National Guidelines for Colorectal Cancer (CRC)

Screening, Diagnosis, Management and Follow up.

1st Edition

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Validated by		**Approved by**	
Name	Dr.Qamra Al Sariri	**Name**	Dr. Badriya Al Rashidi
Designation	Director General	**Designation**	Director General
Signature		**Signature**	
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This Colo-Rectal Cancer task force comprised of:

Name	Title/ Institution
Dr. Suad Sulaiman Al-Kharusi	Consultant - Oncologist and Director of National Oncology Centre at Royal Hospital
Dr. Abdulaziz Mohammed Al-Farsi	Senior. Consultant - Oncologist - Royal Hospital.
Dr. Rashid Mohammed Al-Alawai	Consultant - Colorectal Surgeon & Director General of Khoula Hospital
Dr. Ahmed Hamed Al-Wahaibi	Senior. Consultant - Family Medicine at Primary Health Care Department.
Dr. Ibrahim Khamis AL-Alawi	Senior. Consultant - General & Colorectal Surgeon AT Armed Forces Hospital.
Dr. Itrat Mehdi	Senior. Consultant - Oncologist and Head of Medical Oncology at Royal Hospital
Dr. Najla Abdulamir Al-Lawati	Specialist - Head of Surveillance of NCD.
Dr. Omar AL-Siyabi	Consultant - Gastroenterologist at Royal Hospital.
Dr. Thuraya Nasser Al-Hajri	Consultant - Radiation Oncologist & head of Radiotherapy at Royal Hospital.
Dr. Zaima Yousuf AL-Rawahi	General physician at Hospitals & Specialized Medical Centers Affair, Directorate General of specialized medical care.

Contents

Acronyms

5-FU	5-fluorouracil (anti-cancer drug)
AFP	Alpha fetoprotein
AJCC	American Joint Committee on Cancer
APE	Abdominoperineal excision
APR	Abdominal perineal resection
ASR	Age-standardized rate
ASRs	Age-standardized incidence rates
BCLC	Barcelona clinic liver cancer
BID	Two times a day
BMI	Body Mass Index
BSC	Best supportive Care
C1	Cycle 1
CAGB	Cancer gallbladder
CAPOX	Capecitabine and Oxaliplatin
CBC	complete blood count
CCA	Cholangiocarcinoma
CCD	Charge Coupled Device
cCR	Clinical complete response
CCRT	Concurrent chemoRadiotherapy
CEA	Carcinoembryonic Antigen
CIVI	Continuous intra venous Infusion
cN	Clinical lymph node staging
CR	Complete response
CRC	Colorectal Cancer
CRM	Circumferential resection margin
CRT	ChemoRadiotherapy
CT	Computerized tomography

cT	Clinical tumor staging
CTC / CAT	Computed tomography colonography
d1	Day 1
DCBE	Double-contrast barium enema
DFI	Disease free Interval
DFS	Disease-free survival
dMMR	Deficient mismatch repair
DNA test	Deoxyribonucleic Acid Test
DPD	Dihydropyrimidine dehydrogenase
DRE	Digital Rectal Exam
EAUS	Endoanal Ultrasound
EBRT	External beam radiotherapy
EGFR	Epidermal growth factor Receptors
EMR	Endoscopic mucosal resection
EMVI	extramural venous invasion
ERCP	Endoscopic retrograde chloangio pancreatography
ERUS	Endorectal ultrasound
EUA	Examination under anaesthetic
EUS	Endoscopic ultrasound
FAP	Familial adenomatous polyposis
FISH	Fluoroscent in situ hybridization
FNA	Fine needle aspiration
FOBT	Fecal occult blood test
FOLFOX	Folinic acid, fluorouracil and Oxaliplatin
Fr	Fraction of Radiotherapy
FU	Follow up
GCC	Gulf Cooperation Council
GEJ	Gastroesophageal junction
GIST	Gastrointestinal stromal tumour

Gy	Gray (unit used to measure the total amount of radiation)
H and E	Hematoxylin and Eosin
HCC	Hepatocellular carcinoma
HIPEC	Hyperthermic (or Heated) Intraperitoneal Chemotherapy
HIV	Human immunodeficiency virus
HNPCC	Hereditary nonpolyposis colorectal cancer
HPV	Human Papilloma virus
IBD	Inflammatory bowel disease
IDA	Iron deficiency anemia
IHC	Immunohistochemistry
IV	Intra Venous
LA	Locally advanced
LDH	Lactate dehydrogenase
LE	Local excision
LFT	Liver function test
LN	Lymph node
LVI	Lymphovascular Invasion
M	Metastases
m…	Modified
mCRC	Metastatic colorectal cancer
MDT	Multi-disciplinary Team/tumour board
MRCP	Magnetic resonance cholangiopancreatography
MRF	Mesorectal fascia
MRI	Magnetic Resonance imaging
MSI	Microsatellite instability
MSI-H	Micro satellite instability High
MT	Mutant type
MTB	Mutational tumour burden
N	Nodes

NA	Neoadjuvant
NACT	Neoadjuvant chemotherapy
NART / NARx	Neoadjuvant radiation therapy
NRAS	Neuroblastoma RAS Viral Oncogene Homolog
OD	Once a day
OGD	Oesophago gastro duodenoscopy
OS	Overall Survival
p16	A tumour suppressor protein
PCP	Primary care physician
pCR	Pathologic complete response
PD	Progressive disease
PDGFRA	Platelet derived growth factor receptor antagonist
PD-L1	Programmed death-ligand 1
PET	Positron Emission tomography
PNI	Perineural Invasion
PO	Per Oral
PR	Partial Response
PS	Performance status
pT	Primary tumor
pT4	Pathological stage
PTC	Percutaneous transhepatic cholangiogram
PV	Portal vein
QID	Four times a day
QoL	Quality of life
RAPIDO	Rectal cancer And Preoperative Induction therapy followed by Dedicated Operation
RFA	Radiofrequency ablation
RR	Response rate
RT	Radiotherapy

Rx	Prescription / Treatment
SBRT	Stereotactic body radiation therapy
SCC	Squamous cell carcinoma
SCPRT	short-course preoperative radiotherapy
SD	Stable disease
SMA	Superior mesenteric artery
SMV	Superior mesenteric vein
SRT	Short-course radiotherapy
T	Tumour
TACE	Trans arterial chemoembolization
TARE	Trans arterial radioembolization
TID	Three times a day
TKI	Tyrosine kinase inhibitor
TME	Total mesorectal excision
TNM	Tumour, Nodes, metastasis classification
UICC	Union for International Cancer Control
USG	Ultra sonogram
VEGFR	Vascular endothelial growth factor receptor
WHO	World Health Organization
WT	Wild type

1. Definition

Terms	Definition
Biopsy	Is a sample of tissue taken from the body in order to examine it more closely under a microscope.
Colon cancer	Cancer that forms in the tissues of the colon. Most colon cancers are adenocarcinomas.
Colonoscopy	Is the endoscopic examination of the large bowel and the distal part of the small bowel with a Charge Coupled Device (CCD) camera or a fiber optic camera on a flexible tube passed through the anus. It can provide a visual sight to detect adenomatous polyps and cancer diagnosis (e.g., ulceration, polyps). It also grants the opportunity for biopsy or possible removal of suspected colorectal cancer lesions.
Colorectal cancer	Also known as bowel cancer, colon cancer, or rectal cancer, is any cancer that affects the colon (the longest part of the large intestine) and/or the rectum (the last several inches of the large intestine before the anus).
Colorectal Cancer Screening	Means looking for polyps or cancer in the colon and rectum in people who have no disease-related symptoms.
Colorectal Cancer Screening Services	Evaluation and follow-up of colorectal cancer assessment.
Fecal Immunochemical Test (FIT)	It is a test that investigates the stool sample for the presence of blood or its products in the stool.
Polyp	Is an abnormal growth of tissue protruding from the mucous membrane.
Rectal cancer	A malignant tumor arising from the inner wall of the final part of the large intestine in lower lesion.
Sigmoidoscopy	A procedure in which a physician inserts a viewing tube (sigmoidoscope) into the rectum for inspecting the lower colon and rectum. If an abnormal area is detected, a biopsy can be taken.

CHAPTER ONE

2. Introduction

Colorectal cancer (CRC) is the third most common cancer in men and the second most common cancer in women worldwide, based on GLOBACON 2020 statistics. Significant international variations in the distribution of colorectal cancer have been observed. Globally, the estimated age-standardized rate (ASR) of CRC was 19.5/100000 (23.4/100000 in males and 16.2/100,000 in females).

CRC is ranked as the third most common cancer in the Omani population. It is the most common cancer in males and the third most common cancer in females, based on last published 2019 data from the Oman National Cancer Registry. There was an observed both increase in the trend of the age-standardized incidence rate, and it significantly increased for genders between 1996 and 2019, **(Figure 1)**.

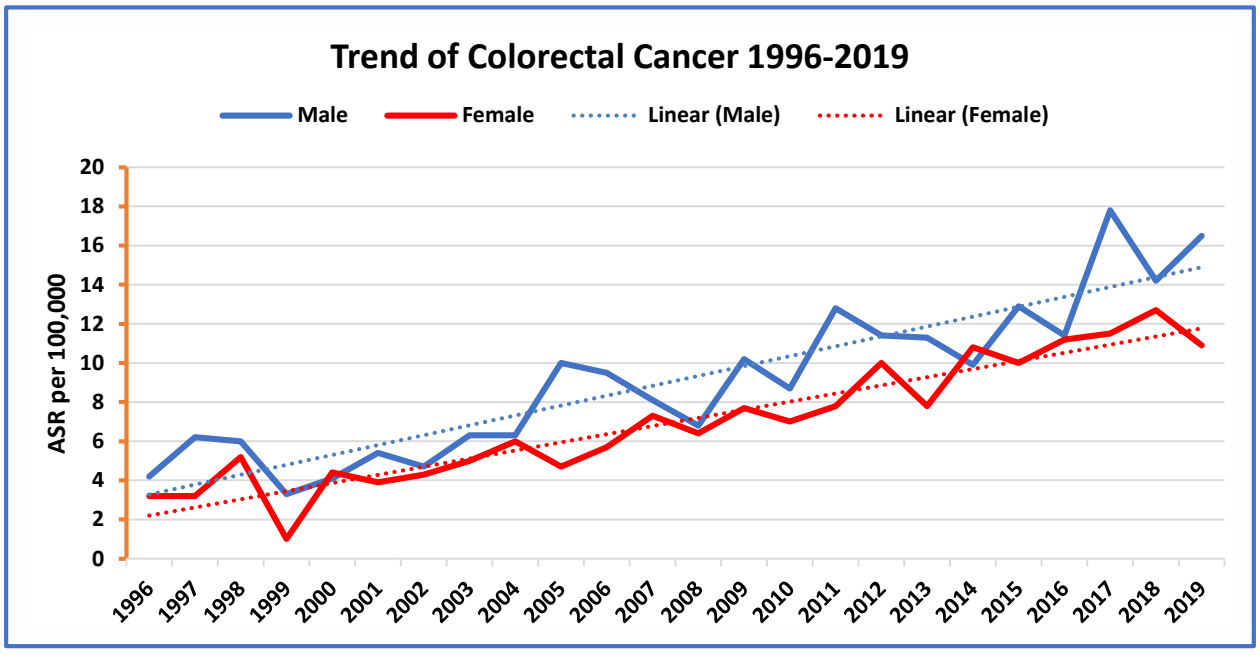
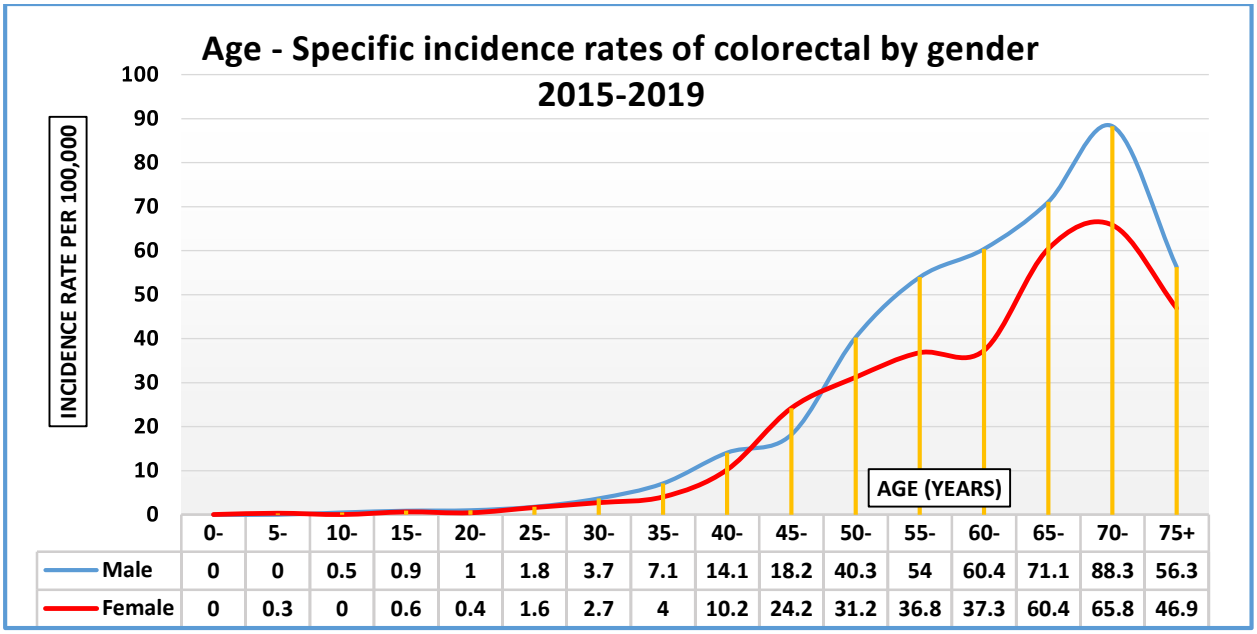


Figure 1: Trends of colorectal cancer (1996-2019)

During the five years (2015-2019), 968 colorectal cancers cases (534 males, 434 females); were reported in Oman. The overall age-standardized incidence rates (ASRs) were 14.5 and 11.3 per 100,000 populations for males and females, respectively. The mean age at diagnosis for men and women was 56 and 57 years, respectively, and the median age was 58 years; **(Figure 2)** illustrates the age-specific incidence rates of colorectal cancer by gender, and age-specific incidence steadily rises to a peak in the **65-70** years' age group.



	0-	5-	10-	15-	20-	25-	30-	35-	40-	45-	50-	55-	60-	65-	70-	75+
Male	0	0	0.5	0.9	1	1.8	3.7	7.1	14.1	18.2	40.3	54	60.4	71.1	88.3	56.3
Female	0	0.3	0	0.6	0.4	1.6	2.7	4	10.2	24.2	31.2	36.8	37.3	60.4	65.8	46.9

Figure 2: Age-specific incidence rates of colorectal by gender (2015-2019)

Based on the latest cancer incidence report in 2019, the total number of colorectal cancer cases was 213 (124 males and 89 females). The estimated age-standardized rate (ASR) of CRC was 16.5/100000 in males and 10.9 /100,000 in females). About 26% of cases were

stage III, and 23% were in stage IV**,** **(Figure 3)**.

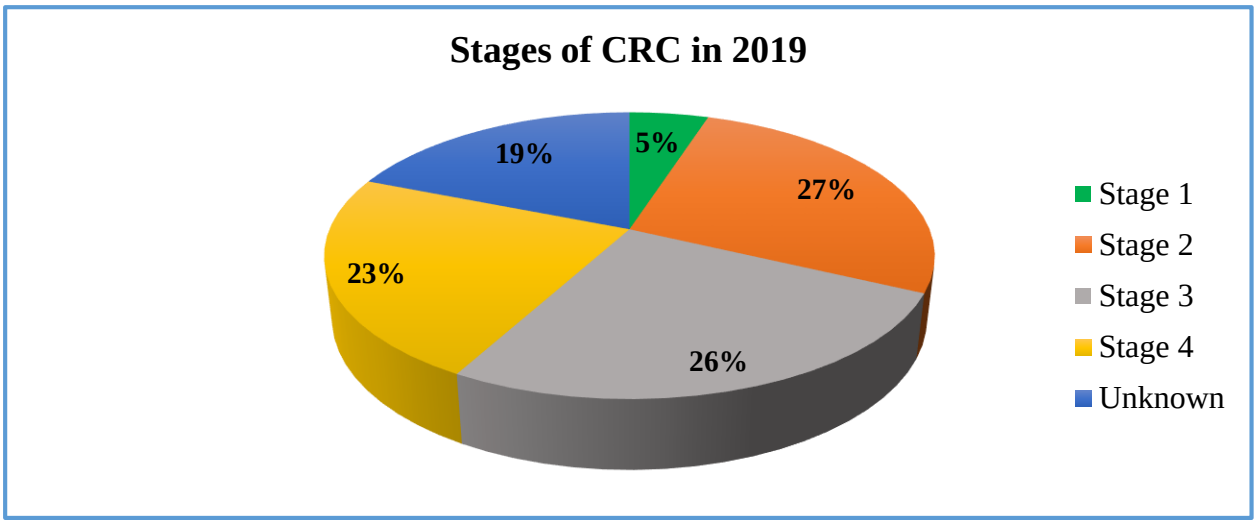


Figure 3: Stages of Colorectal cancer in 2019

Colon Cancer has a 90% 5 years' survival rate when detected early at stage I; this is reduced to 10.3% when diagnosed with metastases at stage IV.

Many of the gastrointestinal symptoms caused by CRC, such as changes in bowel habits are common, but non-specific; and most people presenting with them will not have colon cancer. Unless specific preventive interventions are implemented, the incidence rate of CRC in Oman and the Middle East region will continue to increase due to the increased risk burden arising from a sedentary lifestyle.

- **Expected outcome:**

The implementation of screening programs will result not only in a decrease in incidence, morbidity, and mortality of colorectal cancer but also improve overall survival. The aim is to detect the disease at an earlier stage, ultimately improving the survival rate.

- **Risk factors:**

Colorectal cancer is a preventable disease. Identifying increased risk and high-risk groups is important to perform screening at more frequent intervals than in the average-risk individual whose only risk factor is age. The exact cause of colorectal cancer is unknown, but certain risk factors are strongly linked to the disease development. The risk factors can be categorized into two categories modifiable and non-modifiable risk factors, as shown in **(Table 1)**.

CRC Risk factor		
Non-Modifiable	**Modifiable**	
	Lifestyle Factor	**Nutritional Factors**
- Age- increased risk with aging. - Personal history of colon adenomas (adenomatous polyps). - Family history of colon cancer or adenomas. - Inflammatory bowel disease (Ulcerative colitis & Crohn's colitis) - Diabetes Mellitus. - Race- Africa Americans have higher risk. - Inherited/familial syndromes (FAP & HNPCC).	- Obesity - Smoking - Alcohol consumption - Sedentary lifestyle - Physical inactivity	- Excessive red & processed meat - Low intake of fibers

Table 1: CRC risk factor

- **Screening:**

Organized CRC screening programs aim to identify cancer in asymptomatic patients (when the disease is more likely to be at an early stage). The risk stratification for CRC screening is shown in **(Table 2)**, and **(Table 3)** shows the high risks symptoms.

CRC Screening risk stratification		
Low-Risk	**Average-Risk**	**High-Risk (At any age)**
- Age **<40** years and has no risk factors or family history of colorectal cancer.	- Without prior colorectal cancer or polyps. - Without any of the factors that define high-risk screening.	- Have symptoms of possible colorectal cancer **(Table 3).** - Family or personal history of colorectal cancer.

		- Previous diagnosis of inflammatory bowel disease (discuss with primary physician). - Previously removed pre-cancerous colorectal polyps. - Multiple first-degree relatives with colorectal cancer or precancerous diseases. - Other conditions: Acromegaly, cystic fibrosis, ureterosigmoidostomy, genetic variants.

Table 2: CRC Screening risk stratification

High risk symptoms at any age
- Rectal or abdominal mass. - Rectal bleeding. - Unexplained Weight loss. - Unexplained abdominal pain. - Change in bowel habit. - Iron deficiency anemia.

Table 3: High-risk symptoms at any age

3. Purpose

- To detect cancer at an early and curable stage.
- Reduce incidence and mortality from colorectal cancer through prevention and early detection.
- Reduce the risk of disease & increase the chance of successful treatment.
- Improved pathways from diagnosis to treatment in susceptible populations.
- Ensure that the population receives quality and safe care, and timely referral for diagnosis and/or treatment wherever appropriate.
- Provide knowledge to and allocate the role of PCPs (Primary Care Physicians) in successful Screening Programs and to increase the rate of CRC detection at an early stage.

4. Scope

These guidelines and procedures apply to all Healthcare professionals who participate in comprehensive service-providing for CRC screening facilities in the Sultanate of Oman.

CHAPTER TWO

5. Procedure

5.1. Services provision

5.1.1. The service will be provided at primary health care level, Receiving, and registering adults for the required screening clinic **(Figure 4)**

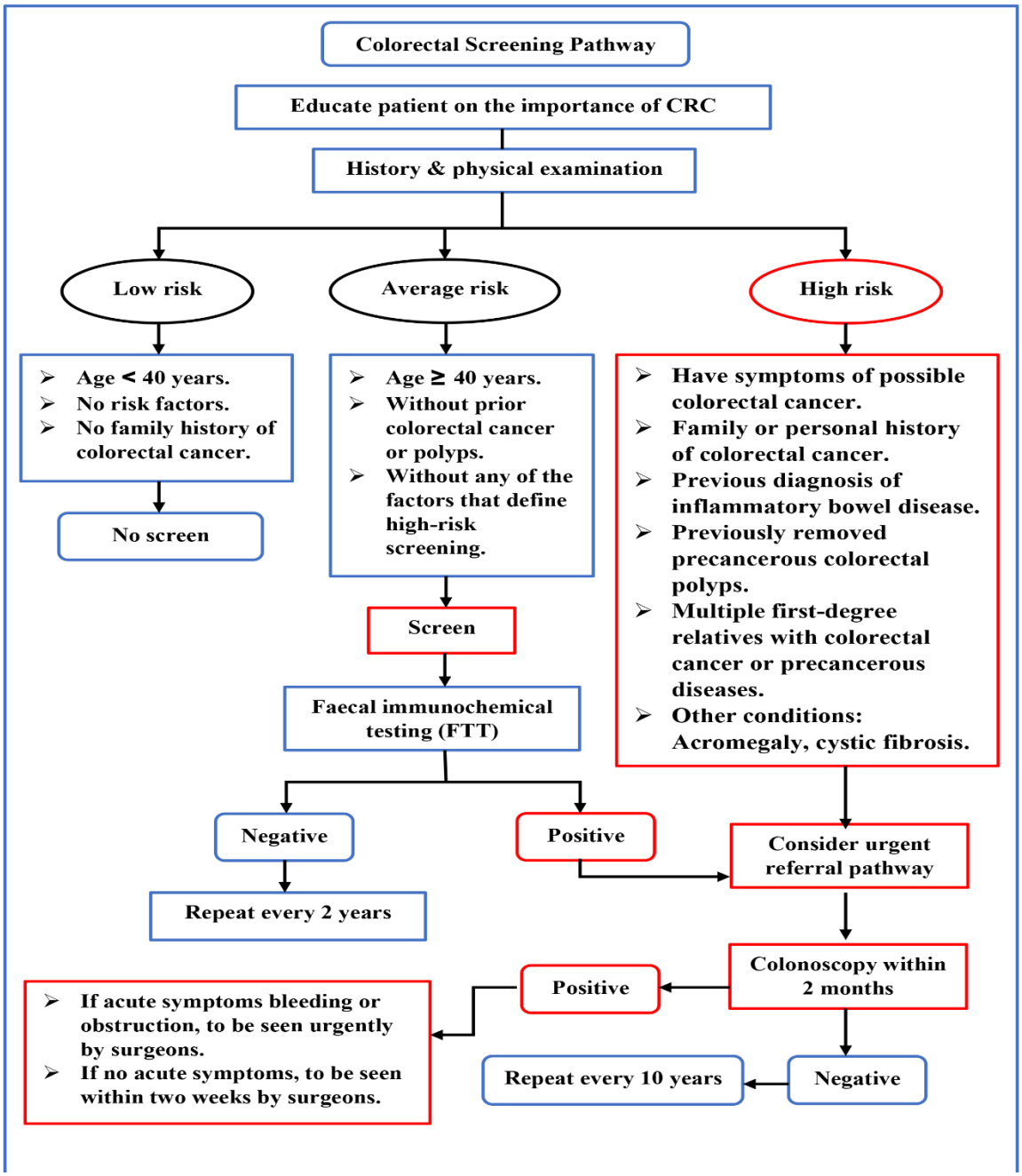


Figure 4: CRC screening pathway

5.2. Colon Cancer

5.2.1. **Diagnosis:**

5.2.1.1. The presenting symptoms are:

a) Altered bowel habits.

b) Localized abdominal pain.

c) Unexplained weight loss.

d) Asthenia.

e) Iron deficiency anaemia.

f) Or symptoms of metastatic disease.

5.2.1.2. A colonoscopy is a standard recommended procedure for diagnosis.

5.2.1.3. If a pre-operative complete colonoscopy is not performed, then it should be done within 3-6 months' intervals after surgery.

5.2.1.4. A standard comprehensive pathology analysis and report are required.

5.2.1.5. Staging includes:

a) Clinical evaluation.

b) CT scan abdomen.

c) MRI (when required for liver assessment, or Rectal Assessment).

d) A pre-operative CEA.

5.2.1.6. PET scan is not routine for staging.

5.2.1.7. Surgical staging: Liver, Lymph nodes, Ascites, extramural spread, at least 12 LNs dissected.

5.2.1.8. Pathology staging as per TNM.

5.2.2. Prognosis:

5.2.2.1. It is determined by stage, grade, LVI, PNI, resection margins, inflammatory infiltrate, and pre-treatment CEA and CA19-9.

5.2.2.2. Molecular characters: MSI/MMR, RAS, NRAS, BRAF, PD-L1, and Ki-67.

5.2.3. Risk Assessment:

5.2.3.1. Loss of chromosome 18q (Negative impact) and MSI/MMR (Positive Impact).

5.2.3.2. MSI-H/dMMR is 10-15% in stage II are low risk of recurrence and not likely to benefit from 5-FU based chemotherapy.

5.2.3.3. There is no predictive marker for chemotherapy in early CRC.

5.2.4. Surgery:

5.2.4.1. Evaluation:

5.2.4.1.1. History and Physical examination.

5.2.4.1.2. laboratory: CBC, LFT, UE1, CEA, CA19-9

5.2.4.1.3. Imaging:

a) CT chest/abdomen/pelvis.

b) In doubtful liver metastasis consider liver MRI.

c) Colonoscopy with tattoo of site Pathology.

d) PET scan if indicated.

5.2.4.2. Special consideration:

5.2.4.2.1. If a pre-operative assessment was not performed, colonoscopy should be performed within 6 months of surgery or as soon as possible after completion of adjuvant therapy.

5.2.4.3. The treatment options are:

5.2.4.3.1. Malignant polyp: Enbloc Colonoscopic polypectomy. Surgical resection indicated if LVI/PNI+ve, grade III, or positive margins. If the stalk is invaded, but margins are free and low grade – Colonoscopic polypectomy is sufficient.

5.2.4.3.2. Invasive carcinoma in sessile polyp needs surgery.

5.2.4.3.3. A laparoscopic resection by an experienced surgeon is recommended when there are no adhesions of prior surgery, not a locally advanced disease.

5.2.4.4. Stage-wise treatment:

a) Stage 0: Local excision, polypectomy, or enbloc resection with larger tumour. Put in the screening program.

b) Stage I: Wide resection anastomosis – No Adjuvant treatment. Only Follow up.

c) Stage II: Wide resection anastomosis – Adjuvant treatment in the high-risk group. Then continue follow up.

d) Stage III: Wide resection with end to end anastomosis – Adjuvant treatment (FOLFOX or XELOX).

5.2.4.5. Postoperative surveillance:

5.2.4.5.1. Clinical assessment and CEA levels to be done at 3-6 months as per most international guidelines.

5.2.4.5.2. CT chest/abdomen/pelvis every 6 to 12 months for the first two years, then annually for up to 5 years.

5.2.4.5.3. Colonoscopy after one year then after 3 and 5 years, if normal.

5.2.4.5.4. Any new and persistent or worsening symptoms warrant the consideration of a possible recurrence and rule it out by appropriate investigations.

5.2.4.6. Tumor-Related Emergencies.

5.2.4.6.1. Perforated colonic tumor.

5.2.4.6.1.1. Right-sided perforation:

a) A right colectomy should be performed.

b) In case of poor general conditions, a resection without anastomosis and terminal ileostomy should be performed.

5.2.4.6.1.2. Transverse/left-sided perforation:

a) Resection with anastomosis, with or without ileostomy, should be attempted.

b) Hartmann's procedure might be considered, keeping in mind the low rate of stoma reversal.

5.2.4.7. Obstructing colon cancer:

5.2.4.7.1. Obstructing colon cancer and curable disease:

a) Colectomy / initial endoscopic stent decompression then interval colectomy/ colostomy (Individualized).

b) High-risk surgical patients, initial stenting followed by optimization for interval colectomy is recommended.

5.2.4.7.2. Obstructing colon cancer and incurable metastatic disease (Palliative).

5.2.4.7.3. Decompressive stent insertion is preferable to colectomy or diversion.

5.2.4.8. Adjuvant treatment recommended for stage III and high-risk stage II:

5.2.4.8.1. High-risk stage II if any of the following is present:

a) Dissected LNs <12 in number.

b) Poorly differentiated tumor.

c) LVI +ve or PNI +ve.

d) Gut Obstruction or perforation.

e) pT4.

f) Positive resection margins.

5.2.4.8.2. Adjuvant chemotherapy should be started within 8 weeks, after surgery if there are no contraindications. (See Appendix 10.1).

5.2.5. Regular follow up improves survival after adjuvant treatment.

5.2.5.1. Clinical Assessment, CEA – every 3 months for 3 years and every 6-12 months in 4th and 5th year.

5.2.5.2. Colonoscopy after 1 year, then every 3-5 years.

5.2.5.3. Pan CT every 6-12 months in first 3 years in high-risk disease.

5.2.5.4. Other assessment as per symptoms.

5.2.6. Metastatic Colorectal Cancer management:

5.2.6.1. Diagnosis:

5.2.6.1.1. Radiologic and biopsy confirmation; A stepwise assessment by the USG, CT, MRI, and PET is useful as per location, indication, and justification.

5.2.6.2. Molecular profiling:

5.2.6.2.1. Archival or fresh tissue can be used. It is preferred to use primary tumour or liver biopsy tissue.

5.2.6.2.2. NRAS and KRAS: Expanded RAS analysis for all considered to be potential candidates for anti-EGFR treatment. A test should be done at an accredited lab, and the turnaround time should be minimal.

5.2.6.2.3. BRAF: Assessed initially to predict prognosis and select the intensity of treatment.

5.2.6.2.4. MSI: To assess for eligibility for immunotherapy.

5.2.6.2.5. Her-2

5.2.6.2.6. PD-L1 or TMB

5.2.6.2.7. UGT1A1 deficiency testing to be done where irinotecan is used in a dose >180 mg/m2.

5.2.6.2.8. Determination of DPD deficiency is not recommended in guidelines before Fluoropyrimidine therapy, unless unexpected, exaggerated toxicity is encountered.

5.2.7. TREATMENT of mCRC Resectable disease:

5.2.7.1. MDT discussion and decision Making is the standard of care.

5.2.7.2. **Oligometastatic Disease:** If potentially curative with R0 resection, surgery is the preferred option. For more extensive oligometastatic disease, initial systemic treatment is advised.

5.2.7.3. Best local treatment (EBRT, RFA, resection with HIPEC, nodal dissection) is personalized based on location, co-morbidities, the objective of treatment, side effects, and expertise available. Lung metastasis is best managed by watchful waiting.

5.2.7.4. **Liver metastasis:** The objective of surgery is complete resection. Stepwise imaging by CT, MRI, and PET help in decision-making.

5.2.7.5. For un-resectable metachronous metastasis, a biopsy is indicated in an unusual site, atypical presentation, or time of relapse is > 3 years after initial diagnosis. Resectable metastasis does not need cytological or pathologic confirmation.

5.2.7.6. **Resectable Liver metastasis:** Resectable with favourable prognosis – upfront surgical resection.

5.2.7.7. In unclear/unfavourable resectable liver metastases tumours – perioperative FOLFOX or CAPOX (3 months prior and 3 months after surgery). Targeted therapy is not justified in this situation. Adjuvant chemotherapy (FOLFOX or CAPOX) is advised in cases with high-risk unfavourable criteria which did not receive pre-operatively

5.2.7.8. Un-resected Conversion Liver Metastasis: Limited liver/lung metastasis in potential candidates for secondary resection, based on response to initial systemic treatment. Respectability should be assessed between 2-4 months of systemic treatment. **(See appendix 10.2).**

5.2.7.9. Conversion systemic protocols are established (re-assess regularly and periodically to avoid overtreatment. In any case, treatment should not exceed 6 months).

5.2.7.10. After conversion and resection, relapse in the liver can be further managed by RFA or SBRT.

5.2.8. Unfavorable or uncommon sites Metastasis (Role of Ablation with or without Surgery):

5.2.8.1. RFA, SBRT, cryoablation, chemoembolization, or radio-embolization (based on location, prognosis, patients' preference, expected survival, available expertise).

a) A decision is to be made in MDT.

b) Limited peritoneal disease – cyto-reductive surgery with HIPEC in experienced high-volume centers. d/s after MDT.

5.2.9. Old age and unfit patients:

5.2.9.1. Fit older patients can be treated as per standard of care.

5.2.9.2. Unfit cases or elder cases: Reduced dose chemotherapy, single fluoropyrimidine plus bevacizumab, Capecitabine, or best supportive care. **(See Appendix 10.2)**.

5.2.10. Prognosis, response, and follow up:

a) RAS, BRAF, MSI is recommended to be done in every case for treatment selection.

b) BRAF mutation is a Negative predictive marker.

c) Assessment every 3 months, when on active chemotherapy.

5.2.10.1. Follow up clinical, CEA, and CT scan every 3-6 months in patients where complete metastatic resection is carried out.

5.3. Rectal Cancer

5.3.1. Diagnosis:

5.3.1.1. Diagnosis is based on DRE, endoscopy, and histopathology confirmation.

5.3.1.2. Rectal cancers are up to 15 cm from the anal verge (Low rectal <5cms, Middle Rectum 5-10 cm, and High rectal 10-15 cm).

5.3.1.3. Management is multi-disciplinary, and decision need to be made in MDT.

5.3.1.4. Work up and staging:

a) Clinical assessment.

b) DRE.

c) Laboratory assessment.

d) CEA.

e) CT chest, abdomen and pelvis or PET scan.

f) EUS if available (Endoscopic u/s).

g) MRI-pelvis.

h) PET may be needed for an extra pelvic disease but should not be used routinely at initial staging.

5.3.1.5. Endoscopy evaluation of rectum and full colon either preoperatively or within 6 months' post-treatment is recommended.

5.3.2. Surgical assessment:

5.3.2.1. Enbloc resection is required for assessing margins and invasion.

5.3.2.2. CRM < 1 mm and TME quality are indicators of outcome.

5.3.2.3. At least 12 LNs need to be assessed. Extra-nodal extension, LVI, PNI, and tumour budding are indicators of prognosis and must be documented.

5.3.3. Management of early-stage CA Rectum:

a) cT1-T2, cT3a/b (Middle or high tumour) N0 or cN1 (in a high rectal tumour).

b) cT2c, cT3a, cT3b: Radical TME.

c) A partial Meso-rectal excision in high rectal tumour.

d) MRI is used to select cases for APR.

e) For cT1-T2 N0 tumours < 4 cm; local excision is suitable only in clinical trials, old age, fragile and high surgical risk patients.

f) TME alone can be done in early favourable cases.

5.3.4. For T3, any N+ with clear CRM (by MRI) (Figure 5)

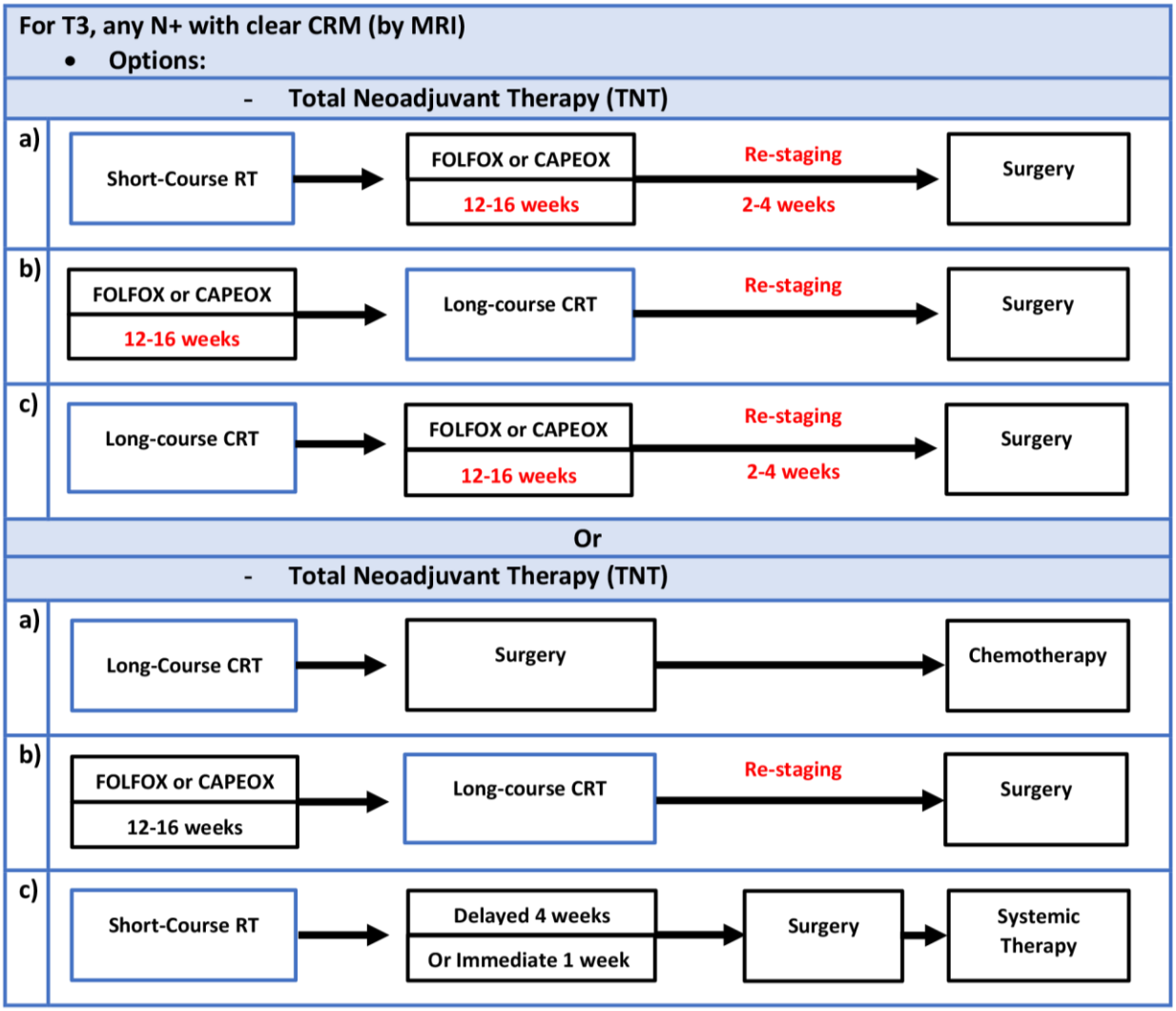


Figure 5: For T3, any N+ with clear CRM (by MRI)

5.3.5. T3, any N with involved or threatened CRM (by MRI), T4, N any or locally unresectable or medically inoperable (Figure 6)

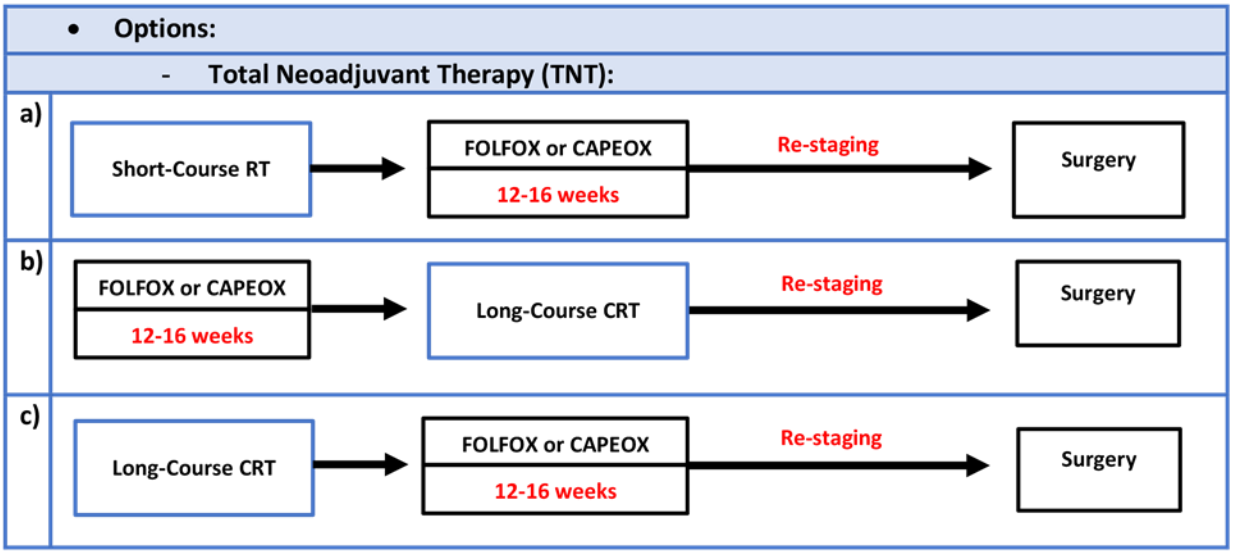


Figure 6: T3, any N with involved or threatened CRM (by MRI), T4, N any or locally unresectable or medically inoperable

5.3.6. Post-Operative-Radiotherapy (Figure 7)

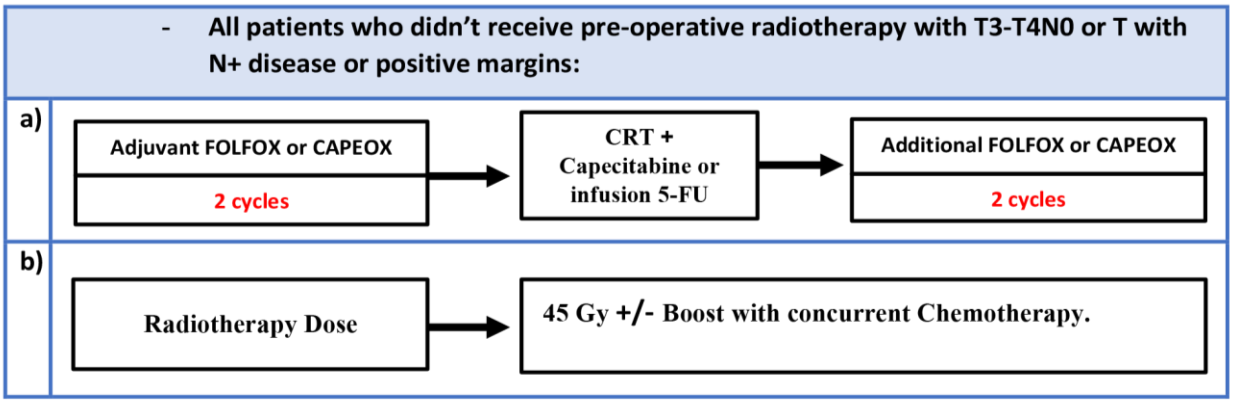


Figure 7: All patients who didn't receive pre-operative radiotherapy with T3-T4N0 or T with N+ disease or positive margins

5.3.7. Special consideration:

- **For T4 un-resectable tumor**	
a)	Consider diverting colostomy if a near or total obstruction.
b)	Consider induction FOLFOX → ChemoRT (55.8 – 59.4Gy + Capecitabine or 5-FU) → resection (if possible).
c)	All patients should receive adjuvant Chemotherapy as per Medical Oncologists' risk assessment and decision.

5.3.8. Locally advanced Rectal Cancer. Radiotherapy section for rectal cancer.

5.3.8.1. Locally Advanced Rectal Cancer: is any ≥ T3, N+ disease. CRM involvement should be considered during pre-operative management.

5.3.8.1.1. Pre-operative Assessment:

a) The proper clinical stage of the patient should be documented prior to starting any therapy.

b) Radiotherapy Indications for Rectal Cancer.

5.3.8.1.2. Pre-operative:

a) Pre-op RT improves local control but not survival

b) T3-T4 N0 or Any T with N+ should receive pre-operative Radiotherapy.

c) CRM measured at the closest distance of the tumor to the mesorectal fascia. Clear CRM: Greater than 1 mm from mesorectal fascia and levator muscles and not invading into the intersphincteric plane.

5.3.8.1.3. Stage IV oligometastatic:

a) Can consider Induction chemotherapy ➔ response assessment with restaging ➔ treat primary with ChemoRT and/ or resection followed by Adjuvant Chemotherapy.

b) Staged or synchronous treatment of liver or lung metastasis (resection preferred, or SBRT) ➔ Adjuvant systemic therapy

5.3.8.1.4. Pelvic recurrence ➔ Individualized options:

a) If no prior pelvic RT, then pre-op ChemoRT (50.4Gy/28 fx + Capecitabine or 5-FU).

b) Followed by surgery.

c) If prior pelvic RT, then surgery or pre-op ChemoRT (30 Gy in 1.2 Gy bid or 30.6 Gy/17 fr + Capecitabine or 5-FU) → surgery.

d) If not fit for surgery, can consider a palliative RT dose.

5.3.8.1.5. Timing of radiotherapy:

a) Pre-Op CRT: TME surgery 6-8 weeks post-CRT.

b) Pre-Op Short course RT: TME 1-week post-RT or 6-8 weeks.

c) Post-Op: CRT after 2 cycles of chemotherapy (to be started 4 weeks' post-op).

5.3.8.1.6. Neoadjuvant Chemotherapy:

a) Fluoro pyrimidine and Oxaliplatin-based regimens in cT3 and cT4 tumours can be used in the mid and upper rectum.

b) NACT alone is not recommended in localized non-metastatic disease.

5.3.8.1.7. Response Assessment after NA Treatment:

5.3.8.1.7.1.Primary tumour: Clinical, Endoscopy DRE, MRI.

5.3.8.1.8. Planned for surgery:

a) Assess CRM and TRG (Tumour Regression Grade) by MRI.

b) CT and PET as indicated.

c) Persistent CRM should be referred to MDT for discussion and enbloc resection.

5.3.8.1.9. cT4 threatened CRM, EMVI should be re-staged at 3 months of original staging.

a) Re-stage also if there is a clinical suggestion of progression.

b) Pathologic response must address pCR, necrosis and regression of EMVI, T and N stages.

5.3.8.1.10. Post-Operative Adjuvant Treatment:

5.3.8.1.10.1. Adjuvant CCRT with Capecitabine:

- Indications include Unexpected adverse histopathology features in a primary resected specimen (Positive CRM, Perforation in the tumour area, incomplete Meso-rectal excision, high-risk of recurrence and NACRT is not given).

5.3.8.1.10.2. Post-operative Chemotherapy after NA treatment

a) High-risk stage II or stage III (Level of evidence Low) Fluoro pyrimidine +/- Oxaliplatin based.

b) **(See Appendix 10.1: Colorectal Cancer Adjuvant chemotherapy protocols).**

5.3.8.1.11. Surgery for rectal cancer

5.3.8.1.11.1. Evaluation:

5.3.8.1.11.2. History and physical exam

5.3.8.1.11.3. Laboratory: CBC, CEA

5.3.8.1.11.4. Imaging:

a) CT chest/abdomen/pelvis\

b) Rectal MRI Consider liver MRI if suspected metastasis, not characterized by the above.

c) Colonoscopy with a tattoo of site Pathology.

5.3.8.1.12. Neoadjuvant option in Rectal Cancer (Figure 8)

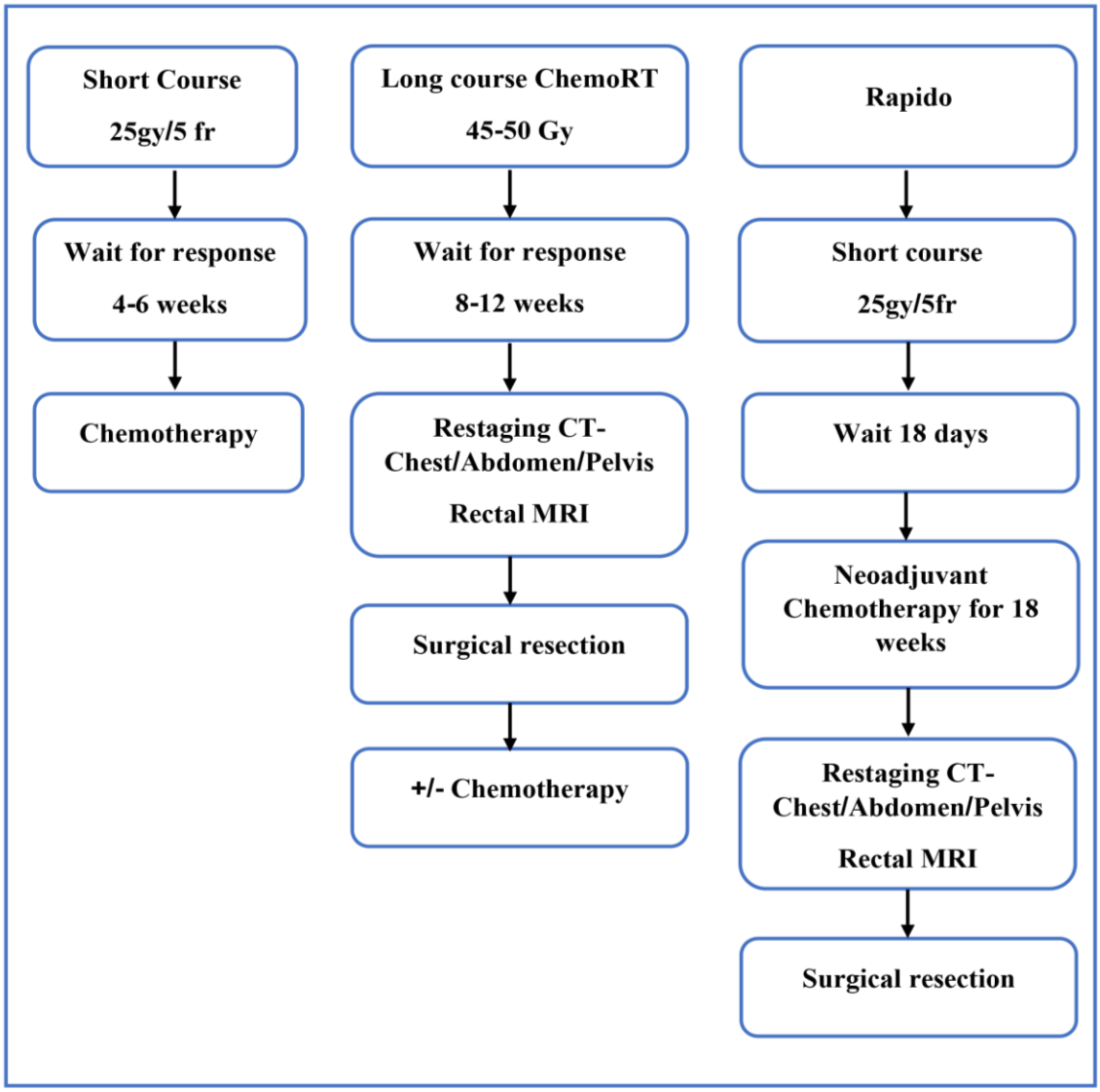


Figure 8: Neoadjavitine option in Rectal Cancer

5.3.8.1.13. Principle of surgical resection (Figure 9)

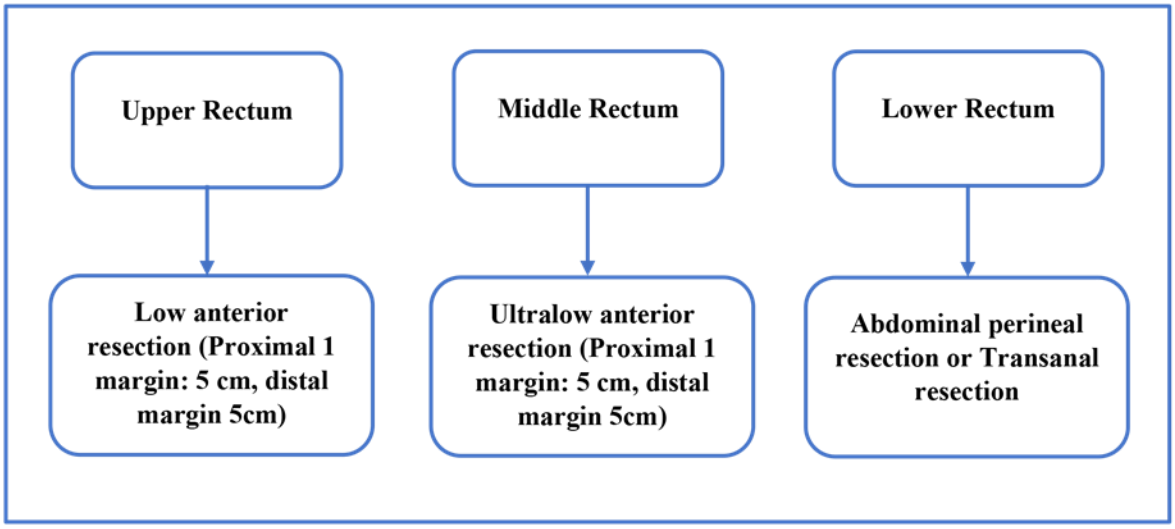


Figure 9: Principle of surgical resection

5.3.8.1.14. Indications for trans-anal excision: only in special conditions (fragile, old age)

a) T1N0.

b) Well differentiated.

c) No lymphatic, vascular, or peri-neural invasion.

d) Less than 4 cm in width.

e) Less than 50% circumferential involvement.

f) Mobile

5.3.8.1.15. Postoperative surveillance:

a) Clinical assessment and CEA every 3 months for the first 1- 2 years.

b) CT chest/abdomen/pelvis every 6 to 12 months for the first 2 years, then annually up to 5 years.

c) Colonoscopy (within 3-6 months after surgery if not completed pre- op), in one year then after 3 and 5 years if colonoscopy normal.

d) Any new and persistent or worsening symptoms warrant the consideration of a recurrence.

5.4. Anal Cancer

5.4.1. **Diagnosis**

5.4.1.1. Presentation: SCC may present as a mass, skin tag, non-healing ulcer, bleeding, pain, discharge, itching, incontinence, or fistulae.

5.4.1.2. A biopsy is needed.

5.4.1.3. Colonoscopy not always indicated.

5.4.2. Staging and assessment:

5.4.2.1. Clinical assessment (Inguinal LNs). DRE. PV examination in females.

5.4.2.2. Proctoscopy and/or EUA.

5.4.2.3. MRI Pelvis or 3D EAUS.

5.4.2.4. CT chest + Abdomen.

5.4.2.5. PET CT is more sensitive for LN and primary tumour.

5.4.2.6. HIV test.

5.4.2.7. Gynecological examination (screen for cervix cancer)

5.4.2.8. Stage with TNM.

5.4.2.9. Loco-regional failure, OS, and DFS are dependent on skin ulceration, LN involvement, male gender, tumour > 5 cm, palpable inguinal LNs and anaemia, and HIV status.

5.4.3. Local/ Loco-regional disease management:

5.4.3.1. MDT discussion and management Decision making.

5.4.3.2. CCRT (5FU, Mitomycin, or cisplatin-based).

5.4.3.3. Salvage surgery.

5.4.4. Management of Localized Cancer:

5.4.4.1. T1-T4, N+, M0 preferred treatment is concurrent chemoRadiotherapy.

5.4.4.2. Local excision with 1-cm margins can be considered for Perianal T1N0, well to moderately-differentiated or selected T2N0 squamous cell carcinoma (SCC) of the perianal (anal margin).

5.4.4.3. Radical pelvic Radiotherapy with concurrent chemotherapy (5-FU + mitomycin) can also consider Capecitabine + mitomycin.

5.4.4.4. Radiotherapy Dose: T1-T2 N0-1: 40-45Gy/28 fr to pelvis, 50,4 Gy /28 fr to Gross disease.

5.4.4.5. T3/4 or N2/3: 40-45Gy/28 fr to pelvis, 54-59.4 Gy /28 fr to Gross disease.

5.4.5. CRRT:

5.4.5.1. CCRT is superior to RT alone.

5.4.5.2. 5FU or Capecitabine with Mitomycin; is recommended along with an RT.

5.4.5.3. Mitomycin is superior to cisplatin.

5.4.5.4. NACT, maintenance or consolidation chemotherapy does not improve outcome and is not recommended.

5.4.5.5. Involved inguinal nodes (even in the absence of clear involvement) are included in the CCRT treatment plan simultaneously.

5.4.5.6. Brachytherapy is not recommended as a single curative entity but may be used as a boost following response to CCRT.

5.4.5.7. The patient should be treated alike irrespective of age.

5.4.6. Post-operative CCRT, where Re-excision is not possible:

5.4.6.1. For excision of perianal skin tags where margins are narrow, incomplete excision, or risk of LN involvement is due to high-risk features.

5.4.6.2. During CCRT, Monitor CBC and Renal functions. Advise cessation of smoking. Always discuss fertility issues with females.

5.4.6.3. CCRT tolerance and compliance can be improved by psychologic/nutritional support, antibiotics, antifungals, analgesics, anti-emetics, and skincare, wherever indicated. **(See Appendix 10.4: CCRT Anorectal)**

5.4.6.4. There are no biomarkers to predict response to CCRT. HPV, p16 can be assessed. Positive cases have better responses, better outcomes and low recurrence rates.

5.4.7. Salvage surgery:

5.4.7.1. Locally persistent, progressive, or recurrent disease at the primary site or inguinal LNs - Consider salvage surgery APE (Anterior pelvic exenteration).

5.4.7.2. Confirm by biopsy and Re-stage (MRI, PET, or CT chest + abdomen to exclude distant metastasis).

5.4.8. Palliative Care and QoL issues:

5.4.8.1. Pain management: opiate and non-opiates analgesics, nerve block, psychotropic medicines, and re-irradiation skincare.

5.4.8.2. Counselling for side effects and sexual health.

5.4.8.3. Diversion in case of fistulae (bladder or rectum).

5.4.9. Response assessment:

5.4.9.1. DRE, biopsy any persistent lesions after 12 weeks of CCRT.

5.4.9.2. Clinical and radiologic assessment of inguinal LNs.

5.4.9.3. A response may continue for 6 months. Closely follow good responders with minimal residual disease.

5.4.9.4. MRI and PET may be needed for assessment.

5.4.9.5. If persistent disease at 26 weeks – biopsy it – Consider Salvage surgery.

5.4.10. Follow up:

5.4.10.1. Patients achieving CR at 8 weeks; Assess 3-6 months for 2 years, then 6-12 months for 5 years.

5.4.10.2. Focus on primary site (by DRE), Inguinal LNs, MRI – every 6 months for 3 years.

5.4.10.3. Biopsy any suspected progressive lesions.

5.4.10.4. Imaging beyond 3 years is not recommended.

5.5. Gastro-Intestinal stromal tumor

5.5.1. Diagnosis

5.5.1.1. A Nodule < 2 cm in the esophagus, stomach, or duodenum can be closely followed up at 3 monthly intervals by EUS.

5.5.1.2. For Rectal small lesions, assessment is done Endorectal US (ERUS) and MRI. Small low-risk lesions can be followed by biopsy. Otherwise, the standard treatment is excision.

5.5.1.3. Tumours > 2ms should be excised following biopsy confirmation.

5.5.1.4. A guided biopsy of an intra-abdominal lesion can be followed by laparoscopic resection in selected eligible cases.

5.5.1.5. A metastatic lesion can be biopsied for pathology confirmation.

5.5.1.6. Diagnosis needs morphology and IHC (CD117 and DOG1 positivity). Mutation analysis (KIT, exon11. Exon 13, exon 17, SDH, NF1, FGFR1, NRAS, KRAS, HRAS, BRAF, NTRK, PDGFRA) is the standard of care, to predict response and select treatment.

5.5.2. Staging:

5.5.2.1. The site, size, mitotic rate, and tumour rupture are the main prognostic factors and guide management decisions.

5.5.2.2. Pan CT is a standard staging investigation. MRI is preferred in rectal GIST.

5.5.3. Local-Regional disease

5.5.3.1. The standard of care is complete R0 resection. No lymph node dissection is indicated in clinically negative LNs.

5.5.3.2. If R0 surgery is not possible or functional impairment is warranted – A pre-operative treatment can be considered to obtain maximal shrinkage before surgery (after 6-12 months).

5.5.3.3. If pre-operative treatment is not effective, then a de-bulking with R1 surgery is justified.

5.5.3.4. Imatinib can be safely given till one day before surgery and resumed after recovery from surgery.

5.5.3.5. A risk stratified (In high risk) 3 years' adjuvant Imatinib is indicated as the standard of care.

5.5.3.6. A rupture at surgery is a definite indication for adjuvant treatment.

5.5.3.7. PDGFRA D842V-mutated GIST does not benefit from Imatinib and should not be used.

5.5.3.8. In NF-1 related and SDH-negative GIST; and KIT/PDGFRA/BRAF wild type GIST, adjuvant treatment should be avoided.

5.5.4. Advanced metastatic disease

5.5.4.1. For inoperable locally advanced and metastatic disease, Imatinib is the standard of care continued indefinitely, even after complete surgical resection. The standard dose is 400 mg daily, escalated to 800 mg daily in exon 9 mutation or after progression on the 400 mg protocol.

5.5.4.2. PDGFRA D842V-mutated GIST preferably needs a clinical trial enrolment.

5.5.4.3. Compliance must be monitored, and regular follow-up is required.

5.5.4.4. Palliative metastasectomy can be considered with symptomatic lesions, but Imatinib must be continued indefinitely.

5.5.4.5. In case of progression or intolerance to Imatinib, second-line Sunitinib should be considered (2 or 4-week protocol).

5.5.4.6. After progression on the 2nd line, the standard 3rd line option is Regorafenib.

5.5.4.7. Imatinib re-challenge or continuation beyond progression is also practiced options.

5.5.5. Response assessment and follow-up:

5.5.5.1. Response assessment needs an experienced multi-disciplinary team.

5.5.5.2. Response/Progression can be in size, density, or necrosis.

5.5.5.3. Common relapses are in the liver or peritoneum.

5.5.5.4. A USG, CT, MRI, or FDG PET scan can be used.

5.5.5.5. A 3-6-month assessment for 3 years during adjuvant treatment, then 3-6 months for a total of 5 years. In low-risk cases, yearly assessment is sufficient.

5.5.5.6. Routine follow-up is not justified in very low-risk cases.

CHAPTER THREE

6. Responsibilities

- Healthcare professionals have a distinct and definite role in educating patients about risk factors for cancers and distinctive screening modalities.

No	Staff	Responsibilities
1	**Laboratory technicians**	Receiving, labeling, and analyzing samples (blood, toxic, tissue etc.)
Primary health Institution Considered a primary intervention in the efforts to promote CRC screening and prevention.		
2	**Health educators**	Provide information on health and health-related issues.
3	**Nurse**	Help identify symptoms and counsel patients about screening, the various ways that screening is done, for example, colonoscopy, stool testing, or gene testing.
4	**Primary care physician (PCP)**	Compliance with screening guidelines.
Secondary Institution		
5	**Gastroenterologist**	Investigate and diagnose the suspicious lesion or primary in the colon.
6	**Surgeon**	Workup and operate on the tumor**.**
7	**Medical Oncologist**	Review the histopathology report and scans; Decide the systemic treatment, and Counseling.
8	**Radiation oncologist**	Review the HPR scans and decide on the role of radiotherapy in the management of rectal GIST.
9	**Oncology nurse**	Administer chemotherapy, radiation treatments, monitoring cancer patients' vital signs, and overall well-being, helping them manage pain and lessen side effects as they undergo treatment.

CHAPTER FOUR

7. Document History and Version Control

Version	Description	Review Date
1	**Initial release**	April 2026
2		
3		

8. References

Title of book/ journal/ articles/ Website
- Colorectal cancer guideline: https://www.nccn.org
- Colorectal cancer guideline: https://www.esmo.org
- CTA Cancer Therapy Advisor: https://www.cancertherapyadvisor.com/
- Dutch TME (Kapiteijn NEJM 2001, Peeters JCO 2005, Peeters Ann Surg 2007, van Gijn Lancet Oncol 2011).
- RAPIDO TRIAL 2020.
- https://journals.lww.com/eurojgh/fulltext/2017/01000/screening_for_colorectal_cancer__the_role_of_the.1.aspx
- https://www.gastrojournal.org/article/S0016-5085%2819%2941479-0/fulltext

9. Appendix

9.1. Appendix: Colon (Colorectal) Ca Adjuvant Protocols

No	Regimen	Dosing
1	**Capecitabine**	**Repeat every 3 weeks for 8 cycle:** - Day 1-14: Capecitabine 850-1250 mg/m^2 orally.
2	**De Gramont**	**Repeat cycle every 2 weeks for a total of 12 cycles:** - **Day 1**: Leucovorin 400 mg/ ^{m2} IV. - **Day 1:** 5-FU 400 mg/ ^{m2} IV. - **Day 1-2:** 5-FU 1200 mg/^{m2} CIVI (Or 2400 mg/ ^{m2} CIVI in 46 hours with infusion pump).
3	**mFOLFOX**	**Repeat cycle every 2 weeks for a total of 12 cycles:** - **Day 1:** Oxaliplatin 85 mg/ ^{m2} IV. - **Day 1:** Leucovorin 400 mg/ ^{m2} IV. - **Day 1:** 5-FU 400 mg/ ^{m2} IV. - **Day 1-2:** 5-FU 1200 mg/ ^{m2} CIVI (Or 2400 mg/ CIVI in 46 hours with infusion pump).
4	**CAPOX**	- **Day 1:** Oxaliplatin 130 mg/ m2 IV. - **Day 1-14:** Capecitabine 1000 mg/ ^{m2} Oral BID. (Repeat cycle every 3 weeks for total 8 cycles).

9.2. Appendix: Colon Ca Advanced or Metastatic Cancer

No	Regimen	Doses
1	**Capecitabine**	- **Day 1-14:** Capecitabine 850-1250 mg/m2 oral. - **Day 1:** +/- Bevacizumab IV 7.5 mg/kg (Every 3 weeks).
2	**CAPOX**	• **CAPOX every 3 week:** - **Day 1:** Oxaliplatin 130 mg/m2 IV. - **Day 1-14:** Capecitabine 1000 mg/m2 Oral. - **Day 1:** +/- Bevacizumab IV 7.5 mg/kg.
3	**Cetuximab (KRAS/NRAS/BRAF Wild type)**	- **Every 2 weeks:** Cetuximab 500 mg/m2 IV.
4	**FOLFRI**	• **FOLFRI every 2 weeks:** - **Day 1:** Irinotecan 180 mg/m2 IV. - **Day 1:** Leucovorin 400 mg/m2 IV. - **Day 1:** 5-FU 400 mg/m2 IV. - **Day 1-2:** 5-FU 1200 mg/m2 CIVI (Or 2400 mg/m2 CIVI in 46 hours with infusion pump). • **Repeat every 2 weeks:** - **Day 1:** +/- Bevacizumab IV 5 mg/kg.
5	**FOLFRI + Cetuximab**	• **FOLFRI + Cetuximab every 2 week:** - **Day 1**: Cetuximab (KRAS/NRAS/BRAF Wild type) 500 mg/m^2 IV. - **Day 1:** Irinotecan 180 mg/m^2 IV. - **Day 1:** Leucovorin 400 mg/m^2IV. - **Day 1:** 5-FU 400 mg/m^2 IV. - **Day 1-2:** 5-FU 1200 mg/m^2 CIVI (Or 2400 mg/m2 CIVI in 46 hours with infusion pump).

6	**FOLFIRI + Panitumumab**	• **FOLFIRI + Panitumumab every 2 weeks:** - **Day 1:** Panitumumab (KRAS/NRAS/BRAF Wild type) 6 mg/kg IV. - **Day 1:** Irinotecan 180 mg/m^2 IV. - **Day 1:** Leucovorin 400 mg/m^2 IV. - **Day 1:** 5-FU 400 mg/m^2 IV. - **Day 1-2:** 5-FU 1200 mg/m^2 CIVI (Or 2400 mg/m^{2}CIVI in 46 hours with infusion pump).
7	**FOLFIRI + Ramucirumab**	• **FOLFRI + Ramucirumab every 2 weeks:** - **Day 1:** Ramucirumab 8 mg/kg IV. - **Day 1:** Irinotecan 180 mg/m^2 IV. - **Day 1:** Leucovorin 400 mg/m^2 IV. - **Day 1:** 5-FU 400 mg/m2 IV. - **Day 1-2:** 5-FU 1200 mg/m^2 CIVI (Or 2400 mg/m^2 CIVI in 46 hours with infusion pump).
8	**FOLFOXIRI**	• **FOLFOXIRI Repeat every 2 weeks:** - **Day 1:** Irinotecan 165 mg/m^2 IV. - **Day 1:** Oxaliplatin 85 mg/m^2 IV. - **Day 1:** Leucovorin 400 mg/m^2 IV. - **Day 1:** 5-FU 400 mg/m^2 IV. - **Day 1-2:** 5-FU 1200 mg/m^2 CIVI (Or 2400 mg/m^2 CIVI in 46 hours with infusion pump). - **Day 1:** And +/- Bevacizumab 5 mg/kg IV.
9	**FOLFOXIRI**	• **FOLFOXIRI Repeat every 2 weeks:** - **Day 1**: Irinotecan 165 mg/m^2 IV. - **Day 1**: Oxaliplatin 85 mg/m^2 IV. - **Day 1:** Leucovorin 400 mg/m^2 IV. - **Day 1:** 5-FU 400 mg/m^2 IV - **Day 1-2:** 5-FU 1200 mg/m^2 CIVI (2400 mg/m^2 CIVI in 46 hours with infusion pump).

		- **Day 1:** and +/- Cetuximab 400 mg IV bolus then 250 mg/m^2 IV (KRAS/NRAS/BRAF Wild type).
10	**FOLFOXIRI**	• **FOLFOXIRI Repeat every 2 weeks:** - **Day 1:** Irinotecan 165 mg/m^2 IV - **Day 1:** Oxaliplatin 85 mg/m^2 IV - **Day 1:** Leucovorin 400 mg/m^2 IV. - **Day 1:** 5-FU 400 mg/m^2 IV. - **Day 1-2:** 5-FU 1200 mg/m^2 CIVI (Or 2400 mg/m^2 CIVI in 46 hours with infusion pump) - **Day 1:** And +/- Panitumumab 6 mg/kg IV (KRAS/NRAS/BRAF Wild type).
11	**Irinotecan**	• **Irinotecan 125, 180 or 350 mg/ m^2 IV weekly, 2 weekly or 3 weekly.** - Bevacizumab can be added in eligible cases 5 mg or 7.5 mg/kg in **2 or 3 weekly protocol.** - **Day 1:** (KRAS/NRAS/BRAF Wild type): Cetuximab 500 mg/m2 IV or Panitumumab 6 mg/kg IV can be added to 2 weekly protocol. - **Day 1:** Ramucirumab 8 mg/kg IV in 2 weekly protocol.
12	**IROX**	- **Day 1:** Oxaliplatin 85 mg/m^2 IV. - **Day 1:** Irinotecan 200 v IV **(every 3 week).** - **Day 1:** Bevacizumab can be added as 7.5 mg/kg IV (in eligible patients).
13	**mFOLFOX6**	- **Day 1:** Bevacizumab 5 mg/kg IV **(every 2 week).** - **Day 1:** (KRAS/NRAS/BRAF Wild type): Cetuximab 500 mg/m^2 IV or Panitumumab 6 mg/kg IV can be added to 2 weekly protocol. - **Day 1:** Ramucirumab 8 mg/kg IV in 2 weekly protocol.

14	**De Gramont**	-
15	**Nivolumab (MSI-H/dMMR)**	- **Every 2 weeks:** Nivolumab (MSI-H/dMMR) 3 mg/kg or 240 mg IV. - **Every 4 weeks:** Nivolumab (MSI-H/dMMR) 480 mg IV.
16	**Pembrolizumab (MSI-H/dMMR)**	- **Every 3 weeks:** Pembrolizumab (MSI-H/dMMR) 2 mg/kg or 200 mg IV.
17	**Nivolumab (MSI-H/dMMR)**	- **Day 1**: Nivolumab (MSI-H/dMMR)3 mg/kg IV. - **Day 1:** Ipilimumab 1 mg/g IV **(Every 3 weeks).**
18	**TAS-1 (Trifluridine + Tipiracil)**	- **Day 1-5:** TAS-1 (Trifluridine + Tipiracil) 35-80 mg/m^2. - **Day 8-12:** TAS-1 (Trifluridine + Tipiracil) 35-80 mg/m^2 **(every 4 weeks).**
19	**Regorafenib**	- **Day 1-2:** Regorafenib 80-160 mg Oral OD **(Every 4 week).**
20	**In Her-2 Amplified and RAS-WT**	- **Day 1:** Trastuzumab 4 mg/kg IV bolus in C1 then 2 mg/kg IV. - **Day 1-7**: Lapatinib 1000 mg oral OD **(weekly cycle).**
21	**In Her-2 Amplified and RAS-WT**	- **Day 1:** Trastuzumab 8 mg/kg IV bolus in C1 then 6 mg/kg IV. - **Day 1:** Pertuzumab 840 mg IV bolus in C1 then 420 mg IV **(three weekly cycle).**

9.3. Appendix: Metastatic Anorectal Ca

No	Regimen/Doses
1	- **Day 1-4:** 5FU 1000 mg/^{m2} CIVI. - **Day 1:** Cisplatin 60 mg/m2 IV (Every 3 weeks).
2	- **Every 2 weeks:** mFOLFOX6.
3	- **Day 1:** Paclitaxel 175 mg/^{m2} IV. - **Day 1:** Carboplatin AUC5 (Every 3 weeks).
4	- **Day 1**: Nivolumab 240 mg IV (Every 2 weeks). **Or** - **Day 1:** Nivolumab 480 mg IV (Every 4 weeks).
5	- **Day 1:** Pembrolizumab 200 mg IV (Every 3 weeks)

9.4. Appendix: CCRT in Localized Anorectal cancer.

No	Regimen/Doses
1	- **Day 1-4 and 29-32:** 5FU 1000 mg/m2 CIVI. - **Day 1:** Mitomycin 10 mg/m2 IV. - **Day 29:** with Concurrent Radiotherapy.
2	- **Day 1-5:** Capecitabine 825 mg/m2 oral BID for 6weeks. - **Day 1:** Mitomycin 10 mg/m2 IV. - **Day 29:** With Concurrent Radiotherapy.
3	- **Day 1-4 and 29-32:** 5FU 1000 mg/m2 CIVI. - **Day 1 and 29:** Cisplatin 75 mg/m2 IV. - **One 56-day** cycle without RT then **another 56-day** cycle with Concurrent Radiotherapy.

9.5. Appendix: Selection guidance in Metastatic Colorectal Cancer

No	First-line options
1	- Doublets (FOLFOX, CAPOX, OR FOLFRI) or triplets (FOLFOXRI in selected cases). - 5FU or Capecitabine used in unresectable asymptomatic or old age patients with co-morbidities.
2	- Bevacizumab can be combined with Capecitabine, 5FU, FOLFOX, FOLFRI (RAS MT), or FOLFOXIRI (BRAF Mutant).
3	- Anti-EGFR is combined with FOLFOX or FOLFRI. Capecitabine-based and bolus 5FU based doublets should not be combined with anti-EGFR.
4	- Anti EGFR antibody: mCRC, Left-sided RAS WT tumours.
5	- Right-sided mCRC RAS WT: Doublet or Doublet + Bevacizumab.
6	- An optimal sequence is still undetermined.
7	- Maintenance or Discontinuation: After induction therapy (6 of CAPOX or 8 of FOLFOX), if good disease and symptom control – maintenance with fluoropyrimidine plus bevacizumab (Bevacizumab alone is not recommended). - Individualization and discussion with the patient are needed.
8	- On clinical/radiologic progression – Proceed with 2nd line in eligible patients (Initial induction protocol can be re-introduced in the absence of significant toxicity and low DFI).
Second Line Treatment	
Valid option with patients of good PS and adequate organ function.	
1	- 2nd line treatment selection is based on treatment received in 1st line.
2	- Backbone chemotherapy should be changed in 2nd line from 1st line.
3	- Patients not exposed to Ant-VEGFR – Bevacizumab is the option.
4	- If patients received bevacizumab previously or show the rapid progression: **a)** Post progression continuation **b)** Aflibercept or Ramucirumab with FOLFIRI (Low DFI or progressive on treatment). **c)** In RAS-WT: Anti-EGFR antibodies with FOLFRI or Irinotecan (Low DFI or progressive on treatment).
Third Line Treatment	
1	- In RAS-WT and BRAF-WT not exposed to anti-EGFR: - Cetuximab or Panitumumab is justified.
2	- Regorafenib or TAS-102 in RAS WT with anti-EGFR (exposed to 5FU, irinotecan, Oxaliplatin, bevacizumab).

9.6. Appendix: The tests used for Colorectal Cancer Screening.

No	Tests
1	Colonoscopy.
2	Computed tomography (CT or CAT) colonography (CT/Virtual colonoscopy).
3	Double-contrast barium enema (DCBE).
4	Faecal immunochemical test (FIT).
5	Faecal occult blood test (FOBT).
6	Sigmoidoscopy.
7	Stool DNA test (sDNA).

9.7. Appendix: Recommendations for Post-Colonoscopy Follow-Up in Average-Risk Adults with Normal Colonoscopy or Adenomas.

Baseline colonoscopy finding	Recommended interval for surveillance colonoscopy	Strength of recommendation	Quality of evidence
Normal	10 y[b]	Strong	High
1-2 tubular adenomas <10 mm.	7-10 y[c]	Strong	Moderate
3-4 tubular adenomas <10 mm.	3-5 y	Weak	Very low
5-10 tubular adenomas <10 mm.	3 y	Strong	Moderate
Adenoma ≥10 mm.	3 y	Strong	High
Adenoma with tubulovillous or villous histology.	3 y[d]	Strong	Moderate
Adenoma with high-grade dysplasia [e].	3 y[d]	Strong	Moderate

>10 adenomas on single examination [e].	1 y	Weak	Very low
Piecemeal resection of adenoma ≥20 mm.	6 mo.	Strong	Moderate

a) All recommendations assume examination complete to cecum with bowel preparation adequate to detect lesions **>5** mm in size; recommendations do not apply to individuals with a hereditary CRC syndrome, personal history of inflammatory bowel disease, personal history of hereditary cancer syndrome, serrated polyposis syndrome, malignant polyp, personal history of CRC, or family history of CRC, and must be judiciously applied to such individuals, favoring the shortest indicated interval based on either history or polyp findings.

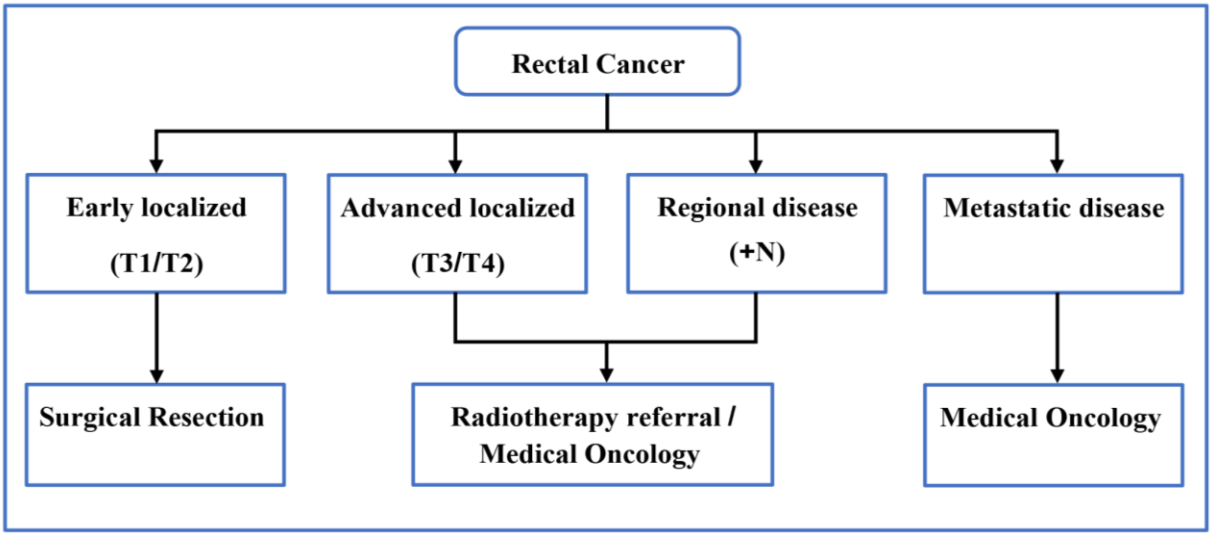
b) Follow-up may be with colonoscopy or other screening modality for average-risk individuals.

c) Patients with recommendations issued before 2020 for shorter than 7- to 10-year follow-up after diagnosis of 1–2 tubular adenomas may follow original recommendations. If feasible, physicians may re-evaluate patients previously recommended an interval shorter than 10 y and reasonably choose to provide an updated recommendation for 7- to 10-year follow-up, taking into account factors such as quality of baseline examination, polyp history, and patient preferences.

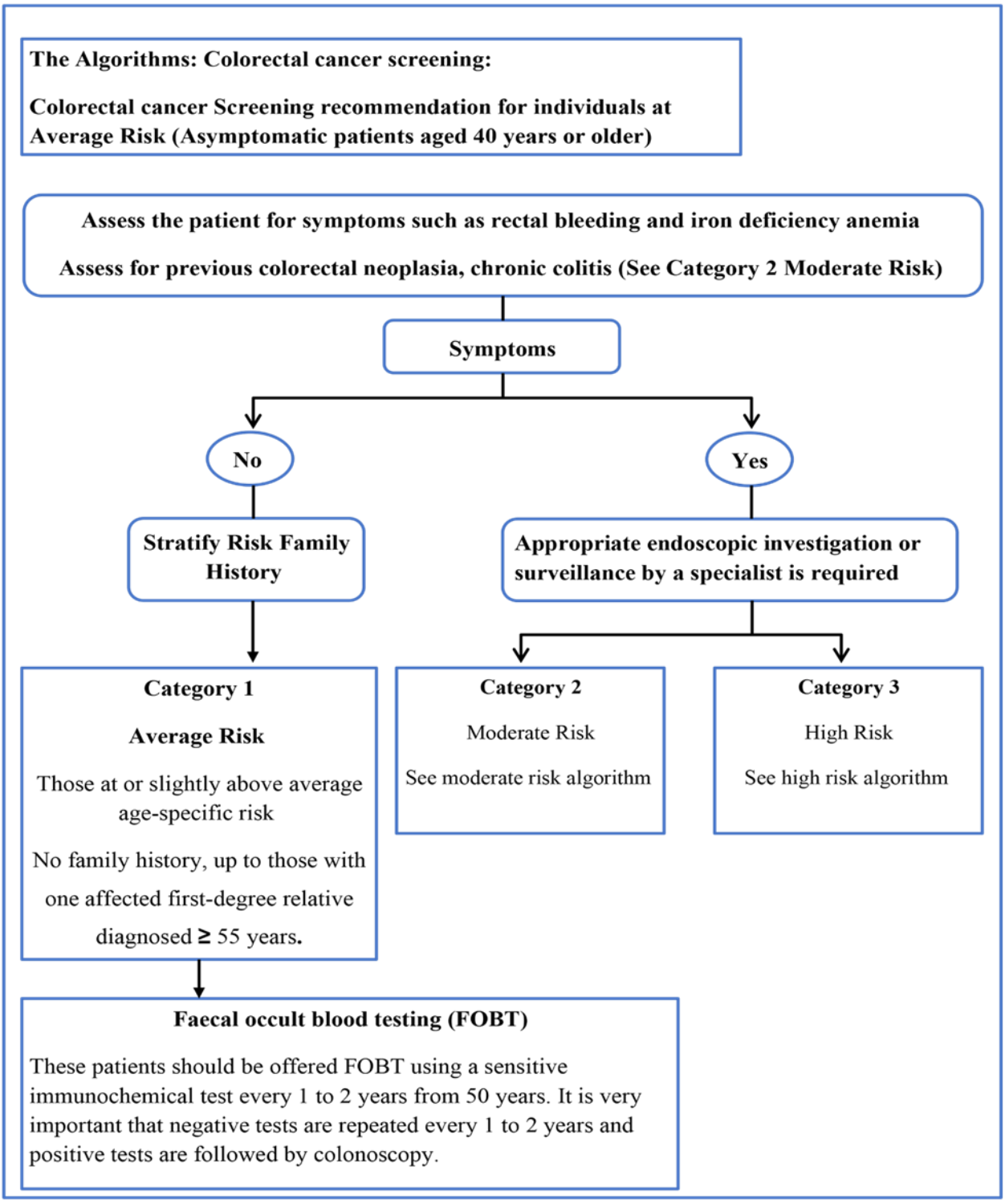
d) Assumes high confidence of complete resection.

e) Patients with **>10** adenomas or lifetime **>10** cumulative adenomas may need to be considered for genetic testing based on absolute/cumulative adenoma number, patient age, and other factors such as family history of CRC.

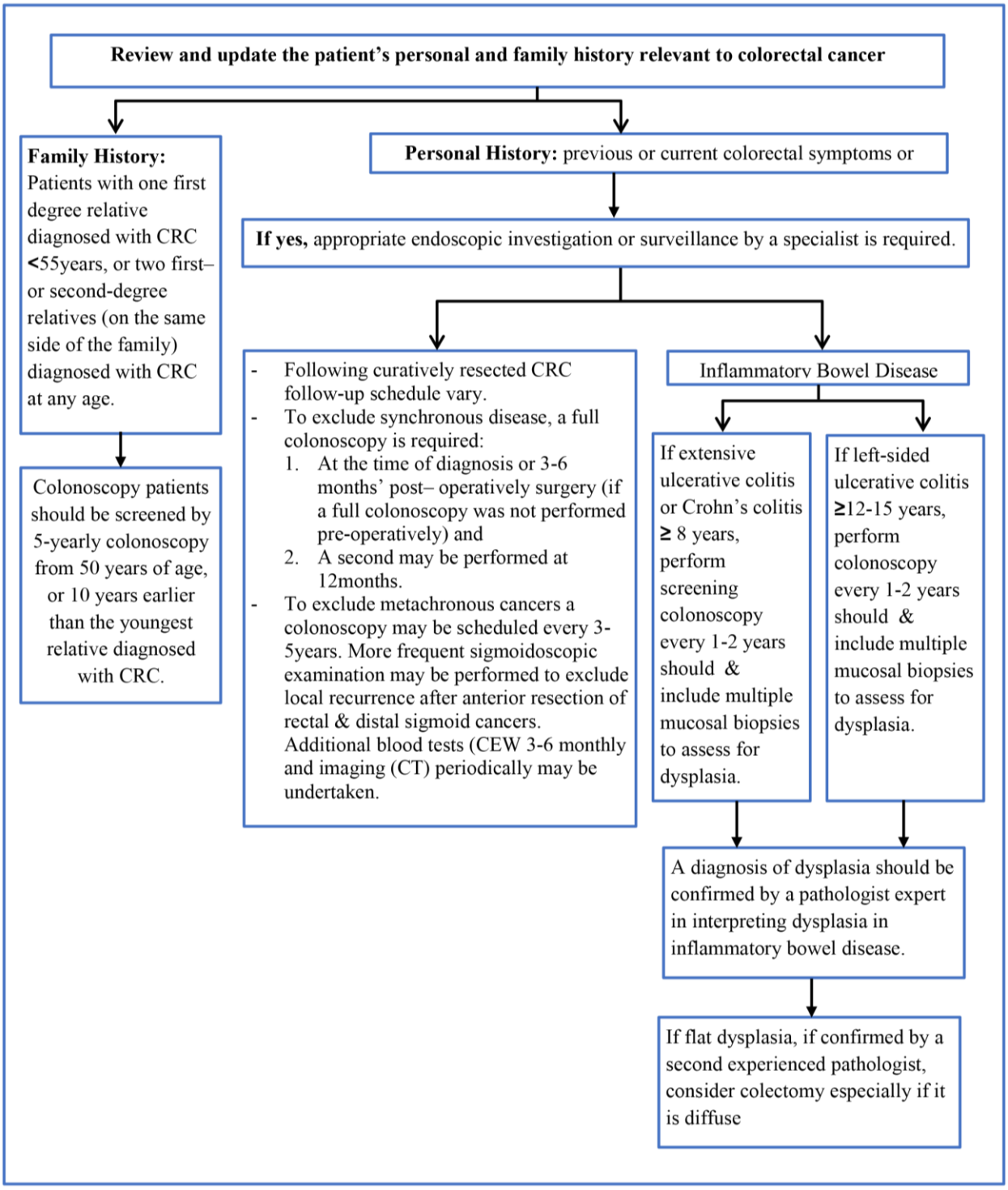
9.8. Appendix: Rectal cancer treatment by stage



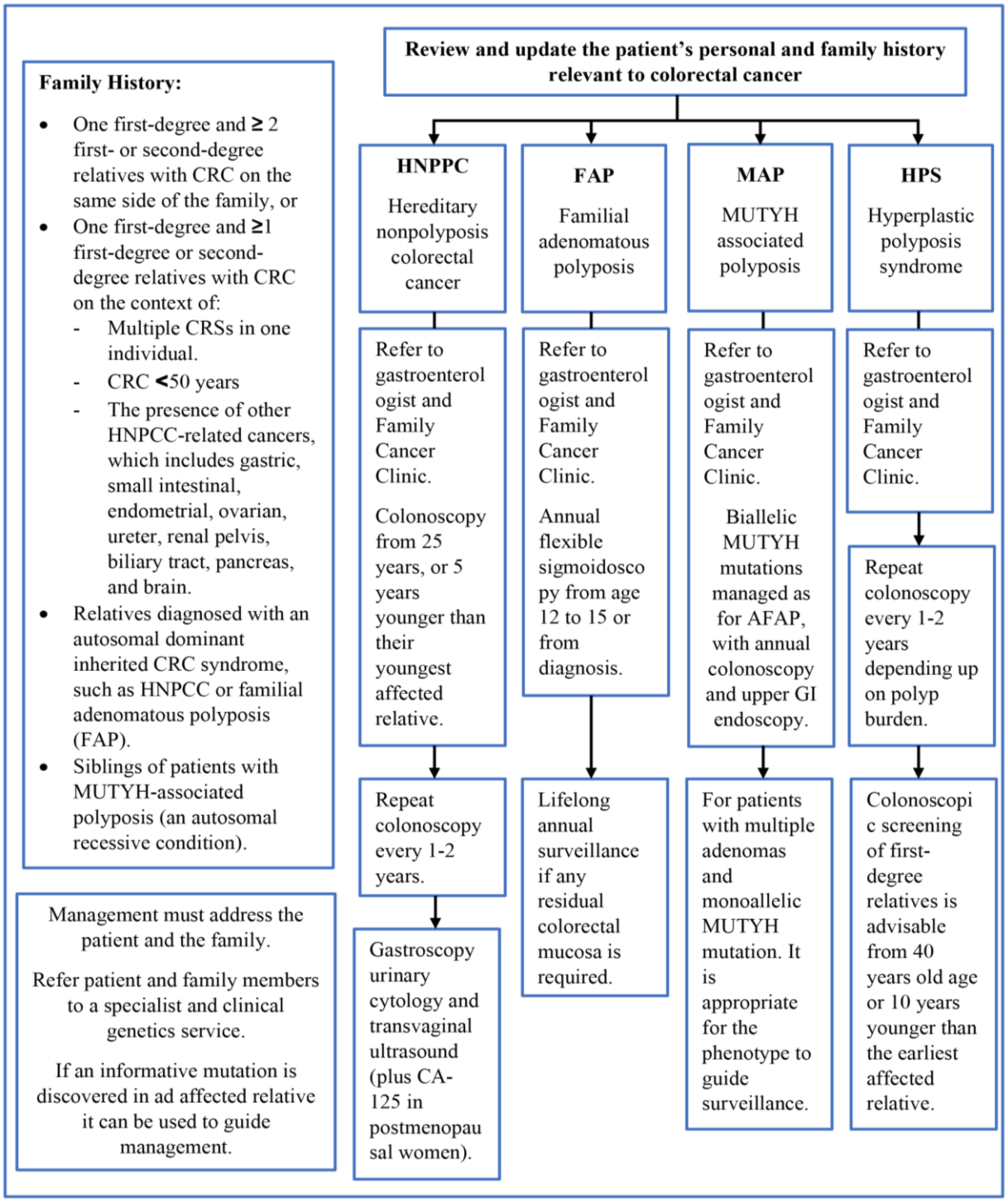
9.9. Appendix: CRC screening recommendation for individuals at Moderate Risk.



9.10. Appendix: CRC screening recommendation for individuals at High Risk.



9.11. Appendix: Indication for urgent referral pathway.



9.12. **Appendix:** Indication for FIT test