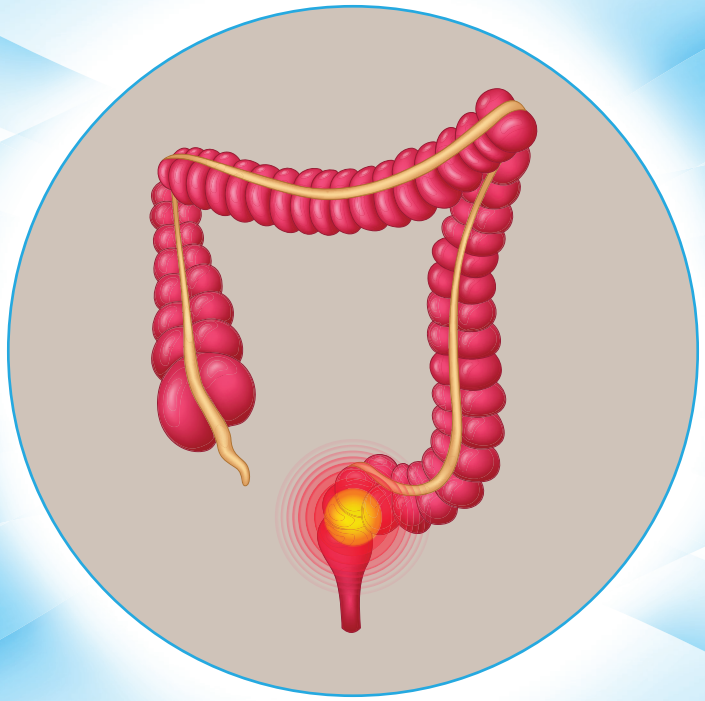
The Association of Colon and Rectal Surgeons of India
(A Section of ASI)



RECTAL CANCER
PRACTICE GUIDELINES 2021

The Association Of Colon And Rectal Surgeons Of India

Practice Parameters Consensus Meeting - 11th Nov 2021, Hotel Renaissance Mumbai

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Foreword

Disorders of the colon and rectum are not only very common but complex too and many a time difficult to treat. The urge to provide best treatment amongst the vast majority available is even more perplexing and frustrating at times. This gets further compounded by the lack of supporting evidences locally. Our members are more guided by evidences produced by other part of the world though it is a well known fact that colorectal disorder occurrences, behaviour and treatment responses may differ across the continents. A need was therefore felt to compile various available literature for some common colorectal disorders and produce them in the form of Practice Guidelines suitable for our members. It is an established fact that treatment modalities guided by the explicit, careful and judicious use of the best evidence available serves as a guide for most appropriate clinical decision making and patient care.

The Association of Colon and Rectal Surgeons of India lead by its team of expert faculties in their respective fields have done some excellent literature search and collated the available experiences to prepare this guidelines for you. We hope this will serve as a ready reckoner for our members in their times of need and help them to combat many litigations too.

I take this opportunity to thank all the contributors for their constant support in this endeavour.

Dr. Niranjan Agarwal
President-ACRSI

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RECTAL CANCER

PRACTICE GUIDELINES 2021

Summary of recommendations

ACRSI recommendations for diagnosis and screening

- A thorough clinical history and examination should be obtained eliciting disease-specific symptoms, associated symptoms, and family history (strong recommendation based on low quality evidence, 1C)
- Fecal occult blood test, fecal immunochemistry, routine laboratory values including CEA levels should be performed for screening as indicated (strong recommendation based on low quality evidence,1C)
- Sigmoidoscopy as a screening test, reduces incidence and mortality of colorectal cancer and should be performed to investigate location of the tumor (strong recommendation based on high quality evidence,1A)
- When possible, all patients with rectal cancer should undergo full colonoscopy for assessing colorectal lesions before rectal cancer management (strong recommendation based on high quality evidence,1A)
- Biopsy is essential in all patients before the start of the treatment (strong recommendation based on moderate quality evidence, 1B)

ACRSI recommendations for staging and imaging

- Rectal cancer staging and re-staging should be routinely performed along with assigning both pre-treatment clinical and post-treatment pathological stages (strong recommendation based on high quality evidence, 1A)
- Clinical staging of the primary tumor by endorectal ultrasound (ERUS) or high resolution rectal magnetic resonance imaging (MRI) should be performed (strong recommendation based on high quality evidence, 1A)
- CT scan of abdomen, pelvis and chest should be preferred to assess the extent of disease and distant metastases (strong recommendation based on moderate quality evidence, 1B)
- All patients with rectal cancer should undergo preoperative radiological staging to assess the metastatic disease (strong recommendation based on low quality evidence, 1C)

ACRSI recommendations for surgical treatment

- Local excision is an appropriate treatment modality for carefully selected T1 rectal cancers without high-risk features (strong recommendation based on high quality evidence, 1A)
- A thorough surgical exploration should be performed, and the findings are suggested to be documented in the operative report (weak recommendation based on low quality evidence, 2C)
- For tumors of the upper rectum, a tumor-specific mesorectal excision should be performed with mesorectum divided ideally no less than 5 cm below the lower margin of the tumor (strong recommendation based on high quality evidence, 1A)
- Total mesorectal excision (TME) should be used for resection of tumors of the middle and lower rectum, either as a part of ultralow anterior resection (uLAR) or as abdominoperineal resection (APR) (strong recommendation based on high quality evidence, 1A)
- Proximal vascular ligation at the origin of the superior rectal artery with resection of all associated lymphatic drainage is appropriate for rectal cancer resections (strong recommendation based on moderate evidence, 1B)
- Extended lateral lymph node dissection should not be done routinely with TME unless associated with clinically suspicious lymph nodes (strong recommendation based on low quality evidence, 1C)
- Intersphincteric resection (ISR)or LAR can be considered instead of APR for low rectal cancer depending on patient choice (weak recommendation based on low quality evidence, 2C)
- After LAR and TME, formation of a colonic reservoir might be considered (weak recommendation based on moderate quality evidence, 2B)
- A diverting ostomy should be considered for patients undergoing a TME for low rectal cancer and for those at high risk for anastomotic leak (weak recommendation based on high quality evidence, 2A)
- Current evidence indicates that laparoscopic TME can be performed with equivalent oncological outcomes compared to open TME when performed by experienced laparoscopic surgeons who possess the necessary technical expertise (strong recommendation based on high quality evidence, 1A)
- Robotic surgery has similar oncological outcomes and better functional outcomes but takes longer operating time compared to laparoscopic resection. However, it should be performed by experienced surgeons (strong recommendation based on high quality evidence, 1A)

Summary of recommendations (contd)

ACRSI recommendations for neoadjuvant and adjuvant chemoradiotherapy

- Neoadjuvant chemoradiotherapy should be used for locally advanced cancers of the mid or distal rectum (strong recommendation based on high quality evidence, 1A)
- Adjuvant chemoradiotherapy should be recommended for selected patients with stage 3 or high-risk stage 2 rectal cancer who are yet to receive neoadjuvant therapy (strong recommendation based on high quality evidence, 1A)
- For patients with stage 3 rectal cancer treated with short-course radiotherapy or no preoperative treatment, CAPOX or FOLFOX is recommended based on patient histopathology (strong recommendation based on moderate quality evidence, 1B)
- Neoadjuvant short-course radiation therapy and long-course chemo radiotherapy are similar in terms of treatment outcomes therefore, the choice should be made based on patient conditions (strong recommendation based on high quality evidence, 1A)

ACRSI recommendations for metastatic rectal cancer

- Based on the patient profile, simultaneous or stage-based approach, or a liver-first approach should be carried out after neoadjuvant therapy followed by the waiting interval in locally advanced rectal cancer patients with synchronous liver metastases (strong recommendation based on high quality evidence, 1A)
- In patients with metachronous metastases, based on chemotherapy history and resectability, local ablation or systemic therapy should be considered (strong recommendation based on moderate quality evidence, 1B)
- Cytoreductive surgery and/or intraperitoneal chemotherapy should be considered in selected patients with peritoneal carcinomatosis in whom R0 resection can be achieved at experienced centers (weak recommendation based on moderate quality evidence, 2B)

ACRSI recommendation for palliation in rectal cancer

- In patients with malignant obstruction, an expanding stent as a bridge-to-surgery can be preferred in a palliative setting (weak recommendation based on low quality evidence, 2C)
- Diverting ostomy should be preferred for obstructing rectal cancer in selective patients in whom low-lying stent placement cause pain and tenesmus (weak recommendation based on low quality evidence, 2C)

ACRSI recommendations for follow-up protocol in rectal cancer

- Clinical assessments including physical examinations and CEA levels should be performed every 3-6 months for 2 years (strong recommendation based on high quality evidence, 1A)
- CT of chest, abdomen and the pelvis should be performed every 6 months in the first 3 years (strong recommendation based on high quality evidence, 1A)
- Complete colonoscopy should be done within the first year, if not performed at time of diagnostic work-up, and it should be followed-up every 3 years (strong recommendation based on high quality evidence, 1A)
- For polyps identified in any colonoscopy, the examination should be repeated every 6-12 months (strong recommendation based on low quality evidence,1C)

Introduction

The prevalence of colorectal carcinoma has increased (9.5%) from 1990 to 2017 across the globe (1,2). In addition, almost 60% of the cases are encountered in developed countries(3). It's prevalence has increased in patients younger than 50 years in many regions globally, and by 2030, incidence rate of rectal cancer is estimated to increase by 124.2% in patients with age 20-34 years, and by 46% in patients with age 35-49 years (4). In India, it's annual incidence rate (AARs) in men is 4.1 per 100 000 (5).

Rectal cancer has distinct environmental associations and genetic risk factors that differ from colon cancer (6). Transformation of the normal rectal epithelium into a dysplastic lesion and eventually, invasive carcinoma, requires a combination of genetic mutations either somatic (acquired) or germline (inherited) accumulated over approximately 10-15years (6). High body mass index (BMI), abdominal fat and type 2 diabetes are its associated risk factors. Additionally, Crohn's disease that affects the rectum, ulcerative colitis and excess intake of red or processed meat, tobacco and alcohol (moderate/heavy) increase the risk for rectal cancer. Data analysis from the Asia-Pacific cohort study collaboration showed that physical activities associated with 28% lower mortality than rectal cancer (7). Family history of rectal cancer increases the risk of occurrence and improves its prognosis after diagnosis (8,9). Data regarding prognostic significance of consuming dairy products is conflicting (10). Moreover, tumor location, presence of lateral pelvic lymph node (LPLN) on preoperative imaging and distant metastasis are risk factors for LPLN metastasis in patients with advanced rectal cancer (11). A study conducted by the Cancer Genome Atlas Network included 224 colorectal tumors and reported similar patterns of genomic alterations in the colon and rectal tissues regardless of their anatomic location and origin (12). It also identified a set of 24 gene mutations in a significant number of cases. In addition to the routinely associated genes (e.g. APC, ARIDIA, TP53, KRAS, and PIK3CA), researchers also identified new genes such as SOX9, FAM123B/WTX, ERBB2 and IGF2 that reportedly regulate cell proliferation and therefore, could serve as potential therapeutic drug targets (12).

Anatomic considerations such as narrow and bony confines of the pelvis make surgical resection more difficult, and the absence of serosa below peritoneal reflection facilitates deeper tumor growth in the peri rectal fat and might contribute to higher rates of locoregional failure of colon cancer (13). Many advances have been made in the diagnosis and management of rectal cancer (1). These include clinical staging with endorectal ultrasound (ERUS) and pelvic magnetic resonance imaging (MRI), operative approaches such as transanal endoscopic microsurgery (TEM), laparoscopic and robotic assisted proctectomy, neoadjuvant and adjuvant therapies, and intense follow-up protocols. Goals of rectal cancer treatment include optimizing disease-free survival (DFS) and overall survival (OS) whilst minimizing local recurrence and toxicity from radiation and chemotherapy. Optimal patient outcomes depend on multidisciplinary approaches in therapy. To standardize patient care, several international clinical practice guidelines (European Society of Medical Oncology [ESMO], American Society of Clinical Oncology [ASCO], National Comprehensive Cancer Network [NCCN], Australia, French, Japanese, Canada, and American Society of Colon and Rectal Surgeons [ASCRS]) have provided evidence-based recommendations for diagnosis and management of rectal cancer. In 2014, the Indian Council of Medical Research (ICMR) also published a consensus document for management of colorectal cancer (5). Despite this, a certain degree of variation across guidelines remain. Considering distinct anatomical differences in etiology and the risks for colon and rectal carcinoma, we aimed to develop clinical practice recommendations for rectal cancer in accordance with the recently published guidelines and updated literature evidence.

Methodology

This practice parameter for rectal cancer management was developed in accordance with the available guidelines and updated evidence for rectal cancer. The authors carried out a literature search on ESMO, ASCO, NCCN, ASCRS, Australia, French, Japanese and Canada Society of Colon and Rectal Cancer guidelines and other relevant high-quality literature available for rectal cancer management. The present guideline was drafted and reviewed by an expert committee and the common consensus statements were derived after discussion and gathering their views during a virtual consensus meeting. This draft was developed after conducting an organized literature search using PubMed, Cochrane database reviews, Google scholar search engines, regulatory resources and guidelines, and recommendations of International societies. The searches were restricted to literatures, articles and abstracts published in English. Keywords used were “rectum cancer”, “diagnosis + rectal cancer” “endorectal ultrasound + rectal cancer”, “MRI + rectal cancer”, “rectal cancer staging”, “lateral recurrence + rectal cancer”, “local excision + rectal cancer”, “TME + rectal cancer”, “APR + rectal cancer”, low anterior resection (LAR) + rectal cancer”, sphincter preserving surgery + rectal cancer”, “ISR + rectal cancer”, “ostomy + rectal cancer”, “colostomy + rectal cancer”, “laparoscopic + rectal cancer”, “robotic + rectal cancer”, “ileostomy + rectal cancer”, “J-pouch + rectal cancer”, “ligation + rectal cancer”, colorectal anastomosis + rectal cancer”, “coloanal anastomosis + rectal cancer”, palliation + rectal cancer”, “brachytherapy + rectal cancer”, “neoadjuvant + rectal cancer”, “short-course chemotherapy + rectal cancer”, "long-course chemotherapy + rectal cancer”, “synchronous rectal liver metastasis", “chemotherapy and regional therapy of hepatic colorectal metastasis", “unresectable rectal cancer metastases”, “peritoneal stripping + peritoneal carcinoma” and “cytoreduction + peritoneal carcinoma".

Systematic reviews and meta-analyses were preferred and were followed by prospective randomized controlled trials (RCTs) for developing this guideline.

A method adopted by the ASCRS was used to derive quality of evidence, wherein 1 was assigned to strong recommendations and 2 to weak recommendations. These recommendations were further categorized based on the level of evidence as 'A' for RCTs without important limitations or overwhelming evidence from observational studies, 'B' for RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise) or exceptionally strong evidence from observational studies, and 'C' for observational studies or case series or consensus opinion of the expert group (Table 1). (14)

Table 1: The GRADE system for grading recommendations (14)

Supporting evidence	Quality of evidence	Grade of recommendation	Quality of evidence
RCTs without important limitations or overwhelming evidence from observational studies	Benefits clearly outweigh risk and burdens or vice versa	1	A
	Benefits closely balanced with risks and burdens	2	A
RCTs with important limitations (inconsistent results, methodologic flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Benefits clearly outweigh risk and burdens or vice versa	1	B
	Benefits closely balanced with risks and burdens	2	B
Observational studies or case series or consensus opinion of the panel	Benefits clearly outweigh risk and burdens or vice versa	1	C
	Uncertainty in the estimates of benefits, risks and burden; benefits, risks, and burden may be closely balanced	2	C

Diagnosis and screening

History, digital examination and blood tests

A detailed history including their family history and risk factors should be obtained and all patients should undergo examination (5). Among many symptoms associated with rectal cancer, most common symptoms are rectal bleeding, diarrhea, constipation/change in bowel habits, weight loss, abdominal pain and anemia. Most rectal cancers develop via the chromosomal instability pathway (CIN), and about 13% are caused by deficient mismatch repair (13). The most common disorders are Lynch syndrome and familial adenomatous polyposis. Therefore, genetic counseling is critical in management, driving surveillance and potential interventions for patients and affected family members (13).

Primary investigations such as fecal occult blood testing, estimation of hemoglobin, liver and renal function tests (RFT), serum carcinoembryonic antigens (CEA) and computed tomography (CT) scan of thorax, abdomen and pelvis should be performed to obtain their functional statuses and to check for metastases (5). A meta-analysis of 9 randomized studies showed that both flexible sigmoidoscopy and fecal occult blood testing reduced colorectal cancer mortality when used as screening tools in asymptomatic patients (15). A systematic review and meta-analysis of 5 studies (N=13 073) showed that fecal immunochemical test (FIT) is highly sensitive (78.6%) for detecting colorectal cancer although its ability to rule out colorectal cancer is higher in symptomatic patients (94.1% [symptomatic] vs. 85.5% [mixed cohort], $P < 0.01$)(16). A Cochrane systematic review and network meta-analysis comparing 12 randomized trials evaluating colorectal cancer screening with guaiac fecal occult blood test (annual, biennial), annual and biennial FIT. Sigmoidoscopy (once only) or colonoscopy (once only) in a healthy population (50-79 years) showed that sigmoidoscopy reduces the incidence of colorectal cancer (RR 0.76, 95% CI: 0.70-0.83). Sigmoidoscopy (RR 0.74, 95% CI: 0.69-0.80),

and annual and biennial guaiac fecal occult blood test (gFOBT) (annual: RR 0.69, 95% CI: 0.56-0.86, biennial: RR 0.88, 95% CI: 0.82-0.93) reduces mortality in colorectal cancer from a 15-year perspective (17). However, a systematic review and meta-analysis of 29 studies (N = 7426) showed that negative gFOBT results associated with the incidence of higher interval colorectal cancer than a negative FIT that supported the use of FIT over gFOBT as a screening tool (18). Increasing age, comorbidities and decrease in functional reverse is associated with early mortality in older patients. Therefore, formal geriatric assessment or any frailty screening tool is recommended before initiating any treatment (19). Blood test for measuring CEA levels should be performed before initiating any elective treatment as rising CEA levels could indicate recurrence of disease and prompt further evaluation. Routine monitoring of CEA and CT scans should be performed for 5 years following surgery (13,20). Digital rectal examination such as perianal soiling, excoriation, protruding mass, tumor distance from anorectal ring, anatomic location, degree of mobility and fixation to surrounding structure should also be performed. In addition, it also helps provide information regarding function and integrity of the sphincter. Liquid biopsy is a minimally-invasive, repeatable technique that could play a significant role in screening, diagnosis, predicting relapse and metastasis, monitor minimal residual disease and chemotherapy resistance in patients with colorectal cancer (21). Systematic review and meta-analysis showed that biopsy has a great diagnostic value in detecting colorectal cancer, monitoring response to chemoradiation and assessing the risk for disease recurrence (22,23).

Colonoscopy

Colonoscopy is the preferred option as it helps to confirm the diagnosis histologically and can be used to endoscopically remove any synchronous polyps. Symptomatic patients with risk factors for colorectal cancer should undergo full colonoscopy or rigid proctoscopy, and in case of obstruction, a virtual colonoscopy might help exclude synchronous colonic tumors (13). A systematic review and meta-analysis of 50 studies (N = 6442, 6779 large polyps) showed that endoscopic resection of large polyps was effective and safe (24). Another systematic review of 7 studies described that safe investigation of isolated changes in bowel habits with flexible sigmoidoscopy reported higher risk for right-sided cancer diagnosis with either an isolated change in bowel habit or a combination of changes in bowel habits with rectal bleeding (25). A systematic review and meta-analysis of 4 RCTs and 10 observational studies suggested that screening by both sigmoidoscopy and colonoscopy helped prevent most deaths from distal colorectal cancer (26). Moreover, observational studies suggested that colonoscopy compared to flexible sigmoidoscopy helps decrease mortality (40%-60%) from cancer of the proximal colon. In case of incomplete colonoscopy, a double-contrast barium enema or CT colonography (CTC) may be used preoperatively (27,28). Moreover, meta-analysis of 6 RCTs (N = 4594) showed significantly higher advance and sessile serrated adenoma detection rate in high-definition white-light endoscopy arm compared to standard-detection colonoscopy arm (40% vs. 30%, respectively P = 0.001)(29). A retrospective study of 3208 patients with colorectal symptoms showed that using only CTC could avoid colonoscopies especially in elderly patients as it provides benefits such as diagnosing relevant extra colonic findings without substantial over-diagnosis (30). Surgical management should be guided by histopathological findings (13).

ACRSI recommendations for diagnosis and screening

- A thorough clinical history should be obtained eliciting disease-specific symptoms, associated symptoms and family history (strong recommendation based on low quality evidence, 1C)
- Fecal occult blood test, fecal immunochemistry, routine laboratory values including CEA levels should be performed for screening as indicated (strong recommendation based on low quality evidence, 1C)
- Sigmoidoscopy, as a screening test, reduces incidence and mortality of colorectal cancer and should be performed to investigate location of the tumor (strong recommendation based on high quality evidence, 1A)
- When possible, all patients with rectal cancer should undergo full colonoscopy for assessing colorectal lesions before rectal cancer management (strong recommendation based on high quality evidence, 1A)
- Biopsy is essential in all patients before the start of the treatment (strong recommendation based on moderate quality evidence, 1B)

Staging and imaging

Clinical staging of rectal cancer helps direct decisions regarding treatment choice. The Union for International Cancer Control (UICC) TNM (tumor [T], nodes [N] and metastases [M]) staging classification (8th edition) (31) is shown in Tables 2 and 3. For rectal cancer staging, both clinical stages (upon which subsequent treatment decisions are made) and the final pathological stage (the most important prognostic factor) should be taken into consideration (32). Although the overall TNM system was developed to stratify patients' prognosis before the advent of neoadjuvant therapy and total mesorectal excision (TME), current data suggests that among patients receiving neoadjuvant therapy, final

pathological stage stratifies DFS. A systematic review and meta-analysis of 17 studies emphasized the prognostic value of tumor regression grades in predicting long-term outcomes-DFS or OS (33). Increasing use of preoperative treatment has led to the requirement of pathological staging and incorporating a "down-staging" effect and the prefix "y" is attached to the pathology report (designated "p") to reflect previous multidisciplinary treatment (34). Preoperative staging should also be prefixed by the staging modality including c: clinical, u: ultrasound, mr: MRI and ct: CT-scan.

Table 2: TNM clinical classification for colorectal cancer (3,13)

T-primary tumor		N-regional lymph nodes		M-distant metastases	
Tx	Primary tumor cannot be assessed	Nx	Regional lymph nodes cannot be assessed	M0	No distant metastasis
T0	No evidence of primary tumor	N0	No regional lymph node metastasis	M1	Distant metastasis
Tis	Carcinoma in situ: invasion of lamina propria	N1	Metastasis in 1–3 regional lymph nodes	M1a	Metastasis confined to one organ (liver, lung, ovary, non-regional lymph node(s)) without peritoneal metastases
T1	Tumor invades submucosa	N1a	Metastasis in 1 regional lymph node	M1b	Metastasis in more than one organ
T2	Tumor invades muscularis propria	N1b	Metastasis in 2–3 regional lymph nodes	M1c	Metastasis to the peritoneum with or without other organ involvement
T3	Tumor invades subserosa or into non-peritonealized pericolic or perirectal tissues	N1c	Tumor deposit(s), i.e. satellites, in the subserosa, or in non-peritonealized pericolic or perirectal soft tissue without regional lymph node metastasis		
T4	Tumor directly invades other organs or structuresb,c,d and/or perforates visceral peritoneum	N2	Metastasis in 4 or more regional lymph nodes		
T4a	Tumor perforates visceral peritoneum	N2a	Metastasis in 4–6 regional lymph nodes		
T4b	Tumor directly invades other organs or structures	N2b	Metastasis in 7 or more regional lymph nodes		

Table 3: Stage-wise grouping of colorectal cancer (3,13)

Stages	T	N	M
0	Tis	N0	M0
I	T1,T2	N0	M0
II	T3, T4	N0	M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
III	Any T	N1, N2	M0
IIIA	T1, T2	N1	M0
	T1	N1c/N2a	
IIIB	T1, T2	N2b	M0
	T2, T3	N2a	

	T3,T4a	N1/N1c	
IIIC	T3, T4a	N2b	M0
	T4a	N2a	
	T4b	N1/N2	
IV	Any T	Any N	M1
IVA	Any T	Any N	M1a
IVB	Any T	Any N	M1b
IVc	Any T	Any N	M1c

Table 4: MRI-based tumor regression grading (mrTRG)(35)

Grade	Response	MERCURY(36)
mrTRG1	Complete response	Linear/crescentic 1–2 mm scar in mucosa or submucosa only
mrTRG2	Good response	No obvious residual tumor signifying minimal residual disease or no tumor
mrTRG3	Moderate response	>50% fibrosis/mucin and visible tumor with intermediate signal intensity
mrTRG4	Slight response	Little areas of fibrosis/mucin but mostly tumor
mrTRG5	No response	Intermediate signal intensity, same appearances as original tumor/tumor regrowth

Work-up: staging and re-staging (ERUS, MRI, CT/PET-CT)

Patients presenting with rectal cancer appropriate for resection require complete staging using colonoscopy for assessing the pathological condition or synchronous lesions of the colon and rectum. Staging and re-staging with conventional colonoscopy (CC), CTC, magnetic resonance colonography (MRC) and positron emission tomography (PET)/CTC are of paramount importance for determining the most appropriate therapeutic method, and in predicting the risk for tumor recurrence and overall prognosis (37).

ERUS and MRI

MRI remains the best choice for staging rectal cancer staging and carrying out response assessment despite recent advanced technologies (38-40). It is important to obtain good quality, high-resolution MRI images that can help the surgeon locate the exact anatomical relation of the tumor to mesorectal fascia and the surrounding structure to obtain complete resection (41-44). Moreover, it was reported that identifying nodal disease with imaging is difficult due to the size of nodes and poor accuracy (45-47). Re-staging patients with rectal cancer following neoadjuvant chemoradiation was also suggested as a recent systematic review and meta-analysis of 8 retrospective studies showed that re-staging altered treatment plan in most patients (48). Recent systematic review and meta-analysis showed that diagnostic accuracy of MRI is high for T3-T4 staging and N staging but has poor sensitivity and specificity (49). ERUS may define treatment for earliest tumors and offer less value in locally advanced rectal cancer (LARC)(13,50-55). A meta-analysis of 6 studies (N = 234) by Chan et al. reported that ERUS and MRI both provide similar accuracy in staging non-metastatic rectal cancer although ERUS was superior to MRI in overall T staging and overall T and N staging after adjusting for MRI (56).

However, accurate detection of involved lymph nodes remains a diagnostic challenge for all imaging modalities. In 2004, a systematic review of 5 studies including 258 biopsy-negative rectal adenomas showed that ERUS demonstrated cancer diagnosis in 81% of the misdiagnosed lesions suggesting it was a useful adjunct to biopsy in preoperative workup of rectal villous adenomas (57). In the same year, a meta-analysis of 90 studies by Bipat and colleagues found that sensitivities and specificities of imaging modalities for nodal staging were comparable: CT, 55% and 74%; ERUS, 67% and 78%; and MRI, 66% and 76%, respectively (58). In 2015, another meta-analysis of 63 studies reported similar findings that ERUS T-stage re-staging accuracy (65%) was non-significantly higher than that of MRI T-staging (52%). However, re-staging ERUS and MRI were equivalent in predicting nodal status (59). Recent systematic review and meta-analysis of 11 studies (N = 1511) showed that ERUS has limited accuracy in distinguishing benign adenomas from T1 rectal cancer (60). Recent retrospective study showed that ERUS can be highly accurate in staging rectal lesions, specifically T1-T2N0 lesions, adenocarcinoma or carcinoid and therefore, could remain a highly accurate staging tool for detecting early rectal carcinoma (61).

Re-staging with MRI

Chest or abdominal CT/MRI and pelvic MRI should be suggested prior surgery for re-staging and prior adjuvant therapy to assess patient's response to primary treatment or resection and during re-evaluation

of conversion to resectable disease. MRI re-staging after neoadjuvant therapy support to assess the distance from anal verge or anorectal junction to lower aspects of remaining tumor, tumor length, residual tumor (high signal T2-weighted images), fibrosis (low signal T2-weighteed images), yT-stage and remaining tumor deposits within mesorectum, yN-stage and number of remaining lymph nodes, any remaining extra-mesorectal lymph nodes (35,47) and smallest radial distance (CRM) between remaining tumor and mesorectal fascia. Moreover, it can provide additional findings such as circumferential location of remaining tumor within the wall, extramural growth extent (for yT3 tumor) and morphology of tumor growth (47). Accurate preoperative assessment of local tumor status following chemoradiotherapy (CRT) is essential in deciding appropriate treatment strategy. Tumor response after CRT can be evaluated by assessing MRI-based tumor regression grade (mrTRG) using an established scoring system and post-treatment T-staging (62). The mrTRG for colorectal cancer is summarized in Table 4.

Tumor circumferential margin (CRM) is defined as the shortest distance between the rectal tumor (including noncontiguous tumor) and the mesorectal fascia (63). Accurate determination of CRM in rectal cancer is important in determining local recurrence risk that could subsequently be prevented by additional therapy (63). The CRM status is an independent prognostic factor and strongly associates with the increased risk of local and systemic recurrence, and survival in patients with rectal cancer (63-65). Decreasing CRM from 20 mm to 1 mm is likely to increase the local recurrence by a factor of 12, risk for developing distant metastasis by a factor of 47 and mortality by 3.7 (66). Patients with rectal cancer and CRM ≤1 mm should receive more postoperative attention depending on their individual situations (65). Only MRI can predict CRM with good accuracy for identifying high- and low-risk patients (67). A prospective study reported that the plane with mesorectal fascia seen on high resolution MRI can accurately and reproducibly correlate with surgical resection margins as clear or affected by tumor, and thus enable selection of preoperative management in patients (39). A systematic review and meta-analysis of 14 studies showed that MRI is valuable for assessing mesorectal fascia involvement in rectal cancer with higher efficacy in patients without preoperative chemotherapy (68). A retrospective review of 20 patients with rectal cancer and TME surgery, with both ERUS and MRI done preoperatively, reported that although MRI is routinely used for preoperative rectal cancer imaging, ERUS could provide additional CRM assessment of mid or distal rectal lesions (69). Recently Ye et al. showed a correlation between ERUs and MRI in predicting the CRM status of 20 patients with mid-low rectal cancer without preoperative chemotherapy, and reported that ERUS can be used along with MRI to predict the CRM in these patients, which appeared highly consistent in 90% of cases (concordant: 95%, Cohen coefficient: 0.608, P = 0.007; correlation coefficient: 0.99, P = 0.0005)(70).

PET-CT scans

The extent of disease and distant metastases can be diagnosed preoperatively using CT scans. Chest CT of patient with T3/T4 mid or lower rectal cancer can detect pulmonary metastases (71). Colorectal cancer with lung metastasis has higher risk for bone (10% vs. 4.5%) or brain (3.1% vs. 0.1%) metastasis than those without lung metastases (72). Knowledge of metastatic patterns may help better guide pre-treatment evaluation of patients; especially indeterminations regarding curative-intent interventions (72). Alternative imaging strategies for patients with contrast allergies may include MRI of the abdomen and pelvis with a non-contrast-enhanced chest CT or fluorodeoxyglucose (FDG)- PET imaging. A retrospective study of 45 consecutive patients with very low adenocarcinoma who underwent CTC with multiplanar reconstruction (MPR) reported that with an arbitrary selection, CTC with MPR could be aligned to the tumor axis to better demonstrate tumor margins consecutively including the deepest section of the tumor (73). Moreover, accuracy of T2 and T3 staging using CTC with MPR surpassed that of MRI and suggests their potential role in preoperative T-staging for very low rectal cancer. When we considered only studies performing contemporary PET/CT, rate of nodal upstaging was 21% (95% CI: 13-30) and TNM stage was altered in 41% of patients (74). Another systematic review and meta-analysis of 10 studies (N = 538) comparing pre- and post-CRT PET/CT scan with histopathological assessment of tumor regression in patients with locally advanced rectal adenocarcinoma also suggested that PET/CT may be an useful addition to the current imaging modalities for assessing treatment response (75). However, there is no definite evidence to support routine clinical use of PET/CTC.

ACRSI recommendations for staging and imaging

- Rectal cancer staging and re-staging should be routinely performed along with assigning both pretreatment clinical and post-treatment pathological stages (strong recommendation based on high quality evidence, 1A)
- Clinical staging of the primary tumor by endorectal ultrasound (ERUS) or high resolution rectal magnetic resonance imaging (MRI) should be performed (strong recommendation based on high quality evidence, 1A)

- CT scan of abdomen, pelvis and chest should be preferred to assess the extent of disease and distant metastases (strong recommendation based on moderate quality evidence, 1B)
- All patients with rectal cancer should undergo preoperative radiological staging to assess the metastatic disease (strong recommendation based on low quality evidence, 1C)

Treatment of rectal cancer

Treatment of rectal cancer is based on its clinical stages. Patients with low-risk, early-stage disease are typically treated with primary surgical therapy. Treatment of locally advanced or high-risk disease requires a multi-disciplinary approach that includes neoadjuvant radiation or chemoradiation followed by surgery.

Surgical techniques

Primary rectal cancer lesions can be treated with surgical techniques depending on the location and extent of cancer. Local procedures include transanal excision, TEM, transanal minimal invasive surgery (TAMIS), intersphincteric resection (ISR), and more invasive procedures include transabdominal resection i.e. anterior resection, low anterior resection (LAR), ultra-low resection with coloanal anastomosis (CAA) and abdominoperineal resection (APR).

Local excision

Local excision is appropriate in patients with early stage T1/N0 cancer (3,76). Transanal excisions with negative margin should be approached for small tumors (<3 cm) which are within 8 cm of the anal verge limited to <30% of rectal circumference with no evidence of nodal involvement. It can be performed with minimal morbidity and mortality by either transanal excision (Parks-type excision) or TEM (76). Transanal excision and TEM involve a full-thickness excision performed perpendicular through the bowel wall into perirectal fat. A meta-analysis reported that TEM may achieve superior oncologic outcomes compared to transanal excision (77). Negative (>3mm) deep and mucosal margins are required and tumor fragmentations should be avoided. The excised segment should be orientated for pathological examination. With the exception of poor operative candidates, patients with positive margins, poor differentiations or invasion into the lower submucosa and patients with T2 lesions should be recommended to undergo radical mesenteric excision (3,76).

Local excision following neoadjuvant therapy for rectal cancer (T2 tumors) might be considered in a clinical trial (78,79). Although there are limited evidence available, CRT or neoadjuvant chemoradiotherapy (NACRT) followed by local excision is reportedly a safe and effective alternative to transabdominal resection in T2N0 distal rectal cancer (50) and in any patient with T/any N rectal cancer who refuse or are unfit for transabdominal resection, respectively (80-82). The CARTS study showed that chemotherapy with TEM had good long-term oncological outcomes and health-related quality of life in patients with early stage (T1-3N0M0) rectal cancer (83). The 5-year results of GECCAR 2 study, a multicenter randomized trial, showed no difference in oncological outcomes between local excision and TME and corroborating its 3-year results suggested that local excision can be proposed in selected patients with small T2/T3 low rectal cancer and a good clinical response post CRT (84).

Primary drawback of local excision is the inability to excise and stage mesorectal lymph nodes as T1 lesions and have a risk of harboring nodal metastasis depending on other histological characteristics (85). Moreover, lymph node metastases in early rectal lesions are unlikely to be identified in an ERUS (86). These observations may underline findings that patients undergoing local excision may have high local recurrence compared to those undergoing radical resection (87-89). In a retrospective study, patients (N = 282) with T1 rectal cancer showed local recurrence rates of 13.2% and 2.7% with local excision and radical excision, respectively (P = 0.001)(88). Similarly, another retrospective study also showed a 12.5% vs. 6.9% recurrence in patients undergoing local excision versus standard resection, respectively (P = 0.003)(87). Recent data analysis with resections for >164 000 patients showed that positive margins were more likely seen with local excisions compared to proctectomy in patients with T1 and T2 stage rectal cancer (23.7% vs. 5.3%,respectively; P < 0.001)(90). Thus, benefits of local excision must be balanced against the risk of local failure for each patient (87). As per the Netherlands cancer registry, local excision is only an oncologically-safe treatment option for patients with pT1 and pT2 tumors with a similar 5-year survival to TME surgery (91). However, systematic review of 25 studies suggested using standardized local excision techniques with caution in case of neoadjuvant chemotherapy (NACT)(92).

With limited data, local resection with TEM might have superior outcomes in stage T1 rectal cancer compared to radical resection (89); however, meta-analyses and retrospective studies reported similar or contradicting results for TEM and TME/resection procedure for oncological outcomes (93-95). Additionally, recent systematic review of 16 retrospective studies showed that although local excision for early-stage rectal cancer is associated with increased local recurrence and decreased OS compared to radical resection, the former might be appropriate for selecting individuals with T1 tumors and no adverse pathologic features (96). Overall, local excision of T1N0 rectal should be done carefully in selective patients as the examination of resection specimen with subsequent transabdominal resection in

patients can have T2 cancer or high risk features.

Radical excision/transabdominal resection

Transabdominal resection is a method that is used for majority of rectal cancers as local excision is suitable for only a small percentage of patients. The procedure for preserving the organ while maintaining the sphincter function is preferred; however, it is not possible in all cases (76). Sphincter preservation may be possible when initial tumor bulk prevented consideration of surgeries and tumor exposure has been improved by CRT. Thus, preoperative CRT may result in tumor downsizing and reduced tumor bulk. Appropriate surgical technique, including sharp mesorectal excision is integral for optimizing oncological outcomes and for minimizing morbidity in these surgeries. TME is a recommended procedure for transabdominal resection, which involves enbloc mesorectum removal with tumor, associated vascular and lymphatic structures, fat tissues and mesorectum fascia via sharp dissection and sparing autonomic nerves (76). The TME approach is designed to remove radical lymphatic drainage regions of the tumor located above the levator muscle. Extension of nodal dissection beyond the resection field is not recommended unless required (76).

For mid and upper rectal lesions, the resection margin extends 4-5 cm below the distal edge of tumor using TME followed by recreation of anastomosis. Permanent colostomy is required when recreation is not possible. To facilitate lymphadenectomy and improve probability of achieving negative CRM, wide TME is recommended (76).Obtaining adequate radial or CRM is critical for local control (97). Risks for CRM positivity increase with advancing T and N stages (65,97,98). Quality of surgery, identified by the proper plane of dissection, also plays a key role in CRM positivity (97,98). For example, among patients registered in the CR-07 study, overall, 11% had CRM involvement and at 3 years, the estimated local recurrence rates were 4% for the group with good plane of dissection compared to13% for those with poor quality of surgery (98).

For low rectum cancer (5 cm above anal verge), APR (a standard procedure) with TME should be done when the tumor directly involves anal sphincter or the levator muscles. Histological studies have compared TME from APR and TME with anterior resection, and specimens have reported significantly more positive CRMs and perforations in APR specimens with the plane of resection lying within the sphincter muscle (more than one third of cases)(99). Therefore, in cases where the attempt to achieve negative margin affects the sphincter and might lead to incontinence, APR is preferred. Studies showed that patients treated with APR had high CRM involvement, high local recurrence and poor prognosis than anterior resection (100,101). A meta-analysis by Peng et al. showed that ISR could be an alternative to APR due to shorter hospital stay, lower morbidity, lesser chances of lymph node metastasis and similar oncological outcomes (102). Meta-analyses and retrospective studies have showed that an extra levator APR may benefit over a conventional APR with significantly low rates of CRM involvement, intra-operative perforation and local recurrence in surgical treatment of low rectal cancer (103-106). Retrospective studies reported worst local control and OS after comparing patient outcomes undergoing APR for rectal cancer. It might be due to the associated risk of high recurrence and death in patients with T3/T4 rectal cancer (107-109). Recent multicenter studies have showed that patients with relatively advanced tumor could benefit from extra levator APR compared to conventional APR for surgical and oncological outcomes in spite of pre-operative radio and chemotherapy effects (110,111). Moreover, the patient's quality of life was found comparable to the sphincter-preserving procedures however, controversial results have also been observed (112-114).

Proximal lymphatic resection for rectal cancer is carried out by removing the blood supply and lymphatics up to the original level of the superior rectal artery via ligating the left colic artery (low tie). Although the lymph node yield may increase in procedures where inferior mesenteric artery (IMA) is ligated (high tie), no significant difference in survival has been reported between the two techniques (high or low tie)(115-117). However, low ligation is recommended owing to lower risk of anastomotic leakage and overall morbidity (116,117). A recent meta-analysis and sequential RCT analysis showed no difference between high and low ligation in terms of oncological outcomes or post-operative mortality and morbidity subject to confounding by using neoadjuvant therapy, adjuvant therapy, disease stages, location of tumor and protective stoma (118). Recent RCTs comparing high tie and low tie showed similar findings in long-term (5-year) OS and DFS outcomes (119). In addition, suspected periaortic lymph nodes should be sent for biopsy; more extended lymph node dissection can be performed at the surgeon's discretion (120). Patients with rectal cancer with positive nodal disease have advanced disease, mostly of the lower rectum. After greater accuracy in preoperative staging, only selected patients are eligible for lateral lymph node dissection (LLND) surgery (121). It includes removing all nodal tissue along the common and internal iliac arteries and improved local control and survival. A systematic review and meta-analyses comparing LLND with conventional surgery found that LLND was associated with increased operative time and increased urinary dysfunction (122-125). However, lateral compartment is an area of significant concern for recurrent disease irrespective of using NACRT for recurrent disease (126). Whereas, recent studies have showed that LLND also decreased local recurrence without NACRT irrespective of survival benefits in advanced lower rectal cancer thus, suggest using NACRT with LLND (127).

Sphincter-sparing surgery

For ultralow rectal cancer, a sphincter-saving procedure allows the safe removal of tumors and spares

the anal sphincter muscles (128). Rates of sphincter-saving surgery have increased from 25% to 75% (129). Distance of the tumor from anal verge is no longer a limit for sphincter-saving resection (128). Sphincter-preserving surgery LAR and ISR are frequently used than APR in treating low rectal cancers (130). LAR syndrome is a major concern that affecting the patient's quality of life in more than half the patients undergoing LAR (131,132). Recent prospective observation study also showed severe bowel dysfunction in patients with low rectal cancer undergoing ultra LAR 36 months after surgery. It also reported old age, gender, adjuvant CRT and ultra LAR are the associated risk factors thus, it should be performed only in selected patients (133). A systematic review and meta-analysis (84 studies) showed that ISR can be considered for patients with low rectal cancer and acceptable oncological outcomes (local recurrence, 6.7%; post-operative mortality, 0.8%; and morbidity, 25.8%) and with diverse and often imperfect functional outcomes (mean number of bowel motion in 24 h: 2.7 in 8 studies)(134). Similar results have been reported in other systematic reviews with ISR that differ from conventional hand-sewn CAA after LAR suggesting that ISR appears to be surgically, oncologically and functionally acceptable for very low rectal cancers all while highlighting the need for more experience and better understanding of oncology, anal physiology and pelvic anatomy to achieve successful outcomes without complications and improved patient survival (135). A retrospective study included patients (N = 111) with advanced rectal cancer treated by NACRT followed by sphincter-saving resection compared those who underwent APR showed that both procedures had similar oncological outcomes (3-year OS, P = 0.948 and disease recurrence, P = 0.107) (136). A cross-sectional study comparing oncological and functional outcomes between ultralow anterior resection (uLAR) and ISR showed that the latter reported severe bowel dysfunction and a higher incidence (75.9% vs. 49.3%, P = 0.16) for major incontinence than the former (137). However, oncological outcomes (OS, 91.7% vs. 91.4%; DFS, 79.2% vs.79%) were comparable in both groups (137). Long-term results of ISR for low rectal cancer in Japan reported similar findings of low mortality and morbidity rates, and good survival rates after ISR. However, local recurrence and postoperative incontinence were relatively high compared to APR or LAR (138). In addition, the local recurrence rates were high with ISR especially in T3 and T4 rectal cancer (138). Modified ISR technique consisting of abandoning colonic J-pouches, transverse coloplasty or defunctioning temporary stoma in favor of direct hand-sewn CAA in highly selective patients with T2/T3 rectal cancer may be an alternative to APR/LAR in accordance with functional (Wexner score 1-year, 8.5; 3-year, 7.2) and oncological perspectives (5-year survival, 93.3%; 3-year DFS, 98%)(139). Retrospective study showed that the new surgical procedure-conformal sphincter-saving operation for very low rectal cancer demonstrated the ability to preserve fecal continence (1-year Wexner score after ileostomy reversal, 5.9 ± 4.3) without compromising oncological outcomes (3-year OS, 100%; 3-year DFS, 83.9%)(140).

Rehabilitation and stoma procedures

Patients with rectal cancer may face functional problems after surgery/chemoradiation that includes urgency, increased bowel frequency, clustering and fecal incontinence. This is commonly encountered after LAR and is attributed partially to the loss of reservoir function of the rectum (141). Risk factors associated with non-closure of the stoma after anterior resection in patients with rectal cancer include old age, ASA score >2, comorbidities, open surgery, surgical complications, anastomotic leakage, stage IV tumor and local recurrence .Thus, patients should be informed prior their operation regarding the non-reversal of the procedure and the joint decision of the surgeon and the patient should be preferred (142). Various surgical techniques have been developed that include colonic J-pouch, transverse coloplasty and side-to-end anastomosis to improve postoperative function.

A systematic review and meta-analysis reported that colonic J-pouch is superior to straight CAA in terms of reduced bowel frequency and the urgency of up to 18 months postoperatively compared to straight CAA. Whereas, transverse coloplasty and side-to-end anastomosis had similar functional outcomes compared to colonic J-pouch (143,144). However, in another multicenter RCT (N = 457) that compared both the procedures showed that colonic J-pouch reconstruction was not superior in terms of reduction in anastomosis leakage and post-operative complications (145). Another multicenter RCT (N = 238) that compared colonic J-pouch and side-to-end anastomosis in patients after resection for rectal cancer reported similar quality of life, functional outcomes and complications for up to 2 years of follow-up in both procedures (146). It was reported that although selecting the procedure may depend on the patient's anatomic considerations and the surgeon's choice, side-to-end anastomosis might be preferred due to ease of construction (146). Similar findings were also reported in another prospective study that compared these two procedures; however, higher anastomotic leakage was seen with colonic J-pouch (147). A systematic review of 8 trials (N = 409) showed that delayed CAA could be an alternative to primary straight CAA in low rectal cancer as it reduced the risk for anastomotic leakage and pelvic sepsis; and there was no need for protective ileostomy and had better functional and oncological outcomes. However, a definitive conclusion awaits further controlled trials (148). Contrastingly, Swiss prospective randomized multicenter trial (SAKK 40/04) (N = 336) that compared end-to-end anastomosis, colonic J-pouch and straight CAA, showed no significant difference between three procedures for composite evacuation and incontinence, and noted that performing reconstruction after rectal surgery depended on the surgeon's preference (149). Moreover, the analysis of quality of life showed significant difference between these reconstruction procedures at 6 and 12 months. Colonic J-pouch was found to be better for short-term (24 months) quality of life (150).

Absence of protective stoma is reportedly associated with high incidence of anastomotic leaks (47%) and reoperation (36%). Thus, a de-functioning stoma could effectively reduce clinical consequences, and it could be recommended in patients undergoing low rectal anterior resection for rectal cancer (151). Anastomotic leaks after anterior resection are associated with decreased survival and significant increase in risk for local recurrence (152). A recent systematic review showed that endoscopic management of anatomical leakage after anterior resection could be considered as an alternative to surgical procedures. Among 75 cases with reported endoscopic repair and endoluminal vacuum device (52%) was the most common technique followed by fibrin glue (25.3%) and over-the-scope-clip/endoclip (22.7%)(153).

Diverting ostomy, either loop colostomy (of transverse colon) or loop ileostomy could lower the anastomotic leak rate (RR, 0.39; P < 0.001) and re-operation rate (RR, 0.29; P < 0.001)(154). A meta-analysis of 5 RCTs showed that protective diversion ileostomy in LAR is beneficial as it decreased the rate of anastomosis leakage by 33% and reoperation by 26% (155). Loop ileostomy is preferred over loop colostomies owing to the ease of reversal of procedure; however, loop ileostomy is associated with increased incidence of high stoma output and dehydration. Stoma prolapse was less frequent with loop ileostomy than with loop colostomy (154). A propensity score-matched retrospective study also showed that loop transverse colostomy associated with low rates of stoma-related complications (48.7% vs. 74.3%, P < 0.001) and stoma reversal perioperative complications (9.01% vs. 24.24%, P = 0.008) compared to loop ileostomy (156). Another systematic review and meta-analysis that compared loop ileostomy with colostomy demonstrated that both procedures had similar overall morbidity (15.6% vs. 20.4%, OR 0.67, P = 0.36, NNT = 21) after both stoma creation and closure however, morbidity reduced with loop ileostomy due to dehydration (3.1% vs. 0%; OR 3.00, P = 0.31, NNT = 33)(157). A recent systematic review and meta-analysis showed the association of LAR syndrome and the use of diverting ileostomy (OR 1.96, P = 0.02) with no consistent difference in patient's quality of life with or without ileostomy (158). A meta-analysis (6 studies) showed that early closure of defunctioning loop ileostomy could be effective and safe (stoma-related complications, OR 0.46, P = 0.02; small bowel obstruction rate, OR 0.11, P < 0.00001; overall morbidity, OR 0.63, P = 0.38) in selected patients without increasing post-operative complications compared to late closure however, strategy to reduce stoma-related complications should be preferred (159). Recent systematic reviews and meta-analysis of the current literature indicated that early ileostomy closure associated with similar complication rates compared to standard closure in patients with an uncomplicated postoperative course and radiologically verified intact distal anastomosis after index surgery (160). Previously the EASY (early closure of temporary ileostomy) trial, a multicenter RCT (N = 112) also showed that early closure ileostomy had fewer complications but had no effect on patient's health-related quality of life (161). Although, limited evidence of systematic review showed temporary loop ileostomy closure during adjuvant chemotherapy following rectal cancer resection may be associated with comparable outcomes to ileostomy closure after adjuvant chemotherapy however, to assess the aptness of using either approaches remains to be seen (162).

Minimal invasive procedures

In rectal cancer surgery, several clinical and patient characteristics have their significant impact on the surgical loco regional tumor clearance (163). Minimally invasive surgery has the potential to reduce perioperative morbidity with equivalent short- and long-term oncological outcomes compared to conventional open approach (163). However, high risk for conversion is evident in patients with bulky and low tumors, male gender and narrow pelvis. Patient characteristics can represent challenges in rectal cancer surgery especially in minimally invasive approaches (163).

Laparoscopy versus open resection

Several RCTs, systematic reviews and meta-analyses have showed clinical, pathological and/or oncological outcomes of laparoscopic resection compared to standard resection procedures. A systematic review and meta-analysis of 14 RCTs compared laparoscopic-assisted rectal resection with open rectal resection and reported significantly reduced blood loss, quicker resumption of oral intake, early return to functions and shorted hospital stay at the expense of long operating time with laparoscopic resection (164). Memon et al. reported that laparoscopic-assisted rectal resection was a safe and effective alternative to open resection however; it should be performed in an established unit with experienced laparoscopic surgeons (164). A systematic review and meta-analysis of 9 RCTs (N = 4126) assessing short- and long-term outcomes of laparoscopic and open surgery showed that short-term outcomes of major and total post-operative complications were lower with laparoscopic surgery, and long-term 5-year survival-rate and DFS rate (positive CRM and number of lymph nodes extracted) were similar for both. Thus, laparoscopic surgery was as safe and effective as open surgery in terms of long-term outcomes but had lower post-operative complications (165). Another systematic review and meta-analysis by M. Pe˛dziwiatr et al. showed similar short- and long-term oncologic outcomes (3- and 5-year DFS, OS and local recurrence) with laparoscopic and open surgery (166). Recent results from the ALaCaRT (Australasian Laparoscopic Cancer of the Rectum Trial) study showed that laparoscopic surgery did not differ from open surgery in efficacy in terms of 2-year DFS (HR 1.17, 95% CI: 0.81-1.68) and OS (HR 1.08, 95% CI: 0.63-1.86) in patients with T1 to T3 rectal adenocarcinoma <15 cm from the anal verge (167). The COLOR II study (N = 1044 patients) showed that based on long-term morbidity

outcomes, laparoscopic surgery for rectal cancer could be considered a routine technique as there was no difference in the risk for bowel obstruction (12.5% vs. 11.9%, P = 1.000), incisional (18.7% vs. 17.0%, P = 1.000) or parastomal hernia (17.4% vs. 9.3%, P = 0.066) (168). However, Martijin et al. reported improved short-term outcomes of laparoscopic surgery in COLOR II study and in patients with rectal cancer within 15 cm from the anal verge without distant metastases and when treated by skilled surgeons, it showed similar safety (morbidity P = 0.424 and mortality P = 0.409), positive resection margins (P = 0.850) and complete resection (P = 0.250) to that of open surgery, and recovery (functional return P < 0.0001and short hospital stay P = 0.036)(169). Moreover, age >65 years, BMI >25 and tumor location between 5-15 cm from the anal verge, were risk factors for converting from laparoscopic to open surgery in patients enrolled in the COLOR II study. Thus, selecting suitable candidates for laparoscopic surgery is essential to prevent intra-operative conversion from laparoscopic to open surgery (170). A Cochrane systematic review and meta-analysis (14 studies, N = 3528) showed that laparoscopic TME and open TME had similar long-term survival outcomes for treating rectal cancer and led to better short-term post-surgical outcomes in terms of recovery from non-locally advanced rectal cancer. Moreover, results also consistently showed similar DFS, OS and local recurrence after at least 3 years and up to 10 years (171). The CLASICC trial reported long-term data of patients with rectal cancer (N = 253) who were randomly assigned to a laparoscopic approach and reported higher rates of radial margin involvement in patients of laparoscopic anterior resection group (12%) compared to open anterior resection group (6%) but this data was statistically insignificant and did not translate into a difference in 5-year rates of local recurrence between both groups (172). These 5-year analyses confirmed oncological safety of laparoscopic surgery for both colonic and rectal cancers. Therefore, using laparoscopic surgery to maximize short-term outcomes does not compromise long-term oncological results (172). The COREAN RCT also found no difference in rates of CRM positivity between open (4.1%) and laparoscopic resection groups (2.9%) (P = 0.77) or in the rate of complete mesorectal resection (P = 0.414) for mid or low rectal cancer (173). It also showed that laparoscopic resection for LARC after preoperative CRT provided similar outcomes in DFS to open resection, thus justifying its use (174). Aleix et al. showed that although other oncological and pathological outcomes were similar for both surgeries, the risk for achieving a non-complete (nearly complete and incomplete) mesorectal excision was significantly higher (RR 1.31; 95% CI: 1.05-1.64; P = 0.02) in patients who underwent laparoscopic resection compared to open resection and needed to be assessed for long-term association with DFS or OS (175). Similarly, Memon et al, in his meta-analysis, compared both surgeries and reported that although laparoscopic resection compares favorably to open resection completeness of TME, +ve CRM, +ve DMR, lymph node harvesting, length of resected specimen and tumor size, significantly higher risk of rectal perforation during laparoscopic resection is a concern for oncological adequacy and safety (176).

Robotics

Recently reported evidence suggests that robot-assisted surgery could overcome several disadvantages of laparoscopic surgery such as high conversion rate, urological and/or sexual complications associated in rectal cancer patients with high BMI, narrow pelvic and bulky tumors. The ROLARR, an international randomized parallel-group trial, compared robotic and laparoscopic surgeries for curative treatment of rectal cancer and showed no superiority (OR 0.614, 95% CI: 0.311-1.211, P = 0.16) of robotic over laparoscopic surgery in terms of conversion rate (177). However, sensitivity analysis revealed that participating doctors were experts in laparoscopic surgery, and some, if not all, were still learning robotic surgery; and treatment effects (OR) decreased by a factor of 0.341 (95% CI: 0.121-0.960, P = 0.042) along with per unit increase in log-number of previous experiences of performing robotic operations by surgeons (177). Several systematic reviews and meta-analyses also showed pathological, functional and oncological outcomes of robotic surgery for rectal cancer. A systematic review (28 studies) that included ROLARR study by Jones et al. compared robotic and laparoscopic TME showed that longer operation time (P = 0.0001), early passage of first flatus (P = 0.002), lower risk of conversion (P = 0.00001) and shorter hospitalization (P = 0.01). In addition, it also showed similar oncological outcomes (recurrence, P = 0.96; numbers of harvested nodes, P = 0.49; and +ve CRM, P = 0.53) and similar length of distal resection margin. Authors concluded that robotic resection was found to be as feasible and oncologically safe as laparoscopic resection (178). Han et al., in his systematic review and meta-analysis (8 RCTs, N = 999), compared robot-assisted proctectomy (n = 495) with laparoscopic proctectomy (n = 504) in patients with rectal cancer. Results indicated that robot-assisted proctectomy was superior for short-term outcomes with similar pathological outcomes, although long-term oncological outcomes remained for better inference (179). Another systematic review of 13 studies (N = 24 526) also reported similar oncological outcomes, and clinical and functional benefits with robotic surgery than open and laparoscopic surgery (180). Milone et al., in a systematic review and meta-analysis (12 studies), showed that robotic approach to rectal resection is better for obtaining complete TME (OR 1.83, 95% CI: 1.08-3.10, P = 0.03) than conventional laparoscopic surgery (181). Moreover, meta-regression showed no association of the patient and tumor characteristics to complete TME (181).

ACRSI recommendations for surgical treatment

- Local excision is an appropriate treatment modality for carefully selected T1 rectal cancers without high-risk features (strong recommendation based on high quality evidence, 1A)
- A thorough surgical exploration should be performed and the findings are suggested to be documented in the operative report (weak recommendation based on low quality evidence, 2C)
- For tumors of the upper rectum, a tumor-specific mesorectal excision should be performed with mesorectum divided ideally no less than 5 cm below the lower margin of the tumor (strong recommendation based on high quality evidence, 1A)
- Total mesorectal excision (TME) should be used for resection of tumors of the middle and lower rectum, either as a part of ultralow anterior resection (uLAR) or abdominoperineal resection (APR) (strong recommendation based on high quality evidence, 1A)
- Proximal vascular ligation at the origin of the superior rectal artery with resection of all associated lymphatic drainage is appropriate for rectal cancer resections (strong recommendation based on moderate evidence, 1B)
- Extended lateral lymph node dissection should not be done routinely with TME unless associated with clinically suspicious lymph nodes (strong recommendation based on low quality evidence, 1C)
- Intersphincteric resection (ISR)or LAR can be considered instead of APR for low rectal cancer depending on patient choice (weak recommendation based on low quality evidence, 2C)
- After LAR and TME, formation of a colonic reservoir might be considered (weak recommendation based on moderate quality evidence, 2B)
- A diverting ostomy should be considered for patients undergoing a TME for low rectal cancer and for those at high risk for anastomotic leak (weak recommendation based on high quality evidence, 2A)
- Current evidence indicates that laparoscopic TME can be performed with equivalent oncological outcomes compared to open TME when performed by experienced laparoscopic surgeons who possess the necessary technical expertise (strong recommendation based on high quality evidence, 1A)
- Robotic surgery has similar oncological outcomes and better functional outcomes but takes longer operating time compared to laparoscopic resection. However, it should be performed by experienced surgeons (strong recommendation based on high quality evidence, 1A)

Neoadjuvant chemoradiotherapy

The NACRT can be either short-course radiotherapy (SCRT) or long-course CRT. A systematic review and meta-analysis of 8 studies compared neoadjuvant radiotherapy (NRT) with no radiotherapy (RT) in patients with stage IV rectal cancers and reported improved local recurrence-free survival rates (RR 1.15; 95% CI: 1.01-1.31, P = 0.03) and 5-year OR (RR 1.31, 95% CI: 1.14-1.89, P = 0.003) benefits with NRT (182). A systematic review and meta-analysis (106 consecutive studies; N = 41 121) showed that preoperative RT/CRT significantly improved local recurrence-free survival however, no improvement in OS or metastasis-free survival was seen. Preoperative RT/CRT also significantly increased the risks for postoperative wound complications, long-term anorectal symptoms and erectile dysfunctions (183). However, NRT/NACRT did not increase the risk for post-operative anastomosis leakage after anterior resection for mid-lower rectal cancer as reported in another systematic review and meta-analysis (23 studies, N = 9675)(184). A systematic review and meta-analysis of 48 studies showed survival benefits for NRT or adjuvant RT in rectal cancer when treated surgically with TME, and reported improved OS and DFS in patients with more than 10% of pT3 tumors; thus RT should be included in the protocol when rectal cancers treated with TEM (185). A systematic review and meta-analysis on dose-escalation of RT showed that >54Gy RT associated with high rates of pathological complete response (pCR) (24.1%, 95% CI: 21.2-27.4) without any increased risk for acute grade 3 toxicity events (186). The pCR approached 25% with moderate escalation of 54-60Gy using moderate inverse planning techniques without an identified clear dose-response relationship (P > 0.05)(186).

A recent systematic review of 17 studies indicated that NACT seems to be an alternative to NACRT for patients with LARC as the former was associated with low anastomotic leak, adequate tumor down-staging, low

local recurrence and high survival rates (187). The N-SOG 03 trial examined the safety and efficacy of neoadjuvant CAPOX (capecitabine combined with oxaliplatin [OXA]) and bevacizumab (bev) without RT followed by curative resection in patients with poor-risk MRI-defined LARC. The OS in this study was 81.3%, and among 29 patients who underwent resection, 5-year OS was 89.7%; progression-free survival, 72.4%; and local-relapse rate was 13.9%. It was reported that NACT alone could be suitable for treating locally advanced rectal cancer due to satisfactory long-term outcomes however, patients with cT4b tumor were not suitable for NACT alone (188). A study that enrolled patients (n = 106) with LARC were given preoperative chemotherapy with folinic acid, 5-fluorouracil (5-FU), OXA and irinotecan (mFOLFOXIRI) followed by adjuvant CT with modified 5-FU, leucovorin and OXA (mFOLFOX6) reported reduced pCR rates (20.4% vs. 17.4%) and tumor down-staging (42.7% vs. 41.3%) compared to patients who were without preoperative long-term RT, respectively. Thus, mFOLFOXIRI was suggested as an possible alternative to CRT in untreated patients with LARC (189). A multicenter, open-label, phase III FOWARC trial to assess the modified infusional mFOLFOX6 with/without RT versus fluorouracil (FU) and radiation in Chinese patients with LARC showed that mFOLFOX6, with/without radiation, had similar 3-year DFS, 3-year local recurrence probability after R0 resection and 3-year OS compared to FU with radiation in patients (190).

A systematic review and meta-analysis of 10 studies (N = 648) showed 5-year OS and DFS of 74.4% and 65.4% in patients who underwent induction chemotherapy and NACRT followed by resection of rectal cancer, respectively. Local recurrence and distant failure rates were 3.5% and 20.6%, respectively; thus total neoadjuvant therapy should be considered in patients with high-risk LARC owing to improved compliance and disease control (191). A prospective phase II COPERNICUS study showed that 8-week OXA/FU NACT followed by SCRT before surgery could be well tolerated with effective tumor downstaging (T-down-staged, 73%; MRI-tumor regression grade, 37%) and 2-year progression-free survival (86.2%)(192). INOVA, a randomized phase II study, compared 2 neoadjuvant strategies (arm A: 12-week bev + FOLFOX-4 followed by bev-5-FU-RT before TME, and arm B: bev-5-FU-RT followed by TME) for LARC. Results showed improved 5-year OS (90.5% vs. 72.7%, respectively) and DFS (70% vs. 63.4%, respectively) in patients from arm A compared to arm B. Thus, bev + FOLFOX-4 could provide survival benefits when followed by bev + 5-FU-RT and TME in LARC (193). Similarly, the Trust trial also reported that neoadjuvant treatment (induction of FOLFOXIRI + bev followed by CRT with fluoropyrimidines (50.4Gy + capcetabine) + bev could be feasible in terms of DFS (2-year DFS: 80.45%, 95% CI: 78.79-82.10) for improvement in distant disease control for LARC (194). A study assessing CAPOX + RT in patients with high-risk LARC showed a 36% pCR or clinical complete response with 17% (leucopenia: 10.6% and radiation dermatitis: 6.4%) common grade 3 adverse events thus, total neoadjuvant treatment could prove effective and safe in these patients (195). Similarly, a multicenter non-randomized phase II study in patients with stage II/III rectal cancer showed that consolidation of mFOLFOX6 after CRT (50Gy) and before TME, increased the compliance to systematic CT and DFS beyond the benefit of improved pCR rates (196). Moreover, the FACT trial also showed high R0 resection rate (91%), pCR rate (11.9%) and sphincter preservation rate (73.8%) with neoadjuvant treatment with mFOLFOX6 for LARC (197). Although CT with neoadjuvant long-course therapy had promising roles, a systematic review by Rosello et al. showed that adjuvant CT could be of value in selected high-risk patients not responding to NART (198); and its routine use in patients with pCR could not be warranted despite non-significant improvements in OS as reported in a systematic review and meta-analysis of 13 studies by Lim et al. (199).

Neoadjuvant chemoradiotherapy and adjuvant therapy regimen

A systematic review and network meta-analysis of 14 RCTs (N = 5599) compared 8 regimens for NACRT: 5-FU alone or with OXA, cisplatin or irinotecan (CPT-11); capecitabine (CAP) alone, or CAP + OXA/CPT-11 and CPT-11 with combined tegafur, 5-chloro-2,4-dihydroxypyridine and potassium oxonate for LARC (200). This meta-analysis indicated that CAP + OXA provided superior clinical results in terms of pCR rate but adding OXA to CAP or 5-FU significantly increased toxicity compared to 5-FU and CAP alone (200). A systematic review and meta-analysis (17 studies) showed that adding OXA to flouropyrimidine-based CRT significantly improved pCR compared to when OXA is not added; however it increased grade 3 toxicities (201). Other treatment strategies that were analyzed included consolidation or induction CT and SCRT that did not show improvement in pCR (201). This further reported that 5-year DFS significantly worsened after SCRT-delay compared to CRT (59% vs. 75.1%, HR 1.93)(201). Another systematic review and meta-analysis (10 RCTs, N = 5599) by Huttner et al. showed NACT intensification with platinum derivatives significantly increased pCR (OR 1.31, 95% CI: 1.10-1.55, P = 0.002) and reduced the distant recurrence (OR 0.78, 95% CI: 0.66-0.92, P = 0.004), however, could not improve OS (HR 0.93, 95% CI: 0.82-1.05, P = 0.23), DFS (HR 0.91, 95% CI: 0.83-1.01, P = 0.07) or local recurrence (OR 0.83, 95% CI: 0.66-1.05, P = 0.12), and was accompanied by grade3/4 toxicities (202). Thus, intensified NACT with the addition of platinum derivatives cannot be recommended routinely as it showed no improvement in OS and DFS, and was associated with increased toxicity; thus, benefits of distant recurrence needed to be elucidated and pCR may be advantageous for high-risk patients (202).

Addition of oxaliplatin

A meta-analysis of 4 RCTs found that adding OXA to neoadjuvant 5-FU-based CRT in patients with LARC showed significantly decreased distant failure (OR 0.76; 95% CI: 0.60-0.97, P = 0.03) with no significant

improvement in OS, DFS or local failure compared to 5-FU CRT (203). Another meta-analysis of 8 RCTs compared OXP-based 5-FU regimen (n = 2887) with 5-FU alone regimen (n = 3216) of NACT and AT in patients (N = 6103) with stage 2/3 rectal cancer. It showed controversial benefits and suggested that it cannot be considered as a standard treatment approach (204). A systematic review and meta-analysis of 10 RCTs (N = 5597) also showed that adding OXA can prolong DFS (HR 0.867, 95% CI: 0.741-0.992, P = 0.000), improve ypCR (RR 1.208, 95% CI: 1.070-1.364, P = 0.002), decrease preoperative metastasis (RR 0.494, 95% CI: 0.256-0.954, P = 0.036) and local recurrence (RR 0.761, 95% CI: 0.616-0.941, P = 0.012). However, no significant difference between the groups with and without OXA was seen in operation rates, R0 resection rates, sphincter-preservation rates, permanent stoma rates, postoperative complications, mortality, OS and improved chemotherapy-related toxicities (205). Thus, NACT with OXP could be both advantageous and disadvantageous to LARC, and its usage should be based on the patient's condition and their tolerance (205).

Addition of capecitabine

A meta-analysis analyzed the effect of CAP and 5-FU on NACT in patients (n = 2916) with LARC from 10 studies and showed that CAP improved pCR (OR 1.34, 95% CI: 1.10-1.63), R0 resection rate (OR 1.92, 95% CI: 1.10-3.36) and nodal downstaging (OR 1.68, 95% CI: 1.11-2.54) whereas, no significant differences were observed overall or in tumor downstaging, 3-year DFS, toxicities during CRT or in sphincter-preservation rates (206). Thus, CAP-based NACT can be safely used for improving pCR, R0 resection and nodal downstaging compared to 5-FU in patients with LARC (206). A prospective study in Indian patients with LARC showed similar response rates and toxicity profiles of CAP-based and 5-FU-based NACT; and suggested to using CAP as an alternative in patients unable to tolerate 5-FU (207).

Addition of capecitabine and oxaliplatin

A RCT including patients (N = 63) with MRI-defined, T3, T4 or N+ histologically proven adenocarcinoma of the rectum within 15 cm from the anal verge, were randomly assigned to receive 50-50.4Gy external beam radiation in 25-28 fractions, and the concurrent CAP 825 mg/m2 twice daily for 5 days a week with/without OXA (60 mg/m2) weekly as the NACRT (CAPOX and CAP group, respectively). The results showed that adding OXA to NACT in LARC led to higher rates of tumor downstaging (59% vs. 42%; P = 0.037) and non-significant improvement in pCR (34% vs.13%, P = 0.072)(208). Long-term results of multicenter JACCRO CC-04: SHOGUN trial that enrolled 45 patients with histopathologically-confirmed LARC (cT3-T4, any N) in Japan showed higher pCR rates (27.3%) with no severe toxicity, good follow-up results, (3-year DFS, 67.5%; 3-year OS, 93% and 3-year local recurrence, 0%) and good loco-regional control (R0 resection rate, 95.5%; T-downstaging, 59.1%; N-down staging, 65.9%; and combined pathological downstaging, 79.5%)(209). Thus, adding OXA to NACT with S-1 in patients with LARC might be feasible and lead to better local control than standard treatment (209). Another multicenter study prospectively assessed long-term outcomes of combined modality in patients with LARC and showed that combined-modality of CAP and OXA prior and concurrent to preoperative pelvic RT followed by TME resulted in high and durable local disease control rate (5-year progress-free survival, 61% [95% CI: 46-73%]; and 5-year OS, 78% [63-87%]) especially, in patients with tumor downstaging (HR 0.16, 95% CI: 0.05-0.56, P = 0.0011) and/or nodal downstaging (HR 0.17, 95% CI: 0.06-0.52, P = 0.0005) however, it was at the cost of relevant long-term toxicity. Although long-term care is required for a proportion of patients with poor gastrointestinal and/or urinary function after multimodality therapy (210).Contrastingly, the 5-year outcomes of the ACCORD 12/0405-PRODIGE 02 trial that compared two NACT regimens (CAP45 [RT 45Gy + CAP] and CAPOX50 [RT 50Gy + CAP and OXA]) for intermediate-risk rectal cancer and showed similar DFS (HR 1.02, 95% CI: 0.76-1.36, P = 0.9), OS (HR 0.87, 95% CI: 0.66-1.15, P = 0.3), local control (HR 0.92, 95% CI: 0.51-1.66, P = 0.7), and reported acceptable levels of late toxicities with both regimens (211).

Short-course and long-course Neoadjuvant chemoradiotherapy

Several systematic review and meta-analyses, and studies compared the effects of long-course and short-course NACRT. One such study compared preoperative short-course RT to long-course CRT and reported better pCR rate (OR 0.05, 95% CI: 0.02-0.18, P < 0.01) with the latter however, this benefit did not translate into higher sphincter-preservation rates (OR 1.62, 95% CI: 0.72-3.67, P = 0.25). Considering similar OS, long-term outcomes and local controls short-course RT could be the treatment-of-choice when pCR is not the aim (212). A systematic review and meta-analysis (4 RCTs) of low-lying rectal cancer compared to short-course versus long-course therapy showed that the latter was similar in reducing risk for local failure compared to short-course therapy (213). A meta-analysis of 8 studies (N = 1475; short course n = 665; long-course n = 810) that compared short-course and long-course neoadjuvant therapy for rectal cancer showed that both treatments were comparable in terms of survival, recurrence and complications. However, the risk for distant metastasis could increase with long-course therapy (OR 2.65, 95% CI: 1.05-6.68)(214). Another meta-analysis of 7 studies (N = 4973) compared preoperative SCRT (5 x 5Gy) with delayed surgery vs. long course therapy for locally resectable rectal cancer, and reported similar treatment benefits in terms of OS (HR 1.30, 95% CI: 0.58-2.89, P = 0.52) or DFS (HR 1.10, 95% CI: 0.73-1.66, P = 0.64)(215). Additionally, the rates for pCR, postoperative complications, grade 3/4 toxicities, local recurrence or distant metastasis were similar between treatments. Sub-group analysis for short-course therapy without adjuvant CT showed that it not only reduced grade 3/4 toxicities but it also significantly decreased OS (P = 0.02) and pCR (P < 0.01)

rates (215). Therefore, preoperative SCRT with delayed surgery was equally effective to preoperative long-course therapy in managing locally resectable rectal cancers (215).

A phase II multicenter RCT FDRT-002 compared long-course NACRT with/without concomitant boost in LARC (stage 2/3)(216). Patients received either pelvic intensity modulated radiation therapy (IMRT) of 50Gy/25Fx concurrently with CAP + OXA or pelvic radiation of 50Gy/25Fx with a concomitant boost of 5Gy to the primary lesion followed by a cycle of XELOX for 2 weeks post completion of CRT followed by definite operation 8 weeks post CRT, and 6 weeks of perioperative CRT cycle of CAP + OXP. Results showed that concomitant boost to OXA-combined NACRT demonstrated slightly higher pCR rates (13.3% vs. 23.3%, P = 0.157), similar local-regional control (P = 0.856), DFS (P = 0.349) and OS (P = 0.553) but led to delayed incision healing (3 vs. 13, P = 0.011) after surgery (216). The post-hoc analysis of FOWARC RCT in patients (N = 220) with LARC showed that long-course neoadjuvant RT (OR 2.20, 95% CI: 1.24-3.91, P = 0.007), height of anastomosis (OR 0.74, 95% CI: 0.63-0.88, P < 0.001) and diverting ileostomy (OR 2.59, 95% CI: 1.27-5.30, P = 0.009) were independent risk factors for postoperative bowel function and quality of life (217). Long-term results of Polish II study that assessed long-course NACRT versus 5x5Gy and consolidation CT (short course) for T3T4 rectal cancer, showed no superiority of long-course NACRT over short-course therapy (218). The 8-year OS (49% vs. 49%, HR 0.90, 95% CI: 0.70-1.15, P = 0.38), 8-year DFS (43% vs. 41%, HR 0.95; 95% CI: 0.75-1.19, P = 0.65), incidence of local failure (35% vs. 32%, HR 1.08, 95% CI: 0.70-1.23, P = 0.60), distance metastasis (36% vs. 34%, HR 1.10, 95% CI: 0.68-1.23, P = 0.54) and late complication rates (grade 3+ 11% vs. 9%, P = 0.66) were similar between short-course/consolidation CT and long-course NACRT patients (218). However, surgery after short-course RT delayed for 4-12 weeks (overall treatment time: 5 -13 weeks) could reduce complications (219). Long-term results of Dutch phase II study evaluated short-course RT followed by NACT of bev, OXA and CAP; and subsequent radical treatment for stage 4 rectal cancer showed that at median 8.1 years of follow-up, OS was 32%; DFS, 28% with median OS of 3.8 (0.5-9.4) years although 5.6%, local recurrence and 80.6%, distant recurrence were seen amongst patients receiving radical treatment(220). This suggested that despite high rates of recurrence, long-term survival could be achieved after NACRT in patients with primary metastatic rectal cancer(220). A single retrospective study assessed the effects of short-course (5 × 5Gy) RT on the local recurrence risk in patients with pT3N1-2 rectal cancer (+ve nodal involvement), and showed that short-course NRT was not associated with local recurrence. However, tumor location under 6 cm from the anal verge (P = 0.03) and the involved lateral margin (P = 0.002) could be contributors towards local recurrence of pT3N1-2M0 rectal cancer (221). A phase II study of near total neoadjuvant therapy (nTNT) of short-course radiation and FOLFOX CT versus conventional NACRT in patients with cT3-4N0-2M0 rectal adenocarcinoma after matched paired analysis showed that patients treated with nTNT had higher tumor downstaging (75% vs. 41%, P < 0.001) and superior distant metastasis-free survival and DFS (85% vs. 68%, P = 0.032) compared to conventional NACRT when matched for tumor location and exact cTNM stage. It also demonstrated a lower risk of recurrence (P = 0.006) with baseline adjustment (222). Moreover, Trans-Tasman Radiation Oncology Group Trial (TROG 01.04) compared adverse events and postoperative complications with preoperative short-course RT versus long-course CRT for T3 rectal adenocarcinoma and showed that the latter reported significantly higher adverse events (all P < 0.05) compared to short-course RT with differences in postoperative complications (50.4% vs. 53.2%, P = 0.68). However, permanent stoma rates (29.8% vs. 38.0%, P = 0.13) and anastomotic leaks (3.5% vs. 7.1%, P = 0.26) were non-significantly lower with long-course therapy with increased perineal wound breakdown rate (50% vs. 38.3%, P = 0.26)(223).

ACRSI recommendations for neoadjuvant chemoradiotherapy and adjuvant therapy

- Neoadjuvant chemoradiotherapy should be used for locally advanced cancers of the mid or distal rectum (strong recommendation based on high quality evidence, 1A)
- Adjuvant chemoradiotherapy should be recommended for selected patients with stage 3 or high-risk stage 2 rectal cancer who are yet to receive neoadjuvant therapy (strong recommendation based on high quality evidence, 1A)
- For patients with stage 3 rectal cancer treated with short-course radiotherapy or no preoperative treatment, CAPOX or FOLFOX is recommended based on patient histopathology (strong recommendation based on moderate quality evidence, 1B)
- Neoadjuvant short-course radiation therapy and long-course chemo radiotherapy are similar in terms of treatment outcomes therefore the choice should be made based on patient conditions (strong recommendation based on high quality evidence, 1A)

Metastatic rectal cancer

About 20%-25% of patients with rectal carcinoma present with synchronous metastatic disease, and 30%-50 % develop metastasis after surgical treatment (224). Diagnosis of metastatic disease is suspected in a patient with rectal carcinoma presenting with systemic symptoms and signs such as sickness and weight loss,

and anorexia in addition to clinical features related to the organ affected by the metastatic disease, and is supplemented by elevated CEA levels. Chest X-ray is routinely done for detecting lesions of more >1 cm or any associated pathology. Ultrasonography (USG) can diagnose most liver metastasis that are >1 cm in size but its sensitivity rate is only 20% for metastasis that are <1 cm in size. CT with intravenous contrast and three-phase examination (non-contrast late arterial and portal veins) is mandatory, and a method of choice for preoperative staging in all patients except in patients with absolute contraindication to the contrast material. CT scan can detect liver metastasis in about 85% of patients. It is useful for assessing respectability, liver volume and treatment response (225). MRI is the chosen method for brain metastasis but owing to high cost, length of the examination and long period of immobility, it is not the first choice for detecting metastatic deposits in other organs. However, it can be useful in picking up small lesions and can precisely identifying pure liquid lesions in the liver. PET scans with/without CT scans can give the anatomical location of metastatic lesions in all parts of the body. It should be advised in patients with suspected metastatic disease where other investigational tools fail or are contraindicated, and in patients who are planned for resection of metastatic disease, to rule out metastasis elsewhere (225,226). Gene testing: RAS status and BRAF V600E mutations is recommended before chemotherapy. However, testing microsatellite instability (MSI) is advised in patients with metastatic disease (227).

Treatment of resectable synchronous metastases

If a patient is fit for surgery, resection (synchronous/staged, depending on feasibility and patient performance) is done that is followed by adjuvant therapy. NACT with/without targeted therapy is advised in some patients to downstage large tumors present at difficult locations and for multiple lesions (228). Multiple resections like that of liver and lung metastasis can be contemplated in fit patients. Choosing the approach (bowel first, liver first or simultaneous) should therefore be based on the patient's condition, the expertise available and facilities available in the given setup. A systematic review and network meta-analysis (1 prospective and 43 retrospective studies, N = 10 848) compared bowel-first approach, simultaneous resection and liver-first approach. The analysis showed that simultaneous approach resulted in higher risk of major morbidity and 30-day mortality. Compared to the bowel-first approach, liver-first approach more frequently failed to complete treatment as planned (34% vs. 6%, respectively) (229). Pairwise and network meta-analysis showed similar 5-year OS between liver-first and bowel-first approaches, and a more favorable 5-year OS after simultaneous resection compared to liver-first approach (OR 0.25-0.90, P = 0.02), and not for the bowel-first approach (229). A meta-analysis of 14 studies that compared simultaneous and staged resection in patients with synchronous colorectal liver metastases reported simultaneous resection to be safe and efficient in treating and avoiding second major operation (lower morbidity rate: OR 0.71, 95% CI: 0.57-0.88, P = 0.002). However, similar post-resection survival rates for simultaneous and staged resections was observed at 1-,3- and 5 years (OR 0.77, 95% CI: 0.52-1.16, P = 0.21; OR 1.12, 95% CI: 0.85-1.47, P = 0.43; OR 1.14, 95% CI: 0.86-1.50, P = 0.37, respectively)(230). Moreover, a meta-analysis comparing simultaneous and delayed resections in patients with synchronous colorectal liver metastases found that the selection criteria for patients undergoing simultaneous or delayed resections differed, that resulted in a discrepancy of the metastatic disease severity being compared between the two (231). Comparable intra-operative parameters, post-operative complications and survival were better with delayed resection; however, reduced length of hospital stay as seen in simultaneous resections could be due to reduced disease severity in these patients (231). Therefore, simultaneous resections can only be considered in patients with limited hepatic disease until evidence comparing these approaches in patients with similar disease severity is available (231).

Evidence also suggested that chemotherapy followed by resection of liver metastases before primary tumor resection may be an effective approach in some patients (227,232). Moreover, neoadjuvant SCRT of T1-T3 primary rectal tumor could be used in selected patients in this setting (227,232). For patients receiving neoadjuvant therapy, surgery/local therapy should be performed 5-12 weeks following the treatment (233,234).

Treatment of unresectable synchronous metastases

Patients with unresectable metastases or with medically inoperable conditions should be treated based on their symptomatic or asymptomatic statuses.

Symptomatic patients are treated with chemotherapy alone or with combined modality of 5-FU/RT, CAP/RT, short-course radiation and resection of the involved rectal segments, diverting colostomy or stenting (235). Primary treatment should be followed by active systemic therapy regimens for advanced metastatic cancer (227). For asymptomatic lung or liver disease deemed unresectable, systemic therapy for advanced/metastatic diseases should be practiced to render the number of patient for resection. Chemotherapy with high response rates should be considered for potentially convertible diseases, and these patients should be reevaluated for resection after 2 months of chemotherapy, and every 2 months thereafter while undergoing their therapy. A prospective database study showed that most patients with synchronous stage IV CRC who have received upfront modern combination of CT, never require palliative surgery (89%) for intact primary tumor thus, supporting the use of CT without prophylactic resection as a standard practice for patients with neither obstructed nor hemorrhaging primary tumor in a setting of metastases (236). A meta-analysis of 21 studies (N = 44226) by Clancy et al. compared the effects of primary

tumor resection with CT alone in CRC with unresectable metastases. The results showed that resection of the primary tumor might confer survival advantage (OR 0.28, 95 % CI 0.165-0.474, P < 0.001) with a mean survival of 6.4 (95% CI: 5.025-7.858, P < 0.001) months in favor of resection of stage IV CRC with unresectable metastases (237). A prospective multicenter phase II NSABP C-10 trial showed that patients with asymptomatic primary tumor and unresectable metastatic disease receiving mFOLFOX6 + bev experienced acceptable morbidity (24-month cumulative morbidity: 16.3%, 95% CI: 7.6-25.1) and a median OS of 19.9 months without upfront primary tumor resection (238). Symptomatic improvements in the primary tumor were observed within 1-2 weeks of first-line systemic CT. Cochrane review of 798 studies showed that primary tumor resection in asymptomatic patients with unresectable stage IV CRC that was managed with CRT was not associated with consistent improvement in OS and resection did not reduce the risk of complications from the primary tumor (239). A systematic review (21 studies) reported that resection of primary tumor might provide survival benefits in stage IV CRC, and suggested that it should be performed based on the tumor burden and performance status rather than on the basis of symptoms (240).

Treatment of metachronous metastases

For documented metachronous metastases that are resectable, metastatic disease on contrast-enhanced CT or MRI, PET/CT scan should be considered for assessing the extent of disease in selected cases of M1 disease for feasibility of surgical cure. In addition, to assess the extent of the condition, PET/CT scan at the juncture is also used to identify sites of extra hepatic diseases that could help preclude surgery (241).

For managing patients with metachronous metastases, their chemotherapy history should be assessed and distinguished from synchronous disease. For patients with resectable metastatic disease, the approach of resection with a 6-month perioperative CT should be chosen based on patient's previous CT regimen. Local ablation procedures can be considered instead of resection, or in addition to resection for liver oligometastases; however, resection is the preferred choice (242). For patients without a history of chemotherapy, FOLFOX or CAPOX is preferred with FLOX, CAP and 5-FU/LV as additional options (243,244). The GONO study, a phase II trial compared FOLFOXIRI with 5-FU/LV and FOLFIRI. The results showed that FOLFOXIRI improved response rates, progression-free survival and OS but with increased yet manageable toxicity in patients with cancer metastases (243). A multicenter randomized phase III trial from the Hellenic Oncology Research Group (HORG) compared FOLFOXIRI with FORFIRI as first-line treatment in metastatic CRC. It showed non-significant improvement in OS (19.5 vs. 21.5 months, P = 0.337) (244). Overall, for patients with unresectable metachronous disease through cross-sectional imaging scan, systemic therapy should be considered based on the previous history of chemotherapy.

Peritoneal carcinomatosis

Colorectal cancer metastasis with peritoneal carcinomatosis is the most important cause for cancer-related death in the world (245). The treatment goal for peritoneal metastases is palliative and primarily, systemic therapy should be considered with palliation or stenting (if needed) for any obstruction (246-248). Several surgical series and retrospective studies showed the role of cytoreductive surgery/peritoneal stripping surgery and peritoneal hyperthermic intraperitoneal chemotherapy (HIPEC) for treating peritoneal carcinomatosis without abdominal metastases (249-253). A systematic review of 19 cohort studies and 13 comparative studies with cytoreduction surgery and HIPEC suggested that this combination treatment has gained acceptance as a standard of care for selected patients with peritoneal metastases from CRC (254). A systematic review (14 studies) showed that cytoreductive surgery combined with perioperative intraperitoneal CT is associated with improved survival (complete cytoreduction: 22%-49%) compared to systemic CT for peritoneal carcinomatosis from colorectal carcinoma (255). A recent systematic review of 20 studies showed that cytoreduction surgery and HIPEC for treating isolated colorectal peritoneal metastases is safe with improved medical survival and DFS (256). Fewer controlled studies associate risks and benefits with the modalities for peritoneal carcinomatosis (256,257). Thus, with limited evidence, complete cytoreduction surgery and/or intraperitoneal chemotherapy can be considered in selected patients for whom R0 resection can be achieved.

ACRSI recommendations for metastatic rectal cancer

- Based on the patient profile, simultaneous or stage-based approach or a liver-first approach should be carried out after neoadjuvant therapy followed by the waiting interval in locally advanced rectal cancer patients with synchronous liver metastases (strong recommendation based on high quality evidence, 1A)
- In patients with metachronous metastases, based on chemotherapy history and resectability, local ablation or systemic therapy should be considered (strong recommendation based on moderate quality evidence, 1B)
- Cytoreductive surgery and/or intraperitoneal chemotherapy should be considered in selected patients with peritoneal carcinomatosis in whom R0

resection can be achieved at experienced centers (weak recommendation based on moderate quality evidence, 2B)

Palliation in rectal cancer

Patients with un-resectable metastasis or those who are medically inoperable, are treated depending on whether they are symptomatic or asymptomatic (76). Symptomatic patients are treated via CT alone, combined modality with CT /RT, short-course radiation, resection of involved rectal segment, diverting colostomy or stenting. Primary treatment should be followed by active systemic therapy regimen for advanced or metastatic disease (258). Advanced colorectal cancer can cause acute colonic obstruction, which is a life-threatening condition that requires emergency bowel decompression. Malignant colonic obstruction is treated using emergency surgery or stoma formation although anastomosis leakage is a major concern for emergency surgery (258). Moreover, despite widespread use of screening programs, colorectal cancer occurs in 7%-29% of cases with bowel obstruction that needs immediate decompression treatment by emergency surgery and is a challenge with a risk for operative mortality (3,259). A systematic review and meta-analysis also showed that local recurrence rates of sigmoid colon cancer is higher than that for rectal cancer, and there is a lack of evidence that describing the palliative resection in sigmoid colon cancer (260). The main priority of intervention in palliative settings is to provide an effective relief without morbidity and to allow rapid return to either palliative chemotherapy or the baseline quality of life (261).

In a study including patients with symptomatic rectal cancer who are not amenable to curative treatment, showed that short-course RT could be an alternative treatment option with 1-, 2- and 3-year colostomy-free survival rates of 100%, 71.4% and 47.6%, respectively; and with cumulative OS rates of 85.2%, 53% and 39.8%, respectively (262). Another study also showed that short-course CRT in malignant rectal cancer could be used as an alternative to palliative surgery as it had an OS of 11.5 months, and required palliative surgery at 2-years (17.5%) and had sustained good palliative effects (67%)(263). However, the regimen of palliative RT in symptomatic rectal cancer, and onset, duration and degree of symptom palliation, quality of life and associated toxicity are concerning (264).

In patients with a limited expected survival in whom targeted anti-angiogenesis agents for systemic therapy can be held after stent placement, endoscopic stents would be preferred with close follow-ups for short-term stent-related perforations and for the likelihood of needing long-term additional endoscopic procedures (261). A systematic review and meta-analysis of 12 studies reported that self-expanding stents are shown to be effective in reducing morbidity and improved palliation in colorectal cancer obstructions although complication rates were higher in stenting for benign obstructions compared to malignant obstructions (265).

Diverting ostomy should also be preferred for obstructing rectal cancer as low-lying stent placements might cause pelvic pain, tenesmus and incontinence. Another systematic review and meta-analysis that examined efficacy of interventions to palliate rectal tenesmus caused by advanced cancer when surgery, RT or CT are no longer treatment options, showed a significant gap in research for palliation of rectal tenesmus and reported that considering its complex pathology, a multimodal approach may be considered (266). Another systematic review of 20 studies also showed a gap in the evidence regarding management of malignant rectal pain and tenesmus (267).

ACRSI recommendation for palliation in rectal cancer

- In patients with malignant obstruction, an expanding stent as a bridge-to-surgery can be preferred in a palliative setting (weak recommendation based on low quality evidence, 2C)
- Diverting ostomy should be preferred for obstructing rectal cancer in selective patients in whom low-lying stent placement causes pain and tenesmus (weak recommendation based on low quality evidence, 2C)

Follow-up protocol

To improve the prognosis by early detection and retrieval of local recurrence and metastases, and to prevent/identify a second rectal cancer, a follow-up and surveillance with clinical examination, imaging and colonoscopy should be performed (13). Colonoscopy is the standard method for diagnosing all types of neoplastic lesions in the rectum irrespective of the indicative clinical situation or tumor size and stage; and it can be used often in early diagnosis of rectal cancer and in follow-ups after detection and treatment of the discovered lesions (20). Intensity of the follow-up will depend on the patient's risk profile, which is defined in follow-up cases for patients diagnosed with stage I or II/III rectal cancer and by those who are disease-free after receiving radical treatment. Clinical examination and pelvic imaging using MRI and/or CT and distant metastases CT of the chest, abdomen and pelvis are recommended (13,20). Data from FACS RCT showed that patients with rectal tumors (particularly, more advanced stages) have a higher risk of recurrence and can benefit more from follow-ups; although <10% may have treatable recurrence (268). Routine use of PET-CT scans as a surveillance is not recommended however, when the recurrence is diagnosed, it may be helpful in defining

other unrecognized disease sites. Systematic reviews and the FACS RCTs showed that surveillance follow-up and 3-5 years of scheduled CEA screening and CT-monitoring increased the rate of surgical resection of recurrence with curative intent although, the optimum modality, intensity and frequency remains undefined (269-271). Moreover, a Cochrane review showed that isolated CEA monitoring is insufficiently sensitive. Routine monitoring of CEA and CT-imaging should be performed up to 5 years following surgery (13,20). The 2018 ASCO resource that stratified the guidelines for treating patients with early-stage colorectal cancer also described that medical history, physical examination, CEA testing, imaging and endoscopy should be performed, with frequency based on settings for post-treatment surveillance (272).

Both rectal cancer surgery and additional pre- or postoperative CRT may result in late sequelae that affects daily function. Long-term treatment side-effects should be monitored including, lower genitourinary toxicities like erectile dysfunction, dyspareunia and urinary incontinence (13,20). Pelvic RT can predispose the patient to bone loss and to an increased risk for bone fracture (273). Although there is only sparse data on patients treated for rectal cancer receiving RT appears to be linked to a greater probability of having a pelvic fracture in this population (273,274). For this reason, CRC survivors who have received pelvic RT should undergo long-term bone density monitoring, appropriate medical treatment for osteopenia and osteoporosis, and careful evaluation following the development of any symptoms that are suggestive of fractures (20). Secondary neoplasms induced by pelvic irradiation are a known but less common complication. A population-based study evaluated risks for cancer prolapse in patients with rectal cancer treated with RT before or after surgery, and reported variable and controversial results (275). A systematic review and meta-analysis of 23 studies also showed an increased risk (RR 1.43, 95% CI: 1.18-1.72) of relapsed rectal cancer following RT to the pelvic region for primary cancer although it was reported that the risk was modest and could not be confirmed for all primary pelvic cancer sites (276). Surveillance should also address social, financial, emotional aspects, practical and functional consequences to maximize the survivors' long-term well-being (20,271,277). Important components include guidelines for proactive detection of likely future effects and an educational program (before and after treatment) to promote engagement with the healthcare system and an appropriate and healthy lifestyle (20). Minimum provisional recommendations for average-risk patients by the 2017 ESMO rectal cancer guidelines suggested clinical assessment- every 6 months for 2 years, completion of colonoscopy- within first year if not done at the time of diagnostic work-up (e.g. if obstruction was present), history and colonoscopy with resection of colonic polyps- every 5 years up to the age of 75 years, minimum two CTs of chest, abdomen and pelvis- for the first 3 years and regular serum CEA tests (at least every 6 months for the first 3 years). High-risk metastases in patients may merit more proactive surveillance for local recurrence (13). Overall, with an ever-increasing number of long-term survivors, monitoring and controlling the sequelae requires involvement and implementation of relationship systems between different levels of care.

ACRSI recommendations for follow-up protocol in rectal cancer

- Clinical assessments including physical examinations and CEA levels should be performed every 3-6 months for 2 years (strong recommendation based on high quality evidence, 1A)
- CT of chest, abdomen and the pelvis should be performed every 6 months in the first 3 years (strong recommendation based on high quality evidence, 1A)
- Complete colonoscopy should be done within the first year, if not performed at time of diagnostic work-up, and it should be followed-up every 3 years (strong recommendation based on high quality evidence, 1A)
- For polyps identified in any colonoscopy, the examination should be repeated every 6-12 months (strong recommendation based on low quality evidence, 1C)

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