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Clinical Practice Guidelines – Gastrointestinal Disease Site

Guideline Title:	Neo-adjuvant Treatment of Stage II and Stage III Rectal Cancer	**Date:**	**(O):** **(R):**	May 23, 2012
Tumor Group:	G. I. Disease Site Group	**Page:**		1 of 8
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 (33).			

Introduction:

In recent years, significant strides have been made in the oncological outcomes of patients with rectal cancer. This has come about with the implementation of improved imaging, better surgical techniques and more targeted radiotherapy and chemotherapy. Presently, neo-adjuvant or preoperative chemoradiation therapy (CRT) followed by total mesorectal excision (TME) has emerged to become the standard treatment for patients with locally advanced rectal cancer.

Despite the recent progress, the treatment of locally advanced rectal cancer still carries the risk of high rates of postoperative complications and long-term morbidity. Toxicities, especially those causing bowel, bladder and sexual dysfunction, are known to have a substantial negative effect on the quality of life of patients. Treatment regimens continue to evolve in the attempt to more precisely target appropriate patients and minimize toxicities without compromising survival and/or disease control.

Question:

1. What treatment should be offered to patients with locally advanced rectal cancer who are eligible for neo-adjuvant therapy?

2. Under what clinical circumstances, would neo-adjuvant short-course radiation therapy be the appropriate choice for patients with locally advanced rectal cancer?

Target Population:

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

Supporting Evidence:

The Rectal SEER Analysis has shown that stage I (T1-2N0) rectal cancers have a 5 year survival rate of 92.1% to 96.6% with TME surgery alone (1). Adjuvant or post-operative therapy is not *typically* indicated for this population. However, as the tumor (T) size and nodal status (N) increases, a corresponding decrease is noted in the 5 year relative survival rate. Therefore, additional therapy in conjunction with TME surgery is reserved for those patients staged and diagnosed with high risk stage II and all stage III rectal cancer. These patients should be reviewed at a multidisciplinary colorectal tumor board for consensus on management.

A detailed review of the evidence has been performed and the optimal treatment options for stage II and III rectal cancer patients are as follows:

Neo-adjuvant versus Adjuvant

Adjuvant CRT with 5-fluorouracil (5FU) has been used for many years in the treatment of locally advanced rectal cancer, and have been shown to reduce the rates of local recurrence (LR) and improve survival. More recently, however, neo-adjuvant CRT has replaced this old treatment standard. This is based primarily on a German study of over 800 rectal cancer patients who were randomized to receive either neo-adjuvant or adjuvant CRT (2). The 5 year study results indicate that there is no significant difference in overall survival between the two arms. However, patients who received neo-adjuvant CRT had a significant decrease in 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.

Expert opinion suggests that the advantages of neo-adjuvant CRT, when surgery is performed 4-6 weeks later, may include:

- tumor regression with down-staging that can potentially permit curative radical resections in locally advanced T4-rectal cancer, and sphincter preservation in low-lying tumors;
- reduction in acute toxicities, thus increasing compliance;
- improved efficacy due to better oxygenation and blood flow to tumor cells;
- ability to evaluate tumor response to therapy (as a means of prognosticating).

The main disadvantage of neo-adjuvant CRT lies with the potential overtreatment of patients with early stage tumors or those who already have metastatic disease, undetectable with present imaging technology, allowing these patients to be exposed to the toxicities of unnecessary treatment (3).

Typically, the current total radiation therapy dose in use for neo-adjuvant CRT of rectal cancer is in the range of 45 Gy to 54 Gy, administered in 25 to 30 fractions over a period of five to six weeks (29-34). Surgery is then performed six to ten weeks following the completion of the radiation therapy. At the Dr. H. Bliss Murphy Cancer Center, the standard of care for neo-adjuvant treatment of rectal cancer is a radiation dose of 50.4 Gy administered in 28 fractions over the course of five and one-half weeks, followed by surgery at four to six weeks after completion of radiation therapy.

Short-Course Preoperative Radiotherapy (SCPRT)

In the last twenty years, three large RCTs (randomized controlled trials) have provided evidence for use of short-course preoperative radiotherapy (SCPRT). The Swedish Rectal Cancer Trial

randomized patients to surgery alone or a short course of 25 Gy given over five fractions for five days (known as 5 X 5 Gy) prior to the standardization of TME surgery (4). The 5 year overall survival rate was improved in the irradiated arm (38%) compared to the non-irradiated arm (30%) ($p = 0.008$), 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 (5). The 5 year recurrence rate of 5.6% in the irradiated arm and 10.9% in the surgery alone arm, but no significant differences were seen in the overall survival rate. A 6 year analysis of this study indicates that the true benefit of SCPRT in terms of LR occurred only in the subgroup of patients with mid-rectal tumors located 5-10cm from the anal verge (6).

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 (CRM). It found an absolute difference in the three year LR rate of 6.2% between the SCPRT arm (4.4%) and the surgery plus selective adjuvant CRT arm (10.6%) ($p < 0.0001$), but no difference in overall survival (7).

The 5 X 5 Gy SCPRT is completed in five days and can then be followed by surgery, which is recommended to take place within 7 days of the last radiation dose. SCPRT does not result in downsizing of tumors or downstaging in terms of nodal status (8).

Neo-adjuvant CRT vs SCPRT

A Cochrane review analyzed four RCTs which compared SCPRT to neo-adjuvant CRT, most of which were carried out in the pre-TME era. It found that neo-adjuvant CRT enhances pathological response and improves local control in resectable stage II and III rectal cancer, but provides no disease-free survival or overall survival benefit (8). A Polish trial which required patients to undergo TME surgery, compared SCPRT and neo-adjuvant CRT and found significantly smaller tumors in the CRT arm and a significantly higher pCR (pathological Complete Response) rate (16.1% vs 0.7%) (p , 0.001) than the SCPRT arm (9). However, there were no differences in overall survival, relapse-free survival, LR rates, or late toxicities, though more acute toxicities were noted in the CRT arm.

Neo-adjuvant CRT should be offered to patients with cT3/4N+ rectal cancer. However, for patients with a predicted clear CRM or low T2N0 disease (approaching the anus), SCPRT may be considered.

Chemoradiation Regimens

5-Fluorouracil (5-FU) based therapy has been the standard of care for neo-adjuvant CRT in the treatment of locally advanced rectal cancer since the 1990s. Infusional 5-FU based CRT has presented some logistical challenges, such as the necessity of central line access with its risk of thrombosis and infection, the inconvenience of the portable infusion pump, frequent visits to the chemotherapy unit, waiting times and need for close coordination between timing of chemotherapy and radiation (10). Recent evidence now suggests that capecitabine, an orally administered fluoropyrimidine, is a viable alternative to infusional 5-FU. Multiple phase II trials using capecitabine and radiation therapy (RT) neoadjuvantly have shown the combination to be well tolerated with an equivalent pathological response rate to the standard infusional 5-FU CRT

(11-13). Few of these studies show a survival advantage for capecitabine however, the pCR rate tends to be significantly higher.

One recent German phase III neo-adjuvant study of capecitabine versus infusional 5-FU CRT achieved its endpoint of non-inferiority between the two arms (14). It found that patients in the capecitabine arm exhibited an higher rate of T-downstaging (52% versus 39%) and negative nodes (71% versus 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.

Recent studies have been investigating the addition of oxaliplatin to fluoropyrimidines in the neo-adjuvant setting of locally advanced rectal cancer, in hopes of improvement in overall outcomes. However, all have concluded that the addition of oxaliplatin significantly increased toxicity without adding benefit to tumor response (15-18). Studies of targeted therapies in the neo-adjuvant setting of locally advanced rectal cancer are ongoing.

Treatment-Related Toxicities
The most common acute toxicities of CRT are gastrointestinal and/or hematological in nature, and can sometimes be severe or even life-threatening. They incude diarrhea, nausea, vomitting, stomatitis, and myelosuppression. The most frequently reported long term side effects after CRT and surgery are urinary dysfunction, altered defecation, pain, fatique and sexual problems, all of which have a negative impact on a patient's quality of life (3,19-21).

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 SCPRT.
- Patients with cT3/4N0/+ rectal cancer are candidates for neo-adjuvant 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 is oral capecitabine but infusional 5-FU is a viable alternative.

Search Strategy:

Literature searches were conducted in PubMed, Embase, and the Cochrane Library, using keywords "rectum cancer" AND "neoplasms" AND "neoadjuvant therapy", as well as an extensive manual search of the reference lists of available literature articles. Guideline searches were also carried out on the websites of the world's most highly respected cancer organizations

and agencies. All selected literature articles and source guidelines were in English and dated after the year 2004 (unless the selection was an earlier landmark study) up to May 2012. The inclusion/exclusion process consisted of selecting guidelines from reputable cancer organizations with preference given to those from Canadian sources where possible. Thirteen source guidelines were identified and conformed to our search criteria (22-34), from which six were selected due to currency, quality of content and/or were Canadian in origin (29-34).

The six identified source guidelines were put through the ADAPTE process (35) with an AGREE II assessment (36), and the National Institute for Health and Clinical Excellence (NICE) guideline was chosen to be adapted for use in our guideline (33). The NICE guideline was selected as the optimal choice due to its applicability, quality and currency of content. Note: 'This adaptation has been produced with permission of NICE. However, NICE has not checked the adaptation to confirm that it accurately reflects the original publication and no guarantees are given by NICE in regard to the accuracy of the adaptation. The NICE guidance that this adaptation is based upon was prepared for the National Health Service in England and Wales. NICE guidance does not apply to Canada and NICE has not been involved in the development or adaptation of any guidance for use in Canada.'

There has been much debate but no consensus on the 'grading of evidence' in Canada. Presently, Canadian experts in the field of guideline development are involved in an ongoing in-depth analysis of the functionality of grading. Until such time as a report is released of their findings, and a consensus reached on whether to assign a grade of recommendation to a guideline, this group has decided to forgo the use of grading.
No competing or conflicts of interest were declared.

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. Teri Stuckless MD FRCPC, Dr. H. Bliss Murphy Cancer Center, St. John's, NL; Telephone 709-777-8097. For access to any of our guidelines, please visit our Cancer Care Program website at www.easternhealth.ca

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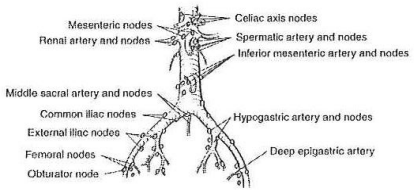
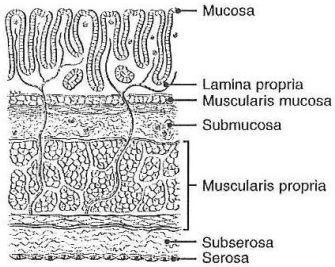
Appendix

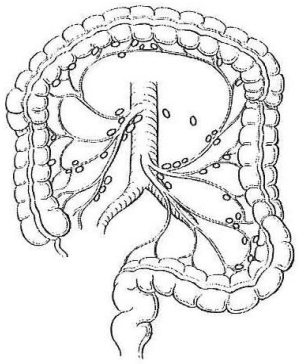
American Joint Committee on Cancer

Colon and Rectum Cancer Staging

7th EDITION







Definitions

Primary Tumor (T)

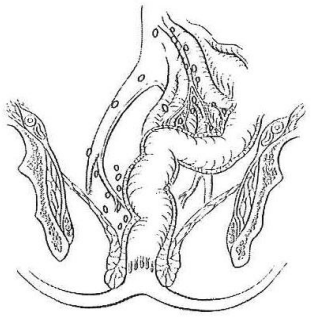
- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- Tis Carcinoma in situ: intraepithelial or invasion of lamina propria[1]
- T1 Tumor invades submucosa
- T2 Tumor invades muscularis propria
- T3 Tumor invades through the muscularis propria into pericolorectal tissues
- T4a Tumor 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.

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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).