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Evidence Based Clinical Practice Guideline on Curable Rectal Cancer - An Update

A Joint Project of the Philippine College of Surgeons and the Philippine Society of Colon and Rectal Surgeons

Catherine S. Co, M.D., F.P.C.S.; Manuel Francisco T. Roxas, M.D., F.P.C.S.; Robert L. Chang, M.D., F.P.C.S.; Marie Dione A. Parreno-Sacdalan, M.D., F.P.C.S.; Armando C. Crisostomo, M.D., F.P.C.S., Carlo C. Cajucom, M.D., F.P.C.S.; Marc Paul J. Lopez, M.D., F.P.C.S.; Hermogenes J. Monroy III, M.D., F.P.C.S. and Maria Lourdes O. Daez, M.D.

Cancers of the colon and rectum are the third most commonly diagnosed cancer in the world.[1] In the Philippines, it is the fourth leading cause of death and new cancer cases in both sexes.[2]

The Philippine College of Surgeons (PCS) and the Philippine Society of Colon and Rectal Surgeons (PSCRS) recognized that the management of rectal cancer is vastly distinct from the management of colon cancer. The management varies from the diagnostic examinations requested, to the use of neoadjuvant therapy and to the type of surgery - total mesorectal excision (TME), with or without sphincter preservation. As early as 2005, an evidence-based clinical practice guideline (EBCPG) was formulated and published in the Philippine Journal of Surgical Specialties (PJSS).[3] Majority of the recommendations in the guideline are still relevant up to the present. However, there are a number of developments and advances in the management of rectal cancer since the literature was last reviewed in 2004.

The objective of this paper was to update the previous guideline with regards the current management of curable rectal cancer.

Specific objectives were: For patients with curable rectal cancer, 1) to determine the diagnostic examinations for pre-operative staging; 2) to define and determine the role of the multidisciplinary team approach; 3) to determine the role of neoadjuvant treatment; 4) to determine the recommended management; 5) to determine the recommended adjuvant treatment and 6) to determine the surveillance regimen to detect recurrence after surgical resection.

It was intended to guide practitioners in General Surgery and Colon and Rectal Surgery working in the Philippines regarding decisions on the management of curable rectal cancer. It was not intended to substitute for individualized and tailored decision-making with regards patient care.

Methodology

The PCS initiated the undertaking by communicating with the PSCRS initially, with the intent to formulate a clinical practice guideline (CPG) on adjuvant therapy for colon and rectal cancer.

In May 4, 2012, the Chair of the PCS Cancer Committee met with the representatives from the PSCRS, Philippine Association of Head and Neck Surgeons Incorporated (PAHNSI) and the Philippine Breast Collaborative group. The delegate from the PSCRS was instructed to relay to the Society, to formulate a national guideline on curable rectal cancer based on the critical appraisal of existing guidelines.

The Technical Working Group (TWG) was formulated and was asked to appraise the guidelines.

The TWG is composed of the following members from the Philippine Society of Colon and Rectal Surgeons:

- Armand C. Crisostomo, MD
- Manuel Francisco T. Roxas, MD

- Robert L. Chang, MD
- Hermogenes J. Monroy, MD
- Carlo C. Cajucom, MD
- Dione A. Parreno-Sacdalan, MD
- Marc Paul J. Lopez, MD
- Catherine S. Co, MD

The following guidelines were appraised: National Comprehensive Cancer Network (NCCN) - Clinical Practice Guidelines in Colon and Rectal Cancer[4], American Society of Colon and Rectal Surgeons - Practice Parameters for Colon Cancer[5], The Association of Coloproctology of Great Britain and Ireland - Guidelines for the Management of Colorectal Cancer[6], National Health and Research Council Australia - Clinical Practice Guideline for the Prevention, Early Detection and Management of Colorectal Cancer[7], Manual Update National Health Services (NHS) - Guidance on Cancer Services Improving Outcomes in Colorectal Cancers[8]. Each of the guidelines were appraised by three evaluators using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) tool. The results of the appraisal were scheduled for presentation to the PCS Cancer and Research Committees.

However, after deliberation, the PCS Cancer and Research Committees decided to update the EBCPG on Curable Rectal Cancer published in 2005.

The TWG is composed of the original members with the addition of Dr. Maria Lourdes O. Daez from the Philippine Society of Gastroenterology.

The EBCPG published in 2005 was reviewed and has the following clinical questions:

- Among patients with rectal cancer, which of the following diagnostic procedures improve pre-operative staging, treatment and outcomes?

Digital rectal exam	CT scan of the abdomen and pelvis
Endoscopy	MRI of the abdomen
Carcinoembryonic antigen	PET scan of abdomen
Chest radiography	Endorectal ultrasound
Liver ultrasound	

- Among patients with rectal cancer, does TME improve survival and decrease local recurrence?
- Among patients undergoing TME, do patients with protecting stomas have better post-operative morbidity/mortality rates compared to those without stomas?
- Among patients with rectal cancer requiring protective stomas after TME, do ileostomies have less stoma related complications compared to transverse loop colostomies?
- Among patients undergoing surgery for rectal cancer, does high ligation of the Inferior Mesenteric Artery (IMA) result in better survival and recurrence rates than those with low ligation?
- Among patients undergoing TME for rectal cancer without pelvic nerve involvement, does autonomic nerve preservation result in better maintenance of sexual and urinary function compared to those without autonomic nerve preservation?
- Among women with rectal cancer undergoing curative surgery, does prophylactic oophorectomy result in better survival and recurrence rates compared to those without prophylactic oophorectomy?
- Among women with rectal cancer undergoing curative surgery, in what clinical situation does en bloc partial posterior vaginectomy result in better survival and recurrence rates?
- Among Stage II and III rectal cancer patients, does preoperative radiotherapy alone (short or long course) result in better survival, lower recurrence rate and better sphincter preservation rate as compared to surgery alone?
- Among Stage II and III rectal cancer patients, does preoperative radiotherapy result in better survival, lower recurrence and complication rates compared to postoperative radiotherapy?

- Among rectal cancer patients undergoing preoperative radiotherapy, does short course therapy result in better survival and recurrence rates compared to long course therapy?

- Does preoperative adjuvant chemotherapy-radiotherapy treatment offer additional advantage over surgery alone or radiotherapy alone?

- Does pre-operative chemotherapy improve survival, decrease recurrence and increase sphincter preservation compared to postoperative chemo-radiotherapy?

- Do Stage I rectal tumors benefit from post-operative chemoradiotherapy, especially those with poor differentiation, lymphatic, vascular, perineural invasion or signet ring cell features?

- Among rectal cancer patients who completed curative treatment, does intensive surveillance result in better overall survival than non-intensive or symptom-directed surveillance, in randomized controlled trials?

The TWG after reviewing the EBCPG 2005 decided on the following questions for the update:

1. What are the recommended diagnostic examinations for pre-operative staging?

2. What is the multidisciplinary team approach and its role in the management of rectal cancer?

3. What is the role of neo-adjuvant treatment?

4. What is/are the recommended treatment/s?

5. What is/are the ecommended adjuvant treatment/s?

6. What is/are the recommended surveillance regimen/s to detect recurrence after surgical resection?

The following terms were defined: rectal cancer, neoadjuvant treatment, adjuvant treatment, total mesorectal excision, wide mesorectal excision and extralevator abdominoperineal resection.

A search of literature was made using Pubmed, Cochrane, Embase, Clinical trials. gov, and the PJSS. Research studies and papers from January 2005 up to June 2012, with no language restriction were retrieved. For diagnostic examinations and the multidisciplinary team approach, systematic reviews and randomized controlled trials were preferred but if none were available, observational studies were retrieved. For the clinical questions on neo-adjuvant therapy, treatment, adjuvant therapy and surveillance, meta-analysis and randomized controlled trials were retrieved.

The search and MESH terms included: rectal cancer, diagnostic staging, computerized tomographic scan, magnetic resonance imaging, PET scan, endorectal ultrasound, multidisciplinary team approach, neoadjuvant treatment, neoadjuvant chemoradiotherapy, neoadjuvant radiotherapy, neoadjuvant chemotherapy, total mesorectal excision, wide mesorectal excision, abdominoperineal resection, evaluation of the surgical specimen, lymph node, circumferential resection margin, minimally invasive surgery, surgery, laparoscopic surgery, adjuvant therapy, surveillance and follow-up.

A total of 46,132 articles were retrieved. There were 160 abstracts reviewed and 110 full text articles obtained. The articles were appraised by two independent evaluators using the appraisal guides for articles on diagnosis and treatment.

On November 7, 2012, the TWG evaluated the current evidence using the Oxford Centre for Evidence-Based Medicine 2011 Level of Evidence[9] and the recommendations were made.

The following members of the TWG were present: Dr. Manuel Francisco T. Roxas, Dr Robert L. Chang, Dr. Dione A. Parreno-Sacdalan, Dr. Catherine S. Co and Dr. Maria Lourdes O. Daez. The members revised the previous EBCPG for presentation to the expert panel.

The revised EBCPG 2013 was evaluated and presented to the expert panel during the PCS 68th

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

The Recommendations were as follows[3]:

Category A	Recommendations that were approved by consensus (at least 75% of the multi-sectoral panel)
Category B	Recommendations that were somewhat controversial and did not meet consensus (consensus <75% of the multi-sectoral panel)
Category C	Recommendations that caused real disagreements among members of the panel (consensus <50% of the multi-sectoral panel)

Annual Clinical Congress on December 5, 2012 held at the Palawan III, Edsa Shangri-La Hotel. The expert panel consisted of the following members:

1. Alejandro C. Dizon, MD
2. Jose Macario V. Faylona, MD
3. Ramon S. Inso, MD
4. George G. Lim, MD
5. Maximo B. Nadala, MD
6. Enrico P. Ragaza, MD
7. Mark R. Kho, MD
8. Daniel L. de la Paz, MD
9. Edgardo C. Cortez, MD
10. Armando C. Crisostomo, MD
11. Ida Marie T. Lim, MD
12. Ma. Luisa D. Aquino, MD
13. Alfred Philip O. De Dios, MD
14. Leonardo O. Ona III, MD
15. Maria Cheryl O. Cucuenco, MD
16. Renato R. Montenegro, MD
17. Alfred Allen E. Buenafe, MD
18. Rex A. Madrigal, MD
19. Alex A. Tan, MD
20. Andrea Joanne A. Torre, MD

21. Alberto B. Roxas, MD
22. Jorge Ignacio, MD (Medical Oncology)
23. Edilberto V. Fragante, MD (Radiation Oncology)
24. Elizabeth A. Nuqui, MD (Pathology)
25. Priscilla B. Caguioa, MD (Meical Oncology)
26. Teresa Sy Ortin, MD (Radiation Oncology)
27. Virgilio P. Banez, MD (Gastroenterology)

The newly revised EBCPG was presented in a Public Forum on December 3, 2013 at the Rosal Room of the Edsa Shangri-La Hotel, during the 69th Annual Clinical Congress of the PCS. The guidelines were accepted with the following comments:

- Question on the need to cite for renumeration of the MDT specialists who participates during an MDT meeting

- Question on who will supervise the laparoscopic rectal resection. It was suggested that a faculty/ fellow certified by their respective society (Philippine College of Surgeons [PCS], Philippine Society of General Surgeons [PSGS], Philippine Association of Laparoscopic and Endoscopic Surgeons [PALES], Philippine Society of Colon and Rectal Surgeons [PSCRS]) to have met the criteria for supervision.

- Question on surveillance using CEA, to state "when applicable", as CEA does not elevate in all cases of rectal cancer.

- Comment on proctoscopy and endorectal ultrasound for those patients who received transanal excision surgery

- Comment on proctoscopy every 6 months for 3-5 years for patients who had low anterior resection or transanal excision

The EBCPG on Curable Rectal Cancer 2013 was presented during the Plenary Session on the Presentation of the CPG Updates on Thyroid, Breast and Rectal Cancer at the Isla Ballroom I and II during the PCS 69th Annual Clinical Congress on December 4, 2013, without any comments.

The final EBCPG on Curable Rectal Cancer 2013 is presented below:

The following terms were defined:

Rectal cancer - histologically verified adenocarcinoma of the rectum located at a distance of up to 12 cm from the anal verge by proctoscopy.[10]

Neoadjuvant treatment - any treatment given prior to surgery, including chemotherapy, radiotherapy, or immunotherapy.

Adjuvant treatment - any treatment given after surgery, including chemotherapy, radiotherapy, or immunotherapy.

Total mesorectal excision - surgical resection of the entire mesentery of the rectum which contains lymphatics and blood supply.[10]

Wide mesorectal excision - surgical resection of the rectum including the mesorectum with a 5 cm distal resection margin.[10]

Extralevator (Cylindrical) APR - technique of abdominoperineal resection where the perineal phase is performed in the prone or lateral position and the mesorectum is approached superior to the levator muscle.[10]

Curable Stage IV disease - rectal cancer primary with distant metastasis to the liver, lung or brain which are deemed potentially resectable for cure.

Clinical Questions

What are the recommended pre-operative evaluation for rectal cancer?
Level of Evidence II, Category A

The following examinations are recommended to accurately stage rectal cancer

- Colonoscopy
- Proctoscopy

- Abdomino-pelvic CT scan with oral, intravenous and rectal contrast
- Chest X-ray or Chest CT scan
- Carcinoembryonic antigen
- For a more detailed evaluation of the rectum: Endorectal ultrasound and/or rectal MRI

All rectal cancer patients should be staged prior to treatment.

For potentially curable Stage IV disease.

- For suspicious liver metastasis, triphasic CT scan views of the liver is recommended
- For suspicious lung metastasis on chest X-ray, Chest CT scan is recommended

Patients diagnosed with rectal tumors need to be adequately staged clinically as the subsequent management relies heavily on the stage of the disease.

Colonoscopy is used to visualize the tumor, determine the location and its physical characteristics, secure biopsies and determine the degree of obstruction of the rectal lumen.[4,10] It is also used to detect for the presence of synchronous tumors in the colon which has an incidence of 2%-8%.[10] A substitute for colonoscopy is CT colonography. CT colonography is a "sensitive, acceptable and equally cost-effective alternative to colonoscopy in patients in whom colonoscopy is contraindicated or undesirable".[11] Additionally, CT colonography is of use in obstructing rectal tumors when the video colonoscope is unable to pass through as it virtually skips the area of obstruction and can visualize the rest of the colon.

Rigid proctoscopy is used to determine accurately the distance of the tumor from the anal verge. This distance is essential in determining the type of surgery to be performed. Comparing flexible sigmoidoscopy or colonoscopy with rigid proctoscopy shows that there is a difference of 2-4cm with the use of colonoscopy. Localization using rigid proctosigmoidoscopy changed the overall treatment in 25% of patients: 21% of lower rectal tumors, 14% of middle rectal tumors, 38% of upper rectal tumors, and 29% of rectosigmoid tumors.[12] For tumors located 11cm-15cm FAV, a wide mesorectal excision is required while tumors located less than or equal to 10 cm from the anal verge, a total mesorectal excision is recommended.

Abdominopelvic CT scan with intravenous, oral and rectal contrast is used to assess resectability of the tumor by determining the depth of involvement, degree of obstruction, extent of invasion to adjacent structures in the pelvic cavity, presence of nodes and stranding in the mesorectum, and document the presence or absence of liver metastasis.[4] It is most useful in locally advanced tumors but has limitations in early rectal tumors, as oftentimes, small tumors are not visualized on CT scan. Triphasic CT scan of the liver is requested to document liver metastasis. Spiral CT scan of the liver with contrast in the portal venous phase (PVP) is adequate for the detection of liver metastasis.[13] For tumors with hypervascular metastases, hepatic-arterial phase contrast should be added in addition to PVP.[13]

Chest X-ray or chest CT scan is used to determine for the presence of lung metastasis. Chest CT scan has the ability to detect pulmonary metastasis with lesions smaller than 10 mm in diameter. A high resolution chest CT scan is preferred for demonstrating the presence and extent of lymphangitis carcinomatosis.[14-15]

Carcinoembryonic antigen (CEA) is a tumor marker which is used to monitor for recurrence. Its use in the preoperative phase is for prognostication. Elevated preoperative CEA levels >/= 5 ng/mL is an independent predictor of overall survival.[16]

Endorectal ultrasound (ERUS) has the following uses: determines the depth of the tumor and presence of nodes. It is highly operator-dependent. A meta-analysis revealed that the accuracy of ERUS for T-staging is 80% to 95% and for N-staging is 70% to 75%. The sensitivity of ERUS in identifying T1, T2, T3 and T4 tumors are 76%-84%, 75%-76%, 88%-96%, and 76%-87%, respectively.[17-19]

A 1.5 Tesla Magnetic Resonance Imaging (MRI) of the pelvis with gadolinium and body coil is recommended to image rectal tumors. MRI demonstrates tumor penetration through the mesorectal fascia with an accuracy of 95%. It is also able to identify the anatomical relationship of the tumor to the circumferential resection margin and shows features such as venous invasion, size of extramural invasion of the primary tumor and

mesorectal or even extramesorectal lymph node involvement. It is also able to confirm the distance of the lower border of the tumor to the anal verge and it is useful to verify whether the puborectalis muscle is or is not involved with tumor. Another potential benefit of MRI staging is the avoidance of unnecessary preoperative treatment in many patients. The accuracy is 60%-86% for T-staging , with a specificity of 92% (CI 90% to 95%) for prediction of a clear margin. The accuracy in evaluating CRM is 100% in T4 tumors, and 97% and 93% for both readers in tumors with a histologically determined tumor-free CRM >10 mm.[17,19-20] The use of ERUS or MRI for a comprehensive evaluation of the rectal cancer in the local setting is primarily limited by its availability in certain hospitals and medical centers.

FDG PET/CT or contrast-enhanced FDG PET/CT has the capability to identify nodal disease remote from the primary site. Its use in the pre-operative staging for primary colorectal cancer (CRC) is limited and the two studies on FDG PET/CT includes small samples of patients.[21] Therefore, there is a lack of data to support the use of FDG PET/CT in the routine staging of all patients diagnosed with primary colorectal cancer.

What is the multidisciplinary team approach and its role in the management of rectal cancer?

Level of Evidence III, Category A

The Multidisciplinary team (MDT) approach is a collaboration among a group of health specialists to develop and implement a comprehensive treatment plan for the patients diagnosed with rectal cancer.

The MDT team composition is based on the availability of specialists.

The MDT should at least include: Surgeon, medical oncologist, radiation oncologist, gastroenterologist and a pathologist.

Treatment planning for all rectal cancer patients should be made after accurate staging and preferably through an MDT consensus.

The MDT arose from the need for quality assurance and control. The treatment of rectal cancer is demanding and requires great skill from the members of the MDT team. Quality surgery, combined with a good pathologic evaluation of the resected specimen, good radiation techniques, administered chemotherapy, together with long-term complete follow-up and functional aspects, are important for quality control.[22-25]

The core MDT members include the colorectal surgeons, general surgeons, hepatobiliary surgeons, gastroenterologists, medical oncologists, radiation oncologists, radiologists, pathologists, geneticists, social workers, oncology and surgical nurses and nurse practitioners, enterostomal therapists and a team coordinator.[23] Plastic surgeons, thoracic surgeons, urologists, and gynecologic oncologists are asked selectively to assist.[23]

The National Institute for Clinical Excellence in London has published guidelines in organizing a multidisciplinary team. Aside from the core members of the MDT, it is recommended to 1) hold weekly meetings set up by the team coordinator, 2) patients data, case notes, diagnostic exam results and pathologic information be made available during the meeting, and 3) cases for discussion to include: new patients diagnosed with colorectal cancer, patients who have undergone resection of a colorectal cancer, patients newly identified with recurrent or metastatic disease, and any other colorectal cancer patients that members of the team feel should be discussed.[23]

High-volume colorectal cancer centers with experienced subspecialty-trained surgeons have reduced mortality and have higher sphincter preservation rates.[23] This trend results in increased survival in those teams with higher site specialization expertise. Comparison of patients managed by the MDT and those without MDT, revealed that MRI was used more often ($P = 0.001$) and TNM staging was more complete ($P<0.001$) as compared to those without MDT.[25] The proportion of patients with advanced disease was higher in the MDT group (88% CT3/N? versus 68%; $P = 0.001$).25 The overall CRM+ rate was 13% and did not differ between the MDT and the non-MDT group ($P = 0.392$).[25]

The treatment strategy was altered after discussion at the MDT meeting in 58.33% of colorectal cancer

patients before operation.[22] The sphincter-preservation and local control of the tumor were better in the neoadjuvant therapy (NT) group than in the control group.[22] The 5-year overall survival rate was also higher in the NT group than in control group (77.23% vs 69.75%, P = 0.049).[22]

The pathologist plays a critical role in judging the quality of the surgery with regards CRM involvement, macroscopic appearance of the surgically resected specimen, reporting the regression grade achieved after chemo-radiation and lymph node harvest. The pathologist can also aid the MDT in the initial and future decisions regarding adjuvant therapy based on the pathologic examination of surgical specimens.[24]

What is the role of neoadjuvant treatment?

- Neoadjuvant treatment is highly recommended for clinically Stage II and III.

  Level of Evidence I, Category A

- The type of neoadjuvant regimen will be determined preferably by the MDT consensus appropriate for each patient.

  Level of Evidence I, Category A

- In case of complete clinical response following neoadjuvant treatment, surgical resection should still be performed.

  Level of Evidence IV, Category A

Neoadjuvant therapy requires giving radiotherapy, chemotherapy or a combination, prior to surgery. Neoadjuvant radiotherapy includes short course (25 Gy in a 5 day course) and long course (54 Gy in a 25 day course) treatment.

When comparing neoadjuvant versus adjuvant radiotherapy, the advantages of neoadjuvant radiotherapy results in enhanced effectiveness in well oxygenated tissues, down-staging of advanced tumors, better treatment compliance, less small bowel in the radiation field, avoidance of directly radiating the healing anastomosis and better ano-rectal function post-operatively.[26]

The addition of chemotherapy enhances the anti-tumor activity of RT and is associated with a 30%-40% histological response in the primary tumor.[27]

The advantages of pre-operative chemoRT in resectable disease include: 1) downstaging or downsizing of tumors close to CRM or sphincter apparatus, 2) enhance R0 and sphincter-preservation rate, and 3) eliminate microscopic systemic disease. The disadvantages are increased local and systemic toxicity and over-treatment of inaccurately staged patients.[27]

Comparing pre-operative chemoRT and pre-operative RT, the local recurrence at 5 years : RT group, 122 of 740 (16.5%) vs CRT group in 71 of 754 (9.4%) (OR 0.53, 95%CI 0.39-0.72, P < 0.001). With regards 5 year survival, RT group 647 of 993 (65.2%) vs CRT group, 644 of 1007 (63.9%). (OR 0.95, 95%CI 0.79-1.14, P = 0.58). 5-year disease free survival - RT group 479/872 (54.9%) vs CRT group 507/881 (57.5%) (OR 1.11, 95%CI 0.92-1.34, P = 0.27). The grade 3-4 treatment related toxicity: RT group 52 of 1017 patients (5.1%) vs CRT 151 of 1015 patients (14.9%) (OR 4.1, 95%CI 1.68-10, P = 0.002) but there was significant heterogeneity (P = 0.005) between the groups. Sphincter preservation: RT group 553 of 1145 patients (48.3%) vs CRT group 583 of 1157 patients (50.4%) (OR 1.09, 95% CI 0.92-1.30, P = 0.32). The 30 day post-operative mortality was RT group 21 of 1117 (1.9%) vs CRT group in 31 of 1122 (2.8%) (OR 1.48, 95%CI 0.84-2.6, P = 0.17). The post-operative morbidity was marginally higher in the CRT group (OR 0.67-1.00, P = 0.05). Regarding anastomotic leak rate, there are no differences in anastomotic leak rate detected (OR 0.62-1.84, P = 0.81). Pathologic complete response of resected specimen : RT group 40 of 1142 patients (3.5%) vs. CRT group 135 of 1142 patients (11.8%) (OR 3.52, 95%CI 2.12-5.84, P < 0.00001).[27]

The complete pathologic response rate after neoadjuvant chemoradiotherapy and surgery as compared to neoadjuvant chemotherapy, chemoradiotherapy and surgery were 34.5% (95% CI: 17.2% to 51.8%) and 32.1% (95% CI: 14.8% to 49.4%).[9] This study was closed prematurely for futility. There was also no statistically significant difference in the

pathological complete response, tumor regression and sphincter preservation.[9] The grade 3/4 toxicity was significantly higher in those given neoadjuvant chemotherapy, chemoradiotherapy and surgery.[28]

The occurrence of grade 3 to 4 adverse events during preoperative treatment was more frequent with oxaliplatin plus fluorouracil and radiation than with radiation and fluorouracil alone (24% v 8% of treated patients; P .001).[10] The rate of pathologic complete responses was 16% in both arms (odds ratio _ 0.98; 95% CI, 0.66 to 1.44; P _ .904).[10] Twenty-six percent versus 29% of patients had pathologically positive lymph nodes (arm A v arm B; P _ .447) and intra-abdominal metastases were found at surgery in 2.9% versus 0.5% of patients (arm A v arm B; P _ .014).[29]

The use of preoperative chemoradiation using capecitabine resulted in a complete pathologic response in 9.3% (95% CI 3-23.1) and an overall downstaging in 74.4% (95% CI 58.5-85). Sphincter sparing surgery was performed in 46.5% (95% CI 31.5-62.2). The toxicity due to capecitabine was moderate and required no treatment interruption.[30]

In a case series of patients pre-operatively evaluated to have T2Nþ, T3N0, or T3Nþ rectal cancer who underwent TME without receiving preoperative chemoradiation, showed a 5-year actuarial LR, DFS, and CSS rates were 9.5%, 65.4%, and 77.8%. Threatened mesorectal fascia at preoperative staging was the only independent preoperative factor that predicted a higher risk for LR (P ¼ .007), shorter DFS (P ¼ .007), and shorter CSS (P ¼ .05). This paper concluded and recommended that for rectal cancer clinically staged as T3N0/Nþ or T2Nþ with a free margin >2 mm from mesorectal fascia may undergo TME alone.[31]

Comparing patients undergoing neoadjuvant radiotherapy using 5 x 5 Gy and surgery in 7-10 days as compared to surgery 4-5 weeks later showed improved 5-year survival rates only in patients with downstaging after preoperative irradiation [90% vs 60% (log rank P=0.004)]. A longer time interval after preoperative radiotherapy did not improve the rate of sphincter-saving procedures and curative resections (R0) despite higher downstaging rate.[32]

Comparing neoadjuvant versus adjuvant chemoradiotherapy with capecitabine showed that after a median follow-up time of 52 months, the 3- and 5-year disease-free survival, overall survival, and cumulative incidence of local recurrence were similar between preoperative and postoperative CRT with capecitabine.[14] The preoperative CRT arm however, had a higher rate of sphincter preservation (68% vs 42%, P ¼ .008).[33]

Comparing 5-fluorouracil and leucovorin with 45 Gy in 25 fractions with a 5.40-Gy boost given pre-operatively and postoperatively showed that the 5-year DFS for preoperative patients was 64.7% v 53.4% for postoperative patients (P _ .011). The 5-year OS for preoperative patients was 74.5% v 65.6% for postoperative patients (P _ .065). A complete pathologic response was achieved in 15% of preoperative patients.[34]

Neoadjuvant radiotherapy shows superior results in terms of local control compared to adjuvant radiotherapy. Neither adjuvant or neoadjuvant radiotherapy impacts overall survival. The use of short course versus long course neoadjuvant radiotherapy remains controversial. There is insufficient data to conclude that neoadjuvant therapy improves rates of sphincter preserving surgery.[35]

Complete clinical response (cCR) is described as patients having no detectable evidence of tumor on clinical examination, or clinical examination and endoscopy after neoadjuvant chemoradiotherapy verified by a negative biopsy of the site of the tumor. This was first reported by Habr-Gama in a series of 118 cCR patients with a potentially resectable low rectal cancer who received preoperative chemoradiation (50.4 Gy combined with 5-FU and folinic acid for 3 consecutive days on the first and last 3 days of radiotherapy), of which 30 patients did not proceed to radical surgery. Twenty-seven (27%) of patients failed locally and proceeded to a salvage resection within 3 to 14 months of the completion of radiation. The local recurrence and survival were found to be similar for those achieving cCR and observed long-term compared with patients with only a partial clinical response but found at surgery to have achieved a pCR. A second study by Habr-Gama of patients with a complete clinical response at eight weeks who were observed rather than proceeding to radical surgery, the mean follow-up was 57.3 months. Two patients (2.8 %) had endoluminal recurrence, and three had systemic metastases.[36]

Several studies have demonstrated that complete clinical response at six weeks is not equivalent to a complete pathologic response. In these studies, at least 50 % of patients who achieve a complete clinical response will have residual microscopic foci in their operative specimen. Local excision alone for T1/T2 rectal cancers have shown that 10%-30% will develop local recurrence and have poor salvage rate when the tumors recur. In 16 patients treated with chemoradiation alone, 37.5% achieved a cCR and were followed in close surveillance by monthly proctoscopy. Five of six patients failed locally after 1 to 10 months only a single patient maintained local control at 34 months.[36] In a series of 51 patients with advanced unresectable or borderline resectable rectal cancer, 10 (19.6%) were clinical complete responders. Of these 8 out of 10 (80%) recurred locally between 3.7 and 8.8 months, and six succeeded in achieving salvage surgery.[36]

What is/are the recommended treatment?
Level of Evidence I, Category A

- Surgical resection is the primary treatment modality for all curable rectal cancer.
- Transanal excisions are a reasonable alternative for T1N0 disease.
- Total Mesorectal Excision (TME) and sphincter preservation is recommended for most middle and lower rectal cancer.
- APR is recommended in the presence of any of the following:
  1) involvement of the external sphincter
  2) involvement of the perianal skin

- Extra-levator technique for APR is recommended to decrease positive circumferential resection margin and perforation rate.
  (Level of Evidence III, Category A)

- Following resection, the surgical specimen should be evaluated by quality measures such as:
  Grading of the TME specimen
  Lymph node harvest
  Circumferential resection margin

Even with the addition of chemotherapy and radiotherapy, surgery remains the primary modality of treatment for rectal cancer. For upper rectal cancer, tumors located 11-15 cm from the anal verge, a wide mesorectal excision with a 5 cm distal resection margin is sufficient. For middle rectal cancers, tumors located 6-10 cm FAV, a total mesorectal excision with a 5 cm distal resection margin is recommended. For lower rectal cancers, tumors 5 cm or less from the anal verge, a total mesorectal excision and a distal resection margin of 2 cm is required.

Transanal excision (TAE) is a reasonable alternative for early rectal cancers. Prerequisites for TAE include tumors less than 4 cm in diameter, tumors occupying less than 40% of the bowel circumference, tumor within 10 cm of the dentate line, tumor freely mobile on digital rectal examination, and T1 or T2 lesions with no regional lymph node involvement on endorectal ultrasound. Local recurrence rate of 5%-33% and survival rate of 57%-100% have been reported in retrospective studies.[10] Risk factors for recurrence include: depth of invasion of the primary tumor, positive surgical margins, histologic grade of the tumor, and the presence of tumor in the regional lymph nodes. The main disadvantage of TAE is the inability to pathologically assess the regional lymph nodes. Microscopic disease can be present in the regional lymph nodes in up to 12% of T1 lesions, 22% of T2 lesions, and 58% of T3 and T4 lesions.[10]

Total mesorectal excision (TME) is recommended for cancers located in the middle and lower rectum. The mesorectum, the mesentery of the rectum which is contained in a fascial envelope together with the blood supply and the lymphatic system, is sharply and completely dissected under direct vision. The 5-year local recurrence risk of patients undergoing a macroscopically complete local resection was 5.6% in case of preoperative radiotherapy compared with 10.9% in patients undergoing TME alone ($P < 0.001$).[37] The overall survival at 5 years was 64.2% and 63.5%, respectively ($P < 0.902$).[37]

Abdominoperineal resection (APR) was associated with an increased risk of CRM involvement [OR 2.52, $P < 0.001$], increased LR rate [HR 1.53, $P = 0.001$] and decreased CSS rate (HR 1.31, $P = 0.002$).[38] APR was also associated with reduced OS compared to the LAR procedure: 59.8% 5-year survival for APR versus 70.1%

for LAR.[38] In patients undergoing APR, it is recommended that the perineal part of the operation be performed with the patient in the prone jack-knife position, with the entire levator muscle resected en bloc with the anal canal and lower rectum.[38] This results in a cylindrical specimen with more tissue covering and surrounding the tumour in low rectal cancer, avoiding "waisting" in TME specimens. Sometimes, a gluteus maximus flap is used to reconstruct the pelvic floor.

Sphincter-preserving rectal surgery, such as low anterior resection, is preferred over an abdominoperineal resection. In patients undergoing LAR, 12% had a positive CRM as compared with 29% after APR. The 5-year OSR in patients with a positive CRM after LAR and APR were, 57.6% and 38.5% ($P < 0.008$).[39] The large proportion of CRM positive resections found in the TME trial after an APR offers an important explanation of the poor outcome in these patients. Tumors that were located anteriorly, advanced T-stage, and higher N-stage were independent risk factors for CRM positivity. Positive CRM, higher T-stage, and higher N-stage were risk factors for LR. In addition to the risk factors for LR, tumors located in the lower rectum and older age were associated with reduced OS.[39]

Survival differed greatly between abdominoperineal resection (APR) and anterior resection (AR; 38.5% v 57.6%, $P <.008$).[40] Low rectal carcinomas have a higher frequency of circumferential margin involvement (26.5% v 12.6%, $P <.001$).[40] More positive margins were present in the patients operated with APR (30.4%) as compared to AR (10.7%, $P <.002$).[40] Furthermore, more perforations were present in these specimens (APR vs AR, 13.7% v 2.5%, $P < .001$).[40]

Following resection, the quality of the TME specimen should be assessed by evaluating the gross appearance of the specimen, number of lymph nodes harvested and the CRM. The gross appearance of the specimen should be objectively evaluated by the surgeon and the pathologist separately. The TME specimen can be evaluated as follows: a) muscularis propria plane, b) intramesorectal plane and c) mesorectal plane. The Muscularis propria plane (previously: poor/incomplete mesorectum), where there is little bulk to the mesorectum with defects down onto the muscularis propria and/or very irregular circumferential resection margin but still reaching to the muscularis propria. The Intramesorectal plane (previously: moderate/moderately complete mesorectum), this plane has moderate bulk to the mesorectum, but with irregularity of the mesorectal surface, moderate coning of the specimen and at no site is the muscularis propria visible. The Mesorectal plane (previously: good/complete mesorectum), this plane has an intact mesorectum with only minor irregularities of a smooth mesorectal surface, no defect is deeper than 5 mm, no coning towards the distal margin of the specimen and smooth circumferential resection margin on slicing.[40]

For Abdominoperineal resection specimens, an additional classification system has been developed for the anal canal: the intramuscular/submucosal plane, sphincteric plane and outside levator plane. The Intramuscular/submucosal plane (IMSM), plane where there is perforation or missing areas of muscularis propria, indicating entry into the muscular tube at this level. In the Sphincteric plane, the CRM is at the surface of the sphincteric muscular tube, but this muscle is intact. In the Outside levator plane, this plane has a cylindrical specimen with the levators removed en bloc.[40]

A minimum number of 12 lymph nodes (LN) is required for anterior resection and total mesorectal excision specimens.[4] The LN yield in patients undergoing neoadjuvant chemoradiotherapy is less than those without neoadjuvant treatment (Mean 9-14.2 vs 13-19.4 $P<0.01$-0.001).[41] The reason for the low LN yield in patients receiving neoadjuvant treatment include inflammation, tissue fibrosis, and/or shrinkage of the LNs.

The specimen is evaluated for involvement of the CRM. CRM is the closest radial margin between the deepest penetration of the tumor and the edge of resected soft tissue around the rectum or from the edge of a lymph node.[4] This has a direct relationship with development of local recurrence. A positive CRM is defined as presence of tumor equal to or less than 1 mm between the edge of the the tumor or LN and the surgical resection plane. A CRM of 2 mm and more is indicative of a negative margin.

Evidence on Minimally Invasive Surgery

- May be considered in the treatment of early rectal cancer

- Because of the higher learning curve for rectal cancer surgery in general and in laparoscopic rectal cancer surgery in particular:

Laparoscopic rectal cancer surgery is recommended to be performed by

1) Surgeons trained in TME (Level of Evidence I, Category A) and extralevator APR (Level of Evidence IV, Category A)
2) Surgeons who have completed at least 20 supervised laparoscopic rectal cancer operations (Level of Evidence III, Category A)

Pre-operative tumor imaging with pelvic MRI, ERUS or a pelvic CT scan is used to assess for adequacy of resectability and if negative circumferential resection margins can be ensured, before considering minimally invasive surgery for rectal cancer.

Comparison of the short-term outcomes of laparoscopic versus open surgery for rectal cancer revealed that the operative time for laparoscopic surgery was significantly longer, by 40.96 min, (weighted mean difference=40.96; 95% CI=25.53-56.38;P<0.00001).[42-44] The intraoperative blood loss and the number of transfused patients in the laparoscopic group were significantly lower than in the open group.[42-44] The length of hospital stay and the time to oral diet were significantly shorter with laparoscopic surgery than with open surgery (P=0.0001 and 0.02, respectively).[42-44]

There was no significant difference in the number of harvested lymph nodes, length of time of parenteral analgesic administration, overall complications, anastomotic leakage, perioperative mortality, positive circumferential resection margin and positive distal resection margin between the two groups.[42-44] There was no significant difference with regarding the cost of surgery between the two procedures. This can be explained by the operating costs being higher and the hospitalization costs were lower in the laparoscopic group as compared to the open surgery group.[42-44]

The conversion rate for laparoscopic to open surgery, ranged from 0% to 34%, with no significant difference between the trials performed by a single institution and those performed by multicenter institutions (P=0.51).[42-44]

Long term oncologic outcomes showed no significant difference in the overall recurrence, local recurrence, distant metastasis, wound site recurrence, overall mortality, cancer-related mortality, and disease-free survival at 3 and 5 years after surgery when comparing laparoscopic and open surgery.[42-44] The urinary dysfunction did not differ significantly between the two groups (odds ratio=1.11; 95% CI=0.57-2.19; P=0.75).[42-44] There was likewise no significant difference in male, female, and both male and female sexual dysfunction between laparoscopic and open groups.[42-44]

Laparoscopic surgery in rectal cancer surgery has inherent difficulties. Foremost of which is the limited dexterity when working in the pelvis. Worth mentioning is the use of robotic surgery in rectal cancer. Robotic surgery has several advantages over laparoscopic surgery including enhanced dexterity, three dimensional field of vision, more intuitive instrument manipulation, superior exposure, dissection and counter-traction, reduced circumferential margin positivity rates, and improved autonomic nerve preservation. Robotic procedures tend to have a longer operative time and cost more. In the only randomized trial comparing robotic with laparoscopic TME surgery, the operating time was found to be increased by only 13 min in robotic TME (217 min and 204.3 min).[45] Robotic surgery also may reduce the length of hospital stay, blood loss, and conversion rates. The complication profiles and short-term oncological outcomes were similar to laparoscopic surgery.

The technique of total mesorectal excision should be mastered during the open technique before venturing in the laparoscopic technique so as not to compromise oncologic outcomes. The American Society of Colon and Rectal Surgeons (ASCRS) and the Society of Gastrointestinal and Endoscopic Surgeons (SAGES) recommend that "laparoscopic proctectomy be considered only when it is within the expertise of trained surgeons who focus on the treatment of rectal cancer. Laparoscopic proctectomy must follow traditional guidelines and standards including adequate mesorectal excision and the achievement of appropriate clear margins".[43] The development of this expertise should include observation of procedures, laboratory experience and graduated clinical responsibility.[43] A minimum of 20

laparoscopic colon operations for a surgeon is required before a surgeon can be included in clinical trials. The learning curve for laparoscopic colectomy have suggested at least 50 cases are required to gain proficiency. Advanced laparoscopic training during residency or fellowship and training on simulators may shorten the learning curve towards proficiency. Mentoring, proctoring and working with an experienced assistant have each been shown to be effective in the adoption of techniques new to a surgeons skill set.

What is the role of adjuvant treatment in the treatment of rectal cancer?

- o Adjuvant therapy for Stage IIB and III results in improved disease free survival. (Level of Evidence I, Category A)

There is no statistically significant impact in giving adjuvant chemotherapy on disease free survival (DFS) for curative cT3-T4 rectal cancer after pre-operative radiotherapy or radiochemotherapy (P <0.5).[47] The treatment effect differed significantly between the ypT0-2 and the ypT3-4 patients (heterogeneity P =.009): only the ypT0-2 patients seemed to benefit from adjuvant chemotherapy (P = .011).[47] The same pattern was observed for overall survival. Only good-prognosis patients (ypT0-2) benefit from adjuvant chemotherapy. Patients in whom no downstaging was achieved did not benefit.

Patients who received pre-operative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone showed a pathological complete response was achieved in 103 (17%) of 591 patients who underwent surgery in the fluorouracil and oxaliplatin group and in 81 (13%) of 606 patients who underwent surgery in the fluorouracil group (odds ratio 1·40, 95% CI 1·02-1·92; P=0·038).47 However, the combination of oxaliplatin and fluorouracil led to more pre-operative Grade 3-4 toxic effects such as diarrhea, nausea and vomiting.

What is/are the recommended surveillance regimen/s to detect recurrence after surgical resection?

(Level of Evidence II, Category A)

- History and physical examination every 3-6 months for 2 years, then every 6 months from the 3rd -5th year then annually thereafter.
- CEA every 3-6 months for 2 years, then every 6 months from the 3rd-5th year then annually thereafter.
- Chest and abdomino-pelvic CT scan annually for 5 years, for patients at high risk of recurrence
- Colonoscopy after 1 year. For incomplete colonoscopy due to an obstructing lesion, colonoscopy should be performed within 6 months following surgery.
- Proctoscopy every 6 months for 5 years, for patients status post low anterior resection

Surveillance regimen followed the NCCN guidelines.[3] Meta-analysis have shown that 80% of tumor recurrences, whether local or systemic recurrence, appears within the first 3 years of the primary resection. The surveillance is intensive during the first 2 years after surgery. History, physical examination and CEA are taken every 3-6 months interval after surgical resection. CT scan of the abdomen-pelvis and chest are requested to detect local or systemic spread. Colonoscopy is used to detect for the presence of intraluminal tumor recurrence and to identify metachronous neoplasms or polyps. Colonoscopy is taken after 1 year, and is repeated after 3 years then every 5 years thereafter. In cases where the colonoscopy showed the presence of villous polyp, polyp >1 cm or with high grade dysplasia, a repeat colonoscopy should be performed after 1 year. Proctoscopy is used to evaluate the anastomotic site in patients who received low anterior resection surgery.

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