

# Rectal Cancer: Current Recommendations on Screening, Diagnostic Investigations and Treatment

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## Abstract

Despite periodic efforts in creating health awareness, no focused screening or early detection programmes for cancers have been strictly implemented within India. Rectal cancers have a relatively low incidence within the Indian population in comparison to those of the Western World. Combined with cancers of the colon, rectal cancers rank amongst the top five digestive malignancies in India with an apparently increasing incidence in sync with urbanization. Notably, if detected early these cancers could be completely cured or at the least treated to prolong survival. We provide a systematic guideline to screen, diagnose and treat rectal cancers.

## Introduction

Rectal cancer is one of the most frequently diagnosed GI malignancies in the Western World, and in combination with colon cancer it ranks third after cancers of the lung and breast in women/prostate in men in incidence and death rates in the United States. In India, rectal cancer is estimated to be the third most common digestive cancer after cancers of the oesophagus and stomach in men, and fourth most common after oesophagus, stomach and gall bladder cancers in women.<sup>1</sup> The incidence of rectal cancer in India is considered moderate-to-low (4-5/100,000 population) as compared to its incidence in the Western hemisphere (12-14/100,000 population).<sup>2</sup> The projected incidence of rectal cancer in India was estimated at 17,445 cases/year in 2001 and has been increasing since.<sup>1</sup> Screening programmes for cancers of the rectum (colon included) are rare in developing nations, like India, due to

which majority of the patients present with locally advanced disease. Surgery still remains the only curative treatment for rectal cancers, however neoadjuvant/adjuvant radiotherapy (RT) and chemotherapy are vital components of multimodal therapy. Fortunately enough, the gradual progression of these cancers allow possible identification of preneoplastic and early neoplastic lesions. Thus, an early and precise diagnosis of rectal cancers with currently available investigative tools create an opportunity to implement an appropriate multimodal therapeutic regimen in the view of achieving a complete cure or at the least prolonging survival in patients. We provide a systematic guideline for the management of rectal cancers-screening recommendations, diagnosis and staging of the disease, and therapeutic options.

## Screening for Rectal Cancer

Screening for rectal cancers, colon included, is strictly advocated in the West due to high prevalence of the disease, and because of the potential cure if preneoplastic or early neoplastic lesions are identified and removed endoscopically or surgically. Table 1 lists current recommendations for colorectal

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**Table 1 : Screening recommendations for rectal cancers, colon included**

Risk category	Screening Test	Age at which screening must begin
Average risk(asymptomatic and no identifiable risk factors-no personal history of colon cancer or adenomatous polyps, no family history of colon cancer, no inflammatory bowel disease and no unexplained anaemia)	One of the following: 1. Faecal occult blood testing (FOBT) annually* 2. Faecal immunochemical test (FIT) annually* 3. Flexible Sigmoidoscopy every 5 years* 4. FOBT + Flexible Sigmoidoscopy every 5 years* 5. Double-contrast barium enema every 5-10 years* <sup>†</sup> 6. Colonoscopy every 10 years	50 years
Family history of colon cancer	One of the following: 1. Double-contrast barium enema every 5 years* <sup>†</sup> 2. Colonoscopy every 10 years	40 years or 10 years younger than the age at which the youngest family member was diagnosed with colon cancer-whichever is earlier
Hereditary Nonpolyposis Colon Cancer (HNPCC)	1. Colonoscopy every 1-3 years 2. Genetic counselling (and optional genetic testing)	21 years
Familial Adenomatous Polyposis (FAP)	1. Flexible Sigmoidoscopy* or Colonoscopy every 1-2 years 2. Genetic counselling (and optional genetic testing)	Puberty
Ulcerative Colitis (UC)	Colonoscopy with biopsy every 1-2 years	7-8 years after the diagnosis of pancolitis, or 12-15 years after the diagnosis of left-sided colitis

\*Positive test demands a prompt colonoscopy. <sup>†</sup>Recommend rigid proctoscopy and flexible sigmoidoscopy to evaluate distal rectum and tortuous sigmoid, respectively.

cancers.

### Staging of Rectal Cancer

Rectal cancers, colon included, are staged following intrabdominal surgical exploration and pathological analysis of the excised specimen(s) (Table 2). Pathologic evaluation must include: tumour histologic grade (G), depth of tumour invasion (T), number of malignant regional lymph nodes (N), assessment of metastasis (M), and the status of proximal and distal margins of the resected tissue. A minimum of 12 regional lymph nodes must be analyzed to precisely stage the tumour. Involvement of the apical lymph

**Table 2 : TNM staging system for colorectal cancer as per american joint committee on cancer<sup>3</sup>**

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
	T2	N0	M0
IIA	T3	N0	M0
IIB	T4	N0	M0
IIIA	T1-T2	N1	M0
IIIB	T3-T4	N1	M0
IIIC	Any T	N2	M0
IV	Any T	Any N	M1

node (most proximal node within 1 cm of vessel ligation at the apex of vascular pedicle) is associated with adverse outcome. Circumferential resection margin (CRM) is the radial margin between the deepest penetration of the tumour and resected soft tissue margin around the rectum. Tumour within 1-2 mm from the transected margin is considered a positive CRM. CRM is a strong predictor of both local recurrence and overall survival, hence its assessment is vital in staging rectal cancer.

#### **Primary Tumour (T)**

- TX Primary tumour cannot be assessed  
 T0 No evidence of primary tumour  
 Tis Carcinoma *in situ*  
 T1 Tumour invades submucosa  
 T2 Tumour invades muscularis propria  
 T3 Tumour invades through the muscularis propria into the subserosa, or into non-peritonealized pericolic or perirectal tissues  
 T4 Tumour perforates visceral peritoneum and/or directly invades other organs/structures

#### **Regional Lymph Nodes (N)**

- NX Regional lymph nodes cannot be assessed  
 N0 No regional lymph node metastasis  
 N1 Metastasis in 1 to 3 regional lymph nodes  
 N2 Metastasis in > 4 regional lymph nodes

#### **Distant Metastasis (M)**

- MX Distant metastasis cannot be assessed  
 M0 No distant metastasis  
 M1 Distant metastasis

#### **Histologic Grade (G)**

- GX Grade cannot be assessed  
 G1 Well differentiated

G2 Moderately differentiated

G3 Poorly differentiated

G4 Undifferentiated

#### **Management of a Malignant Rectal Polyp**

- A polyp with cancer invading the submucosa (T1) is by definition a malignant polyp.
- The polyp site must be marked at colonoscopy if suspicious of cancer or within 2 weeks of the polypectomy when the pathology is known.
- In a malignant polyp (pedunculated or sessile) with favourable histological features (grade 1 or 2 lesions, absence of lymphovascular invasion and negative resection margin), a polypectomy is adequate. However, the option of colectomy must be offered for a sessile polyp since a 10% risk of lymph node metastases has been reported.<sup>4</sup>
- In a malignant polyp (pedunculated or sessile) with unfavourable histological features (grade 3 or 4 lesions, presence of lymphovascular invasion and positive resection margin) or with fragmented specimen or non-assessable margins, transanal or transabdominal polypectomy with en bloc resection of lymph nodes is recommended.
- Total colonoscopy to exclude synchronous polyps and appropriate follow-up surveillance endoscopy must be performed.
- Adjuvant chemotherapy is not recommended for Stage I lesions.

#### **Management of Invasive Nonmetastatic Rectal Cancer**

- Complete staging workup
  - Histopathological tissue examination

- o Total colonoscopy and proctoscopy
- o Complete blood count
- o Chemistry profile
- o Carcinoembryonic antigen (CEA) level
- o Computed tomography (CT) scan of the chest, abdomen and pelvis
- o Note:
  - Positron emission tomography (PET) scan is not recommended in the absence of evidence of metastatic disease.
  - Endorectal ultrasound (US) and endorectal or pelvic magnetic resonance imaging (MRI) may facilitate preoperative staging, with the latter study potentially capable of predicting CRM prior to surgery.
- Surgery for resectable rectal cancer
  - o Transanal excision if the tumour:
    - is small (< 3 cm).
    - is grade 1 or 2 lesion.
    - occupies < 30% of rectal circumference.
    - is within 8 cm of the anal verge.
  - o Radical procedure involving a transabdominal resection, preferably an organ-preserving procedure which maintains sphincter function, if the tumour:
    - is grade 3 or 4 lesion.
    - has positive margins.
    - has lymphovascular or perineural invasion.
  - o Radical procedure depends on the location of primary rectal lesion.
    - Mid-upper rectum:
      - Low anterior resection (LAR) ± colostomy (dependent on possibility of a coloanal anastomosis).
- Low rectum:
  - Total mesorectal excision (TME) + coloanal anastomosis (if intact anal function and adequate distal clearance exists).
    - TME involves en bloc resection of mesorectum and associated lymphovascular structures, fatty tissue and mesorectal fascia, particularly sparing the autonomic nerves.
  - Abdominoperineal resection (APR) + colostomy (if tumour involves the anal sphincter).
    - APR involves en block resection of the rectosigmoid and anus with the surrounding mesentery, mesorectum and perianal soft tissue.
- o Excision and analysis of ≥ 12 lymph nodes to establish a diagnosis of ≥ Stage II rectal cancer is necessary.
  - Apical lymph nodes and those suspicious outside the resection field should also be biopsied.
  - The number of lymph nodes obtained is proportional to the accuracy of staging the cancer, and is vital prognostically in determining disease recurrence and overall survival.
- Neoadjuvant/adjuvant therapy for resectable rectal cancer
  - o Adjuvant therapy of rectal cancer often

includes locoregional treatment due to relatively high risk of locoregional recurrence.

- o Concurrent fluoropyrimidine-based chemotherapy with RT is recommended.
- o RT exerts local tumouricidal effect, reducing tumour mass and facilitating the possibility of a sphincter-sparing resection.
  - The field of radiation must include the following:
    - Tumour/tumour bed with a 2.5 cm margin
    - Presacral nodes
    - Internal iliac nodes
    - External iliac nodes (for T4 tumours)
    - Inguinal nodes (if tumour invades distal anal canal)
  - Recommended doses of radiation are:
    - 45–50 Gy for resectable cancer.
    - > 54 Gy for unresectable cancer.
    - ≤ 45 Gy if small bowel is being irradiated.
  - Apply intensity modulated radiotherapy (IMRT) to concentrate on the tumour site and limit toxicity to the surrounding normal tissue.
  - Intraoperative radiotherapy (IORT) should be considered with T4 tumours or recurrent cancers to facilitate resection.
  - Studies evaluating use of preoperative RT in rectal cancer have shown improved local

control, increased survival and decreased local recurrence rates.<sup>5-7</sup>

- o Combining chemotherapy with perioperative RT increases radiosensitivity, thus potentiating sphincter preservation.
  - Preoperative chemoRT involves infusional 5-FU chemotherapy administered concurrently with radiation.
  - Postoperative chemoRT employs a “sandwich” approach—5-FU-based chemotherapy administered before and after chemoRT regimen.
  - An interval of 5-10 weeks following completion of preoperative chemoRT is recommended prior to surgical resection.
  - Studies evaluating preoperative chemoRT have showed significantly lower local recurrences and increased rate of sphincter preservation, but also its association with increased toxicity.<sup>8, 9</sup>
- o Adjuvant chemotherapy of 6 months duration is also recommended for Stage II and Stage III rectal cancer following neoadjuvant chemoRT/surgery, and it includes:
  - FOLFOX: 5-Fluorouracil (5-FU) + Leucovorin (LV) + Oxaliplatin (OX) (standard of care), or
  - Capecitabine, or
  - 5-FU/LV
- Summarized recommendations for invasive rectal cancer without metastases
  - o T1 or T2 lesions

- Perform a transanal excision of the lesion and review the histopathology.
  - If T1 lesion is well-differentiated, no additional therapy is required.
  - If T1 lesion is poorly-differentiated, or reveals positive margins or lymphovascular invasion, re-resect the lesion transabdominally.
  - If T2 lesion is well-differentiated, or reveals negative margins or no lymphovascular invasion, perform a transabdominal re-resection or administer 5-FU/RT.
- If unable to excise the lesion transanally, perform a transabdominal excision and review the histopathology.
  - If T1 or T2 lesion, no adjuvant therapy is required.
  - If T3 or nodal disease is identified, administer adjuvant chemotherapy with a “sandwich” approach.
- o T3 lesions or lesions with lymph node involvement
  - Perform a transabdominal resection 5-10 weeks following completion of preoperative chemoRT, and subsequent adjuvant chemotherapy of 6 months duration is recommended.
    - If initially treated with transabdominal resection and pathologic evaluation downstages to T1/T2 lesion, only observation is required.
    - If initially treated with transabdominal resection without preoperative chemoRT, 6 months of adjuvant therapy is required.
- o T4 lesions and/or locally unresectable disease
  - Perform a transabdominal resection (if possible) 5-10 weeks following completion of preoperative chemoRT, and subsequent adjuvant chemotherapy of 6 months duration is recommended.
- In unresectable or medically inoperable cancer, palliative therapy involving RT for uncontrolled bleeding, stent insertion for obstruction, or supportive care should be considered.

### **Management of Metastatic Rectal Cancer**

Approximately 50-60% of colorectal cancer patients will develop metastases to the liver, lung and abdominal peritoneum. Almost 15-25% colorectal patients develop synchronous hepatic metastases, and 80—90% of these have unresectable disease at diagnosis. Metastatic disease more frequently develops metachronously following treatment for colorectal cancer, with the liver being the most common site of involvement. Reports of 5-year survival rates for patients with metastatic liver disease without metastatectomy have been shown to approach 0%,<sup>10,11</sup> whereas others have shown 5-year survival rates following hepatic colorectal metastatectomy exceeding 50%.<sup>12, 13</sup>

- Approaches in hepatic metastatectomy
  - o Preoperative portal vein embolization performed to increase volume and function of residual hepatic tissue

- postoperatively.
- o Hepatic resection is performed in two stages for bilobar disease.
  - o Ablative methods (radiofrequency ablation or cryosurgery) are used only in combination with resection and only if negative margins are unattainable by resection alone.
  - Neoadjuvant chemotherapy is increasingly employed in metastatic rectal disease due to its potential to convert unresectable disease to a resectable state.
    - o Following are its advantages and disadvantages:
      - Advantages:
        - Early treatment of micrometastatic disease.
        - Determination of responsiveness to chemotherapy.
        - Avoidance of local therapy for those with early disease progression.
      - Disadvantages:
        - Chemotherapy-induced liver injury.
        - Surpassing a resectable state due to either disease progression or unresponsiveness to chemotherapy.
    - o Recently, bevacizumab has been added to chemotherapy for treatment of unresectable metastatic disease, and at least a 6-week interval between the last dose of bevacizumab and elective surgery is recommended.
    - o Surgery must be performed immediately once the disease becomes resectable, and usually within 3–4

months following initiation of neoadjuvant chemotherapy.

- Treatment for pulmonary metastases is similar to that for the liver, except without the option of hepatic arterial infusion (HAI) device insertion at liver resection for subsequent administration of chemotherapy directly to liver metastases.
- Systemic adjuvant chemotherapy for metastatic disease is recommended following liver or lung resection to eradicate residual micrometastases.
- The goal of treatment in most abdominal/peritoneal metastases is palliative rather than curative, and cytoreductive resection of disseminated carcinomatosis.

#### **Management of Synchronous Metastatic Rectal Cancer**

- Preoperative baseline PET scan must be performed only if prior imaging indicates potentially curable metastatic disease.
- PET scan must not be used to re-evaluate metastatic disease following chemotherapy as it may misinterpret the disease status because of false positive (due to tissue inflammation following surgery or infection) and false negative (due to the presence of necrotic lesions) results.
- Preoperative MRI with intravenous contrast should be considered in potentially resectable hepatic metastases.
- Resectable Synchronous Metastases
  - Preoperative chemoRT (targeted towards primary rectal lesion) and neoadjuvant chemotherapy with bevacizumab-containing regimen (targeted towards metastatic disease) followed by staged metastatectomy and

excision of rectal lesion 5—10 weeks after completion of neoadjuvant chemotherapy should be performed.

- Postoperative chemoRT (“sandwich regimen”) is recommended if preoperative chemoRT is not administered or a high risk for pelvic recurrence exists.
- In case of a resectable solitary pulmonary lesion, excision of the rectal lesion followed by staged thoracotomy and pulmonary nodule resection must be performed.
- In the presence of moderate to severe obstructive symptoms secondary to the primary rectal cancer, its prompt resection is essential.
- Adjuvant chemotherapy of 6 months duration must be offered following complete liver or lung metastatectomy, and HAI therapy in the case of liver metastases only.
- Unresectable Synchronous Metastases
  - Similar treatment algorithm as in resectable synchronous metastases with the exception of preoperative chemotherapy aimed at converting the disease to a resectable state, as well as adjuvant chemotherapy of 6 months duration.
  - Ablation of hepatic metastases at the time of rectal lesion excision should be performed if all metastases can be treated.
  - Symptomatic rectal cancer must be treated with chemotherapy alone, or with chemoRT and resection of the

involved rectal segment or laser canalization or diverting colostomy or stenting.

- Asymptomatic rectal cancer should be treated with chemotherapy for advanced or metastatic disease.
- Unresectable hepatic metastases unresponsive to systemic therapy should receive salvage therapy for advanced or metastatic disease.
- Synchronous abdominal/peritoneal metastases
  - If obstructive symptoms exist a diverting colostomy must be performed followed by chemotherapy.
  - In the absence of obstruction only chemotherapy should be offered.

#### **Management of Metachronous Metastatic Rectal Cancer**

- PET scan must be performed to evaluate and identify sites of metastases.
- Two factors that distinguish management of metachronous metastatic disease from that of synchronous disease are:
  - Evaluation of prior chemotherapy
  - Absence of transabdominal resection
- Resectable disease:
  - If there is no history of prior chemotherapy, neoadjuvant chemotherapy followed by surgery and post-operative chemotherapy is recommended, or
  - If there is history of prior chemotherapy, surgery followed by adjuvant chemotherapy with an alternative regimen is recommended.
- Unresectable disease:
  - Administration of neoadjuvant chemotherapy or change to an alternative regimen if already

receiving one is recommended.

- If converted to a resectable state, metastatectomy should be performed with an additional option of HAI therapy for liver metastases.
- If disease remains unresponsive, subsequent treatment depends on the performance status of the patient and usually involves supportive care.
- Isolated pelvic/anastomotic recurrences are optimally managed by preoperative chemoRT followed by resection if possible.

#### **Chemotherapy for Advanced or Metastatic Rectal Cancer**

- Principles to consider prior to initiation of therapy:
  - Evaluation of the efficacy and safety of chemotherapeutic regimens individualized for each patient.
  - Pre-planned strategies for altering therapy in both the presence and absence of disease progression, or if severe toxicities arise.
- Choice of chemotherapy regimens are:
  - FOLFOX
  - CapeOX: Capecitabine + Oxaliplatin
  - FOLFIRI: 5-Fluorouracil + Leucovorin + Irinotecan
  - 5-FU/LV
- Addition of bevacizumab to fluoropyrimidine-based chemotherapy has produced favourable results,<sup>14, 15</sup> hence is recommended. However, addition of bevacizumab to an alternative therapy is not suggested following clinical failure of a previous bevacizumab-containing regimen.

- Therapeutic options after first progression of the disease are:

- If treated initially with 5-FU/LV-based regimen
  - Irinotecan ± cetuximab
- If treated initially with FOLFOX/ CapeOX-based regimen
  - FOLFIRI ± cetuximab
- If treated initially with FOLFIRI-based regimen
  - FOLFOX/ CapeOX/ cetuximab/ panitumumab
- If treated initially with 5-FU/LV without oxaliplatin or irinotecan
  - FOLFOX/ CapeOX/ FOLFIRI

#### **Post-Treatment Surveillance**

- Successfully treated Stage I—Stage III rectal cancer (no evidence of residual disease).
  - History and physical examination
    - every 3—6 months for 2 years, and then
    - every 6 months for 5 years
  - Carcinoembryonic antigen (CEA) level
    - at baseline, and
    - every 3—6 months for 2 years, and then
    - every 6 months for 5 years (for ≥ T2 lesion)
  - Colonoscopy
    - within 1 year of resection or 3—6 months if not performed preoperatively, and
    - repeat in 3 years if colon is free of polyps followed by colonoscopic surveillance every 5 years, or
    - if first follow-up colonoscopy is abnormal, repeat colonoscopy after 1 year and if colon is free of

- polyps repeat in 3 years followed by colonoscopic surveillance every 5 years
  - o CT scan of the chest, abdomen and pelvis
    - recommended annually every 3 years in Stage III patients at high risk for recurrence, and
    - may be considered annually every 3 years in Stage II patients at high risk for recurrence
- In successfully treated Stage IV patients (no evidence of residual disease) surveillance recommendations are similar except:
  - o CT scan of the chest, abdomen and pelvis
    - every 3—6 months for 2 years, then
    - every 6—12 months for 5 years
  - o Carcinoembryonic antigen (CEA) level
    - at baseline, and
    - every 3 months for 2 years, and then
    - every 6 months for 3—5 years
  - Proctoscopy must be considered every 6 months for 5 years to evaluate for local recurrence at the rectal anastomosis following an LAR.

#### **Managing an Increasing Carcinoembryonic Antigen (CEA) Level**

- Perform the following:
  - o Physical examination
  - o CT scan of the chest, abdomen and pelvis
  - o Colonoscopy
    - If imaging studies are normal, repeat scans every 3 months if symptomatic.

- PET scan may be used to determine if isolated metastases exists despite of negative CT scans.
- PET scan must be considered before surgical resection in suspected recurrence or confirmed metastases by CT, MRI and/or biopsy exists.

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