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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
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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

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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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Evidence-based Series #2-4: Section 2. Part 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: Evidentiary Base: Part 1. Preoperative Therapy

R Wong, K Spithoff, M Simunovic, O Agboola, B Dingle, K Chan, 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: Document Review Summary and Tool for a summary of updated evidence published between 2008 and 2017, and for details on how this Clinical Practice Guideline was ENDORSED.

PRIMARY QUESTION

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

SECONDARY QUESTIONS

1. What is the relative effect of preoperative RT versus:
   a. surgery alone?
   b. preoperative chemoradiotherapy (CRT)?
   c. postoperative CRT?
2. What is the relative effect of preoperative CRT versus other preoperative or postoperative RT (with or without CT)?

Outcomes of interest include overall survival, cause-specific survival, recurrence-free survival, local recurrence, R0 resection, sphincter-preserving surgery, quality of life, acute toxicities, postoperative morbidity (within 30 days of surgery), and late toxicities (>90 days after surgery).

INTRODUCTION

Adenocarcinoma of the rectum is a common malignancy. Together with colon cancer, it is the second most common cancer site in males and the third most common site in females

in Ontario, with approximately 7800 new cases and 3250 deaths per year (1). The mainstay of therapy is surgery.

Since the early 1990s, patients in Ontario with rectal tumours that were stage II and III were advised to receive postoperative CRT, in an effort to avoid local tumour recurrence and improve survival (2,3). For similar treatment goals, certain jurisdictions in Europe have used preoperative RT alone for most patients with rectal cancer, regardless of stage (4-6). Two relevant practice guidelines developed by the Gastrointestinal Cancer Disease Site Group (GI DSG) have been completed and published. A guideline on postoperative RT and/or CT in resected stage II or III rectal cancer was first completed in 1997 and updated in 2001 (3). A preoperative RT guideline for clinically resectable rectal cancer was first completed in 2002 and then updated in 2004 (7). In addition, there have been several systematic reviews evaluating the effectiveness of preoperative RT in rectal cancer. For example, the Colorectal Cancer Collaborative Group conducted an individual patient meta-analysis of 19 randomised controlled trials (RCTs) on preoperative RT that started accrual after 1987 (8), and concluded that preoperative RT, at biological effective dose (BED) ≥30Gy, reduced the risk of local recurrence compared with no RT. Additionally, fewer patients who received preoperative RT died from rectal cancer compared to patients in the control group (45% versus [vs.] 50%; p=0.0003) and short preoperative RT schedules seemed to be at least as effective as longer schedules (including postoperative schedules).

There is evidence that an improved surgical technique for rectal cancer, referred to as total mesorectal excision (TME), dramatically reduces the risks of local and distant disease recurrence (9-13), and therefore may also reduce the potential benefit of preoperative RT. TME involves sharp dissection of the mesorectal fascia—the fascia that envelops the rectal regional lymph nodes. Many of the earlier trials included in published systematic reviews of preoperative RT for rectal cancer did not require TME, and it is difficult to assess whether the results observed in these trials would be similar in patients who do undergo surgery using TME principles. Single-institution case series from surgeons that practice TME report local recurrence risks in the single digits without the use of any CT or RT (9); however, at a multi-institutional or population level, the ability to achieve this deserves validation. For example, despite intense efforts by the investigators, patients in the Dutch TME trial did not always receive high-quality TME surgery. A pathology study by Nagtegaal et al (14) found that the quality of the rectal specimen was suboptimal in 43% of cases. The quality of the TME is important in determining the baseline risk for recurrence and the expected relative effect of preoperative or postoperative therapy.

Preoperative therapy is associated with morbidity risks; therefore, to avoid treating patients with little chance of benefiting from preoperative RT or CRT, appropriate and accurate staging is needed to determine whether or not a patient should be considered for preoperative therapy. A recent Ontario Diagnostic Imaging Guideline summarized evidence on the accuracy of preoperative staging tests for colorectal cancer (15). For rectal cancer, a positive test for tumour penetration through the bowel wall and into perirectal fat will be incorrect approximately 10% of the time with transrectal ultrasound, and 20% of the time with computerized axial tomography CAT scan, magnetic resonance imaging (MRI), or MRI with endorectal coil. A positive test for regional lymph node involvement with tumour will be incorrect approximately 30% of the time with transrectal ultrasound, CAT scan, or MRI, and 20% of the time with MRI with endorectal coil. Moreover, it should be recognized that the results of any imaging test are influenced by the expertise of the involved clinicians (i.e., tests are operator dependent) and this is likely truer for ultrasound than for CT or MRI. Clinical staging in the absence of these modalities would be even less reliable. The incorporation of transrectal ultrasound and/or MRI with endorectal coil to evaluate the T

stage, and the use of CT or MRI of the abdomen to exclude distant metastases is important for the identification of stage II and III patients, for whom the current guideline is intended.

Stage II and III patients are expected to achieve greater benefit from preoperative therapy than those with earlier stage disease. The GI DSG elected to undertake the current guideline to define the role of preoperative RT specifically for these patients, including the optimal way of integrating RT with CT and its relative role versus the postoperative RT approach. Due to the recent publication of a Cochrane review with meta-analysis on preoperative RT with curative surgery for all patients with localized rectal cancer (16), the GI DSG made the decision to use the Cochrane literature review as its evidentiary base rather than perform its own literature search for evidence published between 1966 and 2006. Randomized controlled trials (RCTs) included in the Cochrane review that met the inclusion criteria for this review were retrieved for further analysis in order to provide information specifically on stage II and III disease. A supplementary literature search was conducted to identify studies comparing preoperative CRT to other strategies that were not included in the Cochrane review.

METHODS

The evidence-based series (EBS) guidelines developed by Cancer Care Ontario's Program in Evidence-Based Care (PEBC) use the methods of the Practice Guidelines Development Cycle (17). For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by two members of the PEBC GI DSG and a methodologist.

This systematic review is a convenient and up-to-date source of the best available evidence on preoperative RT or CRT for the management of patients with clinical stage II or III resectable rectal cancer. The body of evidence in this review is primarily comprised of systematic reviews and mature RCT data. That evidence forms the basis of a clinical practice guideline developed by the GI DSG. The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Literature Search Strategy

For the comparison of preoperative RT with surgery alone or other preoperative or postoperative approaches, literature search results for 1966 to December 2006 were adopted from the published Cochrane review by Wong et al (16). The literature review was updated by searching entries to MEDLINE (December 2006 to May week 4 2007), EMBASE (to week 21, 2007), the Cochrane Library (Issue 2, 2007), and the proceedings of the 2007 ASCO meetings for relevant trial reports.

For the comparison of preoperative CRT with surgery or another preoperative or postoperative approach, the literature search strategy described in the Cochrane review was used and article selection was performed specifically to identify articles with preoperative CRT as one of the trial arms.

Relevant articles and abstracts were selected and reviewed, and the reference lists from these sources were searched for additional trials. A search of personal reprint files was also conducted.

Study Selection Criteria

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

1. The article reported on RCTs or systematic reviews of RCTs.

2. The RCT results were reported on patients with clinical stage II or III resectable rectal cancer, although the RCT could have included earlier stage patients. The original intention was to include only studies that involved earlier stage patients if they were stratified by stage. However, there were no studies that incorporated this stratification, so this criterion was modified to include studies where results were reported by stage.
3. The RCTs compared preoperative RT (with or without CT) to surgery alone or an alternative preoperative or postoperative therapy (e.g., preoperative CRT vs. preoperative RT).
4. The article reported on relevant outcomes as described below under the heading Outcomes of Interest.
5. The surgery received by the RCT patients was potentially curative. TME was not mandatory.
6. The RCT or systematic review was reported as a fully published report or published abstract.
7. The RCT or systematic review was reported in English, as translation resources were not available.

Outcomes of interest

The primary outcome of interest was overall survival. Secondary outcomes of interest were cause-specific survival, recurrence-free survival, local control, R0 resection, sphincter preserving surgery, quality of life, acute toxicities, postoperative morbidity (within 30 days of surgery), and late toxicities (>90 days after surgery). If no significant difference in the primary outcome of interest was demonstrated, secondary outcomes were examined to form conclusions. For the comparison of preoperative RT versus surgery alone, the studies using short-course treatments and therapy were not expected to downstage the tumour; therefore, circumferential radial margin (CRM) positivity and sphincter preserving surgery were not expected to differ between groups, and these outcomes were not reported for this comparison.

Statistical methods

Hazard ratios (HRs) were extracted directly from the most recently reported trial results where available. Where they were not reported, HR estimates with 95% confidence intervals (CI) were calculated from the available data, using the methods described by Parmar et al (18). For categorical outcomes, relative risks (RR) were reported. The HR and associated statistics were calculated, where necessary, using an Excel spreadsheet developed by the Matthew Sydes (Cancer Division) method in collaboration with the Meta-analysis Group of the MRC Clinical Trials Unit, London. An HR < 1.0 indicates that patients in the experimental arm had a lower probability of experiencing an event; conversely, an HR >1.0 suggests that patients in the control arm experienced a lower probability of an event.

The number needed to treat (NNT) was calculated from HRs, where appropriate, using the method recommended by Altman et al (19):

$$NNT = 1/[S_c(t)^h - S_c(t)]$$

where

S_c = survival outcome probability in the control group
h = hazard ratio comparing the treatment groups
t = specified time

NNT calculations are sensitive to the baseline risk. A 17% local recurrence rate was observed in the control arm (surgery alone) in the trial by Bosset et al 2004 (20). This was felt to be a

reasonable baseline overall risk for Ontario practice for illustration purposes and was used in calculations of NNT.

Synthesizing the Evidence

A meta-analysis of clinically homogeneous trial results and a sensitivity analysis for quality of TME and RT dose (higher versus lower) were planned. However, due to the limited number of RCTs reporting data for stage II and III rectal cancer in each comparison, the potential bias associated with a pooled estimate for this small subset of trials, and heterogeneity between trials, no meta-analyses were performed.

Study Quality Assessment

Assessment of study quality was performed by extracting key quality characteristics from published trial reports, including declaration of funding source, randomization method, patients' baseline characteristics, statistical power, achievement of target sample size, follow-up, and intention-to-treat (ITT) analysis. These quality characteristics are summarized in a table in Appendix 1. Using the published trial reports to assess quality is limited by the detail of the study methods that were reported by the authors. An assumption is made that if a method was not reported, it was not performed, but this may not be the case. In this systematic review, no attempt was made to contact any authors to clarify the methods reported in the included trials.

RT Dose

Because of the fact that the biological effect of RT dose fractionation varies as a combined effect of dose per fraction, the number of fractions, and the types of tissues under consideration (acute-reacting tissues and tumour versus late-reacting tissues), a method of integrating these components was necessary to facilitate comparison between the different regimens. The concept of BED has been widely employed for this purpose and was used for this review (21,22). BED can be calculated using the following equation:

BED = nd (1+d/a/b)

where

BED = biological effective dose
n= number of fractions
d = dose per fraction
a/b = 10 for tumour and acute reacting tissues
a/b = 3 for late reacting tissues,

where a/b reflects the sensitivity of the respective tissues to radiation injury.

To take into account the effect of altered fractionation regimen, (e.g., multiple fractions per day), a modification of this equation was used for the current document:

BED = nd (1+d/a/b) - Ln2(T-Tk)/ aTp

where

BED = biological effective dose
n= number of fractions
d = dose per fraction
a/b = 10 for tumour and acute reacting tissues
a/b = 3 for late reacting tissues
T = overall time of treatment in days
Tk = time after the start of irradiation when compensatory proliferation begins (estimated to be seven days)
a = average intrinsic radiosensitivity of mucosal basal cells (estimated to be 0.35Gy-1)
Tp = average time of basal cell number doubling (estimated to be 2.5 days) (22,23).

RESULTS

Literature Search Results

Systematic Reviews of RCTs for All Resectable Rectal Cancer

Eight systematic reviews (4,7,16,24-27), including the original version of the PEBC preoperative RT for rectal cancer guideline (7), and the Cochrane review (16), were identified. The Cochrane review focused on preoperative RT versus surgery but also included preoperative RT versus other preoperative or postoperative strategies for resectable rectal cancer. As the Cochrane review was the most recent and most comprehensive of the identified systematic reviews, only the results of this review are discussed further in the current document. Nineteen randomized trials were included in the Cochrane review that compared preoperative RT versus surgery, nine of which compared preoperative RT versus other preoperative or postoperative approaches (Table 1).

The focus of the current review is on patients with stage II and III rectal cancer. However, in selected areas (e.g., preoperative RT vs. surgery alone) trials were almost exclusively designed to include all resectable disease. Within this context, the evidence as it relates to all resectable rectal cancer remains important, while subgroup data limited to stage II and III disease provide additional information to refine the data interpretation as it may apply to the target population. The Cochrane review provided a detailed analysis of the data and a summary of the findings is described. Abbreviations for the names of any cooperative clinical trials groups are provided in Section 2. Part 2, Appendix 3.

RCTs of Stage II or III Rectal Cancer

Six trials fulfilled our inclusion criteria. Only two of the nineteen randomized trials comparing preoperative RT with surgery (5,6) and the three trials comparing preoperative RT with other postoperative or preoperative approaches (20,28,29) included in the Cochrane review met our inclusion criteria (Table 1). Long-term follow-up data have been published for one trial (5) since the publication of the Cochrane review; however, no data are reported specifically for stage II and III patients (30).

Through our supplemental search, one trial comparing preoperative CRT with other preoperative or postoperative strategies, a subject outside the scope of the Cochrane review, was identified that met the inclusion criteria (Sauer et al in 2004, CAO/ARO/AIO94) (31).

Five other trials were identified that did not meet the inclusion criteria but warranted some explanation for their exclusion. Two trials comparing preoperative CRT with postoperative CRT were initiated, (INT 0147 [32] and NSABP-R03 [33]), but were closed early due to poor accrual, and no results are available. Details for these two trials are reported in Appendix 2. The third and fourth trials (34,35) identified investigated whether novel methods (unconventional RT or newer CT agents) of delivering preoperative CRT could improve outcomes but were excluded based on methodological concerns; a randomized phase II trial not designed to make statistical comparisons, conducted by the Radiation Therapy Oncology Group (RTOG) (34), and a trial by Kim et al that included only 14 patients per group and was therefore highly underpowered to detect a difference in outcome (35). Finally, the fifth trial (Studio Terapoa Adivante Retto [STAR]-01) compared intravenous (IV) 5FU with IV 5FU plus oxaliplatin as the CT regimen in combination with RT (36). This trial is reported in the Ongoing Trials (Appendix 3), as only toxicity data in abstract form for a subgroup of patients have been reported to date.

Tables 2 through 4 summarize the trial characteristics (a-tables) and key outcomes (b-tables) for preoperative RT versus surgery alone (Tables 2a and 2b), preoperative RT versus

CRT (Tables 3a and 3b), and preoperative RT versus other approaches (Tables 4a and 4b), respectively.

Table 1. Included studies.

Treatment	Control	No. of studies in Cochrane review	Studies reporting data for Stage II/III patients	Table
Preoperative RT vs. Surgery alone				
Preoperative RT	Surgery alone	19	Kapiteijn 2001 (5) Swedish 1997 (6)	2
Preoperative RT vs. Other				
CRT	Preoperative RT	5	Bujko 2004 (28) Bosset 2004 (20) Gerard 2005 (29)	4
Selective postoperative CRT	Preoperative RT (short)	2	-	-
Preoperative RT (long interval to S)	Preoperative RT (short interval to S)	1	-	-
Preoperative RT (lower dose)	Preoperative RT (higher dose)	1	-	-
Preoperative CRT vs. Postoperative CRT				
Preoperative CRT	Postoperative CRT	NA	Sauer 2004 (31)	5
Preoperative CRT vs. CRT				
Preoperative CRT	Preoperative CRT	NA	-[a]	-

Notes: CRT, chemoradiotherapy; NA, not applicable; No., number; RT, radiotherapy; S, surgery.
a Two studies identified in the literature search for this comparison were not included due to methodological limitations (34,35)

Study Quality

In general, the six RCTs included in this review were of high quality (See Appendix 1). None of the five trials that reported the source of funding was funded by pharmaceutical companies (5,6,20,28,31). Adequate randomization methods were described in five trials (5,6,20,28,31) and were not reported in one trial (29). Sauer et al (31) reported significantly more patients with tumours 5 cm or less from the anal verge in the preoperative therapy group compared with the postoperative therapy group, and the Swedish Rectal Trial (6) reported an unbalanced distribution of tumour stage. All six RCTs reported statistical power calculations and target sample size, and these targets were met in five trials (5,6,20,28,31). The target number of deaths was not reached in one trial (29). Median follow-up ranged from two years (5) to 13 years (6). One trial used an ITT analysis approach and analyzed all randomized patients, including those who were found to be ineligible after randomization (20). Two trials analyzed all eligible patients according to the group to which they were randomized (5,28), one trial analyzed all eligible patients except for six patients who were lost to follow-up (29), one trial analyzed all eligible patients except for nine patients who withdrew consent (31), and one trial analyzed only eligible patients who underwent surgery (6). In this last trial, 1147 patients were randomized, 21 patients were ineligible , and 37 patients did not undergo surgery. Similar numbers of patients were excluded from each treatment arm.

Outcomes

Preoperative RT versus Surgery Alone

Cochrane Review

Nineteen RCTs were identified in the Cochrane review (16) that compared preoperative RT to surgery alone for patients with resectable rectal cancer. There was a modest survival benefit for preoperative RT (HR, 0.93; 95% CI, 0.87-1.00; p=0.04) (14 studies). This translates into an approximately 2% improvement in survival (e.g., from 60% to 62% at eight years). Cause-specific mortality (HR, 0.87; 95% CI, 0.78-0.98; p=0.02) (five trials) and local recurrence also significantly favoured preoperative RT (HR, 0.71; 95% CI, 0.64-0.78;

p<0.00001; NNT, 22; 95% CI, 17-29, assuming a control group local recurrence rate of 17%[1] at five years), although significant heterogeneity across studies was detected for the latter.

There was no significant difference between preoperative RT and surgery alone for curative resectability (RR, 1.02; 95% CI, 1.00-1.05; p=0.06) or sphincter-sparing surgery (RR, 0.94; 95% CI, 0.88-1.04; p=0.3) (15 trials), although both favoured preoperative RT.

Adverse effects were poorly reported in the available RCTs (16). The proportion of patients with no acute adverse effects from RT varied from 20% to 84%, with the most common adverse effect being diarrhea (20%). The proportion of patients with no acute adverse effects after surgery was significantly higher in the surgery-alone group (RR, 0.88; 95% CI, 0.82-0.94; p=0.0002). The incidence of specific toxicity types did not differ significantly between treatment groups, except for pelvic or perineal wound infection, which occurred more frequently in patients who received preoperative RT. Late toxicities were reported in only four RCTs, and late rectal and sexual dysfunctions were significantly more common in patients who received preoperative RT.

RCTs of Stage II or III Disease

Two of the 19 trials included in the Cochrane review presented outcomes separately for stage II and III patients: the Dutch trial by Kapiteijn et al (5) and the Swedish trial (6) (Tables 2a and 2b). Neither trial incorporated stratification by clinical stage as part of the study design. The attempt at examining outcomes for stage II and III patients is subject to bias and should only be considered as supportive evidence. Both trials compared short-course RT (25Gy in 5 fractions) plus surgery to surgery alone, with an interval of one week between RT and surgery. In the Swedish trial (6), TME was not a specified requirement but was in Kapiteijn (5).

The proportion of patients with stage II and III disease were 50% of patients for the Swedish trial (6) and 60% for the Kapiteijn trial (5). There were no significant differences between preoperative RT and surgery alone in overall survival or cause-specific survival for stage II or III patients in the Swedish trial (6). Neither of the trials reported recurrence-free survival; however, both trials demonstrated a significant benefit for local recurrence for stage II and III patients. These observations are consistent with those for preoperative RT including all stages. The magnitude of benefit for local control may be higher when considering stage II and III patients only.

[1] NNT calculation is sensitive to the baseline risk. A 17% local recurrence rate was observed in the control arm (surgery alone) in Bosset 2004 (20) and was used as the baseline risk, assuming this is representative of clinical practice in the population of interest.

Table 2a. Randomized trials of preoperative RT versus surgery alone in stage II/III patients: study characteristics.

Trial	Inclusion criteria	N	Stage				Type of Surgery	RT dose	Median Follow-up
			I	II	III	Other[a]			
Swedish 1997 (6,37)	Location: below sacral promontory resectable	RTS: 583 S: 585	174 147	157 150	123 157	129 131	AP/anterior resection TME:not specified	25Gy in 5 fr BED: 38.7Gy[10]	13 years (Range 11.5-15 years)
Kapiteijn 2001 (5)	Location: below S1-2, Within 15cm from anal verge, resectable	RTS: 924 S:937	265 244	252 245	300 324	107 124	AP/anterior resection TME: yes[b]	25Gy in 5 fr BED: 38.7Gy[10]	24.9 months (Range 1.1-56 months)

Notes: AP, abdominoperineal; BED, biological effective dose; fr, fractions; Gy, gray N, number of patients randomized; RT, radiotherapy; RTS, radiotherapy plus surgery; S, surgery; TME, total mesorectal excision;.

a For the Swedish trial, "other" included non-curatively-resected and ineligible patients. For Kapiteijn et al, "other" included ineligible, stage IV, and unresected patients.

b TME quality review was not performed for all patients.

Table 2b. Randomized trials of preoperative RT versus surgery alone in stage II/III patients: Outcomes.

Trial	Treatment	N	Overall Survival			Cause-specific survival			Local recurrence		
			%	HR (95% CI)	p value	%	HR (95% CI)	p value	%	HR (95% CI)	p value
Swedish 1997 (6,37,38)			overall								
Stage II	RTS	157	38	0.86 (0.65-1.13) [a]	**p=0.27**	69	0.78 (0.54-1.13) [a]	**p=0.19**	6[b]	**0.36 (0.2-0.66)** [a]	**p<0.001**
	S	150	30			59			22		
Stage III	RTS	123	18	0.84 (0.65-1.09) [a]	**p=0.18**	56	0.93 (0.66-1.32) [a]	**p=0.7**	23[b]	0.52 (0.35-0.76) [a]	p<0.001
	S	157	16			52			46		
Kapiteijn 2001 (5)											
Stage II	RTS	252	NR			NR			1.0 [c]	0.29 (0.11-0.75) a	p=0.01
	S	245							5.7		
Stage III	RTS	300							4.3 [c]	0.43 (0.26-0.70) a	p<0.001
	S	324							15.0		

Notes: CI, confidence interval; N, number of patients evaluated; S, surgery; RTS, radiotherapy plus surgery; HR, hazard ratio; NR, not reported.

a Estimated from p value and outcomes based on published data.

b Cumulative local recurrence rate with a median follow-up of 13 years

c 2-year local recurrence rate

Toxicity data are not reported separately for stage II and III patients in either the Kapiteijn or the Swedish trials (5,6). However, the observation of higher risk of acute perineal complications in the acute setting, and late toxicities affecting daily activity, including sexual activity, rectal function, and need for hospital admissions for complications, are expected to be similar to patients with all stages of disease who entered the studies.

The Swedish 1997 RCT provided data on long-term rectal function (38,39). There were more patients with increased stool frequency (20% vs. 8%) and continence problems (50% vs. 24%) (39). The randomized trial by Kapiteijn et al (5) (n=1530) compared health-related quality of life and sexual function between the treatment arms (41). Analysis was based on 990 eligible patients. Health-related quality of life (as measured by the Rotterdam Symptom Checklist) improved over time but did not differ significantly between the treatment arms except on the activity scale. Similarly, there was no treatment effect in the defecation scale. However, sexual function was significantly worse for both males and females. The economic impact of rectal cancer and the effect of preoperative RT were reported for the same trial (40). Of the 292 eligible patients who had paid labour before treatment (total trial sample, 1530), only 61% resumed work at 24 months. Irradiated patients tended to resume work later than non-irradiated patients (between six and 12 months later), although there was no difference after 18 months (40) (Table 3).

Table 3. Summary of key adverse effects for preoperative RT versus surgery alone.

Trial (reference)	Adverse effect	Results
Swedish 1997 (6,38) [a]	Perioperative mortality	4% (RT) vs. 3% (no RT), p=0.3
	Hospital admission during first 6 months from primary treatment	184/572 (RT) vs. 107/575 RR=1.64 95%CI 1.2-2.2 (p=<0.01) [b]
	Late (>6m) hospital admissions after primary treatment	320/572 (RT) vs. 283/575 (p = 0.01). RR not significant.
	Bowel obstruction during late (>6m) hospital admission	42 (RT) vs. 20 RR 1.88 95% CI 1.1-3.2 (p=0.02)
(39) [c]	Median bowel frequency per week	20.5 (RT) vs. 10.0
	Incontinence of loose stool	50% (RT) vs. 24% (p<0.001)
	Urgency with toilet dependence	30% (RT) vs. 6% (p<0.001)
	Emptying difficulties	52% (RT) vs. 36% (p<0.05)
	Impaired social life because of bowel function	30% (RT) vs. 10% (p<0.01)
Kapiteijn 2001 (5,41) [d]	Perineal complications	26% (RT) vs. 18% (p=0.05)
	Defecation scale (in low anterior resection patients)	QoL score 28.7(RT) vs. 29.6 (postoperatively) QoL score 20.8 (RT) vs. 19.5 (at 2 years) p=0.007 for difference in time effect
	Males sexually active (in pts sexually active pts preoperatively [80%])	67% (RT) vs. 76% (p=0.06)
	Females sexually active (in pts sexually active pts preoperatively [52%])	72% (RT) vs. 90% (p=0.01)

Notes: CI, confidence interval; pts, patients; QoL, quality of life; RR, relative risk; RT, radiotherapy; vs, versus..

a Obtained by matching Swedish hospital discharge register with disease-free patients. Minimum time from trial entry 11 years. Analysis of 908 of 1147 patients originally randomized. Data reported at 5 years.

b Difference due to higher rate of infections and gastrointestinal diagnoses in the radiotherapy group compared with the surgery alone group.

c Obtained via mailed questionnaire. Questionnaires were sent to patients who were alive at 5 years (220), of a total sample size of 1168. Responses were received from 171 patients.

d Rotterdam Symptom checklist administered to Dutch patients only (n=1530) (total trial sample 1961) after informed consent, excluding patients with any recurrence during the evaluation period (n = 990). Data collected to 24 months.

Preoperative RT versus Preoperative CRT

Cochrane Review

The Cochrane review by Wong et al (16) identified five RCTs comparing preoperative RT to preoperative CRT, all with 5FU. None of the trials reported a significant difference between treatment groups in overall survival, disease-free survival, or rate of sphincter-sparing surgery. One trial reported significantly higher local recurrence for patients in the preoperative RT-alone arm compared to patients who received preoperative RT plus CT either preoperatively, postoperatively or both. Two RCTs reported higher acute toxicity in the CRT arm compared to the RT-alone arm. No meta-analysis was performed to determine an overall estimate of effect for the addition of CT to RT.

RCTs of Stage II or III Disease

Three of the trials included in the Cochrane review (16) compared preoperative RT with preoperative CRT specifically for stage II and III patients and were included (20,28,29). Two trials addressed the question of a) the role of CT when added to standard fractionation longer course RT (45-50.4 Gy in 25-28 fractions), and one trial addressed b) the relative effect of hypofractionated (short course, 25 Gy in 5 fractions) RT versus CRT conventional fractionation (longer course). TME was recommended in two studies (20,29) and required in the third trial (28), although no trials required a review of the quality of the TME.

a) What is the role of adding CT to standard fractionation longer course RT?

Two studies addressed the addition of CT to standard fractionation (longer course CRT. Bosset et al (EORTC 22921) (20) employed a 2x2 design where the RT was standard for all treatment arms (45Gy in 25 fractions), varying between arms by the way CT was delivered (no CT and preoperative concomitant CT, postoperative CT, or both). Gerard et al (FFCD0203) (29) compared the same RT (45Gy in 25 fractions) with or without CT. Bosset et al required the use of TME, while Gerard et al recommended TME within the protocol (Table 4a).

The addition of CT to standard fractionation RT reduced local recurrence and resulted in higher complete pathological response rates in both trials (Table 5b). There was no significant effect on overall survival or relapse-free survival in either of the trials. These results were accompanied by increased acute toxicities in patients who received CRT. In terms of local recurrence, the absolute recurrence rates for the RT-alone arms were similar at approximately 17%. Results from Gerard et al (29) demonstrated a significantly lower local recurrence rate for patients who received preoperative CRT compared with those who received RT alone (8.1% vs. 16.5%; p=0.004). Furthermore, results from Bosset et al (20) suggest that the timing of the CT is less critical in terms of the local recurrence, with similar local recurrence rates whether CT is delivered concomitantly with RT, postoperatively, or both. Local recurrences rates were 8.7%, 9.6%, and 7.6%, respectively (Table 4b).

Complete pathological response rates in the preoperative RT-alone arms (with 45Gy in 25 fractions; BED, 36.5Gy^{10}) was 4% to 5% in the two trials. With the addition of CT, complete response was significantly increased (11% in one trial [29] and 14% in the second trial [20]). Adverse effects data are reported in Table 5.

b) What is the relative effect of hypofractionated (short course) RT versus CRT conventional fractionation (longer course)?

One trial investigated the effect of short-course RT versus CRT with conventional fractionation for patients with stage II and III rectal cancer (28). Bujko et al compared 25Gy in 5 fractions (BED 38.7Gy^{10}) with 50.4Gy in 28 fractions (BED 40.9Gy^{10}) with CT (5FUFA x 2 cycles). The longer course CRT provided a lower incidence of positive circumferential margins and a higher incidence of complete pathological response rate; however, this was

accompanied by a higher risk of acute toxicities but a non-significant trend in favour of CRT in terms of late toxicities. There was no significant effect on overall survival, relapse-free survival, or local recurrence rates.

A lower incidence of positive circumferential margin appears to be the most important benefit of adopting the longer CRT regimen over the shorter 25Gy in 5 fractions. The rate of positive circumferential margin was reduced from 12.9% to 4.4% ($p=0.017$). The rate of acute grade 3/4 toxicities increased from 3% to 18% ($p<0.001$) (28) (Table 5).

Table 4a. Randomized trials of preoperative RT versus preoperative CRT in stage II/III patients: study characteristics.

Trial	Inclusion criteria	N	CT	Type of Surgery	RT dose	Median Follow-up
a) What is the role of adding CT to longer course RT?						
Bosset 2006 (20)	Location: within 15 cm from anal verge T3-4Nx resectable	RT: 252 CRT: 253 RT+postopCT: 253 CRT+postopCT: 253	Arm 1: no CT Arm 2: preop 2 cycles (conc) Arm 3: postop 2 cycles Arm 4: pre 2 cycles (conc) and postop 2 cycles 5FU 350mg/m2/dx5d FA 20mg/m2/dx5d	AP/anterior/Hartman TME: recommended beginning in 1999 [a]	45Gy in 25 fr BED: 37.5Gy[10]	5.4 years
Gerard (FFCD92-03) 2006 (29)	Location: accessible by digital exam T3-4Nx resectable	CRT: 375 RT: 367	CRT: preop 2 cycles (conc) (+postop x4cycles) RT: preop no CT(+postop x4cycles) 5FU 350mg/m2x5d FA 20mg/m2x5d	TME: Recommended [a]	45Gy in 25fr BED: 37.5Gy[10]	81 months
b) What is the relative effect of short course RT vs. longer course CRT?						
Bujko 2006 (28)	Location: inferior edge palpable on digital exam T3-4 resectable	CRT: 157 RT: 155	CRT: preop x2cycles RT: no CT 5FU 325mg/m2/dx5d FA: 20mg/m2/dx5d	AP/anterior resection/Hartman TME: yes [a]	CRT: 50.4Gy in 28fr BED: 40.9Gy[10] RT: 25Gy in 5fr BED: 38.7Gy[10]	48 months (Range 31-69 months)

Notes: 5FU, 5-fluorouracil; AP, abdominoperineal; BED, biological effective dose; conc, concurrent with radiation; CRT, chemoradiotherapy; CT, chemotherapy; FA, folinic acid; fr, fractions; Gy, gray; N, number of patients randomized; RT, radiotherapy; TME, total mesorectal excision..

[a] No TME quality review was performed.

Table 4b. Randomized trials of preoperative RT versus preoperative CRT in stage II/III patients: outcomes.

Trial	Treatment	N	Overall survival			Recurrence-free survival			Local recurrence			Complete pathologic response (%)	CRM+ (%)	Sphincter preserving surgery (AR) (%)
			%	HR (95% CI)	p value	%	HR (95% CI)	p value	% (95% CI)	Risk (95% CI)	p value			
a) What is the role of adding CT to longer course RT?														
Bosset 2006 (20,44) EORTC22921	CRT[a]	506	65.8	1.02 (0.83-1.26)	p=0.84	56.1[c]	0.84 (0.78-1.13)	p=0.52	CRT: 8.7 (4.9-12.6) RT+ postop CT: 9.6 (5.7-13.5) CRT+postopCT: 7.6 (4.2-11.0) RT: 17.1 (12.3-21.9)	NR	RT vs. others p = 0.002	13.7	8.5	52.8
	RT[b]	505	64.8			54.4[c]						5.3	8.5	50.5
												p<0.0001		p=0.47
												OR 2.84 (1.75-4.59)		
Gerard 2006 (29) FFCD92-03	CRT	375	67.4	0.96 (0.73-1.27)	p=0.684	59.4	0.96 (0.77-1.20)	p=0.96	8.1	RR 0.5 (0.31-0.80)	p=0.004	11.4	6.2	52.4
	RT	367	67.9 (5-year)			55.5 (5-year)			16.5			3.6	6.8	54.4
												p<0.0001	p=0.132	
b) What is the relative effect of short course RT vs. longer course CRT?														
Bujko 2006 (28)	CRT	157	66.2	1.0 (0.69-1.48)	p=0.960	55.6	0.96 (0.69-1.35)	p=0.820	15.6	HR 0.65 (0.32-1.28)	p=0.210	16.1	4.4	58.0
	RT	155	67.2			58.4			10.6			0.7	12.9	61.2
													p=0.017	p=0.57

Notes: AR, anterior resection; CRM, circumferential radial margin; CRT, chemoradiotherapy; CT, chemotherapy; HR, hazard ratio; N, number of patients evaluated; OR, odds ratio; RR, relative risk;. RT, radiotherapy.
a Includes CRT and CRT+postopCT.
b Includes RT and RT+postopCT.
c Disease-free survival.

Table 5. Summary of key adverse effects for preoperative RT versus preoperative CRT.

Trial (reference)	Adverse effect	Results
Bosset (20,43)	Perioperative deaths	2/400 (0.5%) (CRT) vs. 1/398 (0.3%) (RT); not significant
	Adverse effects grade ≥2	217/400 (54%) (CRT) vs. 150/398 (38%); p<0.005
	Late adverse effects	No difference between groups
Gerard (29)	Postoperative death	2% in each arm
	Overall grade 3/4 acute adverse effects	14.9% (CRT) vs. 2.9%; p<0.0001
	Non-hematologic grade 3/4 acute adverse effects	13.5% (CRT) vs. 2.2%
	Late adverse effects	Data not available
Bujko (28)	Grade 3/4 acute adverse effects	18.2% (CRT) vs. 3.2%; p<0.001
	Overall late adverse effects	27% (CRT) vs. 28.3%; RR=1.05 (95% CI, 0.72-1.53; p=0.810)
	Severe late adverse effects	7.1% (CRT) vs. 10.1%; RR=1.43 (95% CI, 0.67-3.07; p=0.360)

Notes: CRT, chemoradiotherapy; RT, radiotherapy; RR, relative risk; CI, confidence interval.

Preoperative RT versus Selective Postoperative RT (with or without CT)

Cochrane Review

Two RCTs (45,46) were identified in the Cochrane review that compared short-course preoperative RT with selective postoperative therapy for patients with resectable rectal cancer (16).

Frykholm et al compared preoperative RT (25Gy in 5 fractions) with selective postoperative RT (40Gy in 20 fractions, one-week gap, 20Gy in 10 fractions) (no CT) for patients with Dukes B or C tumours (45). There were no significant differences between treatment groups in cause-specific mortality or late toxicity but a significant benefit for preoperative RT in local recurrence (HR 1.76 [95% CI 1.11-2.78]) with absolute event rates of 13% (preoperative RT) versus 25% (selective postoperative RT). TME was not specified.

MRC CR07 2006 randomized 1350 patients in a comparison of short-course preoperative RT (25Gy in 5 fractions) with selective postoperative CRT (45Gy in 25 fractions with 5FU) for patients with positive margins (<1mm) (46). TME was a specified requirement. Preliminary results reported in abstract form showed no overall survival difference between treatment groups; however, there was a significant benefit for local recurrence rate in favour of preoperative RT (HR, 2.47; 95% CI, 1.61-3.79; absolute event rates 4.7% preoperative RT vs. 11.1%). Similarly, there was a benefit for preoperative RT in disease-free survival (HR ,1.31; 95% CI, 1.02-1.67). Longer term results from this trial are pending.

RCTs of Stage II or III Disease

Neither of the two studies included in the Cochrane review that compared preoperative RT versus selective postoperative therapy fulfilled our inclusion criteria. Data restricted to stage II and III patients were not separately reported by Frykholm (45), and full reporting for the MRC CR07 2006 trial (46), and whether there is separate reporting relevant to stage II and III patients, is still pending.

Preoperative CRT versus Other Postoperative Approaches

This topic was beyond the scope of the Cochrane review of preoperative RT. One trial was identified in this category, addressing the relative effectiveness of preoperative versus postoperative equivalent CRT (31).

RCTs of Stage II or III Disease

How does preoperative CRT compare with postoperative CRT (similar CRT)?

One randomized trial by Sauer et al compared a preoperative CRT versus a postoperative CRT approach and reported results for patients with stage II and III disease (31) (Table 6). This trial was not included in the Cochrane review because CT was not equivalent between the trial arms (16). RT was 50.4Gy in 28 fractions (BED 40.9Gy^{10}) in the preoperative setting, with an additional boost of 5.4Gy in 3 fractions (BED 44.2Gy^{10}) in the postoperative setting. CT was given concomitantly with the RT on weeks one and five. In addition, postoperative CT (4 cycles) was given.

Despite the intention to accrue clinical T3-4 or node-positive patients only, 18% of patients were TNM pathological stage I in the postoperative CRT group. Compliance to preoperative and postoperative approaches also differed significantly. The proportion of patients who completed a full dose of RT as per protocol was 92% (preoperative) versus 54% (postoperative), and for CT, this was 89% (preoperative) versus 50% (postoperative).

The key benefit observed was in local recurrence rates, favouring preoperative CRT. In addition, there was a benefit for the likelihood of achieving complete pathological response, although the absolute event rate was small. There were no significant differences in overall survival, relapse-free survival, or sphincter-preserving surgery. The toxicity profile was in favour of preoperative CRT.

The local recurrence rate for preoperative versus postoperative CRT was 6% versus 13% (RR, 0.46 [0.26-0.82]; p=0.006). The complete pathological response rate for preoperative CRT was 8%. Acute grade 3/4 toxicity was 27% in the preoperative group versus 40% in the postoperative group (p=0.001), and late grade 3/4 toxicities were 14% versus 24% (p<0.01) (31).

Table 6a. Randomized trial of preoperative CRT versus a postoperative approach in stage II/III patients: study characteristics.

Trial	Inclusion criteria	N	Preoperative regimen		Postoperative regimen		Type of Surgery	Median Follow-up
			CT	RT	CT	RT		
Sauer (CAO/ARO/AIO-94) 2004 (31,47)	Rectal cancer T3/4, or node positive using endoscopic ultrasound and CT Within 16 cm of anal verge.	421 preop 402 postop	5FU infusion wk 1 & 5 + Postoperative 5FU x4 cycles	50.4Gy in 28fr BED=40.9Gy[10]	5FU infusion wk 1 & 5 + 5FU x4 cycles	50.4Gy in 28 fr + 5.4 Gy in 3 fr boost to tumour bed BED = 44.2 Gy[10]	TME with specified standardized technique (no QA)	46 months (Range 3-102) Recruiting patients

Notes: 5FU, 5-fluorouracil; BED, biological equivalent dose; CT, chemotherapy; fr, fractions; Gy, grays; N, number of patients evaluated; QA, quality analysis; RT, radiotherapy; wk, week; TME, total mesorectal excision; .

Table 6b. Randomized trial of preoperative CRT versus a postoperative approach in stage II/III patients: Outcomes

Trial	Treatment	N	Overall survival			Disease-free survival			Local recurrence			Complete pathological response	CRM+	Sphincter preserving surgery (AR)
			%	HR (95% CI)	p value	%	HR (95% CI)	p value	%	RR (95% CI)	p value			
Sauer (CAO/ARO/ AIO-94) 2004 (31,47)	Preop CRT Postop CRT	421 402	76 74 (At 5 years)	0.96 (0.70-1.31)	p=0.8	68 65 (At 5 years)	0.87 (0.67-1.14)	p=0.32	6 13 (At 5 years)	0.46 (0.26-0.82)	p = 0.006	33/415 [a] 0/384 p<0.001	2% 3%	286/415[b] 273/384 p=0.45

Notes: AR, anterior resection; CI, confidence interval; CRM, circumferential radial margin; CRT, chemoradiotherapy; HR, hazard ratio; N, number of patients evaluated; vs., versus..

a Response data reported according to treatment given.

b Authors also reported sphincter preserving surgery in the subgroup deemed necessary to have AP resection preoperatively: 45/116, 39% (preoperative) vs. 15/78, 19%(postoperative); p = 0.004.

DISCUSSION

The ability to provide more accurate preoperative clinical staging with the use of endoscopic ultrasound and MRI has modified the way we approach rectal cancer patients beyond what can be directly inferred from RCTs. Similarly, our understanding of the relationship between the quality of TME surgery and its impact on treatment outcomes is evolving and cannot be directly inferred from existing clinical trials for application in clinical practice.

The limited evidence available specifically for clinical stage II and III rectal cancer patients would dictate that the best evidence for the role of preoperative therapy has to be inferred from the data for all stages. It does appear through our subgroup analysis that there is a possibility that the local control benefit may be further augmented in stage II and III patients, a positive result given the higher risk of local recurrence in such cases.

Table 7 provides a summary of the comparisons, key outcomes, and whether a significant difference was found for patients with stage II and III disease.

Table 7. Summary of key comparisons and outcomes for patients with stage II and III rectal cancer.

Comparison (Reference)	OS	LR	PCR	CRM+	Sphincter Preservation	Acute Adverse Effects[a]	Late Adverse Effects[a]
RT vs. S (5,6)	NS	p<0.05	--	--	--	p<0.05[b]	p<0.05[b]
Longer CRT vs. longer RT (20,29)	NS	p<0.05	p<0.05	NS	NS	p<0.05[c]	--
Longer CRT vs. short RT (28)	NS	NS	--	p<0.05	--	p<0.05[c]	--
Preop CRT vs. postop CRT (31)	NS	p<0.05	p<0.05	--	NS	p<0.05	p<0.05

Notes: OS, overall survival; RFS, relapse-free survival; LR, local recurrence; PCR, pathologic complete response; +CRM, positive circumferential radial margin; RT, radiotherapy; S, surgery; CRT, chemoradiotherapy; preop, preoperative; postop, postoperative; CT, chemotherapy.
a Results for all patients, not only stage II and III disease.
b Favours surgery alone.
c Favours RT without CT.

Data for all patients with resectable rectal cancer indicate that preoperative RT results in a marginal survival benefit of 2% (assuming an expected survival rate of 60%) and a significant improvement in local control compared with surgery alone, but no significant benefit was detected for resectability or sphincter-preserving surgery (16). It should be noted that most of the trials on preoperative RT predate the use of TME-type surgery, and thus one cannot conclude that, if optimal surgery is provided, RT will confer even this marginal survival benefit. Although the Dutch TME trial did go to some lengths to promote proper surgical technique, not all patients received high-quality TME surgery (14). Our analysis of data specifically for patients with stage II and III disease confirmed that the use of preoperative RT decreases the risk of local recurrence in patients with stage II and III disease (5,6); however, no benefit in overall survival or cause-specific survival was demonstrated in the limited data available.

Potential improvements in local control with preoperative RT must be balanced against a greater risk for both acute adverse effects, including pelvic or perineal wound infection, and late adverse effects, including stool frequency and incontinence problems, pelvic fractures, and worsening sexual function. For example, irradiated patients in the Dutch TME trial reported significantly increased rates of fecal incontinence (62% vs.38%) and pad wearing as a result of incontinence (56% vs.33%) compared with patients who received

surgery alone (53). Similarly, 30% of patients who received RT in the Swedish trial reported restrictions in social life because of impaired bowel function compared with 10% of patients in the surgery-alone arm (39). A retrospective cohort study of registry data reported that older women who received RT to the pelvis were at a higher risk for pelvic fracture compared with those who were not irradiated (HR, 1.65; 95% CI, 1.33-2.05) (54). The increased risk for adverse effects should be considered in the decision to administer RT.

What is the role for the addition of CT with standard fractionation (longer course, 45-50.4Gy in 25-28 fractions) RT, specifically in stage II and III patients undergoing TME surgery? There is strong evidence from two trials (20,29), involving a total of 1700 patients, that the addition of CT, compared with RT alone, further enhances local control and the likelihood of achieving a pathological complete response, although at the price of greater acute toxicities. In one trial, it is suggested that the timing of the CT is less important, with benefit observed when CT is given concomitantly, postoperatively, or both (20). However, given the fact that there is a higher pathological complete response rate with concomitant preoperative CRT, it is likely preferable to select the option of CRT concomitantly. Conversely, in certain patients where CT or CT combined with RT will likely result in significant acute toxicities, potentially impairing the patients' ability to complete definitive surgery, one should consider delivering RT alone or deferring CT to the postoperative period.

What is the relative merit of a shorter versus longer course (standard fractionation) preoperative RT? Shorter course RT typically refers to 25Gy in 5 fractions, while longer course (standard fractionation) refers to 1.8 to 2 Gy daily fractions, such as 45Gy in 25 fractions. The biological equivalent dose for these two regimens is in fact quite similar, being $38.7Gy^{10}$ and $37.5Gy^{10}$, respectively. In addition to differences in overall treatment time, the larger dose per fraction predicts for a higher risk of late toxicities. The shorter fractionation is typically followed by surgery within 10 days of the initiation of RT, while the longer course of treatment is typically delivered with CT followed by surgery approximately four to six weeks after completion of RT or CRT. No trial has explored combining CT with the shorter fractionation RT. Shorter versus longer fractionations of RT alone have not been compared directly. Bujko et al (28) compared short-course RT versus long-course CRT (2 cycles). There were no significant differences in key outcomes, including overall survival, relapse-free survival, local recurrence rates, or late toxicities. There were more acute toxicities when using CRT but a higher risk of a positive circumferential margin in the RT-alone arm, although this was not paralleled by an increase in local recurrence rates. Despite the equivalent results on major outcomes, there remains some rationale in favour of the longer course, used in combination with CT, that requires consideration until further evidence is available. It should be noted that, in this trial, there was a relatively small number of patients with tethered tumours (19%) and low lying rectal lesions (abdominoperineal resection rate 35%). ,The limited generalizability of the trial results to patients where positive margins and risk of local recurrence is of greatest concern cannot be ignored. With the superior outcome demonstrated by incorporating CT in the treatment, the use of preoperative long-course CRT represents an approach that can derive the maximal relative benefit. However, for patients where acute toxicities are a major concern, the option of the shorter fractionation should be considered as a reasonable alternative.

What is the relative choice between a preoperative CRT approach versus a postoperative CRT approach? Postoperative CRT has been part of standard practice in Canada for many years. Guideline #2-4 Section 2. Part 2 (*Postoperative Adjuvant Therapy for Resected Stage II or III Rectal Cancer*) recommends the use of postoperative therapy with concurrent CRT in addition to fluoropyrimidine-based CT for patients who have not received preoperative RT. This is expected to improve survival and local control compared to surgery alone or RT alone after surgery. The most powerful evidence guiding the choice between a

preoperative versus a postoperative approach comes from the direct comparison between preoperative and postoperative CRT by Sauer et al (31). The existing evidence would support a preoperative CRT approach. This is expected to provide superior local control benefit, as well as higher pathological complete response rate, with significantly lower acute and late toxicities, within the context of TME surgery. In other words, the preoperative approach provides the greatest relative benefit for the same modalities (CT, RT, and surgery) and dose intensity, but with less toxicity. Could selective postoperative RT (with or without CT) be superior to preoperative RT for higher risk patients? The MRC 07 trial (46) is expected to provide the relevant evidence for whether preoperative RT for higher risk patients is superior to selective postoperative RT (with or without CT). Existing evidence therefore supports the use of preoperative CRT over postoperative CRT when both options are feasible. For patients who are found to have higher risk disease postoperatively, postoperative CRT should be recommended as described in Section 2. Part 2.

What is the most effective way of delivering preoperative CRT? Preoperative 5FU has to date been employed in combination with RT in all trial protocols. Delivery was either five days of IV 5FU/folinic acid (FA) with RT 45 Gy in 25 fractions (20,29) or 5FU infusion during weeks 1 and 5 together with 50.4Gy in 28 fractions (31). While continuous infusional 5FU throughout the course of RT is expected to provide greater synergy between the two modalities and has been increasingly incorporated into clinical practice as well as trial protocols (34,36), the relative efficacy of bolus 5FU and FA versus continuous infusional 5FU in the preoperative setting has in fact not been directly compared. Comparisons of infusional versus bolus delivery of 5FU during RT have been done in the postoperative setting and are discussed in the postoperative guideline discussion (Section 2. Part 2). The optimal way of delivering 5FU in conjunction with RT is unclear, and decisions for individual patients should be based on an informed discussion of the potential risks and benefits for each mode of delivery.

Should postoperative CT be given following preoperative RT with or without CT? There is an obvious paucity of research efforts directed specifically towards answering this question. Bosset et al is the only trial identified that included a comparison of preoperative CRT versus preoperative CRT with postoperative CT (two cycles of 5FU plus FA) (20). No significant difference between the outcomes of these two treatment arms could be observed. Sauer et al (31) used four cycles of 5FU/FA in both treatment arms comparing preoperative versus postoperative CRT. Despite the lack of direct evidence, offering postoperative CT following preoperative RT or CRT is common practice, with the rationale based on indirect evidence. Our evidence-based guideline section on postoperative therapy for patients with pathological stage II or III rectal cancer recommends adjuvant concurrent CRT in addition to fluoropyrimidine-based CT (Section 2. Part 2). Since the benefit of RT, given either preoperatively or postoperatively, is primarily on local control, the survival benefit that is observed with combination postoperative CRT is predominantly attributed to the systemic effect of CT (50). In fact, the next generation of trials assumes the therapeutic benefit of postoperative systemic therapy and focuses on asking the question whether novel postoperative CT regimens are superior to "standard" regimens. For example, the CAO/ARO/AIO-04 trial (See Ongoing Trials, Appendix 3) is designed to examine the relative benefit of adjuvant 5FU with or without oxaliplatin. The ECOGE5204/CRC-04 trial is designed to investigate postoperative oxaliplatin and 5FU/FA with or without bevacizumab in patients who have received preoperative CRT and surgery.

Despite the absence of direct evidence, given the above consideration, the expert opinion of the GI DSG supports the use of postoperative CT in stage II and III rectal cancer following preoperative RT or CRT. Given the potential downstaging effect of standard fractionation preoperative CRT or RT, the decision to use adjuvant CT following surgery and

standard fractionation RT or CRT should be based on clinical staging. The role of post-treatment pathologic staging ("yP" status) or primary tumour response to therapy deserves further study (47). Pathological stage should be used to guide the need for adjuvant therapy in patients receiving hypofractionation (short course) preoperative RT. The optimal choice of CT should be based on the assessment of risk of recurrence. Discussion of the use of capecitabine- and oxaliplatin-based regimens for those patients with a high risk of recurrence are discussed in detail in the postoperative section (Section 2. Part 2).

Can the effect of preoperative CRT be improved by incorporating newer CT agents? This is a question that is being examined in several ongoing trials, with special attention to how irinotecan (CPT11) and oxaliplatin should be incorporated (35,36, Appendix 3). Early attempts to enhance the effect of preoperative CRT by adding newer CT agents active in rectal cancer (i.e., capecitabine, irinotecan, and oxaliplatin) have not yet translated into superior outcomes (34-36); however, longer term results and randomized trial data are pending. Until a superior regimen is identified, 5FU infusion with RT, approximately 50Gy in 25 fractions, remains the standard approach. In most instances, there should be a four to six-week delay from the completion of RT to surgery, to allow patients to recover to an optimal preoperative physiologic state. The exception 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.

Considering all the above evidence, it can be concluded that there is no significant overall survival or relapse-free survival benefit with the use of preoperative RT and different ways of delivering the RT in patients with stage II or III rectal cancer. The reason for considering the use of preoperative RT lies exclusively with the desire to reduce local recurrence rates, which is accomplished at the expense of greater acute and late toxicities. The addition of CT with the longer standard fractionation courses provides a further reduction of local recurrence rates, again at the expense of incremental acute toxicities. For the subgroup of patients who are at higher risk for local recurrence (e.g., where TME with a negative circumferential margin may be difficult to accomplish), the use of preoperative CRT has the additional benefit of a greater likelihood of tumour response, a higher pathological complete response rate, and a lower positive circumferential margin. In these patients, the rationale for the use of preoperative longer course CRT is even stronger. For the same intensity of CRT, the effect is greatest, and with the least acute and late toxicities, when the delivery is done preoperatively.

It cannot be overemphasized that the risk of local recurrence, and therefore the role for preoperative RT with or without CT, depends on, in addition to tumour factors, the quality of the staging workup and the eventual surgery. While late toxicities, in particular rectal and sexual function is anticipated to be higher in patients receiving preoperative RT, this has to be balanced against the desire to reduce the risk of recurrence and the morbidity and mortality of treatment related to subsequent recurrences.

CONCLUSIONS

In summary, for patients with stage II and III rectal cancer, preoperative RT improves local control, and this benefit is likely to be enhanced by the addition of CT. Thus, the use of preoperative CRT likely provides the best strategy to minimize the risk of local recurrence and maximize the likelihood of complete pathological response. Given the potential inaccuracy of preoperative staging and the potential for toxicities related to RT, decisions for multimodality preoperative therapy requires multidisciplinary care as well as joint decision making with patients.

ONGOING TRIALS

The NCI® database of ongoing clinical trials (available from: http://www.cancer.gov/search/clinical_trials/) was searched on May 28, 2007. A listing of relevant trials appears in Appendix 3.

CONFLICT OF INTEREST

Members of the GI DSG who were involved in the development of this systematic review and clinical practice guideline were polled for potential conflicts of interest and declared there were none.

JOURNAL REFERENCES

The following updated practice guideline based on EBS#2-4 has been published by *Clinical Oncology* (© 2010 The Royal College of Radiologists; http://www.clinicaloncologyonline.net/home):

- Wong RKS, Berry S, Spithoff K, Simunovic M, Chan K, Agboola O, et al; Gastrointestinal Cancer Disease Site Group. Postoperative therapy for stage II or III rectal cancer: an updated practice guideline. Clin Oncol (R Coll Radiol). 2010 May;22(4):265-71. doi:10.1016/j.clon.2010.03.002.

Practice Guideline #2-13 was published as:

- Figueredo A, Zuraw L, Wong RK, et al. The use of preoperative radiotherapy in the management of patients with clinically resectable rectal cancer: a practice guideline. BMC Medicine 2003;1:1.

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For a complete list of the Gastrointestinal Cancer DSG members, please visit the CCO website at http://www.cancercare.on.ca/

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Appendix 1. Study quality characteristics.

Trial	Funding	Randomization method	Baseline characteristics	Statistical Power/ Target sample size	Was target sample size met?	Follow-up	ITT analysis
Kapiteijn (5)	Dutch Cancer Society Dutch National Health Council Swedish Cancer Society	Randomized by central office. Permuted blocks of 6. Stratified by centre, expected type of resection.	Balanced	1140 randomized pts (1026 evaluable) for 90% power to detect decrease in LR from 10% to 5% with $p<0.05$	Yes	Median 24.9 mos	All eligible pts analyzed, including protocol violations
Swedish Rectal Trial (6)	Swedish Cancer Society Stockholm Cancer Society Ierzy + Eva Cederbaum Minervafond	Telephone contact with trial centre in 1 of 6 regions. Stratified by hospital.	Unbalanced distribution of tumour stage	1100 pts for 80% power to detect increase in 5-yr survival from 50% to 60%	Yes	Median 13 yrs	Only eligible pts who had surgery analyzed. 58 randomized pts not analyzed.
Bujko (28)	Polish State Committee for Scientific Research	Randomized by telephone to central office. Minimization method. Stratified by centre, character of tumour and type of surgery.	Balanced	316 pts for 80% power to detect a 15% increase in sphincter preservation, $p<0.05$	Yes (312 pts analyzed)	Median 48 mos 2 pts lost to follow-up	4 randomized pts not analyzed for ineligibility. ITT analysis of eligible pts.
Bosset (20)	EORTC NCI Ligue contre le Cancer, Comité du Doubs	Randomized at EORTC centre. Minimization method. Stratified by centre, sex, T stage, tumour location.	Balanced	1011 pts for 80% power to detect 10% difference in 5-yr survival, 2-sided $p<0.05$	Yes	Median 5.4 yrs 12 pts lost to follow-up	All randomized pts analyzed by ITT, including ineligible pts.
Gerard (29)	NR	NR	Balanced	762 pts (323 deaths) for 80% power to detect increase in 5-yr survival from 52% to 62%, $\alpha=0.05$, 2-sided	742 pts analyzed. Did not meet target number of deaths.	Median 81 mos 6 pts lost to follow-up immediately after randomization	20 randomized pts not analyzed, including 14 ineligible and 6 lost to follow-up
Sauer (31)	Deutsche Krebshilfe	Performed by central study centre. Permuted blocks of 14. Stratified by surgeon.	Significantly more pts in preoperative therapy group had tumours 5cm or less from anal verge	680 pts for 80% power to detect 10% difference in 5-yr survival, $\alpha=0.05$, 2-sided	Yes	Median 46 mos 18 pts lost to follow-up	24 randomized pts not analyzed for withdrawal of consent or ineligibility. ITT analysis of eligible and consenting pts.

Notes: EORTC, European Organisation for Research and Treatment of Cancer; ITT, intention-to-treat; LR, local recurrence; mos, months; NCI, National Cancer Institute; NR, not reported; Pts, patients; yrs, years.

Appendix 2. Incomplete trials.

Trial	Inclusion criteria	N	Preoperative regimen		Postoperative regimen		Type of Surgery	Follow-up
			CT	RT	CT	RT		
Preoperative CRT vs. postop CRT								
INT 0147 (32)	Rectal cancer T3/4	NA (target 770)	5FUFA x2 cycles with RT+ Postoperative 5FU FA x4 cycles	50.4Gy in 28fr (Cycle 1 & 2) BED = 40.9Gy^{10}	5FUFA x 6 cycles with RT cycles during cycle 3&4	50.4Gy in 28fr (cycle 3&4) BED = 40.9Gy^{10}	TME not specified Surgeon specify preoperatively (APR, LA, LE)	Closed prematurely due to inadequate accrual
Roh (NSABP-R03) (51,52)	Rectal cancer Dukes B or C	253 (target 990)	5FUFA x3 cycles with RT cycle 2&3 + postoperative 5FY FA x4 cycles	45Gy in 25fr (cycle 2 & 3) BED = 35.2Gy^{10}	5FUFA x7 cycles	45Gy in 25fr (cycle 2&3) BED = 35.2Gy^{10}	TME not specified Surgeon specify preoperatively (APR, LA, LE)	Closed prematurely due to inadequate accrual

Notes: 5FUFA, 5-fluorouracil plus folinic acid; APR, abdominoperineal resection; CT, chemotherapy; fr, fractions; Gy, grays; LA, LE, BED, biological equivalent dose; N, number of patients evaluated; NA, not available; RT, radiotherapy; TME, total mesorectal excision.

Appendix 3. Ongoing randomized controlled trials.

Preoperative FU-based chemoradiation with or without weekly oxaliplatin in locally advanced rectal cancer	
Protocol ID:	Studio Terapia Adiuvante Retto (STAR)- 01
Date last modified:	Unknown
Trial type:	Open-label, multicentre, randomized, Phase III
Primary outcome:	Unknown
Accrual:	410 patients were randomized
Sponsorship:	Unknown
Status:	Preliminary toxicity data presented at ASCO 2007 (36)

Trial testing ftorafur (UFT) associated with neoadjuvant radiotherapy versus radiotherapy alone in rectal adenocarcinoma	
Protocol ID:	CPP276, NCT00207831
Date last modified:	August 16, 2006
Trial type:	Randomized, open label, active control, Phase III
Primary outcome:	Rate of pathologic complete response
Accrual:	Expected enrolment 350
Sponsorship:	Centre Paul Papin, Merck
Status:	Recruiting patients

Phase III randomized study of neoadjuvant chemoradiotherapy comprising radiotherapy and capecitabine with versus without oxaliplatin followed by total mesorectal excision in patients with resectable stage II or III rectal cancer	
Protocol ID:	FRE-FNCLCC-ACCORD-12/0405, EU-20522, NCT00227747
Date last modified:	January 11, 2008
Trial type:	Randomized, active control, Phase III
Primary outcome:	Rate of complete surgical resection
Accrual:	Expected enrolment 590
Sponsorship:	Federation Nationale des Centres de Lutte Contre le Cancer
Status:	Recruiting patients

Phase III randomized study of preoperative chemoradiotherapy comprising radiation therapy and either capecitabine or fluorouracil with or without oxaliplatin in patients with resectable rectal cancer	
Protocol ID:	NSABP-R-04, NCT00058474, CALGB-NSABP-R-04
Date last modified:	January 17, 2008
Trial type:	Randomized, active control, Phase III
Primary outcome:	Loco-regional control, assessed by evidence of tumour at 3 years
Accrual:	Expected enrolment 1606
Sponsorship:	NCI, CALGB
Status:	Recruiting patients

Prospective Randomised Multicenter Phase-III-Study: Preoperative Radiochemotherapy and Adjuvant Chemotherapy With 5-Fluorouracil Plus Oxaliplatin Versus Preoperative Radiochemotherapy and Adjuvant Chemotherapy With 5-Fluorouracil for Locally Advanced Rectal Cancer	
Protocol ID:	CAO/ARO/AIO-04, German Cancer Aid (no. 106759), NCT00349076
Date last modified:	December 14, 2007
Trial type:	Randomized, open label, active control, Phase III
Primary outcome:	Disease-free survival at 3 years
Accrual:	Expected enrolment 1200
Sponsorship:	University of Erlangen-Nürnberg
Status:	Recruiting patients.

Phase III Randomized Study of Preoperative Radiotherapy Versus Selective Postoperative Chemoradiotherapy in Patients With Operable Rectal Cancer	
Protocol ID:	MRC-CR07, EU-98008, CAN-NCIC-C016, ISRCTN28785842, NCT00003422, C016
Date last modified:	December 25, 2007
Trial type:	Randomized, Phase III
Primary outcome:	Local recurrence
Accrual:	Expected enrolment 1800
Sponsorship:	Medical Research Council, National Cancer Institute of Canada
Status:	Ongoing, not recruiting patients, preliminary results published (46)

Evidence-based Series #2-4 Version 2: Section 2. Part 2

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: Evidentiary Base: Part 2. Postoperative Therapy

S Berry, RB Rumble K Spithoff, A Figueredo, B Cummings, and Members of 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: Document Review Summary and Tool for a summary of updated evidence published between 2008 and 2017, and for details on how this Clinical Practice Guideline was ENDORSED.

QUESTION

What is the role of postoperative adjuvant radiotherapy (RT) and/or chemotherapy (CT) for patients with resected stage II or III rectal cancer in terms of improving survival and delaying local recurrence?

INTRODUCTION

Surgery is the primary treatment for localized carcinoma of the rectum, but resection is followed by local or distant relapses in about 50% of patients, leading to premature death due to the disease. The efficacy of surgery is constrained by the lack of serosa over the lower rectum and by the inability to obtain wide radial resection margins because of the presence of the bony pelvis. However, surgery can have a substantial impact on rates of local recurrence (1). Rectal resection using the total mesorectal excision (TME) technique, involving sharp dissection of the mesorectal fascia, is associated with low rates of local recurrence for patients with rectal cancer (2-4). Local recurrences are often disabling due to pelvic pain and infection. For these reasons, reduction in local recurrences, as well as distant metastases, is a major goal for adjuvant therapy for resected rectal cancer.

Many randomized controlled trials (RCTs) have addressed the issue of adjuvant treatment in rectal cancer. Buyse et al (5) synthesized the results of trials of adjuvant therapy for colorectal cancer published up to 1987. In this meta-analysis, neither RT nor CT decreased the odds for death; however, a subgroup analysis demonstrated that rectal cancer patients had better survival results from adjuvant CT than colon cancer patients. In 1990, an NIH Consensus Conference reviewed the available evidence and recommended the use of combined RT and CT for the treatment of stages II and III rectal cancer (6). Since then,

multiple new trials of adjuvant RT and CT have become available; therefore, the NIH report is primarily of historical interest and a rigorous synthesis of current data with an evidence-based guideline is needed.

A practice guideline report on the role of postoperative adjuvant RT and/or CT for patients with resected stage II or III rectal cancer was originally completed by the PEBC Gastrointestinal Cancer Disease Site Group (GI DSG) in 2000 (9). The original guideline recommended that patients with resected stage II or III rectal cancer should be offered adjuvant therapy with the combination of RT and CT, including 5-fluorouracil (5FU) but not semustine. To integrate important new evidence into the original guideline, the GI DSG decided to update the document - this document replaces the December 2000 guideline.

In 2003, the PEBC GI DSG published a separate practice guideline on the role of preoperative RT in rectal cancer (7) and an updated review of this topic can be found in Section 2. Part 1 of this document. There is an increasing body of evidence that preoperative therapy results in lower rates of local recurrence and a better toxicity profile than a postoperative approach for certain patient groups. However, since not all patients are considered candidates for preoperative RT, a systematic review of the evidence for postoperative therapy is still warranted.

Some of the literature for adjuvant therapy in this disease setting includes patients with both rectal and colon cancer. This clinical practice guideline considers only study reports that included rectal cancer patients only or that allowed data to be extracted on rectal cancer patients separately from colon cancer patients. Because portal venous infusion of CT is not routinely used for patients with resected stage II or III rectal cancer, only systemic CT will be considered in this review of the evidence.

METHODS

The evidence-based series (EBS) guidelines developed by Cancer Care Ontario's Program in Evidence-Based Care (PEBC) use the methods of the Practice Guidelines Development Cycle (8). For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by one member of the PEBC Gastrointestinal DSG and methodologists.

This systematic review is a convenient and up-to-date source of the best available evidence on postoperative adjuvant RT and/or CT for resected stage II or III rectal cancer. The body of evidence in this review is primarily comprised of mature randomized controlled trial (RCT) data. That evidence forms the basis of a clinical practice guideline developed by the Gastrointestinal DSG. That evidence forms the basis of the recommendations developed by the GI DSG. The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Literature Search Strategy

Searches were conducted for the years from 1988 to September (week 2) 2007 on MEDLINE, 1996 through to week 38, 2007 on EMBASE, October 2002 on CANCERLIT, and through to Issue 3, 2007 of the Cochrane Library, using the MeSH terms "rectal neoplasm", "colorectal neoplasm", "drug therapy", "adjuvant chemotherapy", "adjuvant radiotherapy", "combined modality therapy", and the text word "adjuvant". These search terms were combined with search words for the following publication types: randomized controlled trials, meta-analyses, and systematic overviews. Personal reprint files were also searched and citations from retrieved articles were reviewed. Abstracts published in the proceedings of the 1999 through 2007 annual meeting of the American Society of Clinical Oncology (ASCO)

and the 1999 through 2006 annual meeting of the American Society for Therapeutic Radiation and Oncology (ASTRO) were also searched for relevant information. The National Cancer Institute (NCI) database (http://www.cancer.gov/search/clinical_trials/) was searched for relevant ongoing clinical trials on December 10, 2007.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

1. The RCTs enrolled patients with stage II or III rectal carcinoma who had undergone resection with curative intent. Information on tumour staging is found in Appendix 1. While many of the available studies reported on patients with colorectal cancer, this review considered only studies that presented data for patients with stage II or III rectal carcinoma separately from colon cancer patients.
2. Syntheses of evidence were in the form of systematic overviews and meta-analyses of RCTs.
3. Studies were published in the English language, as translation resources were not available.

Synthesizing the Evidence

Where possible, the data were pooled to estimate the overall effect on both survival and local control for the following comparisons: RT versus observation alone, CT versus observation alone (systemic and oral), combined chemo-radiotherapy (CRT) versus observation, CT versus RT, CT versus CT, CRT versus RT alone, CRT versus CT alone, and CRT versus CRT. The results for patients with stage II and III rectal cancer were combined in meta-analyses for this report in the manner in which data were presented in the published reports. It was not possible to separate results of stage II versus those with stage III disease. Individual patient data were not available for these analyses. When survival and disease-free survival were not reported, they were estimated from published graphs (*estimated data)*. Where available, data for five-year survival and disease-free survival were abstracted and reported. Data on local recurrence reported at the time of follow-up in each study were pooled even though follow-up times were different across studies. Combining data in this way assumes a constant hazard ratio of risks between the groups being compared (10).

The study results were pooled using Review Manager 4.2.7 (RevMan Analyses 1.0.2; version date: November 2003; © 2003 the Cochrane Collaboration), which is freely available through the Cochrane Collaboration[2]. Results are expressed as relative risk ratios (RR), where RR <1.0 indicates lower risk of an event in the experimental treatment group, RR >1.0 indicates lower risk in the control group, and RR=1 indicates no difference in risk between the groups (11).

The numbers need to treat (or harm) (NNT) for study results were calculated from the RRs with the Visual Rx NNT calculator freely available online (http://www.nntonline.net/), using the methodology described by Cates (12).

RESULTS

Literature Search Results

Twenty-nine relevant RCTs were identified and included in the review (13-41). Only the primary publications of trial results were included, except where secondary publications

[2] RevMan Analyses [Computer program]. Version 1.0.2 for Windows. In: Review manager (RevMan) 4.2.7. Oxford (England): The Cochrane Collaboration, 2003.

reported data that were not included in the primary report (42-46). In addition, a systematic overview of adverse effects (47) and six meta-analyses of RCTs (48-53) were obtained and included. The trials are grouped according to treatment modality: RT versus observation alone, CT versus observation alone (systemic and oral),, combined CRT versus observation, CT versus RT, CT versus CT, CRT versus RT alone, CRT versus CT alone, and CRT versus CRT (Table 1). Details of the specific CT and RT regimens from each trial are presented in Appendix 2. Abbreviations for the names of any cooperative clinical trials groups are provided in Appendix 3.

Study Quality

None of the identified RCTs were double-blinded or placebo-controlled, and only 15 provided information about target sample size calculations and statistical power to detect a significant difference in outcome between treatment groups (9,16,19,22,25,26,29,32,33,35,37,39,40,45,46). Method of randomization was often not reported, particularly in older studies. Six studies also included patients with colon tumours or patients with stage I disease (22,27,29,30,35,37); therefore, data extracted for the purpose of this review represents subgroup analyses for these studies. It is likely that the majority of these studies did not have sufficient statistical power to detect a significant difference in outcomes for subgroup analyses.

Surgical Techniques

Most trial reports included in this systematic review did not comment on the surgical techniques used, other than to say that "curative" or "complete" surgery was a requirement for trial entry. It is likely that currently recommended standards of surgery, including total mesorectal excision (TME), were not met in all the trials discussed (54).

Table 1. Evidence included in this guideline report.

Treatment / Comparisons	Number of trials (References*)	References included in pooled results		Summary of Results
		Mortality	Local Failure	
Randomized Trials				
RT versus observation	**7** (13-16,18,23,24)	13-19	13-19	Table 2
Systemic CT versus observation	**6** (13,14,22,29,38,40)	16,17,20-22	16,17,21,22	Table 3
Combined CRT versus observation	**2** (13,25)	16,25	16,25	Table 4
CT versus RT	**3** (13,14,17)	16,17,26	16,17	Table 5
Comparison of two systemic CT regimens	**5** (27,30,35-37)	*No pooling performed*		Table 6
Combined CRT versus RT alone	**4** (13,17,20,32,42)	16,26,30-32	16,30-32	Table 7
Combined CRT versus CT alone	**3** (13,17,28)	16,26,33	16,33	Table 8
Combined CRT versus another combined CRT regimen	**8** (19,21,26,31,33,34,39,41 ,45,46)	*No pooling performed*		Table 9
Meta-analyses				
Adverse events	(47)			-
Radiotherapy versus observation	(51)			Appendix 4
Chemotherapy versus observation	(48-53)			Appendix 4

* Three trials contained multi-arm interventions (13,14,17) and thus appear in multiple categories.

Radiotherapy versus Observation

Seven trials were obtained that compared postoperative RT with observation alone in patients with resected rectal cancer (13-16,18,23,24). One trial included patients with both rectal and rectosigmoid cancer (18). Results are presented in Table 2. None of the trials

detected a significant benefit in overall or disease-free survival for RT. One of the trials (MRC) did detect a significant benefit in local failure favouring RT.

The dose of RT varied from 4000 cGy in 20 days to 4800 cGy in 25 to 27 days, and a perineal or pelvic boost dose was added in two trials (14,16). There is no suggestion that the variations in RT dose over this range had any effect on survival or local recurrence rates. Radiation fields were comparable in all trials.

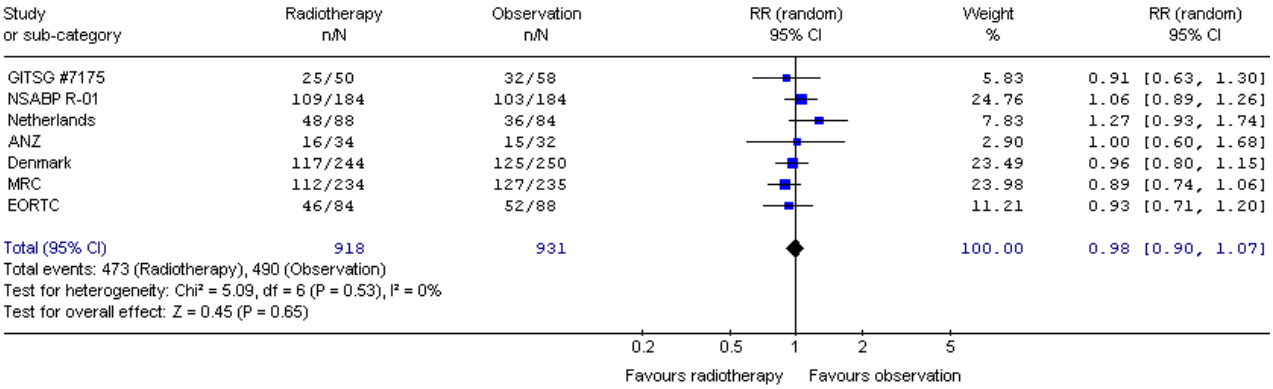
Pooling the data on the 1849 patients included in the seven trials did not detect a difference between RT and observation alone for overall survival (RR, 0.98; 95% confidence interval [CI], 0.90 to 1.07; p=0.65) (Figure 1); however, a statistically significant difference was detected in favour of RT for local failure (RR, 0.78; 95%CI, 0.65, 0.95; p=0.01) (Figure 2).

Table 2. Randomized trials of radiotherapy versus observation.

Trials	Median follow-up (months)	Treatment Allocation	# Pts	Local Failure %	p-value	Disease-free survival %	p-value	Overall survival %	p-value
GITSG # 7175	NR	Obs	58	24‡		46†		44†	
1988 (13)		RT	50	20‡	NS	52†	NS	50†	NS
NSABP R-01	64	Obs	184	25		30		44	
1988 (14)	(mean)	RT	184	16	NS	44	NS	41	NS
Netherlands *	38	Obs	84	33		47		57	
1991 (15)		RT	88	24	NS	35	NS	45	NS
ANZ	52	Obs	32	22		40	-	53¶	
1991 (16)	(mean)	RT	34	24	NS	44		53¶	NS
Denmark	60	Obs	250	27		NR	-	50¶	
1992 (18)		RT	244	28	NS			52¶	NS
MRC	48	Obs	235	34		45		46	
1996 (23)		RT	234	21	0.001	48	NS	52	NS
EORTC	85	Obs	88	34		45†		41†	
1997 (24)		RT	84	30	NS	47†	NS	45†	NS

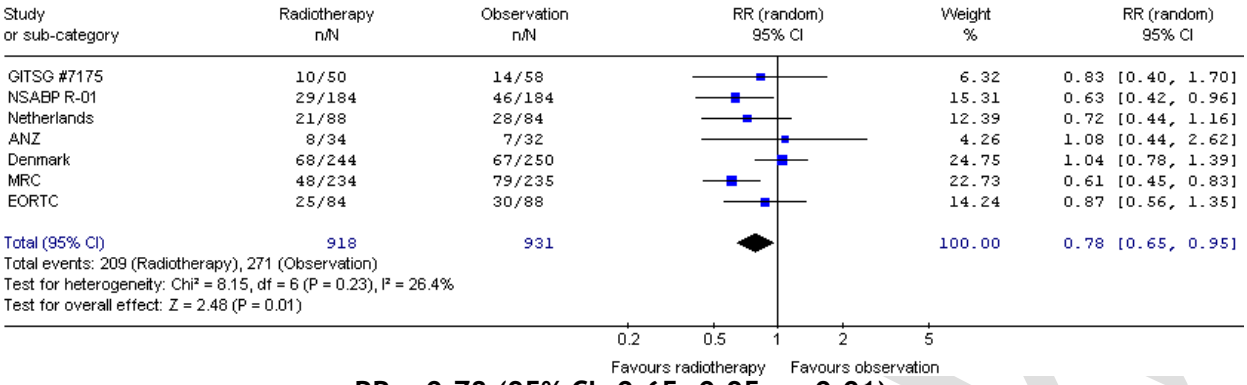
Notes: # Pts, number of patients; CT, chemotherapy; NR, data not reported; NS, not statistically significant; Obs, only observation after surgery; RT, radiotherapy.
* Interim analysis.
†Estimated from survival curves.
‡Includes patients with locoregional and locoregional + distant recurrence.
¶ Calculated from crude # of deaths.
For details about treatment regimens see Appendix 2. For full names of trials and trial groups see Appendix 3.

Figure 1. Meta-analysis of RCTs comparing radiotherapy to observation alone: mortality relative risk ratio (random effects model).



RR = 0.98 (95% CI, 0.90-1.07; p=0.65)

Figure 2. Meta-analysis of RCTs comparing radiotherapy to observation alone: local failure relative risk ratio (random effects model).



RR = 0.78 (95% CI, 0.65- 0.95; p=0.01)

Systemic Chemotherapy versus Observation

Six trials were obtained comparing postoperative CT with observation alone in patients with resected rectal cancer (13,14,22,29,38,40). Results are presented in Table 3. Three trials used standard intravenous administrations (13,14,29), while three Japanese studies used oral regimens (22,38,40). Only one of the three studies examining intravenous CT detected a significant difference in overall survival favouring treatment compared to observation (NSABP R-01). All three trials examining oral CT regimens detected significant overall survival differences favouring treatment compared with observation (CCCSG, NSAS-CC01, Hamaguchi). None of the three studies examining intravenous CT detected significant differences in local failure between treatment arms; however, one study investigating an oral regimen detected a significant difference favouring adjuvant CT compared to observation.

Pooling data from the three trials (776 patients) testing intravenous CT regimens detected a statistically significant benefit favouring systemic CT for overall survival (RR, 0.85; 95% CI, 0.73-0.98; p=0.03) (Figure 3). Pooling data from the two trials (768 patients) testing oral CT regimens for which sufficient data were available also detected a statistically significant benefit favouring oral CT for overall survival (RR, 0.63; 95% CI, 0.51-0.77; p=<0.00001) (Figure 3). Pooling data from all six of the CT versus observation-alone trials (1544 patients) detected a highly significant benefit for CT in overall survival (RR, 0.75; 95% CI, 0.65-0.88; p=0.0003) (Figure 3).

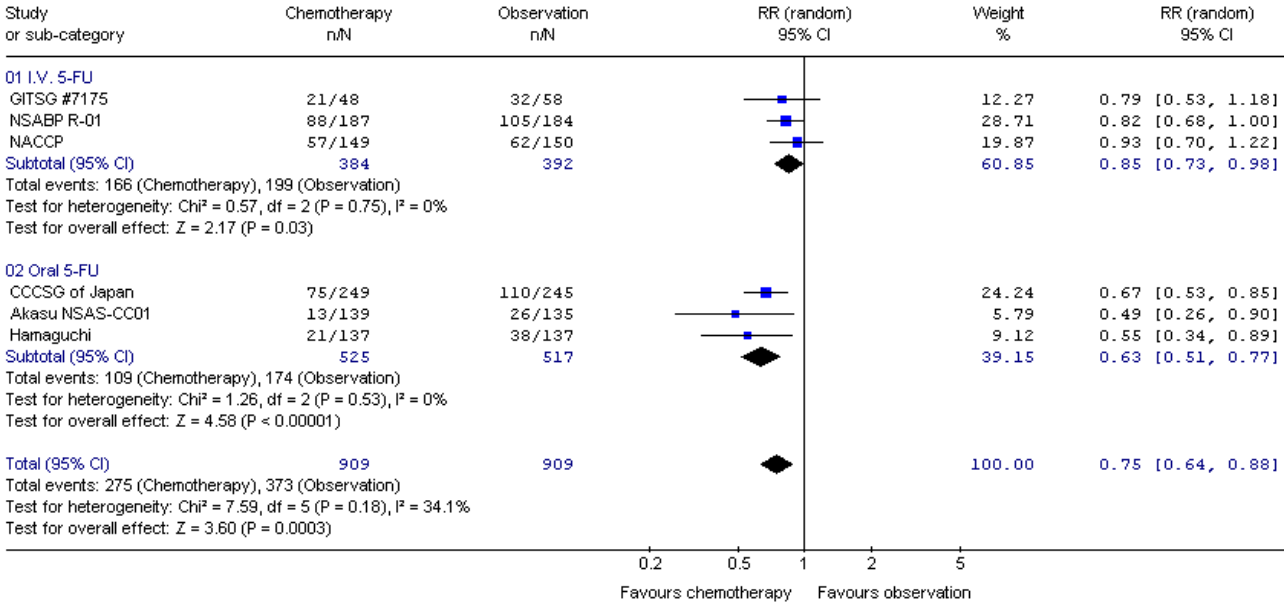
Pooling data from the two trials (477 patients) testing intravenous CT regimens that reported local failure data did not detect a statistically significant difference between CT and observation alone for local failure (RR, 0.90; 95% CI, 0.65-1.24; p=0.5) (Figure 4). Pooling data from two trials (768 patients) testing oral CT regimens detected a highly significant benefit favouring oral CT for local failure (RR, 0.58; 95% CI, 0.41-0.81; p=0.002) (Figure 4). Pooling data from all four of the CT versus observation alone trials (1245 patients) detected a significant benefit favouring CT for local failure (RR, 0.74; 95% CI, 0.55- 0.98; p=0.04) (Figure 4), a positive result that was heavily influenced by the oral CT trials.

Table 3. Randomized trials of systemic chemotherapy versus observation.

Trials	Median follow-up (months)	Treatment Allocation	# Pts	Local Failure %	p-value	Disease - free survival %	p-value	Overall survival %	p-value
Intravenous 5FU									
GITSG # 7175 1988 (13)	NR	Obs MF	58 48	24‡ 27‡	NS	46† 51†	NS	44† 57†	NS
NSABP R-01 1988 (14)	64 (mean)	Obs MOF	184 187	25 21	NS	30 42	0.006	43 53	0.05
NACCP 2001 (29)	57	Obs* FU-Lev*	150 149	NR	-	47II 52II	-	59 62	NS
Oral fluoropyrimidines									
CCCSG of Japan 1995 (22)	>60	Obs MIFU-2	245 249	21§ 12§	0.002§	51 70	<0.05	55 70	<0.05
Akasu 2006 ¶ NSAS-CC01(38)	36	Obs UFT	135 139	10 6	NR	60II** 78II **	0.0014	81 ** 91 **	0.0048
Hamaguchi 2007 (40)	74	Obs UFT	274 total	NR	-	56 69	0.034	72 85	0.033

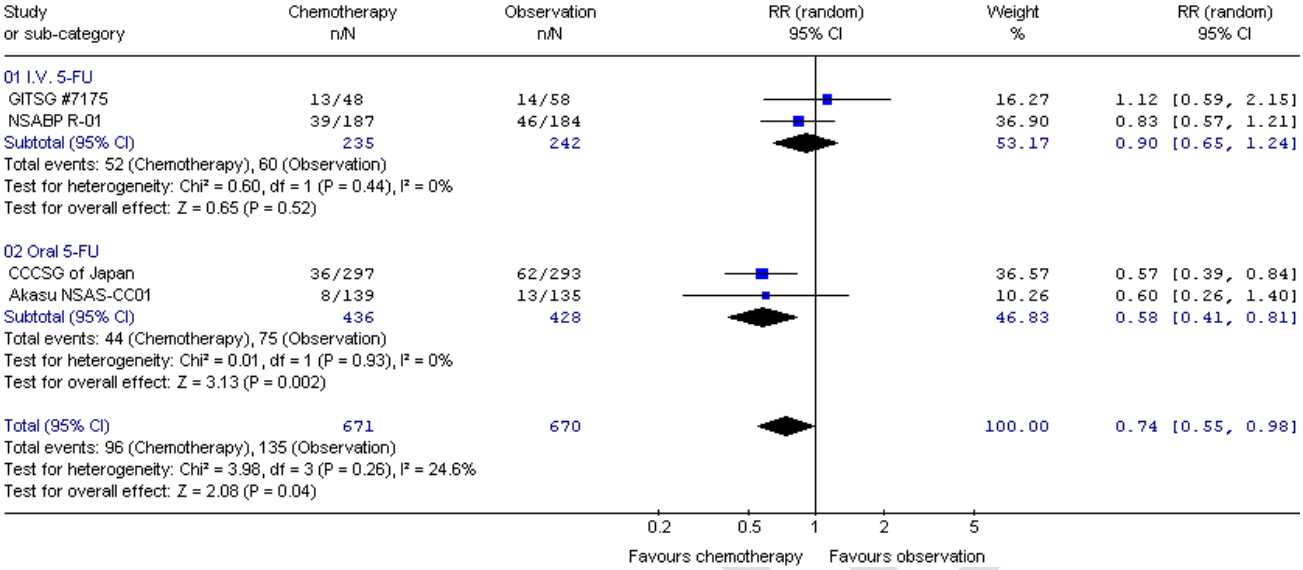
Notes: # Pts, number of patients; MF, 5FU and semustine; MOF, 5FU, semustine and vincristine; MIFU-2, 5FU plus mitomycin C; NS, not statistically significant; Obs, only observation after surgery.
*Almost 50% of patients received RT
†Estimated from survival curves.
‡Includes patients with locoregional and locoregional + distant recurrence.
§ Includes patients with Dukes class A rectal cancer
¶ Results are from an interim analysis
II Recurrence-free survival data
** 3-year data.
For details about treatment regimens see Appendix 2. For full names of trials and trial groups see Appendix 3.

Figure 3. Meta-analysis of RCTs comparing chemotherapy versus observation alone: mortality relative risk ratio (random effects model).



IV CT **RR = 0.85 (95% CI, 0.73-0.98; p=0.03)**
Oral CT **RR = 0.63 (95% CI, 0.51-0.77; p<0.00001)**
Total **RR = 0.75 (95% CI, 0.65-0.88; p=0.0003)**

Figure 4. Meta-analysis of RCTs comparing chemotherapy to observation alone: local failure relative risk ratio (random effects model).



IV CT **RR = 0.90 (95% CI, 0.65-1.24; p=0.52)**
Oral CT **RR = 0.58 (95% CI, 0.41-0.81; p=0.002)**
Total **RR = 0.74 (95% CI, 0.55-0.98; p=0.04)**

Combined Chemotherapy plus Radiotherapy versus Observation

Two trials were obtained that tested combined CRT versus observation alone (13,25). Results are presented in Table 4. One of the two trials detected a statistically significant benefit favouring adjuvant treatment with combined CRT for survival in the primary analysis performed nearly 6.5 years after the last patient entered the study (GITSG #7175) (13), and one trial detected a statistically significant benefit favouring CRT for local failure (Tveit) (25). In the GITSG #7175 trial, the survival benefit favouring CRT was no longer present after an adjustment for covariates in a secondary analysis (16), In this study, another covariate-adjusted analysis was performed that indicated a significant benefit in time to recurrence favouring patients assigned to CRT (p=0.005) but no significant difference between groups in local recurrence (11% versus [vs.] 24%; p=0.08).

After an observation period of four to eight years, the Tveit (NARCPG) trial (25) detected a significant decrease in local recurrence (12% vs. 30%; p=0.01) as well as improvement in five-year overall survival (64% vs. 50%; p=0.05) and five-year recurrence-free survival (64% vs. 46%; p=0.01).

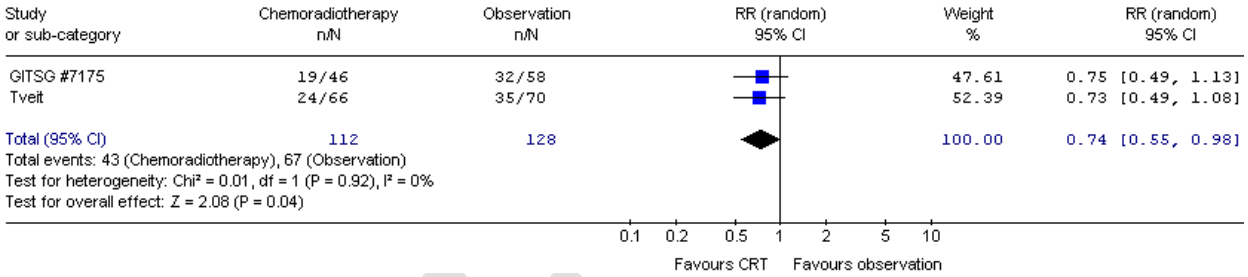
Pooling the results of the two trials (240 patients) demonstrated significant improvements in survival (RR for death, 0.74; 95% CI, 0.55-0.98; p=0.04) (Figure 5) and local recurrence (RR, 0.42; 95% CI, 0.23-0.75; p=0.004) (Figure 7).

Table 4. Randomized trials of combined radiotherapy and systemic chemotherapy versus observation.

Trials	Median follow-up (months)	Treatment Allocation	# Pts.	Local Failure %	p-value	Disease-Free Survival %	p-value	Overall Survival %	p-value
GITSG #7175 1988 (13)	NR*	Obs RT+MF	58 46	24‡ 11‡	NR	46† 70†	NS†	44† 59†	0.01
Tveit 1997 (25)	>60	Obs RT+FU	70 66	30 12	0.01	46¶ 64¶	0.01	50 64	0.05

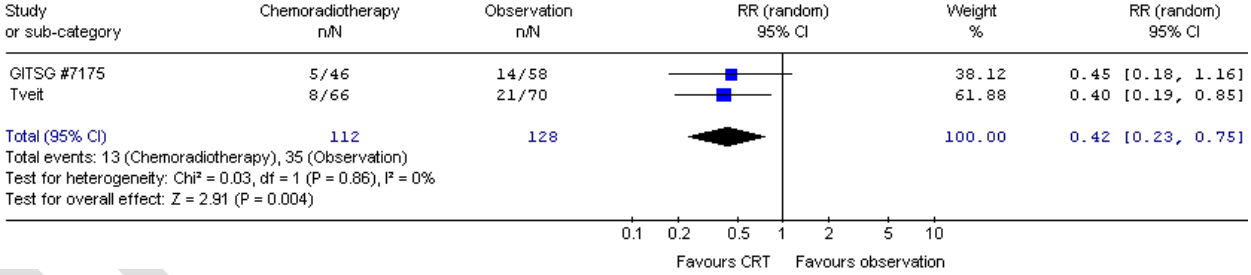
Notes: # Pts, number of patients; MF, 5FU and semustine; NR, data not reported; NS, not statistically significant; Obs, only observation after surgery; Stage B and Stage C refer to Dukes' stages.
* Minimum follow-up 6.5 years.
† Estimated from survival curves.
‡Includes patients with locoregional and locoregional + distant recurrence.
¶ Recurrence-free survival data.
For details about treatment regimens see Appendix 2. For full names of trials and trial groups see Appendix 3.

Figure 5. Meta-analysis of RCTs comparing combined chemotherapy and radiotherapy to observation alone: mortality relative risk ratio (random effects model).



RR = 0.74 (95% CI, 0.55-0.98; p=0.04)

Figure 6. Meta-analysis of RCTs comparing combined chemotherapy and radiotherapy to observation alone: local failure relative risk ratio (random effects model).



RR = 0.42 (95% CI, 0.23-0.75; p=0.004)

Systemic Chemotherapy versus Radiotherapy

Three trials compared systemic CT to RT alone (13,14,17). Results are presented in Table 5). None of the trials detected a statistically significant difference between CT and RT for either overall survival or local failure.

Pooling data from the three trials (627 patients) testing CT against RT showed a significant benefit in overall survival for CT compared with RT (RR, 0.85; 95% CI, 0.73-0.99; p=0.03) (Figure 7). Pooling the data from the two trials (469 patients) that provided data did not detect a difference between treatments for local failure (RR, 1.32; 95% CI, 0.92-1.91;

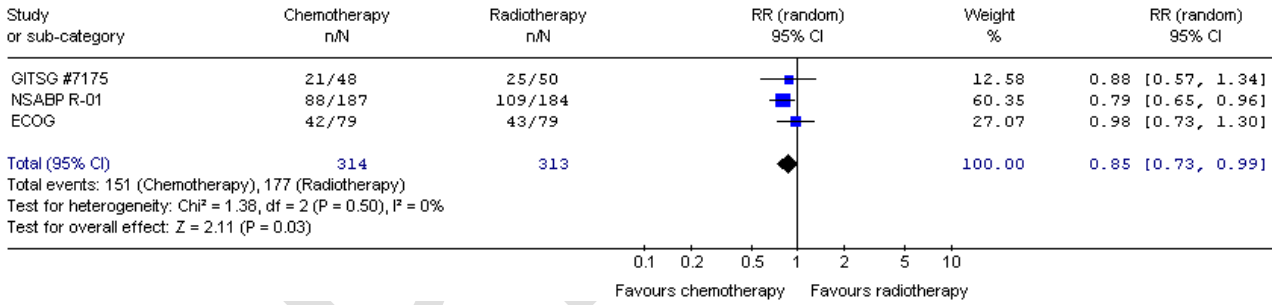
p=0.14) (Figure 8). Data gathered from the ECOG trial (26) that was estimated as the number of patients per treatment arm were not reported.

Table 5. Randomized trials of systemic chemotherapy versus radiotherapy.

Trials	Median follow-up (months)	Treatment Allocation	# Pts	Local Failure %	p-value	Disease - free survival %	p-value	Overall survival %	p-value
GITSG # 7175 1988 (13)	NR	RT CT(MF)	50 48	20* 27*	NS	52† 51†	NS	50† 57†	NS
NSABP R-01 1988 (14)	64 (mean)	RT CT (MOF)	184 187	16 21	NS	44 42	NS	41 53	NS
ECOG 1991 (17)	NR	RT CT (MF)	79‡ 79‡	NR	-	40 45	NS	46 47	NS

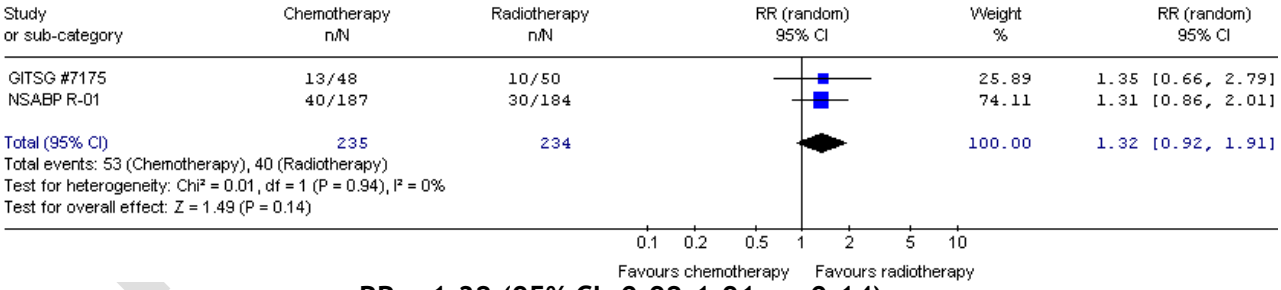
Notes: # Pts, number of patients; CT, chemotherapy; MF, 5FU and semustine; MOF, 5FU, semustine and vincristine; NR, not reported; NS, not statistically significant; Obs, only observation after surgery; RT, radiotherapy.
*Includes patients with locoregional and locoregional + distant recurrence.
†Estimated from survival curves.
‡Patients were randomized to three treatment arms (RT, CT or RT+CT). A total of 248 patients were eligible and 237 were evaluable, but number of patients per treatment arm was not reported. Estimated numbers (79 patient per arm) were used for the meta-analysis conducted for this report.
For details about treatment regimens see Appendix 2. For full names of trials and trial groups see Appendix 3.

Figure 7. Meta-analysis of RCTs comparing chemotherapy to radiotherapy: mortality relative risk ratio (random effects model).



RR = 0.85 (95% CI, 0.73-0.99; p=0.03)

Figure 8. Meta-analysis of RCTs comparing chemotherapy to radiotherapy: local failure relative risk ratio (random effects model).



RR = 1.32 (95% CI, 0.92-1.91; p=0.14)

Comparison of Two Different Chemotherapy Regimens

Five trials were obtained that tested different regimens of CT against each other (27,30,35-37). Results are presented in Table 6. Two trials compared one IV CT regimen against another (35,36), two trials compared different oral CT-based regimens (27,30), and one trial compared IV CT with versus without additional oral CT (36).

Four of the trials (27,30,35,37) reported rectal cancer patients data in subgroup analyses. None of the four trials that reported survival data detected a statistically significant difference between treatment arms for overall survival. Two trials (35,36) reported data for local failure in rectal cancer patient data separately from colon cancer patients. No difference between treatment arms for local failure was reported. One trial reported significantly improved disease-free survival for patients whose CT was administered by continuous venous infusion compared to bolus infusion (35). No pooling was performed due to the non-comparable differences in the treatments examined and insufficient reported data.

Table 6. Randomized trials comparing two different chemotherapy regimens.

Trials	Median Follow-Up (months)	Treatment Allocation	#Pts	Local Failure %	p-value	Disease-Free Survival %	p-value	Overall Survival %	p-value
With intravenous 5FU									
Chau 2005 (35)	55	5FU/LV bolus 5FUCVI	167 156	11 11	NS	58 74	<0.05	65 79	NS
Tsavaris 2005 (36)	96	5FU/LV 5FU+Lev	75 75	34 37	NR	63* 63*	NS	70* 70*	NS
With oral fluoropyrimidines									
Iwagaki 2000 (27)	>60	HCFU HCFU +5FUCVI	75 76	NR	-	59 73	0.218	NR	-
Iwamoto 2001 (30)	72?	HCFU MIFUCVI+HCFU	118 total	NR	-	NR	-	72 85	0.095
Kotake 2005 (37)	54	5FUCVI 5FUCVI+HCFU	81 80	NR	-	70 78	NS	NR	NS

Notes: 5FUCVI, 5FU continued venous infusion; HCFU, 1-hexylcarbamoyl-5FU; Lev, levamisole; LV, leucovorin; MIFUCVI,1-hexylcarbamoyl-5FU + 5FUCVI + mitomycin C; NR, not reported; NS, not statistically significant.
* Estimated from survival curves.

Combined Chemotherapy plus Radiotherapy versus Radiotherapy

Four trials compared CRT to RT alone (13,17,20,32,42). Results are presented in Table 7. Only one of the four trials (NCCTG #79-47-51) (20,42) detected a statistically significant survival benefit for CRT compared with RT alone. One of the three trials that reported local failure data detected a reduction in local failure rates by CRT compared to RT alone (20).

Pooling the data from the four trials (676 patients) did not detect any significant difference between the treatment groups for overall survival (RR, 0.95; 95% CI, 0.67-1.34; p=0.75) (Figure 9a). Pooling the data from the three trials (518 patients) that provided data detected no statistically significant benefit of CRT compared with RT alone for local failure (RR, 0.74; 95% CI, 0.40-1.38; p=0.34) (Figure 10a). Estimated data from the ECOG trial were used because the number of patients per treatment arm was not reported.

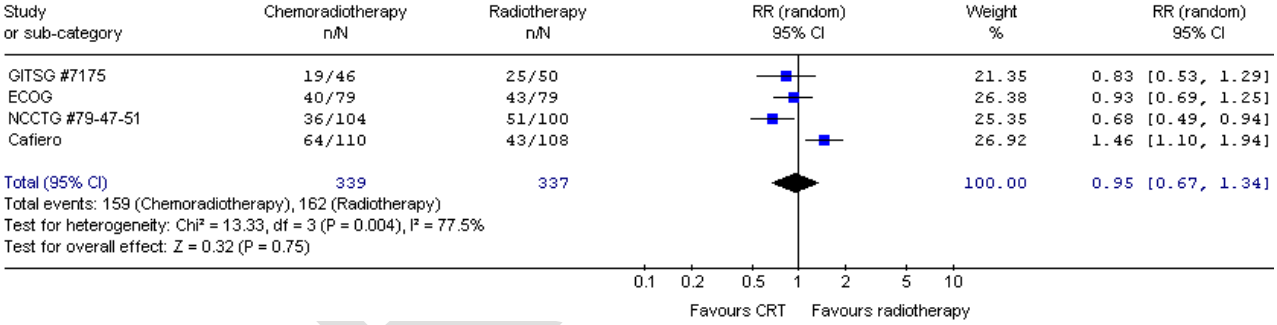
The trial by Cafiero et al (32) was the only trial that administered RT and CT sequentially; the other three trials administered RT concurrently with CT. The Cafiero trial, reported an imbalance in stage III disease between treatment arms (47.2% in the RT arm compared to 67.3% in the CRT arm). In addition, 41% of patients in the CRT arm either stopped CT (32%) or never started CT (9%) (32). The imbalance in study arms and the inability to start or complete the CRT regimen may have had an impact on the study outcome. Due to the different CRT scheduling and significant methodologic issues with this trial, the meta-analyses were also performed without the data from the Cafiero trial. Pooled data of the three remaining trials (16,26,30,31) detected a significant benefit for CRT on overall survival (RR, 0.81; 95% CI, 0.67-0.99; p=0.04) (Figure 9b). Pooled data of the two trials that provided data (16,30,31) also detected a significant benefit for CRT on local failure (RR, 0.54; 95% CI, 0.32-0.90; p=0.02) (Figure 10b).

Table 7. Randomized trials of combined radiotherapy plus systemic chemotherapy versus radiotherapy.

Trials	Median follow-up (months)	Treatment Allocation	# Pts	Local Failure %	p-value	Disease-free survival %	p-value	Overall survival %	p-value
GITSG #7175 1988 (13)	80	RT RT+MF	50 46	20* 11*	NR	52‡ 70‡	NS	50‡ 59‡	NS
ECOG 1988 (14)	108	RT RT+MF	79† 79†	NR	-	40 46	NS	46 50	NS
NCCTG #79-47-51 1991 (20,42)	60	RT RT+MF	100 104	25 14	0.036	37 59	0.002	49 65	0.043
Cafiero 2003 (32)	58	RT RT+FU-Lev	108 110	9 13	NS	34 22	0.66	60 42	0.18

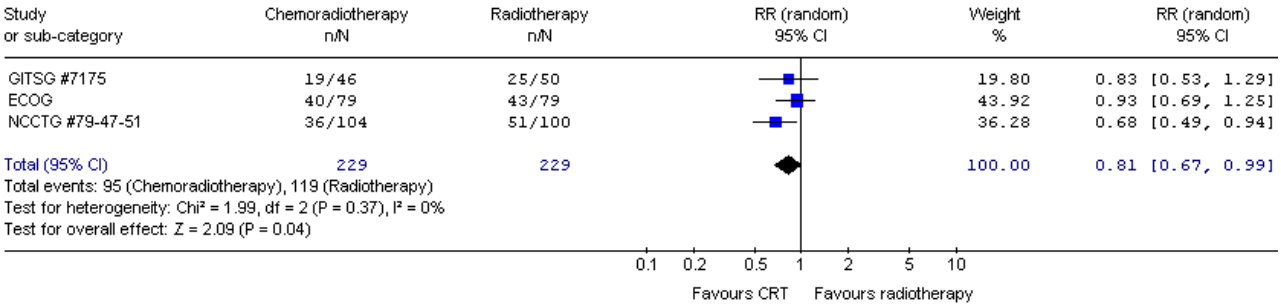
Notes: # Pts, number of patients; RT, radiotherapy; CT, chemotherapy; MF, 5FU and semustine; NR, data not reported; NS, not statistically significant.
* Includes patients with locoregional + distant recurrence
†Patients were randomized to three treatment arms (RT, CT or RT+CT). A total of 248 patients were eligible and 237 were evaluable, but number of patients per treatment arm was not reported. Estimated numbers (79 patients per treatment arm) were used for the meta-analysis conducted for this report.
‡ Estimated from survival curves.
For details about treatment regimens see Appendix 2. For full names of trials and trial groups see Appendix 3.

Figure 9a. Meta-analysis of RCTs comparing combined chemotherapy and radiotherapy to radiotherapy alone: mortality relative risk ratio (random effects model).



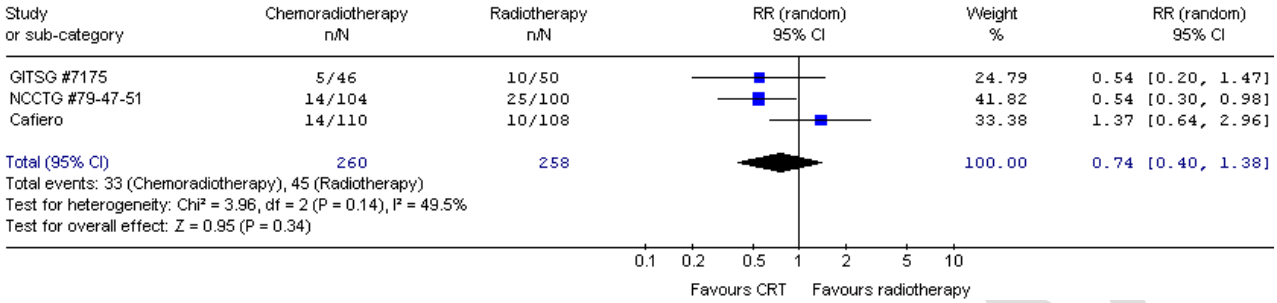
RR = 0.95 (95% CI, 0.67-1.34; p=0.75)

Figure 9b. Meta-analysis of RCTs (without Cafiero et al) comparing combined chemotherapy and radiotherapy to radiotherapy alone: mortality relative risk ratio (random effects model).



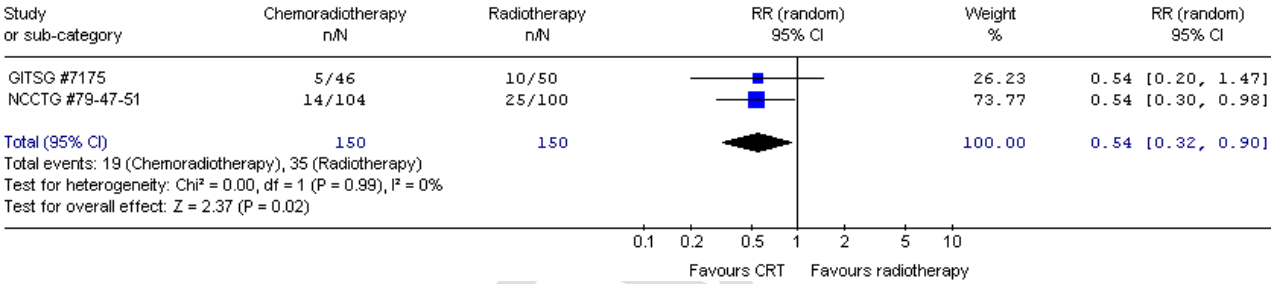
RR = 0.81 (95% CI, 0.67-0.99; p=0.04)

Figure 10a. Meta-analysis of RCTs comparing combined chemotherapy and radiotherapy to radiotherapy alone: local failure relative risk ratio (random effects model).



RR = 0.74 (95% CI, 0.40-1.38; p=0.34)

Figure 10b. Meta-analysis of RCTs (without Cafiero et al) comparing combined chemotherapy and radiotherapy to radiotherapy alone: local failure relative risk ratio (random effects model).



RR = 0.54 (95% CI, 0.32-0.90; p=0.02)

Combined Chemotherapy plus Radiotherapy versus Chemotherapy

Three trials were obtained that tested CRT against CT alone (13,17,28). Results are presented in Table 8. None of the trials detected significant differences between CRT compared with CT alone for either overall survival or local failure.

The NSABP R-02 trial (28) differed from the other trials obtained as the CT alone regimen varied between the male and female patients: female patients received 5FU plus leucovorin, and male patients were randomly assigned to 5FU, semustine, and vincristine (MOF) or 5FU plus leucovorin. Although this trial did not detect a significant benefit in either overall survival or disease-free survival, a significant reduction in the cumulative incidence of loco-regional recurrence was evident for patients randomized to combined CRT compared with CT alone (RR, 0.57; 95% CI, 0.36-0.92; p=0.02), an absolute decrease of 5% (from 13% with CT alone to 8% with CRT at five years). Modifying 5FU with leucovorin was associated with a significant benefit in disease-free survival compared with MOF (55% versus 47% at five years (p=0.009), but there was no significant difference in overall survival between the two types of CT (65% versus 62% at five years; p=0.17).

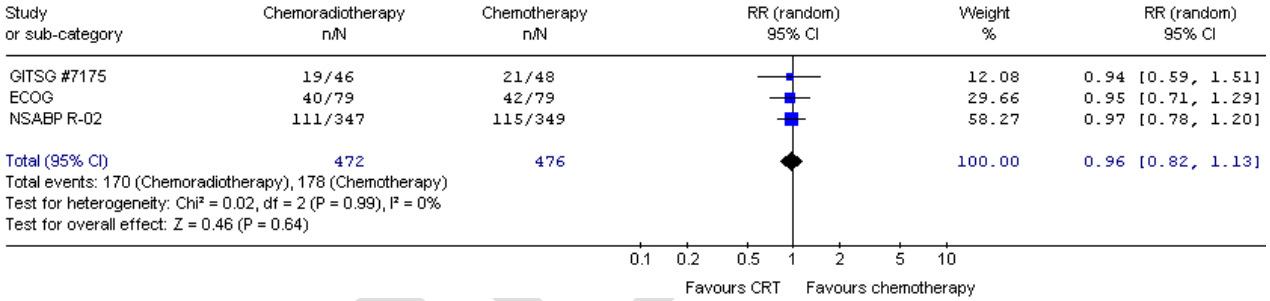
Pooling the data from the three trials (948 patients) did not detect a significant difference between CRT compared with CT alone for overall survival (RR, 0.96; 95% CI, 0.82-1.13; p=0.64) (Figure 11), but a significant difference was detected for local failure (RR, 0.58; 95% CI, 0.38-0.87; p=0.008) (Figure 12). Estimated data from the ECOG trial were used because the number of patients per treatment arm was not reported.

Table 8. Randomized trials of combined radiotherapy plus systemic chemotherapy versus systemic chemotherapy alone.

Trials	Median follow-up (months)	Treatment Allocation	# Pts	Local Failure %	p-value	Disease - free survival %	p-value	Overall survival %	p-value
GITSG #7175 1988 (13)	NR	MF	48	27‡	NS	51	NS	57	NS
		RT+MF	46	11‡		70		59	
ECOG 1991 (17)	108	MF	79†	NR	-	45	NS	47	NS
		RT+MF	79†			46		50	
NSABP R-02 2000 (28)	93 (mean)	FUFA or MOF	349	13	0.02	55*	0.90	67*	0.89
		RT + FUFA or MOF	347	8		58*		68*	

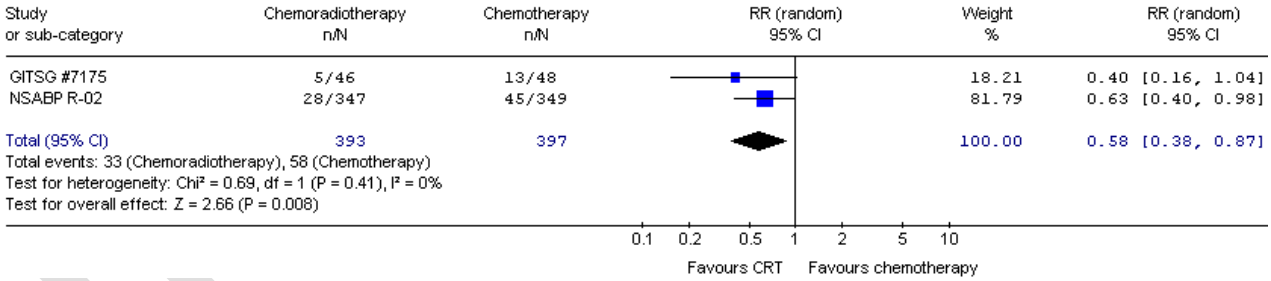
Notes: # Pts, number of patients; RT, radiotherapy; MF, 5FU and semustine; MOF, 5FU, semustine and vincristine; FUFA, 5FU plus leucovorin; NR, data not reported; NS, not statistically significant.
†Patients were randomized to three treatment arms (RT, CT or RT+CT). A total of 248 patients were eligible and 237 were evaluable, but number of patients per treatment arm was not reported. Estimated numbers were used for the meta-analysis conducted for this report.
‡ Includes patients with locoregional and locoregional + distant recurrence
* Estimated from survival curves.
For details about treatment regimens see Appendix 2. For full names of trials and trial groups see Appendix 3.

Figure 11. Meta-analysis of RCTs comparing combined chemotherapy and radiotherapy to chemotherapy alone: mortality relative risk ratio (random effects model).



RR = 0.96 (95% CI, 0.82-1.13; p=0.64)

Figure 12. Meta-analysis of RCTs comparing combined chemotherapy and radiotherapy to chemotherapy alone: local failure relative risk ratio (random effects model).



RR = 0.58 (95% CI, 0.38-0.87; p=0.008)

Comparison of Different Chemotherapy plus Radiotherapy Regimens

Eight trials were obtained that tested varying regimens of CRT against each other (19,21,26,31,33,34,39,41,45,46). Results are presented in Table 9. Only one of the trials (NCCTG 86-47-51 trial) (21) detected a statistically significant difference between treatments in favour of RT given with infusional 5FU compared with RT given with bolus 5FU for overall survival. None of the trials detected a significant difference between treatments for local failure. In the five trials containing an RT plus 5FU-alone arm (19,21,26,39,45), no significant

benefit was reported with the addition of other agents, including folinic acid, levamisole, semustine, and interferon alpha (IFNα).

In the four-arm NCCTG 86-47-51 trial (21) infusional and bolus 5FU delivery were compared against each other in regimens that all included RT. Patients randomized to the bolus 5FU treatment arm were further randomized to test semustine compared with no semustine, and again to test the effectiveness of semustine given before or after RT. The addition of semustine to bolus 5FU did not improve outcomes. The administration of infusional 5FU resulted in a significant overall survival benefit compared with bolus 5FU (p=0.005). Infusional 5FU was associated with lower overall relapse rates (37% versus 47%; p=0.01) and lower distant metastasis rates (31% versus 40%; p=0.03). In contrast, the Intergroup trial 0144 (39) did not detect a significant difference between infusional and bolus 5FU in relapse-free survival or overall survival.

The trial reported by Lee et al (41,46) tested the optimal sequence of CT and RT. All patients received the same regimen of eight cycles of CT at four-week intervals. At seven years, no significant between early RT and late RT was detected for DFS (72% versus 63%; p=0.157) or overall survival (71% versus 68%; p=0.855).

No pooling was performed due to the non-comparable differences in the treatments examined.

Table 9. Randomized trials comparing two or more regimens of systemic chemotherapy, both combined with radiotherapy (RT).

Trials	Median follow-up (months)	Treatment Allocation	# Pts	Local Failure %	p-value	Disease-free survival %	p-value	Overall survival %	p-value
GITSG #7180 1992 (19)	70	RT+MF RT+FU	95 104	17‡ 16‡	NS	48 53	0.20	53 59	0.58
NCCTG 86-47-51 1994 (21)	46	RT+FUbol RT+FUinf	332 328	NR	-	53¶ıı 63¶ıı	0.01	60ıı 70ıı	0.005
		RT+MF(bol+inf) RT+FU(bol)	226 219	9 11	NS	56†¶ıı 58†¶ıı	0.31	66†ıı 62†ıı	0.78
Tepper INT 0114 1997 (31,45)	89	RT+FU RT+FUFA-ld RT+FU+Lev RT+FUFA+Lev	421 425 426 424	12‡ 9‡ 13‡ 9‡	NS	54 56 52 54	NS	62 67 61 64	NS
Fountzilas HeCOG 1999 (26)	59	(RT+FU) (RT+FU)+FUFA-hdx6	109 111	13 13	NS	54 64	0.53	62 64	0.75
Gennatas HeCOG 2003 (33)	NR	RT+FUFA-id RT+FUFA+IFNα	104 103	NR	-	34 36	NS	38 39	NS
Lee/Kim Korea 2002 (41,46)	94	RTd1+FUFA-ld RTd57+FUFA-ld	135 139	2* 6*	0.136 *	72** 63**	0.157	71** 68**	0.855
Staib FOGT-2 2004 (34)	NR	RT+FU+Lev RT+FUFA+Lev RT+FU+Lev+IFNα	280 291 222	12‡ 9‡ 12‡	>0.05	NR	NR	71†† 79†† 72††	NS
Smalley INT-0144 2006 (39)	68	FUbol, RT+FUinf, FUbol FUinf, RT+FUinf, FUinf FUbol, RT+FUFAbol +Lev, FUbol	626 607 623	8 4.6 7	NR	62 62 57	NS	68 71 68	NS

Notes: # Pts, number of patients; FU, 5-fluorouracil (5FU); FUbol, by bolus; FUFA, 5-flourrouracil plus folinic acid or leucovorin; FUinf, by infusion; MF, 5FU and semustine; (RT+FU), 5FU given only during RT; IFNα, interferon alpha; Lev, levamisole; NR, data not reported; NS, not statistically significant; RT, radiotherapy; Tx, treatment.
†Estimated from survival curves.

‡ Includes patients with locoregional and locoregional + distant recurrence, data from publically available online presentation slides.
* Local failure data reported only in full publication (46) at 37 months median follow-up
¶ Recurrence-free survival data.
II Four-year data.
** Seven-year data
†† Three-year data
For details about treatment regimens see Appendix 2. For full names of trials and trial groups see Appendix 3.

Table 10. Pooled results of adjuvant treatments for rectal cancer patients.

Treatment Comparison	Mortality				Local Recurrence			
	# Trials (Ref.)	# Pts	RR for death (95% CI)	Number needed to treat/harm* (95% CI)	# Trials (Ref.)	# Pts	RR for local recurrence (95% CI)	Number Needed to treat/harm* (95% CI)
RT vs. Obs	7 (13-16,18,23,24)	1849	0.98 (0.90,1.07)	NNT 95 (NS)	7 (13-16,18,23,24)	1849	0.78 (0.65, 0.95)	NNT 16 (10, 69)
IV + Oral CT vs. Obs	5 (13,14,22,29,38)	1544	0.75 (0.65, 0.88)	NNT 10 (7, 21)	4 (13,14,22,38)	1341	0.74 (0.55, 0.98)	NNT 20 (12, 249)
CRT vs. Obs	2 (13,25)	240	0.74 (0.55, 0.98)	NNT 8 (5, 97)	2 (13,25)	240	0.42 (0.23, 0.75)	NNT 6 (5, 14)
CT vs. RT	3 (13,14,17)	697	0.85 (0.73, 0.99)	NNT 12 (7,176)	2 (13,14)	469	1.32 (0.92, 1.91)	NNH 19 (NS)
CRT vs. RT	3 (13,17,20)	458	0.81 (0.67, 0.99)	NNT 11 (6,193)	2 (13,20)	300	0.54 (0.32, 0.90)	NNT 10 (5, 43)
CRT vs. CT	3 (13,17,32)	948	0.96 (0.82, 1.13)	NNT 68 (NS)	2 (13,17,32)	790	0.58 (0.38, 0.87)	NNT 17 (12, 53)

Notes: CT, chemotherapy; CT+RT, chemotherapy plus radiotherapy; Obs, observation after surgery; NS, not significant; RR, relative risk ratio; RT, radiotherapy; vs., versus.
* Number of patients needed to prevent (NNT) or cause (NNH) one event, calculated from the relative risk

Adverse Effects

Systematic Review of Adverse Effects

Ooi et al (47) reviewed the adverse effects reported in nine randomized trials of postoperative RT and six randomized trials of postoperative CRT. These trials were identified through a MEDLINE search from 1966 to 1998. The mortality rates ranged from 0% to 5% after postoperative RT and from 0.3% to 18% after postoperative CT plus RT. Diarrhea, nausea, skin reactions, radiation cystitis, and fatigue were common adverse effects after postoperative RT. Five to 11% of patients experienced small-bowel obstruction following postoperative RT. Postoperative CRT was associated with acute gastrointestinal and hematologic adverse effects that may be severe or life-threatening, and delayed adverse effects from RT included radiation enteritis (4%), small-bowel obstruction (5%) and rectal stricture (5%).

Adverse Effects in RCTs of Combined Modality Chemoradiotherapy

Individual trial reports similarly demonstrated greater incidence of adverse effects in patients who received combined CRT than those who received only CT or only RT. In the GITSG 7175 trial (13), severe or worse non-hematologic adverse effects were higher in the combined modality arm (35%) than in patients who received CT alone (15%) or RT alone (16%). In addition, leucopenia was more common among CRT patients than among patients receiving CT alone (26% versus 13%) (13). Miller et al (43), further reporting toxicity on the NCCTG trial by Krook et al (20) found a significant increase in severe or life-threatening diarrhea with the combination of RT and concurrent bolus 5FU CT compared with RT alone (22% versus 4%, p=0.001). Low anterior resection was associated with increased rates of all grades of diarrhea (p<0.001), and severe or life-threatening diarrhea (p=0.006) compared with abdominoperineal resection. Similar findings were reported by Miller et al (44) based on events in the NCCTG trial by O'Connell et al (21). The risk of severe diarrhea with 5FU administration during RT

was higher in patients who had a low anterior resection compared with those who had an abdominoperineal resection (grade 3 diarrhea, 23% versus 10%; p<0.001).

In terms of the toxicities observed for different methods of delivering 5FU in conjunction with RT, the NCCTG trial demonstrated that severe diarrhea was observed more frequently when 5FU was given as an infusion concurrently with RT than when 5FU was given as a bolus injection (24% versus 14%), while the reverse was true for severe leucopenia (2% with infusional 5FU versus 11% with bolus 5FU) (21) (Table 11). The Intergroup 0144 trial (39) demonstrated significantly higher grade 3 to 4 hematologic toxicity in patients who received bolus 5FU compared to patients who received only continuous venous infusion CT (49% to 55% for bolus 5FU arms versus 4% in the continuous venous infusion arm). However, even though grade 3 to 4 hematologic toxicities were higher in the bolus arms, the rates of grade 3 to 4 infections were only slightly lower in the continuous infusion arm (9 to 10% for bolus 5FU arms versus 6% in the continuous venous infusion arm). Grade 3 to 4 gastrointestinal toxicities were similar between all treatment groups in the Intergroup 0144 trial.

Table 11. Adverse effects for different methods of delivering 5FU.

Trial	Adverse effect	Bolus 5FU	CVI 5FU
NCCTG (21)	Severe or life-threatening diarrhea	14%	24%
	Leukopenia (<2000/mm^3)	11%	2%
INT 0144 (39)	Grade 3/4 hematologic toxicity	55%	4%
	Grade 3/4 infection	10%	6%
	Grade 3/4 GI toxicity	41%	42%

Notes: 5FU, 5-fluorouracil; vs, versus; CVI, continuous venous infusion.

Overviews of Adjuvant Trials in Rectal Cancer

Six published meta-analyses of adjuvant therapy for colorectal cancer were identified and included (48-53). Meta-analyses that did not report results separately for patients with rectal cancer were excluded. Results are summarized in Table 11 (Appendix 4). One meta-analysis compared postoperative RT with surgery alone (51), two compared IV systemic CT with surgery alone (48), and four compared oral fluoropyrimidines with surgery alone (49,50,52,53)

In general the results of the published meta-analyses were in agreement with those of the current review. An individual patient data (IPD) meta-analysis comparing postoperative RT with surgery alone reported no significant survival benefit; however, there was a significant benefit for RT in five-year isolated local recurrence (51). For the comparison of postoperative CT with no postoperative CT, a meta-analysis of rectal cancer patients from three trials reported a significant survival benefit for CT (48). Generally, the four meta-analyses by Sakamoto et al (49,51,52,62) demonstrated an overall survival and disease-free survival benefit for oral fluoropyrimidines compared with surgery alone, although not all analyses were able to detect a statistically significant difference between groups.

DISCUSSION

The goal of this systematic review was to determine the optimal adjuvant treatment strategy for patients with resected stage II and III rectal cancer with overall survival and local failure rates as the outcomes of interest.

While both RT (Figures 1 and 2) and CT (Figures 3 and 4) as single modalities improve outcomes compared to surgery alone, the pooled analyses performed in this overview reveal that combined modality therapy with both CT and RT is the optimal adjuvant therapy for patients with resected stage II and III rectal cancer. Although no significant difference was

detected between CRT and CT for overall survival (Figure 11), a significant benefit for CRT on local failure was observed in the pooled analysis (Figure 12). A significant benefit in overall survival and local failure was detected for CRT compared to RT alone (Figure 9b and Figure 9b) when a methodologically flawed trial (32) that used sequential rather than concurrent CRT was excluded from the pooled analysis. The fact that all trials in this pooled analysis used concurrent RT and CT suggests that this should be the preferred method of delivering combined modality therapy.

Adjuvant treatments, especially CRT regimens, are associated with significant acute and chronic toxicity (43,44,47) that need to be discussed with patients as part of the informed discussion regarding adjuvant treatment of rectal cancer. Enteritis, diarrhea, bowel obstruction or perforation, and fibrosis within the pelvis are associated with RT. Delayed adverse effects from RT include radiation enteritis, small bowel obstruction and rectal stricture. A greater number of hematological and non-hematological adverse effects are associated with CT plus RT than with CT alone or RT alone. Postoperative combined CT plus RT is associated with acute gastrointestinal and hematologic adverse effects that may be severe or life threatening (47).

In the five trials containing an RT plus 5FU-alone arm (19,21,26,39,45), no significant benefit was reported with the addition of other agents, including folinic acid, levamisole, semustine, and interferon alpha (IFNα). Other promising agents, such as capecitabine and oxaliplatin, have not been thoroughly studied in randomized trials of rectal cancer patients. A trial examining the role of oxaliplatin (e.g., ECOG-E3201) was closed early due to poor accrual. This agent is emerging as a standard of care with no additional studies in the postoperative setting anticipated, bypassing the traditional evidentiary development path. While the DSG would normally be reluctant to recommend a therapy in the absence of definitive evidence, it is reasonable to consider oxaliplatin and capecitabine here. Specifically, despite the fact that there is currently no direct randomized evidence for these newer agents in rectal cancer, there is evidence for the benefits of capecitabine and oxaliplatin in the adjuvant therapy of resected colon cancer (55,56). Given the biologic similarity between colon and rectal cancer in terms of their histology, tissue of origin, patterns and risk of systemic recurrence, and the fact that these two diseases are treated the same when they metastasize, the adjuvant systemic therapy of rectal cancer has been led by advances in the adjuvant therapy of colon cancer. The CAO/ARO/AIO-04 trial (See Ongoing Trials, Appendix 3) is designed to examine the relative benefit of adjuvant 5FU with or without oxaliplatin. However, in North America, based on the extrapolation of data from the adjuvant colon trials, oxaliplatin-based postoperative therapy has been accepted as a standard and in the current NCIC CTG-endorsed Intergroup trial for rectal cancer, (ECOG-E5204) patients in both arms are receiving oxaliplatin based adjuvant therapy. Given the benefits observed with capecitabine and oxaliplatin based therapy in the adjuvant treatment of colon cancer (see Evidence-Based Series [EBS] #2-29), it is reasonable and appropriate to offer patients with resected rectal cancer at high risk of systemic recurrence (as described in EBS #2-29) the same adjuvant systemic therapy as their counterparts with colon cancer.

What is the optimal way of delivering CT during RT? Two trials (21,39) compared the administration of 5FU by continuous venous infusion to bolus administration during RT treatment. In terms of efficacy, the NCCTG trial (21) demonstrated a significant benefit for the continuous venous infusion group on both disease-free survival and overall survival, while the Intergroup 0144 trial (39) reported no significant difference between groups receiving infusional or bolus 5FU. In both trials, severe hematologic toxicity was significantly higher in the treatment arms containing bolus 5FU compared to the continuous venous infusion 5FU arms (Table 11). However, in the Intergroup trial, this decreased myelosuppression translated into only slightly lower rates of grade 3/4 infections in the continuous infusion

arms (Table 11) (39). The Intergroup trial showed similar rates of grade 3/4 GI toxicity in all treatment arms, while the NCCTG trial (21) demonstrated higher rates of severe diarrhea when continuous infusion 5FU was given in conjunction with RT. Given these conflicting results for both efficacy and toxicity, neither method of administering 5FU in conjunction with RT is clearly superior in terms of efficacy or toxicity, and decisions for individual patients should be based on an informed discussion of the potential risks and benefits of each mode of delivery.

A growing body of evidence is emerging to support the use of preoperative, neoadjuvant treatment strategies for resectable rectal cancer—practitioners are urged to review the evidentiary base for preoperative therapy (Section 2. Part 1) for further discussion of preoperative CT and RT.

A substantial number of trials included in this systematic review were conducted before the adoption of the TME technique or did not report on surgical techniques used; therefore, it is likely that many trials did not use current standards for resection of rectal tumours. There is evidence that the use of TME drastically reduces the risk of local recurrence compared with conventional resection (54). Single-institution case series and retrospective chart reviews have demonstrated that the proper performance of TME can result in local recurrence risks in the single digits without the use of CT or RT. There are no data in the postoperative setting to determine whether the current recommendation for postoperative CRT holds if optimal surgery is performed. For patients who undergo TME with negative resection margins and who have favourable prognostic characteristics, the incremental benefit of RT may be small. For these patients, a discussion of the trade-offs between toxicities associated with therapy and the potential benefits is particularly crucial.

In summary, patients with resected stage II and III rectal cancer who have not received preoperative RT should be offered adjuvant therapy with concurrent CRT in addition to fluoropyrimidine-based CT; however, further studies are needed to optimize therapy even further. For potential participation, patients should be made aware of active trials at the institutions where they are treated.

ONGOING TRIALS

The National Cancer Institute (NCI) database (available from: http://www.cancer.gov/search/clinical_trials/) was searched for relevant ongoing clinical trials on December 10, 2007. A listing of relevant trials appears in Appendix 5. One preliminary report (59) was obtained and is included in this ongoing trials section. As no efficacy data was available for this preliminary report, it is not included in the main document.

CONFLICT OF INTEREST

Members of the GI DSG involved in the development of this evidence-based series were polled for conflicts of interest and declared that there were none.

JOURNAL REFERENCES

The following updated practice guideline based on EBS#2-4 has been published by *Clinical Oncology* (© 2010 The Royal College of Radiologists; http://www.clinicaloncologyonline.net/home):

- Wong RKS, Berry S, Spithoff K, Simunovic M, Chan K, Agboola O, et al; Gastrointestinal Cancer Disease Site Group. Postoperative therapy for stage II or III rectal cancer: an updated practice guideline. Clin Oncol (R Coll Radiol). 2010 May;22(4):265-71. doi:10.1016/j.clon.2010.03.002.

Practice Guideline #2-13 was published as:

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For a complete list of the Gastrointestinal Cancer DSG members, please visit the CCO Web site at http://www.cancercare.on.ca/

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Appendix 1. Comparison of staging systems for colorectal cancer.

AJCC	UICC	Astler-Coller	Dukes'
Stage I Tumour invades submucosa T1, N0, M0	**Stage IA** T1, N0, M0	**A**	**A**
Tumour invades muscularis propria T2, N0, M0	**Stage1B** T2, N0, M0	**B1**	
Stage II Tumour invades through muscularis propria into the subserosa, or into nonperitonealized pericolic or perirectal tissues T3, N0, M0	**Stage II** T3, T4, N0, M0 (T3a with fistula) (T3b without fistula)	**B2**	**B**
Tumour perforates the visceral peritoneum, or directly invades other organs or structures T4, N0, M0			
Stage III Any degree of bowel wall with regional node metastasis Any T, N1-3, M0	**Stage III** Any T, N1, M0	**C1/C2**	**C**
Stage IV Any invasion of bowel wall, with or without regional lymph node metastasis, but with evidence of distant metastasis Any T, and N,M1	**Stage IV** Any T, any N, M1	**D**	

Notes: AJCC, American Joint Commission on Cancer; UICC, International Union Against Cancer

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Appendix 2. Treatment administration and dosage schedules in randomized trials.

Radiotherapy versus observation	
GITSG 7175 (13)	40 to 48 Gy over 4.5 to 5.5 weeks
NSABP R-01 (14)	46 to 47 Gy over 5 weeks
Netherlands (15)	50 Gy over 5 weeks
ANZ (16)	45 Gy over 5 weeks
Denmark (18)	50 Gy over 7 weeks
MRC (23)	40 Gy in 20 fractions
EORTC (24)	32 Gy by antero-posterior portals and 14 Gy by lateral fields over 30 to 38 days
Chemotherapy versus observation	
GITSG 7175 (13)	MF: Semustine 130 mg/m^2 orally on day 1; 5-FU by intravenous bolus injection (IVB) 325 mg/m^2 on days 1 to 5 and 375 mg/m^2 on days 36 to 40. Repeat cycle every 10 weeks for 18 months
NSABP R-01 (14)	MOF: Semustine 130 mg/m^2 orally on day 1; vincristine 1 mg/m^2 on days 1 and 36; and 5-FU by IVB 325 mg/m^2 on days 1 to 5, and 375 mg/m^2 on days 36-40. Repeat cycle every 10 weeks for 18 months
CCCSG-Japan (22)	Mitomycin C by IVB 6 mg/m^2 on days 7 and 14 postoperatively, then bimonthly; 5-FU orally 200 mg/m^2/day starting on day 14. Continue for 6 months
NACCP (29)	5-FU 450 mg/m^2 days 1 to 5 and starting on day 28 once weekly, plus levamisole 50 mg three times daily for 3 days repeated every 2 weeks; to complete one year of treatment
Akasu et al, Japan (38)	UFT 400 mg/m^2/day for 5 days out of every 7 for one year following resection
Hamaguchi (40)	UFT 400 mg/m2/day for 5 days per week for one year
Chemoradiotherapy versus observation	
GITSG 7175 (13)	40 to 44 Gy over 5 weeks; 5-FU by IVB 500 mg/m^2 first 3 days and last 3 days of RT; starting on day 70, semustine and 5-FU as in CT above
Tveit for NARCPG (25)	46 Gy in 23 fractions plus 5-FU IVB 500 or 750 mg total dose (cut of body surface 1.75 m^2) 30 minutes before radiation fractions 1, 2, 11, 12, 21 and 22
Chemotherapy versus radiotherapy	
GITSG 7175 (13)	**CT:** MF: Semustine 130 mg/m^2 orally on day 1; 5-FU by intravenous bolus injection (IVB) 325 mg/m^2 on days 1 to 5 and 375 mg/m^2 on days 36 to 40. Repeat cycle every 10 weeks for 18 months **RT:** 40 to 44 Gy over 5 weeks; 5-FU by IVB 500 mg/m^2 first 3 days and last 3 days of RT; starting on day 70
NSABP R-01 (14)	**CT:** MOF: Semustine 130 mg/m^2 orally on day 1; vincristine 1 mg/m^2 on days 1 and 36; and 5-FU by IVB 325 mg/m^2 on days 1 to 5, and 375 mg/m^2 on days 36-40. Repeat cycle every 10 weeks for 18 months **RT:** 46 to 47 Gy over 5 weeks
ECOG 4276 (17)	**CT:** 5-FU plus semustine; neither dose nor schedule available **RT:** Neither dose nor schedule available
Chemotherapy versus chemotherapy	
Igawaki et al. (27)	CT-1: HCFU 300 mg/day, starting on day 14 for 52 weeks CT-2: 5-FU 333 mg/m^2/day by continuous IV infusion on days 0 to 3 and 6 to 9, followed by HCFU as above
Iwamoto for the TSGCCC, Sendai (30)	**CT-1:** HCFU 300 mg/day, starting on day 14 and given for 52 weeks **CT-2:** Mitomycin C 6 mg/m^2 IVB day plus 5-FU 180 mg/m^2/day by continuous IV infusion on days 1 to 6, and followed by HCFU as treatment A
Chau et al. (35)	**CT-1:** 5-FU 300mg/m^2/day for 12 weeks by continuous IV infusion **CT-2:** 5-FU 425 mg/m^2 by bolus and LV 20 mg/m^2 on days 1-5 every 4 weeks for six cycles
Tsavaris et al (36)	**CT-1:** LV 20 mg/m2 IV bolus and 5-FU 425 mg/m^2 IV bolus (immediately after LV) on days 1-5, repeated every 4 weeks for 6 cycles **CT-2:** 5-FU 425 mg/m^2 IV bolus days 1-5 and after 4 weeks weekly 5-FU 425 mg/m^2 IV bolus plus levamisole tablets 50 mg t.i.d. for 3 days every 2 weeks for 12 months
Kotake et al (37)	**CT-1:** 5-FU CVI 24 hrs 320 mg/m2/day for 14 days, oral HCFU 300 mg/day from the fourth post0operative week for one year

	CT-2: 5-FU CVI 24 hrs 320 mg/m2/day for 14 days
Chemoradiotherapy versus radiotherapy	
GITSG 7175 (13)	**CRT:** 40 to 44 Gy over 5 weeks; 5-FU by IVB 500 mg/m^2 first 3 days and last 3 days of RT; starting on day 70, semustine and 5-FU as in CT above. Repeat cycle every 10 weeks for 18 months. **RT:** 40 to 44 Gy over 5 weeks
ECOG 4276 (17)	**CRT:** 5-FU plus semustine and RT; neither dose nor schedule available. **RT:** Neither dose nor schedule available
Krook et al NCCTG 79-47-51 (20)	**CRT:** Semustine 130 mg/m^2 orally on day 1, and 5-FU by IVB 300 mg/m^2 on days 1 to 5, and 400 mg/m^2 on days 36 to 40. RT 4500 cGy over 5 weeks starting on day 68, with 5-FU by IVB 500 mg/m^2 first 3 days of the first and fifth week of RT. Repeat 5-FU and semustine regimen as above starting on day 131. Regimen was given for six months **RT:** 4500 cGy over 5 weeks
Cafiero for PARCG, Genoa, Italy (32)	**CRT:** 5-FU 450 mg/m^2/day 1-5 and after day 28 weekly plus levamisole 50 mg three times a day every 2 weeks, both for one year; RT same dose, start week 2 **RT:** 50 Gy in 25 fractions; start day 1
Chemoradiotherapy versus chemotherapy	
GITSG 7175 (13)	**CRT:** 40 to 44 Gy over 5 weeks; 5-FU by IVB 500 mg/m^2 first 3 days and last 3 days of RT; starting on day 70, semustine and 5-FU as in CT above **CT:** Semustine 130 mg/m^2 orally on day 1; 5-FU by intravenous bolus injection (IVB) 325 mg/m^2 on days 1 to 5 and 375 mg/m^2 on days 36 to 40. Repeat cycle every 10 weeks for 18 months
ECOG 4276 (17)	**CRT:** 5-FU plus semustine and RT; neither dose nor schedule available. **CT:** 5-FU plus semustine; neither dose nor schedule available.
NSABP, R-02 (28)	**CRT:** All patients received chemotherapy. Females received leucovorin 500 mg/m^2 followed by 5-FU 500 mg/m^2 once weekly for 6 weeks in 8-week cycles, repeated 6 times. Males were randomized to the same chemotherapy or to 5-FU 375 mg/m^2 days 1-5 and 36-40 and semustine 130 mg/m^2 day 1 of 8-week cycles, repeated 5 times, plus RT 45Gy in 25 fractions plus 5.4 Gy boost; during RT, chemotherapy was limited to 5-FU 400 mg/m^2 the first 3 and last 3 days of RT **CT:** All patients received chemotherapy. Females received leucovorin 500 mg/m^2 followed by 5-FU 500 mg/m^2 once weekly for 6 weeks in 8-week cycles, repeated 6 times. Males were randomized to the same chemotherapy or to 5-FU 375 mg/m^2 days 1-5 and 36-40 and semustine 130 mg/m^2 day 1 of 8-week cycles, repeated 5 times
Chemoradiotherapy versus chemoradiotherapy	
GITSG 7180 (19)	**CRT-1:** 4140 cGy over 23 days with 5-FU by IVB 500 mg/m^2 for 3 days during the first and last week of RT; after a 5-week rest, semustine 100 mg/m^2 orally on day 1, and 5-FU by IVB 325 mg/m^2 on days 1 to 5, and 375 mg/m^2 on days 36 to 40. Repeat cycle of chemotherapy every 10 weeks. Total treatment duration was initially 20 months but later reduced to 1 year **CRT-2:** RT with concurrent 5-FU as in CRT treatment; after a 5-week rest, 5-FU by IVB 350 mg/m^2 on days 1 to 5; repeat cycles of chemotherapy every 4 weeks, 4 times. 5-FU doses were increased by increments of 50 mg/m^2 per cycle. Total duration of treatment was five months
O'Connell et al for NCCTG 86-47-51 (21)	**CRT-1:** 4500 cGy over 5 weeks with 5-FU by IVB 500 mg/m^2 for 3 consecutive days during weeks 1 and 5 of RT; semustine 130 mg/m^2 orally on day 1 and 100 mg/m^2 on day 134; 5-FU by IVB 350 mg/m^2 on days 1 to 5, 400 mg/m^2 on days 36 to 40, 300 mg/m^2 on days 134 to 138, and 350 mg/m^2 on days 169-173 **CRT-2:** As CRT-1 except 5-FU during RT given as a protracted intravenous infusion at a dose of 225 mg/m^2/day for 5 weeks **CRT-3:** 4500 cGy over 5 weeks with 5-FU by IVB 500 mg/m^2 for 3 consecutive days during weeks 1 and 5 of RT; 5-FU by IVB 500 mg/m^2 on days 1 to 5 and 36 to 40, 300 mg/m^2 on days 134-138, and 350 mg/m^2 on days 169 to 173

	CRT-4: As CRT-3 but 5-FU during RT given as a protracted intravenous infusion at a dose of 225 mg/m^2/day for 5 weeks. Total duration of these 4 treatments is 6 months
Fountzilas et al for HeCOG (26)	**CRT-1**: RT 45Gy plus boost 5.4 Gy in 28 fractions by multiple fields plus 5-FU 400 mg/m^2 for 3 days in the first and last week of RT **CRT-2:** RT plus 5-FU as above plus leucovorin 500 mg/m^2 plus 5-FU 500 mg/m^2 weekly for 6 weeks in 8-week cycles; one cycle before RT+5-FU and 3 cycles following RT
Tepper (31)	**CRT-1:** All patients received RT starting on day 57, receiving 45 Gy in 25 fractions through multiple fields and boosts of 5.4 Gy, plus 5-FU 500 mg/m^2 days 1-5, 36-40, 57-59, 85-87, 134-138 and 169-173 **CRT-2:** All patients received RT starting on day 57, receiving 45 Gy in 25 fractions through multiple fields and boosts of 5.4 Gy, plus 5-FU 425 mg/m^2 plus leucovorin 20 mg/m^2 in the same schedule as CRT-1; dose of 5-FU decreased to 400 mg/m^2 during RT **CRT-3:** All patients received RT starting on day 57, receiving 45 Gy in 25 fractions through multiple fields and boosts of 5.4 Gy, plus 5-FU 500 mg/m^2 as in CRT-1 added with levamisole 50 mg three times a day for 3 days, repeated every 2 weeks **CRT-4:** All patients received RT starting on day 57, receiving 45 Gy in 25 fractions through multiple fields and boosts of 5.4 Gy, plus 5-FU and leucovorin as in CRT-2 plus levamisole as in CRT-3
Gennatas et al. for HeCOG (33)	**CRT-1:** 5-FU 425 mg/m^2 plus leucovorin 20 mg/m^2 days 1-5 and 29-33; 5-FU 400 mg/m^2 plus leucovorin 20 mg/m^2 days 57-60 and 85-66, and 5-FU 375 mg/m^2 plus leucovorin 20 mg/m^2 on days 134-138 and 169-173 **CRT-2:** Same treatment as above plus interferon alpha-2b, 5x10up6 IU SC times 3 during each week of chemotherapy
Staib et al, Germany (34)	**CRT-1:** Postoperative loading course: 5-FU 450 mg/m^2 d1-5 (arms A and C) or 5-FU 450 mg/m^2 plus leucovorin 200 mg/m^2 d1-5 (arm B). Lev was administered orally at 150 mg/d d1-3, every 2 weeks. After 4 weeks the treatment was continued weekly for one year. RT was given over a 6-week period postoperatively in a three-field technique up to a dose of 45-50,4 Gy in 1,8 Gy fractions 5x per week administered along with a 20% reduction in 5-FU dose, plus 5-FU once per week plus levamisole. **CRT-2:** Postoperative loading course: 5-FU 450 mg/m^2 d1-5 (arms A and C) or 5-FU 450 mg/m^2 plus leucovorin 200 mg/m^2 d1-5 (arm B). Lev was administered orally at 150 mg/d d1-3, every 2 weeks. After 4 weeks the treatment was continued weekly for one year. RT was given over a 6-week period postoperatively in a three-field technique up to a dose of 45-50,4 Gy in 1,8 Gy fractions 5x per week administered along with a 20% reduction in 5-FU dose, plus 5-FU plus Lev, modulated with leucovorin d1, week 1 **CRT-3:** Postoperative loading course: 5-FU 450 mg/m^2 d1-5 (arms A and C) or 5-FU 450 mg/m^2 plus leucovorin 200 mg/m^2 d1-5 (arm B). Lev was administered orally at 150 mg/d d1-3, every 2 weeks. After 4 weeks the treatment was continued weekly for one year. RT was given over a 6-week period postoperatively in a three-field technique up to a dose of 45-50,4 Gy in 1,8 Gy fractions 5x per week administered along with a 20% reduction in 5-FU dose, plus 5-FU plus Lev, modulated with IFNa at 6 million units 3 times during week one only
Smalley et al for INT-0144A, Intergroup trial, (39)	**CRT-1** B 5-FU 2 five day cycles q28d before (500 mg/m^2/d) and after (450 mg/m^2/d) XRT (50.4 to 54 Gy) plus 5-FU via PVI 225 mg/m^2/d during XRT **CRT-2** PVI 5-FU (300 mg/m^2/d) 42d before and 56d after identical XRT + PVI as arm 1 **CRT-3** B 5-FU + FA (20 mg/m^2) in 2 five day cycles q28d before (425 mg/m^2 5-FU) and after (380 mg/m^2 5-FU) XRT + bolus 5-FU (400 mg/m^2) + FA d1-4 of week 1,5 of XRT + LEV 150 mg/d d1-3,14-16 each cycle before and after XRT
Lee et al., Korea (46)	**CRT-1**: RT 45 Gy in 25 fractions starting on day 1 plus chemotherapy with 5-FU 375 mg/m^2 and leucovorin 20 mg/m^2 on days 1 to 3 and then days 1 to 5 of monthly courses of chemotherapy **CRT-2:** Chemotherapy as above; RT to start on day 57. Both chemotherapy regimens were given for 6 months

Appendix 3. Clinical trial groups.

Abbreviation	Clinical Trial Group
ANZ	Australia and New Zealand Bowel Cancer Trial
AXIS	Adjuvant X-ray and 5-fluorouracil Infusion Study
CCCSG (Japan)	Colorectal Cancer Chemotherapy Study Group of Japan
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
FOGT	Forschungsgruppe Onkologie Gastrointestinaler Tumoren
GITSG	Gastrointestinal Tumour Study Group
HeCOG	Hellenic Cooperative Oncology Group
MRC (UK)	Medical Research Council
NACCP	Netherlands Adjuvant Colorectal Cancer Project
NARCPG	Norwegian Adjuvant Rectal Cancer Project Group
NCCTG (US)	North Central Cancer Therapy Group
NSABP (US)	National Surgical Adjuvant Breast and Bowel Project
NSAS (Japan)	National Surgical Adjuvant Study
SAKK	Swiss Group for Clinical Cancer Research

Appendix 4. Published systematic reviews and meta-analyses of adjuvant therapy for colorectal cancer.

Review, year (reference)	Patient Population	Data source	Treatment	# of RCTs in analysis (# of patients)	References of included RCTs	Results
Radiotherapy versus observation						
Colorectal Cancer Collaborative Group (CCCG), 2001 (51)	Rectal cancer	IPD	Postop RT vs. surgery alone	8	13-17,19,26, one not included in PEBC review	4.6% reduction in mortality favouring RT (SE 5.9, p>0.05). Significant reduction in 5-year isolated local recurrence for RT (15.0% vs. 22.9%, p=0.0002). Overall risk reduction for isolated local recurrence was 36.9%, not affected by age or disease stage.
IV systemic chemotherapy versus observation						
Dube, 1997 (48)	Colorectal cancer (rectal cancer subgroup)	Published data	Postop CT vs. no CT (one trial CRT vs. RT)	3 in rectal subgroup	16,17,31	Mortality OR, 0.64 (95% CI, 0.48-0.85; p<0.05), favouring CT. Absolute 5-year OS increase 9%.
Oral systemic chemotherapy versus observation						
Sakamoto, 1999 (49)	Colorectal cancer (rectal cancer subgroup)	IPD	Oral fluoropyrimidines (5FU+MMC, tegafur+MMC, carmofur) vs. surgery alone	3 (4960 pts total, 2310 rectal cancer pts)	21, two not included in PEBC review	DFS RR, 0.77 (95% CI, 0.66-0.89; p=0.0003) favouring CT for rectal cancer pts. OS RR, 0.87 (95% CI, 0.73-0.99; p=0.049) favouring CT for rectal cancer pts.
Sakamoto, 2001 (50)	Stage II or III colorectal cancer (rectal cancer subgroup)	IPD	Carmofur vs. surgery alone or other CT	3 (614 pts total, 267 rectal cancer pts)	None included in the PEBC review	DFS RR, 0.72 (95% CI, 0.47-1.09; p>0.05) for rectal cancer pts. OS RR, 0.67 (95% CI, 0.43-1.06; p>0.05) for rectal cancer pts.
Sakamoto, 2004 (52)	Colorectal cancer (rectal cancer subgroup)	IPD	Oral fluoropyrimidines vs. surgery alone	3	NR	Mortality HR, 0.92 (95% CI, 0.79-1.07; p>0.05) favouring oral CT for rectal cancer pts. DFS HR, 0.83 (95% CI, 0.73-0.95; p<0.05) favouring oral CT for rectal cancer pts.
Sakamoto, 2007 (53)	Rectal cancer	IPD	UFT vs. surgery alone	5 (2091)	NR	Mortality HR, 0.82 (95% CI, 0.70-0.97; p=0.02) favouring UFT. DFS HR, 0.73 (95% CI, 0.63-0.84; p<0.0001) favouring UFT. Local relapse-free survival HR, 0.68 (95% CI, 0.53-0.87; p=0.0026) favouring UFT.

Notes: 5FU, 5-fluorouracil; CI, confidence interval; CT, chemotherapy; DFS, disease-free survival; HR, hazard ratio; IPD, individual patient data; IV, intravenous; OS, overall survival; LEV, levamisole; LV, leucovorin calcium; MMC, mitomycin C; NR, not reported; OR, odds ratio; PEBC, Program in Evidence-based Care; SE, standard error; pts, patients; PVI, portal venous infusion; RR, relative risk; RT, radiotherapy; TNM, see Appendix 1 for staging information; UFT, tegafur-uracil.

* Update of Buyse et al meta-analysis (5) to 1990.

† Unclear whether this meta-analysis is a combined analysis of trials included in Sakamoto 1999 and 2004 (49,62).

Appendix 5. Ongoing trials.

5FU/LV vs. LV5FU2 + CPT11 in Stage II-III Resected Rectal Cancer	
Protocol ID:	AERO-R98, NCT00189657, R98 Intergroup Trial [France]
Last date modified:	September 12, 2005
Trial type:	Multicentre, treatment, randomized, open label, active control, parallel assignment, safety/efficacy study
Accrual:	600 patients will be accrued
Primary endpoint:	Disease-free survival
Sponsorship:	Association Européenne de Recherche en Oncologie, Aventis Pharmaceuticals, Pfizer
Status:	Recruiting, preliminary report available (59)
Expected completion	Not reported

Randomized Phase III Clinical Study Comparing Postoperative UFT+LV, UFT+LV/UFT and UFT+LV+PSK/UFT+PSK Therapies for Stage III Colorectal Cancer	
Protocol ID:	HGCSG-CAD, NCT00209742
Last date modified:	October 30, 2007
Trial type:	Treatment, randomized, open label, active control
Accrual:	340 patients will be accrued
Primary endpoint:	3-year disease-free survival
Sponsorship:	Hokkaido Gastrointestinal Cancer Study Group
Status:	Recruiting
Expected completion	October 2008

Randomized Phase III Trial Comparing Adjuvant Oral UFT/LV to 5-FU/l-LV in Stage III Colorectal Cancer	
Protocol ID:	JCOG-0205-MF, NCT00190515, C000000193
Last date modified:	May 31, 2007
Trial type:	Treatment, randomized, open label, active control, parallel assignment, safety/efficacy study
Accrual:	1100 patients were to be accrued
Primary endpoint:	Disease-free survival
Sponsorship:	Japan Clinical Oncology Group, Japanese Ministry of Health, Labor and Welfare
Status:	Ongoing, no longer recruiting patients
Expected completion	November 2011

Phase III Randomized Study of Adjuvant Tegafur-Uracil Versus Observation Only in Patients With Curatively Resected Stage II Colorectal Cancer	
Protocol ID:	TMDU-BRI-CC-05-01, NCT00392899
Last date modified:	November 9, 2007
Trial type:	Treatment, randomized, active control
Accrual:	2000 patients will be accrued
Primary endpoint:	Disease-free survival
Sponsorship:	Tokyo Medical and Dental University
Status:	Recruiting
Expected completion	Not reported

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: EBS Development Methods and External Review Process

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: Document Review Summary and Tool for a summary of updated evidence published between 2008 and 2017, and for details on how this Clinical Practice Guideline was ENDORSED.

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based guidelines, known as Evidence-based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

The Evidence-Based Series

This EBS is comprised of three sections:

- *Section 1: Guideline Recommendations.* Contains the clinical recommendations derived from a systematic reviews of the clinical and scientific literature and its interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.
- *Section 2. Evidentiary Base: Part 1. Preoperative Therapy.* Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on preoperative therapy for rectal cancer and the conclusions reached by the Group or Panel.
- *Section 2. Evidentiary Base: Part 2. Postoperative Therapy.* Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on postoperative therapy and the conclusions reached by the Group or Panel.
- *Section 3: EBS Development Methods and External Review Process.* Summarizes the evidence-based series development process and the results of the formal external review of the draft version of Section 1: Recommendations and Section 2. Evidentiary Base: Part 1 and Part 2.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This EBS was developed by the GI DSG of the CCO PEBC. The series is a convenient and up-to-date source of the best available evidence on preoperative or postoperative therapy for stage II or III rectal cancer, developed through review of the evidentiary base, evidence synthesis, and input from external review participants in Ontario. The GI DSG is comprised of medical oncologists, radiation oncologists, surgeons, and a community representative. A complete list of DSG members can be found on the CCO website at http://www.cancercare.on.ca/english/toolbox/qualityguidelines/diseasesite/gastro-ebs/gastro-dsg/

Disease Site Group Consensus Process

Discussions by the members of the GI DSG concerning the draft recommendations involved the following:

1. Current data suggest that CRT should be part of the adjuvant treatment of stage II and III rectal cancer as it does improve both local recurrence and survival.
2. A major debate developed about whether RT should be administered before or after surgery. Preoperative short-course RT seems better where local control and toxicity are concerned compared to a standard five-week course of postoperative RT. However, using preoperative RT may lead to the treatment of some patients who do not need it and may interfere with the selection for chemotherapy if disease stage is altered, although recent evidence demonstrates that stage is not altered when short-course RT is followed by surgery within 10 days (3).
3. The role of CT alone or combined with RT needs to be clarified. Two areas of concern are the need for adjuvant CT for stage II patients and the duration of CT for stage III patients. The members of the GI DSG felt it was crucial to support clinical trials addressing these issues.
4. Some members felt that local recurrence rates after surgery in the reviewed trials were much higher than rates expected by current standards that include total mesorectal excision (TME).
5. The survival advantage of adjuvant treatments for rectal cancer is small and the side effects significant; further improvements in effective therapy are needed.

6. There was unanimous agreement that patients should be informed of the emerging data from ongoing adjuvant therapy trials and that they should be encouraged to participate in clinical trials.
7. There was considerable debate and discussion about the contents of the qualifying statement indicating that oxaliplatin and capecitabine should be considered. While there was general agreement, some members disagreed with including treatments not supported by direct evidence.

Report Approval Panel

Prior to the submission of this EBS draft report for external review, the report was reviewed and approved by the PEBC Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues. Key issues raised by the Report Approval Panel included:

Preoperative Therapy

- Two trials reported outcome data only for patients who underwent surgery. The authors should consider whether this introduces substantial bias and whether patients receiving preoperative therapy experienced toxicities that precluded therapy, making their exclusion from analysis inappropriate.

Postoperative Therapy

- Additional information on study quality should be added.
- Clarification was requested regarding the shape of the survival curve and whether a continuous and consistent pattern of events can be expected over the course of follow-up. Clarification is needed regarding the time point at which the data points were selected for extraction and whether this was consistent between trials.
- The authors should indicate how many trials were excluded due to the unavailability of data for patients with rectal cancer and whether the exclusion of these studies may have biased the results.
- A more systematic description of toxicities and a broader discussion of the trade-offs associated with therapy would be helpful.
- The authors should indicate which meta-analyses published by other groups were based on individual patient data and which were based on published data. The authors should also describe the degree of overlap in the studies included in these published meta-analyses and the current review.
- The preference for concurrent chemotherapy and radiotherapy over sequential therapy should be stated in the recommendations.
- The authors should consider providing evidence that out-of-date surgery was used and cite the standards for current surgical techniques. They should also declare whether the recommendations still hold as stated even if better surgery was performed.
- The meta-analysis of chemotherapy versus observation reports subtotals for oral and intravenous chemotherapy and an overall total. The authors should consider removing the overall pooled estimate as this is redundant.
- A comment about dose and delivery of radiotherapy should be considered in the recommendations.
- The authors should consider updating the literature search.
- The authors should clarify whether the data presented in the tables is subgroup data or the entire trial data.

- The optimal administration of 5FU is not clear. A summary of the different toxicity profiles would be useful.
- The original version of the guideline should be described in the document.

Overall Comment
- As the topic of therapy for rectal cancer is complex, the authors should consider providing a figure that outlines what they believe to be the optimum sequences of therapy and cite each component to the appropriate section of the guideline or another guideline.

Modifications and Responses to Report Approval Panel Comments

The following modifications and responses were made to address key issues raised by the Report Approval Panel:

- Additional details regarding patients excluded from the analysis for the Swedish Rectal Trial (4) and the Sauer et al trial (5) were added to the text of Section 2. Part 1. In the Swedish Rectal Trial, similar numbers of patients did not undergo surgery in each group, and the authors did not feel that the exclusion of these patients biased the analysis.
- A brief paragraph on study quality characteristics was added to the Results section of Section 2. Part 2.
- In stage II and III rectal cancer, the majority of events occur within three to five years. In general, there is a continuous and consistent pattern of events, and it is reasonable to assume a constant hazard ratio. This assumption is supported by data from trials in colon cancer (6). For this reason, the authors consider it reasonable to report and pool the data at the time of follow-up. Where available, five-year overall survival and disease-free survival were extracted and reported in the tables. A note was added to the tables to indicate the trials for which five-year data were not available or were not appropriate due to length of follow-up. Meta-analyses of mortality data were updated to include the five-year data.
- Trials including colon cancer patients were excluded from the CT versus Observation arm (one trial), PVI CT versus Observation arm (six trials), and the CT versus CT arm (two trials). The authors do not believe that the exclusion of these trials biased the results obtained.
- The Adverse Effects section of Section 2. Part 2 was modified to provide an overview of the toxicities and to focus detailed discussion of toxicities to those most relevant to discussion of the efficacy data.
- The discussion of published systematic reviews in Section 2. Part 2 was revised to clarify which meta-analyses used individual patient data and which used published data. In addition, a description of which studies were included in each meta-analysis was added. Meta-analyses that did not report data specifically for patients with rectal cancer were removed.
- The recommendations were modified to state that concurrent chemoradiation is recommended over sequential therapy.
- A number of trials included in this document were conducted before the adoption of the TME technique. A reference to the NCI guidelines for colorectal surgery was added (7). There are no data in the postoperative setting to determine whether the current recommendations would still hold if better surgery was performed. Data indicate that preoperative radiotherapy provides benefits even with TME, but it is unclear whether this could be extrapolated to the postoperative adjuvant setting.
- There was some disagreement between GI DSG members regarding whether IV and oral chemotherapy trials should be pooled together in a meta-analysis or analyzed

separately. Both the pooled subtotals for IV and oral chemotherapy and the overall pooled estimate were retained to satisfy both points of view.
- The DSG decided not to include an additional statement regarding the dose and delivery of radiotherapy in the recommendations as dose information for specific studies is available in the appendix sections of Section 2. Part 1 and Section 2. Part 2.
- The literature search was updated to September 2007.
- The authors reported in the Results section which trials present data from subgroup analyses.
- Randomized trials and published systematic reviews of CT by portal venous infusion were removed because this method of CT administration is no longer routinely used in Ontario.
- A summary table of toxicity data for bolus versus continuous venous infusion 5FU was added to Section 2. Part 2 (Table 11), and a reference to this table was added to the Recommendations in Section 1.
- A statement regarding the original version of the postoperative therapy guideline completed in 2000 was moved from the Methods section to the Introduction in Section 2. Part 2. Additional details regarding the recommendations in the original guideline were added.
- The authors decided not to add a table outlining the preferred treatment options and sequence of therapy. It was felt that such a table would complicate the document rather than simplify the recommendations.

External Review by Ontario Clinicians

Following the review and discussion of Section 1: Recommendations and Section 2: Evidentiary Base of this EBS and review and approval of the report by the PEBC Report Approval Panel, the GI DSG circulated Sections 1 and 2 to external review participants in Ontario for review and feedback. Box 1 summarizes the draft recommendations and supporting evidence developed by the GI DSG.

BOX 1:
DRAFT RECOMMENDATIONS (approved for external review April 28, 2008)
Preoperative Therapy
- Preoperative chemoradiotherapy (CRT) is preferred, compared to preoperative RT 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.

- For patients receiving postoperative CRT, the optimal way of administering 5-fluorouracil (5FU) during CRT—via continuous infusion or bolus 5FU—is not clear, since neither method is definitively superior in terms of efficacy or toxicity (See Section 2. Part 2, Table 11 for a description of differential toxicity patterns). Either method of administration can be considered appropriate, and treatments for individual patients should be based on an informed discussion of the potential risks and benefits of each mode of delivery.
- 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 based on an assessment of their risk of recurrence.

QUALIFYING STATEMENTS

- Recommendations for preoperative therapy presuppose adequate preoperative staging investigations, including transrectal ultrasound and/or magnetic resonance imaging (MRI) with endorectal or surface coil to assess the T and 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. There are insufficient data in either the preoperative or postoperative setting to determine whether the current recommendations hold if optimal surgery is performed.
- In most instances, there should be a four to six-week delay from the completion of RT to surgery, to allow patients to recover to an optimal preoperative physiologic state. The exception 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.
- Oxaliplatin-based CT and capecitabine have emerged as recommended treatments for the postoperative adjuvant therapy of high-risk colon cancer (see PEBC Evidence-based Series Guideline #2-29). Patients with resected rectal cancer at similarly high risk of systemic recurrence should be offered the same systemic adjuvant therapy as their counterparts with resected colon cancer, based on the recommendations of Guideline #2-29. The rationale for this statement, in the absence of direct evidence for these agents in rectal cancer, is described in more detail in the Discussion section of the systematic review for postoperative therapy (Section 2. Part 2).
- The rationale for the opinion that patients who have received standard fractionation 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.

Methods

Feedback was obtained through a mailed survey of 129 external review participants in Ontario (27 medical oncologists, 19 radiation oncologists, and 84 surgeons). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The survey was mailed out on April 28, 2008. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The GI DSG reviewed the results of the survey.

Results

Forty-seven responses were received out of the 129 surveys sent (36% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the participants who responded, 33 indicated that the report was relevant to their practice or organizational position, and they completed the survey. Key results of the feedback survey are summarized in Table 1.

Table 1. Responses to eight items on the feedback survey.

Item	Number (%)		
	Strongly agree or agree	**Neither agree nor disagree**	**Strongly disagree or disagree**
The rationale for developing a guideline, as stated in the "Introduction" section of the report, is clear.	32 (97)	1 (3)	
There is a need for a guideline on this topic.	31 (94)	1 (3)	1 (3)
The literature search is relevant and complete.	31 (94)	2 (6)	
The results of the trials described in the draft report are interpreted according to my understanding of the data.	31 (94)	2 (6)	
The draft recommendations in the report are clear.	31 (94)	2 (6)	
I agree with the draft recommendations as stated.	31 (97)	1 (3)	
This report should be approved as a practice guideline.	29 (88)	1 (3)	3 (9)
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?	**Very likely or likely**	**Unsure**	**Not at all likely or unlikely**
	31 (94)	1 (3)	1 (3)

Summary of Written Comments

Ten respondents (30%) provided written comments. In addition to minor comments and editorial suggestions, the main points contained in the written comments were:

1. The guideline should address whether tumours of the upper rectum or rectosigmoid need preoperative therapy.
2. A statement should be added about whether preoperative CRT should affect the decision regarding temporary stomas.

3. The recommendation that preoperative CRT is preferred over preoperative RT to reduce local recurrence is not supported by the Polish study comparing long course RT with chemotherapy versus short course RT without chemotherapy. This trial showed that that short course RT is equivalent in local recurrence to long course CRT.
4. The last phrase of the recommendation, "…that patients who have received preoperative CRT or RT should receive postoperative chemotherapy based on an assessment of their risk of recurrence," should be deleted. All patients have been staged preoperatively; therefore, it is a given that their risk deserves postoperative chemotherapy. Postoperative pathology plays no role in decision making at present based on evidence.
5. One respondent suggested that a comment should be made regarding the use of capecitabine.
6. One respondent questioned whether TOTAL mesorectal excisions is always appropriate and suggested that the term "mesorectal excision" be used.
7. The guideline should be quite emphatic that patients should undergo optimal staging of local disease and preoperative Rx considered for stage II and III. The draft wording is a little soft.
8. Evidence has shown that endorectal coil is not necessary for optimum sensitivity and specificity in preoperative imaging. The guideline mentions that technique as if it is the gold standard and some readers might mistakenly think that MRI without endorectal coil is not worthwhile.
9. The guideline recommends CAT Scan to assess the mesorectal margin. While a CAT Scan might be able to detect flagrant examples of a threatened margin, it is not an appropriate test for this. The guideline should not create the illusion that CAT Scan is an adequate local staging tool.
10. Although proper TME was not scored in the Dutch short course RT trial, the investigators did go to some lengths to promote proper techniques. This should be acknowledged.
11. A delay beyond 10 days from completion of short course preoperative RT to resection is to be avoided. The statement about "ideally within 10 days" should be strengthened by rationale (i.e., morbidity, technical difficulty).
12. Determination of clinical stage remains a problem and it is not clear that the RCTs which meet inclusion criteria by reporting on stage II and III really staged patients well prior to trial inclusion (i.e., Swedish and Dutch trials).
13. It is not clear from the preamble in Section 2 Part 1 (Preoperative Evidentiary Base) that the inclusion criteria of reporting stage II and III separately were followed in eliminating many of the Cochrane reviewed trials. Some trials that did not meet these criteria were then discussed.
14. One respondent disagreed strongly with the qualifying statements that there are insufficient data to determine whether the current recommendations hold if optimal surgery is performed. The Dutch TME trial answered that question and further recent trials support it.
15. One respondent questioned whether the formula used to calculate biological equivalent dose was correct, citing a reference to an article with a different formula (8).

Modifications/Actions

1. The ability to define what is considered upper rectum or rectosigmoid is controversial. While there is some evidence from the Dutch trial (8) to support the lack of benefit for radiation to decrease local recurrence when tumours were in the upper rectum, there

is insufficient evidence to provide specific recommendations based on location of tumour.

2. There is no significant evidence to suggest that preoperative RT increases risk of anastomotic leak.
3. The recommendation was modified to "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," for clarification.
4. The phrase "…based on an assessment of their risk of recurrence" was removed.
5. There is insufficient evidence to make a specific recommendation regarding the use of capecitabine.
6. The Qualifying Statements indicate that the use of total mesorectal excision principles should be followed. This includes TME for low lesions, partial TME for higher lesions (i.e., at least 5 cm of mesorectum distal to the leading edge of the tumour). More detailed deliberation on this issue is available in the surgery guideline for colorectal cancer developed by the Surgical Oncology Program (9).
7. The first Qualifying Statement specifically addresses the importance of preoperative staging. In addition, the inaccuracy inherent with preoperative staging is highlighted in the second Qualifying Statement.
8. The Qualifying Statement was modified to read "surface OR endorectal coil" to highlight that either is appropriate.
9. A separate guideline on imaging for colorectal cancer has been developed (10). Limited studies comparing MRI with CAT scan to assess margins showed no differences. If neo-adjuvant treatments are to be decided based on T or N category, the guidelines are clear that preoperative MRI is needed, with or without transrectal ultrasound (TRUS).
10. A statement was added to acknowledge that the Dutch trial did attempt to promote proper surgical technique; however, there are good data to indicate that optimal surgical technique was not followed.
11. Early unpublished data from the Dutch trials have suggested higher risk of cardiac perioperative morbidity in patients who undergo surgery within 10 days of preoperative RT. This has suggested that adherence to surgery within 10 days may not be ideal. In the absence of clear published evidence in either direction, the authors have elected to leave this aspect of the recommendation less rigid.
12. The authors agree with this statement. However, the evidence presented is the best available to guide therapy. The inclusion criteria for both the Swedish and Dutch trials targeted resectable and curable tumours, which may tend to favour the inclusion of smaller tumours within these trials. It is likely that the issue of "suboptimal" staging tools would always be an issue when long-term data is a key outcome of interest.
13. The authors assume the respondent is referring to Section 2 Part 1 page 6 "RCTs of SII or III rectal cancer," paragraph 2. These trials were identified through a supplemental literature search and are borderline in terms of meeting the inclusion criteria. The authors felt it was important to explain to the reader why these trials were excluded from the analysis. The comment "…warrants explanation" was added to emphasize the purpose of this section.
14. The phrase "There are insufficient data in either the preoperative or postoperative setting to determine whether the current recommendations still hold if optimal surgery is performed" was deleted. This statement was intended to highlight the issue that quality of TME is challenging both within a clinical trial setting, and in clinical practice. The role of radiotherapy merits further study when uniformly high quality

TME can be consistently conducted at a population level. The authors agreed that this statement may detract from the interpretation of the recommendations.

15. Suwinski et al provided a prospective estimation of the alpha/beta ratio for rectal cancer (11). The data are interesting but for this method to be generally accepted and applied, further confirmation with prospective large datasets is warranted. The authors have therefore preserved their original approach to calculate biological equivalent dose for this version of the guideline.

Policy Review

A draft of the evidentiary base for postoperative therapy (Section 2. Part 2) with recommendations was submitted to the Committee to Evaluate Drugs (CED)/CCO subcommittee in 2006 to inform a decision on the funding of oxaliplatin for colorectal cancer.

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the GI DSG and the Report Approval Panel of the PEBC. Updates of the report will be conducted as new evidence informing the question of interest emerges.

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Evidence-based Series 2-4 Version 3: Section 4

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 Summary Review

S Berry, R Wong, C Agbassi and the Gastrointestinal Cancer Disease Site Group

Review Date: December 5, 2018

The 2008 guideline recommendations are

ENDORSED

This means that the recommendations are still current and relevant for decision making.

OVERVIEW

The original version of this guidance document was released by the Program in Evidence-based Care (PEBC), Cancer Care Ontario, in 2008. In 2013, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist (JB) conducted an updated search of the literature from 2006 to 2011 and the data supported the 2008 recommendations. Please see Appendix A for the 2013 document summary and review table.

In December 2016, this document was reassessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist (CA) conducted an updated search of the literature. Two clinical experts (RW and SB) reviewed and interpreted the new eligible evidence and proposed the existing recommendations could be endorsed. The Gastrointestinal Cancer Disease Site Group convened and on March 13, 2018 the recommendations found in Section 1 (Clinical Practice Guideline) were endorsed.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Questions Considered

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

2. What is the role of postoperative adjuvant radiotherapy (RT) and/or chemotherapy (CT) for patients with resected stage II or III rectal cancer in terms of improving survival and delaying local recurrence?

Literature Search and New Evidence

The new search (January 2013 to January 2017) yielded 28 references representing 12 pooled/meta-analysis and 15 RCTs were found. Brief results of these publications are shown in the tables below.

Impact on the Guideline and Its Recommendations

The two clinical reviewers (SB and RW) noted that although the approach to treatment has altered in some instances from what the original recommendations state, the new evidence does not, at the present time, support changing the recommendations. The reviewers proposed that in almost all cases the recommendations could be endorsed, but new qualifying statements should been added in Section 1 to highlight emerging issues around the treatment of rectal cancer.

During Expert Panel review, the Expert Panel members voted in support of endorsing the 2008 guideline, but some of their comments required consideration by the clinical reviewers. Concerns were expressed about the timing between neoadjuvant treatment and surgery and the role of short-course RT in preoperative treatment, the role of oxaliplatin-based adjuvant chemotherapy, the need for chemoradiotherapy in some patients with upper rectal tumour, and watchful waiting for patients with clinical response after preoperative chemoradiotherapy.

In response to suggestions from the Expert Panel review, the following modifications were made:

- A qualifying statement was modified describing the length of delay between the completion of RT and surgery, advising a delay between 7 and 11 weeks resulted in no difference in DFS or OS (GRECCAR trial), but that the GRECCAR trial results should be interpreted with caution.
- With respect to chemoradiation therapy, the recommendation for the use of 5FU bolus administration was removed, because bolus therapy is no longer appropriate and the emergence of capecitabine or infusional 5FU as the preferred regimens based on randomized trial data (NSABP R-04).
- A qualifying statement was modified clarifying the use of oxaliplatin-based adjuvant therapy based on updated results from the ADORE trial. To address comments of the expert panel that oxaliplatin-based therapy should be reserved for ypN+ tumours, subgroup analyses were included to appropriately inform decisions.
- A qualifying statement was added advising that patients without features suggestive of high risk of local or distant recurrence on MRI should be discussed in a multidisciplinary cancer conference to address the need for chemoradiotherapy.
- A qualifying statement was added advising that patients with clinical complete response after preoperative chemoradiotherapy should only be offered watchful waiting in the context ofa clinical trial, given discordant results of the retrospective studies of these patients.

Document Review Tool

Number and Title of Document under Review	**2-4 Preoperative or Postoperative Therapy for the Management of Patients with Stage II or III Rectal Cancer**
Current Report Date	November 4, 2013
Clinical Expert	Scott Berry and Rebecca Wong
Research Coordinator	Chika Agbassi
Date Assessed	December 14, 2016
Approval Date and Review Outcome (once completed)	March 13, 2019 ENDORSED

Original Question(s):

3. 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])?

4. 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.

Study Selection Criteria:

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

4. The RCTs enrolled patients with stage II or III rectal carcinoma who had undergone resection with curative intent. Information on tumour staging is found in Appendix 1. While many of the available studies reported on patients with colorectal cancer, this review considered only studies that presented data for patients with stage II or III rectal carcinoma separately from colon cancer patients.
5. Syntheses of evidence were in the form of systematic overviews and meta-analyses of RCTs.
6. Studies were published in the English language, as translation resources were not available.

Search Details:

- January 2013 to January 2017 (MEDLINE, EMBASE)
- January 2013 to January 2017 On-going trial (ClinicalTrials.gov)

Summary of new evidence:

Of 4077 total hits from MEDLINE and EMBASE, 27 references representing 12 pooled/meta-analysis and 15 RCTs were found. Details from the included trials are summarized in the tables below.

Clinical Expert Interest Declaration: The Clinical experts declare no competing interest.	
1. Does any of the newly identified evidence contradict the current recommendations? (i.e., the current recommendations may cause harm or lead to unnecessary or improper treatment if followed)	No
2. Does the newly identified evidence support the existing recommendations?	Yes. There may be some evidence that adjuvant chemotherapy after neoadjuvant chemo radiotherapy is not necessary. However, the evidence is not strong enough to change the current recommendations.
3. Do the current recommendations cover all relevant subjects addressed by the evidence? (i.e., no new recommendations are necessary)	The nonoperative approach of treatment for patients with complete response following neoadjuvant CRT is a worthwhile topic to address but it is outside the scope of this guideline.
Review Outcome as recommended by the Clinical Expert	ENDORSE
DSG/GDG Commentary	In response to feedback from the GI DSG, modifications and additions were made to the qualifying statements accompanying the recommendations.

Pooled/Meta-analysis			
Author	**Objectives (number of trial/ number of patients)**	**Included Studies**	**Conclusion**
Bujko et al. 2015[1]	To evaluate the use of adjuvant chemotherapy in patients who received preoperative CRT. (9/5108)	**FU vs observation** EORTC 22921 (Case 2002, Bosset 2014), Italian trial (Bosset 2014), Proctor/script study(Sanato 2014) Chronicle study (Breugom 2015), QUASAR Study (Nimeiri 2013, QUASAR Collaborative group 2007), **FU vs FU-OX** PETACC-6 (Glynne-Jones 2014, Schmoll 2014), CAO/ARO/AIO-4 (Schmoll 2013, Rodel 2012), ADORE (Rodel 2014), ECOG E3201(Hong 2014)	The scientific evidence supporting the use of postoperative chemotherapy in patients with rectal cancer is not strong
An et al 2013[2]	To evaluate the short term efficacy and toxicities of adding OX to FU in CRT of LARC. (4/3863)	ACCORD (Gerard 2010), AIO-04 (Rodel 2012), NSABP R-04 (Roh 2011), STAR-01 (Aschele 2011)	Adding weekly OX to FU in neoadjuvant CRT appeared to increase the pCR rate and reduces the rate of intra-abdominal or perioperative metastases

Zhou et al 2014[3]	To evaluate the safety and efficacy of short term CRT with immediate surgery versus long term CRT with delayed surgery. (12/2187)	Read2001, Vironen2005, Bujko2006, Klenova2007, Eitta2010, Pettersson2010, Inoue2011, Guckenberger2012, Krajcovicova2012, Ngan2012, Yeh2012, Casalta-Lopes2013,	Short term CRTT with surgery is as effective as long term CRT in terms of OS, DFS, LR, DM and sphincter preservation rate.
Rahbari et al. 2013[4]	To assess the effectiveness and safety of neoadjuvant radiotherapy in the management of rectal cancer. (22/10961)	**Neoadjuvant therapy vs. surgery alone** MRC 1 (W Duncan1984), MRC 2, SRCT (Swedish rectal cancer trial1997), Stockholm I (Cedermark 1995), Stockholm II (Martling 2001), TME trial (Kapiteijn 2001), Dahl 1990, NWRCT (Marsh 1994), Reis 1989, Goldberg 1994, Petersen 1998, VASAG I (Higgins 1975), VASOGII (Gerard 1988), GTCCG , Kilgerman 1972, Toronto (rider 1977), Illenyi 1994 **Neoadjuvant CRT vs. Neoadjuvant** Bujko 2006, FFCD 9203 (Gerard 2006), GTCCG (boulis-wassif 1984), EORTC (Bosset 2006), Latkauskas 2012.	Neoadjuvant radiotherapy improves local control in patients with cancer particularly when CRT is administered.
Shaikh et al 2014[5]	To determine whether differences exist in LR, OS and DFS between patients treated with CRT+LE and CRT+RS. (7/1301)	Bannon 1995, Bonnen 2004, Callender 2010, Caricato 2006, Habr-Gama 1998, Huh 2008, Kundel 2010	There was no statistical difference in the LR, OS and DFS rates observed between patients treated with LE and RS for rectal cancer preoperative CRT.
Breugom et al 2015[6]	To compare adjuvant CT with observation for patients with rectal cancer (4/1196)	I-CNR-RT (Sainato2014), PROCTOR-SCRIPT (Breugom 2014), EORTC 22921 (Bosset 2014) CHRONICLE(Glynne-Jones 2014)	**Compared with observation,** adjuvant fluorouracil-based CT did not improve OS. However adjuvant CT may be beneficial to patients with a tumour 10-15 cm from the anal verge.
Zhao et al 2015[7]	To evaluate the efficacy of OX/FU-based adjuvant CT based on a comparison with fluorouracil-based adjuvant CT for patients with rectal cancer. (4/2793)	CHRONICLE(Glynne-Jones 2014, AIO-04 (Rodel 2012 & 2014), PETACC-6 (Schmoll 2013 & 2014) ADORE (Hong 2014)	Adjuvant OX/FU-based chemotherapy can improve the DFS of patients after neoadjuvant CRT and radical surgery, compared with adjuvant fluorouracil-based chemotherapy.
Burbach et al 2014[8]	To quantify the pCR rate after preoperative CRT with doses of P60 Gy in patients with LARC (18/1106)	Marks 1993, Meade 1995, Movsas 1998, Mohiuddin 2000, Rouanet 2002, Pfeiffer 2005, Jakobsen 2006, Mohiuddin 2006, Movsas 2006, Ho-Pun-Cheung 2007, Sun Myint. 2007, Jakobsen 2008, Lindebjerg 2009, Vestermark 2008, Maluta 2010, Jakobsen 2012, Vestermark 2012, Engineer 2013	Dose escalation above 60 Gy for locally advanced rectal cancer results in high pCR-rates and acceptable early toxicity
Loos et al 2013[9]	To determine the impact of preoperative CT on long-term anorectal, sexual, and urinary function (25/6548)	Fichera2001, Bonnel2002, Chatwin2002, Duijvendijk2002, Amin2003, Ammann2003, Nathanson2003, Welsh2003, Marijnen2005, Peeters2005, Prabhudesai2005,Temple2005, Pietsch2007, Murata2008, Selvindos2008, Ito2009, Morino2009, Parc2009, Cana2010, Garlipp2010, Song2010, Zugor2010, Denost2011, Varpe2011.	Current evidence demonstrates that preoperative CRT negatively affects anorectal function after TME
De Caluwé et al 2013[10]	To compare preoperative RT with preoperative CRT in patients with resectable stage II and III rectal cancer	Bosset2006, Boulis-Wassif1984, Bujko2006, Gerard2006, Latkauskas2011,	Compared to preoperative RT alone, preoperative CRT enhances pathological response and improves local control in resectable stage II and III rectal cancer, but does not benefit disease free or overall survival.

Liu et al 2016[11]	To compare the efficacy and safety of capecitabine plus radiation with 5-FU plus RT as neoadjuvant treatment in LARC. (9/3141)	Hofheinz2012, O'Connell2014, Chen2012, Chan2010, Yerushalmi2006, Das2006, Kim2007, Ramani2010, Kim2006	Capecitabine wasmore efficient than 5-FU in terms of tumor response in neoadjuvant treatment for patients with LARC and favourably low toxicity with the exception of HFS.
Qin et al 2014[12]	To assess the effects of preoperative CRT on anastomotic leak after rectal cancer resection (7/3375)	Cedermark1995, Gates1996, Park2011, Sauer2003, Marijnen2002, Sebag-Montefiore2009, SRCT1993.	Current evidence demonstrates that preoperative CRT did not increase the risk of postoperative anastomotic leak after rectal cancer resection in patients.

Published Randomized Controlled Trials

Reference(Trial)	Intervention	Population/Follow-up	Outcomes/Results
Preop RT (with or without CT) vs. surgery alone			
Wiltink et al 2014[13]	Preop RT + TME vs TME alone n = 606	Surviving patients with rectal cancer treated with pRT and evaluated for HRQL using a questionnaire combining EORTC QLQ-C30, EORTC QLQ-CR29 and additional questions **Med Follow-up: 14yr**	**QoL:** There were no significant differences in the functioning scales and global health status mean scores. 50.5% in the preoperative RT reported erection difficulties compared to 29.8% in the TME group
Sainato et al., 2014[14]	Observation (n=294) vs. CT alone (n=296)	Patients with LARC (Clinically T3-T4) treated with RT + nCT + S **Med Follow-up:** 63.7m	**OS(5yr):** 70% vs. 69%, (HR 1.045; 95% CI 0.775 to 1.410; p = 0.772) **DFS(5yrs):** 63% vs. 65%; (HR 0.977;95% CI 0.724 to 1.319; p = 0.882) **LRR:** 5% vs. 2%. **DM:** 21% vs 19.6%
Preop RT (with or without CT) vs preop CRT			
Bosset et al 2014[15]	Group A: Preop RT vs. Group B: Preop CRT and Group C: Preop RT + postop CT vs. Group D: Preop CRT + postop CT n= 1011	clinical stage T3 or T4 resectable rectal cancer **Med Follow-up:** 10.4yr	**Group A vs B** **OS (10yr):** 49·4% (44·6 to 54·1) vs. 50·7% (45·9 to 55·2). HR 0·99 (0·83 to 1·18) p=0·91 **DFS (10yr):** 44.2% (39.5 to 48.8) vs. 46.4% (41.7 to 50.9) HR 0.93 (0.79 to 1.10) p=0.38 **LR (10yr):** 22·4% (17·1 to 27·6) vs 11·8% (7·8 to 15·8) **DM(10yr):** 39·6% (33.5 to 45.8) vs. 33.4% (27.5 to 39.3) **Group C vs. D** **OS (10yr):** 51·8% (47·0 to 56·4) vs. 48·4% (43·6 to 53·0), HR 0·91(0·77 to 1·09) P=0·32 **DFS (10yr):**47·0% (42·2 to 51·6) vs. 43·7% (39·1 to 48·2). HR 0·91(0·77 to 1·08) p=0·29 **LR (10yr):** 14·5% (10·1-18·9) vs. 11·7% (7·7 to 15·6) **DM(10yr):** 35·9% (29·9 to 41·9) vs. 34·1% (28·2 to 40·1)
Delbaldo et al 2014[16] (R98 trial)	Preop RT + LV/5-FU2 + irinotecan vs. Preop RT + LV/5-FU	Patients with histologically proven and optimally resected adenocarcinoma of the rectum.	**OS (5yr):** 75% vs 74 % HR = 0.87. P = 0.433. **DFS(5yr):** 63% vs 58%; HR = 0.80, P = 0.154. **Neutropenia (grade 3-4):** 33% vs 6%, P = 0.03

Allegra et al 2015 [17] O'Connell et al 2014[18] (R-04 trial)	Preop RT + FU (225mg/ m^2) ± Ox (50 mg/m^2) vs. Preop RT + Cap (825 mg/m^2) ± Ox (50 mg/m^2) N= 1608	Patients with clinical stage II or III rectal cancer **Med Follow-up: nr**	**5-FU group vs. Cap group** **DFS(5yr):** 66.4% vs 67.7%; p=0.70 **OS (5yr):** 79.9% vs 80.8%; p=0.61 LRR (3yr): 11.2% vs 11.8%; p=0.98 **pCR: 20**.7% vs. 17.8%; p=**0**.14 **SSS:** 59.4% vs. 59.3%; p= 0.14 **SD:** 21.3%; vs. 21.1%; P=0.95 **(FU or Cap) + Ox vs. no Ox** **DFS(5yr):** 69.2% vs 64.2%; p=0.34 **OS (5yr):** 81.3% vs 79.0%; p=0.38 **LRR** (3yr): 11.2% vs 11.8%; p=0.70 **pCR:** 19.5% vs. 17.8%; p=**0.42** **SSS:** 57.1% vs. 61.0%; p= 0.24 **SD:** 17.9%; vs. 23.5%; P=0.20
Hong et al 2014[19]	Arm A: four cycles of 5-FU + Lv (300mg/m^2/20 mg/m^2) n=161 **vs.** Arm B: 8cycles of Ox (85 mg/m^2) + Lv (200 mg/m^2) + 5-FU(400 mg/m^2) on day 1 and 5-FU infusion 2400 mg/m^2 for 46 hr every 2 weeks n-160	Patients with stage II/III colorectal cancer (62 with rectal cancer) **Med Follow-up:** 38.2m	**DFS (3yrs):** 62.9% (55.4 to 70.4) vs. 71.6% (64.6 to 78.6); HR 0.66 (95% CI 0.43-0.99); p = 0.047 **OS (3yrs) :** 85.7% (95% CI 80.3 to 91.1) vs. 95% (95% CI 91.6 to 98.4); HR, 0.46% (95%CI 0.22 to 0.97) p=0.036
Schmoll et al 2016[20] Schmoll et al 2014[21] PETC Trial [ABSTRACT]	Arm 1: PreOp RT + Cap + PostOp Cap vs. Arm 2: Preop Cap + Ox + postOp Cap + Ox n = 1094	Patients with rectal adenocarcinoma within 12 cm from the anal verge, T3/4 and/or node-positive, with no evidence of metastatic disease and considered either resectable at the time of entry or expected to become resectable, **Med Follow-up:** 52months	**pCR**: 11.3% vs 13.3%; p = 0.31 **SP:** 70% vs 65%; p = 0.09 **Toxicity**: 3/4 toxicity occurred in 15.1% of patients in arm 1 vs. 36.7% in arm 2.
Sclafani et al 2014 [22] EXPERT-C [ABSTRACT]	Preop CRT + CAPOX + post op CAPOX vs Preop CRT + CAPOX + post op CAPOX + Cetuximab N= 164	**Med Follow-up:** 63.8 months	**CR:** 15.8% vs 7.5% p = 0.31 **DFS (5yr):** 78.4 vs 67.5 p = 017 **OS(5yr):** 83.8% vs 70 p = 0.20
McCollum et al [23] [ABSTRACT]	Preop RT + FU (225mg/ m^2) vs Preop RT + FU (225mg/ m^2) + Cet	T3/T4 LARC patients	**PCR**: 28.3% (17.5 to 41.4) vs 26% (16.3 to 39.1) **RFS (5yr):** 65% vs 61% **OS (5yr):** 66% vs 83% **LRR :** 3% vs 4%
Preop RT (with or without CT) vs. postop CT			
Breugom et al 2014[24] PROCTOR-SCRIPT	Preop CRT (5-FU- based) vs Postop CRT (5-FU/LV or Cape) n=437	Patients with histologically proven stage II or III rectal adenocarcinoma **Med Follow-up:** 5yr	**OS (5ys):** 79.2 % vs 80.4; HR 0.93, (0.62 to 1.39) P = 0.73 **DFS:** 55.4% vs 62.7%; HR 0.80 (0.60 to 1.07) P=0.13 **OR:** 40.3 vs. 36.2%; HR 0.88 (0.64 to 1.20) P= 0.43 **LRR:** 7.8% vs. 7.8%; HR 1.17 (0.55 to 2.50) P= 0.69 **DM:** 38.5 vs. 34%: HR 0.87 (0.63 to 1.20) P= 0.39
Glynne-Jones et al 2013[25] (Chronicle trial)	Preop CRT vs. Preop CRT + Postop CT n=113	aged >18 years, with histologically confirmed rectal adenocarcinoma, located ≤15 cm from the anal verge, or below the peritoneal reflection **Med Follow-up:** 44.8m	**OS:** 88% vs. 87% HR 1.18, (0.43 to 3.26) P = 0.75 **DFS:** 71% vs. 78%; HR 0.80, (0.38 to 1.69) P = 0.56 **LRR:** 27% vs. 22%

Fernandez-Martos et al 2015[26]	Preop CRT+ postop CT vs Preop CRT n=108	Patients with distal or middle third, T3-T4 and/or N+ rectal adenocarcinoma selected by MRI **Med Follow-up:** 69.5mo	**OS:** 78% (63.6% to 87.1%) vs. 75% (61% to 84.1%) P= 0.64 **DFS:** 64% (49.5% to 75.8%) vs. 62 (48% to 73.4%) P= 0.85 **LR:** 2% (0 to 10.2) vs. 5% (1.1 to 14.8) 0.61 HR 0.51 (0.13 to 1.86) p = 0.64 **DM:** 21% (11 to 34.7) vs. 23% (12.9 to 36.4) p = 0.79
Rodel et al 2014 [27] (CAO/ARO/AIO-04) [ABSTRACT]	Preop CRT (5FU) + Postop CRT (5FU) Preop CRT (5FU/OX) + Postop CRT (OX/LV/5FU) n = 637	Patients with cT3/4 or cN+ rectal cancer **Med Follow-up:** nr	**DFS(3yrs):** 71.2% (67.6% to 74.9%) vs 75.9% (72.4% to 79.5%), P=0.03 **G3/4 toxicity:** 23% vs 26% P=0.14.
Hebbar et al 2014[28]	Arm A: 12 cycles of FOLFOX4 (oxaliplatin 85 mg/m2) Arm B: r 6 cycles of FOLFOX7 (oxaliplatin 130 mg/m2) Followed by 6 cycles of FOLFIRI (irinotecan 180 mg/m2). n = 284	patients with resectable or resected metastases **Med Follow-up:** 67mos	**OS (5yr):** 69.5% in arm A, and 66.6% in arm B. HR = 1.07, (0.68 to 1.70) P = 0.764 **Med OS:** 51.8mos in arm A and 37.8mos in arm B. HR = 1.14 (0.75 to 1.73) P = 0.53. **DFS (3yrs):** 43.5% vs. 44.1% **Med DFS:** 22.4mos (16.5 to 37.5) in arm A and 24.3(19.3 to 39.9) in arm B HR = 0.94, 95% CI 0.70 to 1.26; P = 0.679).

Ongoing Trials

Protocol ID	Official Title	Intervention/ Comparison	Status	Estimated Study Completion Date	Last Updated
NCT02031939	Randomized Controlled Study on Optimize Neoadjuvant Chemoradiotherapy for Locally Advanced Rectal Cancer	Capecitabine combine with oxaliplatin vs standard chemoradiotherapy	Recruiting	January 2023	April 26, 2017
NCT02964468	Multicenter Dose-escalation Trial of Radiotherapy in Patients With Locally Advanced Rectal Cancer	3DCRT treatment (sequential boost) vs. Radiation: Dose Escalation Intensity Modulated Radiotherapy treatment	Recruiting	November 2018	November 16, 2016
NCT02551237	A Phase III Study Evaluating Two Neoadjuvant Treatm (1week - 25Gy) in Patient Over 75 With Locally Advanced	RT (50Gy) + capecitabine vs. RT (25Gy)	Recruiting	March 2030	March 18, 2016
NCT01952951	A Randomized Phase II Trial of Preoperative Chemoradiation (Preop CRT) Followed by CapOx (Capecitabine Plus Oxaliplatin) Versus Preop CRT Alone for Locally Advanced Rectal Cancer (LARC)	CRT + CT vs. CT	Ongoing, not recruiting	December 2019	September 13, 2017
NCT02288195	Phase III Study of Neoadjuvant Chemotherapy With Capecitabine and Oxaliplatin Versus Chemoradiation for Locally Advanced Rectal Cancer Patients	CRT vs CT	Recruiting	June 2024	October 13, 2016
NCT02921256	A Phase II Clinical Trial Platform of Sensitization Utilizing Total Neoadjuvant Therapy (TNT) in Rectal Cancer	FOLFOX6 + RT + capecitabin vs. FOLFOX6 + RT + capecitabine + veliparib	Recruiting	April 30, 2019	September 25, 2017
NCT02533271	Phase III Study of Short-term Radiotherapy Plus Neoa in Locally Advanced Rectal Cancer	Short-course radiotherapy with neoadjuvant chemotherapy vs. Long-term chemoradiotherapy	Recruiting	August 2025	August 26, 2015
NCT02605265	A Randomized Phase III Trial of Capecitabine With or Without Irinotecan Driven by UGT1A1 in Neoadjuvant Chemoradiation of Locally Advanced Rectal Cancer	CRT vs CRT + irinotecan	Recruiting	December 2020	December 7, 2016
NCT02340949	Induction FOLFOX With or Without Aflibercept Followed by Chemoradiation in High Risk Locally Advanced Rectal Cancer. Phase II Randomized, Multicenter, Open Label Trial	Induction FOLFOX with or without aflibercept	Ongoing, not recruiting	February 2020	February 3, 2017
NCT01804790	Randomized Phase III Study Comparing Preoperative	neoadjuvant mFolfirinox	Recruiting	January	June 17,

	Chemoradiotherapy Alone Versus Neoadjuvant Chemotherapy With Folfirinox Regimen Followed by Preoperative Chemoradiotherapy for Patients With Resectable Locally Advanced Rectal Cancer	followed by preop CRT vs. preop CRT		2022	2016
NCT02008656	A Phase II Multicenter Randomized Trial Evaluating 3-year Disease Free Survival in Patients With Locally Advanced Rectal Cancer Treated With Chemoradiation Plus Induction or Consolidation Chemotherapy and Total Mesorectal Excision or Non-operative Management	induction neoadjuvant chemotherapy arm vs. consolidation neoadjuvant chemotherapy arm	Recruiting	November 2018	August 15, 2017
NCT02363374	Induction Chemotherapy Before or After Preoperative Chemoradiotherapy and Surgery for Locally Advanced Rectal Cancer: A Randomized Phase II Trial of the German Rectal CancerStudy Group	Arm A: Induction CT followed by CRT before surgery Arm B: Combined CRT followed by three cycles CT before surgery	Recruiting	March 2023	August 21, 2017
NCT02031939	Randomized Controlled Study on Optimize Neoadjuvant Chemoradiotherapy for Locally Advanced Rectal Cancer	Standard CRT vs. Induction CT + standard CRT+ gap CT	Recruiting	January 2023	April 26, 2017
NCT02167321	Adjuvant Chemotherapy With FOLFOX After Total Mesorectal Excision for Locally Advanced Rectal Cancer; an Open-label, Multicenter, Prospective, Randomized Phase 3 Trial	Arm A : standard nCRT Arm B : adjuvant FOLFOX	Recruiting	May 2021	January 11, 2017

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Members of the Expert Panel

Name	Affiliation	Declarations of Interest
Tim Asmis	Medical Oncology, Ottawa	Fellowship funding from Roche
Mala Bahl	Medical Oncology, Grand River	No interests to declare
Jim Biagi	Medical Oncology, Kingston	No interests to declare
Kelvin Chan	Medical Oncology, Odette	No interests to declare
Charles Cho	Radiation Oncology, Southlake	No interests to declare
Kristopher Dennis	Radiation Oncology, Ottawa	No interests to declare
Mark Doherty	Medical Oncology, Odette	No interests to declare
Tarek Elfiki	Medical Oncology, Windsor	No interests to declare
Valerie Francescutti	Surgical Oncology, Hamilton	Owner of an incorporated medical professional practice
Julie Hallet	Surgical Oncology, Odette	Received honoraria from Novartis Oncology and Ipsen Biopharmaceuticals Canada for speaking at institutional rounds across Ontario. This was not a speaker bureau. The companies had no influence on the content of the slides or the talks. Unrestricted research grant from Canada Health Infoway: $50,000.00 Unrestricted educational grant from Baxter Corporation: $3,000.00
Nazik Hammad	Medical Oncology, Kingston	No interests to declare
Khalid Hirmiz	Radiation Oncology, Windsor	No interests to declare
Raymond Jang	Medical Oncology, Princess Margaret	Research funding from Ipsen
Derek Jonker	Medical Oncology, Ottawa	
Paul Karanicolas	Surgical Oncology, Odette	Consultant with and research support from Sanofi
Erin Kennedy	Surgical Oncology, Mt Sinai	Principal Investigator: Canadian Partnership Against Cancer Rectal Cancer Project 2014-2017 Non-operative management for locally advanced low rectal cancer CIHR 2016-2021
Aamer Mahmud	Radiation Oncology, Kingston	No interests to declare
Brandon Meyers	Medical Oncology, Hamilton	No interests to declare
Fayez Quereshy	Surgical Oncology, Princess Margaret/Toronto Western	No interests to declare
Jolie Ringash	Radiation Oncology, Princess Margaret	No interests to declare
Mark Rother	Medical Oncology, Peel	No interests to declare
Marko Simunovic	Surgical Oncology, Hamilton	No interests to declare

Stephen Welch	Medical Oncology, London	No interests to declare
Raimond Wong	Radiation Oncology, Hamilton	No interests to declare
Kevin Zbuk	Medical Oncology, Hamilton	Received travel support from Amgen

Literature Search Strategy:

Medline

1. meta-Analysis as topic/
2. meta analysis.pt.
3. (meta analy$ or metaanaly$).tw.
4. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview).tw.
5. (systematic adj (review$ or overview?)).tw.
6. (exp Review Literature as topic/ or review.pt. or exp review/) and systematic.tw.
7. or/1-6
8. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
9. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
10. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
11. (study adj selection).ab.
12. 10 or 11
13. review.pt.
14. 12 and 13
15. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
16. (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
17. random allocation/ or double blind method/ or single blind method/
18. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
19. or/15-18
20. (phase II or phase 2).tw. or exp clinical trial/ or exp clinical trial as topic/
21. (clinical trial or clinical trial, phase II or controlled clinical trial).pt.
22. (20 or 21) and random$.tw.
23. (clinic$ adj trial$1).tw.
24. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
25. placebos/
26. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
27. (allocated adj2 random).tw.
28. or/23-27
29. 7 or 8 or 9 or 14 or 19 or 22 or 28
30. exp rectal cancer/
31. exp colorectal cancer/
32. rectal: neoplasm:.kw.
33. (rectal: cancer or rectal: carcinoma: or rectal: tumo?r: or rectal: malignan:).tw.
34. (rectal: cancer or rectal: carcinoma: or rectal: tumo?r: or rectal: malignan:).kw.
35. rectal neoplasms/rt, su, th
36. Colorectal neoplasms/rt, su, th
37. or/30-36
38. (adjuvant or neoadjuvant or neo adjuvant or post operativ$ or postoperativ$ or pre operativ$ or preoperativ$ or following surgery or after surgery or post-surgery or before surgery or pre surgery or pre-surgery or operable or stage 2A or stage 2 A or Stage IIA or stage II A or stage 2 or stage II or stage 3A or stage 3 A or stage IIIA or stage III A or stage 3 or stage III or stage II-III or stage 2-3).tw.
39. 29 and 37 and 38

40. limit 39 to english

41. limit 40 to human

42. limit 41 to yr="2013 -Current"

Embase

1. exp Meta Analysis/ or exp Systematic Review/

2. (meta analy$ or metaanaly$).tw.

3. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview).tw.

4. (systematic adj (review$ or overview?)).tw.

5. exp Review/ or review.pt.

6. (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.

7. (study adj selection).ab.

8. 5 and (6 or 7)

9. or/1-4,8

10. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.

11. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.

12. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/

13. randomization/ or single blind procedure/ or double blind procedure/

14. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.

15. or/12-14

16. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/

17. 16 and random$.tw.

18. (clinic$ adj trial$1).tw.

19. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.

20. placebo/

21. (placebo? or random allocation or randomly allocated or allocated randomly).tw.

22. (allocated adj2 random).tw.

23. or/18-22

24. 9 or 10 or 11 or 15 or 17 or 23

25. (editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/

26. 24 not 25

27. exp rectal cancer/

28. exp colorectal cancer/

29. rectal: neoplasm:.kw.

30. (rectal: cancer or rectal: carcinoma: or rectal: tumo?r: or rectal: malignan:).tw.

31. (rectal: cancer or rectal: carcinoma: or rectal: tumo?r: or rectal: malignan:).kw.

32. rectal neoplasms/rt, su, th

33. Colorectal neoplasms/rt, su, th

34. or/27-33

35. (adjuvant or neoadjuvant or neo adjuvant or post operativ$ or postoperativ$ or pre operativ$ or preoperativ$ or following surgery or after surgery or post-surgery or before surgery or pre surgery or pre-surgery or operable or stage 2A or stage 2 A or Stage IIA or stage II A or stage 2 or stage II or stage 3A or stage 3 A or stage IIIA or stage III A or stage 3 or stage III or stage II-III or stage 2-3).tw.

36. 24 and 34 and 35

37. limit 36 to english

38. limit 37 to human

39. limit 38 to yr="2013 -Current"

DEFINITIONS OF REVIEW OUTCOMES

1. **ARCHIVE** – ARCHIVE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is out of date or has become less relevant. The document will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of our website and each page is watermarked with the words "ARCHIVED."

2. **ENDORSE** – ENDORSE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is still useful as guidance for clinical decision making. A document may be endorsed because the Expert Panel feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **UPDATE** – UPDATE means the Clinical Expert and/or Expert Panel recognizes that the new evidence pertaining to the guideline topic makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The Expert Panel advises that an update of the document be initiated. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making, unless the recommendations are considered harmful.

APPENDIX A: DOCUMENT SUMMARY AND REVIEW CONDUCTED IN 2013

Evidence-based Series #2-4 Version 2: Section 4

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 Summary Review

R Wong, J Brown, and the Gastrointestinal Cancer Disease Site Group

Review Date: November 1, 2013

The 2008 guideline recommendations are

ENDORSED

This means that the recommendations are still current and relevant for decision making.

OVERVIEW

The original version of this guidance document was released by Cancer Care Ontario's Program in Evidence-based Care in 2008.

In September 2013, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist conducted an updated search of the literature. A clinical expert reviewed and interpreted the new eligible evidence and proposed the existing recommendations could be endorsed. The Gastrointestinal Cancer Disease Site Group endorsed the recommendations found in Section 1 (Clinical Practice Guideline) in October 2013.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Questions Considered

1. Following appropriate preoperative staging tests, should patients with resectable stage II/III rectal cancer be offered preoperative radiotherapy (RT) (with or without chemotherapy [CT])?
2. What is the role of postoperative adjuvant radiotherapy (RT) and/or chemotherapy (CT) for patients with resected stage II or III rectal cancer in terms of improving survival and delaying local recurrence?

Literature Search and New Evidence

The new search from January 2007 to September 2013 yielded 38 RCTs (18 RCTs for preoperative therapies, 12 RCTs for a combination of preoperative and postoperative therapies and eight RCTs for postoperative therapies) evaluating the management of patients with stage II or III rectal cancer. There were 10 meta-analyses found in the literate review and 10 ongoing studies identified from clinicaltrials.gov. Brief results of these searches are shown in the Document Review Tool.

Impact on Guidelines and Its Recommendations
The new data supports existing recommendations. Hence, the Gastrointestinal Cancer Disease Site Group ENDORSED the 2008 recommendations on the use of preoperative or postoperative therapy for the management of patients with stage II or III rectal cancer

Document Review Tool

Number and title of document under review	2-4: Preoperative or Postoperative Therapy for the Management of Patients with Stage II or III Rectal Cancer
Current Report Date	July 15, 2008
Clinical Expert	Dr. Rebecca Wong
Research Coordinator	Judy A Brown
Date Assessed	September 23, 2011
Approval Date and Review Outcome (once completed)	October 31, 2013 (ENDORSE)

Original Question(s):
Preoperative
Following appropriate preoperative staging tests, should patients with resectable stage II/III rectal cancer be offered preoperative radiotherapy (RT) (with or without chemotherapy [CT])?
Postoperative
What is the role of postoperative adjuvant radiotherapy (RT) and/or chemotherapy (CT) for patients with resected stage II or III rectal cancer in terms of improving survival and delaying local recurrence?

Target Population:
Patients with resectable stage II/III rectal cancer
Study Section Criteria:
Preoperative
Articles were selected for inclusion in this systematic review of the evidence if they
met the following criteria:

1. The article reported on RCTs or systematic reviews of RCTs.
2. The RCT results were reported on patients with clinical stage II or III resectable rectal cancer, although the RCT could have included earlier stage patients. The original intention was to include only studies that involved earlier stage patients if they were stratified by stage. However, there were no studies that incorporated this stratification, so this criterion was modified to include studies where results were reported by stage.
3. The RCTs compared preoperative RT (with or without CT) to surgery alone or an alternative

preoperative or postoperative therapy (e.g., preoperative CRT vs.preoperative RT).
4. The article reported on relevant outcomes as described below under the heading Outcomes of Interest.
5. The surgery received by the RCT patients was potentially curative. TME was not mandatory.
6. The RCT or systematic review was reported as a fully published report or published abstract.
7. The RCT or systematic review was reported in English, as translation resources were not available.

Postoperative

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

1. The RCTs enrolled patients with stage II or III rectal carcinoma who had undergone resection with curative intent. While many of the available studies reported on patients with colorectal cancer, this review considered only studies that presented data for patients with stage II or III rectal carcinoma separately from colon cancer patients.
2. Syntheses of evidence were in the form of systematic overviews and meta-analyses of RCTs.
3. Studies were published in the English language, as translation resources were not available.

Search Details:

January 2007 to September 2013 (Medline Aug wk 1 and Embase wk 30)
January 2009 to September 2013 (ASCO Annual Meetings)
January 2007 to September 2013 (clinicaltrials.gov)
January 2007 to September 2013 Cochrane Library

Brief Summary/Discussion of New Evidence:

There were 1,780 articles identified from Medline and Embase, along with 380 conference abstracts from ASCO and 33 trials from clinicaltrials.gov up for consideration.

RCTs

Eighteen RCTs (19 articles and 12 abstracts) examining *preoperative* therapies were identified. Of those trials evaluating preoperative radiotherapy, one compared RT to surgery alone and six compared RT to other preoperative RT or chemo radiotherapy (CRT) adjuvant treatments. One compared CRT to surgery alone and 9 compared CRT to other preoperative CRT adjuvant treatments.

Twelve RCTs (15 articles and 8 abstracts) compared various *preoperative and postoperative* approaches.

Eight RCTs (8 articles and 2 abstracts) evaluated *postoperative* therapies. One trial compared two different types of postoperative RT regimes. Three compared CRT to surgery alone and three compared CRT to CT postoperative adjuvant treatments. One study examined optimal sequence of postoperative adjuvant chemotherapy and RT using early and delayed times to surgery.

Meta-analyses

Ten meta-analyses were identified. Five examined articles assessing preoperative RT and preoperative CRT and three looked at postoperative CT versus surgery alone. One examined studies comparing different regimens of preoperative CRT and one looked at studies examining preoperative and postoperative RT and CRT.

There were 10 ongoing studies identified from clinicaltrials.gov.

Preoperative Therapies (18 RCTs)

Preop Therapies - RT vs. Surgery Alone (1 RCT)			
Trial/ Reference	**Intervention**	**Population/Follow-up**	**Outcomes/Results**
Dutch Colorectal Cancer Group Van Gijn et al., 2011(1) **See also:** Kusters et al., 2010 (2) deBruin et al., 2006 (3) Peeters et al., 2007 (4)	SRT (n=897) TME preceded by 5 x 5 Gy RT **vs.** Surgery alone (n=908): TME alone (ratio 1:1)	Patients with resectable RC without evidence of distant disease (tumours below the level of S1/S2 with an inferior tumour margin located 15 cm or less from the anal verge) **Follow-up:** 11.6 yrs (median)	Overall (10 yr) **OS**: 48% vs. 49%, p=0.86 **CSD:** 28% vs. 31%; p=0.20 **LR:** 5% vs. 11.0%, p<0.0001 Stage II(10 yr) **OS**: 50% vs. 55%, p=0.242 **LR:** 5% vs. 8%, p=0.212 Stage III (10 yr) **OS**: 39% vs. 37%, p=0.526 **LR:** 9% vs. 19.0%, p<0.0001
Preop Therapies - RT vs. RT (3 RCTs)			
Trial/ Reference	**Intervention**	**Population/Follow-up**	**Outcomes/Results**
Lyon R96-02 Ortholan et al., 2012 (5)	EBRT (n=43): neoadjuvant EBRT 39 Gy in 13 fractions **vs.** EBRT+CXRT (n=45): the same EBRT with CXRT boost, 85 Gy in three fractions	Patients with T2 to T3 carcinoma of the lower rectum **Follow-up:** 11 yrs (median)	**OS:** 56% vs.55%, p = 0.85 **LR:** 15% vs.10%, p = 0.69 **DFS:** 54% vs.53%, p = 0.99 **cPR:** 3% vs. 26% **CRPC:** 63% vs. 29%; p<0.001
Trans-Tasman Radiation Oncology Grp trial 01.04 Ngan et al., 2012 (6)	SC (n=163) pelvic RT 5 x 5 Gy in 1 wk, early surgery, & six courses of adjuvant CT. **vs.** LC (n=163) 50.4 Gy, 1.8 Gy/fraction, in 5.5 wks, with continuous infusional 5-fu 225 mg/m^2 per dy, surgery in 4 to 6 wks, & 4 courses of CT	Patients had ultrasound- or magnetic resonance imaging-staged T3N0-2M0 rectal adenocarcinoma within 12 cm from anal verge **Follow-up:** 5.9 yrs (median)	**OS:**74% vs. 70%, HR=1.12 (95% CI: 0.76-1.67) p=0.62 **LR (3yr):** 7.5% vs. 4.4% (95%CI: 2.1 to 8.3)p=0.24 **DRR:** 27% vs. 30%, p=0.92 **(for LC:SC):** HR=1.04 (95% CI, 0.69 to 1.56) **LTX**: NS
Wzietek et al., 2013 (7) (ASCO 506)	HART (n=122) pelvis irradiated 2x/dy to the total dose of 42 Gy in 1.5 Gy/fx over 18 dys **vs.** HYPO (n=116) 39 Gy in 3.0 Gy/fx over 17 dys Post-op CT (PCT) given to ypN+ pts	Patients with cT3-4 resectable adenocarcinoma of the rectum **Follow-up:** 3.1 yrs (median)	**OS:** RR=0.97, p=0.72 **LC:** RR=1.08, p=0.44 **PC:** 26.2% vs. 31%, p=0.41
Preop Therapies - RT vs. CRT (4 RCTs)			
Trial/ Reference	**Intervention**	**Population/Follow-up**	**Outcomes/Results**
Bujko et al., 2007 (8)	RT (n=145) 5 x 5 Gy with immediate surgery. **vs.** CRT (n=146) 50.4 Gy, 5-5-fu, leucovorin) with delayed surgery	Patients with Stage cT3 or resectable cT4 tumor **Follow-up:** 4 yrs (median)	**DFS:** HR=1.05 (95% CI: 0.73-1.51) **DM:** HR=1.17 (95% CI: 0.77–1.78) **LR:** HR=1.45 (95% CI: 0.74 – 2.84)

Bujko et al., 2011 (9) (ASCO 167)	RT (n=29) 25 Gy in 5 fractions over one wk+ 4 Gy boost **vs.** CRT (n=22) 50.4 Gy in 28 fractions+ 5.4 Gy boost in 3 fractions given concurrently with 5-Fu and leucovorin	Patients with G1-2 rectal adenocarcinoma <3-4 cm; flat raised cT1, cT2 or borderline cT2/cT3; cN0. Mucosa at the tumour edges **Follow-up:** 2 yrs (median)	**pCR:** 38% and 55%; p=0.238.
Gamelin et al., 2009 (10) (ASCO 4014)	RT (n=87): RT alone (RT) (1.8 Gy/d, 45 G total) 5 dys/w for 5 wks **vs.** CRT (n=90): with daily UFT 300 mg/m²+ leucovorin 75 mg for 5 wks	Patients with RAC stage T3 (T4 if anal extension) N<2, M0 **Follow-up:** 22.3 mos (median)	**pCR:** 3.4% VS. 13.3%; p=0.0182 **SPR:** 57.6% VS. 72.4% **TX(GIII):** 4% vs. 8.9% **TX(GIV):** 2% vs. 3.5% **PFS(1yr):** 82.6% vs. 91.7% **OS:** 91.4% vs 95.3%
Latkauskas et al., 2012 (11)	SRT (n=37) with delayed surgery: RT 25Gy/5fr, 5Gy per fraction over 5 dys **vs.** CRT (n=46): Rt 50Gy/25fr,1.8–2Gy per fraction over 5 wks with CT 5-Fu/Lv (400 mg/m2 5-fl 20 mg/m2 Leucovorine) during the first and last wk of RTV surgery after 6 wks.	Patients with resectable stage II and III rectal adenocarcinoma **Follow-up:** NR	**SPR:** 70.3%vs 69.6%; P=0.342 **PC:** 40.5% vs. 26.1%; P=0.221 **ROR:** 86.5% vs. 91.3%; p=0.734 **pCR**: 2.7% vs. 21.8%, p=0.03
Preop Therapies - CRT vs. CRT (9 RCTs)			
Trial/ Reference	**Intervention**	**Population/Follow-up**	**Outcomes/Results**
STAR-01 Aschele et al., 2011 (12) **See also:** Aschele et al, 2009 (CRA4008) (13)	CRT+fl (n=379) pelvic radiation (50.4 Gy in 28 daily fractions) & concomitant infused 5-fu (225 mg/m(2)/d) **vs.** CRTfl+xoa (n=368): above combined with oxaliplatin (60 mg/m(2) wkly x 6;	Patients with resectable, locally advanced (cT3-4 &/or cN1-2) adenocarcinoma of the mid-low rectum **Follow-up:** NR	**TX:** 8% vs. 24%,p<0.001 **pCR:** 16% in both arms; OR= 0.98 (95% CI: 0.66-1.44) *P*=.904
Hofheinz et al., 2012 (14) **See all:** Hofheinz et al, 2011 (ASCO 3504) (15) Hofheinz et al., 2009 (ASCO 4014) (16)	CRT+capecitabine (n=197) 2 cycles of capecitabine (2500 mg/m(2) dys 1-14, rep dy 22), + CRT (50.4 Gy+ capecitabine 1650 mg/m(2) dys 1-38), + 3 cycles of capecitabine. **vs.** CRT+5-fu (n=195) 2 cycles of bolus 5-fu (500 mg/m^2 dys 1-5, rep dy 29), + CRT (50.4 Gy+ infusional 5-fu 225 mg/m^2 daily), then 2 cycles of bolus 5-fu.	Patients aged 18 yrs or older with pathological stage II-III locally advanced RC **Follow-up:** 52 mos (median)	**OS (3yr):** 87% (95%CI:81%-91%) vs. 83% (95%CI:77%-88%) **OS (5yr):** 76% (95%CI:67%-82%) vs. 67% (95%CI:58%-74%) p=0.0004 **OS (5yr):** 5-fu vs. cap - HR 1.5 (95% CI: 1.00–.228). **OS(7yr):** 71% (95%CI:60%-79%) vs. 58% (95%CI:47%-67%) **DFS (3yr)**: 75% (95%CI:68%-81%) vs. 67% (95%CI:59%-73%) p=0.071 **DFS (5yr)**: 68% (95%CI:60%-74%) vs. 54%(95%CI:45%-62%) **LR:** 6% vs. 7%, p=0.67; p=0.665 **DM:** 18.8% vs 27.7%; p=0.0037
Danish Colorectal Cancer	Arm A (n=99): 50.4 Gy in 28 fractions	patients with	**PC:** NS

Group Jakobsen et al., 2012 (17) **See also:** Jakobsen et al., 2011 (ASCO 3512) (18)	to the tumor and pelvic lymph nodes **vs.** Arm B (n=95): same treatment supplemented with an endorectal boost given as high-dose-rate brachytherapy (10 Gy in 2 fractions) Concomitant CT, uftoral 300 mg/m^2 and L-leucovorin 22.5 mg/dy, added to both arms on treatment dys.	resectable T3 and T4 tumors with a circumferential margin of ≤ 5 mm on magnetic resonance imaging **Follow-up:** NR	**TX**: NS **CPRR:** NS **ROR (T-3 tumors):** 90% vs. 99%; p=0.03 **RMR: (tumor regression gr, 1+2):** 29% vs. 44%; (P=0.04)
Marechal et al., 2012 (19)	Arm A (n=29) wk CRT with 5-5-fu (5-FU) continuous infusion followed by surgery **vs.** Arm B (n=28) induction oxaliplatin, folinic acid & 5-fu followed by CRT & surgery.	Patients with T2-T4/N+ rectal adenocarcinoma	**ypT0-1N0 rate:** 34.5% (95% CI: 17.2% - 51.8%) vs.32.1% (95% CI: 14.8% - 49.4%) – **study closed early due to futility**
Radition Therapy Oncology Grp (RTOG-0012) Mohiuddin et al., 2011 (20) (ASTRO 190) **See also:** **M**ouhiddin et al., 2006 (21)	Arm 1 (n=50): CVI 5-fu, 225 mg/m^2 per dy, 7 dys per wk+ pelvic HRT 45.6 Gy at 1.2 Gy b.i.d., .6 hour interval+ a boost to the tumor of 9.6 Gy for T3 and 14.4 Gy for fixed T4 cancers **vs.** Arm 2 (n=53): CVI 5-fu 225 mg/m^2 per dy Mondy to Fridy, 120 hours per wk+ Irinotecan (CPT-11) 50g/m^2 once wkly x 4+ pelvic RT 45 Gy at 1.8 Gy per dy and boost to the tumor of 5.4 Gy for T3 and 9 Gy for fixed T4 cancers	Patients with clinical T3/T4 distal RCs **Follow-up:** Arm 1 6.4 yrs Arm 2 7.0 yrs in (median)	**pCR:** 33% vs. 27% **LR:** 16% vs. 17% **OS:** 62% vs. 75% **DFS:** 52% vs. 57% **DSS:** 78% vs. 85% **LTX:** NS
Tunio et al., 2010 (22)	treated initially with concurrent capecitabine (825 mg/m^2 oral twice daily) and pelvic EBRT (45 Gy in 25 fractions), then randomized to Grp A (n = 17): grp to receive 5.5-7 Gy x 2 to gross tumor volume (GTV) and **vs.** Grp B (n = 19): EBRT grp to receive 5.4 Gy x 3 fractions to GTV with EBRT. Oral capecitabine was given at 825 mg/m^2 bid for the duration of RT	Patients with locally advanced RC (≥T3 or N+) **Follow-up:** 18 mos (median)	**cPR of T stage (ypT0):** 59% vs. 15.8%; p <0.0001 **ORR:** 68.15 vs. 66.04%; **SPR:** 66.7% vs. 50%; p <0.01 **LTX (GR1&2):** 17.6% vs. 21.1% **ATX (GR3):** 70.6% vs. 42.1%
Valentini et al., 2008 (23)	PLAFUR (n=83) cisplatin, 5-fu, and RT cisplatin (60 mg/m^2) given dys 1 and 29, with prolonged infusion of 5-5-fu (1,000 mg/m^2) on Dys 1-4 and 29-32,+ concurrent RT (50.4 Gy in 1.8-Gy fractions daily). **vs.** TOMOX-RT (n=81): raltitrexed, oxaliplatin, and RT (raltitrexed (3 mg/m^2) and oxaliplatin (130 mg/m^2) was given on Dys 1, 19, and 38 with the same RT regimen as used for PLAFUR)	Patients with cT3 and/or N+ resectable rectal carcinoma **Follow-up:** NR	**TRG1-2** : 41.0% vs. 51.9%; p=0.162 **ypTO rate** 24.1% vs. 35.8%; p=0.102 **ATX (GR3-4):** 7.1% vs. 16.4% **SPS:** 87.9% vs. 86.4%
Villacampa et al., 2012 (24) (ASCO 3571)	Arm A (n=44) concurrent RT 45Gy/25f/5 wks + CAP (825mg/m^2/b.i.d.) + BEV every 2 wks	Patients with LARC (Stages II-III assessed by MRI) and ECOG PS	**TX (GR3-4):** 18 % vs. 13%; p=0.50 **PC:** 43% vs. 37%

	(5 mg/kg for 3 doses) **vs.** Arm B (n=46) the same schedule without BEV Surgery was scheduled 6-8 wks after completing CRT	<2	**pCR:** 16% vs 11%; p=0.54 **ROR:** 96% vs. 96%; p=1.0 **SSS:** 61% vs. 67%; p=0.66
Radiation Oncology Grp 0247 Wong et al., 2012 (25) **See also:** Wong et al., 2011 (ASCO 3517) (26) Wong et al., 2008 (27)	Arm 1 (n=52) wkly RT (50.4 Gy in 1.8-Gy fractions) with concurrent capecitabine (1,200 mg/m^2/dy Mondays through Friday) and irinotecan (50 mg/m^2 wkly in four doses) **vs.** Arm 2 (n=52) concurrent capecitabine (1,650 mg/m(2)/d Mondy through Fridy) and oxaliplatin (50 mg/m^2 wkly in five doses)	Patients with Stage T3 or T4 RC of <12 cm from the anal verge **Follow-up:** unclear	**pCR:** 10% vs. 21% **TDR:** 52% vs. 60% **NDR:** 46% vs. 40% **TX (GR3-4 -hem):** 9% vs. 4% **TX (GR3-4 –non-hem):** 26% vs. 27%
Preop Therapies - CT vs. Surgery Alone (1 RCT)			
Trial/ Reference	**Intervention**	**Population/Follow-up**	**Outcomes/Results**
KODK4 Okabayashi et al., 2012 (28)	PreCT (n=41) wkly administration of tegafur suppositories (grp A) **vs.** Surgery alone (n=51) no wk treatment (grp B)	98 patients with clinical T3/4 colorectal cancer (35 had rectal cancer). **Follow-up:** 80.9 +/- 31.0 mos (median) and 64.5 +/- 28.8 mos	**OS (5yr):** 91.4% vs. 73.2% (p=0.051) **DFS (5yr):** 89.3% vs. 70.3% (p=0.045) **DMR**: 7.4% vs. 23.4% (p=0.03) **LR:** 4.6% vs. 8.2 (p = 0.68)
ATX Acute Toxicity; **cPR** complete pathological remission; **CPRR** complete pathologic remission rate; **CRPC** cumulated rate of permanent colostomy; **CSD** cause specific death; **DFS** Disease-free (or recurrence-free Survival); **DMC** Distant metastasis control; **DMFS** Distant Metastasis Free Survival**; DMR** Distant Metastasis Rate (or DM); **DRR** Distant Recurrence Rate; **DSM** disease Specific Mortality; **G/GR** grade; **HR** hazard ratio; **LC** local control; **LR** Local recurrence; **LFR** Local Failure Rate; **LTX** late toxicity; **NDR** Nodal Downstaging Rate; **NS** not stated; **OM** Overall mortality**; ORR** Overall Radiographic Response**; OS** Overall survival; **PFS** progression free survival; **pCR** pathologic complete response; **PC** Postoperative complications; **PM** Postoperative Mortality; **RMR** Rate of major Response; **ROR** RO Resection; **RR** relative risk; **SPS** Sphincter Preservation Surgery (or SPR or SSS); **TDR** Tumor Downstaging Rate; **TR** Tumor Regression; **TRG** Tumor Regression Grade; **TX** toxicity; **ypT** pathologic tumour stage; **yr(s)** year(s)			

Preoperative and Postoperative therapies

PreRT& Post RT vs. Post RT vs. Surgery alone (1 RCT)			
Trial/ Reference	**Intervention**	**Population/Follow-up**	**Outcomes/Results**
Zhang et al., 2008 (29)	Group A (n=92): wk accelerated hyperfractionation (15 Gy/6f/3d) followed by conventional postop fractionation (D_T35-40 Gy/3.5-4 wks). **vs.** Group B (n=98) postop RT (D_T 50 Gy/5 wks) vs. Group C (n=70) Surgery alone	Patients with stage II (117 patients) and stage III (143 patients) rectal carcinoma **Follow-up:** 5 yrs	**LR:** 5.4% vs.16.3% vs. 64.3%; P = 0.017 **DMR**: 6.5% vs. 28.6% vs. 31.4%; P = 0.001 **OS (3yr):** 86.9% vs. 62.2% vs. 51.4% , p=0.001 **OS (5yr):** 68.5% vs. 54.1% vs. 41.4% , p=0.003 **GRI& II radiation enterocolitis (GrA&B):** 7.6% vs. 6.1%
Preop RT vs. Preop CRT & postop CT (1 RCT)			
Trial/ Reference	**Intervention**	**Population/Follow-up**	**Outcomes/Results**

EORTC Bosset et al., 2013 (ASCO 3560) (30) **See also:** Collette et al., 2007 (31)	four treatment arms Arm 1 preop RT (n=199) **vs.** Arm 2 preop RT + 2 CT courses (n=204) **vs.** Arm 3 preop RT + 4 postop CT courses (n=190) **vs.** Arm 4 preop RT-CT + postop CT.(Preop RT 45 Gy over 5 wks (n=192) (A one 5-dy course of CT consisted of 5-FU 350 g/m^2 and Leucovorin 20 mg/m^2d)	Patients with resectable T3-T4 M0 rectal cancer **Follow-up:** 10.4 yrs (median)	**Arm2,4 vs Arm 1,3** **OS:** p=0.91 **DFS**: p=0.38 **DM:** NS **Arm2,4 vs Arm 1,2** **OS:** p=0.32 **DFS:** p=0.29 **DM:** NS **Arm1 vs Arm 2,3&4** **LR:**17.4% vs. 9%, p=0.0044 **DM:** NS
Preop RT vs. postop CRT (2 RCTs)			
Trial/ Reference	**Intervention**	**Population/Follow-up**	**Outcomes/Results**
The Medical Research Council CR07/National Cancer Institute of Canada Clinical Trials Group C016 (MRC CR07/NCIC CTG C016) trial Sebag-Montefiore et al., 2009 (32) **See also:** Stephens et al., 2010 (33) Quirke et al, 2006 (34)	PreRT (n=674): pre-RT of 25 Gy 5 consecutive daily fractions followed by surgery within 7 dys. **vs.** PostCRT (n=676): Initial surgery, postop concurrent chemoRT of 45 Gy in 25 fractions + (moly (5-FU 370–425 mg/ m^2, d1–5 every 28d) or wkly (5-FU 370–425mg/m^2 1x/wk) schedule combined with 20 mg/m^2 LV with each 5-FU)	Patients with operable adenocarcinoma of the rectum (NOT SURE ABOUT STAGE) **Follow-up:** 4 yrs (median)	**OS:** HR=0.91 (95%CI: 0.73-1.13) p=0.40 **DFS:** HR=0.76 (95%CI: 0.62-0.94) p=0.013; AD (3yrs) 6.0% (95% CI 5.3-6.8) (77.5% vs. 71.5%) **LR:** HR=0.39 (95%CI: 0.27-0.58) p<0.0001; AD (3 yrs) 6.2% (95% CI 5.3-7.1) (4.4% vs 10.6%
Taher et al, 2006 (35)	Group I (n=26): surgery followed by RT(50Gy/5 wks, 2Gy/fraction, 5 dys/wk) + CT **vs.** Group II (n=26) RT (46Gy/4.5 wks, 2Gy/ fraction, 5 dys/wk) followed by surgery±postop CT	Patients with previously untreated rectal cancer, Duke's stage B&C **Follow-up:** 10 yrs	**OS (10yr):** (63% vs. 60%, p=0.698) **DMFS:** 88% Vs. 72%; p=0.16 **DFS:** 65% vs. 66%, p=0.816 **LFR:** 8% vs. 305, p=0.057 **TX:** NS **PC:** NS
Preop CRT vs. postop CRT (5 RCTs)			
Trial/ Reference	Intervention	Population/Follow-up	Outcomes/Results
ACCORD Gerard et al., 2012 (36) **See also:** Gerard et al., 2011 (37) Gerard et al., 2010 (38) Gerard et al., 2009 (ASCO LBA4007) (39)	PreCRT (n=153) wk CT-RT with CAP45 (45-Gy RT for 5 wks with concurrent capecitabine) or **vs.** PostCRT (n=153) CAPOX50 (50-Gy RT for 5 wks with concurrent capecitabine & oxaliplatin)	Patients with T3-4 Nx M0 resectable rectal cancer **Follow-up:** 3 yrs	**OS:** 87.6% vs. 88.3%, p=NS **DFS:** 67.9% vs. 72.7%, p=NS **SOS:** 13.9% vs.19.2%, p=0.09; HR=0.32 (95% CI: 0.21-0.50) **LR:** 6.1% vs. 4.4%, p=NS **LTX (GR3-4):** 6.5% vs. 5.4%, p=NS
Kaçar et al., 2008 (40)	PRECRT (n=26): 4500-5040 cGy in 25-28 fr, 5x/wk to the pelvis + 5-FU 425mg/m^2 + leucovorin 20mg/m^2/dy; surgery 5-8wks after completion of CRT **vs.** POSTCRT (n=25): 2-4wks after wounds healed: 5040cGy in 30fr + 540-cGy boost to tumour bed + 4-6 (5-FU	Patients with stage II or III who did not display distant metastasis or peritoneal dissemination **Follow-up:** Mean 25.5 (mos) ± 12.6	**OS (4yr):** 86% vs. 60%; p=0.520 **DFS(4yr)**: 56% vs. 51%; p=0.707 **LR:** 15.4% vs. 20%, p=0.726

	425mg/m^2 + leucovorin 20mg/m^2/dy for 5 dys)		
Park et al, 2011 (41)	PreCRT (n=107): 46 Gy in 23 fr to whole pelvis +boost dose of 4 Gy in 2 fr + C 825mg/m^2, 2x/dy + 4wks after surgery: 4 x (C 2500mg/m^2/d/14d, 1 wk break) or 4 x (bolus 5-FU/LVa) **vs.** PostCRT (n=113): 50Gy in 25 fr to whole pelvis + C 825mg/m^2, 2x/dy + 4wks after CRT: 4 x (C 2500mg/ m^2/d/14 d, 1 wk break) or 4 x (bolus 5-FU/LVa)	Patients with locally advanced rectal cancer (cT3, potentially resectable cT4 or N+) **Follow-up:** 52 mos (median)	**OS (5yr):** 83% vs. 85%, p=0.6204 **DFS (5yr):**: 73% vs. 74%, p=0.8656 **LR(5 yr):** 5% vs. 6%, p=0.3925 **DM (5yr):** 23% vs. 24%, P=0.7384 **LTX(5yr):** 8% vs. 3% p=0 .350 **SPS (5yr):** 80% vs 72%, P=0.248 Patients with Low Lying tumors **SPR:** 68% vs 42%, P = .008
NSABP R-03 Roh et al., 2009 (42)	PreCRT (n=123): 5-FU 500mg/m^2 1x/wk for 6 wks + LV 500mg/m^2 1x/wk for 6 wks + 45Gy in 25 fr + 5.40Gy boost + 5-FU 325mg/m^2/5d + LV 20mg/m^2/5d (1st & 5th wk of RTX); surgery 8 wks after completion of CRT **vs.** PostCRT (n=131): CT after recovery from surgery or 4 wks after surgery; 5-FU 500mg/m^2 1x/wk for 6 wks + LV 500mg/m^2 1x/wk for 6 wks + 45Gy in 25 fr + 5.40Gy boost + 5-FU 325mg/m^2/5d + LV 20mg/m^2/5d (1st & 5th wk of RT)	Patients with clinical T3 or T4 or node-positive rectal cancer **Follow-up:** 8.4 yrs (median)	**OS (5yr):** 74.5% vs. 65.6% HR=0.69 (95% CI: 0.47-1.03) p=0.065 **DFS (5yr):** 64.7% vs. 53.4% HR=0.63 (95% CI: 0.44-0.90) p=0.011 **LR:** HR=0.86 (95% CI: 0.41-1.81) p=0.693 **SPS:** 47.8% vs. 39.2%, p=0.227 **PC:** 25% vs. 22.6, NS **TX:** balanced between grps with exception of diarrhea.
CAO/ARO/AIO-04 Sauer et al., 2012 (43) **See also:** Rodel et al., 2012 (44) Roedel et al.; 2011 (ASCO LBA35050) (45)	PreCRT (n=404): wk CRT (50.4 Gy) with 5-FU (1 g/msq/dys 1-5, 29-33), surgery, and adjuvant 5-FU (500 mg/msq/dys 1-5, 4 cycles) **vs.** PostCRT (n=395) the same schedule of CRT used postop.	Patients with histologically proven carcinoma of the rectum with clinically staged T3-4 or any node-positive disease **Follow-up:** 46 mos (median)	**OS;** 59.6% vs. 59.9%, p=0.85 **LR:** 7.1% vs. 10.1%, p=0.048 **DM (10yr):** 29.8% vs. 29.6%; p=0.9 **DFS:**: 68.1% vs. 67.8%, HR, 0.94; 95% CI, 0.73 to 1.21; p=.65 **ROR:** NS; **PO:** NS **pCR:** 13.1% vs. 17.6%, p=0.033
Preop CRT vs. Preop CRT & postop CT (1 RCT)			
Trial/ Reference	**Intervention**	**Population/Follow-up**	**Outcomes/Results**
PETACC-6 trial (on-going NCT00766155) Schmoll et el., 2013 (46) (ASCO 3531)	Arm 1 (n=547) wk CRT (45 Gy in 25 fractions) with capecitabine (825 mg/m^2 twice daily), followed by 6 cycles of adjuvant CT with capecitabine (1000 g/m^2 twice daily/dys 1-15 every three wks) **vs.** Arm 2 (n=547) the same regimen with the addition of oxaliplatin before (50 mg/m^2 dys 1, 8, 15, 22, 29) and after surgery (130 mg/m^2 dy 1, every three wks)	Patients with rectal cancer within 12 cm from the anal verge, T3/4 and/or node-positive, with no evidence of metastatic disease and considered either resectable at the time of entry or expected to become resectable after wk CRT **Follow-up:** NR	**TX(G3-4):** 15.1% vs. 36.7% **ROR:** 92% vs. 86.3% **pCR:** 11.3 vs. 13.3% (p=0.31) **SPR:** 70% vs. 65% (p=0.09) **PC:** 38% vs. 41%
Preop CRT & postop CT vs. Preop CRT & postop CT (1 RCT)			

Trial/ Reference	Intervention	Population/Follow-up	Outcomes/Results
Minkyu Jung et al. 2012 (47) (ASCO 511) **(on-going NCT01269216)**	FL group (n=) wk radiation (45-50.4 Gy in 25-28 daily fractions) and concomitant CT with bolus injections of 5-FU 400 mg/m^2/dy and LV 20 mg/m^2/dy for 3 consecutive dys every 4 wks for 2 cycles (FL group), **vs.** IS group (n=) irinotecan 40 mg/m^2 on dys 1, 8, 15, 22, 29 and S-1 35mg/m^2 twice on the dy of irradiation (Mondy-Fridy) (IS group). Curative surgery was performed for about 4-8 wks after the completion of chemoRT. Postop CT regimen is FL	Patients with resectable, locally advanced (cT3-4 and/or cN positive) adenocarcinoma of rectum **Follow-up:** NR	**pCR:** 17.2% vs. 24.2% (p=0.1) **TX(G3-4):** 1.4% vs. 7.0% (p=0.095)
Induction CAPOX + Preop CRT vs. Preop CRT + postop CAPOX			
Trial/ Reference	**Intervention**	**Population/Follow-up**	**Outcomes/Results**
GCR-3 Grupo cancer de recto 3 study Fernadez-Martos 2011 (48)(ASCO 3552) **See also:** Fernadez-Martos 2010 (49) Fernadez-Martos 2009 (50)	arm A (n=37) CRT with capecitabine, oxaliplatin, & concurrent radiation followed by surgery & four cycles of postop adjuvant CAPOX **vs.** arm B (n=54) induction CAPOX followed by CRT & surgery	Patients with locally advanced rectal cancer (tumors extending to within 2mm of, or beyond, the mesorectal fascia (ie, an involved or threatened circumferential resection margin; lower third (_6 cm from the anal verge) cT3 tumors; resectable cT4 tumors; and any cT3N+) **Follow-up:** 39.3 mos (median)	**3 yr** **OS:** 90% (95% CI: 77-96) vs. 81%(95% CI: 68-89) p= 0.18 **DFS:** 68% (95% CI, 53-80) vs. 70% (95% CI, 55-80) (p=0.97) **LR:** 21.2 vs. 21.4, p=0.6036
ATX Acute Toxicity; **CCM** Cause Specific Mortality**; DFS** Disease-free (or recurrence-free Survival); **DMFS** Distant Metastasis Free Survival**; DMR** Distant Metastasis Rate (or DM); **G/GR** grade; **HR** hazard ratio; **LR** Local recurrence; **LFR** Local Failure Rate; **LTX** late toxicity; **OM** Overall mortality**; ORR** Overall Radiographic Response**; OS** Overall survival; **NS** not stated; **pCR** pathologic complete response; **PC** Postoperative complications; **RMR** Rate of major Response; **ROR** RO Resection; **SOS** Sterilization of the Operative Specimen; **SPS** Sphincter Preservation Surgery (or SPR);			

Postoperative Therapies (8 RCTs)

Postop Therapies - RT vs. RT (1 RCT)			
Trial/ Reference	**Intervention**	**Population/Follow-up**	**Outcomes/Results**
Kornmann et al, 2010 (51)	5-FU (n=282) levamisol and local irradiation with 50.4Gy **vs.** 5-FU+FA (n=291) levamisol and local irradiation with 50.4Gy. **vs.** 5-FU+IFN (n=223) levamisol and local irradiation with 50.4Gy.	Patients with R(0)-resected rectal cancer (UICC stage II & III) **Follow-up:** 4.9 yrs (median)	**OS(5yr):** 60.3% (95% CI: 54.3–65.8) vs 60.4% (95% CI: 54.4–65.8) vs. 59.9% (95% CI: 53.0–66.1) **OS Stage II:** 77.1% (95%CI: 71.5 – 81.7) **LR:** 16.7% (95% CI: 12.3–22.5) vs 13.6% (95% CI: 9.6-19.0) vs. 17.1%

Postop Therapies - RT vs. RT (1 RCT)			
Trial/ Reference	**Intervention**	**Population/Follow-up**	**Outcomes/Results**
			(95% CI: 12.2-23.8) **DFS:** 54.4% (95% CI: 48.2–60.1) vs 58.0% (95% CI: 51.9–63.6) vs. 56.5% (95% CI: 49.5–63.0) **DSM:** 36.2% vs. 33.7% vs 33.6% **TX (WHO III&IV):** 31.5% vs. 27.7 vs 58.1% (p<0.001)
Postop Therapies - CT vs. surgery alone (3 RCTs)			
Trial/ Reference	**Intervention**	**Population/Follow-up**	**Outcomes/Results**
Dahl et al., 2009 (52) Norwegian Gastrointestinal Cancer Group (NGGG)	PostCRT(n=214)5-FU (450mg/m^2) for 5 consecutive d + levamisole 50mg, 3x daily for d1-3; after, 5-FU wkly from d28: 450mg/m^2 for 48 wk + levamisole 50mg, 3xdaily for 3 dys every 14 dys **vs.** Surgery alone (n=211)	Patients with stage II & III colorectal cancer (225 with rectal cancer) **Follow-up:** 5 yrs	**OS:** 71% (95% CI: 65-78) vs. 66% (95% CI: 60-73) p=0.40 **DFS(3yr):** 73% (95% CI: 67-79) vs. 67% (95% CI: 61-74) **DFS(5yr):** 58% (95%CI: 44%-71%) vs.37% (95%CI: 23%-50%) p=0.012 **CSS (5yr) :** 65% (95%CI: 53%-78%) vs. 47% (95%CI: 33%-61%) p=0.032 (**NOTE:** these outcomes are for colon and rectal combined, but study says looked at them separately and did not find any differences on these outcomes in the 2 groups)
Hamaguchi et al., 2011 (53) National Surgical Adjuvant Study of Colorectal Cancer (NSAS-CC)	UFT Group (n=140) surgery + UFT (400 mg/m^2/dy), given for five consecutive dys per wk for 1 yr. **vs.** Surgery alone (n=136)	patients with stage III colorectal cancer (n=276 with rectal) **Follow-up:** 36 mos (median)	**OS:** HR=0.60 (95% CI: 0.38 vs. 0.97) p=0.034 **RFS**: HR=0.66 (95%CI: 0.45-0.97) p=0.033 **TX:** NS
QUASAR Collaborative Group, 2007 (54)	CT group (n=474) Surgery + 5-FU + L-folinic acid (either high dose 175mg IV or low dose 25mg IV) six 5d courses every 4 wk or 1x/wk for 30wk **vs.** Surgery alone (n=474)	Patients with Stage II colorectal cancer (948 with rectal cancer) **Follow-up:** 5.5 yrs (median)	**LR:** RR= 0.68 (95% CI 0.52–0.88; p=0.004) **OM:** RR=0.77 (95%CI 0.54–1.00; p=0.05
Postop Therapies - CT vs. CRT (3 RCTs)			
Trial/ Reference	**Intervention**	**Population/Follow-up**	**Outcomes/Results**
Hata et al., 2008 (55)	Arm A: 5-FU + CDDP (n=30): 5-FU 320mg/m2 + CDDP 3.5mg/m^2 daily for 21 + 5 FU (200mg/body daily for 2 yrs) **vs.** Arm B: 5-FU (n=32): Oral 5-FU exclusively (200mg/body daily for 2 yrs) starting 3wk after surgery	Patients with stage II/III colorectal cancer (62 with rectal cancer) **Follow-up:** 78.0 & 76.4 mos (median)	**DFS :** 60.0% vs. 59.4%; HR, 0.98 (95%CI : 0.48% vs.2.16)p=0.961 **OS :** 73.2% vs. 68.6%; HR, 1.26 (95%CI :0.50%-3.20%)p=0.623 **Stage II** **DFS(5yr)** 77.8% vs. 87.8%;

Postop Therapies - RT vs. RT (1 RCT)			
Trial/ Reference	**Intervention**	**Population/Follow-up**	**Outcomes/Results**
			p=0.209 **OS(5yr):** 86.5% vs. 95.1%; p=0.182 **Stage III** **DFS(5yr)** 62.4% vs. 70.3%; p=0.428 **OS(5yr):** 71.0% vs. 73.0%; p=0.850
HCOG Kalofonos et al., 2008 (56)	Arm A (n=119): wkly administration of IRI 80 mg/m^2 I IV, LV 200 mg/m^2 and 5FU 450 mg/m^2 bolus **vs.** ArmB (n=127) LV 200 mg/m^2 and 5FU 450 mg/m^2 IV bolus	Patients who underwent complete surgery for stages B2 & C rectal adenocarcinoma with neither gross nor microscopic evidence of residual disease. **Follow-up:** 52 mos (median)	**OS:** HR=0.73 (95% CI: 0.46-1.15) p=0.129 **DFS:** HR=0.92 (95% CI: 0.63-1.34) **LRFS:** 94% vs. 94%, p=0.837
Koda et al. 2011 (57) (ASCO 515) Koda et al. 2013 (ASCO 520) (58)	UFT group (n=NR): (400mg/m^2/dy, 5d/wk for 1 year, starting within 6wks after resection **vs.** S-1 group (n=NR): (80mg/m^2/dy, 28d per 6wks) for 1 year, starting within 6wks after resection	stage III colorectal patients (# rectal NR but outcomes given separately for rectal) **Follow-up:** 30.7mos (median)	**LR:** 11/25 vs. 4/21; p<0.01
Postop Therapies - Timing of CRT (1 RCT)			
Trial/ Reference	**Intervention**	**Population/Follow-up**	**Outcomes/Results**
Kim et al., 2011 (59)	Early CRT (n=155): 8 x (5-FU 375mg/m^2/dy + LV 20mg/m^2/dy at 4 wk intervals) + pelvic RT of 45 Gy in 25 fr, starting 1st cycle of CT **vs.** Late CRT (n=153): 8 x (5-FU 375mg/m^2/dy + LV 20mg/m^2/dy at 4 wk intervals) + pelvic RT of 45 Gy in 25 fr, starting 3rd cycle of CT	Patients with Stage II or III rectal cancer **Follow-up:** 121 mos (median)	**OS (10 yrs):** NS **DFS (10yrs):** 71% vs. 63%; p = 0.162 **LR:** 26.7% vs. 35.3%; p=0.151

CSS Cause-specific survival**; DFS** Disease-free (or recurrence-free Survival); **DSM** disease Specific Mortality; **HR** hazard ratio; **LR** Local recurrence; **LRFS** Local Relapse-free survival; **NS** not stated; **OM** Overall mortality**; OS** Overall survival; **RFS** Recurrences-free Survival; **RR** relative risk; **TX** toxicity; **yr(s)** year(s)

Meta-Analysis (n=10)

Pre-op RT vs. Pre-op CRT				
Reference	**Intervention**	**RCT Population**	**N of Studies**	**Results**
Caluwe et al., 2013 (60)	pre-op RT **vs.** Pre-op CRT	Resectable stage II or III rectal cancer patients	5 RCTs	**OS**: at 5 yrs - OR=1.05 (95% CI: 0.88-1.27), p=0.58 **DFS**: at 5 yrs OR=0.90 (95% CI: 0.74-1.09),p=0.27 **LR**: at 5 yrs OR=0.53 (95% CI: 0.39-0.72), p<0.0001 **SPS**: OR=1.09 (95% CI: 0.92-1.30), p=0.32 **OM:** OR=1.48 (95% CI: 95% CI: 0.83-2.63), p=0.18 (30dy) **PM:** OR=0.82 (95% CI: 0.67-1.00), p=0.05 – 4 studies **TX:** OR=4.10 (95% CI: 1.68-10) (grade III/IV), p=0.002 **pCR:** OR= 3.52 (95% CI: 2.12-5.84), p<0.000001
Latkauskas et al., 2010 (61)	Pre-op RT **vs.** pre-op ChRT	Patients with stage II and III resectable rectal cancer	4 RCTs	**OS**: OR = 1.0744 (95% CI: 0.87–1.30), P = 0.4647 **CSS:** OR = 1.0436, P = 0.6309 **LR:** OR = 0.6988, P = 0.2447 **SPS**: OR = 1.0075, P = 0.9324 **PMor:** OR = 1.2284, P = 0.0662 **ROR**: OR = 1.404, P = 0.1756 **cPR:** OR = 3.0296 (95% CI: 1.95–4.72), P < 0.0001 **TX**: OR = 4.0 (95% CI: 1.74–9.19), P=.0011
	Pre-op SRT **vs**. Preop ChRT		5 RCTs	**OS**: OR = 1.2302, P = 0.4307 **LR:** OR = 1.4216, P = 0.2554 **SPS**: OR = 1.2686, P = 0.4384 **ROR**: OR = 2.73 (95% CI 1.71–4.35), P < 0.0001
McCarthy et al., 2012 (62)	CRT **vs** RT	Patients aged over 18 years undergoing preoperative CRT or RT followed by surgery for locally advanced non-metastatic rectal cancer. (Locally advanced non-metastatic cancer defined as stage 3 rectal tumours)	6 RCTs	**OS**: OR = 1.01 [95% CI: 0.85-1.20), p=0.88, at 4-5 yrs **LR:** OR 0.56 (95% CI: 0.42-0.75) P<0.0001 **SPR**: OR 1.01 (95% CI: 0.86-1.20) P=0.87 **LTX:** OR 0.88 (95% CI: 0.50-1.54) P=0.65 **OM**: 1.73 (95% CI: 0.88-3.38), p=0.11 30 dys
Wong et al., 2007 (63)	PRT **vs.** Surgery alone	Studies designed for patients of any age with a localized resectable carcinoma of the rectum	19 RCTs	**OM:** HR=0.93 (95%CI: 0.87-1.0) [NS when using CCCG data - individual ptient data] **CSM:** HR=0.87 (95%CI: 0.78-0.98) **LR:** HR=0.71 (95%CI: 0.64-0.78) **SPS**: HR=0.94 (95%CI: 0.88-1.04) **LX:** NR
	PRT vs. Other strategies		9 RCTs	No pooled data for this group
Pre-op CRT vs Surgery Alone				
Reference	**Intervention**	**RCT Population**	**N of studies**	**Results**

Viani et al., 2011 (64)	Group 1 RCTs with a BED >30 Gy_{10} and a short RT schedule vs. Surgery alone vs.	Studies that included only rectal carcinoma, defined by tumors located within 15 cm of the	4 RCTs	**OM:** OR=0.87 (95%CI: 0.76-0.99) p=0.03 **SPR:** OR=1 (95%CI: 0.87-1.14) p=0.97 **LR:** OR=0.53 (95%CI: 0.41-0.69) p<0.00001
	Group 2 RCTs with BED >30 Gy_{10} and a long RT schedule vs. Surgery alone vs.	pectinate line or anal verge on sigmoidoscopy, or rectosigmoid tumors without metastases.	7 RCTs	**OM:** OR=0.77 (95%CI: 0.61-0.99) p=0.04 **SPR:** OR=0.65 (95%CI: 0.48-0.88) p=0.005 **LR:** OR=0.38 (95%CI: 0.32-0.46) p<0.00001
	Group 3, RCTs with BED ≤ 30 Gy_{10} and a short RT schedule vs. Surgery alone Vs.		4 RCTs	**OM:** OR=0.93 (95%CI: 0.75-1.16) p=0.51 **SPR:** OR=0.91 (95%CI: 0.7-1.19) p=0.5 **LR:** OR=0.86 (95%CI: 0.66-1.13) p=0.29
	Group 4 RCTs with BED ≤ 30 Gy_{10} and a long RT schedule vs. Surgery alone		6 RCTs	**OM:** OR=0.98 (95%CI: 0.81-1.19) p=0.86 **SPR:** OR=0.97 (95%CI: 0.72-1.31) p=0.83 **LR:** OR=0.95 (95%CI: 0.74-1.22) p=0.67
Post-op Ct vs Surgery Alone				
Reference	**Intervention**	**RCT Population**	**N of Studies**	**Results**
Petersen et al., 2012 (65)	Any post-op CT **vs.** surgery alone	Patients with non-metastatic rectal cancer	21 RCTs	**OS (all):** HR=0.83 (95%CI: 0.76-0.91) p=0.0003 (all patients) **OS (stage II 2 studies):** HR=0.78 (95%CI: 0.62-0.97) p=0.03 **OS(stage III -3 studies):** HR=0.92 (95%CI: 0.78-1.09) p=0.36 (stage III -3 studies) **DFS (all):** HR=0.75 (95%CI: 0.68-0.83) p<0.00001 **DFS (stage II study):** HR=0.69 (95%CI: 0.51-0.94) p=0.02 **DFS(stage III -3 studies):** HR=0.67 (95%CI: 0.54-0.83) p=0.0002
Sakamoto et al., 2007 (66)	surgery alone vs. Surgery + post-op UFT versus	IPD meta-analysis from RCTs for resected rectal cancer without evidence of distant metastasis (Dukes A,B,C)	5 RCTs	**OS(5yrs):** HR=0.82 (95%CI: 0.70-0.97) p=0.02 – all **OS:** HR=0.60 Dukes A, HR=0.79 Dukes B, HR=0.86 Dukes C (p=0.495 heterogeneity test) **DFS:** HR=0.73 (95%CI: 0.63-0.84) p<0.0001 – all **RFS:** HR=0.68 (95%CI: 0.53-0.87) p=0.0026 - all
Wu et al., 2012 (67)	surgery combined with postoperative adjuvant CT vs.	patients were diagnosed with colorectal cancer and pathologically	4 RCTs for rectal cancer	**OS :** HR=0.72 (95%CI: 0.61-0.86) p=0.0002 – 5 yrs **DFS:** HR=0.34 (95%CI: 0.22-0.51) p<0.00001 – 5 yrs

	surgery alone	confirmed as stage Dukes' B or stage II (T3–T4, N0, M0); (3) without any anticancer therapy before surgery		
Pre-op CRT vs. Pre-op CRT				
Reference	**Intervention**	**RCT Population**	**N of Studies**	**Results**
An et al., 2013 (68)	Pre-op CRT with OX/FU **vs.** Pre-op CRT with FU alone	Patients with LARC, of whom 49.7% patients received the experimental treatment, FU plus OX.	4 RCTs	**pCR:** OR=1.20 (95% CI: 1.01-1.42) p=0.04 **TX:** OR=2.29 (95% CI: 1.31-4.00) p=0.004 – GR3/4 **PS:** OR=1.05 (95% CI: 0.90-1.21) p=0.55 **OM:** OR= 0.90 (95% CI: 0.35-2.35) p=0.84 – 60 dys
Pre-op/Post-op CRT/RT				
Reference	**Intervention**	**RCT Population**	**N of Studies**	**Results**
Fiorica et al., 2010 (69)	Pre-op RT **vs.** Pre-op CRT	Patients with resectable, histologically-proven, rectal adenocarcinoma without metastases	7 RCTs,	**OS:** RR=1.02 (95% CI: 0.94-1.09) p=0.68 (5 yr) **LC:** RR=1.05 (95% CI: 1.01-1.10) p=0.02 (5 yr) **DMC:** RR=0.97 (95% CI: 0.93-1.02) p=0.21 (5 yr)
	Post-op RT **vs.** Post-op CRT		4 RCTs	**OS:** RR=1.09 (95% CI: 0.83-1.41) p=0.54 (5 yr) **LC:** RR=0.96 (95% CI: 0.80-1.16) p=0.66 (5 yr) **DMC:** RR=1.11 (95% CI: 0.94-1.31) p=0.22 (5 yr)
	Pre-op RT **vs.** Post-op CRT		2 RCTs	**OS:** RR=0.96 (95% CI: 0.90-1.03) p=0.28 (5 yr) **LC:** RR=0.93 (95% CI: 0.90-0.96) p<0.00001 (5 yr) **DMC:** RR=0.95 (95% CI: 0.84-1.07) p=0.42 (5 yr)

CSS Cause-specific survival**; DFS** Disease-free (or recurrence-free Survival); **DMC** Distant metastasis control; **dy(s)** day(s); **HR** hazard ratio; **LC** local control; **LR** Local recurrence; **LTX** late toxicity; **NR** not reported; **NS** not stated; OM Overall mortality**; OR** odds ratio; **OS** Overall Rate; **pCR** pathologic complete response; **PM** Postoperative Mortality**; PS:** Permanent Stoma; **ROR** RO Resection; **RR** relative risk; **SPS** Sphincter Preservation Surgery (or SPR); **TX** toxicity

Ongoing Trials

Intervention	Official title	Status	Protcol ID	Completion date	Last updated
SC RT and combination CT (capecitabine and oxaliplatin) vs. pre-op LC CRT	Randomized Multicentre Phase III Study of Short Course Radiation Therapy Followed by Prolonged Pre-operative Chemotherapy and Surgery in Primary High Risk Rectal Cancer Compared to Standard Chemoradiotherapy and Surgery and Optional Adjuvant Chemotherapy.	Recruiting	NCT01558921	June 2016	June 14, 2013
Preop hyperfractionated RT vs. preop CRT	Preoperative Hyperfractionated Radiotherapy Versus Combined Radiochemotherapy for Patients With Locally Advanced Rectal Cancer: a Phase III Randomized Trial.	Not yet open for recruitment	NCT01814969	December 2016	March 18, 2013
CRT (5-FU/FL) vs.	A Randomized Phase II Study of Neoadjuvant Chemoradiotherapy	Recruiting	NCT01269216	February 2017	March 20, 2012

Intervention	Official title	Status	Protcol ID	Completion date	Last updated
CRT (5-FU/TS) + postop CT	With 5-FU/Leucovorin (FL) vs. TS-1/Irinotecan in Patients With Locally Advanced Rectal Cancer				
Neoadjuvant FOLFOX, with combined modality CRT vs. Preop combined modality CRT	A Phase II/III Trial of Neoadjuvant FOLFOX, With Selective Use of Combined Modality Chemoradiation Versus Preoperative Combined Modality Chemoradiation for Locally Advanced Rectal Cancer Patients Undergoing Low Anterior Resection With Total Mesorectal Excision	Recruiting	NCT01515787	July 2017	June 24, 2013
Preop RT vs. Preop CRT (5-FU and leucovorin) (with or without postop CT)	Four Arms Phase III Clinical Trial For T3-T4 Resectable Rectal Cancer Comparing Pre-Operative pelvic Irradiation To Pre-operative Irradiation Combined With Fluorouracil And Leucovorin With Or Without Post-Operative Adjuvant Chemotherapy	Unknown	NCT00002523	NR	July 20, 2011
Preop RT vs. Preop CRT (5-FU and leucovorin)	Preoperative Radiotherapy With or Without Concurrent Chemotherapy (5-Fluorouracil and Leucovorin) in T3-4 Rectal Cancers - Randomized Trial	Ongoing, but not recruiting	NCT00296608	NR	May 1, 2012
Preop CRT (oxaliplatin, capecitabine with cetuximal) vs. Preop CRT (oxaliplatin, capecitabine without cetuximal)	A Multicentre Randomised Phase II Clinical Trial Comparing Oxaliplatin (Eloxatin), Capecitabine (Xeloda) and Pre-Operative Radiotherapy With or Without Cetuximab Followed by Total Mesorectal Excision for the Treatment of Patients With Magnetic Resonance Imaging (MRI) Defined High Risk Rectal Cancer	Unknown	NCT00383695	NR	January 12, 2010
Preop CRT (capecitabine with oxaliplatin) vs. Preop CRT (capecitabine without oxaliplatin)	Prospective Randomized Phase III Study of Concurrent Capecitabine and Radiotherapy With or Without Oxaliplatin as Adjuvant Treatment for Stage II and III Rectal Cancer	Recruiting	NCT00714077	December 2013	May 28, 2013
Preop CRT (5-FU and oxaliplatin) vs. Preop CRT (5-FU)	Prospective Randomised Multicenter Phase-III-study: Preoperative Radiochemotherapy and Adjuvant Chemotherapy With 5-Fluorouracil Plus Oxaliplatin versus Preoperative Radiochemotherapy and Adjuvant Chemotherapy With 5-Fluorouracil for Locally Advanced Rectal Cancer	Ongoing, but not recruiting	NCT00349076	December 2013	October 5, 2012
Preop CT + Postop CT (capecitabione & Oxaplatin vs. Capecitabine Alone	Preoperative Chemoradiotherapy and Postoperative Chemotherapy With Capecitabine and Oxaplatin vs.Capecitabine Alone in Locally Advanced Rectal Cancer (PETACC-6)	Unknown	NCT00766155	NR	September 28, 2011

Clinical Expert Interest Declaration:

Professional Interest, Publication

Instructions. For each document, please respond YES or NO to all the questions below. Provide an explanation of each answer as necessary.	
4. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed?	No
5. On initial review, a. Does the newly identified evidence support the existing recommendations? b. Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary?	a) Yes b) Yes [maybe - there are some potential questions regarding radiotherapy doses)
6. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary:	No
7. Do the PEBC and the DSG/GDG responsible for this document have the resources available to write a full update of this document within the next year?	No (Maybe - will be discussed at the DSG meeting next week but not a higher priority that the two already identified in EBS series)
Review Outcome	Endorse

DSG/GDG Approval Date	October 31, 2013
DSG/GDG Commentary	

New References Identified

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Search Strategy:

Medline

1. meta-Analysis as topic/
2. meta analysis.pt.
3. (meta analy$ or metaanaly$).tw.
4. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview).tw.
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6. (exp Review Literature as topic/ or review.pt. or exp review/) and systematic.tw.
7. or/1-6
8. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
9. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
10. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
11. (study adj selection).ab.
12. 10 or 11
13. review.pt.
14. 12 and 13
15. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/

16. (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
17. random allocation/ or double blind method/ or single blind method/
18. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
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20. (phase II or phase 2).tw. or exp clinical trial/ or exp clinical trial as topic/
21. (clinical trial or clinical trial, phase II or controlled clinical trial).pt.
22. (20 or 21) and random$.tw.
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24. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
25. placebos/
26. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
27. (allocated adj2 random).tw.
28. or/23-27
29. 7 or 8 or 9 or 14 or 19 or 22 or 28
30. exp rectal cancer/
31. exp colorectal cancer/
32. rectal: neoplasm:.kw.
33. (rectal: cancer or rectal: carcinoma: or rectal: tumo?r: or rectal: malignan:).tw.
34. (rectal: cancer or rectal: carcinoma: or rectal: tumo?r: or rectal: malignan:).kw.
35. rectal neoplasms/rt, su, th
36. Colorectal neoplasms/rt, su, th
37. or/30-36
38. (adjuvant or neoadjuvant or neo adjuvant or post operativ$ or postoperativ$ or pre operativ$ or preoperativ$ or following surgery or after surgery or post surgery or before surgery or pre surgery or pre-surgery or operable or stage 2A or stage 2 A or Stage IIA or stage II A or stage 2 or stage II or stage 3A or stage 3 A or stage IIIA or stage III A or stage 3 or stage III or stage II-III or stage 2-3).tw.
39. 29 and 37 and 38
40. limit 39 to english
41. limit 40 to human
42. limit 41 to yr="2006 -Current"

Embase

1. exp Meta Analysis/ or exp Systematic Review/
2. (meta analy$ or metaanaly$).tw.
3. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview).tw.
4. (systematic adj (review$ or overview?)).tw.
5. exp Review/ or review.pt.
6. (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
7. (study adj selection).ab.
8. 5 and (6 or 7)
9. or/1-4,8
10. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
11. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
12. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
13. randomization/ or single blind procedure/ or double blind procedure/

14. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
15. or/12-14
16. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
17. 16 and random$.tw.
18. (clinic$ adj trial$1).tw.
19. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
20. placebo/
21. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
22. (allocated adj2 random).tw.
23. or/18-22
24. 9 or 10 or 11 or 15 or 17 or 23
25. (editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/
26. 24 not 25
27. exp rectal cancer/
28. exp colorectal cancer/
29. rectal: neoplasm:.kw.
30. (rectal: cancer or rectal: carcinoma: or rectal: tumo?r: or rectal: malignan:).tw.
31. (rectal: cancer or rectal: carcinoma: or rectal: tumo?r: or rectal: malignan:).kw.
32. rectal neoplasms/rt, su, th
33. Colorectal neoplasms/rt, su, th
34. or/27-33
35. (adjuvant or neoadjuvant or neo adjuvant or post operativ$ or postoperativ$ or pre operativ$ or preoperativ$ or following surgery or after surgery or post surgery or before surgery or pre surgery or pre-surgery or operable or stage 2A or stage 2 A or Stage IIA or stage II A or stage 2 or stage II or stage 3A or stage 3 A or stage IIIA or stage III A or stage 3 or stage III or stage II-III or stage 2-3).tw.
36. 24 and 34 and 35
37. limit 36 to english
38. limit 37 to human
39. limit 38 to yr="2006 -Current"

COCHRANE

1. exp rectal neoplasms/
2. exp rectal cancer/
3. rectal: neoplasm:.kw.
4. (rectal: cancer or rectal: carcinoma: or rectal: tumo?r: or rectal: malignan:).tw.
5. (rectal: cancer or rectal: carcinoma: or rectal: tumo?r: or rectal: malignan:).kw.
6. rectal neoplasms/rt, su, th
7. Colorectal neoplasms/rt, su, th
8. or/1-7
9. (adjuvant or neoadjuvant or neo adjuvant or post operativ$ or postoperativ$ or pre operativ$ or preoperativ$ or following surgery or after surgery or post surgery or before surgery or pre surgery or pre-surgery or operable or stage 2A or stage 2 A or Stage IIA or stage II A or stage 2 or stage II or stage 3A or stage 3 A or stage IIIA or stage III A or stage 3 or stage III or stage II-III or stage 2-3).tw.
10. 8 and 9
11. limit 10 to yr="2006 -2014"

ASCO Annual Meeting - searched http://www.ascopubs.org/search with keywords: Resectable Rectal carcinoma

Clinicaltrials.gov – searched http://clinicaltrials.gov/ct2/home with keywords: Resectable Rectal carcinoma