



Localized Rectal Cancer: Indian Consensus and Guidelines

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Abstract

The rising incidence of colorectal cancer (CRC) in India, particularly the prevalence of rectal cancer over colon cancer (0.7:1), has been a growing concern in recent decades; especially notable is the trend of increasing cases among young CRC patients. Given the diverse treatment approaches for rectal cancer globally and the varying economic capacities of patients in low to middle-income countries (LMICs) like India, it is essential to establish consensus guidelines that are specifically tailored to meet the needs of these patients. To achieve this, a panel comprising 30 eminent rectal cancer experts convened to conduct a comprehensive and impartial evaluation of existing practices and recent advancements in the field. Through meticulous scrutiny of published literature and a consensus-building process that involved voting on pertinent questions, the panel formulated management strategies. These recommendations are the result of a rigorous, evidence-based process and encapsulate the collective wisdom and judgment of leading authorities in the field.

Keywords

- Indian consensus and guidelines
- early rectal cancer
- MRI
- MSI

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide. According to Globocan data 2020,¹ in India, CRC accounted for 6.7% (89,937) of all cancer cases and 7.7% (65,068) of all deaths, with a cumulative risk of 1.85. The incidence of CRC in India has been increasing over the past few decades, with the National Cancer Registry Programme (NCRP) estimating 70,220 new cases in 2020. Men are more commonly affected than women, with an incidence rate of 10.8 per 100,000 men and 7.5 per 100,000 women. According to a recent study presented in the *Journal of Clinical Oncology* by All India Institute of Medical Sciences, the prevalence and incidence of rectal cancer in India are observed to be higher than colon cancer, with colon to rectal cancer ratio being 0.7:1.² Further analysis showed that the mean age at presentation for colon cancer was 51 years, whereas for rectal cancer, it was 45 years. Notably, a considerable proportion of patients qualified as young CRC (diagnosed at or before the age of 40 years), accounting for 34.7% of the total patient cohort. Among this group of young CRC patients, rectal cancer was observed more frequently than colon cancer, with proportions of 41.3 and 25.4%, respectively. In light of different approaches to rectal cancer treatment worldwide, such as variations in the strategies recommended by organizations like the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO), and the differing financial situations of patients in India, including some who are covered under government schemes while others face out-of-pocket expenses, it is necessary to develop consensus guidelines that are tailored to the needs of our population. Our initial step toward promoting collaboration involved gathering and scrutinizing the published literature in order to produce an informative guide specifically tailored to rectal cancer patients in low- or middle-income country such as India.

Methodology

Our recommendations for rectal cancer management (►Tables 1–11; ►Fig. 1) were derived from the existing guidelines established by NCCN and ESMO. To ensure a comprehensive and unbiased assessment, we gathered a panel of 30 renowned experts in the field of rectal cancer and requested their participation in voting on relevant questions. (►Supplementary) All panel members were urged to vote on every question, with those with potential conflicts of interest advised to abstain from voting on that particular issue. The panel then discussed the recommendations, highlighting areas of substantial disagreement or controversy. After incorporating recent advances and rectifying any inaccuracies, the revised recommendations were circulated to all panel members via email for further review. In accordance with the ESMO guideline methodology, each recommendation is accompanied by a level of evidence and grade of recommendation, which reflect the strength of the available evidence and the degree of agreement among experts, respectively³ (►Appendix). These assessments are further substantiated by a consensus determined by the number of experts who agreed to a given recommendation relative to the total number of experts who voted. These rigorous standards ensure that these recommendations are grounded in a thorough and systematic evaluation of the available evidence, and reflect the collective expertise and judgement of the leading experts.

Screening

Globally, individuals between the ages of 65 and 74 years are the most commonly diagnosed group with CRC.⁴ However, it is estimated that approximately 1 in 10 newly diagnosed cases of CRC are observed in individuals who are below 50 years of age.⁵ The incidence of CRC, specifically adenocarcinoma, has risen by almost 15% between 2000 to 2002 and

Table 1 Indian consensus and guidelines: screening

Guidelines	LoE	GoR	Consensus
Statement 1 ^{2,7}			
CRC screening may be done for adults (without any family history of cancer) between the age of 40 to 75 years ^{1,2}	V	A	22/26
Statement 2 ⁷			
Stool-based tests or direct-visualization tests are acceptable for screening as long as they are performed as per the recommended frequency ◦ Stool-based tests are cheap and freely available. FIT is preferred over gFOBT and should be repeated once every year ◦ Flexible sigmoidoscopy can be performed once every 5 years ◦ Colonoscopy can be performed once every 10 years (if no adenoma or carcinoma detected)	I	A	24/25
Statement 3 ⁸			
Currently, there is no role of ctDNA based screening for colorectal cancers	Expert opinion	Expert Opinion	26/27

Abbreviations: CRC, colorectal cancer; FIT, fecal immunohistochemical test; gFOBT, guaiac-based fecal occult blood test; GoR, grade of recommendation; LoE, level of evidence.

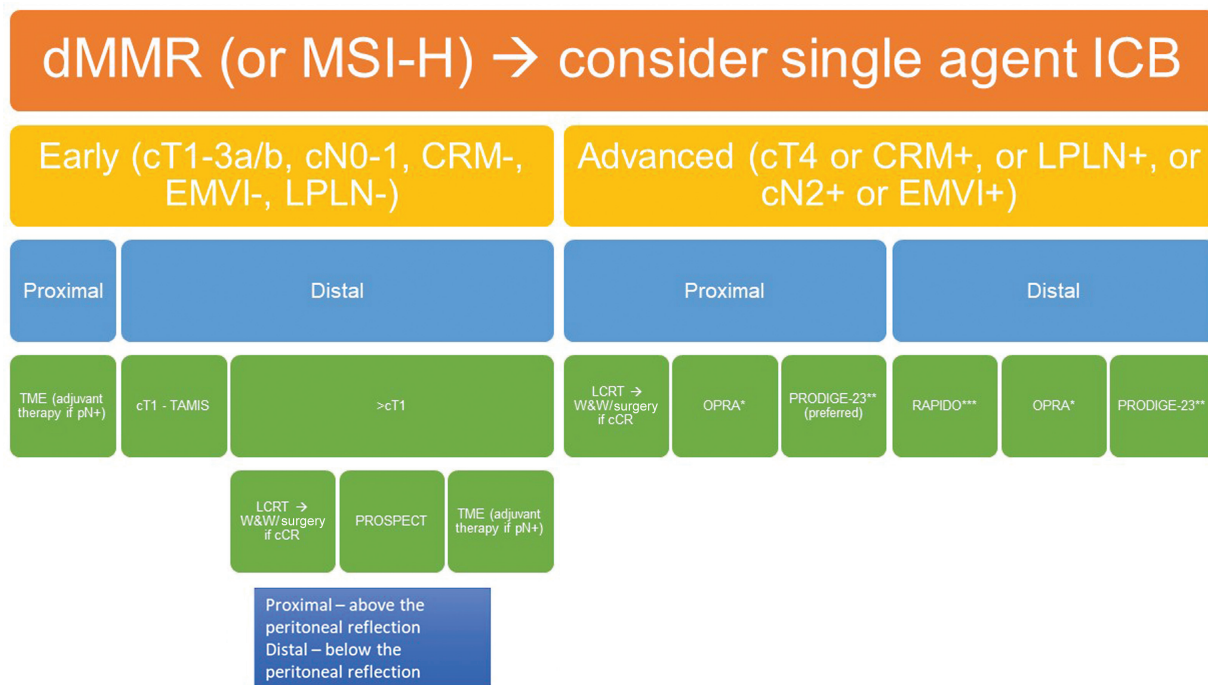


Fig. 1 An algorithm for management of localized rectal cancer. TME – Total mesorectal excision; TAMIS – Transanal minimally invasive surgery; LCRT – 1.8 Gy x 25# radiotherapy with chemotherapy (capecitabine); PROSPECT – perspective FOLFOX and selective RT followed by TME; PRODIGE-23 – Induction mFOLFIRINOX for 2 to 3 months → LCRT → TME or W&W (if cCR); RAPIDO– SCRT→ Consolidation CAPOX or FOLFOX for 3 to 4 months → TME or W&W (if cCR); OPRA – LCRT → Consolidation CAPOX or FOLFOX for 3 to 4 months →TME or W&W (if cCR); cCR – Clinically complete response. * preferred if the goal is to achieve cCR for W&W approach; * preferred if N2 or EMVI where risk of distant failure high. Adjuvant FOLFOX or COPOX after TME. *** may have higher local recurrence compared to LCRT.

2014 to 2016 among adults aged between 40 and 49 years,⁶ leading to a renewed focus on young onset CRC.

CRC typically originates from precancerous polyps located in the colon and rectum. Effective screening tests can detect these polyps or identify CRC in its early stages. A panel of experts has reached a consensus with a high level of confidence that screening for CRC in adults aged between 40 and 75 years provides a favorable overall outcome. Additionally, the panel agrees that screening adults aged 76 years or older, who have previously undergone screenings, still offers a modest benefit. Lastly, individuals who have never undergone CRC screening are more likely to experience advantages from the screening process.

These guidelines pertain to individuals aged 40 and above who do not display any symptoms and are considered to have an average risk of developing CRC. Average risk refers to individuals who have not previously been diagnosed with CRC, adenomatous polyps, or inflammatory bowel disease. Furthermore, it includes individuals who do not have a personal or family history of hereditary cancer predisposition syndromes, such as Lynch syndrome or familial adenomatous polyposis, which substantially increase the likelihood of developing CRC.

Consistent with the guidelines provided by the US Preventive Services Task Force,⁷ the panel advises the following recommended time intervals for screening using stool-based and direct visualization tests: a yearly administration of the high-sensitivity fecal immunochemical test (FIT), a screening interval of 5 years for flexible sigmoidoscopy, and a screening

interval of 10 years for colonoscopy. It should be emphasized that if the results of the FIT-based screening test indicate a positive finding, follow-up with colonoscopy is necessary to fully realize the benefits of screening.

Although circulating tumor DNA (ctDNA)-based tests have shown promise in assessing patient treatment and prognosis, there is currently minimal evidence to support the use of ctDNA-based screening tests in detecting CRC.⁸ Therefore, the panel confers opinion that ctDNA-based screening tests for CRC are of limited usefulness at present (► **Table 1**).

Genetic Testing

The panel had a broad consensus that genetic counseling should be advised to every patient with CRC, regardless of age at cancer diagnosis or family history of cancer. However, due to limited availability of genetic testing and counseling services at all tiers in the healthcare system and the cost of testing being a deterrent to the patient, it was noted that provision of genetic counseling for all patients may not be available in certain centers.⁹ Nonetheless, efforts should be made to provide pretreatment genetic counseling due to its impact on treatment stratification, prognosis, surgical intervention, and prevention of cancer in other family members.¹⁰

Lynch syndrome, formerly known as hereditary non polyposis CRC, is the most common hereditary cancer predisposition syndrome that is caused due to variants of the

Table 2 Indian consensus and guidelines: genetic testing

Guidelines	LoE	GoR	Consensus
Statement 4 ^{9,10}			
Genetic counseling could be offered to every patient with colorectal cancer, preferably before the start of treatment. For those who are not ready to consider genetic issues at diagnosis, efforts could be made to offer again at follow-up to address issues of surveillance and other primary tumors	III	C	25/27
Statement 5 ¹¹			
- Genetic testing should be performed according to age, cancer history/ pathology, tumor MSI/ MMR status, and family history. - Germline MMR genes are the most frequently mutated genes; other moderate-to-high-penetrance gene testing are to be considered only when deemed appropriate by a genetic counselor / physician	II	A	29/29

Abbreviations: GoR, grade of recommendation; LoE, level of evidence; MMR, mismatch repair; MSI, microsatellite instability.

mismatch repair (MMR) genes, chiefly—*MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*. Germline testing for these genes individually or as part of a broader sequencing panel may be offered to patients with age of diagnosis less than 50 years, those with first and or secondary relatives with a history of Lynch syndrome-associated cancers, those who have synchronous or metachronous cancer, or those who are deemed high risk based on Amsterdam II or revised Bethesda criteria by genetic counsellor and/or treating clinician.¹¹

Practice of genetic counseling and germline testing should be in adherence to the latest national and/or international guidelines. The clinical utility of identification of moderate penetration gene/s in multigene testing is still lacking and this needs to be discussed with patients in both the pre- and post-testing counseling. For those patients who are not ready to undergo genetic testing at diagnosis, access to genetic counseling and testing should be offered again at follow-up to address issues of surveillance, risk of other primary tumors, and risk stratification for the relatives. Patients and their first-degree relatives with a pathogenic or likely pathogenic variant(s) in one of the MMR genes can be offered post-test genetic counseling regarding their risk of cancer by site, age, and affected MMR gene together with approaches to surveillance and cancer prevention interventions in order to reduce risk of cancer^{12,13} (► **Table 2**).

Staging

The expert panel recommended that all patients diagnosed with early rectal cancer undergo a comprehensive evaluation, which should include a complete physical examination, blood tests to assess complete blood count, liver function tests (LFTs), renal function tests, and serum carcinoembryonic antigen (CEA) levels. This evaluation should also assess the patient's performance status to determine their operative risk. In addition to a digital rectal examination (DRE), patients should also undergo sigmoidoscopy or full-length colonoscopy to exclude synchronous colonic tumors.

DRE is crucial in determining the location of rectal cancers in relation to the anal margin and for planning primary surgery or a neoadjuvant approach. Abnormal LFTs, particularly

elevated levels of alkaline phosphatase, may indicate liver pathology and suggest the possibility of liver metastases. Significantly elevated serum CEA levels should raise suspicion of metastasis, and additional clinical imaging for further staging evaluation should be considered.

The preferred staging system for CRCs is the tumor, node, metastasis (TNM) staging system, developed by the combined American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control.¹⁴ In the 8th edition of the AJCC Cancer Staging Manual, T1 tumors are characterized by involvement of the submucosa, while T2 tumors infiltrate into the muscularis propria. T3 tumors penetrate through the muscularis propria, and T4a tumors directly penetrate to the surface of the visceral peritoneum, while T4b tumors directly invade or are adherent to other organs or structures.

The regional lymph node classification includes N1a, which is characterized by 1 positive lymph node; N1b, characterized by 2-3 positive lymph nodes; N2a, characterized by 4-6 positive nodes; and N2b, characterized by 7 or more positive nodes. Additionally, tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis (i.e., satellite tumor nodules) have been classified as N1c. Within each T stage, survival is inversely correlated with N stage, with N0 being the lowest stage, followed by N1a, N1b, N2a, and N2b.

In rectal cancer, it is noteworthy that the T stage has more prognostic value than the N stage. Some experts have proposed subdividing T3 disease based on the distance of tumor spread from the muscularis propria, although this is a matter of debate. T3 tumors with more than 5 mm of invasion beyond the muscularis propria (i.e., T3c disease) have been found to have an inferior cancer-specific survival rate of approximately 54%, compared to 85% when the depth was 5 mm or less.¹⁵

The updated guidelines for the treatment of rectal cancer from ESMO incorporate depth of extramural invasion beyond the muscularis propria as a factor in treatment allocation using the T3 subdivision system.¹⁶ However, AJCC and NCCN do not stratify decision making for T3N0 disease according to depth of extramural invasion. The panel recommends that a further subclassification of T3 based on available evidence

may prove valuable in preventing both over-treatment and inadequate treatment. Therefore, the depth of extramural invasion beyond the muscularis propria should be taken into consideration when making treatment decisions for rectal cancer that may improve patient outcomes.

Imaging plays a critical role in preoperative staging for rectal cancer, as it individualizes treatment strategy for each patient. The panel recommends that endoscopic rectal ultrasound (EUS) be used for early T1 tumors¹⁷ that are suitable for transanal endoscopic microsurgery (TEM), as it can determine if a lesion is confined to the mucosa or submucosa. However, for lesions greater than T1, the panel does not mandate the use of EUS as there is no additional benefit. The panel recommends the use of pelvic magnetic resonance imaging (MRI) for accurate locoregional clinical staging.¹⁸ Pelvic MRI has proven to be the best modality so far for assessing the depth of tumor penetration, determining the T substage, detecting extramural vascular invasion (EMVI), estimating the presence of local lymph nodal metastases, predicting the risks of local recurrence and synchronous/metachronous distant metastases, providing accurate images of soft tissue structures in the mesorectum, including the mesorectal fascia, and providing information useful in predicting the circumferential resection margin (CRM) before radical surgery.¹⁹ EMVI, in particular, portends a poor prognosis and serves as a predictor of distant metastasis.²⁰ The panel's recommendation is supported by the MERCURY trial²¹ which confirmed that high-resolution T2 sequence MRI can accurately assess the CRM preoperatively and differentiate patients with low- and high-risk disease. The rectum can be divided into three segments based on their anatomical position on MRI. A low rectal tumor is characterized as a tumor whose inferior margin is positioned at or below the pelvic sidewall's musculus levator origin.²² The mid-rectum is positioned between the low rectum and the inferior-most point of the anterior peritoneal reflection and the high rectum is located above the mid-rectum and below the sigmoid "take-off".²³ Patients with MRI-clear CRM had higher 5-year overall survival (OS) compared to those with MRI-involved CRM 62.2 versus 42.2%, respectively (hazard ratio [HR], 1.97; 95% confidence interval [CI], 1.27–3.04). Preoperative MRI imaging also predicted disease-free survival (DFS; HR, 1.65; 95% CI, 1.01–2.69; $p < 0.05$) and local recurrence (HR, 3.50; 95% CI, 1.53–8.00; $p < .05$). To ensure a comprehensive report, a standard proforma for MRI and pathology can be followed, and radiology departments can refer to the European Society of Gastrointestinal and Abdominal Radiology consensus guidelines for standardized MRI imaging of rectal cancer.²⁴

The panel considers contrast-enhanced computed tomography (CT) scan of the pelvis as an inferior modality to MRI in T and N staging, and for predicting CRM due to its poor sensitivity.²⁵ Therefore, it is not the preferred choice for local staging of rectal cancer. However, in centers where MRI is unavailable or has limitations such as low field strength (i.e., $<1.5T$), unavailability of phased-array surface coils, lack of a standardized Rectal MRI protocol or expertise to interpret MRI images, the panel recommends a contrast-enhanced CT scan of the pelvis over an inferior quality MRI

or substandard reporting with an understanding that it is a suboptimal modality and every attempt should be made to obtain a standard rectal MRI scan of the patient.

The panel recommends that preoperative imaging should be done in all cases to rule out distant metastases. CT scan of the chest and abdomen is recommended for this purpose. In case CT abdomen is being done, a plain CT scan of the thorax suffices; however, if CT abdomen is being done in the same setting, then CT thorax with contrast along with CT abdomen with contrast is acceptable.

The panel consensus is that positron emission tomography (PET) scan is not recommended for preoperative staging of rectal cancer. However, it may be used to assess an indeterminate finding on a contrast-enhanced CT scan or in patients with a strong contraindication to intravenous contrast and locally extensive disease who require beyond-total mesorectal excision (TME) surgery. In addition, it may be beneficial when used in conjunction with MRI liver in patients at high risk of multiple metastases, and for RT target delineation in radiotherapy planning. Bone scan and brain imaging are not routinely indicated unless patient is symptomatic (►Table 3).

Histopathological Examination

The pathologic staging of rectal cancers depends on proper examination of resected surgical specimen. So, a detailed and proper histopathology report of the pathologic evaluation of rectal cancer is needed. A histopathological report (histopathological examination [HPE]) should include (i) gross description of the specimen and tumor, (ii) grade of differentiation of tumor, (iii) depth of penetration and extension of the tumor to the adjacent structures (T), (iv) number of positive regional lymph nodes and number of regional lymph nodes evaluated (N), (v) the presence of distant metastases to other organs including non-regional lymph nodes (M), (vi) the status of proximal, distal, circumferential (radial), and mesenteric margins,^{26,27} (vii) neoadjuvant treatment effect,²⁸ (viii) lymphovascular invasion,²⁹ (ix) perineural invasion,^{30,31} and (x) the number of tumor deposits.^{32–35}

Rectal cancer is classified according to the 8th edition of the AJCC TNM staging system. During the grossing of the specimen, it is important to record the distance of the tumor extending outside the muscularis propria into the perirectal tissue, as well as to identify the area in which the tumor spreads closest to the CRM. It is necessary to assess at least 12 lymph nodes in patients who have not undergone neoadjuvant treatment.^{36–38} It is reported in literature that high-grade tumor budding in pT1 CRC or malignant polyps is associated with an increased risk of lymph node metastasis. The most important resection margin for rectal cancer is the CRM. When reporting involvement of the CRM, it should be noted that it is considered involved if it is located less than or equal to 1 mm from the tumor-free margin. It is important to measure the CRM from the primary tumor and express the measurement in millimeters for accuracy.^{36,39} If a positive lymph node or a tumor deposit is closer to the margin, a second CRM measurement should be made and reported.^{26,27,40–42} Currently, it is not recommended to

Table 3 Indian consensus and guidelines: staging

Guidelines	LoE	GoR	Consensus
Statement 6 ^{23,28}			
Location and physical characteristics of the primary rectal tumor should be documented by DRE and flexible sigmoidoscopy / colonoscopy. Lower rectum is when the tumor is below 5cm from the anal verge, mid-rectal tumors are situated at 5 to 10 cm from the anal verge and tumors lying above 10 cm from the anal verge are upper rectal tumors. Alternatively, the rectum can be divided into three segments based on their anatomical position on MRI. A low rectal tumor is characterized as a tumor whose inferior margin is positioned at or below the pelvic sidewall's musculus levator origin. The mid-rectum is positioned between the low rectum and the inferior-most point of the anterior peritoneal reflection and the high rectum is located above the mid-rectum and below the sigmoid "take-off"	I	A	28/28
Statement 7 ³⁸			
Full blood count, liver, and renal function tests, serum CEA and CT scan of thorax and abdomen / pelvis (if MRI pelvis could not be done) should be carried out to define functional status and presence of metastases	I	A	30/30
Statement 8 ²¹			
Pelvic MRI (rectal protocol) is the gold standard test to locally stage the rectal tumor. Also, assessment of CRM and EMVI is most accurate with MRI and predicts high risk of distant metastasis and local recurrence	I	A	31/31
In places with resource constraints and unavailability of MRI, CECT pelvis may be done with the understanding that it is a suboptimal modality and every effort should be made to arrange for MRI	Expert opinion	Expert opinion	
Statement 9 ¹⁷			
EUS is appropriate for early T1 tumors where TEM can be performed. It is of no added benefit for advanced tumors	II	A	31/31
Statement 10 ³⁸			
Routine use of PET-CT is not indicated	Expert opinion	Expert opinion	28/31
Statement 11 ^{21,38}			
UICC TNM (8th edition) should be followed and documented accurately before starting any treatment	I	A	27/29
Further classification of cT3 may be helpful in risk stratifying patients for appropriate treatment strategy	II	B	

Abbreviations: CEA, carcinoembryonic antigen; CECT, contrast-enhanced computed tomography; CRM, circumferential resection margin; CT, computed tomography; DRE, digital rectal examination; EMVI, extramural vascular invasion; EUS, endoscopic ultrasound; GoR, grade of recommendation; LoE, level of evidence; MRI, magnetic resonance imaging; PET-CT, positron emission tomography -computed tomography; TEM, transendoscopic microsurgery; UICC TNM, Union for International Cancer Control -Tumour, Node, Metastasis staging system.

routinely report the tumor regression grade after neoadjuvant treatment. However, it is crucial to report pathologic complete response (pCR) to assess the efficacy of the neoadjuvant treatment.²⁸ Tumor budding is defined as the presence of a single cell or a cluster of four or fewer neoplastic cells as detected by routine staining at the advancing edge of an invasive carcinoma.⁴³ Tumor deposits, also known as satellite nodules, are irregular and discrete tumor deposits that are located in the perirectal fat, but are away from the leading edge of the tumor. These nodules are located within the lymphatic drainage of the primary tumor. They are not counted as lymph nodes replaced by tumor as there is no lymph node tissue associated with these nodules. The number of tumor deposits should be mentioned in the pathology report.^{32–35,44,45} The presence of perineural invasion is associated with worse prognosis.^{30,31,45–48} Immunohistochemistry (IHC) testing for

MMR should be performed on all rectal cancers for the discussion of genetic counseling and the role of immunotherapy.^{49–53} IHC is not recommended for the routine histopathology reporting; however, if there is a doubt about the morphology, IHC testing can help exclude the possibility of other cancers such as neuroendocrine or melanoma (► **Table 4**).

Risk Adapted Treatment

Every case should be discussed in multidisciplinary tumor boards (MDT) at the time of diagnosis and staging, a multimodality treatment plan should be documented at the beginning based on local institutional policies, resources, and waitlist for locoregional therapy. The MDT should consist of a surgical oncologist, a medical oncologist, a radiation

Table 4 Indian consensus and guidelines: HPE

Guidelines	LoE	GoR	Consensus
Statement 12 ²⁶			
T1 tumors can be subdivided into pedunculated and sessile. Pedunculated tumors must have the grade, presence of LVI and presence of tumor budding documented to predict the risk of lymph node metastasis. PNI if present should be recorded. For sessile tumors, the level of infiltration into the sm and the width of invasion compared with the width of the cancer should be assessed	I	A	28/28
Statement 13 ^{26,28,29}			
For advanced tumors, ◦ The quality and grade of TME specimen should be assessed and preferably photographed ◦ Histologic subtyping should be done as per WHO classification, 5th edition ◦ At least 12 lymph nodes must be assessed (for patients undergoing upfront surgery only) ◦ Tumor deposits (non-nodal, non-neural, non-lymphatic deposits), if present, should be documented ◦ Proper documentation of margins- circumferential resection margin, distal longitudinal and proximal longitudinal, (or additionally any other in extended resections) in mm (millimeters) is required; PNI, LVI, and tumor budding must be reported ◦ If preoperative therapy was administered, TRG using Mandard, Dworak or College of American Pathologist should ideally be documented	I	A	30/30
Statement 14 ^{49,52}			
MMR testing by IHC or MSI-PCR should be performed on all rectal cancers for the purposes of genetic counseling as well as discussion of the use of immunotherapy	II	A	29/30
Statement 15 ³⁷			
◦ IHC is not routinely recommended, however if there is a doubt on morphology, especially in poorly differentiated tumors, mesenchymal or other tumors, (e.g., neuroendocrine, melanoma, lymphoma, and GIST) must be excluded ◦ HER2 testing is not recommended for the purpose of treatment or as a prognostic marker ◦ KRAS / NRAS / BRAF testing is not recommended for the purpose of treatment or as a prognostic marker.	Expert opinion	Expert opinion	30/31

Abbreviations: BRAF, v-raf murine sarcoma viral oncogene homolog B1; GIST, gastrointestinal stromal tumor; HER2, human epidermal growth factor receptor 2; HPE, histopathological examination; GoR, grade of recommendation; IHC, immunohistochemistry; KRAS, Kirsten rat sarcoma viral oncogene homolog; LoE, level of evidence; LVI, lymphovascular invasion; MMR, mismatch repair; MSI, microsatellite instability; NRAS, neuroblastoma ras viral oncogene homolog; PCR, polymerase chain reaction; PNI, perineural invasion; sm, submucosa; TME, total mesorectal excision; TRG, tumor regression grading; WHO, World Health Organization.

oncologist, a radiologist, a pathologist, a psychological counsellor, a geneticist, and a dietician. In case of unavailability of the MDT at the local place, virtual tumor boards (VTB) for difficult and complicated cases should be consulted. Such well-structured VTB facility organized by the National Cancer Grid ensures access to specialized consultations, enhancing the collaborative management of cancer patients.

Risk Adapted Therapy for Very Early and Early Tumors

There are a variety of surgical approaches available for the treatment of primary rectal cancer lesions.^{54,55} The selection of the appropriate method depends on several factors such as the location, extent, and stage of the disease. These methods include polypectomy, transanal local excision, and TEM. More invasive procedures that involve transabdominal resection, such as low anterior resection (LAR), proctectomy

with TME and coloanal anastomosis, and abdominoperineal resection (APR) are also available.^{54,55}

For early rectal cancers, such as cT1N0 without adverse features like grade 3, venous invasion, and LVI+ (lymphovascular invasion), local excisional procedures such as TEM are considered appropriate as a single modality.^{56–58} TEM allows for more accurate en bloc, full-thickness local excision of rectal tumors than local excision and can provide similar oncological outcomes as TME in pT1sm1 (clinical cN0) rectal cancers without compromising anorectal function. A meta-analysis in 2015 confirmed that TEM has superior oncologic outcomes compared to transanal local excision in early cancers.⁵⁹ During these excision, tumor fragmentation should be avoided and negative deep (>3 mm) and mucosal margins are required.

Local procedures, such as sphincter-sparing procedures, cause minimal morbidity and mortality and result in early postoperative recovery.^{60,61} However, they have certain

limitations, such as the absence of pathologic staging of nodal involvement. Endorectal ultrasound is also unable to identify lymph node micrometastases in early rectal lesions.⁶² As a result, patients undergoing local excision have a higher local recurrence rate than those undergoing radical resection.^{61,63,64}

Careful patient selection is crucial for local excision of T1, N0 rectal cancer. It is also important to carefully examine the resection specimen, and consider subsequent transabdominal resection for patients found to have T2 disease or high-risk features. In some cases, local radiotherapy such as brachytherapy or contact therapy (Papillon technique) can be considered as an alternative to local surgery,⁶⁵ either alone or in combination with chemoradiotherapy.

Patients with rectal cancer who are not suitable for local surgery should undergo transabdominal resection. Whenever possible, sphincter preservation surgeries are preferred, although they may not be feasible in all cases. Tumors such cT2c/T3a/b should be treated by radical TME surgery due to the higher risks of recurrence and mesorectal lymph node involvement.⁵⁸ TME is the standard surgery and involves the en bloc removal of the mesorectum, associated lymphatic and vascular structures, fatty tissue, and mesorectal fascia while sparing the autonomic nerves.^{55,60,66} In cases of high rectal cancer, a partial mesorectal excision with a distal margin of at least 5 cm of mesorectum may be considered.

When the tumor involves the anal sphincter or the levator muscles or when margin-negative resection would result in

loss of anal sphincter function, an APR with TME should be performed, which involves en bloc resection of the recto-sigmoid, rectum, anus, surrounding mesentery, mesorectum (TME), and perianal soft tissue, and necessitates creation of a colostomy.⁶⁷ Preoperative radiotherapy with or without chemotherapy may be considered for low lying tumors needing an APR to achieve a complete clinical response (CCR) and pursue a “watch-and-wait” (W&W) strategy to avoid a stoma, but it is not a routine recommendation.

The decision of laparoscopic or open surgery should be based on surgeon’s experience with the technique, the location and stage of the cancer, and patient related factors such as obesity and previous open abdominal surgery. Robotic-assisted rectal cancer surgery provides some technical advantages for surgeons compared with conventional laparoscopy, but it has not shown to impact survival for the patients. Lateral pelvic lymph node dissection is not routine unless persistently involved on postneoadjuvant therapy imaging. Lateral pelvic nodes are often invaded if multiple mesorectal nodes are involved⁶⁸ (►Table 5).

Risk Adapted Therapy for Intermediate Risk (IR) Rectal Cancer [cT3a/b (Very Low, Levators Clear, MRF Clear or (cT3a/b in Mid- or High Rectum, cN1-2 (not Extranodal), no EMVI]

Although upfront surgery is still the mainstay of treatment for early rectal cancer, neoadjuvant therapy is becoming increasingly important for downstaging the disease and

Table 5 Indian consensus and guidelines: risk adapted therapy for very early and early tumors

Guidelines	LoE	GoR	Consensus
Statement 16 ^{59,65}			
Very early tumors			26/30
cT1N0 with no additional risk factors (like LVI, G3) may be considered for TEM/local excision	I	A	
EBRT with or without brachytherapy boost can be considered as an alternative to surgery	III	B	
Statement 17 ^{120,121}			
Early rectal tumors not suitable for local excision (cT1–cT2; cT3 if middle or high, N0 (or also cN1 if high), MRF clear, no EMVI)			25/30
TME is the standard treatment option	I	A	
For ultra-low-lying tumors needing an APR and if patient wishes to avoid a stoma, one may consider using preoperative radiotherapy with or without chemotherapy to achieve a CCR and pursue W&W strategy	III	B	
Statement 18 ⁶⁸			
• In selecting laparoscopic or open surgery, the surgeon should consider his/her experience with the technique, the stage and location of the cancer and patient factors such as obesity and previous open abdominal surgery • Robotic-assisted rectal cancer surgery provides some technical advantages for surgeons compared with conventional laparoscopy but has not shown to impact survival for the patients • Lateral pelvic lymph node dissection is not routine unless persistently involved on postneoadjuvant therapy imaging	Expert opinion	Expert opinion	28/29

Abbreviations: APR, abdominoperineal resection; CCR, complete clinical response; EBRT, external beam radiation therapy; EMVI, extramural vascular invasion; GoR, grade of recommendation; LoE, level of evidence; MRF, mesorectal fascia; LVI, lymphovascular invasion; TEM, transanal endoscopic microsurgery; TME, total mesorectal excision; W&W, watch-and-wait.

reducing the risk of local recurrence.⁶⁹ Before the era of total neoadjuvant therapy (TNT), one of the largest meta-analysis involving more than 3000 patients with rectal cancer confirmed increased PCR rates, decreased local recurrences and distant metastasis rates with the use of neoadjuvant long-course chemoradiotherapy (LCRT).⁷⁰ However, the criteria for choosing the subset of patients benefitting the most from neoadjuvant therapy are not well defined in the IR group. There are considerable differences of opinion regarding the two approaches. The support for upfront surgery in this subset of patients, where the tumors are proximal and do not threaten the mesorectal fascia, comes from the favorable rates of low local recurrences after TME in the Dutch trial and several other retrospective analyses.^{29,71–74} Though there is ample support for neoadjuvant therapy in advanced cT3c/d and cT4 patients with threatened mesorectal fascia, its role in other indications is debatable. Of particular interest here are the patients with radiologically positive nodes.

The advent of improved imaging modalities such as EUS and MRI gives a better picture of CRM. However, their utility in predicting a node's malignant versus reactive nature based on its morphology and size is controversial.^{75,76} However, it can be agreed that there is no prognostic importance of involved lymph nodes on preoperative MRI assessment, on the risk of local recurrence. If the surgeon carries out a good quality TME with en-bloc excision of the mesorectum, the chances of local recurrence are low.⁷⁷ The updated guidelines for the treatment of rectal cancer from the ESMO suggest that patients with a depth of invasion beyond the muscularis propria, that is, 5 mm or less, are appropriate candidates for upfront surgery rather than neoadjuvant therapy, even if they are node-positive, as long as the levators are not threatened, the mesorectal fascia is clear, and there is no extranodal extension.¹⁶ The American Society of Clinical Oncology (ASCO) Annual Meeting Plenary Session showcased the outcomes of the PROSPECT trial, a randomized phase 3 study, revealing significant findings in the treatment of locally advanced rectal cancer (LARC; cT2N+ or cT3N0/+). The trial demonstrated the noninferiority of neoadjuvant 5-fluorouracil and oxaliplatin (FOLFOX), in combination with selective application of 5-fluorouracil chemoradiotherapy

(5-FU CRT), compared to 5-FU CRT alone. Among approximately 1,200 patients enrolled in the study, the 5-year DFS rate was 80.8% in the experimental arm, while it stood at 78.6% in the standard arm. Notably, despite 90% of patients in the experimental arm avoiding radiotherapy, no additional local recurrences were observed.⁷⁸ Therefore, we recommend a carefully selected subset of intermediate-risk patients to be considered for upfront surgery where the surgeon is convinced of an adequate TME with complete mesorectal excision. Neoadjuvant therapy can be reserved for the remaining candidates where there is a suspicion that the quality of the surgery will be compromised (► **Table 6**).

Risk Adapted Therapy for Locally Advanced Rectal Cancer [cT3c/d or Very Low Localization, Levators Threatened, MRF Clear, cT3c/d Mid-Rectum, cN1–N2 (extranodal), EMVI +]

LARC are defined as tumors that involve the subserosa or extend into nonperitonealized pericolic or perirectal tissues, or tumors that involve other organs or structures and/or perforate the visceral peritoneum. Additionally, tumors with EMVI on rectal MRI are also classified as LARC. These tumors carry an increased risk of local recurrence and/or synchronous and subsequent metastatic disease.⁷⁹ In the case of preop contrast-enhanced MRI showing the features mentioned above, the risk of local recurrence and metastasis is high, and these patients are candidates for neoadjuvant therapy. If such patients undergo upfront surgery, they have a high chance of an R+ resection leading to increased local recurrences. There are two different schedules of preoperative therapy that are standards of care worldwide namely LCRT and short-course RT (SCRT). LCRT with LCRT in the neoadjuvant setting became the standard of care (compared to adjuvant CCRT) after the results of the German trial were first published in 2004, while the role of SCRT was first established in the Swedish trial as early as in 2005.

Choice of Short-Course RT versus Long-Course RT

SCRT with a 25 Gy total dose at 5 Gy/fraction during 1 week is followed by immediate surgery (< 10 days from the first radiation fraction) or delayed surgery. LCRT with a

Table 6 Indian consensus and guidelines: risk adapted therapy for intermediate risk (IR) rectal cancer

Guidelines	LoE	GoR	Consensus
Statement 19 ^{29,71,81,82,91,104–106}			
Intermediate/more locally advanced rectal cancers [cT3 (very low, levators clear, MRF clear) or (cT3 in mid- or high rectum, cN1-2 (not extranodal), no EMVI]			25/31
Upfront surgery for carefully selected subset of intermediate risk patient (early T3, non-bulky)	II	B	
SCRT → TME	II	A	
LCRT → TME	II	A	
SCRT → chemotherapy for 3 to 4 months → TME	II	B	
Perioperative chemotherapy → LCRT / SCRT → TME	II	B	
Perioperative chemotherapy → TME (especially for cT3 mid rectal tumors with N0 or N1)	II	B	

Abbreviations: EMVI, extramural vascular invasion; GoR, grade of recommendation; LoE, level of evidence; LCRT, long-course radiotherapy; MRF, mesorectal fascia; SCRT, short-course radiotherapy; TME, total mesorectal excision.

recommended dose of 45 to 50 Gy in 25 to 28 fractions, a boost with 5.4 Gy in 3 fractions, can be considered for preoperative RT if the CRM is threatened, and for postoperative RT routinely with 5.4 to 9.0 Gy in 3 to 5 fractions according to CRM. Several institutes worldwide, including India, have adopted SCRT as their standard of care, especially with newer trials highlighting a higher rate of adverse events in the LCRT arm with no difference in postoperative complications.⁸⁰ Further support of SCRT followed by delayed surgery was demonstrated by the Stockholm trial, which was a phase 3, randomized, noninferiority trial⁸¹ and another phase III trial by Bujko et al.⁸² The Stockholm III study demonstrated that SCRT with a delayed surgical approach is noninferior when compared to SCRT followed by immediate surgery. Although there was a slightly higher occurrence of acute radiation-related side effects in the former group, the rates of postoperative complications were nearly the same in both groups; hence, SCRT with delayed surgery is an acceptable alternative to SCRT with immediate surgery.⁸¹

Currently, there are no established guidelines specifying which clinic-radiological substages would benefit the most from SCRT or LCRT in LARC. The decision to use a preoperative approach in LARC is primarily based on the risk of having a positive margin resection at TME surgery. If there is a predicted risk of a positive margin or R+ resection status, chemoradiation therapy (LCRT) may be recommended.⁸³ For above group patients, LCRT is associated with higher R0 resection rates compared with RT alone.⁸⁴ These recommendations are challenged by the findings of a recent trial where even if the predicted margin is at risk (CRM $\leq$ 1 mm or fixed cT3 tumors), similar R0 resection rates and DFS are achieved by both SCRT or LCRT followed by chemotherapy with oxaliplatin/leucovorin/fluorouracil and by surgery.⁸⁵

The management of upper rectal cancer remains debated, with limited studies analyzing the impact of neoadjuvant treatment in this specific population. Current evidence lacks consensus due to the inclusion of different rectal tumor locations in previous trials and the known impact of tumor location on outcomes. While some guidelines (ESMO) suggest treating upper rectal cancers as colon cancer without neoadjuvant treatment, there is disagreement among experts who argue that patients with cT4 tumors of the upper rectum may benefit from neoadjuvant chemoradiation therapy (CRT) or chemotherapy alone. A recent retrospective study in France demonstrated comparable survival outcomes between patients who received radiotherapy and those who did not. Interestingly, the cohort receiving neoadjuvant CRT experienced a higher incidence of postoperative sepsis and other complications.⁸⁶

Choice of Chemotherapy with RT

Continuous intravenous infusion of 5-FU or oral capecitabine during CRT is recommended rather than bolus 5-FU^{87,88} Capecitabine is therapeutically equivalent to infusional FU when used during concomitant LCRT, but with a different toxicity profile.⁸⁸ However, its oral formulation makes it easier to administer with a higher compliance rate. Though adding oxaliplatin to LCRT may improve the pCR rates and

DFS in some patients, several meta-analyses proved it enhances the acute toxicities.⁸⁹ Adding a platinum agent increased grade 3 or 4 toxicities, including diarrhea, nausea, neurosensory toxicity, and fatigue. As there is no improvement in survival in several randomized trials testing, this combination precludes oxaliplatin as a radiosensitizer. It is not recommended to be added to fluoropyrimidine-based LCRT outside of a clinical trial.^{90,91}

Though some nonrandomized trials suggested the benefit of adding irinotecan to the LCRT regimen, the same could not be shown in an Radiation therapy oncology group (RTOG) trial.⁹² Biological molecularly targeted agents have not been successfully integrated into LCRT. There is discord regarding the early reports concerning the benefit of adding cetuximab or panitumumab, two humanized monoclonal antibodies targeting the epidermal growth factor receptor, to conventional FU-based CRT.^{93,94} Similarly, the use of bevacizumab (a humanized monoclonal antibody targeting the vascular endothelial growth factor [VEGF] or aflibercept (a recombinant fusion protein that functions as a decoy receptor, preventing VEGFA, VEGFB, and placenta growth factor from binding to their receptors) in addition to conventional FU-based LCRT has had mixed results.^{95,96} Thus, their addition to standard LCRT is not recommended due to the paucity of completion of phase III studies.

To summarize, neoadjuvant RT or LCRT is a crucial component of locally advanced mid/low stage II/III rectal cancers, and it reduces the rate of local recurrence without impacting the OS. There is little benefit from adding preoperative SCRT or LCRT to upper rectal cancers (>12 cm from the anal verge) above the peritoneal reflection, and it should be treated as colon cancer (–Table 7).

Risk Adapted Therapy for Very Advanced Tumors [cT3 with any MRF Involved, Any cT4a/b, Lateral Node +]

SCRT has not been perused for the candidates as mentioned above. Involvement of lateral pelvic lymph nodes is an independent poor prognostic feature and addressing it surgically is controversial.⁶⁸ Also, any CRM+ (either due to tumor or lymph node) has in general higher risk of local recurrences.²⁷ It is recommended that such cases be treated with a long course of concurrent chemoradiotherapy and then be considered for surgery followed by adjuvant chemotherapy. (TME and more extended surgery if needed due to tumor overgrowth). However, depending on the treating clinician's discretion, total neoadjuvant therapy (TNT- see below) (TNT) is also feasible for this subset of patients. It is given as a treatment option in the latest NCCN guidelines for unresectable and medically operable tumors (–Table 7).

TNT Approach

TNT should be considered for all LARCs, especially clinical T4 disease, local extension to pelvic side walls and sacrum or close or involved CRM, N2 disease, lateral pelvic node involvement, or in presence of EMVI. These tumors are unlikely to undergo curative resection without multivisceral resection; hence, such patients require preoperative treatment to shrink the

Table 7 Indian consensus and guidelines: risk adapted therapy for locally advanced and very advanced rectal cancer

Guidelines	LoE	GoR	Consensus
Statement 20 ^{91,104–106}			
Locally advanced rectal cancers [cT3 or very low localization, levators threatened, MRF clear, cT3 mid-rectum, cN1–N2 (extranodal), EMVI +].			27/27
LCRT → TME	II	A	
SCRT → chemotherapy for 3 to 4 months →TME	II	A	
Perioperative chemotherapy → LCRT / SCRT →TME	II	A	
Statement 21 ^{88,90,93–95}			
Oral capecitabine is preferred over 5-FU-based regimens as a chemotherapy partner for LCRT	II	A	27/28
It is not recommended to add oxaliplatin to fluoropyrimidine during LCRT	Expert opinion	Expert opinion	
Addition of irinotecan or biological agents (like bevacizumab and cetuximab/panitumumab) is not recommended to standard LCRT	Expert opinion	Expert opinion	
Statement 22 ⁸⁶			
Upper rectal tumors (above the peritoneal reflection) have limited benefit from preoperative radiotherapy and may be considered for upfront surgery	III	C	25/26
Alternatively, if cT4a/b, one may consider neoadjuvant chemoradiotherapy	III	C	
Statement 23 ¹¹²			
Very advanced tumors (cT3 with any MRF involved, any cT4a/b, lateral node +)			22/25
TNT approach is preferred in this situation.	II	A	
Preoperative LCRT followed by surgery (TME and more extended surgery if needed due to tumor overgrowth)	II	B	
It is advisable to conduct 8 to 12 weekly imaging evaluation to assess the poor responders to neoadjuvant treatment and consider them for definitive surgery	III	A	

Abbreviations: 5-FU, 5-fluorouracil; EMVI, extramural vascular invasion; GoR, grade of recommendation; LoE, level of evidence; LCRT, long-course radiotherapy; MRF, mesorectal fascia; SCRT, short-course radiotherapy; TEM, transanal endoscopic microsurgery; TME, total mesorectal excision; TNT, total neoadjuvant therapy.

cancer away from the threatened margin, that is, the MRF/CRM. Without preoperative treatment, surgery is likely to lead to either an R1 or an R2 resection.⁸⁴ A treatment approach, which includes courses of both chemoradiotherapy (chemoRT) and chemotherapy given as neoadjuvant therapy before definitive surgery, has been the therapy of choice in recent times. This approach, called TNT, was initially tested in small phase II trials and later in larger phase III trials.^{97–103}

The TNT approach consists of two approaches: the induction chemotherapy approach and the consolidation approach. The induction chemotherapy approach involves using FOLFOX/CAPOX or FOLFIRINOX for 12 weeks (as per PRODIGE-23),¹⁰⁴ followed by LCRT or SCRT. A 7-year update of PRODIGE 23 revealed a notable 5.1% increase in DFS through TNT, alongside a significant 5.8% improvement in OS compared to the standard approach of LCRT followed by surgery; both strategies were supplemented by adjuvant FOLFOX chemotherapy.¹⁰⁵ The consolidation approach involves using SCRT (preferred) or LCRT, followed by FOLFOX (5-FU, leucovorin, oxaliplatin) or CAPOX (capecitabine and oxaliplatin) for 12–16 weeks. The RAPIDO trial enrolled 920 patients who were randomized into two arms: one receiving SCRT followed by chemotherapy (6 x CAPOX or 9 x FOLFOX) and then TME, and the other following the conventional sequence of LCRT followed by TME with optional adjuvant chemotherapy (8 x CAPOX or 12 x FOLFOX).

Despite comparable 3-year OS and locoregional failure (LRF) rates, the experimental arm displayed nearly doubled pCR rates and a noteworthy 6.8% reduction in distant metastasis at the 3-year mark.^{106,107} However, the 5-year update of the RAPIDO trial revealed an increase in the risk of local relapse in the experimental arm.¹⁰⁶ It is not clear whether it is better to start with chemotherapy, then follow with LCRT, or vice versa when following a TNT approach. In the Organ Preservation of Rectal Adenocarcinoma trial, 324 patients were divided into two arms: one received induction chemotherapy followed by LCRT, while other had received LCRT followed by consolidation chemotherapy. Chemotherapy consisted of 4 months of CAPOX or FOLFOX. The 3-year DFS was similar in both arms and the primary endpoint of the study (DFS between TNT and selective WW versus historical controls) was not met. However, a trend emerged where chemoradiation followed by consolidation chemotherapy correlated with a higher rate of organ preservation (3-year TME-free survival: 41 vs. 53%).⁸⁵

The TNT approach has been shown to offer several benefits, including the potential to prevent or eliminate micrometastases early on, a higher rate of achieving pathologic complete response, longer progression-free survival,^{103,108–111} minimizing the duration for need of an ileostomy,¹¹¹ facilitating resection, and improved tolerance and completion rates of chemotherapy.^{99,103,104,108} In some cases, neoadjuvant

Table 8 Indian consensus and guidelines: TNT

Guidelines	LoE	GoR	Consensus
Statement 24 ^{60,108,110,112}			
Locally advanced rectal tumors with CRM threatened or involved (either due to primary or lymph node) can be considered for TNT approach	II	A	23/25
Statement 25 ²⁰			
Patients with EMVI may benefit from TNT approach as they have more risk for distant metastasis. Treating them with systemic chemotherapy earlier may reduce the risk of recurrence	III	B	21/28
Statement 26 ^{104,105,107}			
Any mid / low lying tumors above cT3/4 or cT1-2 with cN+ may be considered for TNT approach	II	A	25/27
Statement 27 ^{109,111}			
For early ultra-low lying rectal tumors, TNT approach may be acceptable if the goal is to achieve CCR and avoid permanent stoma	III	C	25/28

Abbreviations: CCR, complete clinical response; CRM, circumferential resection margin; EMVI, extramural vascular invasion; GoR, grade of recommendation; LoE, level of evidence; TNT, total neoadjuvant therapy.

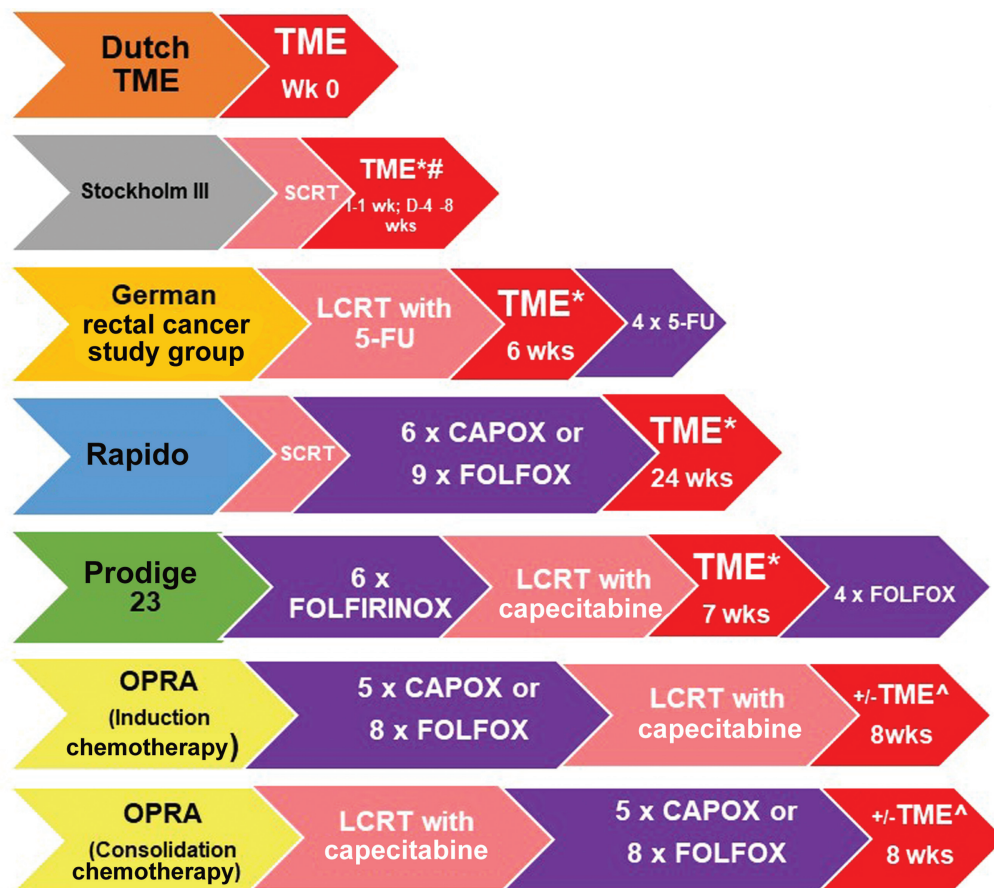


Fig. 2 Timing of total mesorectal excision (TME) in various pivotal trials. TME, Total mesorectal excision; SCRT, Short course radiation therapy – 5 x 5 Gy over 5 days; LCRT, Long course chemoradiation; 5-FU, 5-Fluorouracil; FOLFOX, 5-FU, Oxaliplatin; FOLFIRINOX, 5-FU, Oxaliplatin, Irinotecan; CAPOX, Capecitabine, Oxaliplatin; RAPIDO, Radiotherapy and preoperative induction therapy followed by dedicated operation; OPRA, Organ preservation in rectal adenocarcinoma. *Timing from end of RT; #I-immediate – 1 wk; D-delayed – 4 to 8 wks; ^Timing from end of TNT; Wks – Weeks.

therapy may even eliminate the need for surgery if a complete response is achieved. For early ultra-low lying rectal tumors, the TNT approach may be acceptable if the goal is to achieve CCR and avoid a permanent stoma (►Table 8).

Timing of Surgery (►Fig. 2)

The optimal timing of surgery after SCRT is debatable, and there is no consensus on the best approach. Most of the

significant trials described above, which compared SCRT followed by surgery versus surgery alone⁸³ or SCRT versus LCRT before surgery,⁸² used an interval to surgery of 7 days after completion of SCRT. On the other hand, the further surgery if needed due to tumor overgrowth, the median interval time for surgery in the Dutch TME trial was 11 days. Some studies have reduced the time to 3 days, citing the cause of treatment-related leukopenia contributing to poor wound healing after delayed surgery.^{112,113} Similar to the ESMO guidelines, we recommend that either approach (immediate surgery <10 days after the first RT fraction or delayed surgery four to eight weeks after the end of RT) is acceptable.¹⁶ The optimal interval between completion of neoadjuvant CRT and surgery in rectal adenocarcinoma is also not established. Updated guidelines from the ESMO provide no specific recommendation other than to state that in practice, there is a wide variation in the timing of surgery, with intervals ranging from 4 to 12 weeks. Prolonging this interval may not only enhance the rate of pCR but also provide an opportunity for tumor repopulation. Moreover, delaying surgery can also postpone the administration of postoperative chemotherapy. The benefits of longer intervals must therefore be carefully weighed against the potential risk of subsequent metastases.¹⁶

Adjuvant Therapy

Postoperative CRT could be considered in patients with adverse histopathological features after upfront surgery—like positive CRM, perforation in the tumor area, incomplete mesorectal resection, nodal deposits with extracapsular spread close to the MRF, or if preoperative RT has not been given in patients with high risk of local recurrence.¹¹⁴ The rates of local failure with surgery alone range from 15 to 30% with T3N0 stage II disease compared to T1 and T2 disease where it is less than 10%. The failure rate increases up to 65% with node positive status in T3/T4 disease. The suggested chemotherapy partner for treating the patient is infusional 5-FU or capecitabine at a dose of 825 mg/m² twice daily, 5 days a week. The bolus 5-FU is not recommended because of the major hematological toxicity associated with it. Moreover, the results of the GITSG and NCCTG trials have shown that RT alone after surgery is an inferior option with a lack of survival benefit when compared to chemoradiotherapy (CRT).¹¹⁵ Oxaliplatin should not be used concurrently with radiotherapy.

The available randomized controlled trials and meta-analyses have not provided clear evidence on the benefit of adjuvant chemotherapy, as the methods used in these trials for answering this question are not standard. Additionally, there is a lack of data to strongly support the use of adjuvant chemotherapy in patients with rectal cancer who have received neoadjuvant chemoradiotherapy.¹¹⁴ As such, there are variations in the recommendations for adjuvant therapy between American and European nations. The NCCN recommends the use of adjuvant therapy irrespective of the outcomes of neoadjuvant chemoradiotherapy. On the other hand, the ESMO recommends adjuvant chemotherapy for

high-risk patients with pathological stage II and stage III disease. According to a retrospective propensity score matched analysis conducted over a period of 6 years using the National Cancer Database in the USA, there is limited benefit in patients who achieve a complete pathological response after neoadjuvant chemoradiotherapy (CRT).¹¹⁶ The Indian Society of Medical & Paediatric Oncology recommends the discretion of physicians when deciding whether to observe patients with pCR or to administer adjuvant chemotherapy to all other patients. In the adjuvant setting, the recommended regimen is a combination of 5-FU and oxaliplatin, based on data from the phase II Adjuvant Oxaliplatin in Rectal Cancer (ADORE) trial.¹¹⁷ Since International Duration Evaluation of Adjuvant therapy study included exclusively colon cancer patients, there is no strong evidence to comment on duration of chemotherapy for the rectal cancer patients. The panel recommends to give a total of 6 months of chemotherapy including the period of chemoradiation¹¹⁸ (► Table 9).

W&W Strategy

De-escalation strategies are being researched in oncology to gain better quality of life without compromising the survival outcomes. Patients with LARC do suffer from significant surgical toxicities like bowel dysfunction, perianal discharge, and LAR syndrome. W&W strategy is being practiced in many institutions wherein patients who have obtained complete clinical response after neoadjuvant concurrent chemoradiotherapy is observed for local recurrence and surgical morbidities are obviated. W&W merits discussion in this important policy document. In the meta-analysis by Dossa et al on published literature primarily on retrospective studies, there was no difference between W&W and surgery in terms of OS in patients who had achieved complete clinical response.¹¹⁹ However, the risk of local recurrence remains high, with rates as high as 30%, although nearly 85% of these local recurrences can be salvaged.¹²⁰ The international registry on W&W database collected data on over 1,000 patients and found that the majority (88%) of recurrences occurred within the first 2 years, and 97% of recurrences were in the rectum wall. Some studies have shown that the OS may be inferior with the W&W strategy.¹²¹

Considering the morbidity of up to a 90% rate of LAR syndrome, which includes symptoms like tenesmus, perianal discharge, increased stool frequency, pain, and fecal incontinence,¹²² many patients would not agree for surgery and/or stoma. Newer approaches like total neoadjuvant treatment question the role of universal surgery for all paradigm for LARC. “Wait” is acceptable, but how to “watch” in our setup is a big challenge. The W&W strategy requires intense monitoring or surveillance for local recurrence like DRE, endoscopy, and MRI. These investigations are limited by their sensitivity and specificity. Repeated biopsies are not recommended. The majority of local recurrences in rectal cancer patients who undergo W&W can be successfully treated surgically, as shown by retrospective studies and IWWD data. In absence of strong prospective data and limitations

Table 9 Indian consensus and guidelines: adjuvant therapy

Guidelines	LoE	GoR	Consensus
Statement 28 ¹¹⁴			
Postoperative CRT could be selectively used in patients with unexpected adverse histopathological features after primary surgery—e.g., positive CRM, perforation in the tumor area, incomplete mesorectal resection, extranodal deposits or nodal deposits with extracapsular spread close to the MRF, or in other cases with high risk of local recurrence if preoperative RT has not been given	Expert opinion	Expert opinion	22/23
Statement 29 ^{116,117}			
It is reasonable to consider adjuvant ChT in rectal cancer patients after preoperative CRT/RT with residual disease	II	B	20/24
For patients achieving PCR after preoperative therapy, observation is a reasonable option	II	B	
Statement 30 ¹¹⁸			
If adjuvant chemotherapy is planned, a doublet chemotherapy (CAPOX or FOLFOX) may be preferred; however, single-agent capecitabine is an acceptable alternative	II	B	22/26
Duration of chemotherapy should not be more than 24 weeks (total including preoperative regimen)	II	B	

Abbreviations: CAPOX, capecitabine and oxaliplatin; ChT, chemotherapy; CRM, circumferential resection margin; CRT, chemoradiotherapy; FOLFOX, 5-fluorouracil and oxaliplatin; GoR, grade of recommendation; LoE, level of evidence; MRF, mesorectal fascia; PCR, pathological complete response; RT, radiation therapy.

of intense follow-up, patient selection remains a key here. Tumors located in the lower and mid-rectum that require TME can be considered for W&W, especially for patients who wish to avoid permanent stoma.

The concept of W&W is applicable to operable cases and can also be extended to medically inoperable cases, where addressing comorbidities like heart disease and diabetes mellitus can be combined with reassurance on the W&W strategy. W&W is a promising nonsurgical option for selected patients, and prospective large sample studies are needed to fill the lacuna in literature to support its universal adoption (→Table 10).

Surveillance

The purpose of post-treatment surveillance in rectal cancer is to detect the recurrence of the disease at an early stage, allowing for timely curative interventions. The recommendations for transanal local excision patients include proctoscopy with EUS or contrast-enhanced MRI every 3 to 6 months for the first 2 years, then every half-yearly for a total of 5 years. Colonoscopy at 1 year after surgery with repeat intervals based on status of adenoma and based on expert opinion is recommended for them as well as those with stage I nonLynch rectal cancer.¹²³

Stage II and III patients are recommended for intensive postoperative surveillance due to a risk of 5 to 30% recurrence rate. A recent study reported that 95% of CRC recurrences occur within 5 years post-treatment,¹²⁴ while data from 20,898 patients in 18 colon cancer trials found that 80% of recurrences occur within the first 3 years.¹²⁵ Unfortunately, surveillance strategies such as imaging or CEA screening

did not offer a significant survival advantage over a symptom-based approach for these patients.¹²⁶ The COLOFOL trial of 2509 patients with stage II or III CRC found no significant difference in 5-year overall or CRC-specific mortality between high-frequency and low-frequency surveillance approaches.¹²⁷ A meta-analysis reported a sensitivity of 68% and specificity of 97% for a CEA cutoff of 10 ng/mL; however, it showed limitations in detecting recurrences within the first 2 years post-treatment.¹²⁸ Surveillance protocol recommendations for non-Lynch patients with stage II to III rectal cancer include physical examination and CEA screening every 3 to 6 months for 2 years, then every 6 months for 5 years, along with chest/abdominal/pelvic CT every 6 to 12 months for 5 years based on expert opinion.

Lynch syndrome-associated CRCs present at a younger age, are predominantly right-sided, and progress rapidly from adenoma to cancer. Regular colonoscopy is the only effective surveillance protocol, with a decrease in CRC mortality of up to 72%. Guidelines recommend colonoscopy every 2 to 3 years starting as early as at age of 25 years for the patients with molecular confirmation of Lynch syndrome. More stringent surveillance may be warranted for MLH1 and MSH2 gene carriers as compared to MSH6 and PMS2.¹²⁹ Aspirin, has been found to be associated with reduced CRC risk in Lynch syndrome carriers. We aim to systematically promote this intervention for all Lynch syndrome carriers and recommend low-dose aspirin 100 to 150 mg for at least 2 years.¹³⁰

The application of PET/CT in disease surveillance is not advisable due to potential hazards such as unwarranted medical interventions following false positive results and unjustified radiation exposure.^{131,132} While studies have

Table 10 Indian consensus and guidelines: W&W—Indian consensus and guidelines

Guidelines	LoE	GoR	Consensus
Statement 31 ^{119–121}			
A NOM approach may be considered in centers with experienced multidisciplinary teams after a careful discussion with the patient about their risk of recurrence	III	A	23/25
NOM should only be offered to patients achieving CCR as defined by • DRE • Scopy and biopsy if required • MRI	Expert opinion	Expert opinion	
Statement 32 ^{126,128}			
Careful surveillance is essential for those considering a W&W approach to treat tumor regrowth in a timely manner ◦ DRE, flexible sigmoidoscopy, and CEA every 3 to 4 months for the first 2 years, then every 6 months for years 3 to 5 (with photographs); ◦ MRI every 3 to 4 months for the first 2 years, then every 12 months for years 3 to 5; ◦ CT chest/abdomen/pelvis twice a year for 2 years, then once a year for years 3 to 5; ◦ And colonoscopy once at year 1 and again at year 5;	II	A	26/26
Statement 33 ⁵³			
If patient has dMMR or MSI-H, one may consider single agent PD-1/PDL-1 therapy for 6 months	III	A	24/27
Statement 34 ¹¹⁹			
For locally advanced tumors, one may consider brachytherapy boost to augment the chances of cCR in order to pursue W & W strategy. However, it must be done in expert centers only	III	C	23/25

Abbreviations: CCR, clinical complete response; CEA, carcinoembryonic antigen; CT, computed tomography; dMMR, deficient mismatch repair; DRE, digital rectal examination; GoR, grade of recommendation; LoE, level of evidence; MRI, magnetic resonance imaging; MSI-H, microsatellite instability-high; NOM, nonoperative management; PD-1, programmed cell death protein 1; PDL-1, programmed cell death ligand 1; W&W, wait and watch.

Table 11 Indian consensus and guidelines: surveillance—Indian consensus and guidelines

Guidelines	LoE	GoR	Consensus
Statement 35 ^{123,126}			
For patients with Transanal local excision only ◦ Proctoscopy (with endoscopic ultrasound [EUS] or MRI with contrast) every 3–6 months for the first 2 y, then every 6 months for a total of 5 years ◦ Colonoscopy at 1y after surgery • If advanced adenoma, repeat in 1 year • If no advanced adenoma, repeat in 3 years, then every 5 years	Expert opinion	Expert opinion	25/25
Statement 36 ¹³¹			
For patients with stage-I rectal cancer (non-Lynch) ◦ Colonoscopy at 1 year after surgery • If advanced adenoma, repeat in 1 year • If no advanced adenoma, repeat in 3 years, then every 5 years	Expert opinion	Expert opinion	25/25
Statement 37 ^{128,131}			
For patients with stage II to III rectal cancer (non-Lynch) • History and physical examination every 3–6 months for 2 years, then every 6 months for a total of 5 years • CEA every 3–6 months for 2 years, then every 6 months for a total of 5 years • Chest/abdominal/pelvic CT every 6–12 months for a total of 5 years	Expert opinion	Expert opinion	22/27

(Continued)

Table 11 (Continued)

Guidelines	LoE	GoR	Consensus
Statement 37 (a) ¹²⁹			
For patients with/ without prior history of rectal cancer and are known Lynch syndrome carriers (germline pathogenic MMR gene variant carriers)			26/26
MLH1, MSH2, and MSH6 gene carriers: 2-3 yearly colonoscopy surveillance is recommended	III	A	
PMS2 gene carriers: 5-yearly colonoscopy surveillance may be considered, in order reduce colorectal cancer incidence and mortality	III	B	
There is no evidence to support different colonoscopic intervals between men and women	III	A	
MLH1 and MSH2 gene carriers: age of initiation for colonoscopy surveillance is recommended to be 25 years	III	A	
MSH6 and PMS2: age of initiation for colonoscopy surveillance is recommended to be 35 years	III	B	
Statement 38 ¹³²			
PET-CT is not recommended for surveillance.	Expert opinion	Expert opinion	27/28
Statement 39 ¹³³			
Role of ctDNA-based surveillance is promising but cannot be recommended as part of routine clinical practice	Expert opinion	Expert opinion	27/28
Statement 40 ¹³⁰			
Chemoprevention with low-dose aspirin 100 to 150mg for a minimum duration of 2 years in Lynch syndrome carriers (germline MMR pathogenic variant carriers) with/without prior history of cancer is recommended to reduce risk of cancer	III	B	28/28

Abbreviations: CEA, carcinoembryonic antigen; CT, computed tomography; ctDNA, circulating tumor DNA; MLH1, MutL homolog 1; MMR, mismatch repair; MRI, magnetic resonance imaging; MSH2, MutS homolog 2; MSH6, MutS homolog 6; PET-CT, positron emission tomography/computerized tomography; PMS2, postmeiotic segregation increased 2.

shown that ctDNA detection can predict cancer relapse with high accuracy and earlier than radiologic imaging or CEA, the current evidence for its value in post-treatment surveillance is limited by small sample sizes and lack of validation cohorts. Ongoing trials are aimed at establishing ctDNA-based surveillance strategies and determining if early diagnosis impacts survival¹³³ (→ **Table 11**).

Authors' Contributions

Bhawna Sirohi and Viraj Lavingia were involved in concept and design. All the authors have helped in definition of intellectual content, literature search, manuscript preparation, manuscript editing, and manuscript review.

Patient Consent

No, as in this article, the guidelines presented are derived from a comprehensive literature review and expert consensus.

Conflict of Interest

As mentioned in the individual forms separately by each author.

All authors have read and approved the manuscript, met the requirements for authorship, and believe that the manuscript represents honest work.

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