,4] It is difficult to determine what the ideal ratio of anterior resection to APR should be, but it is recommended that the overall proportion of resectable rectal cancers treated by APR should be less than 30%. If distal clearance of 1cm can be achieved, a low rectal cancer may be suitable for anterior resection. If a surgeon has any doubt regarding the choice between these two operations, an experienced second opinion should be sought.

Recommendation grade - C

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Local excision of early localized tumours

Early tumours are neoplasms limited to the rectal wall (c/p T1– 2 N0 M0). They represent 3–5% of rectal cancers, and include small, exophytic, mobile tumours without adverse pathologic factors (i.e., high grade, blood or lymphatic vessel invasion, colloid histology, or the penetration of tumour into or through the bowel wall) and can be adequately treated with a variety of local therapies. In patients with early rectal cancer, the choice of treatment is complete local excision or TME, and depends on the risk of lymph-node involvement, which is associated with the depth of invasion of the tumour in the rectal wall.

The role of mucosectomy alone

Early carcinomas limited to T1sm1, with well/good differentiated tumours, no evidence of blood or lymphatic

vessel invasion and negative margins, can be safely and effectively resected by endoscopic mucosal resection (EMR)[1]. However, there is not enough evidence to recommend this procedure as the standard treatment. After EMR, pathologic analysis of submucosa infiltration is essential to assess the completeness of the resection[1].

The role of local excision alone

Local excision—transanal excision or endoscopic microsurgery for tumours in the upper-third layer of the submucosa (T1Sm1) and some in the middle layer (T1Sm2)—is valuable if excision is completed with adequate margins[2-4]. Patients with T1 small, exophytic, mobile tumours without adverse pathologic factors (i.e., high grade, blood or lymphatic vessel invasion, sm3) can be adequately treated with local excision alone, preferably a TEM procedure[5,6].

Technically, the use of local excision requires that there is a non-obstructing tumour and its dimension is less than half of the lumen and/or size is less than 4 cm of diameter[6]. The specimen after local excision has to be carefully analyzed to evaluate its integrity, the depth of invasion in the bowel wall, the absence of margin infiltration both laterally and deeply, and the presence of adverse pathologic factors: high grade, blood or lymphatic vessel invasion.

When the muscular layer is involved by the tumour (T2), the risk of positive lymphatic nodes ranges between 15% and 20%. Local excision alone is an inappropriate procedure. It should only be integrated with combined treatment (radiotherapy + chemotherapy), preferably preoperatively, when major surgery is contraindicated or refused.

In early localized tumours Transanal Endoscopy Microsurgery (TEM) may emerge as a technically reliable

option to remove the full thickness of rectal wall and to evaluate the completeness of the removed specimen[5,6]. Local excision is associated with less anorectal and genitourinary dysfunction and better quality of life compared with radical surgery. Local excision is not indicated in patients with cT3 tumour due to the usually large dimension of the primary lesion and the high incidence of positive nodes (30–50%).

At least half of the patients who undergo salvage abdominoperineal resection (APR) for local recurrence after local excision and/or radiotherapy can be cured: however, if these patients had been offered definitive surgery as the first treatment, cure rates would be higher. A standard resection done a few weeks after a local excision, when high risk predictive factors are present in operative specimen, does not compromise the oncological results compared to a standard resection done as the initial treatment in patients. However, depending on the tumour location, this may compromise the ability to perform a sphincter-sparing operation.

Local excision in rectal cancer is appropriate only for pT1 cancers which are graded well or moderately well differentiated and less than 3cm in diameter. Subsequent histopathological examination of cancers treated by local excision may, however, identify a proportion which require more radical surgery. **Recommendation grade B**

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Extended Resections

Extended resections, including exenterative surgeries are usually considered for T4 rectal cancer Locally advanced tumours are defined as neoplasms extending beyond the rectal wall with unresectable infiltration to surrounding organs or structures, and/or perforation of the visceral peritoneum (c/p T4 N0–2 M0). **The role of extended surgery**

A rectal cancer is defined as unresectable if a potentially curative surgical resection is not feasible. The evaluation of resectability depends on the extent of the operation the surgeon is able to perform as well as the degree of morbidity the patient is willing to accept. The heterogeneity of the presentation and a definition of resectability based on clinical criteria rather than on objective criteria make it difficult to compare between series[1]. It is important for

the surgeon to recognize preoperatively the extent of tumour invasion into other organs and/or the pelvic sidewall for documentation prior to preoperative radiation and to establish a plan for en bloc resection[2].

From the surgical point of view, R0 resection represents the most important parameter to achieve the best long-term outcome in T4 rectal cancer in terms of overall survival, disease-free survival and local control. After total pelvic exenteration, the morbidity rate is higher than 50% and includes: pelvic abscess or fistulas, sepsis, leak of the perineal suture, anastomotic leak, perineal wound infection, intestinal obstruction and pulmonary disease. Physiological age and the absence of co-morbidities appear to be more acceptable when selecting patients for exenteration than chronological age[3].

When partial resection of involved organs enables removal of all tumour (en bloc resection), a limited resection (without total pelvic exenteration) could be performed[2]. With a minimum consensus it was agreed that when the trigone of bladder or the prostate is involved, Total Pelvic Exenteration is recommended for all patients, irrespective of the response to preoperative treatment. This involves the removal of the rectum, bladder, lower ureters, internal genital organs and bilateral internal iliac vessels en bloc to achieve a negative margin and complete clearance of lymphatics[2].

A R0 total pelvic exenteration is a potentially curative operation for patients with advanced pelvic cancer: 5-year overall survival is acceptable (52–60%)[3], but it results in high morbidity and impaired quality of life. Even if radical resection includes an extended lymphadenectomy with high ligation of the inferior mesenteric artery and lateral nodes dissection, the role of lateral lymphadenectomy has

yet to be determined. Surgery extended to lateral pelvic nodes is associated with significant morbidity[2, 4-6] .

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Management of patients presenting as emergencies

More than one fourth of colon cancer presents in emergency as perforation or obstruction. Acute malignant

colonic obstruction is most common cause of large bowel obstruction (54 – 78%) associated with significant morbidity and mortality. [1]

Neoplastic obstruction affects the left colon most often, and about half of the carcinomas of the splenic flexure present in obstruction. Second most common cause is other non-colonic malignancies such as ovarian, endometrial, bladder, or prostate cancer either from +direct invasion or metastatic tumor deposits. Perforation associated with CRC is less common and prevalence is between of 2.6% and 6.5%. Caecal perforation with distension is a dreaded complication in 1.7% to 18% of patients with a mortality of 50%. [2, 3].

In general the outcome in the obstructed patients is always being poor than the non obstructed patients [4] **(Level of Evidence 2B)**

Presentation

Classically these patients present with colicky pain in abdomen, distension, vomiting and hemodynamic instability. Clinical examination, Biochemical and hematological investigations are necessary to assess the resuscitation that is required for stabilization before any treatment can be offered. Pre-operative factors which affect the postoperative mortality are: age, gender, Americal Society of Anasthesiology grading, nature of obstruction (benign / malignant), site of obstruction (proximal / Distal), condition of proximal colon, peritonitis, preoperative transfusion, preoperative renal failure, laboratory data (hematocrit < 30, Hb < 10gm%, Total Count >15000) [5]

Investigations

Plain X-ray abdomen – It is the simplest investigation that can diagnose large bowel obstruction

CECT scan – It is the investigation of choice. It is useful in determining anatomical position of the obstruction and also can highlight perforation, intra-abdominal sepsis and collections and also distant metastases. The sensitivity, specificity and accuracy of CT scan are 71%, 71% and 71% respectively.

MRI – Emerging as an alternative to CT scan, but rarely used outside clinical trials. The sensitivity, specificity and accuracy for MR imaging was 95%, 100% and 96% respectively. [6] **(Level of Evidence 2B)**

Management

Acute Obstruction

There is been a dilemma always regarding the approach in a patient presenting with acute obstruction. The options available are – [7]

1. DEFUNCTIONING STOMA - The simplest would be the formation of a defunctioning colostomy or caecostomy as an emergency step which will relieve the obstruction and allows recovery and a delayed resection once the patient becomes stabilized. Disadvantage is that the definitive resection is left with a covering stoma for which closure is required as a third surgery. Also, Adjuvant treatment is delayed in presence of malignancy inside. It is advocated only in patients with high anesthesia risk; sepsis and/or pressor requirement before surgery; difficult abdomen (severe adhesions, morbidly obese, history multiple prior operations) or lack of proper infrastructure.

2. TWO STAGE PROCEDURE - which is resection and formation of a proximal end colostomy, with closure of the rectal stump or with creation of a distal mucous fistula as described by Hartman. It requires subsequent closure but as primary is removed, adjuvant treatment can be instituted. Disadvantage is that some patients may never come up for reversal of the hartmann.
3. RESECTION WITH PRIMARY ANASTMOSIS - Resection of the tumor with primary anastomosis with or without covering stoma. on-table colonic irrigation with or without colonoscopy can be used to rule out synchronous lesions such as polyps.

   Preferred option whenever possible as it is curative and can avoid second major surgery and adjuvant treatment can be instituted early.
4. COMPLETE COLONIC RESECTION – Resection of entire colon proximal to the obstructing tumour and creation of an ileo-sigmoid or ileo-rectal anastomosis. Added advantage of this procedure is removal of synchronous tumors. This should only be done if patient is haemodynamically stable and with documented diseased or at risk proximal colon.

In patients with right sided lesions right hemicolectomy is the standard of care in emergency situation with or without anastmosis.

For left sided lesions debate is still open. Study by Lee et al compared the morbidity in resections of right-sided lesions and left-sided lesions, they concluded that resection with primary anastmosis for left-sided obstructing growths should not be discounted. [8]

(Level of Evidence 2A)

Retrospective analysis suggests that there is no significant excess morbidity or mortality with immediate resection as compared with staged procedure, so whenever possible primary excision of the growth should be done. [9,10] **(Level of Evidence 2A)**

when emergency resections were compared with elective resections, the emergency patients had far poorer prognosis as compared with non-obstructed elective resections as shown in studies of Zucchetti et al and Omejc et al.[11,12] **(Level of Evidence 2A)**

Resection rates are less in emergency situations as compared to the elective surgeries (85% Vs 77%). Curative resections are also less in emergency situations (70% Vs 60%) [13] **(Level of Evidence 2B)**

Intraoperative blood transfusion is said to have harmful effect on the survival in CRC patients. This is more relevant in cases of emergency surgeries as blood loss is generally more in emergency operations. [14,15] **(Level of Evidence 2B)**

In an emergency colorectal surgery, strongest predictors for 30 day mortality were ASA score and age. Predictors for early postoperative complications were faecal contamination during surgery and ASA score. Strongest predictor for 3 year mortality after emergency surgery was malignant disease. Other predictors for long-term outcome were procedures performed and degree of specialization of the surgeon.[16]

Another factor which is important in primary anastmosis is serum albumin which is the marker of nutritional status of the patient. Hypoalbuminemia is an important determinant in choice of treatment and whether primary anastmosis is to be done. [17] **(Level of Evidence 2B)**

Intra-operative colonic lavage (ICL) came into vogue in 1980's. Its advantage was making an anastomosis on a prepared bowel but the problem was prolonged operative time, the risk of spillage and contamination, increased post-operative complications and the need for increased expertise. RCT from the SCOTIA group concluded that segmental resection following ICl is the preferred treatment however, it did not show any difference in mortality or morbidity. [18] **(Level of Evidence IB)**

Perforation

Second important presentation of malignancy in emergency is perforation. Removal of the perforated segment with proximal stoma with distal mucous fistula or hartmann should be done. Attempt should not be made to anastmose in sick patient with peritonitis. A retrospective study of more than 1500 patients showed that aggressive management can give around 60% survivals. In patients with perforation, main cause of death is sepsis with postsurgical mortality being 12%. Generally causes of the poorer outcome in cases of perforation are sepsis and malignancy, plus the combination of preexisting comorbidity and pathophysiologic disturbances. [19] **(Level of Evidence 2B)**

Bleeding

Patient can present with bleeding with large colonic growth in which management depends upon general condition of the patient. In cases which are hemodynamically stable excision with or without primary anastomosis is the treatment of choice.[20] But in patients which are unstable, angioembolisation can be considered as an emergency measure with surgery after stabilisation.

Major complication of angioembolisation is colonic ischemia. [21] **(Level of Evidence 2B)**

Metallic stenting for colonic obstruction

Self-expanding metallic stents have been introduced as a treatment for LBO secondary to tumors. Stents can be used in two fashions :

1) as a "bridge" to definitive surgical treatment by allowing bowel preparation and resuscitation . It also allows time for disease evaluation
2) as a "permanent" palliative treatment for unresectable lesions and in patients with metastatic disease in whom resection of the primary will not improve survival.[22] **(Level of Evidence 2B)**

In patients with advanced disease, the long-term outcomes are poor, especially in those with other medical problems. Urgent or emergent surgery in this setting is associated

with a high morbidity and a mortality that ranges from 9% to 27%. The use of stents avoids this morbidity and allows patients to begin chemotherapy at the earliest.

Palliation of patients with advanced malignancy can be difficult. Surgery may be considered inappropriate in this group of patients as they are often frail and with co-morbidities. All palliative procedure has been shown to have a significantly higher mortality rate. For patients in end stage, SEMS offer better quality of life than the one with colostomy.

In addition, patients with large bowel obstruction secondary to noncolonic pelvic malignancies (e.g., bladder, prostate or ovarian carcinoma) or metastatic disease (e.g., breast carcinoma) can be helped with SEMS.

SEMS can be utilized for lesions anywhere in the colon however, most of the stenting has been done for left sided lesions. Lower rectal lesion is difficult to stent if it is very close to the anal sphincter. If placed too low, then it may cause tenesmus, rectal pain and fecal incontinence. So it is recommended that stents should be placed at least 2 cm above the anal canal.

A review (published in 2002) of all colonic stent papers published between 1990 and 2000, there were 262 patients who underwent attempted stent placement as a bridge to surgery – 223 (85%) were successfully placed and 95% of the 223 underwent a one-stage elective operative resection. Stent has complications in form of perforation(4%), reobstruction (10%) and migration (10%) of patients, but overall it offered good palliation and it is safe and effective as bridge to surgery [23] **(Level of Evidence 2A)**

A comparison by Law et al of stenting vs. emergency surgery as palliative treatment

modality for left-sided incurable colonic obstructions. Of 61 patients, 31 were treated with surgery and 30 with metal stents. The group that was stented had fewer patients who

Intensive care requirement (1 vs. 11), and the hospital stay (4 vs. 8 days) was less in stented group.[24] **(Level of Evidence 1B)**

Feasibility of stent placement was shown in metaanalysis of 54 case series representing 1198 patients, 791 patients were stented for palliation with overall 93% success rate .Failure rate was high in proximal lesions. Causes of failure were stent malpositioning, migration, stool impaction, or perforation. Recurrent obstruction, 7.3% at median of 24

weeks, was mostly due to tumor overgrowth and was treated endoscopically in most cases. Perforation occurred in 3.7% and was mainly due to pre-stenting dilatation. Other complications were stent malpositioning and bleeding. [25] **(Level of Evidence 2B)**

A decision analysis between stenting and emergency surgery showed 23% fewer operative procedures per patient, an 83% reduction in stoma requirement (7% vs. 43%), and lower procedure related mortality (5% vs. 11%) so as lower cost ($45,709 vs. $49,941) with colonic stent.[26] **(Level of Evidence 2A)**

So metal stenting is a feasible alternative for diversion stoma in case of large bowel obstruction as it gives better quality of life for the patient, without the psychological repercussions of a colostomy, and it appears to be cost-effective. [27] **(Level of Evidence 1B)**

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CHAPTER-6

Radiation In Rectal Cancer

Introduction

Combined modality preoperative chemo-radiation in patients with stage II and III rectal cancer is currently has being advocated as the preferred approach, with the goals of down-staging clinical tumor (T) and nodal (N) status, increasing both the curative resection rates and the ability to perform sphincter-sparing surgery, improving the number of patients obtaining a complete pathological response and decreasing local recurrence rate. Regimens are modulated to retain the benefits while, minimizing morbidity of combined modality therapy including preservation of bowel continence, genitourinary function and anastomotic leak and mortality after surgery. The evidence presented here targets the principles and benefits obtained by combining chemotherapy with pre-operative radiation for rectal cancer.

The preference for pre-operative over postoperative and short versus long courses of radiation in rectal cancer is discussed in Chapter.

I. Risk of local recurrence (LR) in rectal cancers and selection of patients for neo-adjuvant therapy:

A. Circumferential margin (CRM) positivity and LR:

CRM positivity is a strong predictor of local recurrence and overall survival [1-4].

B. Clinical nodal disease status and risk of recurrence:

There is level 2 evidence to suggest that low-risk (T1-2N+ or T3N0) rectal cancer have a significantly favourable outcomes compared to high-risk (T3N+ or T4Nany) with 7 year survival (70% v/s 45%) and local recurrence (9% versus 18%) respectively [5]. The same study showed that lymph node LN ratio (positive nodes divided by total number of nodes examined is a strong predictor of survival [6]. Hence, stage II and III rectal cancers are selected for pre-operative neo-adjuvant therapy.

C. Importance of pathological complete response after neo-adjuvant therapy (pCR):

There is level 2 evidence to suggest that:

- Pathological response after CTRT is an important predictor of disease recurrence [7,8,9].
- Responders to neo-adjuvant therapy who achieve down-staging to ypT0-2 derive survival benefit in terms of DFS and OS benefits from post op adjuvant chemotherapy, suggesting that neo-adjuvant therapy provides survival advantage in responders[10].
- Patients with stage II and III rectal cancer who achieve pCR (ypT0N0) also have a very favourable prognosis [7-9,11].

D. Choice of pre-operative modality to select stage II and III rectal cancers for neo-adjuvant therapy:

Accurate staging is a prerequisite prior to neo-adjuvant therapy to avoid the possibility of over-treating early tumors due to use of inaccurate staging modalities[12-15].

- CT scan is not considered to be appropriate method for T stage evaluation [16,17].
- There is level 1a evidence to suggest that EUS and MRI have similarly high sensitivity for T2 stage (94%) although EUS has a higher and specificity (86% v/s 69%) [16].
- There is level 1a evidence that EUS and MRI have advantage to evaluate soft tissue structures in the mesorectum and thereby have a potential to predict an R0 resection, with EUS being superior to MRI [17-18].
- For N stage: the sensitivity and specificity of CT (55%, 74%), MRI (66%, 76%), EUS (67%, 78%), hence none of the three modalities are superior to one another for N stage evaluation in rectal cancer[16-18].
- Disadvantage of EUS and MRI is the high degree of operator dependence.

II. Impact of combining chemotherapy with preoperative radiation therapy in resectable stage II and III rectal cancer :

- There is level 1a evidence that the addition of FU based chemotherapy (CT) to preoperative radiation (RT) significantly improved
  - o 1. The rate of complete pathological response (OR 2.52-5.27, $P < 0.001$) [19].

- 2. The incidence of local recurrence at five years (OR 0.39-0.72, P < 0.001) [19].

- There is level 1a evidence that addition of FU based CT to RT failed to provide benefit for DFS (OR 0.92-1.34, P = 0.27) and OS (OR 0.79-1.14, P = 0.58) at five years [19].
- There level 1a evidence that addition of FU based CT to RT significantly increased [19].
  - 1. Grade III and IV acute toxicity (OR 1.68-10, P = 0.002) [19].
  - 2. But did not affect postoperative morbidity (anastomotic leaks) or mortality[19].
- There is level 1a evidence to suggest that the impact of addition of FU based CT to RT leading to improved pCR rates but this did not translate into higher sphincter preservation rate (OR 0.92-1.31, P = 0.29) [19, 20].
- There is level 2 evidence to suggest that a select group of patients who achieve down-staging (ypT0-2) after preoperative CTRT have improved 5 year DFS [8,9,10] overall survival [8, 10]. These results suggest that the same prognostic factors may drive both tumor sensitivity for the primary treatment and long-term clinical benefit from further adjuvant CT.
- There is level 1b evidence to suggest that preoperative CTRT combination improves curative resection rates to upto 86-98% [19-25].

III. Impact of combining chemotherapy with preoperative radiation therapy in unresectable stage II and III rectal cancer :

- There level 1a evidence that preoperative RT alone does not improve rates of curative resection [26].

§ There is level 1b evidence that preoperative CTRT improves R0 resection rates in T3 and T4 rectal cancers [19-25].

IV. Choice of chemotherapy regime combined with radiation

- Bolus FU v/s FULV :
  - o There is level 1b evidence to suggest that bolus FU alone is non-inferior to FU-Leucovorin (FULV) and FU –levamiosole (FULEM) combinations administered concomitant with radiation in terms of local recurrence, DFS and OS [27].
- Bolus FU v/s Infusional FU:
  - o There is level 1b evidence that bolus FU is equivalent to infusional FU administered concurrently with radiation in terms of DFS and OS [28]. However the hematological toxicity of bolus FURT was found to be higher compared to infusional FU [28].
  - o There is level 2 evidence to suggest that infusional FU combined with radiation is possibly associated with higher OS in node positive rectal cancer [29].
- Capecitabine RT v/s Bolus FURT:
  - o There is level 1b evidence that when combined with radiation, capecitabine is non-inferior to both, bolus FU [30, 31] and FULV [32] in terms of down-staging, pCR rates and toxicity profile.
  - o There is level 2 evidence that when combined with radiation, capecitabine is non –inferior to infusional FU in terms of down-staging, pCR rates and toxicity profile[33].

- Combining FU or capecitabine with oxaliplatin (FOLFOX or CAPOX):
    - There is level 1b evidence to suggest that addition of oxaliplatin to capecitabine concurrently with radiation does not improve the pCR rates but only increases toxicity [30].
    - There is level 1b evidence to suggest that addition of oxaliplatin to continuous infusion FU regimes concurrently with radiation does not improve the pCR rates but only increases toxicity [34].
    - There is level 1b evidence that addition of oxaliplatin to capecitabine concurrently with radiation however, significantly downstages the tumor along with reduction in CRM positive status [30].
- Combining FU with Irinotecan (FOLFIRI)
    - There is level 3 evidence from a phase I/II study that FOLFIRI combined with radiation could achieve pCR in 25% of cases [35].
- Combining FU with cetiximab
    - There is level 3 evidence from a phase II study reported a down-staging to ypT0-2N0 in 44% of patients [36].
- Combining FU with Bevacuzumab
    - There is level 3 evidence form a small phase I study reporting good pathological after combined bevacizumab and FU use with preoperative radiation [37].

V. Risk of toxicity with pre-operative combined modality chemo-radiation.

- There is level 1a evidence that toxicity is significantly increased when FULV or single agent FU is combined with radiation compared to radiation alone [19].
- There is level 1b evidence to suggest that FOLFOX and CAPOX significantly increases toxicity compared to FU alone without additional therapeutic benefit, when combined with radiation [30, 34].

VI. Grades of recommendation for use of chemotherapy with preoperative radiation for stage II and III rectal cancer.

§ A: Combined modality neoadjuvant therapy using chemotherapy with radiation should be used as standard of care in all stage II and III rectal cancers .

§ A: Chemotherapy using bolus FU is recommended in combination with radiation.

§ A: Capecitabine can be used to replace bolus and infusional FU in combination with radiation

§ A: Combining oxaliplatin with bolus FU, infusional FU or capecitabine in chemoradiation regimes is not recommended.

§ B: The use of targetted monoclonal antibodies (Bevacizumab, Cetuximab) in combination with FU based regimes as radiosensitizers for preoperative radiation is experimental and should be used only in the setting of clinical trials.

Radiation for Resectable Rectal Cancers

Postoperative adjuvant chemoradiotherapy significantly improves local control and overall survival as compared to surgery alone or surgery and radiotherapy for stage II/III rectal cancers and was recommended as standard of care in 1990 NIH consensus conference (1). The potential for higher rates of sphincter preservation has provided the rationale for using preoperative chemoradiotherapy for rectal cancers. Randomized trials comparing postoperative and preoperative radiation demonstrated the benefit of preoperative approach in improving sphincter preservation and local control (2-4), an effect maintained even in patients undergoing Total Mesorectal Excision (TME) (5). The recommendations and guidelines for radiation for resectable rectal cancers are as follows

Stage I

Role of adjuvant chemoradiotherapy

Patients with cT1-2 tumours are candidates for upfront surgery. No adjuvant treatment is indicated for those who have pT1-2pN0 tumours on final histopathology. Adjuvant chemoradiation is reserved for those for patients with adverse pathological features (margin positive, node positive, T3 on histopathology). Adjuvant treatment for these patients includes 5FU or capecitabine based chemoradiotherapy followed by 5FU/Leucovorin (or capecitabine and oxaliplatin)

Role of Definite Radiation (+/-chemo)

Radiotherapy alone can be offered to medically inoperable patients or who refuse surgical treatment. The schedule and regimen of chemoradiation is similar to preoperative chemoradiation. The radiation portals should include

primary tumour with 2 cm margins and perirectal, internal iliac and presacral lymph nodes. External iliac lymph nodes should routinely be excluded. A dose of 45-50 Gy/ 25 fractions/5 weeks is recommended. Wherever feasible multiple fields should be used to limit dose to adjacent bowel. In select T2 tumours additional boost of 10-16 Gy to the primary tumour may be used to improve local control. However the evidence is limited and a definitive recommendation requires further studies.

Stage II/III

Preoperative chemoradiotherapy followed by TME and/or adjuvant chemotherapy is indicated for all patients with stage II/III rectal cancers. Radiotherapy portals are similar to early stage disease. External iliac lymph nodes should be included in tumours reaching the anal verge and for tumors extending into GYN or GU structures. Preoperative radiation doses should be no more than 45-50 Gy/25 fractions and should be combined with concomitant 5FU based chemotherapy. All patients should be counseled regarding adverse impact on fertility and premature menopause following pelvic radiation. Option for pretreatment sperm banking/ovarian transposition should be given before initiating radiation.

What is the optimal radiotherapy schedule for rectal cancers: Preoperative or Postoperative?

Five randomized trials have investigated the role of preoperative vs postoperative radiotherapy. Of these 2 trials closed prematurely (NSABP R-03 and RTOG 94-01) due to poor accrual. The recommendations are hence based on results of the remaining 3 trials. The first trial was conducted in the pre-TME era. Investigators at Uppsala (3) randomized 471 patients with resectable rectal cancer

to receive either preoperative (25.5 Gy/5 fractions/1week and surgery within one week of RT) or selective postoperative radiotherapy to stage B2 and above (60 Gy/ 8 weeks). Surgery comprised of standard surgical excision at that time (Not TME). No adjuvant chemotherapy used in this trial. Local recurrence rates at 5 years (22% vs 13%, p=0.002) favoured the use of preoperative radiotherapy. Though higher perineal wound sepsis was observed in preoperative group (33% vs 18%, p=0.01), no difference was observed in late toxicity in either arms. There was no reported difference in overall and cancer specific survival.

More recently 2 randomized trials have been reported in patients scheduled to undergo TME (German (4) and MRCCR07/NCIC CTG(2) trials). While the primary endpoint of German trial (4) focused on detecting 10% difference in 5 yr overall survival, the sample size calculations of MRC/ NCIC trial (2) were based on detecting 10% differences in local recurrence rates at 2 years. The German trial randomized 823 patients (T3 or T4 or node positive tumours) to preoperative chemoradiotherapy (50.4Gy/28 fractions with fluorouracil given as continuous infusion of 1000 mg per square meter per day during week 1 and week 5 of radiotherapy) followed by surgery within six weeks or to similar postoperative chemoradiotherapy. Though there was an imbalance in the number of distal rectal cancers in the two arms (preop vs postop 39% vs 30%;p=0.008) the local recurrence rate was lower in the preoperative arm (6% vs 13%;p=0.006). The sphincter preservation rate was higher in the preoperative arm (39% vs 19%; p=0.004). However no difference was observed in 4 year overall survival (76% vs 74%;p=0.80) (4)

MRC-CR07/NCIC CTG randomized 1350 patients with resectable rectal cancer to receive either a short course

preoperative radiotherapy (25 Gy/5 fractions/1 week) followed by TME or to selective postoperative chemoradiotherapy. Most patients with stage III disease received adjuvant chemotherapy. The study reported decreased local recurrence rate (4.4% vs 10.6%; p=0.0001) and improved 5 year disease free survival with preoperative radiotherapy (73.6% vs 66.7%; p=0.01). Sphincter preservation was not used as one of the outcome measures and differences have not been reported (2).

Is radiotherapy needed for patients planned for TME?

Most of the trials comparing preoperative radiotherapy and surgery or surgery alone were conducted in the pre TME trial. The Dutch trial evaluates the role of preoperative radiotherapy in patients undergoing TME. A total of 1860 patients were randomized to either short course preoperative radiotherapy (5X5 Gy) and TME or to TME alone. No chemotherapy was allowed. At a median follow up of 6.1 years the local recurrence rate was reduced in patients undergoing preoperative radiotherapy (5.6% vs 10.9%; p<0.001). Overall survival at 5 years was 64.2% and 63.5%, respectively (p= 0.902). Subgroup analyses showed significant effect of radiotherapy in reducing local recurrence risk for patients with nodal involvement, for patients with lesions between 5 and 10 cm from the anal verge, and for patients with uninvolved circumferential resection margins(5).

Should preoperative radiotherapy be combined with chemotherapy?

Four randomized controlled trials (6-9) and subsequent metaanalyses (10-12) evaluated the role of addition of chemotherapy to preoperative radiotherapy. Of these three

trials employed TME as the standard surgical technique. Though there were considerable variation in the radiation schedule and time to surgery, on pooled analysis the addition of chemotherapy improved the pathological response rates (11.8% vs 3.5%; p=0.0001) and decreased 5 yr recurrence rates (9.4% vs 16.5%) however with increased rates of acute grade III/IV toxicity (14.9% vs 5.1%; p=0.0002). The difference in local control rates did not translate into benefit in overall survival (10).

Is prolonged preoperative chemoradiation superior to shorter radiation fractionation schedule?

Polish randomized trial evaluated the role of short vs prolonged fractionation. A total of 316 patients were randomized to short fractionation (5X5 Gy) followed by TME within 7 days or prolonged chemoradiation (50.4 Gy/28 fractions) concomitantly with two course of bolus 5FU and leucovorin followed by TME within 4-6 weeks. The type of surgery was decided after neoadjuvant treatment. Though tumour downsizing was greater in prolonged chemoradiation this did not translate into difference in sphincter preservation rates (58% vs 61% p=0.57) (8). There was no difference in quality of life, sexual and anorectal function in either arm (13)

What is the optimal time between preoperative radiation and surgery?

The optimal time between preoperative radiotherapy and TME has been evaluated by Lyon R 90-01 randomized trial (14). The study randomized patients to short (2 weeks) or long interval (6-8 weeks) for surgery after neoadjuvant radiation (39 Gy/13 fractions/2.5 weeks). The sample size of 206 was based on 20% expected difference in sphincter

preservation rates. Higher pathological response rates were observed in the long interval arm (26% vs 10.3%; $p=0.005$), however this did not translate into statistically significant difference in sphincter preservation rates (75.5 vs 67.7%). Unplanned subgroup analyses favoured the use of longer interval in low lying rectal cancers (within 5 cm of anal verge) (69% vs 79%). There was no difference in postoperative morbidity, local control and overall survival.

Does response to preoperative chemoradiotherapy predict improved outcomes?

Following preoperative chemoradiation 15-27% patients have complete pathological response (15). A pooled analysis of outcomes of 3105 patients undergoing preoperative chemoradiotherapy in various prospective/retrospective studies demonstrated improved disease free survival in those achieving pathological complete response (83.3% vs 65.6%; $p<0.0001$). The effect of pathological complete response on disease free survival was not modified by any of the other variables (16).

Recommendations:

1. Upfront surgery should be used for early T1-2 tumours. Those with corroborating histopathology and no adverse pathological features do not need adjuvant treatment. (Level III, Grade B)
2. Preoperative radiotherapy improves sphincter preservation rate and local control in patients with resectable cancer and should be favoured over postoperative chemoradiotherapy. Postoperative radiotherapy should be considered in patients with rectal cancer who did not receive preoperative radiotherapy and who are at high risk of local

recurrence. When postoperative radiotherapy is indicated, a schedule of 45Gy in 25 fractions over five weeks with 5FU based chemotherapy is recommended (1) (Level 1b, Grade A).

3. Preoperative improves local control even after TME and should be routinely offered to patients with stage II/III resectable rectal cancers. (Level 1b, Grade A).
4. The addition of chemotherapy to preoperative radiotherapy improves local control. (Level 1a, Grade A).
5. Short and prolonged fractionation provides equivalent sphincter preservation rates (Level 1b, Grade A). Resource sparing short fractionation may be used to optimize resources in large volume radiation oncology centers. However prolonged course of chemoradiation should be preferred in locally advanced bulky tumors with borderline fixity on clinical examination since tumor shrinkage is desired in these patients to facilitate R0 resection.
6. Long interval between neoadjuvant treatment and surgery leads to higher pathological response rates. Overall there is no difference in short and long interval in terms of sphincter preservation (Level 1b, Grade A). However longer intervals may be considered in those with low lying bulky rectal cancers.
7. Complete pathological response following neoadjuvant chemoradiotherapy is an independent predictor of 5 year disease free survival (Level IIa, Grade B). Strategies to improve pathological complete response should be evaluated in patients with resectable rectal cancers.

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Radiotherapy in locally advanced unresectable or recurrent rectal cancers

Locally advanced tumours, extending beyond the rectal wall with infiltration to surrounding organs or structures, and/or perforation of the visceral peritoneum (c/p T4 N0-2 M0), may not be resected completely due to tumour fixation. In patients with rectal cancer that present with locally advanced yet still non metastatic disease, the aim of the neoadjuvant treatment is to downstage the tumor in order to achieve R0 resection. Approximately 50–84% of patients are able to undergo a resection with negative margins after radiation therapy. [1-3].

A recently published randomized trial in patients of unresectable rectal cancer by Brændengen et al (NORDIC trial), demonstrated that the addition of chemotherapy to radiotherapy improved resectability, local control, time to treatment failure, and cancer-specific survival in patients with unresectable rectal cancer[3]. In that study an R0 resection was performed in 82 patients (84%) in the CRT group and in 74 patients (68%) in the RT group (P =0.009). A R0 total pelvic exenteration is a potentially curative operation for patients with advanced pelvic cancer: 5-year overall survival is acceptable (52–60%), but it results in high morbidity and impaired quality of life.. Leve of evidence [IV, A].

Recommendation

These patients should receive long course pre-operative chemoradiation (Level 1b, Grade A). This includes radiation

in the range of 50–54 Gy plus 5FU-based chemotherapy with the goal of increasing the rate of R0 resection. It is important for the surgeon to recognize pre-operatively the extent of tumour invasion into other organs and/or the pelvic sidewall for documentation prior to pre-operative radiation and to establish a plan for en bloc resection. The high incidence of metastases in unresectable patients is the rationale for the use of adjuvant chemotherapy after chemoradiation and surgery although there is no direct clinical trial evidence to support its use.

In very old patients (‡80–85 years) and in patients not fit for radiochemotherapy (CRT), 5 X 5 Gy with a delay of _8 weeks before surgery can be an option, presently under clinical validation [4,5]. This regime of radiotherapy can also be offered to patients requiring palliation for relief of symptoms as pain and bleeding. Level of evidence [IV, C].

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Reirradiation for recurrent rectal cancers

Rectal cancer patients treated with radiotherapy and surgery can have a local recurrence risk of about 5 to 20%, depending on the T and N stage. Reirradiation could potentially improve local control in patients with recurrent rectal cancer previously treated with radiation therapy. Use of hyperfractionated radiotherapy 1.2 Gy fraction twice daily to a dose of 40-45Gy with concurrent chemotherapy using Inj 5FU has been shown to be effective in some retrospective and phase II studies. The reported overall 5 yr survival rate ranges from 19% -47%. In the patients who underwent R0 surgical resection, the 5 Year survival rate was 67%.

Recommendation

In cases of recurrent rectal cancers requiring reirradiation, the treatment should be aimed to render the tumors surgically resectable. Therefore concomitant chemoradiation should be offered to a dose of 40 – 45 Gy. Both acute and late toxicity can be lowered by using smaller field sizes. (Level IIA Grade B)

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CHAPTER-7

Adjuvant Chemotherapy In Clorectal Cancer

Majority of adjuvant chemotherapy trials in CRC have combined both colon and rectal cancers for the same stage of disease. There are no trials reporting rectal cancers separately or as a subgroup. Hence all results for colon cancer apply to rectal cancers as well and will be presented as a consolidated evidence for "Adjuvant chemotherapy in CRC".

SELECTION OF DATA: The present evidence and recommendations are based on publications between 1988 and 2010. Clinical trials published before 1987 [72] have been reported as a meta-analysis. This was excluded since stage could not be examined due to the lack of standardization of staging methods.

EVIDENCE AND RECOMMENDATIONS: include

I. General principles of adjuvant therapy in stage II and II CRC.

a. Impact of Interval between surgery and initiating adjuvant chemotherapy

b. Duration of adjuvant chemotherapy
c. Relationship between 3-5 year DFS and OS
d. High risk CRC: Use of prognostic and predictive factors in selecting patients for chemotherapy
e. Choice of chemotherapy regime
f. Adjuvant therapy in elderly patients

II. Benefit of adjuvant chemotherapy in stage III CRC.

III. Benefit of chemotherapy in stage II CRC.

I. adjuvant therapy in stage II and II CRC.

A. Interval between surgery and initiating adjuvant chemotherapy:

- The standard interval between surgery and initiation of chemotherapy in most clinical trials is 5 weeks.
- Evidence: There is a level 2 evidence for a significant survival advantage for patients starting chemotherapy within 8 weeks of surgery [1, 34].
- Recommendation: B: Adjuvant chemotherapy for CRC using FULV regime should be initiated within 8 weeks of surgery.
- Applicability in India: A

B. Duration of adjuvant chemotherapy

- Optimal duration of adjuvant treatment, comparing two durations of 5-Fu based adjuvant treatment, 6 months versus 9 to 12 months has been evaluated.
- Evidence:

- There is level 1a evidence to that shorter duration of 5FU based chemotherapy(3-6 months) compared with longer duration (9-12 months) is not associated to poorer DFS (RR=0.96, CI: 0.90-1.02) or OS (RR = 0.96 ;CI: 0.91-1.02)[2].
- Note: There level 1b evidence to suggest that 5-fluorouracil and levamisole combination for 12 months is as effective as 5-fluorouracil plus high- or low-dose leucovorin for six months [3-7].

- Recommendation: A: Adjuvant chemotherapy for CRC using FULV regime CRC is can be reduced to 6 months.
- Applicability in India: A

C. DFS and OS as primary endpoints for adjuvant therapy clinical trials:

- The traditional end point for clinical trials of adjuvant CRC treatment has been 5 year OS.
- Evidence:
  - There is level 1a evidence that 3-year DFS was an excellent predictor of 5-year OS results and could be an appropriate primary end point for adjuvant studies in stage III CRC [8].
  - There is level 1a evidence that there was no association between DFS and OS stage II CRC, hence an improvement in DFS may not translate into improved OS with extended follow up required to evaluate true OS benefit [9,10]. This observation is also maintained in stage II high risk CRC patients with poor pathological prognostic factors,

suggesting the need to evaluate predictive factors for benefit from chemotherapy [45].

- There is level 1a evidence to suggest that prolonged survival after recurrence reduces the association between 3-year DFS and 5-year OS in stage II and III CRC [10].

- Recommendation:
  - A: 3 year DFS can be used as primary end-point in adjuvant treatment trials in stage III CRC
  - A: 3 year DFS should not be used as surrogate for 5 year OS in adjuvant treatment trials in stage II CRC
- Applicability in India: A

D. Prognostic and Predictive Factors in CRC

1. Introduction

- Prognostic Factors identify high risk group of patients and are linked to survival (DFS, OS).
- Predictive Factors correlate with response to treatment and thereby impact survival.
- Pathological factors identified as prognostic factors have not been validated as predictive tools for benefit from adjuvant therapy.

2. Pathological Prognostic factors:

i. T stage:

- There is level 1a evidence that T stage (T4 vs T3 HR-2.58) is a significantly independent prognostic factor in stage II and stage III CRC[11-15]

ii. Lymph node examination:

- There is level 1a evidence to suggest that number of lymph nodes examined is prognostic of survival in stage II and III CRC [16].

- There is level 1a evidence to suggest the number of positive nodes is an independent prognostic factor in stage III CRC and is associated with worse outcomes dependant number of positive nodes. (HR- N1 =2.1, HR- N2 = 4.2). N2 nodes have 4 times increased risk of relapse and 5 times lower survival, N1 have 2 times increased risk of relapse and 2 times worse survival [12].
- There is level 2 evidence to suggest the following:
- Examination of 12 or more lymph nodes is associated with improved survival, relative to < 12 nodes (HR = 0.83) [17.]
- Patients with 12 or more nodes examined tend to do better regardless of whether they were treated at hospitals with high or low overall node examination rates [17].
- Nodal status (0 positive nodes and > 12 nodes examined, 0 positive nodes and < 12 nodes examined, 1 to 3 or > 4 positive nodes) as the most significant clinical/pathologic predictor of DFS (*P*_.001)[18].
- There is significant interaction between stage of disease and number of nodes recovered [19.]
- Survival improved with increasing number of nodes examined (8–12 nodes - RR = 0.46, 13–17 nodes -RR = 0.76, nodes >/= 18 -RR =0.79)[18, 19].
- The association between survival and nodal count is stronger in stage II (HR= 0.69) than in stage III (HR = 0.89) patients [19].
- Stage B patients with < 7 nodes in the specimen have both significantly shorter DFS and OS [19].

iii. Pathological factors independently prognostic for survival in stage II and III CRC include:

- There is level 2 evidence [20, 21] to suggest that venous invasion (HR- 2.7), peritoneal invasion (HR- 2.8), tumor perforation (HR – 9.8), margin involvement (HR – 2.6) and high grade pathology (HR -1.3) are independent prognostic factors in stage II CRC.

iv. Pathological factor independently prognostic in stage II and III CRC:

- There is level 1a evidence that high grade tumor are associated with poor DFS and OS in stage II and III CRC (univariate analysis) [12].

3. Molecular Prognostic factors

i. MMR gene status: dMMR (MSI- H) v/s pMMR (MSI-L or MSS)

§ MSI-H is found in 15-17% of all sporadic CRC [22]. There is level 2 evidence to suggest the following:

o dMMR tumors are associated with a 15% or better overall survival in patients with locally advanced CRC (stage II and III) with an HR = 0.67; (95% CI, 0.58 to 0.78) compared to proficient MMR (pMMR) [22]

o The effect of MSI on prognosis is independent of patient selection, and is maintained in both adjuvant and advanced settings [22].

o Based on interaction test between MMR status and stage (stage II and III CRC), MMR status is found to be a significantly independent prognostic factor for stage II CRC, but not for stage III CRC [14]

- In stage II CRC dMMR (defective MMR-dMMR) is independently protective (MSI-H v/s MSS : HR- 0.31) [15] .

ii. 18qLOH:

- The somatic LOH (loss of heterozygosity) at chromosome 18q, a site containing genes related to CRC has been associated with a poorer outcome in patients with CRC compared with that in patients with tumors retaining both parental alleles at 18q [14, 23,24,25].
- Level 2 evidence suggests that, 18qLOH MSI is a significantly independent prognostic factor in stage II but not in stage III CRC based on test for interaction between, prognostic marker and stage in stage II and III CRC [14].

iii. P53 status: Level 2 evidence suggests that, p53 status a significantly independent prognostic factor in stage III CRC based on test for interaction between, prognostic marker and stage in stage II and III CRC [14]

iv. Recurrence Score (RS): Clinically validated multigene assay in stage II CRC reveals [15]:

- Of the 48 prognostic genes, 7 have been identified and used to develop the recurrence score which has been clinically validated in stage II CRC.
- The RS is significantly predictive of DFS ($p=0.01$) and OS ($p=0.04$)
- RS retains prognostic significance independent of MMR status, T stage, nodes examined, grade, and lymphovascular invasion.
- The Recurrance risk increases monotonically with increasing RS. The estimated recurrence rates are RS- Low: 12%, RS-IM: 18%, RS-High: 22%.

4. Pathological Predictive Factors:

- T stage: There is level 1a evidence that there is lack of significant interaction between T stage and treatment, suggesting that adjuvant therapy provides similar significant benefit in both T3 and T4 patients [12]. Hence T4 stage is not a useful predictor of treatment benefit.
- High Tumor Grade:
- There is level 1a evidence to suggest that there is lack of significant interaction between tumor grade and treatment, suggesting that tumor grade is not predictive of response to adjuvant chemotherapy [12].
- N0 v/s N1 v/s N2 Status:
- There is level 1a evidence for a significant interaction between treatment and nodal status, indicating that the magnitude of benefit varies depending on nodal status [12].
- For DFS, the HR estimates when comparing treatment to control by nodal subgroup include- 0 nodes: HR - 0.831; 1 to 4 nodes: HR - 0.60; > 5 nodes: HR - 0.60.
- For OS, the HR estimates include: 0 nodes: HR - 0.85; 1 to 4 nodes: HR- 0.66; > 5 nodes, HR - 0.65.
- Note: Thus, there is no difference in outcomes between N1 and N2 status with regard to DFS and OS.

5. Molecular Predictive Factors

i. MMR gene status:

- MMR status is presently the only validated predictive marker for outcome of adjuvant chemotherapy in CRC [14].

- Level 2 evidence suggests that there is a significant interaction between MMR status and treatment efficacy for DFS and OS, indicating that the effect of treatment differs in stage II and III CRC by based on MMR status MMR status [14, 26].
- DFS and MMR status

CRC Stage	dMMR	pMMR
II	HR – 2.3 (No benefit; potential harm)	HR – 0.84 (No benefit)
III	HR – 1.01 (No benefit)	HR – 0.64 (Beneficial)

- OS results were similar to DFS results except in stage II disease with dMMR status, the OS is reduced (HR = 2.95) suggesting that chemotherapy is harmful in this group.

ii. 18qLOH: Level 2 evidence suggests that 18qLOH does not have a predictive value in stage II CRC [14,24].

6. Clinical Relevance of Differentiating Prognostic from Predictive factors:

Results of a recent clinically validated multigene assay in stage II CRC reveals [15, 18].

- 7/48 recurrence risk genes and 6/ 66 chemotherapy benefit genes have been selected to create the final recurrence score (RS) and treatment score algorithms, respectively.
- The correlation between these two scores is low, suggesting that the genes associated with recurrence and adjuvant treatment benefit may be different.

- Hence, patients may need to be stratified twice - first on the basis of risk and second on the basis of probability of responding to adjuvant chemotherapy treatment.
- Presently the predictive score is available for FULV based therapy and not for FOLFOX or FOLFIRI therapy.
- There is weak interaction between gene expression and stage suggesting the probability that the current anatomic-based staging system lacks a strong biologic basis [12]. Similar, level 1a, 2 evidence of interaction between stage and treatment has been identified [12, 45].
- Recurrance Score (RS), T4 stage and MMR status are independently prognostic factors in CRC.

7. Recommendations for Clinical Application of Prognostic and Predictive factors:

A: In stage II CRC, recurrence Score, T4 stage, MMR status and, 18qLOH can be used to counsel patients regarding prognosis in terms of DFS and OS.

A: In stage III CRC, T4 stage, nodal status and p53 can be used to can be used to counsel patients regarding prognosis in terms of DFS and OS.

B: Lymphovascular embolisation, perforation, obstruction can be used to counsel patients regarding prognosis in terms of DFS and OS in adjuvant treatment trials for stage II.

B: In patients with stage II CRC, MMR gene status can be used to counsel patients regarding benefit from adjuvant FULV chemotherapy in terms of DFS and OS.

8. Applicability in India:

A: T4, Nodal status, lymphovascular embolisation, perforation, obstruction

B: MMR gene status

C: 18qLOH, p53, Recurrence Score and Treatment Score (Oncodyx Multigene Assay CRC)

E. Choice of chemotherapy regime

1. Systemic Chemotherapy

i. 5-FULV versus FU LEM (levamisole):

- There is level 1b evidence for equivalent activity of 5-fluorouracil plus levamisole and 5-fluorouracil plus leucovorin regimens [3-7].
- There is level 1b evidence that 5-fluorouracil and levamisole for 12 months is as effective as 5-fluorouracil plus high- or low-dose leucovorin for six months [3-7].

ii. FU combined with low dose versus high dose leucovorin

- There is level 1a evidence to suggest that higher-dose leucovorin (folinic acid) produced no extra benefit in these regimens over that from low-dose leucovorin [27, 28].

iii. Safety and QOL: 5-Flurouracil with either low dose leucovorin or levamisole.

- There is level 1b evidence to suggest that the toxicity of Fu combined with either leucovorin or levamisole is mild to moderate with 5% requiring hospitalization with treatment related mortality of 0.5% [30].
- There is no detrimental effect on QOL [31].

iv. Bolus FULV – four weekly v/s once a week schedule

- There is level 1a evidence to suggest that the once-weekly regimen is much less toxic and as effective as the four-weekly schedule [30, 32].
- The above evidence also suggested that the toxicity of 5-FULV adjuvant therapy could be reduced substantially by weekly scheduling without compromising efficacy [30, 32].

v. Protracted Venous Infusion (PVI- FULV) versus Bolus FULV

- There is level 1 b evidence to suggest that PVI – FULV for 12 weeks is equivalent in efficacy to bolus FULV (lowdose LV) for six months in terms of DFS and OS [34, 35, 36].
- Also, PVI-FULV adjuvant-based therapy is relatively less toxicity than bolus FULV with better QoL [33-36].
- The major drawbacks of c PVI FULV is catheter-associated complications [34 - 36].

vi. FOLFIRI versus FULV (addition of irinotecan to FULV)

- There is level 1b evidence to suggest that integration of irinotecan with FULV as a adjuvant treatment strategy for patients with stage III disease has no advantage compared with 5-FU alone and therefore should not be given in the adjuvant setting [42-44].

vii. FOLFOX4 or FLOX versus FULV (addition of Oxaliplatin to FULV Mayo or Roswell Park regimes):

The results of MOSAIC trial[45] (Mayo Regime; FOLFOX4) were similar to that of NSABP-C07[46]

(Roswell Park Regime, FLOX) trial. The results of MOSAIC trial are presented here.

- Benefit in Stage III CRC: There is an absolute benefit in 5 yr DFS of 5.9% (HR= 0.78) and in 6 yr OS of 4.2% (HR=0.80) in patients with stage III CRC
- Benefit in Stage II CRC: There is an absolute benefit in 5 yr DFS of 3.8% (HR= 0.84), which does not translate into OS benefit with an 6 yr OS absolute benefit of 0.1% (HR=1.00) in all patients with stage II CRC
- Benefit in Stage II CRC with Pathological Poor Prognostic Factors: There is an absolute benefit in 5 yr DFS of 7.7% (HR= 0.72) which does not translate into benefit in OS with a 6 yr OS of 2.0% (HR=0.91) in stage II CRC patients with high risk pathological prognostic factors (T4, tumor perforation, bowel obstruction, poorly differentiated tumor, venous invasion, or less than 10 lymph nodes examined).

viii. Addition of Targetted therapy to FOLFOX regime

- There is level 1 evidence to suggest that Bevacizumab for 1 year with modified FOLFOX6 does not significantly prolong 3 year DFS in stages II and III CRC [47].
- There is level 1 evidence to suggest that the addition of Cetuximab to modified FOLFOX6 resulted in impaired DFS and a trend toward impaired OS in mKRAS resected stage III colon cancer [48].

ix. Replacing FULV with Oral Capecitabine

- There is level 1 to suggest that capecitabine alone

is equivalent to FULV combination (Bolus Mayo Clinic regime) in terms of efficacy (DFS, OS) and QOL with patients preferring oral chemotherapy [49-52].

- In terms of toxicity profile, capecitabine is associated with significantly fewer adverse events than fluorouracil plus leucovorin. Neutropenia requiring medical intervention, grade 3 or 4 stomatitis, diarrhea and alopecia was less and hand-foot syndrome was more with capecitabine as compared to FULV [49, 52].

2. Immunotherapy

i. Immuotherapy As Adjunct to Systemic Chemotherapy: Levamisole, Interferon or BCG vaccine in addition to FULV.

- There is level 1b evidence that addition of levamisole to FULV does not improve survival but only adds to toxicity [5-7, 27, 28] .
- There is level 1a evidence that addition of interferon to FULV does not improve survival [29].
- There is level 1b evidence that addition for BCG to systemic chemotherapy is not superior to chemotherapy alone [64, 65].

ii. Immunotherapy (autologous tumour cell-BCG vaccine) compared to surgery alone

- There is level 2 evidence that use of autologous tumour cell-BCG vaccine (BCG mixed with altered tumor cells) provides no benefit in DFS and OS in both stage II CRC [66,67] and stage III CRC [66] .
- There is level 1a evidence to suggest that autologous tumour cell-BCG vaccine with >70% of viable cells and a dose of 107 tumour cells per immunization significantly improved DFS in

stage II CRC who developed an induration of >5mm at the site of the inoculum [68].

- The difference noted was due to diffrenet immunogenicity of the vaccine and T-cell immunity of the host [68].

iii. Immunotherapy Edrecolomab- Mab-17A) compared to surgery alone

- There is level 1b evidence that monoclonal antibody 17A (Edrocolomab) improves DFS and OS in stage III CRC [69].
- There is level 1b evidence that Mab-17A does not improve outcomes in stage II CRC [70, 71].

iv. Immunotherapy versus systemic therapy:

- There is no evidence comparing systemic chemotherapy with immunotherapy (autologous tumour cell-BCG vaccine or Mab-17A).

3. Regional (Portal Venous Infusion and Intraperitoneal) Chemotherapy

- Portal Venous Infusion FU versus surgery alone (observation)
- There is level 1a evidence to suggest that Portal Venous Infusion of FU does not improve DFS, marginally improves OS and does not have an impact on hepatic recurrances in Stage II and III CRC [37-41] compared to observation
- Intraperitoneal Chemotherapy versus surgery alone (observation)
- There is level 2 evidence to suggest that intraperitoneal chemotherapy improves DFS and OS compared to observation in stage III CRC [62].
- There is level 2 evidence to suggest that

intraperitoneal chemotherapy improves DFS in stage II without any benefit in OS. [63].

- Regional Chemotherapy versus Systemic therapy
- There is no data to ascertain the advantage of portal venous infusion therapy or intraperitoneal chemotherapy over systemic chemotherapy.

Recommendations for Systemic Chemotherapy regimes

A: FOLFOX4 for 6 months is the preferred as adjuvant chemotherapy regime in patients with stage III CRC.

A: Weekly FULV (low dose LV) for 6 months can be considered as standard chemotherapy in patients with stage II CRC.

A: Patients with stage II CRC should not be routinely offered FOLFOX4 as adjuvant chemotherapy.

A: FOLFOX 4 for 6 months can be offered to stage II CRC patients with high risk pathological prognostic factors with an intention to improve DFS.

A: FOLFOX 4 should not be stage II CRC patients with high risk pathological prognostic factors with an intention to improve OS.

A: FULV (low dose LV) combination can be replaced by capecitabine and FOLFOX 4 can be replaced by XELOX in adjuvant therapy for CRC.

A: Protracted venous infusion therapy using FU for 3 months is an alternative to standard FULV (low dose LV) for 6 months for adjuvant treatment of CRC.

A: Immunotherapy using interferon, levamisole or should not be used alone nor as adjunct to systemic adjuvant chemotherapy regimes in CRC.

Applicability In India: A

Recommendations for Regional (Portal Venous infusion and Intraperitoneal) Chemotherapy

A: Regional chemotherapy- both portal venous infusion and intraperitoneal chemotherapy cannot be recommended at present for adjuvant treatment of CRC.

Applicability In India: C

Regional chemotherapy such as intraperitoneal and portal venous infusion chemotherapy as an adjuvant for colon cancer has not been used because of the technical difficulties of the procedures and similar results from systemic chemotherapy.

Recommendations for Immunotherapy:

A: Autologous tumour cell-BCG vaccine in stage II CRC and Edrocolomab in stage III CRC cannot be recommended for adjuvant therapy since

- There is no evidence comparing these with systemic chemotherapy.
- Efficacy of the autologous tumor cell-BCG vaccine is dependent on a responsive host and an active vaccine.

Applicability In India: C – preparation of an effective autologous tumour cell-BCG vaccine is a complicated procedure requiring a dedicated laboratory to obtain an active vaccine and a responsive host.

F. Adjuvant Chemotherapy in Elderly (>70 years) CRC Patients

1. Introduction:

Elderly patients > 65 years are less likely to receive adjuvant therapy [53]. Questions are: Are the

benefits of CT dependant on age? Do elderly experience more toxicity than others?.

2. Evidence
   - FULV/ capecitabine in elderly: There is level 1a evidence to suggest that there is significant interaction between age and the efficacy of treatment. Elderly patients do not receive the same treatment benefit as young patients in DFS and OS [30],[54]. There is no difference in toxicity except leucopenia is more frequent in elderly [55].
   - FULV v/s FOLFOX4 in elderly: There is level 1a evidence to suggest that older patients treated with FOLFOX receive short term DFS benefit which disappears over time, providing no OS benefit due to competing causes of death [54, 56].
   - FULV v/s FOLFIRI in elderly: There is level 1a evidence to suggest that FU compared to combination of FU with irinotecan has no benefit in DFS, OS and TTR (HR- 1.09) in elderly patients with stage III CRC [54].
3. Recommendation for systemic adjuvant chemotherapy in elderly :

   A: FULV or oral capecitabine is a reasonable option for adjuvant therapy in elderly patients with stage II and III CRC.
4. Applicability In India: A

II. BENEFIT OF ADJUVANT THERAPY IN STAGE III CRC

1. Evidence
   - There is level 1a evidence to suggest that adjuvant systemic chemotherapy using FULV

improves DFS (absolute benefit of 18% HR-0.55) and OS (absolute benefit of 12% HR-0.71) by 30-40% in patients with stage III CRC [4, 60, 61].

- There is level 1b evidence to suggest that adjuvant systemic chemotherapy using FOLFOX4 is superior to FULV and improves DFS (absolute benefit of 6%, HR-0.78) and OS absolute benefit of 4% , HR-0.80) by 30-40% in patients with stage III CRC [45,46]. While, level 1b evidence suggests that FOLFIRI is not superior to FULV in stage III CRC [42,43, 44].

2. Recommendation:

   A: All patients with stage III CRC should be treated with adjuvant systemic chemotherapy using the FOLFOX 4 regime

3. Applicability In India: A

III. BENEFIT OF ADJUVANT THERAPY IN STAGE II CRC

1. Source of Evidence:
   - Source: Since the relatively good prognosis of this group of patients is relatively good (75-80% survival at 5 years without adjuvant therapy) ideally a sample size of > 4,000 assessable patients is required to detect a 4% difference in survival advantage . Such a large trial is not conducted till date [57].
   - However, there is level 1 evidence to suggest that adjuvant therapy is effective in stage II colon cancer.
   - The most direct evidence for the above is from meta-analysis showing lack of significant interaction between treatment

effect and stage and similar relative risk reduction in stage II and stage III disease [12, 40, 58]. Similar, indirect evidence is obtained for subgroup analysis and relative risk reduction in different stages of the disease in subgroup evaluation of metanalysis of randomized trials and relatively large randomized trials demonstrating a definite but small benefit as shown below[59].

1. Quantum of Benefit
   - The improvement in 3-5 year DFS is 2-8% and in 5year OS is 2-3% [59] in patients receiving FUFA [59,30] or FOLFOX therapy [45, 49].
2. Dilema in advocating adjuvant chemotherapy for stage II CRC in clinical practice:
   - At present improvements in disease-free and, perhaps, in overall survival are modest. At best, only one of eight to 20 treated patients will benefit, whereas the remainder will receive treatment with no benefit.
   - The important question is whether this small benefit might prove to be clinically significant for recommendation as standard therapy and whether any subgroups can be identified who will derive a larger benefit.

3. Selecting patients with stage II CRC for adjuvant therapy:

i. Selection based on Predictive factors: Predictors of FUFLV adjuvant therapy are continuing to evolve:

a. MMR status: is presently the only clinically validated predictive factor for benefit from FULV adjuvant therapy in stage II CRC [15].

- There is level 2 evidence to suggest that the role of MMR in FULV chemotherapy:
    - Stage II patients with dMMR (MSI-H) tumors have no benefit in DFS (HR = 2.30) and reduced OS (HR = 2.95) after adjuvant FUFA therapy.
    - In stage II pMMR (MSS or MSI-L) tumors there was no benefit in DFS (HR = 0.84) and OS after adjuvant FUFA therapy.
- There is no available evidence to assess the predictive value of MMR status in for benefit from FOLFOX adjuvant therapy in stage II CRC patients.

b. Role of Recurrance score and Treatment Score (Oncodyx Multigene Assay) [15,18]:
    - The recurrence score is a significantly independent prognostic factor for DFS and OS and has a weak association with treatment score.
    - The treatment score independently predicts benefit from FULV based adjuvant therapy. Treatment score predictive value for FOLFOX regime is unknown.
    - Whether MMR gene status as a predictive factor of treatment benefit is independent of the treatment score is unknown at present[15].

c. Recommendations for use of predictive factors in stage II CRC:
    B: MMR status should be in an all patients with stage II CRC to estimate the benefit of FULV adjuvant therapy regime.

B: Stage II patients with MSI-H (dMMR) should not be treated with FULV adjuvant therapy.

B: At present, pMMR status should not be used as a sole risk factor to recommend FULV adjuvant treatment for patients with stage II disease.

d. Applicability of Predictive factors In India:

B: MMR gene status; C: Treatment Score

ii. Selection based on Prognostic factors

a. Definition of high risk based on pathological factors: At least one of these factors present- T4, tumor perforation, bowel obstruction, poorly differentiated tumor (high grade), venous invasion, or less than 10 lymph nodes examined.

b. Systemic FUFA regime for high risk prognostic factors:

- There is level 2 to suggest that the 5-year risks of death for an untreated patient with stage II disease with high-risk features is 30% with survival benefit of 5·4% with FUFA therapy [30].

c. Systemic FOLFOX4 regime for high risk prognostic factors:

- There is level 2 evidence to suggest that FOLFOX4 chemotherapy improves DFS (absolute benefit in 5 yr DFS of 7.7%; HR = 0.72) in patients with high risk prognostic factors in stage II CRC but this benefit does not translate into improved overall survival (absolute benefit in 6 yr OS of 2.0%; HR = 0.91) compared to FULV therapy [45].

d. Recommendation for use of prognostic factors:
    B: Stage II CRC with high risk pathological prognostic factors should be offered FULV based adjuvant therapy.
    B: Stage II CRC with high risk pathological prognostic factors may be offered FOLFOX4 as adjuvant chemotherapy with an intention to improve disease free survival.
    B: Stage II CRC with high risk pathological prognostic factors should not be offered FOLFOX4 as adjuvant chemotherapy with an intention to improve overall survival.
e. Applicability of Prognostic Factors In India: A

iii. Age as a selection factor independent of poor prognostic factors:

a. Evidence:
    - There is level 1b evidence to suggest that the 5-year mortality without chemotherapy is 20%, a reduction in the relative risk of death of 18% (95% CI 5–30) translates into an absolute improvement in survival of 3·6%.
    - Also, chemotherapy seems to prevent a proportion of recurrences and deaths, rather than just delaying them, which makes the life-years gained more substantial, especially for younger patients [30].

b. Rationale for benefit in young patients:
    - For a 50-year-old, who would have a life

expectancy of 30 more years if not dying of their cancer, reducing their 5-year risk of cancer death by 3·6% (eg, from 20% to 16·4%) would increase their life expectancy by about a year. By contrast, a sustained 3·6% improvement in survival for a 75-year-old, with a life expectancy of about 10 years, would increase their life expectancy by only 4 months. If a 2-month deduction is made for loss of quality-adjusted life during chemotherapy, the average QALYs gained are 10 plus 2 months.

c. Recommendation :

A: All young patients with stage II CRC should be offered adjuvant therapy based on high risk prognostic and predictive factors for adjuvant therapy.

d. Applicability In India: A

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CHAPTER-8

Palliative Chemotherapy

The decision for planning palliative chemotherapy in a case of advanced CRC should be taken by a Multidisciplinary team. [IV, C] Metastatic disease should be confirmed by appropriate radiological investigations (discussed elsewhere in this guideline). A histological diagnosis is essential prior to starting chemotherapy. The only exception is in patients with resectable metastases in whom histological diagnosis is not required due to a low chance of seeding.[1] Patient evaluation should include assessment of the performance status, organ function and a detailed history of co-morbid illnesses. All patients planned for chemotherapy should be assessed by a nutritionist and advised regarding diet and supplements.

Palliative chemotherapy can improve both, the progression free survival and overall survival and should be considered in all patients. However, chemotherapy rarely leads to a cure and involves significant costs. It can also be associated with side effects leading to morbidity. Hence patients and care givers should be counseled in detail prior to planning the chemotherapy. Counseling should include, but not be limited to the treatment options available, the cost

involved, the expected benefits and risks and overall prognosis. Counseling should be done in the outpatient clinic using written patient information material whenever possible.

A) FIRST LINE CHEMOTHERAPY

Chemotherapy is the mainstay of treatment for advanced CRC (ACRC). It has been shown to improve both the progression free survival (PFS) and overall survival (OS) in randomized trials. [Ia, A] The median OS, for ACRC is approximately 6-8 months with best supportive care (BSC). The use of bolus 5Flourouracil (5 FU) prolonged it to 10-12 months. Subsequently regimens that added bolus Leucovorine (LV) or used infusional LV- 5 FU prolonged the median OS to about 14 months. The median OS has progressed to almost 20 months with the addition of Oxaliplatin or Irinotecan to LV-5FU containing regimens and using them in a sequential manner after progression. During the last few years, biological therapies targeting Vascular Endothelial Growth Factor (Bevacizumab) and the Epidermal Growth Factor Receptor (Cetuximab, Panitumumab) have further improved the response rates (RR) up to 50%, the PFS up to almost 1 year and the OS now touches 2 years [2].

Sequential treatment remains a valid option for some patients with ACRC. [Ib, A] The optimum use of chemotherapy for ACRC is still being defined. The use of combination protocols as first-line therapy is associated with a significant improvement in median survival of 3.5 months.[3] Although combination chemotherapy is widely used as first line treatment, large, randomized studies have also shown that a staged approach of initial single-agent 5FU treatment upgraded to combination when required is non-inferior to first-line combination chemotherapy[4,5].

However, studies on sequential treatment did not use targeted agents and most patients in these studies were not exposed to all 3 active agents (Fluorouracil, Oxaliplatin, Irinotecan) during the entire course of treatment. The ideal subgroup for treatment with single agent 5 FU is unclear. It could be a possible first line treatment option in patients with multiple metastases and good to moderate performance status, less aggressive disease or comorbid conditions[6].

Randomized studies have shown more efficacy and less toxicity with bimonthly LV-infusional 5FU in patients with ACRC without any change in the survival and it is recommended over the monthly bolus LV- 5FU regimen[7]. [Ib, A] A combination of 5FU with Leucovorine (LV) along with Irinotecan or Oxaliplatin is superior to 5 FU + LV alone. Both Oxaliplatin and Irinotecan based regimens show similar efficacy. [Ib, A]

A randomized phase III study (GERCOR) investigated two sequences: LV, 5 FU, and Irinotecan (FOLFIRI) followed by LV, 5 FU and Oxaliplatin (FOLFOX6), and FOLFOX6 followed by FOLFIRI in ACRC [8]. Both sequences achieved a prolonged survival and similar efficacy. Thus the sequence of drugs used as first line and second line treatment seems to be unimportant in terms of impact on survival. [Ib, A] The toxicity profiles are different for FOLFIRI and FOLFOX. Mucositis, nausea/ vomiting, diarrhea and alopecia are seen more frequently with FOLFIRI, and neutropenia and neurosensory toxicity are more frequent with FOLFOX.

FOLFOXIRI can be considered as another active but toxic first line chemotherapy option. [Ib, A]. 6 months of chemotherapy with FOLFOXIRI (5-FU, LV, Irinotecan, and Oxaliplatin) improved the RR, radical surgical resection of metastases, PFS and OS compared with FOLFIRI in a phase

III randomized controlled trial (RCT).[9] The absolute benefit in survival at 5 years with FOLFOXIRI was 7% and it was associated with increased, but manageable, toxicity (peripheral neurotoxicity and neutropenia).

Due to a better toxicity profile, Oxaliplatin + 5-FU/LV could be preferred as the first-line treatment for ACRC. [Ia, A] A meta-analysis of 7 studies of 5FU-LV with Oxaliplatin and Irinotecan based chemotherapy showed that the Oxaliplatin + 5FU/LV regimens was associated with lower toxicities and equal efficacy to the Irinotecan+ 5-FU/LV regimens [10].

There are a number of Oxaliplatin based chemotherapy regimens available which differ in terms of the 5FU administration and dose. These have a predictable safety profile and acceptable tolerability, regardless of the 5 FU regimen.[11] **[Ib, A]**

XELOX / CapOx (CAP and Oxaliplatin) is non-inferior to FOLFOX-4 as a first-line treatment for ACRC, and may be considered as a routine treatment option for appropriate patients.[12,13] **[Ia, A]** FOLFOX-4 is associated with more grade 3/4 neutropenia and febrile neutropenia , and XELOX with more grade 3 diarrhea and hand-foot syndromes (HFS) . A major issue with CAP containing regimens is that the standard dose of CAP (1 g/m2 twice daily on days 1–14 of a 21 day cycle) is not universally tolerable. CAP tolerance varies between regions and individuals and the doses may need tailoring accordingly.

The 3 commonly used Irinotecan containing regimens (FOLFIRI, mIFL and CapeIRI) were compared in a RCT.[14] **FOLFIRI was associated with a superior PFS and OS and should be the preferred Irinotecan-based regimen in first-line ACRC. [Ib, A]** CapeIRI was associated with higher rates

of severe vomiting, diarrhea, and dehydration and the CapeIRI arm was discontinued due to toxicity concerns.

Targeted therapy:

An important advance in the management of ACRC has been the introduction of targeted treatments. There are 3 drugs which are presently approved for treatment of ACRC. Bevacizumab is a humanized monoclonal antibody against vascular endothelial growth factor (VEGF). Cetuximab is a mouse-human chimeric monoclonal antibody targeting the epidermal growth factor receptor (EGFR) and Panitumumab is a fully human monoclonal antibody against the EGFR.

Bevacizumab:

In addition to its direct anti-angiogenic effects, Bevacizumab (BEV) can also improve the delivery of chemotherapy by altering tumor vasculature and decreasing the elevated interstitial pressure in tumors. The addition of BEV to IFL combination chemotherapy resulted in a 4.7 month improvement in median OS and a 10% improvement in the PFS in patients with ACRC in a RCT [15]. [Ib, A]

However, studies using Oxaliplatin based regimens with BEV showed conflicting results. One study evaluating XELOX/ FOLFOX4 with BEV failed to show an improvement in the OS or RR[16]. Most patients were not treated until progression and this might have been responsible for the poor results. In the TREE-2 study patients with untreated ACRC were randomly assigned to 3 different Oxaliplatin containing regimens [mFOLFOX6, bFOL or CapOx (CAP with Oxaliplatin)] with BEV [11]. Treatment was continued until disease progression or unacceptable toxicity. First-line Oxaliplatin and 5 FU based therapy plus BEV resulted

in a median OS of 23.7 months as compared to 18.3 months with chemotherapy alone. **[Ib, A]**

In a single arm phase 2 study, the combination of BEV with FOLFOXIRI was safe and well tolerated with promising results in terms of PFS [17]. **[IIb, B]** A phase 3 study for the comparison of FOLFOXIRI plus BEV with FOLFIRI plus BEV is in progress.

When using an Irinotecan based regimen with BEV, an infusional 5FU schedule should be preferred. [Ib, A] In a phase III RCT (BICC-C study) the median OS was significantly greater for patients who received FOLFIRI and BEV (28.0 months) when compared with mIFL and BEV (19.2 months). The 1-year survival was 87% and 61% respectively.[14, 18]

Apart from the clinical trials there are 2 large prospective observational studies of BEV with chemotherapy in routine clinical practice (BEAT, BRiTE) showing similar efficacy and safety profile as seen in the clinical trials with a median OS of 22.7 months[19, 20] .

Continued VEGF inhibition with BEV beyond initial progressive disease (PD) can result in significant prolongation of survival. [IIb, B] In the observational BRiTE study, previously untreated patients with ACRC who had PD were classified into three groups: no post-PD treatment, post-PD treatment without BEV (no BBP), and BBP (BEV beyond progression). Median OS was 25.1 months and median PFS 10.0 months in the overall BRiTE population. Median OS rates were 12.6, 19.9, and 31.8 months in the no post-PD treatment, no-BBP, and BBP groups, respectively.

A Cochrane database systematic review[21] and 2 meta-analyses[22, 23] showed that the addition of BEV to

chemotherapy of ACRC prolongs both PFS and OS in first- and second-line therapy. [Ia, A] The objective response rate (ORR) was significantly higher on the BEV-containing arm. While differences in treatment-related deaths and 60-day mortality were not significant, higher incidences in grade III/IV hypertension, arterial thromboembolic events and gastrointestinal perforations were observed in the patients treated with BEV. However, the side effects are predictable and manageable and do not compound the incidence or severity of toxicities from chemotherapy.

Cetuximab:

In a phase 3 RCT (CRYSTAL), Cetuximab plus FOLFIRI improved the PFS of patients with wild type KRAS (WT KRAS) tumors when used in the first-line treatment for ACRC. There was no significant difference in the OS[24]. The rate of surgery for metastases was higher in the Cetuximab–FOLFIRI group (7.0% vs. 3.7%), as was the rate of R0 resection. Among patients with WT KRAS tumors, the RR in the Cetuximab–FOLFIRI group was significantly higher (59.3% vs. 43.2%).The grade 3/4 adverse events more frequent with Cetuximab were skin reactions, infusion-related reactions and diarrhea. [Ib, A]

Another RCT evaluating FOLFOX-4 with or without Cetuximab as first line treatment of ACRC (OPUS) showed a higher ORR for Cetuximab plus FOLFOX-4 (46% v 36%).[25] In patients with WT KRAS tumors, the addition of Cetuximab to FOLFOX-4 signiûcantly increased the ORR (61% v 37%), approximately doubled the R0 resection rate and lowered the risk of disease progression (hazard ratio 0.57) compared with FOLFOX-4 alone. [Ib, A]

The CELIM study evaluated RR and resectability in ACRC with unresectable liver metastases using Cetuximab with FOLFOX-6 or FOLFIRI.[26] The RR was significantly higher in

WT KRAS tumors as against KRAS mutated (MT KRAS) tumors (70% vs. 41%). The resectability rates increased (32% to 60%) post chemotherapy. [Ib, A]

The MRC COIN study evaluated the addition of Cetuximab to FOLFOX / CapOx when given as ûrst-line therapy, but showed results contrary to earlier studies.[27] In the WT KRAS group, PFS was 8.6 months in both arms. OS was >17 months in both arms, but was much shorter than the range of 20-24 months reported in earlier trials In the WT KRAS group, the ORR in the Cetuximab arm was higher (64% vs. 57%). In the group with MT KRAS, PFS and OS were worse in the Cetuximab arm. The addition of Cetuximab to chemotherapy did not improve OS or PFS in WT KRAS. [Ib, A] Cetuximab is likely to benefit patients who received FOLFOX as opposed to CapOx, those with limited metastatic disease, and those who were WT KRAS.

The efficacy (PFS and OS) of Cetuximab is significantly associated with KRAS mutation status[28]. In a phase 3 RCT, treatment with Cetuximab significantly improved median OS (9.5 vs. 4.8 months) and PFS (3.7 vs. 1.9 months) in patients with WT KRAS tumors and not in patients with MT KRAS tumors.

In patients with WT KRAS tumors, Cetuximab added to chemotherapy improves the RR, PFS and respectability in the first line setting. Patients with a tumor having MT KRAS do not benefit. KRAS testing should be done in all patients who will be potential candidates for Cetuximab therapy and Cetuximab should only be considered in patients with WT KRAS. [Ia, A].

Panitumumab:

Panitumumab is a fully human antibody against the EGFR. Panitumumab monotherapy efficacy (RR, PFS, OS benefit)

in ACRC is confined to patients with WT KRAS tumors.[29] KRAS status should be considered in selecting patients with ACRC as candidates for Panitumumab therapy. [1b, A]

In the PRIME study, Panitumumab-FOLFOX4 as first line treatment for ACRC significantly improved median PFS compared with FOLFOX4 (9.6 v 8.0 months) in patients with WT KRAS tumors[30]. A non-significant increase in median OS was also observed (23.9 v 19.7 months). In patients with MT KRAS tumors, median PFS and OS were lower in the panitumumab-FOLFOX4 arm. [Ib, A]

A systematic review of 12 RCTs showed that Cetuximab and Panitumumab improve PFS and OS for patients with ACRC expressing WT KRAS. There is no clear evidence of a benefit of anti-EGFR antibodies, either for PFS or OS for patients with MT KRAS[31]. [Ia,A] The benefit for WT KRAS tumors varies with the chemotherapy used (some difference in the effect with Oxaliplatin or Irinotecan and by choice of Fluoropyrimidine). The significant benefit on OS may be limited to trials using infusional 5FU.

2 meta-analysis of 7 RCTs each using Cetuximab also showed that, in patients with WT KRAS, Cetuximab-based therapy improves PFS and OS resulting in better ORR vs. non-Cetuximab therapy[32, 33]. Its most common and severe AE is skin toxicity that is predictable and manageable. [Ia, A]

Use of two Monoclonal Antibodies targeting both VEGF+EGFR:

The addition of Cetuximab or Panitumumab to BEV along with Oxaliplatin or Irinotecan based chemotherapy resulted in significantly shorter PFS, increased toxicity and inferior quality of life. Mutation status of the KRAS

gene was a predictor of outcome in the Cetuximab group. These combinations are not recommended for the treatment of ACRC in clinical practice. [Ib, A]

Although an earlier randomized phase II study evaluating the combination of Irinotecan, Cetuximab and BEV in patients with Irinotecan-refractory ACRC showed promising results in terms of improved time to tumor progression (TTP), RR and OS, phase III studies (BOND 2) showed that combining EGFR and VEGF inhibition has deleterious effects and this combination is not recommended [34]. [Ib, A]

A phase III RCT (CAIRO 2) showed that the median PFS and Quality of life scores were lower and the grade 3/ 4 adverse events higher in the XELOX, BEV and Cetuximab group as compared to the XELOX and BEV group.[35] The OS and RR did not differ significantly. Patients with MT KRAS tumors who were treated with Cetuximab had significantly decreased PFS. [Ib, A]

Another phase III RCT (PACCE) evaluated Panitumumab added to BEV and Oxaliplatin or Irinotecan based chemotherapy as first-line treatment for ACRC.[36] The median PFS and OS were worse for the Panitumumab arm. KRAS analyses showed adverse outcomes for the Panitumumab arm in both wild-type and mutant groups. [Ib, A]

B) SECOND LINE CHEMOTHERAPY

Second line chemotherapy with Oxaliplatin or Irinotecan based regimens improves the RR and prolongs the PFS and OS. [Ia, A] Present data do not suggest superiority of a particular treatment sequence over the other. [Ib, A]

In a GERCOR study[8], second line FOLFOX 6 was given after progression on FOLFIRI and FOLFIRI given after progression on FOLFOX 6. Both regimens achieved a prolonged survival and similar efficacy. [Ib, A] Another phase II RCT compared CapIri and CapOx as second-line treatment in patients with ACRC, pretreated with a CAP-based combination regimen.[37] The PFS and OS were prolonged to a similar extent with both regimens. Thus, CapIri and CapOx are both effective and tolerable second-line treatment regimens after CAP-based first-line combination therapy [Ib, A]. Severe diarrhea is more frequently associated with second-line CapIri. Oxaliplatin-mediated sensory neurotoxicity after first-line CapOx was reversible under second-line CapIri.

IROX provides an additional option for patients who experience treatment failure with single-agent ûuoropyrimidine therapy. [Ib,A] In patients with ACRC previously treated with 5 FU-LV or CAP as adjuvant or ûrst-line treatment, Irinotecan plus Oxaliplatin (IROX) is superior to Irinotecan alone in prolonging significantly the median OS (13.4 vs. 11.1 months), RR (22% vs. 7%), and median TTP (5.3 vs. 2.8 months).[38] There was an increased incidence of granulocytopenia, diarrhea, and sensory disturbances associated with IROX.

A Cochrane database systematic review of 7 RCTs using second-line chemotherapy for the treatment of ACRC showed that second-line chemotherapy is effective in prolonging TTP and OS in patients with ACRC [39]. [Ia, A]

Bevacizumab:

The addition of BEV to FOLFOX4 improves the median OS to 12.9 months, the median PFS to 7.3 months and RR to 22.7% for patients with ACRC who have been

previously treated with 5FU and Irinotecan[40]. Using BEV as monotherapy results in poorer RR and OS compared to chemotherapy alone and is not recommended. [Ib, A]

Cetuximab:

A combination of Cetuximab and Irinotecan improved the RR (22.9 %), median TTP (4.1 months) and median OS (8.6 months) [41]. Cetuximab has clinically significant activity when given either alone or in combination with Irinotecan in patients with Irinotecan-refractory ACRC. [Ib, A]

Panitumumab:

In patients who have failed first line chemotherapy for ACRC, Panitumumab plus FOLFIRI significantly improved median PFS (5.9 months) and RR (35%) in WT KRAS population as compared to FOLFIRI alone.[42] A non-significant trend toward increased OS was observed; (median OS: 14.5 months vs. 12.5 months). In patients with MT KRAS, there was no difference in efficacy. [Ib,A]

C) CONTINUUM OF CARE IN PATIENTS ON CHEMOTHERAPY

Palliative chemotherapy using conventional cytotoxic drugs and monoclonal antibodies has radically changed the prognosis of ACRC with the median OS almost reaching 2 years. However toxicity of chemotherapy often makes it difficult to continue chemotherapy even in patients who are responding well. Cost of chemotherapy and quality of life (QOL) are other issues involved. Considering the wide range of chemotherapeutic options available and the relatively long survival, using the available treatment options judiciously so as to maximize patient benefit and optimize costs and toxicity is essential.

While patients having tumor related symptoms that affect the QOL will require the most active regimens available that causes rapid tumor shrinkage and palliation, these regimens have significant toxicity and cannot be given continuously even if the response persists. Many other patients will have minimal tumor related symptoms and in these patients, chemotherapeutic drugs should be used in a manner so as to limit the side effects, improve or maintain the QOL and prolong survival.

Although combination protocols using 5FU-LV with either Irinotecan or Oxaliplatin are currently regarded as standard first-line therapies in ACRC, analysis of data from 7 large phase 3 RCTs revealed that the median OS is significantly correlated with the percentage of patients who received all three drugs in the course of their disease but not with the percentage of patients who received any second-line therapy.[3] Hence, the more treatment options are available for treatment, the longer patients will live if they have access to these options. [43]

The challenges in practice when managing patients with ACRC lie in deciding the sequence of agents to be used and in adjusting the intensity of initial therapy (which will yield good response rates, and thus, palliation of tumor related symptoms) with the adverse events which will generally follow and which may compromise the patient's QOL. Thus, rather than follow rigid lines of treatment, a better option is an individualized treatment plan that will maximize benefit (prolong survival and maintain QOL as long as possible) and optimize side effects and treatment related costs while ensuring that all potentially effective treatment options are available to a patient along the lines of a continuum of care.[43]

A number of trials have evaluated different approaches regarding the sequence and duration of palliative chemotherapy. The 'Stop and go' approach involves stopping all chemotherapy drugs after a fixed number of cycles so as to have chemotherapy free intervals, until progression. Maintenance chemotherapy involves stopping some agents and continuing the others. The On-Off strategy involves intermittent administration of chemotherapy. Another strategy reutilizes previously used drugs in different combinations.

The MRCC trial compared efficacy of continuous and intermittent chemotherapy after 12 weeks of LV-5FU based regimens.[44] Patients on intermittent chemotherapy had significantly fewer serious adverse events with no significant difference in OS. The trial showed no clear evidence of a benefit in continuing therapy indefinitely until disease progression. It may be safe to stop chemotherapy after 12 weeks and re-start the same treatment on progression in patients with chemo sensitive ACRC. [Ib, A] However this trial did not use drugs like Oxaliplatin and Irinotecan and so it is unsure if the results can be extrapolated to regimens using these drugs.

The OPTIMOX2 study compared chemotherapy discontinuation with maintenance therapy with LV/5FU after six cycles of mFOLFOX7 chemotherapy in the first-line treatment of ACRC.[45] mFOLFOX7 was reintroduced after tumor progression. The planned complete discontinuation of chemotherapy had a negative impact on duration of disease control and PFS compared with the maintenance therapy strategy. The results from this trial suggest that chemotherapy discontinuation cannot be decided before therapy is initiated in patients with ACRC. [Ib, A]

The MRC COIN trial compared intermittent CT (iCT) with FOLFOX/ CapOx for 3 months initially, with further 3-month courses upon progression to standard continuous chemotherapy.[46] .The iCT arm had signiûcantly less adverse events and better QOL with patients spending less weeks on treatment (median 15 vs. 25 weeks). The median OS was 1.3 months less for the iCT arm. Speciûed non-inferiority could not be proved. The small difference in survival needs to be balanced against the reduced toxicity observed with iCT. [Ib, A]

The OPTIMOX1 study evaluated intermittent Oxaliplatin treatment based on FOLFOX7 which was compared to FOLFOX4.[47] FOLFOX7 was given for six cycles, followed by maintenance without Oxaliplatin for 12 cycles, and reintroduction of FOLFOX7. There was no significant difference in the median PFS, OS and RR. Grade 3 or 4 toxicity was lower in the intermittent Oxaliplatin arm. Oxaliplatin can be safely stopped after six cycles in a FOLFOX regimen without compromising the efficacy. [Ib, A]

The CONcePT trial tested if an intermittent Oxaliplatin (IO) schedule of mFOLFOX7/ BEV allows patients to remain on therapy longer compared to a conventional Oxaliplatin (CO) "treat-to- failure" approach.[48] In the IO arms, patients alternated every 8 cycles with and without Oxaliplatin. The IO arm had significantly longer time to treatment failure (5.6 vs. 4.2 months) along with a trend toward longer PFS and reduced neurotoxicity (10 vs. 24%). CONcePT demonstrated that IO is associated with a significant improvement of TTF, without compromising PFS. [Ib, A]

About 60% of ACRC patients discontinue Oxaliplatin prior to disease progression, due to cumulative neurotoxicity.

The OPTIMOX1 & CONcePT trials provide evidence that intermittent Oxaliplatin-based therapy should be considered in the first-line treatment of ACRC as it can extend time on first-line therapy for Oxaliplatin-based combinations. [Ib, A]

The Spanish MACRO TTD trial compared 6 cycles of XELOX-BEV followed by continuation treatment with XELOX-BEV versus single-agent BEV until disease progression.[49] The hazard ratio for PFS did not meet the criteria for non-inferiority. There was no difference in the OS or adverse event profiles in the 2 arms. Maintenance therapy with single agent BEV can be an appropriate option following induction XELOX-BEV in patients with ACRC. [Ib, A]

A randomized GISCAD trial compared the efficacy of intermittent and continuous FOLFIRI, both administered until progression, in the first line treatment of ACRC.[50] The OS, PFS and the toxicity were comparable in the two groups. Second-line Oxaliplatin-based treatment was administered in a similar percentage (66%) in the two arms. Intermittent therapy with FOLFIRI does not diminish the efficacy of treatment. [Ib, A]

D) THIRD LINE CHEMOTHERAPY

Cetuximab improves OS and PFS and preserves QOL measures in patients with ACRC in whom other treatments have failed. [Ib, A] In a phase 3 RCT in patients who have been previously treated with a 5FU, Irinotecan, and Oxaliplatin, Cetuximab prolonged the median OS (6.1 vs. 4.6 months) and preserved QOL compared to best supportive care (BSC) [51]. A rash of grade 2 or higher was strongly associated with improved survival. [Ib, A]

In another RCT, patients with ACRC who have progressed after standard chemotherapy had a significantly

prolonged PFS and RR with Panitumumab compared to BSC[52]. There was no difference in the OS. Skin toxicities, hypomagnesaemia, and diarrhea were the most common toxicities observed. [1b,A]

E) LIVER LIMITED DISEASE

Almost one third of patients with CRC present with liver-limited metastases of which 15-20% would be primarily resectable. The 5 year survival post resection for CRC liver metastases is 25 - 50 %. There are 3 possible presentations of patients with colorectal liver metastases (CLM): patients with resectable metastatic disease, patients with metastases that are initially unresectable and those patients with extensive disease who are unlikely ever to become resectable. Poor prognostic factors for patients with liver metastases are multiple metastases, >5 cm in diameter, synchronous presentation, lymph node-positive primary and high tumor marker levels.[53]

Patients with a small (<2-cm) solitary metastasis and good prognostic features should probably go for upfront surgery, particularly if there is a risk that the metastasis may disappear after chemotherapy, making resection difûcult. [IV, C]

Other patients (both with resectable and unresectable CLM) which would include a majority of the patients, should be treated upfront with chemotherapy. Perioperative chemotherapy improves the 3 year DFS and should be considered. [Ia, A] In a meta-analysis of 8 trials in patients with resected stage IV CRC, a subset analysis on intra-arterial chemotherapy showed no survival benefit. Trials involving systemic chemotherapy showed a survival benefit (HR, 0.74) [54] and a significant recurrence-free survival benefit. The toxicities of chemotherapy were acceptable in most trials. [Ia, A] In an RCT, perioperative

chemotherapy using 6 cycles of FOLFOX4 for patients with initially resectable CLM did not improve the resection rates. The absolute increase in rate of PFS at 3 years was 7.3% [55]. Postoperative complications occurred more often after chemotherapy than after surgery. [Ib, A]

An analysis of a cohort of patients resected for solitary, metachronous, resectable CLMs where patients who received at least 3 cycles of Oxaliplatin- or Irinotecan-based chemotherapy before liver surgery was compared with those who were resected upfront. There were higher postoperative complications in the chemotherapy group (37.2 vs. 24%). Preoperative chemotherapy did not influence the OS or DFS. Postoperative chemotherapy, improved OS and DFS in patients with metastases of size e"5 cm but not in patients with metastases <5 cm.[56] [III, B]

Preoperative chemotherapy can downsize tumors and control micro-metastases, weeding out patients with aggressive disease who will have a poor prognosis. Patients tolerate chemotherapy better. However chemotherapy can have toxic effects on the liver and preoperative chemotherapy can delay surgery and increase perioperative morbidity.

Adjuvant chemotherapy should be considered in most patients especially those who have not received preoperative chemotherapy. [Ib, A] An RCT evaluating LV-5FU as adjuvant therapy after resection of CLM, showed an improved in the 5 year DFS in the chemotherapy group.[57] A trend towards increased OS was observed. [Ib, A] A pooled analysis of 2 phase III trials (FFCD Trial 9002 & ENG trial) using LV-5FU for resected CLM showed that adjuvant chemotherapy was independently associated with both PFS and OS in multivariable analysis[58]. There was a marginal statistical significance for median PFS and OS in favor of adjuvant chemotherapy.

The total duration of chemotherapy probably should be limited to a maximum of 6 months to include both pre- and postoperative chemotherapy. [IV, C]

Patients whose liver metastases may be rendered resectable by chemotherapy should be considered for a chemotherapy regimen that is most effective (high RR and prolonged PFS). As the RR correlates with the resection rates, the regimens with highest RR should be preferred. The possible regimens could be FOLFOX/ FOLFIRI/ FOLFOXIRI alone or with a biological agent (Cetuximab/ Bevacizumab /Panitumumab). [Ib, A] The treatment should be chosen taking into account the KRAS status (anti EGFR therapy will benefit only patients with WT KRAS), duration to surgery and presence of obstructive symptoms (Bevacizumab can caused increased bowel perforations and an interval of 6 weeks needs to be maintained between Bevacizumab injections and surgery) and the performance status (which will affect tolerance to chemotherapy especially regimens like FOLFOXIRI). In an analysis of studies that enrolled patients with metastases confined to the liver, 24-54% of patients were resected following chemotherapy. A strong correlation was found between RR and the resection rate.[59]. [Ia, A]

In the CELIM RCT, patients with non-resectable CLM received Cetuximab with either FOLFOX6 or FOLFIRI [26]. In a retrospective analysis, a partial or complete response was noted in 70% patients with KRAS WT tumors versus 41% patients with KRAS-MT. Resectability rates significantly increased from 32% to 60% after chemotherapy. [Ib, A]

A phase II prospective study (POCHER) assessed the efficacy of Cetuximab plus chronomodulated Irinotecan, 5FU, LV and Oxaliplatin (chrono-IFLO) administered as neoadjuvant chemotherapy to increase the resectability of CLM.[60] 79% patients had PR. Complete resection was done in 63%

after a median 10 cycles of chemotherapy. Median PFS was 13 months and median OS 37 months with 2-y survival of 68% in the entire population and 80.6% in resected patients. Diarrhea was the limiting toxicity. [IIb, B]

A single arm study using FOLFIRINOX in unresectable CLM showed a RR of 70.6%. 82.4% underwent hepatic resection and 26.5% achieved R0 resection[61]. Two-year overall survival was 83%. FOLFIRINOX, has an acceptable toxicity profile and shows a high response rate in CLM. [IIb, B]

The data from the CELIM and POCHER studies and also from the previously described CRYSTAL and OPUS studies[24, 25] have shown that the addition of Cetuximab to infusional 5FU based chemotherapy regimens signiûcantly improves the PFS, RR (59-70%), and resectability (R0 resection rate) in ACRC patients, compared with chemotherapy alone. Thus, FOLFIRI/FOLFOX plus Cetuximab should be the ûrst-line therapy option for patients with WT KRAS tumors, with BEV substituting for Cetuximab in patients with MT KRAS or unknown KRAS status. [Ib, A]

Patients whose liver metastases will never be resectable should be considered for a continuum of care strategy as described earlier (Section C), so as to optimize chemotherapy with respect to survival, toxicity and costs. [IV, C]

Liver damage can occur following neo-adjuvant chemotherapy but it is generally not clinically significant if the patients are not over treated. BEV treatment is manageable if proper care is taken including maintenance of a 6 week interval between BEV injections and surgery. Surgery should be performed at the earliest so as to minimize the hepatic toxicity of chemotherapy. [IV, C]

The currently available evidence does not support the clinical or investigational use of Fluoropyrimidine-based HAI alone for the treatment of patients with unresectable CLM. A Cochrane database systematic review of 10 RCTs comparing hepatic arterial infusion (HAI) to systemic chemotherapy for the treatment of unresectable CLM showed that the greater RR obtained with HAI does not translate into a survival advantage over Fluoropyrimidine alone systemic chemotherapy [62]. **[Ia, A]**

CHEMOTHERAPY REGIMENS AND DOSES:

Regimen	Drugs, doses and schedule
LV5FU2 regimen[47]	2-hour infusion of l-LV 200 mg/m2 or dl-LV 400 mg/m2 followed by an FU 400mg/m2 bolus and 46-hour 3,000mg/m2 infusion every 2 weeks
FOLFOX4[47]	2-hour infusion of Leucovorin isomers l-LV (100 mg/m2) or dl-LV (200mg/m2) followed by an FU bolus (400mg/m2) and 22-hour infusion (600mg/m2) for 2 consecutive days every 2 weeks, with Oxaliplatin (85mg/m2) as a 2-hour infusion on day 1.
FOLFOX6[8]	Oxaliplatin 100 mg/m2 on day 1, given as a 2-hour infusion in 500 mL dextrose 5%, concurrent with l-LV 200 mg/m or dl-LV 400 mg/m2 as a 2-hour infusion, and followed by bolus FU400mg/m2 and a 46-hour infusion FU 2,400 mg/m2 , every 2 weeks
mFOLFOX6[11]	Oxaliplatin 85mg/m2 IV with LV 350mg IV over 2 hours plus FU400mg/m2 IV bolus and 2,400mg/m2 continuous infusion over 46 hours every 2 weeks

FOLFOX7[47]	2-hour infusion of l-LV 200 mg/m2 or dl-LV 400 mg/m2 followed by an FU 46-hour infusion of 2,400 mg/m2 every 2 weeks, with Oxaliplatin 130 mg/m2 as a 2-hour infusion on day 1, every 2 weeks
bFOL[11]	Oxaliplatin 85 mg/m2 IV on days 1 and 15 and LV 20 mg/m2 IV over 10 to 20 minutes followed by FU 500 mg/m2 IV push on days 1, 8, and 15 every 4 weeks
CapOx/ XelOx[11]	Oxaliplatin 130mg/m2 IV on day 1 and Capecitabine 1,000 mg/m2 orally twice daily on days 1 to 15 every 3 weeks
FOLFIRI[14]	Irinotecan, 180 mg/m2 IV over 90 min; LV, 400 mg/m2 IV over 2 h; 5 FU, 400 mg/m2 IV bolus; FU, 2,400 mg/m2 IV continuous infusion over 46 h every 2 weeks
IFL[15]	Irinotecan 125 mg/m^2 IV infusion, with bolus 5 FU and Leucovorine, (Fluorouracil 500 mg/m2 and Leucovorin 20 mg/m2) once weekly for 4 weeks; cycle repeated every 6 weeks
mIFL[14]	Irinotecan, 125 mg/m2 IV over 90 min on days 1 and 8; LV, 20 mg/m2 IV bolus on days 1 and 8; FU, 500 mg/m2 IV bolus on days 1 and 8 every 3 weeks
CapIri[14]	Irinotecan, 250 mg/m2 IV over 90 min on day 1; Capecitabine, 1,000 mg/m2 by mouth twice per day on days 1-14 every 3 weeks

FOLFOXIRI[17]	Irinotecan 165 mg/m^2 on day 1, Oxaliplatin 85 mg/m^2 on day 1, folinate 200 mg/m^2 on day 1, and 5FU 3200 mg/m^2 for 48 h continuous infusion starting on day 1 and repeated every 2 weeks
IROX[38]	Oxaliplatin 85 mg/m2 administered as a 120-minute intravenous [IV] infusion followed by Irinotecan 200mg/m2 administered as a 30- or 90-minute IV infusion every 3 weeks
Irinotecan[38]	Irinotecan 350mg/m2 administered as a 90-minute IV infusion every 3 weeks
Bevacizumab[19]	5 mg/kg every 2 weeks (5-FU-based regimens) or 7.5 mg/kg every 3 weeks (Capecitabine-based regimens). Bevacizumab is administered i.v., initially over 90 min. If the ûrst infusion is well tolerated, the second is delivered over 60 min; if the 60-min infusion is well tolerated, all subsequent infusions are delivered over 30 min.
Cetuximab[35]	400 mg/m^2 of Cetuximab , given intravenously on day 1 of the first treatment cycle, followed by 250 mg/m^2 of Cetuximab given weekly thereafter.
Panitumumab[30]	6 mg/kg intravenously (IV) over 1 hour at every 2 weeks on day 1 before infusional 5FU chemotherapy. If tolerated, subsequent infusions can be administered over 30 minutes

MMC+5FU with radiation for anal canalcancer	Mitomycin 10mg/m2 IV bolus Day 1 and Day 29 5FU 750-1000 mg/m2/d IV, days 1-4 and 29-32 with concurrent RT for 5 weeks
Cisplatinum+5FU for metastatic anal canal cancer	Cisplatin 100 mg/m2 IV Day 2 5FU 750-1000 mg/m2/d IV days 1-5 Repeat every 4 weeks

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CHAPTER-9

Other Local Treatment Modalities

Sterotactic Body Radiation Therapy (SBRT) for Liver Metastasis

Stereotactic Body Radiotherapy (SBRT) is a novel treatment modality which delivers very high doses of radiation to primary or metastatic tumors at various extra cranial sites (like liver) with high precision. While whole liver has modest tolerance to radiation (30-35 Gy/1.5-2 Gy per fraction)(1), partial liver volume can tolerate very high doses of radiation (60 in 3 fractions over one week) without the risk of radiation induced liver disease such that excellent local control of solitary or oligo metastasis can be achieved (2, 3) (Level III, Grade B). Though no comparative or randomized studies are available between SBRT and other established modalities for treatment of liver metastasis from CRCs, quality assured prospective studies using high dose SBRT have reported 24 months local control rates of 57-92% (4-7) that are similar to metastatectomy(8, 9), transarterial chemotherapy (TACE) (10) or Radiofrequency Ablation (RFA) (11). SBRT hence provides noninvasive means of delivering local ablative therapy for liver metastasis from CRC. (Level III, Grade B).

Eligibility Criteriae

1. Resectable/ Unresectable Solitary Metastasis not more than 8 cm in greatest dimension.
2. Resectable/ Unresectable metastatic lesions not more than 3-4 in number and not more than 3 cm in maximum dimension.
3. Partial response following Radiofrequency Ablation (RFA) or Transarterial Chemoembolisation (TACE)
4. Recurrence after metastatectomy, RFA or TACE alone or in combination.
5. Liver metastasis with sub diaphragmatic/ perihilar/ perivascular location or complicated with Portal Vein Thrombosis (i.e. not amenable for RFA/TACE).

Contraindications

1. Previous abdominal irradiation.
2. Less than 700 cc of normal liver (after excluding target volume for radiation)
3. Active viral hepatitis/ clinically significant liver failure.

Techniques for SBRT

SBRT can be executed in radiation oncology facilities with Linear Accelerator with 3DCRT/IMRT facility with or without body frame/respiratory gating (2) or active breathing control (Level III, Grade B). In the absence of breathing control systems individualized tumor movement should be assessed prior to ascertaining target volume. Availability of high precision image guided units like Cyberknife, Tomotherapy, Novalis may provide opportunities of better dose conformity however is not mandatory. In either case high emphasis on stringent quality assurance for treatment execution is strongly recommended (12).

SBRT: Target Delineation

Gross Tumor Volume (GTV): Should be delineated on contrast enhanced images immediately acquired after intravenous injection.

Clinical Target Volume (CTV) : Additional 5-7 mm margins are necessary (13) (Level IV, Grade C) however many institutions do not adapt any margins(3) beyond GTV while treating liver metastasis (Level III, Grade B)

Internal Target Volume (ITV): In institutions with access to 4D CT Simulation ITV should be generated for all phases of respiration. Alternatively fluoroscopic record of respiratory movement may be obtained on a conventional simulator.

Planned Target Volume (PTV): 5-15 mm margin may be used depending on whether or not breathing modulation is applied. Wherever available respiratory gating and active breathing control should be adopted as it facilitates SBRT delivery within 3 mm PTV margin (14) (Level III, Grade B)

SBRT : Dose Fractionation Schedules

Significant improvement in local control has been reported with increasing doses of radiation. SBRT studies have reported 3 year local control of 8.1%,59% and 89.3% for SBRT dose of <36 Gy, 36-54 Gy and 54-60 Gy (15) (Level IV, Grade C). While it's important to meet dose volume criteriae of normal structure (especially for normal liver outside the target), it's clear that ability to deliver high doses may be associated with good to excellent in-field tumor control rates. Very high doses of SBRT (60 Gy/3 fractions/one week) may be delivered provided at least 700 cc of normal liver receives no more than 15 Gy and the maximum dose to small bowel, spinal cord and kidneys is restricted below their tolerance threshold (2) (Level III,

Grade B).The prescription isodose for SBRT has varied from 65-95% isodose line and needs individualization on the basis of dose to the adjacent normal organs.

Local Control Rates with SBRT

As enumerated above dose response relationship exists in terms of local control. Prospective studies have employed varying doses. Following is the summary from quality assured prospective studies

SBRT in patients pretreated with Surgery, RFA and TACE

SBRT can be safely executed in patients who have undergone metastatectomy or RFA at an earlier date provided that dose to uninvolved normal liver is restricted below the prescribed threshold. Patients who have undergone systemic chemotherapy or TACE at an earlier date can be treated with SBRT. However, if TACE or chemotherapy is planned immediately before or after SBRT it's advisable to have a minimum gap of 2 weeks between the two modalities.(3)

Applicability in Indian Scenario

The infrastructure and personnel needs for SBRT necessitate execution within tertiary care or specialized centers with access to Linear Accelerator with 3DCRT/IMRT facilities. Recommendations of Task Group 101 should be followed for execution of quality assured SBRT (12). While no direct cost efficacy analyses exist within the Indian scenario, the cost efficacy is expected to be superior to other competing modalities for treatment of liver metastasis from CRC.

Level of Application in Indian Scenario: A-B

Author	Level	Prescription Isodose (%)	Dose	No: of pts/ F/Up (mths)	Local Control	Grade III/IV Toxicity
Bloomgren(16)	III	65%	20-45 Gy/2-4#	17/ 9.6	1 yr:95%	11%
Wulf	III	65%	30 Gy/3#	23/ 9	1yr: 76% 2yr: 61%	None
Herfarth	III	80%	14-26/1#	33/ 5.7	1yr:71%	None
Mendez R	III	65%	37.5Gy/3#	14/ 12.9	1 yr: 100% 2 yr: 86%	Grade III:21%
Kavanagh	III	80-90%	60 Gy/3#	21/19	1.5: 93%	None
Katz	III	80%	50 Gy/5#	69/ 14.5	20mths: 57%	None
Gunven	IV	65%	20-45Gy/2-4#	7/ 117	5-14yr:100%	None
Rusthoven	III	100%	36-60 Gy/3#	47/ 16	1 yr :95 % 2 yr :92 %	None
Lee	III	100%	27.7-60 Gy/6 #	70/ 10.8	1 yr: 71%	Grade III:10%
TMH Series unpublished	III III	60-70%	30-37.5Gy/3#	7/ 9	1yr: 50%	None

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Radiofrequency Ablation for Hepatic Metastases of Colorectal Carcinoma

Radiofrequency ablation (RFA) is one of the most promising thermal ablation techniques and has beenhas been used as a treatment for primary and metastatic liver tumors. Hepatic lesions which are inoperable due to extent or multinodularity of disease or concurrent medical disability are suitable for RFA [2] if they fall in following selection criteria [1 , GOE IV]

1) Preferentially patients with =/< 5 lesions can be treated with RFA
2) The lesion should be </= 3cm at its longest axis to achieve best rates of complete ablation
3) No extrahepatic disease or whatever limited extra hepatic disease , should be curable. [1]

Tumors located on the surface of liver, adjacent to gall bladder or bowel and adjacent to blood vessels can be treated in more experienced hands as the rate complications and incomplete ablation are more at these locations. The absolute contraindication for patients otherwise falling in the above selection criteria is uncorrectable coagulopathy. [3, GOE IV]. Relative Contraindications for RFA are as follows:

A. Tumour located <1 cm from the main biliary duct (due to risk of delayed stenosis of the main biliary tract);
B. Intrahepatic bile duct dilation;
C. Bilioenteric anastomosis; and

RFA is an effective local abalative technique and is relatively safe with low mortality rate (0%-2%) [4, GOE III]. Reported mortality of RF ablation is much less than that of surgical resection o% - 0.5% and 0% to 6.6% respectively [5]. Long-term survival in three series including patients with tumor each d" 5 cm, the 5-year survival rate ranged 24-44% at 5 years [22, 23, 26]. When RFA was performed in patients with small (d"4 cm) solitary hepatic colorectal metastases, a 40% 5-year survival rate was demonstrated [6]. This conclusion is supported by the interim analysis of a randomized controlled trial comparing chemotherapy plus RFA versus chemotherapy alone in CRC metastatic to the liver [7, GOE Ib]. The overall survival rates in their studies approach those of surgical resection [5, GOE III]. Solbiati et al [8] reported the results of RFA to treat 179 hepatic metastases in 117 patients with colorectal carcinomas. In their study, the median survival was 36 months and the 1, 2 and 3- year survival; rates were 93, 69 and 46%, respectively.

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CHAPTER-10

Squamous Cancer of Anal Canal

Introduction

Carcinoma of Anal Canal is a relatively uncommon malignancy constituting only 4% of all lower alimentary tract cancers and 1.6% of all digestive system malignancies with peak age incidence between 55-65 years (1). In India, anal canal malignancies accounts for 0.46% of all cancers (2). Upto 36% patients present with advanced T3-T4 disease with synchronous inguinal lymph node metastasis in upto 11% of patients (3). The relative risk of anal cancer is reported to be 37.7- 84.4 times in patients with Acquired Immunodefficiency Syndrome (4)

Historically the standard treatment of anal cancer was abdominoperineal resection (APR) with an estimated 5 year survival of 40-70%. The use of concurrent chemoradiotherapy is associated with 5 year disease free survival of 50-70% and allows sphincter and function preservation in 2/3rd of the patients and is accepted as the current standard of care(5-7). (Level Ib, Grade A)

Staging Investigations:

Mandatory

Digital Rectal Examination and Biopsy.

FNAC of enlarged inguinal nodes.

Chest X Ray or CT Thorax.

CT/MRI of Abdomen/Pelvis.

Optional

PET-CT scan

(The role of PET scan and/ or sentinel lymph node biopsy for sentinel lymph node assessment remains investigational and is not recommended for routine lymph node staging (8) (Level III, Grade B)

Other Pretreatment Investigations

HIV testing with CD4 counts in patients testing positive for HIV.

Routine Complete Blood Count/Biochemistry.

Pretreatment Procedures

Sperm Banking

Ovarian Transposition/ Choice of posttreatment hormone therapy.

Defunctioning colostomy in those with vaginal involvement.

Stage Wise Treatment Recommendations:

T1N0

Local excision remains the standard of care for very early T1 lesions in patients in whom adequate excision can be performed without compromising sphincter function

(Level III, Grade C). If sphincter function is at risk than 5FU/Mitomycin based concurrent chemoradiotherapy should be considered. Radiation dose should be at least 45-50 Gy. Boost may not be needed for early lesions.

T2-T4/N0/N+

The recommendations are based on phase III randomized studies (5-7)

Chemoradiotherapy with 5-Flourouracil (5-FU) and Mitomycin C is recommended as the first line of treatment. Addition of chemotherapy to radiation leads to 19-22% improvement in 4 year local control from 43-52% to 65-71%) ((5, 7) and 32% improvement in colostomy free survival (5). Mitomycin independently contributes towards improving locoregional control and colostomy free survival. Though hematological toxicity increases from 7 to 20% with addition of Mitomycin it should not be omitted from concurrent chemoradiotherapy (6). (Level Ib, Grade A). Salvage surgery (APR) should be reserved for those who fail this regimen. Complete regression may take 3-6 months. The decision regarding surgical salvage should be deferred to more than 6 months after chemoradiotherapy. In all cases biopsy should be done before proceeding with radical salvage surgery.

Is there any role of neoadjuvant chemotherapy prior to chemoradiation?

The role of neoadjuvant chemotherapy has been evaluated in phase III randomized trial (RTOG-9811) (9). The study randomized patients to either neoadjuvant cisplatin and 5 FU followed by 5FU/ Cisplatin based chemo radiotherapy or 5 FU/Mitomycin C based chemo radiotherapy alone. At a median follow up of 30 months there was no difference in local control or overall survival. None of the other

ongoing trials are independently evaluating neoadjuvant chemotherapy.

Recommendation: The available evidence does not support the use of neoadjuvant chemotherapy prior to chemo radiotherapy (Level Ib, Grade A)

Is Cisplatin superior to Mitomycin C for concurrent chemoradiotherapy?

RTOG 9811 (9) used cisplatin in the investigational arm, however the interpretation of results was confounded by the use of neoadjuvant chemotherapy in the same arm precluding direct comparison of cisplatin with mitomycin C. The ACT II trial (10) randomizes patients to mitomycin C and cisplatin and to receive maintenance 5FU/ cisplatin chemotherapy or not. The final results of ACT are awaited.

Recommendation: There is insufficient evidence to support the use of cisplatin over mitomycin C. In the absence of robust evidence 5FU/mitomycin C based chemoradiotherapy remains the standard of care.

What is the optimal boost dose, overall treatment time?

The total dose, overall treatment time (OTT) and schedule of radiotherapy has varied within the published randomized trials precluding uniform recommendations.

Is Boost Mandatory?

While the EORTC studies uniformly used boost for all patients after a planned gap of 6 weeks (5), The RTOG (6) and UKCCCR (7) studies used boost irradiation only for patients who had biopsy proven or clinically residual disease after phase I of irradiation. The boost dose in the aforesaid studies has varied from 9 Gy to 20 Gy delivered

either through conventionally fractionated external beam irradiation or an interstitial implant. There is no randomized evidence evaluating the benefit of boost dose towards improving local control or colostomy free survival. Retrospective evaluation of outcomes of UKCCCR Phase III randomized study questions the benefit of boost after a 6 week gap (11). Hence the ongoing UKCCCR studies (ACT II) (10) have omitted the planned gap between phase I radiation and boost. Retrospective evaluation of outcomes at our own institution demonstrates improved local control and colostomy free survival with higher doses when no planned treatment gap was incorporated (12) None of the ongoing studies evaluate the question of boost vs no boost however FFCD ACCORD-3 study is investigating the role of low (15 Gy/8 fractions) vs high dose boost (20-25 Gy/11-14 fractions) (13).

Recommendation:

On the basis of available data boost is recommended for all patients with T3 and T4 tumours and T1/2 tumours with residual disease after phase I (45-50 Gy). Planned gaps should be avoided and boost initiated as early as feasible (Level III, Grade B)

Overall Treatment Time.

While the European philosophy has relied on split course radiotherapy, American trials have avoided planned interruptions during RT; however mandate reassessment for residual disease for addition of boost after a short gap (6, 9). Pooled data from RTOG 8704 and RTOG 9811 studies show that prolonged OTT was positively associated with time to colostomy failure. OTT >53 days was associated with reduction in colostomy free survival ($p=0.05$) (14) (Level IIa, Grade B). Retrospective evaluation

of UKCCCR data suggests lower incidence of locoregional relapse when overall treatment time was maintained less than 2 months. This effect persisted after adjusting for baseline covariates (29% vs 61%;o=0.01) (11) (Level IIB, Grade B).

Recommendation:

Though there is no randomized data evaluating the effect of gap, retrospective evaluation of data from randomized studies suggests that planned gap should be avoided while delivering chemo radiotherapy for anal cancer (Level III, Grade B)

Should intensity modulated radiotherapy (IMRT) be recommended as a standard treatment technique for chemoradiotherapy in anal canal.

High incidence(14-47%) of grade III skin toxicity (i.e. moist desquamation) has been observed in patients undergoing chemo radiotherapy, often leading to treatment interruption and loss of treatment intensity (5-7). On analysis of our institutional data 37% incidence of acute grade III skin toxicity was observed (12). Newer techniques like IMRT can substantially reduce normal tissue doses (15) and can thereby decrease incidence of skin toxicity to less than 10%. Prospective clinical data also supports the use of IMRT for reducing acute hematological and bowel toxicity (16, 17). The benefit of IMRT in reducing late effects is not known

Recommendations:

IMRT reduces on treatment acute toxicity and interruptions during chemo radiotherapy (Level III, Grade B). Wherever feasible IMRT should be offered. Centers that lack facility for IMRT should use conformal techniques to reduce

marrow and small bowel doses or consider referral to centers with access to IMRT facilty.

Important considerations in HIV Positive patients

Prospective studies comparing response and toxicity in HIV positive and negative cohort have reported heterogenous outcomes. No differences has been observed in initial response rate and 5 year overall survival of HIV negative and positive cohort. However, the local control rates have been consistently lower in the HIV positive cohort (38%-81% vs 78%-90%)(18-20). Heterogeneity has also been observed in reported acute toxicity rates. While few single institutional studies have identified no difference in acute toxicity between HIV positive and negative patients (19, 20) a relatively large multicentric study recorded higher grade III-IV toxicity with 5FU/mitomycin C based chemoradiotherapy (skin toxicity: 35% vs 17%;p=0.04; hematological toxicity 33% vs 12%;p0.08) often translating into prolonged OTT. No correlation was observed between toxicity ,local response rates and CD4 counts. Within the same study no severe hematological toxicity was observed in HIV positive patients receiving cisplatin/5FU based chemo radiotherapy (18).

Recommendation:

Though single institutional studies have reported safety of 5FU/mitomycin C based chemoradiotherapy in HIV positive patients on antiretroviral treatment (with moderate to low CD4 counts) caution is recommended while executing treatment. Higher acute toxicity may be anticipated. 5FU/Cisplatin based chemoradiotherapy may be associated with lower hematological toxicity. Integration of newer radiation techniques is recommended for toxicity reduction. Lower rates of sphincter preservation

in the reported studies necessitate appropriate patient counseling regarding higher chance for need of salvage surgery. (Level III, Grade B)

Applicability of Recommendations in Indian Scenario:

A 20 year review of our institutional data (1985-2005) of 257 patients confirms the efficacy and safety of 5FU/ mitomycin based chemoradiotherapy within the Indian population(12). No prospective data with newer radiation techniques is available. Prospective studies integrating IMRT should be undertaken

Level of Applicability

Concurrent chemoradiotherapy for Ca Anal Canal: Level A

IMRT for Ca Anal Canal: Level B

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APPENDIX-1

Tata Memorial Centre - COLONIC CARCINOMA REPORT
(not to be used for APTIs, low ANTs and rectosigmoid colectomy)
Name : .....Hospital no: ..... Report no: .....
Grossed by:.....Reported by:.....Consultant:.....

GROSS DESCRIPTION

Received a specimen of Total colectomy / Right hemicolectomy / left hemicolectomy / Sigmoid colectomy measuring cm in length. An ulceroproliferative / infiltrative tumour measuring cm is seen in the _____. It is _____ cm from the proximal and _____ cm from the distal resection margin. It involves the bowel circumferentially / partly in anterior quadrant / partly in posterior quadrant. The tumour is seen invading the wall of colon up to the . Tumour site perforation is present (pT4) / absent.

_____ regional lymph nodes are dissected from the specimen at the level of the tumour and _____ lymph nodes are dissected above the level of the tumour, _____ lymph nodes are dissected below the level of the tumour _____ apical nodes are dissected. Grossly, the lymph nodes are ech, grey / firm, whitish.

The terminal ileum measures cm and shows no abnormality
Appendix measures _____ cm and shows _____.

Sections:

APPENDIX-2

Tata Memorial Centre - COLONIC CARCINOMA REPORT

(not to be used for APRs, low ARs and rectosigmoid colectomy)

Name : .....Hospital no: ..... Report no: .....

Grossed by:.....Reported by:.....Consultant:.....

HISTOLOGY

Total colectomy / Right hemicolectomy / left hemicolectomy / Sigmoid colectomy (post chemotherapy and radiotherapy)

differentiated adenocarcinoma of the colon/ rectum. Tumour

invades the .....(pT)

Lymphovascular emboli are not seen / seen.

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

Doughnuts are free of / involved by tumour.

Lymph Nodes at the level of tumour:

Lymph nodes above the level of tumour:

Lymph nodes below the level of tumour:

Apical nodes:

Rest of the colonic segment shows _____

The terminal ileum

The appendix

IMPRESSION

Total colectomy / Right hemicolectomy / left hemicolectomy / Sigmoid colectomy (post chemotherapy and radiotherapy)

Adenocarcinoma; Completely resected (R0) / R1 / R2

TNM (UICC 7th edition) T N / yT yN

Signature:

Registrar: Consultant: Date:

APPENDIX-3

TNM; AJCC 7th Edition

T1 into the submucosa and not beyond
T2 into the muscularis propria and not beyond
T3 through the muscularis propria into subesrosa, serosa is free
T4a perforates visceral peritoneum
T4b directly invades other organ or structures

N1: Metastasis in 1 to 3 regional lymph nodes.
N1a:1 node
N1b: 2 – 3 nodes
N1c: satellites in subserosa, *without* regional nodes,
N2 Metastasis in 4 or more regional lymph nodes ,N2a: 4 – 6 nodes, N2b: 7 or more

Distant metastasis M1
M1a one organ
M1b > one organ or peritoneum

Tumour regression grading system (TRG score):
TRG 1 No viable cancer cells
TRG 2 Single cells or small groups of cancer cells
TRG 3 Residual cancer outgrown by fibrosis
TRG 4 Significant fibrosis outgrown by cancer
TRG 5 No fibrosis with extensive residual cancer

Please note that TNM 7h edition has deleted pM0 and pMX categories as part of pathology report

APPENDIX-4

AJCC Staging of Anal Canal Ca

Primary Tumor:

Tx: Primary tumor cannot be assessed.

T0: No evidence of primary tumour.

Tis: Carcinoma in Situ (Bowen's disease, high grade squamous intraepithelial lesion,anal intraepithelial neoplasia II-III)

T1: Tumor 2 cm or less in greatest dimension.

T2: Tumor more than 2 cm but not more than 5 cm in greatest dimension.

T3: Tumor more than 5 cm in greatest dimension.

T4: Tumor of any size invading any organ (s). e.g, vagina,urethra, bladder.

Note: Direct invasion of rectal wall, perirectal skin, subcutaneous tissue or the sphincter muscle is not classified as T4.

Regional Lymph Nodes

Nx: Regional lymph nodes cannot be assessed.

N0: No regional lymph node metastasis.

N1: Metastasis in perirectal lymph nodes.

N2: Metastasis in unilateral internal illiac and /or inguinal lymph node (s).

N3: Metastasis in perirectal and inguinal lymph nodes and/ or bilateral internal iliac and/or inguinal lymph nodes.

Distant Metastasis:

M0: No evidence of distant metastasis.

M1: Distant Metastasis.

Stage Groupings

	T	N	M
Stage 0:	Tis	N0	M0
Stage I:	T1	N0	M0
Stage II:	T2	N0	M0
	T3	N0	M0
Stage IIIA:	T1-3	N1	M0
	T4	N0	M0
Stage III B:	T4	N1	M0
	Any T	N2-3	M0
Stage IV:	Any T	Any N	M1

APPENDIX-5

Commonly Used Combination Regimens

Adjuvant therapy

- Oxaliplatin + 5-fluorouracil + leucovorin ($FOLFOX_4$)
- Capecitabine with or with out radiation
- 5-Fluorouracil + leucovorin (weekly schedule, low dose leucovorin)
- LV5FU (Mayo regimen)

Neo-Adjuvant therapy

- Oxaliplatin + 5-fluorouracil + leucovorin ($FOLFOX_4$)
- Irinotecan + 5-fluorouracil + leucovorin (FOLFIRI regimen)
- Along with cetuximab in K-RAS Wild type.
- Along with bevazucimab in K-RAS muted

Metastatic disease

- Capecitabine
- Capecitabine + oxaliplatin (CAPEOX)
- Oxaliplatin + 5-fluorouracil + leucovorin ($FOLFOX_6$)

- Oxaliplatin + 5-fluorouracil + leucovorin (mFOLFOX$_7$)
- FOLFOX$_4$ + bevacizumab
- Irinotecan + 5-fluorouracil + leucovorin (FOLFIRI regimen)
- Capecitabine + Inrinotecan (CAPEIRI)
- Cetuximab monotherapy or combined with FOLFOX/ FOLFIRI

Anal canal

- Mitomycin C + 5 5-fluorouracil + radiation (Primary treatment
- Cisplatin + 5-fluorouracil (Palliative treatment)