Indian Council of Medical Research consensus document for the management of colorectal cancer

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Access this article online

Quick Response Code:

Website: www.ijmpo.org

DOI: 10.4103/0971-5851.142031

EXECUTIVE SUMMARY

- This document is based on consensus among the experts and best available evidence pertaining to the Indian population and is meant for practice in India.
- Evaluation of a patient with newly diagnosed colorectal cancer (CRC) should include essential tests: A complete colonoscopy with biopsy, imaging (for colon cancer: Contrast-enhanced computed tomography (CECT) scan of the chest, abdomen and pelvis and for rectal cancer: Magnetic resonance imaging (MRI) of the pelvis, or an endoscopic ultrasound (EUS), with a chest and abdomen CECT), complete blood counts, liver and kidney function tests, carcinoembryonic antigen (CEA) and carbohydrate antigen 19.9 (CA19.9).
- For patients with localized colon cancer, resection is the treatment of choice, with consideration given to adjuvant chemotherapy for the patient with stage III and high-risk Stage II cancers.
- In patients with early rectal cancer (T1/T2, N0) surgery is the treatment of choice.
- Patients with locally advanced rectal cancer (T3/T4, N1, circumferential resection margin (CRM) threatened or involved) benefit from neoadjuvant therapy. Short course radiotherapy can be given if the CRM is not threatened. Others should undergo long course chemoradiotherapy. Adjuvant therapy is given to all patients receiving neoadjuvant therapy.
- Patients with potentially resectable metastatic liver limited disease should undergo synchronous or staged metastatectomy, along with neoadjuvant and adjuvant chemotherapy.
- Nonresectable metastatic disease must be assessed for chemotherapy versus best supportive care on an individual basis.
- Clinical examination and serum tumor markers are recommended at each follow-up visit, with imaging only done when either is abnormal or rising. Colonoscopic surveillance is also recommended for these patients.

INCIDENCE

Colorectal cancer is the third most common cancer in men and the second most common in women worldwide.[1] However, in India, colon cancer ranks 9th and rectal cancer 10th among the most common cancers in men. For women, rectal cancer does not figure in the top 10 cancers, whereas colon cancer ranks 9th.[2] In 2013, the highest adjusted incidence rate (AAR) in men for CRCs was recorded in Thiruvananthapuram (4.1), followed by Bengaluru (3.9) and Mumbai (3.7). In women, the highest AAR was recorded in Nagaland (5.2), followed by Aizwal (4.5).[2]

PURPOSE

Several international consensus guidelines are available for the management of CRC, but none specific for India. It may not be possible to apply these international guidelines to the Indian population owing to differences in the incidence and biology of disease, socioeconomic factors,

and availability of resources. Therefore, it is essential to formulate reliable, evidence-based guidelines that are applicable to Indian patients, keeping in mind the socio-cultural diversity, distribution of resources and availability and accessibility to health-care.

DIAGNOSIS AND STAGING

Evaluation of a patient with a CRC is aimed at pathological confirmation of the diagnosis and an accurate staging of the disease. Essential tests, which need to be done in all patients, include a complete colonoscopy with biopsy, imaging (CECT scan of the chest, abdomen and pelvis for colon cancers and MRI of the pelvis, or a EUS, with a chest and abdomen CT for rectal cancer, complete blood counts, liver and kidney function tests, CEA and CA19.9.

In metastatic disease, histological confirmation of primary neoplasms is preferable, but if this is not feasible, histological confirmation of the metastatic lesion is mandatory before definitive therapy. RAS mutation testing is recommended for patients with metastatic disease as mutations in the RAS gene predict a lack of response to therapy with cetuximab and panitumumab[3,4,5] BRAF mutation testing is currently not recommended.

If index colonoscopy has not been complete, the same should be done within a 3-month period after resection to exclude synchronous lesions or polyps. If this is not possible, a double-contrast barium enema for total colon examination is essential. If CT scan of the chest and abdomen are not feasible, a chest radiograph and abdominal ultrasonography may be done prior to treatment.

Indications for positron emission tomography-CT include suspected recurrence on the basis of increasing tumor marker levels or clinical symptoms,[6,7] diagnosis and staging[8,9] and before curative resection of metastatic disease.[7]

Staging should be done with American Joint Committee on Cancer staging manual[10] and patients should be assigned a TNM stage.

TREATMENT PLAN

Treatment decisions are based on the stage. All new cases of CRC should be discussed at the tumor board or at multidisciplinary team meetings and the treatment strategy should be confirmed.

Treatment of non-metastatic disease

Colon cancer

In the majority of patients with localized disease, resection is the treatment of choice, with consideration given to adjuvant chemotherapy following resection. In patients not fit for major surgery, one has to make a decision between chemotherapy or best supportive care. In patients presenting with obstruction, a stent or a defunctioning stoma may be used as a bridge to surgery.

Occasionally, patients will present with local disease that has infiltrated adjacent structures; in these cases, the use of preoperative chemotherapy may be considered.

The use of adjuvant chemotherapy depends on the final histopathologial stage of the disease. All patients with stage III disease should be offered oxaliplatin and fluoropyrimidine (5-fluorouracil [5-FU] or capecitabine) based adjuvant chemotherapy for a period of 6 months.[11] Patients with stage II disease with the following high risk features can be considered for 5-FU or capecitabine based adjuvant chemotherapy: Number of lymph nodes sampled <12; poorly differentiated tumor; vascular, lymphatic or perineural invasion; close, indeterminate, or positive margins; tumor presentation with obstruction or tumor perforation; pT4 stage.[11,12] Macrosatellite instability testing should be considered for patients with T3N0 tumors and patients with microsatellite stable disease may be offered adjuvant chemotherapy.[13] Elderly patients (>75 years of age) should be offered single agent adjuvant chemotherapy with 5-FU or capecitabine.[11]

Patients who have undergone margin-positive resection can be considered for radiotherapy.

Rectal cancer

For T1N0 lesions <3 cm in size, within 8 cm from the anal verge, involving <30% of the circumference, well or moderately differentiated adenocarcinoma with no angiolymphatic invasion, local excision is the ideal treatment. This may or may not be full thickness.

Rectal T1 tumors beyond the reach of a trans-anal excision, but <4 cm in size, mobile, and involving less than a third of the circumference can be considered for transanal endoscopic microsurgery (TEMS) excision. Excision is a full thickness, and local nodal excision is possible.[14] However, TEMS requires special expertise and equipment and should not be attempted without training.

For T1 lesions not amenable to local excision, T2N0 lesions and some early T3 lesions where the CRM is not threatened, low anterior resection (LAR) is the surgery of choice. However, if the tumor is within 5 cm of the anal verge, abdomen perineal excision (APE) is the surgery of choice. There is no role for neoadjuvant therapy in these patients with early disease.

For patients with T3 lesions, some T4 lesions with only vaginal or peritoneal involvement, and node-positive lesions, where the CRM is not threatened, short-course preoperative radiotherapy can be recommended, followed by surgery, since this reduces local recurrence rates[15]: 25 Gray (Gy), 5 Gy/fraction for 1-week followed by surgery (<10 days from the first fraction) is a convenient, simple, and low-toxic treatment.[15]

For T3/T4lesions, node positive lesions, where the CRM is threatened, patients can be offered long-course neoadjuvant chemo-radiotherapy (NACTRT) to decrease the local recurrence rate, improve disease-free survival and increase sphincter preservation rates.[16] Standard NACTRT refers to a dose of 46-50.4 Gy together with 5-FU given either as bolus injections with leucovorin during radiation or oral capecitabine, 825 mg/m^2 PO twice daily or prolonged continuous infusion 5-FU (likely better than bolus 5-FU).[17] Surgery should be performed 6-10 weeks after completion of NACTRT. The pathological complete remission rate post NACTRT ranges from 20% to 30% and correlates with prolonged survival.[18]

The nature of surgery would depend on the location of the tumor. Tumors within 5 cm of the anal verge usually require APE whereas more proximal tumors require an anterior resection or a LAR. A distal margin of at least 2 cm is desirable. Total mesorectal excision (TME) extending 4-5 cm below the distal edge of the tumor or a complete TME should be performed. When performing an APE an attempt must be made to obtain a cylindrical specimen without "waisting" at the pelvic floor.

The need for adjuvant chemotherapy should be based on the initial radiological (MRI, if available) staging, and not on post-treatment pathological staging. Indications for adjuvant therapy are as follows: Adverse factors on histology, T3 disease or higher, N1 disease, lymphovascular or perineural invasion, and in general, receipt of NACTRT. Patients with T2N0 disease have only a 5% benefit with chemotherapy.[19]

The current recommendation is 6 months of perioperative treatment.

The regimens recommended are the same as those used in colon cancer. In the case no neoadjuvant therapy is given, adjuvant therapy depends on the histology with CTRT being reserved for patients with involved CRM and adjuvant chemotherapy for those with high-risk features. Adjuvant therapy should be started as early as possible once the operative wound is healed as every 4-week delay in treatment decreases survival rates by 14%.[20]

Laparoscopic resection may be considered, if available, if there is no locally advanced disease and no acute obstruction or perforation. Patients at high risk for prohibitive abdominal adhesions should not be treated using the laparoscopic approach, and in patients who are found to have adhesions during laparoscopic exploration, conversion to open procedure is recommended. Robotic surgery for rectal cancer has theoretical advantages but is not recommended at present. The ROLAAR trial will provide some evidence for or against robotic surgery.

Treatment of metastatic disease

Patients with metastatic CRC can be divided into four groups.

1. The first group is patients with resectable/potentially resectable metastatic disease at presentation. All patients with metastatic disease isolated to a single organ site may be considered for resection, and occasionally, patients with small volume metastatic disease involving two sites may also be considered. In these patients, immediate surgical resection is usually recommended, provided the patients are medically fit. Neoadjuvant chemotherapy is an acceptable alternative approach.[21] Adjuvant (postoperative) chemotherapy is also recommended for these patients, in an attempt to reduce the rate of recurrence.[22]
2. The second group is patients with unresectable disease at presentation that becomes potentially resectable after downstaging (conversion) with systemic therapy. The aim is to convert unresectable liver metastatic disease to resectable disease. The National Institute for Health and Care Excellence, United Kingdom, has recommended a combination of cetuximab[23] plus FOLFOX (or cetuximab with FOLFIRI if oxaliplatin is not tolerated or contraindicated) for patients fit for surgery with disease isolated to the liver (and resected or potentially operable primary colorectal tumor) that is initially unresectable. Other options include combination chemotherapy with Capecitabine-oxaliplatin or FOLFIRINOX with or without the use of bevacizumab.

   Re-evaluation for conversion to resectable disease should be considered every 2 months after preoperative chemotherapy, provided all original sites are amenable to resection. Curative resection will not be possible in many cases, and it is important that patients are aware of this fact. Following hepatic resection, if further hepatic recurrence develops, repeat resection may be considered.

   Given the rationale that these patients have a high risk of recurrence and that chemotherapy may reduce this recurrence risk, these patients are frequently offered adjuvant chemotherapy, despite the lack of data from randomized trials. Some patients with limited lung and liver metastases may be selected for staged metastasectomy following chemotherapy for advanced disease.

3. The third group is patients who have potentially resectable metastatic disease, but who are not candidates for surgical resection because of co-morbidity or poor performance status. In these circumstances, nonsurgical treatment strategies like radiofrequency ablation to the liver or lung or stereotactic radiotherapy to the liver should be considered. This should be only considered when all measurable metastatic lesions can be treated.[24]
4. The last group is patients with unresectable metastatic disease. In these cases, curative treatment is not possible, but many patients will benefit in terms of both quality-of -life and survival from the use of systemic chemotherapy and supportive measures, with a median overall survival rate approaching more than 2 years in recent studies. Evidence suggests that greater benefit is achieved if patients are treated early, before becoming symptomatic.

Hereditary colorectal cancer

Approximately, 5% of all CRCs can be attributed to a hereditary genetic predisposition, including Lynch syndrome (hereditary nonpolyposis colon cancer [HNPCC]) and familial adenomatous polyposis (FAP) among others. Genetic risk assessment for hereditary CRC (HNPCC or FAP) and referral for genetics evaluation should be considered in patients with CRC below 50 years or gastrointestinal cancer before the age of 40 years, uterine cancer before the age of 45 years, multiple gastrointestinal polyps, two separate primary cancers (colorectal, endometrial, gastric, ovarian, urinary tract, hepatobiliary, small bowel, skin and brain) or a family history of colorectal or uterine cancer and a first-degree relative with any of the cancers listed above or a polyposis syndrome. Individuals who fulfill the Amsterdam criteria must also undergo genetic testing.[25]

FOLLOW-UP

The aim of follow-up is to detect recurrences early as well as to assess any complication due to surgery/radiotherapy/chemotherapy especially second cancers. For cancers treated with curative intent-the follow-up is every 3 months in the 1st year, every 6 months until 5 years and then annually. This consists of a clinical examination and measurement of CEA or CA19.9 levels (whichever was raised at diagnosis), radiologic imaging and colonoscopic surveillance at year 1 and 3. If polyps are noted and treated, colonoscopy should be undertaken every 6-12 months until polyp-free status is achieved. For patients with metastatic disease in remission, imaging is considered only if signs/symptoms suggest disease progression or if rising levels of tumor markers are noted.

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How to cite this article: Sirohi B, Shrikhande SV, Perakath B, Raghunandharao D, Julka PK, Lele V, *et al*. Indian Council of Medical Research consensus document for the management of colorectal cancer. Indian J Med Paediatr Oncol 2014;35:192-6.
Source of Support: Nil. **Conflict of Interest:** None declared.