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Evidence-Based Series 2-4 Version 3 REQUIRES UPDATING

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Preoperative or Postoperative Therapy for the Management of Patients with Stage II or III Rectal Cancer

Members of the Gastrointestinal Cancer Disease Site Group

An assessment conducted in August 2020 indicated that Evidence-based Series (EBS) 2-4 Version 3 REQUIRES UPDATING. It is still appropriate for this document to be available while this updating process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

EBS 2-4 Version 3 is comprised of 4 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/31891

Section 1: Clinical Practice Guideline
Section 2. Part 1: Evidentiary Base: Part 1. Preoperative Therapy
Section 2. Part 2: Evidentiary Base: Part 2. Postoperative Therapy
Section 3: EBS Development Methods and External Review Process
Section 4: Document Review Summary and Review Tool

March 13, 2019

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Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Original version July 2008	1966-2007	Full Report	Web publication	NA
Version 2 Oct 2013	2008- 2013	New data found in Section 4: Document Summary and Review Tool (Appendix A)	Updated web publication	2008 recommendations are **ENDORSED**
Current Version 3 Mar 2019	2013-2017	New data found in Section 4: Document Assessnebt and Review	Updated web publication	2008 recommendations are ENDORSED

Evidence-Based Series #2-4 Version 3: Section 1

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Preoperative or Postoperative Therapy for the Management of Patients with Stage II or III Rectal Cancer: Guideline Recommendations

R Wong, S Berry, K Spithoff, M Simunovic, K Chan, O Agboola, B Dingle, RB Rumble, B Cummings, and the Gastrointestinal Cancer Disease Site Group

Report Date: July 15, 2008
This report replaces previous versions of
Practice Guidelines #2-3 and #2-13

These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making. Please see Section 4 and Appendix A for a summary of updated evidence published between 2008 and 2017, and for details on how this Clinical Practice Guideline was ENDORSED. Modifications made in 2019 to the content of this recommendations section are shown in highlighted text.

QUESTIONS

1. Following appropriate preoperative staging tests, should patients with resectable clinical stage II or III rectal cancer be offered preoperative radiotherapy (RT) (with or without chemotherapy [CT])?

2. What is the role of postoperative RT and/or CT for patients with resected stage II or III rectal cancer who have not received preoperative RT, in terms of improving survival and delaying local recurrence?

TARGET POPULATION

These recommendations apply to adult patients with clinically resectable or resected stage II or III rectal cancer.

RECOMMENDATIONS

Preoperative Therapy

- Preoperative chemoradiotherapy (CRT) is preferred, compared to preoperative RT (standard fractionation: longer course: 45-50.4Gy in 25-28 fractions) alone, to decrease local recurrence.
- Preoperative CRT is preferred, compared with a postoperative approach, to decrease local recurrence and adverse effects.

- For patients with relative contraindications to CT in the preoperative period, acceptable alternatives are preoperative standard fractionation (longer course; 45-50.4Gy in 25-28 fractions) or hypofractionation (short course; 25Gy in 5 fractions) RT alone followed by surgery guided by the risk of adverse effects.
- Patients eligible for preoperative RT+/-CT should also be considered for adjuvant CT.

Postoperative Therapy

- Patients with resected stage II or III rectal cancer who have not received preoperative RT should be offered postoperative therapy with concurrent CRT in addition to fluoropyrimidine-based CT. The evidence reviewed demonstrates that this treatment improves survival and reduces local recurrence rates compared to observation alone or RT alone after surgery.
- Informed discussions regarding the potential advantages of adjuvant therapy also need to address the significant acute and long-term toxicity that can potentially occur with combined treatment with RT and CT.
- It is the expert opinion of the Gastrointestinal Cancer Disease Site Group (GI DSG) that patients who have received preoperative CRT or RT should receive postoperative CT.

QUALIFYING STATEMENTS

- Recommendations for preoperative therapy presuppose adequate preoperative staging investigations, including transrectal ultrasound and/or magnetic resonance imaging (MRI) with surface or endorectal coil to assess the T category, MRI with surface or endorectal coil to assess the N category, a good digital rectal exam, computerized axial tomography (CAT) scan or MRI to assess the mesorectal margin, CAT scan or MRI of the abdomen to assess for potential metastatic or stage IV disease, and chest x-ray for pulmonary imaging.
- Potential inaccuracies of preoperative testing on tumour staging should be discussed with patients to allow them to make informed decisions (1).
- The eventual rectal surgery is expected to include total mesorectal excision (TME) principles. The quality of surgery greatly influences the potential benefits of preoperative treatments. A substantial number of trials included in the evidentiary base did not use currently recommended standards of surgery, including TME.
- The rationale for the opinion that patients who have received standard fractionation (45-50.4Gy in 25-28 fractions) preoperative RT+/-CT should be offered postoperative CT in the absence of direct evidence for this is described in more detail in the Discussion section of the systematic review for preoperative therapy (Section 2. Part 1).
- Enteritis, diarrhea, bowel obstruction or perforation, and fibrosis within the pelvis are associated with RT. Delayed adverse effects from RT include radiation enteritis (4%), small bowel obstruction (5%), rectal stricture (5%), pelvic fracture, and worsening sexual and bowel function. A greater number of hematological and non-hematological adverse effects are associated with CT plus RT than with CT alone or RT alone. Combined CT plus RT is associated with acute gastrointestinal and hematologic adverse effects that may be severe or life threatening.

QUALIFYING STATEMENTS – Added to the 2019 Endorsement:
(See Section 4 for details about the modifications)

- *Capecitabine or infusional 5FU are the preferred regimens for use in CRT (2). Choice of regimen should be based on an informed discussion or risks, benefits, and convenience of these regimens with the patient.*
- *In most instances, there should be a delay of more than 7 weeks but less than 11 weeks from the completion of RT to surgery, to allow for maximum downstaging of the tumour and facilitate TME surgery with a negative CRM. The GRECCAR trial*

suggested that a delay of 11 weeks was associated with poorer quality of the mesorectal excision, however the results of this trial remain controversial. (3,4). With respect to pathological response, the trial grouped patients in an unconventional manner (complete vs almost complete + incomplete). If patients had been categorized in the more common grouping (complete + almost complete vs incomplete), the results might not have been significantly different. Furthermore, the trial did not report the proportion of patients with <1 mm tumour circumferential margin.

- *The exception to delay of surgery is the use of short-course RT where, in relatively healthy patients, surgery can occur immediately following RT, and ideally within 10 days of the initiation of RT.*
- *In choosing between fluoropyrimidine monotherapy and oxaliplatin-based adjuvant therapy, oxaliplatin-based adjuvant chemotherapy is recommended for patients based on the results of the ADORE trial (5). This trial demonstrated a statistically significant DFS benefit for the overall trial population of patients with ypT3/4 or ypN+ tumours, and a statistically significant improvement in OS in the yPN2 subgroup.*
- *The value of neoadjuvant therapy for patients with an upper rectal tumour (>10 cm) and no MRI features suggesting a high risk of local or distant metastases should be discussed in a multidisciplinary cancer conference.*
- *Patients with clinical complete response after preoperative chemoradiotherapy should only be offered watchful waiting in the context of a clinical trial.*

KEY EVIDENCE

Preoperative Therapy

- Two trials (6,7) comparing preoperative RT versus surgery alone for patients with resectable rectal cancer, including stage I to IV patients, presented outcomes separately for stage II and III patients. Subgroup analyses showed a significant local control benefit for preoperative RT in these patients. This is consistent with the local control benefit for all resectable rectal cancer patients reported in a Cochrane review (8) (hazard ratio [HR], 0.71; 95% confidence interval [CI], 0.64-0.78; number needed to treat [NNT], 22; 95% CI, 17-29, assuming a control group local recurrence rate of 17% at five years).
- Two trials (9,10) comparing preoperative CRT with standard fractionation longer course RT for patients with stage II and III rectal cancer found a local recurrence benefit and improved complete pathological response rate for patients who received CRT.

Postoperative Therapy

- Twenty-nine RCTs, six meta-analyses on adjuvant RT and/or CT in stage II and III resected rectal cancer, and a review of the adverse effects of adjuvant RT and CT were reviewed. Some multi-arm trials contributed to more than one comparison. Data on overall survival and local failure were pooled for the following comparisons: RT versus observation alone, CT versus observation alone (systemic and oral), combined CRT versus observation, CT versus RT, CRT versus RT alone, and CRT versus CT alone (See Table 1).

Preoperative versus Postoperative Therapy

- One trial (11) comparing preoperative versus postoperative CRT (with 4 cycles of postoperative 5FU CT) for patients with clinical stage II and III rectal cancer showed superior local recurrence rate (relative risk [RR], 0.46; 95% CI, 0.26-0.82; from 6% to 13%) and lower acute and late toxicities in favour of preoperative CRT.

Table 1. Outcomes of randomized controlled trials included in the clinical practice guideline: adjuvant therapy following resection for stage II or III rectal cancer patients.

Comparison	Number of trials	Comparisons examined	Number of trials pooled	Pooled results RR (95% CI; p-value)
RT vs. Obs	7	Survival	7	0.98 (0.90, 1.07; p=0.65)
		Local failure	7	0.78 (0.65, 0.95; p=0.01)
CT vs. Obs	6	Survival (IV+oral)	6	0.75 (0.65, 0.88; p=0.0003)
		Local failure (IV+oral)	4	0.74 (0.55, 0.98; p=0.04)
CRT vs. Obs	2	Survival	2	0.74 (0.55, 0.98; p=0.04)
		Local failure	2	0.42 (0.23, 0.75; p=0.004)
CT vs. RT	3	Survival	3	0.85 (0.73, 0.99; p=0.03)
		Local failure	2	1.32 (0.92, 1.91; p=0.14)
CT vs. CT	5	*No pooling performed*		
CRT vs. RT	3*	Survival	3	0.81 (0.67, 0.99; p=0.04)
		Local failure	2	0.54 (0.32, 0.90; p=0.02)
CRT vs. CT	3	Survival	3	0.96 (0.82, 1.13; p=0.64)
		Local failure	2	0.58 (0.38, 0.87; p=0.008)
CRT vs. CRT	8	*No pooling performed*		

Notes: CI, confidence interval; CRT, chemoradiotherapy; CT, chemotherapy; IV, intravenous; Obs, observation; RR, relative risk ratio; RT, radiotherapy; vs., versus.
* A fourth randomized trial was excluded from the meta-analysis. See details in Section 2 Part 2, page 11.

RELATED GUIDELINES

- Evidence-Based Series #2-29: Adjuvant Systemic Chemotherapy for Stage II and III Colon Cancer Following Complete Resection.
- Evidence-Based Series #17-4: Optimization of Surgical and Pathological Quality Performance in Radical Surgery for Colon and Rectal Cancer: Margins and Lymph Nodes.

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