CANCERCare
A PROGRAM OF EASTERN HEALTH

Clinical Practice Guidelines - Gastrointestinal Disease Site

Guideline Title:	Neo-Adjuvant Treatment of Stage II and Stage III Rectal Cancer - **Summary**	**Date:**	**(O):** **(R):**	May 23, 2012
Tumor Group:	G. I. Disease Site Group	**Page:**		1 of 5
Issuing Authority:	Dr. Jehann Siddiqui Clinical Chief, Cancer Care Program	**Date Signed:**		Oct 21,2013
Adapted From:	National Institute for Health and Clinical Excellence "Colorectal cancer: The diagnosis and management of colorectal cancer" guideline, Nov 2011 (10).			

Target Population:

These recommendations apply to patients with a pathological confirmed diagnosis of locally advanced rectal cancer following appropriate radiological staging.

Recommendations:

The following recommendations of the Eastern Health G. I. Disease Site Group apply to patients with a pathologically confirmed cancer of the rectum and who have undergone appropriate preoperative staging:

- Pretreatment multidisciplinary discussion of pathologically confirmed cases of rectal cancer is strongly encouraged.
- Patients with stage I rectal cancers require surgical intervention only. Patients with T2N0 cancers that encroach upon the anal canal may be considered for short-course preoperative radiotherapy (SCPRT).
- Patients with cT3/4N0/+ rectal cancer are candidates for neo-adjuvant (preoperative) chemoradiation therapy (CRT) (typically, consisting of 50.4Gy in 28 fractions with concurrent capecitabine).
- Patients with cT3N0 rectal cancer, with a predicted clear resection margin, or contraindications to chemotherapy may be considered for SCPRT.
- The neo-adjuvant CRT regimen chemotherapy of choice would be oral capecitabine but infusional 5-fluorouracil (5-FU) is a viable alternative.

Supporting Evidence:

Neo-adjuvant CRT has replaced the old standard of adjuvant (postoperative) CRT with 5-fluorouracil (5FU) in the treatment of locally advanced rectal cancer based primarily on a German study comparing the two in the rectal cancer setting (1). The 5 year results indicated that there was no significant difference in overall survival between the two arms. However,

patients who received neo-adjuvant CRT had a significant decrease in local recurrence (LR) rates (6% versus 13%; p=0.006), as well as fewer acute (27% versus 40%; p=0.001) and chronic toxicities (14% versus 24%; p=0.01), in comparison to those who received adjuvant therapy.

In the last twenty years, three large randomized controlled trials have formed the basis of evidence for use of SCPRT (2-4). The 5 X 5 Gy SCPRT is a short course of 25Gy given over five days and can then be followed by surgery, which is recommended to take place within 7 days of the last radiation dose. The rationale for its use is that the short time period for delivery of the dose may interfere with the effects of accelerated cellular repopulation. SCPRT does not result in apparent downsizing of tumors or downstaging in terms of nodal status (5). The Swedish Rectal Cancer Trial randomized patients to surgery alone or 5 X 5 Gy treatment plan in the era prior to the standardization of total mesorectal excision (TME) surgery (2). The results indicated that the 5 year overall survival rate was improved in the irradiated arm with 38% compared to 30% in the non-irradiated arm ($p = 0.008$), while the LR rate was 9% versus 26% ($p < 0.001$), respectively. The Dutch Colorectal Cancer Group Trial also randomized patients in a similar manner to either SCPRT and TME surgery or TME surgery alone (3). The results were a 5 year LR rate of 5.6% in the irrated arm and 10.9% in the surgery alone arm but no significant differences seen in the overall survival rate. Finally, the Medical Research Council CR07/National Cancer Institute of Canada – Clinical Trials Group trial randomized their resectable study population to either SCPRT followed by TME surgery or TME surgery followed by adjuvant CRT for only those patients with a pathologically positive circumferential resection margin. It found an absolute difference in the 3 year LR of 6.2% between the SCPRT arm (4.4%) and the surgery plus selective adjuvant CRT arm (10.6%) ($p < 0.0001$), but again no differences in overall survival in either arm (4).

Multiple phase II trials using capecitabine and radiation therapy neo-adjuvantly have shown the combination to be well tolerated with an equivalent pathological response rate to the standard infusional 5-FU CRT (6 - 8). Few of these studies show a survival advantage for capecitabine however, the pathological complete response rate tends to be significantly higher. Currently, there is limited phase III data validating the use of capecitabine in the neo-adjuvant setting. One recent German phase III neoadjuvant study of capecitabine versus infusional 5-FU CRT achieved its endpoint of non-inferiority between the two arms (9). It found that patients in the capecitabine arm exhibited an higher rate of T-downstaging (52% vs 39%) and negative nodes (71% vs 56%). Significantly less leukopenia was observed in the capecitabine arm but more hand-foot syndrome. Stomatitis/mucositis, diarrhea, nausea/vomiting, and radiodermatitis were not significantly different between both arms. This study did suggest that given the safety profile and trend for improved downstaging in the neo-adjuvant setting, which may potentially improve the possibility of sphincter preservation surgery, capecitabine should replace 5-FU as neo-adjuvant treatment of locally advanced rectal cancer.

Qualifying Statements:

Expert opinion suggests that the advantages of the neo-adjuvant approach, when surgery is performed 4-6 weeks following the last cycle of chemotherapy, may include:

- tumor regression with down-staging and downsizing that can potentially permit curative radical resections in locally advanced T4-rectal cancer, and sphincter preservation in low-lying tumors;

- may also be useful in resectable rectal cancer since neo-adjuvant irradiation is associated with less toxicities than adjuvant irradiation, therefore enabling more patients to receive the full-dose regimen;
- oxygen tension within the tumor may be higher before surgery since surgical resection compromises the regional blood flow. This may allow the tumor to be more radiosensitive by decreasing the more radioresistant hypoxic fraction;
- complete pathological response rates up to 10%-25% can be achieved.

Disclaimer:

These guidelines are a statement of consensus of the G. I. Disease Site Group regarding their views of currently accepted approaches to diagnosis and treatment. Any clinician seeking to apply or consult the guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment.

Contact Information:

For more information on this guideline, please contact Dr. Terri Stuckless MD FRCPC, Dr. H. Bliss Murphy Cancer Center, St. John's, NL; Telephone 709-777-8097. For the complete guideline on this topic or for access to any of our guidelines, please visit our Cancer Care Program website at www.easternhealth.ca

Literature Support:

1. Sauer R, Becker H, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med. 2004;351(17):1731-1740.
2. Folkesson J, Birgisson H, et al. Swedish Rectal Cancer Trial: Long lasting benefits from radiotherapy on survival and local recurrence rate. J Clin Oncol. 2005;23(24):5644-5650.
3. Van Gijn W, Marijnen CAM, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicenter, randomized controlled TME trial. Lancet Oncol. 2011;12:575-582.
4. Sebag-Montefiore D, Stephens RJ, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): A multicenter, randomized trial. Lancet. 2009;373:811-820.
5. Ceelen WP, Van Nieuwenhove Y, et al. Preoperative chemoradiation versus radiation alone for stage II and III resectable rectal cancer. Cochrane Database of Systematic Reviews 2009, Issue 1. Art.No.:CD006041. DOI: 10.1002/14651858.CD006041.pub2.
6. Kim JC, Kim TW, et al. Preoperative concurrent radiotherapy with capecitabine before total mesorectal excision in locally advanced rectal cancer. Int J Radiation Oncol Biol Phys. 2005;63(2):346-353.
7. Das P, Lin EH, et al. Preoperative chemoradiotherapy with capecitabine versus protracted infusion 5-fluorouracil for rectal cancer: A matched-pair analysis. Int J Radiation Oncol Biol Phys. 2006;66(5):1378-1383.
8. Desai SP, El-Rayes BF, et al. A phase II study of preoperative capecitabine and radiation therapy in patients with rectal cancer. Amer J Clin Oncol. 2007;30(4):340345.
9. Hofheinz R, Wenz F, et al. Capecitabine (cape) versus 5-fluorouracil (5-FU)-based neoadjuvant chemotherapy for locally advanced rectal cancer (LARC): Safe results of a randomized, phase III trial (abst. 4014). J Clin Oncol. 2009;27:15S.

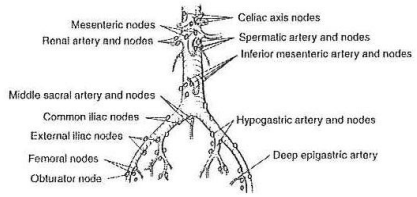
10. Hyslop J, Paul A, et al. Clinical Guideline: The diagnosis and management of colorectal cancer. National Health Service. November 2011. www.nice.org.uk

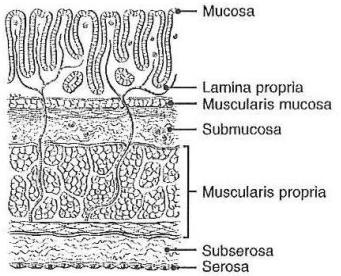
Appendix

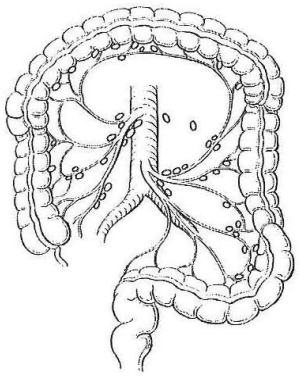
American Joint Committee on Cancer

Colon and Rectum Cancer Staging

7th EDITION







Definitions

Primary Tumor (T)

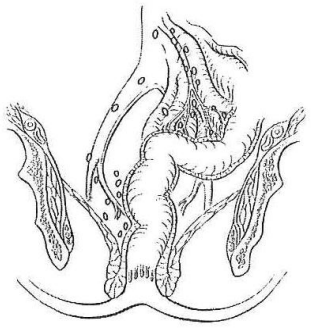
- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- Tis Carcinoma in situ: intraepithelial or invasion of lamina propria[1]
- T1 Tumor invades submucosa
- T2 Tumor invades muscularis propria
- T3 Tumor invades through the muscularis propria into pericolorectal tissues
- T4a Tumor penetrates to the surface of the visceral peritoneum[2]
- T4b Tumor directly invades or is adherent to other organs or structures[2,3]

Regional Lymph Nodes (N)[4]

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Metastasis in 1–3 regional lymph nodes
- N1a Metastasis in one regional lymph node
- N1b Metastasis in 2–3 regional lymph nodes
- N1c Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
- N2 Metastasis in 4 or more regional lymph nodes
- N2a Metastasis in 4–6 regional lymph nodes
- N2b Metastasis in 7 or more regional lymph nodes

Distant Metastasis (M)

- M0 No distant metastasis
- M1 Distant metastasis
- M1a Metastasis confined to one organ or site (for example, liver, lung, ovary, nonregional node)
- M1b Metastases in more than one organ/site or the peritoneum



ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage	T	N	M	Dukes*	MAC*
0	Tis	N0	M0	–	–
I	T1	N0	M0	A	A
	T2	N0	M0	A	B1
IIA	T3	N0	M0	B	B2
IIB	T4a	N0	M0	B	B2
IIC	T4b	N0	M0	B	B3
IIIA	T1–T2	N1/N1c	M0	C	C1
	T1	N2a	M0	C	C1
IIIB	T3–T4a	N1/N1c	M0	C	C2
	T2–T3	N2a	M0	C	C1/C2
	T1–T2	N2b	M0	C	C1
IIIC	T4a	N2a	M0	C	C2
	T3–T4a	N2b	M0	C	C2
	T4b	N1–N2	M0	C	C3
IVA	Any T	Any N	M1a	–	–
IVB	Any T	Any N	M1b	–	–

NOTE: cTNM is the clinical classification, pTNM is the pathologic classification. The y prefix is used for those cancers that are classified after neoadjuvant pretreatment (for example, ypTNM). Patients who have a complete pathologic response are ypT0N0cM0 that may be similar to Stage Group 0 or I. The r prefix is to be used for those cancers that have recurred after a disease-free interval (rTNM).
* Dukes B is a composite of better (T3 N0 M0) and worse (T4 N0 M0) prognostic groups, as is Dukes C (any TN1 M0 and Any T N2 M0). MAC is the modified Astler-Coller classification.

ajcc®

American Cancer Society®

Financial support for AJCC 7th Edition Staging Posters provided by the American Cancer Society

Notes

[1] Tis includes cancer cells confined within the glandular basement membrane (intraepithelial) or mucosal lamina propria (intramucosal) with no extension through the muscularis mucosae into the submucosa.

[2] Direct invasion in T4 includes invasion of other organs or other segments of the colorectum as a result of direct extension through the serosa, as confirmed on microscopic examination (for example, invasion of the sigmoid colon by a carcinoma of the cecum) or, for cancers in a retroperitoneal or subperitoneal location, direct invasion of other organs or structures by virtue of extension beyond the muscularis propria (that is, a tumor on the posterior wall of the descending colon invading the left kidney or lateral abdominal wall; or a mid or distal rectal cancer with invasion of prostate, seminal vesicles, cervix, or vagina).

[3] Tumor that is adherent to other organs or structures, grossly, is classified cT4b. However, if no tumor is present in the adhesion, microscopically, the classification should be pT1-4a depending on the anatomical depth of wall invasion. The V and L classifications should be used to identify the presence or absence of vascular or lymphatic invasion, whereas the PN site-specific factor should be used for perineural invasion.

[4] A satellite peritumoral nodule in the pericolorectal adipose tissue of a primary carcinoma without histologic evidence of residual lymph node in the nodule may represent discontinuous spread, venous invasion with extravascular spread (V1/2), or a totally replaced lymph node (N1/2). Replaced nodes should be counted separately as positive nodes in the N category, whereas discontinuous spread or venous invasion should be classified and counted in the Site-Specific Factor category Tumor Deposits (TD).