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The Use of Preoperative Radiotherapy in the Management of Patients with Clinically Resectable Rectal Cancer

Practice Guideline Report #2-13

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ORIGINAL GUIDELINE: December 12, 2002
MOST RECENT LITERATURE SEARCH: January 2004
NEW EVIDENCE ADDED TO GUIDELINE REPORT: January 2004

Based on the publication peer-review process and updating procedures, the Gastrointestinal Cancer Disease Site Group has modified this practice guideline report. The revised sections are labelled UPDATE.

SUMMARY

Guideline Questions

Should patients with resectable rectal cancer receive preoperative radiotherapy to improve survival and prevent or delay local recurrence? Should preoperative radiotherapy replace the present common practice of postoperative combined radiotherapy and chemotherapy?

Target Population

These recommendations apply to adult patients with clinically resectable rectal cancer. This report does not consider the use of preoperative radiotherapy to convert locally advanced, initially unresectable rectal cancer to resectable cases, to preserve the anal sphincter or to delay the need for colostomy.

Update

Recommendations

- Preoperative radiotherapy is an acceptable alternative to the standard practice of postoperative radiotherapy for patients with stage II and III resectable rectal cancer.
- Both preoperative and postoperative radiotherapy decrease local recurrence but neither improves survival as much as postoperative radiotherapy combined with chemotherapy. Therefore, if preoperative radiotherapy is used, chemotherapy should be added postoperatively, at least for patients with stage III disease.

Qualifying Statement

- Patients who choose preoperative radiotherapy as a treatment option instead of postoperative combined radiotherapy and chemotherapy need to be made aware that, because pathological stage is unknown until surgery is performed, many patients who will not benefit from treatment will be exposed to the risk of radiation-induced morbidity and mortality.

Methods

Entries to MEDLINE (1966 to January week 1 2004), EMBASE (1980 to week 3 2004), CANCERLIT (1983 to October 2001), the Cochrane Library (Issue 3, 2003), and the proceedings of the 1998 to 2003 annual meetings of the American Society of Clinical Oncology and the 1999 to 2003 annual meetings of the American Society for Therapeutic Radiology and Oncology were searched for relevant trial reports. 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. The Physician Data Query (PDQ) clinical trials database on the Internet was searched for reports of on-going trials.

Evidence was selected and reviewed by four members of the Practice Guidelines Initiative's Gastrointestinal Cancer Disease Site Group and the methodologists. This practice guideline report has been reviewed and approved by the Gastrointestinal Cancer Disease Site Group, which is comprised of medical and radiation oncologists, surgeons, a pathologist, a hematologist, a gastroenterologist and community representatives.

The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each guideline report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Key Evidence

- Randomized trials demonstrate that preoperative radiotherapy followed by surgery is significantly more effective than surgery alone in preventing local recurrence in patients with resectable rectal cancer, and may also improve survival. However, because the pathological stage is unknown until surgery is performed, preoperative therapy requires the treatment of most rectal cancer patients and, consequently, exposes many patients, who will not benefit, to the risk of radiation-induced morbidity and mortality.
- A single trial, using surgery with total mesorectal excision, has shown that preoperative radiotherapy induces a greater than 50% decrease in local recurrence.
- Results of trials comparing preoperative radiotherapy with the commonly used postoperative radiotherapy plus chemotherapy are not available for review at this time.

Future Research

- Patients with evidence of locally advanced but resectable rectal cancer should be encouraged to participate in randomized clinical trials evaluating the role of preoperative radiotherapy versus postoperative radiotherapy and chemotherapy combined.
- As optimal surgery including total mesorectal excision can also reduce the probability of locally recurrent rectal cancer, this surgical modality should be tested against the value of adjuvant radiotherapy in a randomized trial.

Related Guideline

Practice Guidelines Initiative Practice Guideline Report #2-3: *Postoperative Adjuvant Radiotherapy and/or Chemotherapy for Resected Stage II or III Rectal Cancer*.

For further information about this practice guideline report, please contact: Dr. Jean Maroun, Chair, Gastrointestinal Cancer Disease Site Group, Ottawa Regional Cancer Centre, General Division, 501 Smyth Road, Ottawa, Ontario, K1H 8L6; TEL (613) 737-7000, ext. 6708; FAX (613) 247-3511.

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PREAMBLE: About Our Practice Guideline Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle.[1] The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis, and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee, whose membership includes oncologists, other health providers, patient representatives, and Cancer Care Ontario executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network that is expected to consult with relevant stakeholders, including CCO.

Reference:

[1] Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

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FULL REPORT

I. QUESTIONS

Should patients with resectable rectal cancer receive preoperative radiotherapy to improve survival and prevent or delay local recurrence? Should preoperative radiotherapy (RT) replace the present common practice of postoperative combined RT and chemotherapy (CT)?

II. CHOICE OF TOPIC AND RATIONALE

Adenocarcinoma of the rectum is a common malignancy that originates in the last 15 centimetres of the large bowel where most of the external surface is not covered by peritoneum but rather is directly surrounded by connective-adipose tissue. Resection of the rectum and surrounding tissues can cure approximately 50% of patients; the other half will eventually die of the disease. Surgical failure is related to distant micrometastases that are not apparent and/or to incomplete local resection. Local recurrences increase in frequency and survival decreases as the tumour penetrates through the rectal wall and extends to regional lymph nodes (1). These prognostic factors form the basis for the TNM staging system widely used to advise therapy (see Appendix I for tumour staging).

Meticulous dissection of perirectal tissues en bloc with total mesorectal excision (TME) decreases local relapse (2). Pre- and postoperative RT has also been used to reduce local recurrence, which is associated with pelvic pain and rectal obstruction, and to prevent disease dissemination from the local site, thereby improving survival. Other goals of RT are to convert inoperable tumours into resectable cases, to preserve the anal sphincter and to avert a colostomy (3). The advantages and disadvantages of preoperative and postoperative RT have been well described (3). The principal advantage of postoperative RT is that it is given only to patients at high risk of recurrence according to well-investigated prognostic factors, pathological stages II and III (B2 and C). Major incentives for preoperative RT originate from a variety of perspectives. Biologically, a tumour with an undisturbed circulation and oxygenation has a better chance for full radiation effects. Moreover, a tumour reduced in size and with the surrounding tissues sterilized facilitates surgery and reduces potential tumour dissemination. A more practical incentive is the possibility of using an equally effective five-day course of high-dose fraction preoperative RT instead of a 25-30 day standard postoperative course of RT.

Another practice guideline developed by the Gastrointestinal Cancer Disease Site Group (DSG), first completed in 1997 and updated in 2001, reviewed the effects of postoperative RT and/or CT in resected stage II/III rectal cancer (4) (see the Abstract of the guideline report in Appendix II). This guideline recommended the combined use of postoperative radiation and CT as the preferred treatment for resected stage II and III rectal cancer. This combined treatment improved the local recurrence rate by 50% and the 5-year survival rate by 42%. The same guideline discouraged the use of radiation therapy alone as adjuvant treatment because it only decreased local recurrence rates. For the present report, we initially reviewed only the effect of RT, given before definitive surgery, on survival and local recurrence. Following advice received from practitioner feedback and from our resource group, we have also included a discussion of preoperative RT compared with postoperative combined RT plus CT. This report does not consider the use of preoperative RT to convert locally advanced, initially unresectable rectal cancer into resectable cases, to preserve the anal sphincter or to delay the need for colostomy.

III. METHODS

Guideline Development

This practice guideline report was developed by the Practice Guidelines Initiative (PGI) of the Program in Evidence-based Care (PEBC), using the methods of the Practice Guidelines Development Cycle (5). Evidence was selected and reviewed by four members of the PGI's Gastrointestinal Cancer DSG and methodologists. This practice guideline report is a convenient and up-to-date source of the best available evidence on preoperative RT for clinically resectable

rectal cancer, developed through systematic reviews, evidence synthesis and input from practitioners in Ontario. The body of evidence in this report is primarily comprised of mature randomized controlled trial data; therefore, recommendations by the DSG are offered. The report is intended to promote evidence-based practice. The PGI is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

External review by Ontario practitioners was obtained through a mailed survey consisting of items that address the quality of the draft practice guideline report and recommendations and whether the recommendations should serve as a practice guideline. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee.

The PGI has a formal standardized process to ensure the currency of each guideline report. This consists of the periodic review and evaluation of the scientific literature, and where appropriate, integration of this literature with the original guideline information.

Literature Search Strategy

MEDLINE (1966 to December 2001), CANCERLIT (1983 to October 2001) and the Cochrane Library (Issue 4, 2001) were searched with no language restrictions. "Rectal neoplasms" (Medical subject heading [MeSH]), "colorectal neoplasms" (MeSH) and the text word "rectal cancer" were combined with "radiotherapy" (MeSH) and the following phrases used as text words: "preoperative", "neoadjuvant", "radiotherapy", "radiation", "irradiation". These terms were then combined with the search terms for the following study designs or publication types: practice guidelines, meta-analyses and randomized controlled trials. The Physician Data Query (PDQ) clinical trials database on the Internet (http://www.nci.nih.gov/search/clinical_trials/) and the proceedings of the 1998 to 2001 annual meetings of the American Society of Clinical Oncology (ASCO) and the 1999 to 2001 annual meetings of the American Society for Therapeutic Radiology and Oncology (ASTRO) were searched for reports of new or ongoing trials. 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.

Update

In January 2004, the literature search was updated for the MEDLINE (to January week 1 2004), EMBASE (1980 to week 3 2004), and Cochrane Library (Issue 3, 2003) databases. The 2003 ASCO and ASTRO abstracts were also searched for relevant trial reports. Additionally, the PDQ database was also searched for relevant on-going and recently closed clinical trials.

Inclusion Criteria

Trials of preoperative RT in resectable rectal cancer are characterized by multiple methodological problems because two treatments are combined (RT and surgery) to affect a heterogeneous condition (various populations and stages of rectal carcinoma) and to achieve a variety of goals (downstaging, improving resectability, decreasing local and possibly distant recurrences and improving survival). Cummings (6) detailed many of the pitfalls that marred early trials, including deficiencies in trial design, eligibility criteria, treatment standardization and reporting of results. We used this critique to develop standard criteria for the selection of trials of preoperative RT for rectal cancer. Studies were included in the overview of the evidence if they met all of the following criteria:

1. Patients were randomly assigned to preoperative RT versus surgery alone or an alternative treatment.
2. The study population was well defined. Studies preferably included only rectal carcinoma, defined by tumours located within 15 centimetres of the pectinate line on sigmoidoscopy, or rectosigmoid tumours. Patients were screened for metastases and co-morbidity by clinical and imaging procedures and were assessed as surgically resectable for cure.
3. Treatments were described clearly, including RT dose, fractionation, duration, field size and

portals of irradiation. Timing of surgery after completion of RT was clearly set. General surgical principles were described.

4. Compliance with treatments and follow-up were described.
5. Treatment outcomes were reported for overall survival and/or local failure. Other outcomes were recorded if available. These included adverse effects (morbidity and mortality), downstaging (decrease in the proportion of cases with stage III disease) and resectability (total and curative).

Update

Inclusion criterion 2. was modified for clarity, and now reads as follows:

2. The study population was well defined. Studies preferably included only rectal carcinoma, defined by tumours located within 15 centimetres of the pectinate line or anal verge on sigmoidoscopy, or rectosigmoid tumours. Patients were screened for metastases and co-morbidity by clinical and imaging procedures and were assessed as surgically resectable for cure.

Synthesizing the Evidence

Trials of preoperative RT versus surgery alone were pooled using the software package Metaanalyst[0.998] (Dr. Joseph Lau, Boston, MA, USA). Overall mortality, local failure, tumour resectability, tumour downstaging and adverse effects were pooled in separate analyses for all studies, where data was available. Reported figures or estimates obtained from tables or graphs were used. For calculation of survival and local failure, all eligible patients were considered in the denominator, based on intention to treat. All deaths at the time of reporting, regardless of cause, were included in survival calculations. Patients with local failure included those with non-resected as well as those with recurrent disease. Only resected cases were considered in the calculation of downstaging.

Data were pooled using the random effects model as the more conservative estimate of effect (7). Results were expressed as risk ratios (RR) with 95% confidence intervals (CI), where a RR less than 1.0 favours preoperative RT and a RR greater than 1.0 favours surgery alone. Odds ratios (OR) and absolute risk differences (RD) were also calculated.

Heterogeneity of results among trials was expected in view of the different treatments used and populations tested, as well as the wide time interval and geography across which these trials were conducted. For example, the RT prescription may affect the results. RT doses greater than 30 Gy_{10} are considered necessary, and pelvic fields are as effective as extended fields. Moreover, the use of three or more RT beams will lessen toxicity, and short delays of surgery after RT will not demonstrate downstaging. Thus, these factors were investigated with sensitivity analyses to see whether there was an impact on results. Outcomes of predetermined groups of patients were examined initially by the graphic method described by L'Abbe et al (8) and RR calculated. For sensitivity analyses the following factors were examined:

Treatment effects:

- Biologically effective dose (BED) of RT (less than 30 Gy_{10} versus equal to or greater than 30 Gy_{10}). BED was calculated using the formula (9) $BED=nd\ (1+d/\alpha/\beta)$, where n=number of fractions, d=dose per fraction, $\alpha/\beta=10$ for tumour effect and acute reactions and $\alpha/\beta=3$ for late reactions, with no time correction (not needed for late reactions) because parameters were not available and usual ranges are quite wide;
- RT fraction size (standard fractions up to 2.5 Gy/day versus high fractions of 5 Gy/day);
- Contemporary RT prescription, defined as studies employing multiple-field technique and target volume confined to the pelvis (i.e., excluding studies employing parallel pair arrangements or including para-aortics); and
- Delay of surgery after completion of RT (less than seven days versus eight or more days).

Population effects:

- Studies including a range of rectal cancer cases versus those including only advanced disease.

Sensitivity analyses were also performed for all five of the meta-analyses (overall survival, local failure, tumour resectability, downstaging and adverse effects) considering only trials with high design quality. The quality of the 14 eligible randomized trials of preoperative RT versus surgery alone in operable rectal cancer was scored independently. Five assessors assessed each trial using the Detsky instrument (10). This questionnaire addresses five domains of study quality: randomization process, outcomes measure, patient eligibility, treatment description and statistical procedures. The 14 questions on the Detsky instrument can be answered "adequate", "inadequate" or "partial" and scored 1, 0 or 0.5, respectively. The final score of each trial is a ratio of the observed points divided by the total number of questions answered. The results from the five assessors were averaged for a final score. Trials with Detsky instrument scores greater than 0.5 were considered to be of high quality.

Update

Where the Metaanalyst$^{0.998}$ (Dr. Joseph Lau, Boston, MA, USA) software program was used to perform all meta-analyses and produce all figures in the original guideline, in the manuscript and this update version, Review Manager 4.2.1 (© Update Software) (which is freely available through the Cochrane Collaboration) was used. All figures and tables in this practice guideline have been updated to reflect the latest information as presented in the manuscript.

At the suggestion of one of the peer reviewers, the first bullet under treatment effects was changed to include a correction for time and now reads as follows in both the manuscript and this update:

- Biologically effective dose (BED) of RT (less than 30 Gy_{10} versus equal to or greater than 30 Gy_{10}). BED was calculated using the Linear Quadratic formula (9) and the parameters suggested for time correction (1u):
  BED *time* = $nd\ (1+d/\alpha/\beta) - \gamma/\alpha\ (T - Tk)$
  where n=number of fractions, d=dose per fraction, α/β=10 for tumour effect and acute reactions and α/β=3 for late reactions, γ/α = repair rate set at 0.6 Gy/day and T = total treatment time and Tk = initial delay time set at 7 days.

IV. RESULTS

Literature Search Results

The literature search identified 24 trials. Nineteen trials compared preoperative RT plus surgery to surgery alone (11-28,37) and five trials compared preoperative RT to alternative treatments (29-33). Two meta-analyses compared preoperative RT versus surgery alone (34,35).

Update

Updating activities obtained an additional five reports (1u-5u). Two of these trials were abstract reports of RCTs (1u,2u). The trial by Bujko et al (1u) compared preoperative radiotherapy versus preoperative chemoradiotherapy. The trial by Gerard et al (2u) compared two different regimens of preoperative radiotherapy.

At the suggestion of the peer reviewers chosen by *BMC Medicine* prior to publication, two additional papers (3u,4u) were also obtained. The first paper (3u) described the BED formula with a correction for time, and the second (4u) was a review paper describing the morbidities associated with postoperative combined RTCT.

The final report (5u) is an update of an on-going trial included in the original practice guideline (European Organization for Research and Treatment of Cancer [EORTC] 22921).

Preoperative Radiotherapy versus Surgery Alone

Four of the 19 trials of preoperative RT compared with surgery alone were excluded from

the review (11-15). The remaining 15 trials are described in Table 1.

Preliminary results of one trial have been reported in Russian (11), but the report and results were difficult to interpret. This trial was excluded until more mature results are available and it is clear that the trial meets the inclusion criteria. Three trials had major violations to the inclusion criteria. The Memorial Hospital trial included both randomized as well as non-randomized patients in the analysis (12). The Veterans Administration Surgical Oncology Group (VASOG) Trial I included patients who may have had apparent metastases and did not allow for an analysis excluding this group of patients (13). The Essen trial was described in summary form and was a failed trial of preoperative plus postoperative RT treatment due to difficulties with compliance (14).

Of the 14 remaining trials of preoperative RT compared with surgery alone (15-28), one trial (17) contributed to two comparisons (single fraction preoperative RT versus surgery alone; multiple fractions preoperative RT versus surgery alone) and one (27) included 316 patients who were also included in another trial (28). Neither report described results for these patients separately from those who were included in only one of the two trials. Reports of three trials (16,21,22) did not provide data on compliance with treatment. This was not considered to be a major violation to the inclusion criteria, and these trials were included. Where results have been reported or updated in more than one publication, only the most recent publication is listed.

The 14 trials that were reviewed are presented in Table 1. All trials included patients with resectable rectal cancer. Two trials also included patients with rectosigmoid tumours (15,18). Some trials excluded patients with small tumours (24,27,28) or were limited to those with locally advanced tumours (22,25,26) or those requiring abdomino-perineal resection (18). Patients excluded were those with evidence of distant metastases, previous malignancy or previous RT.

Surgery was performed from within a few hours to 40 days following the preoperative RT course, but most surgeries were done within one to four weeks of preoperative RT. The description of surgical procedures was very general except for the distinction between palliative and curative procedures. Radiation was delivered mainly by anterior and posterior portals. Only recent trials used three or four radiation portals (26-28). Radiation fields were primarily pelvic, but some trials used extended guitar-shaped fields up to L2 (15,19,20,24). The total radiation dose and the fractionation schedules were quite different across studies, ranging from 5 Gy in a single treatment to over 5000 cGy in five weeks.

Compliance with treatments was generally well described. Follow-up data were collected prospectively in all but one trial (16). The follow-up schedule was described for all trials except one (15). The rate of patients lost to follow-up was 16% in one trial (23), while the remaining trials reported greater than 90% compliance with follow-up. The median follow-up at the time of the trial report was five years or more in most trials.

Addendum

The Dutch Colorectal Cancer Group report results after a median follow-up of 24.9 months, which is much shorter than for other trials, and numbers of patients with events cannot be determined (37). Therefore, this trial is not included in the meta-analysis. This study, which included patients with rectal cancer not fixed or amenable to local excision, standardized surgery with TME. Patients were randomized to surgery alone or surgery preceded by RT (bottom row, Table 1) (37). The recurrence rate was significantly lower in patients receiving preoperative RT (2.4% vs. 8.2%; $p<0.001$), but overall survival was the same for both treatment groups. In a multivariate subgroup analysis, tests for interaction between tumour location, TNM stage and treatment were not significant, suggesting that treatment effect was similar for all the subgroups analyzed.

Table 1. Randomized trials of preoperative radiotherapy (RT) versus surgery alone in resectable rectal cancer.

Trial (Reference)	No. of Patients Randomized RT / no RT (Analyzed)	RT Prescription*	Biologically Effective Dose (Gy_{10})	Compliance with RT† 0 <1 >1	Surgical Delay after RT (Days)	Median Follow-up (Months)	Study Quality Score‡
Yale (15)	15 (15) / 16 (16)	45 in 25 2 fields, G	53.1	NA 7% NA	2-42	>60	0.29
Toronto (16)	60 (60) / 65 (65)	5 in 1 2 fields, P	7.5	NR NR NR	0	72	0.55
MRC-I (17)	549 (549) / 275 (275)	5 in 1 or 20 in10 2 fields, G	7.5 or 24.0	2% 6% NA	<7	>60	0.66
VASOG-II (18)	180 (180) / 181 (181)	31.5 in 18 2 fields, G	37.0	7% 11% 4%	~40	60	0.70
Norway (19)	159 (155) / 150 (145)	31.5 in 18 2 fields, G	37.0	1% NA NA	<21	54	0.80
EORTC (20)	236 (231) / 230 (228)	34.5 in 15 2 fields, G	42.4	1% NA NA	1-69	>72	0.67
Brazil (21)	34 (34) / 34 (34)	40 in 20 2 fields, P	48.0	NR NR NR	7	120	0.48
Hungary (22)	171 (171) / 165 (165)	40 in 20 or 50 in 25 2 fields, P	48.0 60.0	NR NR NR	42	>60	0.44
ICRF-UK (23)	228 (228) / 239 (239)	15 in 3 2 fields, P	22.5	NA 10% NA	<2	60	0.64
Stockholm-I (24)	424 (424) / 425 (425)	25 in 5 2 fields, G	37.5	NA 12% NA	<7	107	0.74
MRC-II (25)	139 (139) / 140 (140)	40 in 20 2 fields, P	48.0	1% 5% 4%	<7	>60	0.83
NW-UK (26)	143 (143) / 141 (141)	20 in 4 3 field, P	30.0	NA 1% 3%	<7	96	0.57
Sweden (27)	583 (573) / 585 (574)	25 in 5 3-4 fields, P	37.5	3% 1%§ NA	<7	>60	0.82
Stockholm-II (28)	272 (272) / 285 (285)	25 in 5 4 fields, P	37.5	-------5%-----	<7	50	0.88
Dutch (37)	924 (908) / 937 (897)	25 in 5 (5) 4 fields, P	37.5	3% 2% NR	<7	24.9	0.81

Note: EORTC indicates European Organization for Research and Treatment of Cancer; ICRF-UK, Imperial Cancer Research Fund United Kingdom; MRC, Medical Research Council; NW-UK, Northwest Region Rectal Cancer Group United Kingdom; VASOG, Veterans Administration Surgical Oncology Group.

*Total dose in Gy, number of fractions, number of treatment fields, target volume (G, guitar-shaped; P, pelvic).

†0 indicates per cent of patients receiving no treatment; <1, percent receiving less than planned treatment; >1, percent receiving more than planned treatment.

‡Based on independent assessment by five reviewers using the Detsky instrument (10).

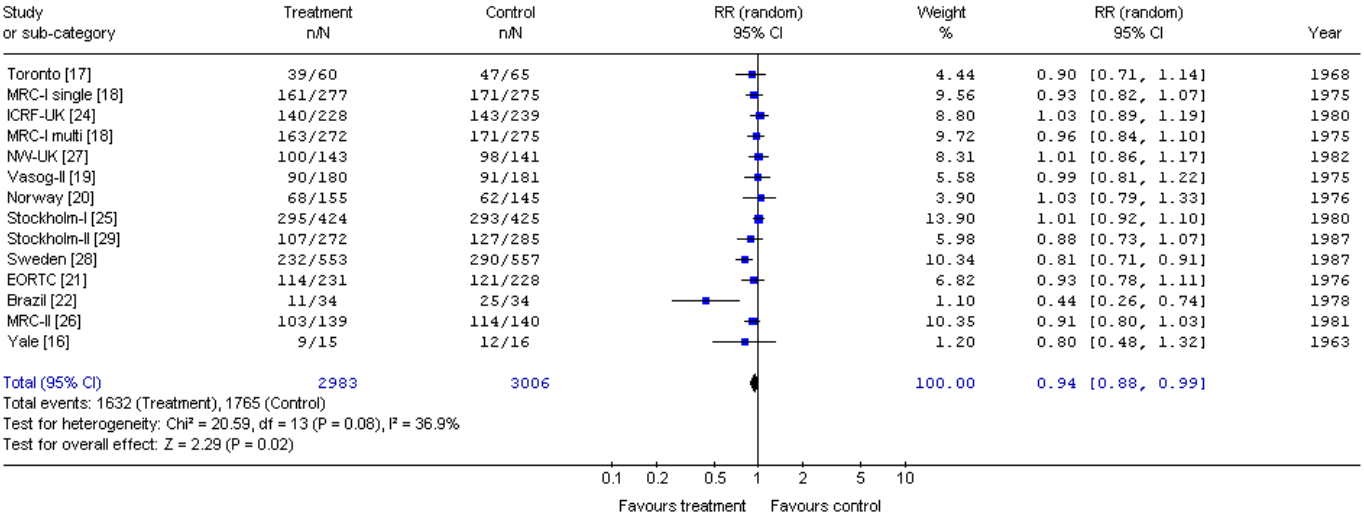
§5% of patients also received RT over >7 days, and 8% of patients received radiation through a 2 portal beam.

Pooled Results of Trials Comparing Preoperative Radiotherapy to Surgery Alone

Overall Survival

Survival was reported for all trials except one (22). Survival results for only resected cases were reported for one trial (27). The overall mortality risk ratio favoured preoperative RT (RR, 0.94; 95% CI, 0.89 to 0.99; p=0.021), results that correspond to an absolute risk difference of 4% (95% CI, 0.7% to 7.5%; p=0.018). There was significant heterogeneity across trials (X^2=20.30; p<0.10). As observed in Figure 1, most heterogeneity derived from a study from Brazil (21); removal of this study resulted in non-significant heterogeneity, and the results were similar (RR, 0.95; 95% CI, 0.91 to 0.99; p=0.012).

Figure 1. Meta-analysis examining preoperative radiotherapy for patients with resectable rectal cancer: overall mortality.



Overall risk ratio = 0.94 (95% CI, 0.89 to 0.99; p=0.02)

Local Failure

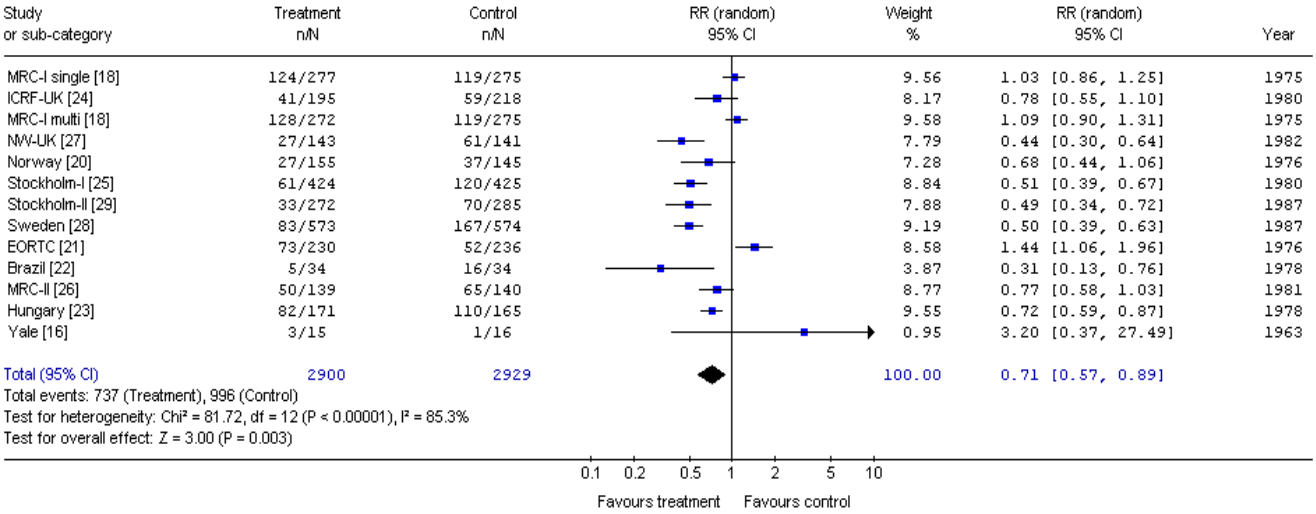
Local failure rate was calculated for all trials as the number of patients unable to have tumour removal as well as those with recurrent disease after resection. The overall risk ratio favoured preoperative RT (RR, 0.71; 95% CI, 0.57 to 0.89; p=0.0025), with an absolute risk reduction of 8.6% (95% CI, 3.1% to 14.2%; p=0.0024). There was significant heterogeneity when local failure rates were pooled across trials (X^2=80.38; p<0.001). Figure 2 displays the local failure risk ratios with the trials arranged in ascending order of the RT dose (BED) used. There was no treatment effect in the analysis of three trials of preoperative RT using doses of 7.5 to 24.0 BED (RR, 1.01; 95% CI, 0.87 to 1.17; p=0.92), while trials using doses greater than or equal to 30 BED had evidence of reduced local failures (RR, 0.64; 95% CI, 0.49 to 0.82; p=0.00047).

Update

This section was re-written as follows:

Local failure rate was calculated for all trials as the number of patients unable to have tumour removal as well as those with recurrent disease after resection. The overall relative risk ratio favoured preoperative RT (RR, 0.71; 95% CI, 0.57 to 0.89; p=0.0025) with an absolute risk reduction of 8.6% (95% CI, 3.1% to 14.2%; p=0.0024). There was significant heterogeneity when local failure rates were pooled across trials (X^2=81.72; p<0.001). Figure 2 displays the local failure risk ratios with the trials arranged in ascending order of the RT dose (BED) used. There was no treatment effect in the analysis of three trials of preoperative RT using doses of 7.5 to 26.8 BED (RR, 0.95; 95% CI, 0.79 to 1.11; p=0.58), while trials using doses greater than or equal to 30 BED had evidence of reduced local failures (RR, 0.63; 95% CI, 0.48 to 0.83; p=0.0011) with significant heterogeneity being detected.

Figure 2. Meta-analysis examining preoperative radiotherapy for patients with resectable rectal cancer: local failure.



Overall risk ratio = 0.71 (95% CI, 0.57 to 0.89; p=0.003)

Tumour Resectability

Total tumour resectability between the treatment arms was not significantly different when 12 trials (14 comparisons) involving 5923 patients were pooled (RR, 1.00; 95% CI, 0.99 to 1.00; p=0.36). Pooling of 14 trials (16 comparisons) involving 6816 patients detected no significant difference in curative resections for preoperative RT compared with surgery alone (RR, 0.99; 95% CI, 0.98 to 1.01; p=0.59). There was no significant heterogeneity among trials included in either pooled analysis.

Downstaging

There was an overall significant decrease in the incidence of stage III rectal cancer among patients randomized to preoperative RT compared with surgery alone, but there was significant heterogeneity among the pooled results (X^2=38.41; p<0.001) (Figure 3). Radiation dose, or its fractionation, and timing of surgery did not affect the results**.**

Update

This section was re-written as follows:

There was an overall significant decrease in the incidence of stage III rectal cancer among patients randomized to preoperative RT compared with surgery alone, but there was significant heterogeneity among the pooled results (X^2=38.57; p<0.001) (Figure 3). Neither radiation dose, or its fractionation, nor timing of surgery affected results**.**

Adverse Effects

Preoperative RT did not significantly increase 30-day postoperative mortality compared with surgery alone (RR, 1.33; 95% CI, 0.87 to 2.05; p=0.19). These results showed significant heterogeneity of trial results (X^2=23.29; p<0.05) (Figure 4). Results were not affected by radiation dose.

Postoperative morbidity was similar across trials and consisted mainly of delay of perineal wound healing and infection. The pooled results for postoperative morbidity also demonstrated significant heterogeneity (X^2=62.74; p<0.001) (Figure 5). Results were not different for patients receiving high or low dose RT or delay to surgery of <7 or >8 days.

Update

The first paragraph in this section was re-written as follows:

Preoperative RT did not significantly increase 30-day postoperative mortality compared with surgery alone (RR, 1.33; 95% CI, 0.87 to 2.05; p=0.19). These results showed significant heterogeneity of trial results (X^2=23.35; p<0.05) (Figure 4). Results were not affected by radiation dose.

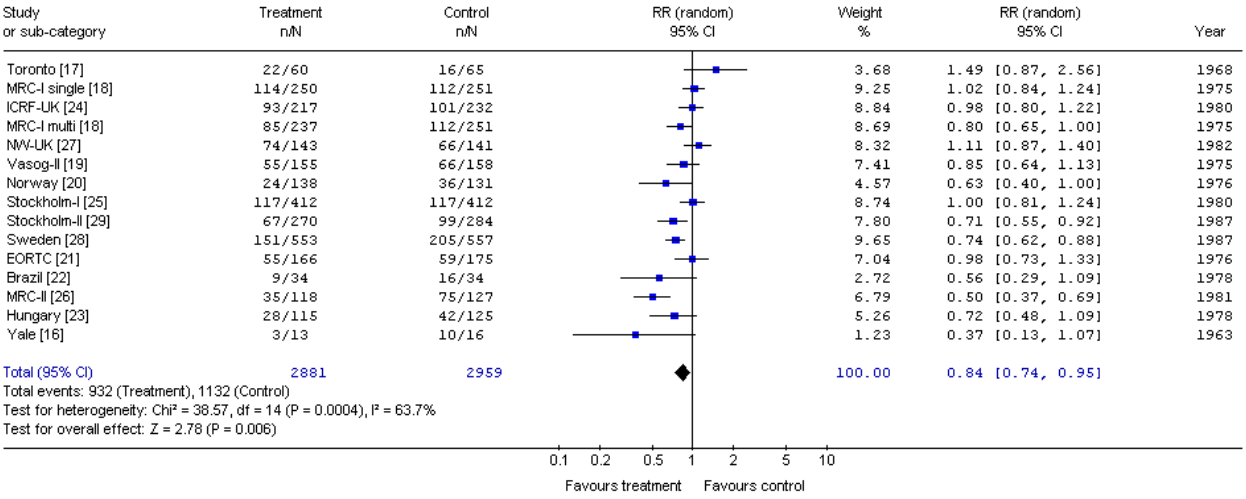
Sensitivity Analysis

Sensitivity analyses were conducted to test the robustness of the conclusions of the five pooled analyses above (overall survival, local failure, tumour resectability, downstaging, adverse effects) when excluding the three studies with quality scores of less than 0.5 (15,21,22). Results of the pooled analyses of the best quality studies were not different from the results considering all studies (data not shown). Details of the quality assessment results using the Detsky instrument can be found in Appendix III.

Published Meta-analyses

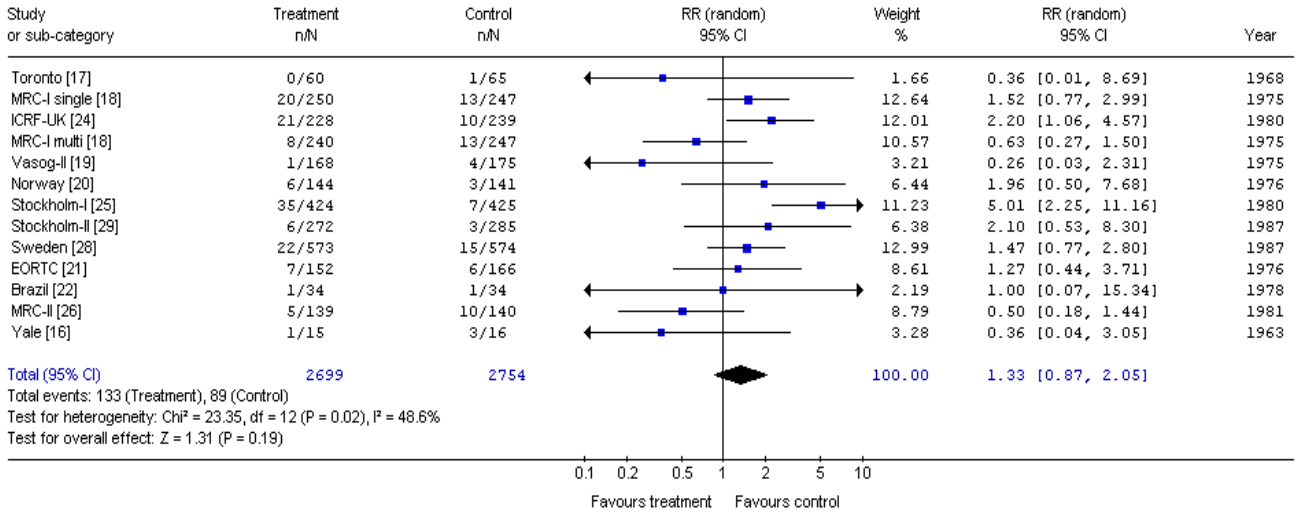
Subsequent to the completion of our analysis, two groups (34,35) published literature-based meta-analyses of trials comparing preoperative RT to surgery alone for resectable rectal cancer. The Camma et al (34) meta-analysis followed a methodology similar to ours. In the analysis, however, there was also an investigation of patient subgroups (Dukes' stages A, B and C, and male sex) and a regression analysis for overall survival (but not for other outcomes). The following regression variables were used: BED, stage of disease, male sex, study publication year, study size, allocation concealment and handling of withdrawals. This meta-analysis considered 12 published trials (13,15,16,18-21,23-27): it included the VASOG-I trial (13), which we excluded, and it did not include a trial from Hungary (22) nor the single-fraction RT arm from the MRC-I trial (17). All comparisons were made using odds ratios. Camma et al (34) detected a significant reduction in overall mortality with preoperative RT (Table 2). In a subgroup analysis, the decrease in mortality occurred in patients with Dukes' stages B and C but not in patients with stage A disease. No interaction was found between RT dose and survival (BED <30 or >30; p=0.53). In the regression analysis none of the factors used as variables had a significant impact on survival. Cancer-specific mortality and local recurrences were also reduced by the use of preoperative RT.

Figure 3. Meta-analysis examining preoperative radiotherapy for patients with resectable rectal cancer: incidence of stage III tumours.



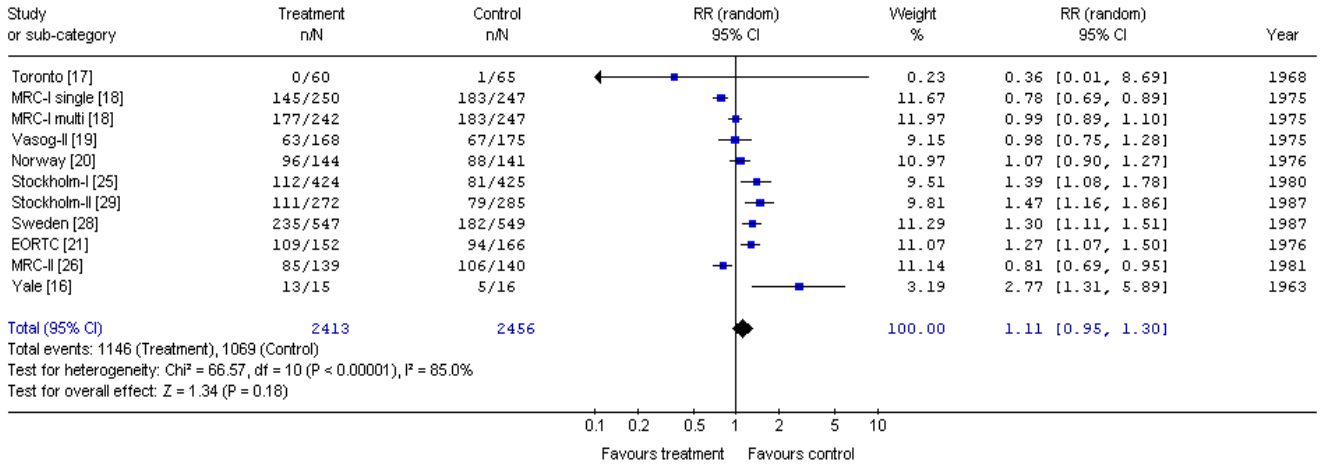
Overall risk ratio = 0.84 (95% CI, 0.74 to 0.95; p=0.006)

Figure 4. Meta-analysis examining preoperative radiotherapy for patients with resectable rectal cancer: 30-day postoperative mortality.



Overall risk ratio = 1.33 (95% CI, 0.87 to 2.05; p=0.19)

Figure 5. Meta-analysis examining preoperative radiotherapy for patients with resectable rectal cancer: postoperative morbidity.



Overall risk ratio = 1.11 (95% CI, 0.95 to 1.30; p=0.18)

(Table 2) but distant metastases were not. The overall rate of postoperative adverse events was higher in patients receiving preoperative RT (57.4% versus 42.4%; p<0.001). The 30-day postoperative mortality was not significantly different between patients receiving preoperative RT and those having only surgery. Camma et al (34) concluded that preoperative RT reduced overall and cancer-specific mortality rates, and particularly local recurrence rates, while not affecting distant metastases. Postoperative mortality was not affected by the use of preoperative RT, in spite of a higher rate of adverse events in patients so treated.

The Colorectal Cancer Collaborative Group (35) identified trials of adjuvant pre- and postoperative RT started before January 1, 1987. This group's search yielded 19 trials of preoperative RT that included five trials not included in our review. These additional five trials included two trials that used pre- plus postoperative RT (14,30), one trial that included patients

with metastatic disease (13), another that combined RT with 5-FU administration (32), and a Japanese trial published in 1989. Analysis was done by the log-rank method for overall and disease-specific mortality and for all (including isolated) recurrences. The overall yearly death rate was 5.6% (standard error ±3.3). All recurrences and isolated recurrences were significantly decreased by preoperative RT at 5 years (45.9% vs. 52.9% and 12.5% vs. 22.2%, respectively) and at 10 years (55.1% vs. 60.8% and 16.7% vs. 25.8%, respectively). There was significant heterogeneity between the results of the 12 trials analyzed (p=0.002), which was explained by the greater efficacy of RT at higher biologically effective dose (>30 Gy). The reduction in local recurrence was proportionally similar for the various stages of the disease and not affected by either sex or age. A multivariate analysis was not done (35).

The results of the published meta-analyses (34,35) and the one conducted for this systematic review are shown in Table 2.

Table 2. Results of three meta-analyses of preoperative radiotherapy versus surgery alone in resectable rectal cancer.

Outcome	Pooled Results Odds Ratio, 95% Confidence Interval and p value		
	Camma et al (34)	**CRCCG (35)***	**Present Review**
Overall Mortality	0.84 (0.72, 0.98) p=0.03	0.95 (0.86, 1.06) p=0.34	0.85 (0.74, 0.97) p=0.019
Local Failure	0.49 (0.38, 0.62) p<0.001	0.58 (0.42, 0.80) p=0.00008	0.62 (0.45, 0.85) p=0.0029
30-day Postoperative Mortality	1.38 (0.86, 2.32) p=0.22	NR NR	1.42 (0.90, 2.23) p=0.13

Note: CRCCG indicates Colorectal Cancer Collaborative Group.
* ORs calculated from data shown in Figure 1 (34).

Preoperative Radiotherapy versus Alternative Treatments

Preoperative Radiotherapy versus Postoperative Adjuvant Radiotherapy in High Risk Cases

In a multi-institutional randomized trial in Sweden, patients with operable rectal cancer were randomized to preoperative RT, or to selective postoperative RT if the pathological stage was II or III (29,36). Overall survival was the same for both treatment groups. When only patients with radical resection were considered, local recurrence was less likely for those receiving preoperative RT (11% vs. 22%; p=0.02) (Table 3). Postoperative complications, both early (29) and late (36), were significantly more frequent after higher-dose postoperative RT. The investigators emphasized that a short course of high-fraction preoperative RT is preferable to a standard course of postoperative RT. Preoperative RT was better in reducing local recurrence rates and was associated with lower morbidity.

Two other randomized trials have investigated the benefit of preoperative RT in patients who also received postoperative RT if the pathological stage was II or III (30,31) (Table 3). In a study by the Radiation Therapy Oncology Group (RTOG), investigators randomized patients to a single dose of 500 cGy preoperatively and gave 45 Gy postoperatively to all high-risk patients (30). After more than five years of follow-up, survival and local failure were similar in patients with or without preoperative RT. The preoperative RT dose in this trial was very small and has been shown to be ineffective (16,17). German investigators performed a similar but smaller trial using a higher preoperative RT dose (31). Patients were randomized to immediate surgery or to receive 16.5 Gy in 5 fractions preoperatively. After surgery, patients at high risk of local recurrence (T4 stage, R1-2 or intraoperative tumour perforation) also received 41.4 Gy if they

had preoperative RT or 59.8 Gy if they did not have preoperative RT. In a multivariate analysis of local recurrence, the only significant variable was staging (International Union Against Cancer [UICC]) (p=0.0003), while preoperative RT and T4 stage had non-significant effects (p=0.08 and 0.07, respectively). In a similar analysis of survival, three variables were significant: age (p=0.0003), UICC stage (p=0.001) and residual disease status (p=0.01). Preoperative RT had a non-significant effect (p=0.078). These last two trials indicate that selective postoperative RT annuls any potential positive effect of preoperative RT in low dose.

Preoperative Radiotherapy Alone versus Preoperative Radiotherapy Plus Chemotherapy

An early randomized trial by the European Organization for Research and Treatment of Cancer (EORTC) (32) compared preoperative RT with or without CT. Fluorouracil by bolus injection was given for 4 days during the first week of the radiation course. The trial was marred by many difficulties, with 27% of the cases being ineligible or not evaluable. The combined treatment did not reveal any advantage over RT alone (Table 3). Of interest was a marginally significant decrease in liver metastases for patients receiving preoperative combined treatment (p=0.06).

Update

The trial by Bujko et al (1u), reported in abstract form, randomized 316 patients to either preoperative radiotherapy (5 Gy_{10} for 5 days) followed immediately by surgery or preoperative chemoradiotherapy (50.4 Gy_{10} total, 1.8 Gy_{10} per fraction, plus two courses of bolus 5-FU and leucovorin calcium) followed by delayed surgery. The main outcome of interest was distal intramural margin spread. The researchers hypothesized that because downstaging cannot occur after the 5x5 treatment, distal intramural margin spread would be no different than surgery alone. Results detected a significant difference in distal intramural margin spread between the two treatment arms favouring treatment with combined chemoradiotherapy followed by delayed surgery (p=0.006). Survival data was not provided in this preliminary report. Final results will be included when available.

Preoperative Radiotherapy with Surgery at Different Intervals

One trial by French investigators tested whether the delay of surgery after the completion of preoperative RT is important (33) (Table 3). Operable patients with rectal tumours accessible to digital rectal examination (stage T2-3, NX, M0) received preoperative RT (39 Gy_{10} in 13 fractions over 17 days through 3 fields) and were randomized to surgery after a short (two-week) or a long (six- to eight-week) interval. The only significant difference in outcomes, favouring the long over the short delay, was the higher proportion of patients with a clinical tumour response (partial plus complete) (53.1% versus 71.7%; p=0.007) and pathological downstaging (10.3% versus 26%; p=0.005). The three-year local failure and survival rates were not significantly different.

Update

Preoperative Radiotherapy versus Alternative Preoperative Radiotherapy Regimen

A trial by Gerard et al (3u), reported in abstract form, randomized 88 patients to either preoperative external beam radiotherapy (39 Gy_{10} in 13 fractions over 17 days) compared to the same regimen with an endocavitary x-ray boost (85 Gy_{10} in 3 fractions over 21 days). In both treatment arms, surgery was performed after a delay of five weeks. At 28 months of follow-up, no difference in survival, local-control, or post-operative complications was detected.

Table 3. Randomized trials of preoperative radiotherapy compared to alternative treatments in rectal cancer.

Trial (Reference)	Treatment			No. Patients	Local Failure (%)	Survival Rate At 5 years (%)
	Preoperative RT	Surgery Delay	Postoperative RT (Delay)			
Pahlman & Glimelius (29)	5.1 Gy x 5	1 week	60 Gy in 54* (4-6 weeks)	236 235	22% 33% p=0.012	43% 37% p=0.43
RTOG (30)	0.5 Gy x 1	1 day	45-51 Gy* (2-6 weeks)	175 178	32% 32% p=NS	43% 32% p=NS
Herrmann et al (31)	3.3 Gy x 5	1-2 days	41.5 Gy in 48* 59.8 Gy in 56* (6-14 weeks)	48 46	25% 39% p=0.142	49% 37% p=NS
EORTC (32)	2.3 x 15 2.3 x 15 + 5-FU	2 weeks 2 weeks	NR NR	121 126	15% 15% p=NS	59% 46% p=0.06
Francois et al (33)	3.0 Gy x 13 3.0 Gy x 13	2 weeks 6-8 weeks	NR NR	99 102	9% 9% p=NS	78%† 73%† p=NS

Note: NS indicates not statistically significant; RTOG, Radiation Therapy Oncology Group; NR, not reported.
* Radiation given only to high-risk cases (stages II and III).
† 3-year survival rate.

Addendum

A recently published trial, coordinated by the Dutch Colorectal Cancer Group, included patients with rectal cancer not fixed or amenable to local excision. This study used standardized surgery with total mesorectal excision and randomized patients to surgery alone or surgery preceded by RT (37). Nine hundred and twenty-four patients were randomized to surgery alone and 937 to preoperative RT consisting of 25 Gy in 5 fractions. The analysis of results is based on 908 patients allocated to surgery alone and 897 patients allocated to preoperative RT. After a median follow-up of two years, the recurrence rate was significantly lower in patients receiving preoperative RT (2.4% vs. 8.2%; $p<0.001$), but overall survival was the same for both treatment groups. In a univariate subgroup analysis, the risk of local recurrence was significant for tumours with an inferior margin $\leq$ 5cm ($p<0.05$) from the anal verge, an inferior margin 5.1 to 10cm ($p<0.001$) from the anal verge, TNM stage II tumours ($p<0.01$) and TNM stage III tumours ($p<0.001$). In a multivariate subgroup analysis, tests for interaction between tumour location, TNM stage and treatment were not significant, suggesting that treatment effect was similar for all the subgroups analyzed.

These early results of the trial would indicate that even with optimal surgery (total mesorectal excision) the rate of local recurrence can be reduced by preoperative RT. As the absolute difference in recurrence rates is 5.8%, 17 patients would require treatment to prevent or delay one local recurrence. It would be beneficial to know more about the toxicity, especially long-term anal dysfunction. Results of this trial were not added into the meta-analysis because the trial only reported two-year median follow-up data.

V. INTERPRETIVE SUMMARY

Results of three meta-analyses (Table 2) indicate that preoperative RT compared to surgery alone significantly decreases the risk of local failure and overall mortality. The absolute reduction in local failure is 8.6% (95% CI, 3.1% to 14.2%) while the absolute reduction in overall mortality at five years is only 3.5% (95% CI, 1.1% to 6.0%). Early results of the Dutch trial (37) confirm the decrease in local recurrence with preoperative RT, even after optimal surgery with TME. The improved results of recent trials can be explained by better patient selection and radiation prescription. Swedish investigators, comparing the results of the Stockholm-I (25) and Stockholm-II (29) trials of preoperative RT, determined that the overall survival of patients was significantly affected negatively by a high 60-day postoperative mortality rate (38). This high early

fatality rate was due to an excessive number of infectious, cardiovascular and thromboembolic events. This excess in mortality was attributed to the delivery of similar doses of radiation by larger versus smaller volumes, and by two rather than multiple radiation portals, and to patient characteristics such as evidence of ischemia by electrocardiogram (ECG) and poor performance status. An increase in morbidity was also observed and consisted of venous thromboembolism, femoral neck and pelvic fractures and intestinal obstruction. A subgroup of patients who participated in the Swedish trial (27) completed a questionnaire about anorectal dysfunction. Bowel disturbances led to social restrictions in 30% of patients who received preoperative RT compared with 10% of patients who received surgery alone ($p<0.01$). The abnormalities included more frequent bowel movements, urgency and incontinence. No single factor could be identified to explain the complications, but the authors suggested a radiation effect on the anal sphincter itself or on its nerve supply (39). Similar anorectal dysfunction has been reported after postoperative RT combined with CT (40).

Preoperative RT in high fractions has been compared with standard low-fraction postoperative adjuvant RT (29). The overall survival was the same for both treatment groups, but the local recurrence and morbidity rates were lower for preoperative RT. While preoperative RT was given to all cases, postoperative RT was given only to high-risk cases (stages II and III), a group equal to half the number of cases treated with the preoperative approach. Although the recipients were high-risk cases, the increased morbidity with postoperative RT may also be related to the higher total radiation dose.

The use of preoperative RT in small doses did not decrease the indications for postoperative adjuvant RT (30,31). One older trial using four bolus injections of 5-FU during the preoperative RT reported increased postoperative mortality and decreased overall survival (32). The cause for this toxicity is not known and has not been observed in subsequent trials of combined therapy. The delay of surgery after preoperative RT for more than two weeks decreased the rate of stage III disease but had no impact on resectability, local recurrence or survival (33).

Update

Along with providing the BED formula with a correction for time, Glimelius et al (3u), in a retrospective analysis of preoperative and postoperative RT trials, observed a similar reduction in local failure when the dose of radiation was higher in the postoperative than in the preoperative setting.

Also, a review article by Ooi et al (4u) was obtained at the suggestion of the peer reviewer's that described anorectal dysfunction associated with postoperative RT combined with CT.

ONGOING TRIALS

Preoperative RT versus Surgery Alone

1. A total of 1,400 patients will be entered in a multi-centre randomized trial of total mesorectal excision with versus without preoperative RT in primary rectal cancer (DUT-KWF-CKVO-9504, EU-96020, EORTC-40971). Patients randomized to the surgery arm will receive postoperative RT if resection is incomplete. A feasibility analysis of the first 500 randomized Dutch patients has been published (41). A significantly higher rate of postoperative infective complications (36% versus 27%; $p=0.04$) and greater blood loss (median 1200 ml versus 800 ml; $p<0.001$) was found for the group of eligible patients who had preoperative RT plus total mesorectal excision compared with the group who had total mesorectal excision alone. There were no other significant differences in postoperative morbidity or mortality. Two-year results of this trial were made available (37), and appear in the Addendum section of this report.

Preoperative RT versus Alternative Treatments

1. An Intergroup trial (INT #R9401) investigates patients with clinically transmural (T3+) resectable rectal cancer. Patients are randomized to preoperative RT (50.4 Gy) combined with 5-fluorouracil (5-FU) plus low-dose leucovorin given for five days at monthly intervals, with two courses given concurrently with the RT and the other four courses subsequent to surgery, or the same RT given during the third postoperative month plus the same 5-FU plus leucovorin CT for six postoperative cycles (42-44).
2. A National Surgical Adjuvant Breast and Bowel Project trial (NSABP # R-03) also investigates patients with clinically transmural (T3+) resectable rectal cancer. Patients are randomized to preoperative RT (50.4 Gy) preceded by six weekly cycles of 5-FU plus high-dose leucovorin, two cycles one month apart during RT, and six further weekly cycles postoperatively, or the same combined treatment all given postoperatively (42-44).
3. An EORTC trial (41) also investigates patients with clinically transmural (T3+) resectable rectal cancer. Patients are randomized to four treatment arms: 1) preoperative RT alone (45 Gy); 2) preoperative RT as above combined with two 5-day courses of 5-FU plus low-dose leucovorin four weeks apart; 3) preoperative RT alone as above followed postoperatively by four 5-day courses of 5-FU plus leucovorin 28 days apart; or 4) preoperative RT combined with 5-FU plus leucovorin as in 2) followed by four 5-day courses of 5-FU plus leucovorin 28 days apart.
4. In the AXIS trial conducted by the United Kingdom Coordinating Committee on Cancer Research (UKCCCR), patients with colorectal cancer are randomized to receive or not receive immediate postoperative CT by portal vein infusion. Patients with rectal cancer may also be randomized to preoperative or postoperative RT with or without concurrent CT. An early report, providing estimated data based on preliminary results on 3681 patients, is available (45). There is also a report available from a single centre in the AXIS trial that used preoperative RT in two 500 cGy fractions per day for five days with concurrent 5-FU 300 mg/m2/day by continuous intravenous infusion for the duration of RT, and surgery 15 days later (46). Of the 138 patients entered in this centre and followed for three years, 66 received only surgery; and of these 66, 27 (41%) have recurred and 21 (32%) have died. Among the 68 patients in this single-centre study who received preoperative RT, 41 patients showed tumour shrinkage and none have recurred. Among 27 patients in this single-centre study with no tumour response, seven patients (25%) have recurred and six (22%) have died. Interestingly, these early results suggest RT responsiveness as a prognostic factor for recurrence and survival.
5. As of February 2000, Sauer et al (47) recruited 546 patients in a German multicentre phase III trial of preoperative versus postoperative combined CT and RT. As of February 2000, 417 patients were evaluable, and median follow-up was 22 months. The investigators reported that preoperative combined therapy was well tolerated and was not associated with a higher risk for perioperative and postoperative morbidity. A blinded analysis of all patients was conducted, and two-year overall survival was 89%. Long-term results are not yet available.
6. A MRC trial (MRC-CR07, EU-98008) is recruiting 1800 patients in a phase III randomized, multicentre study of preoperative RT versus selective postoperative chemoradiotherapy in patients with operable rectal cancer. Patients are randomized to receive preoperative RT (arm 1) or postoperative chemoradiotherapy (arm 2). Patients may then receive adjuvant CT as per local policy. Patients are to be followed every three months for one year, every six months for two years and then annually thereafter.
7. An EORTC trial (EORTC-22921) is recuiting 992 patients in a phase III randomized, multicentre study of preoperative RT with or without 5-FU combined with leucovorin calcium (CF) and/or postoperative 5-FU/CF in patients with resectable adenocarcinoma of the rectum. Patients are to be stratified according to centre, sex, tumour location and stage. This will be a four-arm trial comparing preoperative RT versus preoperative RT +

preoperative CT versus preoperative RT + postoperative CT versus concurrent preoperative RT/CT. Patient follow-up will occur every six months.

Update

Preliminary results (5u) obtained indicate that preoperative chemoradiotherapy, compared to preoperative radiotherapy alone, increases the frequency and severity of acute toxicity. Surgical outcomes between the two groups were similar. Final results will be included when available.

VIII. DISEASE SITE GROUP CONSENSUS PROCESS

The discussion of the Gastrointestinal Cancer DSG focused on results from recent trials of preoperative RT in Europe that demonstrated significant improvements in local failure and survival rates. These results, achieved with a short course of radiation (5 fractions) and with less toxicity than standard longer courses of radiation, have prompted the widespread use of this treatment modality in Europe and more recently in North America. Some treatment centres in Ontario have started phase II studies of preoperative RT, in some cases with concurrent CT.

There are, however, some concerns about the widespread use of preoperative RT. Some potential risks of the treatment seem preventable. The use of radiation given in smaller volumes and with multiple fields, instead of the past practice of two fields, has been shown to decrease both early postoperative morbidity and mortality (24,27,28). The exclusion of patients with poor performance status and those with ischemic changes in the ECG (38) reduced both mortality and morbidity in the first two months. More difficult to predict is long-term anorectal dysfunction, which restricts the social life of one third of survivors in some series following both pre- and postoperative adjuvant RT (39). Another concern is that some of the preoperatively irradiated patients would not have required this treatment based on the postoperative staging of the disease. Furthermore, the prognostic value of the postoperative staging of irradiated patients remains uncertain, although downstaging does not occur after the short course of preoperative RT. The postoperative pathological staging is very important to determine the need for adjuvant CT, which improves survival and reduces local recurrence (4).

Is preoperative RT an acceptable option to be offered to patients for adjuvant treatment in resectable rectal cancer? The previous recommendations from this group for patients with resected stages II and III rectal cancer was postoperative RT plus CT. This combined treatment has been demonstrated to significantly reduce local failure by 50% (95% CI; 8% to 73%) and improve patient survival by 42% (95% CI; 8% to 63%) in patients with stage II and III rectal cancer when compared to postoperative RT alone (Appendix II). In similar patients, postoperative RT alone compared to observation after surgery decreased local recurrences by 27% (95% CI; 4% to 45%) but did not improve survival. Postoperative RT alone is, therefore, discouraged (Appendix II). Preoperative RT alone, when compared to surgery, has been shown to decrease local failure by approximately 50% and to improve survival by approximately 15% (Table 2). The improvement in local recurrence occurs even after optimal surgery with TME (see Addendum). ~~In~~ A single trial (29,36) detected less local recurrence (11% versus 22%, p=0.02) and less morbidity with preoperative short-course RT than with conventional postoperative RT alone. From these results, it can be inferred that preoperative RT is a better treatment choice than postoperative RT plus CT, with less local failures and less morbidity. A comparison of preoperative RT followed by postoperative CT versus combined postoperative RT plus CT is presently being investigated in clinical trials but mature results are not yet available for review, and therefore, a definite recommendation cannot be made at this time.

While we confirm our recommendation for combined postoperative RT plus CT for resected patients with stage II and III rectal cancer, based on the evidence from the Swedish and Dutch trials (27,41) preoperative RT (followed by CT for at least patients with stage III) is an alternative, provided the patient is made aware of the potential benefits and drawbacks. Benefits are the decrease in local failure and in treatment morbidity. Local failure is an important outcome

in rectal cancer, as recurrences are associated with significant disability. Drawbacks are the need to use preoperative RT in most patients compared to RT administered according to postoperative staging and the possibility that patients not requiring radiation may develop treatment-associated complications.

Physicians should encourage patients to participate in clinical trials of the primary treatment of rectal cancer. These trials should require the best possible surgery, the confirmation of the accuracy of clinical staging versus pathological staging and the use of measures of quality of life. Patients must also be clearly advised of the differences between treatment approaches.

IX. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

Draft Recommendations

Based on the evidence above, the Gastrointestinal Cancer DSG drafted the following recommendations:

Target Population

These draft recommendations apply to patients with clinically resectable rectal cancer.

Draft Recommendations

- Randomized trials demonstrate that radiotherapy followed by surgery is significantly more effective than surgery alone in preventing local recurrence in patients with resectable rectal cancer and may also improve survival. However, because pathological stage is unknown until surgery is performed, preoperative therapy requires the treatment of most rectal cancer patients and, consequently, exposes many patients, who will not benefit, to the risk of radiation-induced morbidity and mortality.
- Postoperative radiotherapy for patients with stage II/III rectal cancer is as effective in prolonging survival as preoperative radiotherapy for all rectal cancer patients regardless of stage of disease. For this reason, postoperative radiotherapy combined with chemotherapy should remain the standard treatment.
- Patients with evidence of locally advanced but resectable rectal cancer should be made aware of the trade-offs of preoperative and postoperative radiotherapy, and they should be encouraged to participate in randomized clinical trials evaluating the primary treatment of rectal cancer.

Practitioner Feedback

Based on the evidence contained in the original report and the draft recommendations presented above, feedback was sought from Ontario clinicians.

Methods

Practitioner feedback was obtained through a mailed survey of 155 practitioners in Ontario (30 medical oncologists, 21 radiation oncologists, 100 surgeons and four gastroenterologists). The survey consisted of 21 items evaluating the methods, results and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Gastrointestinal Cancer DSG reviewed the results of the survey.

Results

A total of 97 responses were received out of the 154 surveys sent (63% response rate). Responses included returned completed surveys as well as phone fax, and email responses. Of the practitioners who responded, 79 (81%) indicated that the report was relevant to their

clinical practice and completed the survey. Key results of the practitioner feedback survey are summarized in Table 4.

Table 4. Practitioner responses to eight items on the practitioner feedback survey.

Item	Number (%)*		
	Strongly agree or agree	**Neither agree nor disagree**	**Strongly disagree or disagree**
The rationale for developing a clinical practice guideline, as stated in the "*Choice of Topic*" section of the report, is clear.	74 (94%)	3 (4%)	2 (3%)
There is a need for a clinical practice guideline on this topic.	71 (90%)	7 (9%)	1 (1%)
The literature search is relevant and complete.	69 (87%)	7 (9%)	2 (3%)
The results of the trials described in the report are interpreted according to my understanding of the data.	68 (87%)	6 (8%)	2 (3%)
The draft recommendations in this report are clear.	71 (90%)	4 (5%)	4 (5%)
I agree with the draft recommendations as stated.	67 (85%)	4 (5%)	8 (10%)
This report should be approved as a practice guideline.	54 (68%)	14 (18%)	10 (13%)
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**
	63 (80%)	7 (9%)	7 (9%)

* Percentages may not add up to 100% due to missing data.

Summary of Main Findings

Of the 79 respondents, 68% agreed that the document should be approved as a practice guideline and 80% agreed that they would use it in their own clinical practice.

Forty-three (54%) respondents provided written comments. The main points contained in the written comments were:

1. Several respondents expressed concern with the statement in the recommendations that "Postoperative RT for patients with stage II/III rectal cancer is as effective in prolonging survival as preoperative radiotherapy for all rectal cancer patients regardless of stage of disease". These respondents noted that preoperative versus postoperative RT was not the topic of this guideline and randomized trials addressing this issue are still ongoing.
2. Respondents also questioned the recommendation that "postoperative radiotherapy combined with CT should remain the standard treatment". They argued that if the results of the ongoing trials demonstrate that preoperative and postoperative RT are equally effective, then one treatment should not be recommended over the other as the standard treatment. Several respondents raised the question of the role of total mesorectal excision.

Modifications/Actions

1. Practitioner feedback indicated a need to clarify the role of preoperative RT in the context of the companion guideline recommending postoperative RT plus CT for stage II and III rectal cancer (4). In this context, the magnitude of benefits and drawbacks of preoperative and postoperative RT with and without CT are further discussed in the Consensus section.

Practice Guidelines Coordinating Committee Approval Process

The revised version of the guideline was circulated to 11 members of this group. Seven members returned ballots: five approved the guideline report as written and two members approved the guideline conditional on the DSG addressing suggestions for revision. The suggestions referred to the recommendations and the meta-analyses.

One member expressed concern that the recommendations did not follow the evidence by not recommending preoperative RT. Preoperative RT should be an option with a qualifying statement that patients should be made aware of the adverse effects. Another member felt that in regard to the meta-analyses there was confusion between exploring sources of heterogeneity versus conducting a subgroup analysis to examine a hypothesis stated *a priori*, and thought that

the additional meta-analyses to find out the impact on statistical heterogeneity should be left out. This member stressed that, although it may be of interest to examine a subgroup to test a hypothesis determined *a priori*, the analyses must be conducted properly using a regression procedure (as used by Camma et al (34)), as it is inappropriate to conduct a meta-analysis of a subgroup, and then further divide the studies into another subgroup without using a regression approach. Another member recommended moving the summary of Camma's literature-based meta-analysis to the beginning of the Results section.

Modifications/Actions

The Gastrointestinal Cancer DSG decided to modify the guideline recommendations to include preoperative RT as an option to be discussed with patients as an alternative to postoperative RT. In regard to the meta-analyses of subgroups, these were limited to *a priori* hypotheses only, and statistical heterogeneity was explored by visual analysis of the meta-analysis figures. The discussion of Camma's literature-based meta-analysis was left as is, as the lead author decided it read better after the description of the trials and Gastrointestinal Cancer DSG meta-analyses. One member of the PGCC did not approve the guideline, even after these requested modifications were made. Other editing suggestions were considered and acted upon.

Peer Review Feedback

A summary of the major comments appears below. Where the same issue was raised by both reviewers, the issue and the response appear only once.

While one reviewer acknowledged that this was a well performed meta-analysis based on summary data, he did request the following issues be addressed:

- The BED calculations used in the guideline should include a correction for time, and a reference was provided (1u).
- Downsizing (downstaging) is not a problem with short-course preoperative RT, but this is not mentioned in the practice guideline.
- The statement in the guideline that preoperative RT overtreats patients versus postoperative RT is misleading, as patients treated postoperatively may already have been cured by surgery.

The second reviewer had concerns with the guideline, and after revision, the manuscript still did not meet his approval. The manuscript was then submitted to a BMC Central editor for adjudication, after which the document was accepted without revisions. His comments are listed below:

- He believed that the authors were biased in favour of postoperative RTCT in terms of survival, and that a fairer comparison would have included only trials using preoperative RT doses likely to kill any micrometastases present.
- He recommended that we include in the guideline a statement that modern imaging techniques (e.g., MRI) make preoperative staging as efficacious as postoperative pathologic staging; therefore, patients not needing treatment will not be exposed to RT.
- He stated that he thought:
  - The recommendations were the result of a bias favouring postoperative RT in North American clinicians.
  - There was selection bias in consideration of deaths, and the Gastrointestinal Cancer DSG used a different methodology than the Colorectal Cancer Collaborative Group (35) used in their overview.
  - The Gastrointestinal Cancer DSG should address the issue that the Stockholm trial was a subgroup of the Swedish trial; therefore, the quality-of-study score should be the same for both trials.

- The external review was biased in favour of postoperative RT, whereas in Europe, preoperative RT would have been recommended.

Modifications/Actions

In response to the comments from the first reviewer, the Gastrointestinal Cancer DSG made the following changes in the manuscript:

- In response to the BED calculations requiring a correction for time, the Gastrointestinal Cancer DSG agreed and calculations were redone using the parameters suggested in Glimelius et al. (1u).
- In response to downsizing (downstaging) not being a problem with short-course preoperative RT, the Gastrointestinal Cancer DSG agreed, and the text has been changed.
- In response to the issue of overtreatment with preoperative RT versus postoperative RT, the Gastrointestinal Cancer DSG agreed but acknowledged that it is a question of numbers; more patients will be overtreated with preoperative RT than with postoperative RT. This is clearly stated in the text.

With respect to the comments from the second reviewer, the Gastrointestinal Cancer DSG made the following changes in the manuscript:

- While the second reviewer believed that the authors were biased in favour of postoperative RTCT in terms of survival, stating that we should consider only trials using preoperative RT doses likely to kill any micrometastases present, we think CT adds to the survival benefit regardless of the RT dose. Unfortunately there is no direct comparison of preoperative RT versus postoperative RTCT to describe.
- In response to the statement that modern imaging techniques make preoperative staging as efficacious as postoperative pathologic staging, the authors are not aware of any randomized trials comparing these methods.
- In response to the statement that the recommendations were the result of a strong bias favouring postoperative RT in North American clinicians, we acknowledge that combined RTCT is the current standard treatment for most physicians in North America. However, in also recommending preoperative RT for some patients, our clinical practice guideline departs from tradition.
- In response to the statement that there was selection bias in consideration of deaths and that the Gastrointestinal Cancer DSG used a different methodology than the Colorectal Cancer Collaborative Group used in their overview, we agree. The difference was the result of a methodological criterion, necessary because in preoperative trials randomization occurs prior to surgery. All eligible patients should be amenable to radical surgery; if surgery cannot be done, it is a failure. We agree that this may favour results of postoperative trials versus those of preoperative trials.
- In response to the issue that the Stockholm trial was just a subgroup of the Swedish trial and the quality-of-study scores should be the same for both trials, we acknowledge that the Stockholm trial was a subgroup of the Swedish trial and state that in the text, including noting the overlapping number of patients. In regard to the quality-of-study scores, these were done with the published figures, and the results were different.
- In response to the statement that the external review was biased in favour of postoperative RTCT, we agree; this is geographical variation in practice.

Approved Practice Guideline Recommendations

These practice guideline recommendations reflect the integration of the draft recommendations with feedback obtained from the external review process. They have been approved by the Gastrointestinal Cancer DSG and the Practice Guidelines Coordinating Committee.

Recommendations

Key Recommendations

- The standard of practice recommended for patients with stage II and III rectal cancer is postoperative adjuvant treatment combining radiotherapy plus chemotherapy.
- Preoperative radiotherapy may be an acceptable alternative to postoperative radiotherapy that should be presented to patients as an option. Postoperative chemotherapy is still recommended for stage II and III patients.

Qualifying Statement

- Patients who choose preoperative radiotherapy as a treatment option instead of postoperative combined radiotherapy and chemotherapy need to be made aware that because pathological stage is unknown until surgery is performed many patients, who will not benefit from treatment, will be exposed to the risk of radiation-induced morbidity and mortality.

Update

Upon consideration of the recently published results of the Dutch Colorectal Cancer Group report (37), the Gastrointestinal Cancer DSG modified the recommendations to support preoperative RT as an alternative to standard postoperative combined treatment.

Recommendations

- Preoperative RT is an acceptable alternative to the standard practice of postoperative RT for patients with stage II and III resectable rectal cancer.
- Both preoperative and postoperative RT decrease local recurrence but neither improves survival as much as postoperative RT combined with CT. Therefore, if preoperative RT is used, CT should be added postoperatively, at least for patients with stage III disease.

Qualifying Statement

- Patients who choose preoperative RT as a treatment option instead of postoperative combined RT and CT need to be made aware that because pathological stage is unknown until surgery is performed many patients, who will not benefit from treatment, will be exposed to the risk of radiation-induced morbidity and mortality.

X. PRACTICE GUIDELINE

This practice guideline reflects the most current information reviewed by the Gastrointestinal Cancer DSG.

Target Population

These recommendations apply to adult patients with clinically resectable rectal cancer. This report does not consider the use of preoperative RT to convert locally advanced, initially unresectable rectal cancer to resectable cases, to preserve the anal sphincter or to delay the need for colostomy.

Update

Recommendations

- Preoperative RT is an acceptable alternative to the standard practice of postoperative RT for patients with stage II and III resectable rectal cancer.
- Both preoperative and postoperative RT decrease local recurrence but neither improves survival as much as postoperative RT combined with CT. Therefore, if preoperative RT is used, CT should be added postoperatively, at least for patients with stage III disease.

Qualifying Statement

- Patients who choose preoperative RT as a treatment option instead of postoperative combined RT and CT need to be made aware that because pathological stage is unknown until surgery is performed many patients, who will not benefit from treatment, will be exposed to the risk of radiation-induced morbidity and mortality.

Future Research

- Patients with evidence of locally advanced but resectable rectal cancer should be encouraged to participate in randomized clinical trials evaluating the role of preoperative RT versus postoperative RT and CT combined.
- As optimal surgery including total mesorectal excision can also reduce the probability of locally recurrent rectal cancer, this surgical modality should be tested against the value of adjuvant RT in a randomized trial.

Related Guideline

Practice Guidelines Initiative's Practice Guideline Report #2-3: *Postoperative Adjuvant Radiotherapy and/or Chemotherapy for Resected Stage II or III Rectal Cancer*.

XI. JOURNAL REFERENCE

Figueredo A, Zuraw L, Wong RK, Agboola O, Rumble RB, Tandan V, and the members of Cancer Care Ontario's Program in Evidence-based Care's Gastrointestinal Cancer Disease Site Group. The use of preoperative radiotherapy in the management of patients with clinically resectable rectal cancer: a practice guideline. *BMC Med*. 2003; Nov 24;1(1):1. (6 October 2003). Available at: http://www.biomedcentral.com/1741-7015/1/1.

XII. ACKNOWLEDGMENTS

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For a complete list of the Gastrointestinal Cancer Disease Site Group members and the Practice Guidelines Coordinating Committee members, please visit the CCO Web site at: http://www.cancercare.on.ca/access_PEBC.htm/

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Update

This section includes all references obtained from the peer-review prior to publication and updating activities.

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Appendix I. Comparison of staging systems for colorectal cancer.

AJCC	UICC	Astler-Coller	Dukes′
Stage I Tumour invades submucosa T1, N0, M0 Tumour invades muscularis propria TG2, N0, M0	Stage IA T1, N0, M0 Stage1B T2, N0, M0	A B1	A
Stage II Tumour invades through muscularis propria into the subserosa, or into nonperitonealized pericolic or perirectal tissues T3, N0, M0 Tumour perforates the visceral peritoneum, or directly invades other organs or structures T4, N0, M0	Stage II T3, T4, N0, M0 (T3a with fistula) (T3b without fistula)	B2	B
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 indicates American Joint Commission on Cancer; UICC, International Union Against Cancer.

For further information about the specifics of these staging systems, please see Cohen AM, Minsky BD, Schilsky RL. Colon Cancer. In: DeVita V Jr, Hellman S, Rosenberg SA, editors. *Cancer: Principles & Practice of Oncology*. Philadelphia:JB Lippincott;1997:1144-251.

Appendix II. Practice Guideline Report # 2-3.

Postoperative Adjuvant Radiotherapy and/or Chemotherapy for Resected Stage II or III Rectal Cancer

ORIGINAL GUIDELINE: September 25, 1998 UPDATE: December, 2001
This summary integrates the original practice guideline with the most current information (labeled NEW).

Guideline Question
What is the role of post-operative adjuvant radiotherapy and/or chemotherapy for patients with resected stage II or III rectal cancer in terms of improving survival and delaying local recurrence?
Target Population
These recommendations apply to adult patients with resected stage II or III rectal cancer.
Key Evidence
Twenty-five randomized controlled trials (RCTs), four meta-analyses, two evidence-based consensus statements on adjuvant radiotherapy and/or chemotherapy in stage II and III resected rectal cancer, and a review of the adverse effects of adjuvant radiotherapy and chemotherapy were reviewed. Some multi-arm trials contributed to more than one of the comparisons listed below. Interventions included radiotherapy (RT), systemic chemotherapy (CT), combined treatment (CT+RT), and portal vein infusion chemotherapy (PVI). In 1997, pooled analyses were performed by the guideline authors for RCTs of RT versus observation, CT versus observation, CT versus RT, CT+RT versus CT alone, and CT+RT versus RT alone. Effect sizes were expressed as odds ratios (OR) with 95% confidence intervals (CI).

RT versus observation (8 RCTs): The pooled results of seven RCTs of RT alone versus observation detected a benefit in local control for RT (OR [for local failure], 0.73; 95% CI, 0.55 to 0.96; p=0.022), but there was no significant survival benefit (OR [for death], 0.92; 95% CI, 0.77 to 1.11; p=0.40). Preliminary analysis of an eighth RCT, published recently in abstract form, indicated no significant survival benefit for RT versus observation (hazard ratio, 0.95; 95% CI, 0.69 to 1.31; p=0.69).

CT versus observation (6 RCTs and 2 meta-analyses): The pooled results of three studies comparing CT with observation revealed a significant survival benefit for CT (OR [for death], 0.65; 95% CI, 0.51 to 0.83; p=0.0006), but no benefit in local control (OR [for local failure], 0.71; 95% CI, 0.44 to 1.16; p=0.17). All three of the RCTs located during updating found no significant survival benefit, but one found a significant improvement disease-free survival for CT versus observation. A published meta-analysis found significant survival benefit favouring adjuvant chemotherapy (OR, 0.64; 95% CI, 0.48 to 0.85), but one of the three RCTs included in this meta-analysis compared CT+RT versus RT. A published meta-analysis of individual patient data from 2310 patients with rectal cancer found that the mortality risk ratio was 0.857 (95% CI, 0.734 to 0.999; p=0.049) and the disease-free survival risk ratio was 0.767 (95% CI, 0.656 to 0.882; p=0.0003) favouring adjuvant chemotherapy with oral fluoropyrimidines compared with observation.

CT versus RT (3 RCTs): None of the three RCTs of CT versus RT found a benefit for overall survival or disease-free survival. The pooled results of the three RCTs confirmed no survival benefit (OR [for death], 0.80; 95% CI, 0.58 to 1.10; p=0.17).

CT by PVI versus observation (3 RCTs and 1 meta-analysis): A published meta-analysis of individual patient data from 673 patients with rectal cancer revealed a 4% reduction in the annual odds of death at five years treated with PVI (p-value not reported).

CT+RT versus observation (2 RCTs): A covariate-adjusted comparison of CT+RT compared with observation revealed significantly improved time to recurrence with CT+RT in one trial (p=0.005). A second RCT found a significant decrease in local recurrence rates (12% versus 30%; p=0.01) as well as improvement in 5-year overall survival (64% versus 50%; p=0.05) and 5-year recurrence-free survival rates (64% versus 46%; p=0.01) favouring CT+RT.

CT+RT versus RT (3 RCTs): Pooled analysis of three trials of CT+RT versus RT revealed a benefit

for CT+RT for both survival (OR, 0.58; 95% CI, 0.37 to 0.92; p=0.019) and local control (OR, 0.50; 95% CI, 0.27 to 0.92; p=0.025).

CT+RT versus CT (3 RCTs): Pooled results from two trials showed no significant survival benefit for CT+RT versus CT (OR=0.80; 95% CI, 0.48 to 1.32; p=0.37). In a third trial, the addition of radiotherapy to chemotherapy did not significantly improve disease-free survival (hazard ratio, 0.99; 95% CI, 0.80 to 1.22; p=0.90) or overall survival (hazard ratio, 0.98; 95% CI, 0.78 to 1.24; p=0.89).

Comparison of CT+RT regimens (6 RCTs): When CT with 5-FU was given concurrently with RT, continuous intravenous infusion (CII) was more effective than the drug administered by bolus. The addition of semustine to 5-FU was ineffective. Two trials found no improvement in survival when levamisole or leucovorin was added to 5-FU. Preliminary results of two randomized trials have been published in abstract form. In the first, the addition of interferon alfa-2b to adjuvant 5-FU, leucovorin and RT was not associated with significant improvements in recurrence or survival rates. The second trial failed to show a significant difference between six and 12 months of 5-FU plus medium-dose folinic acid in terms of relapse rates, disease-free survival and overall survival.

Adverse effects: Enteritis, diarrhea, bowel obstruction or perforation, and fibrosis within the pelvis were associated with radiotherapy. Delayed adverse effects from radiotherapy included radiation enteritis (4%), small-bowel obstruction (5%) and rectal stricture (5%). A greater number of hematological and non-hematological adverse effects were associated with CT+RT than with CT, RT or observation. Postoperative CT+RT was associated with acute gastrointestinal and hematologic adverse effects that may be severe or life-threatening.

Recommendations

- Patients with resected stage II or III rectal cancer should be offered adjuvant therapy with the combination of radiotherapy and chemotherapy.
- If the goal of adjuvant therapy is to improve survival, there is no evidence to support the use of radiotherapy alone.
- There is evidence that chemotherapy should include 5-fluorouracil (5-FU), but not semustine.
- During the concurrent component of combination therapy, intravenous infusion with 5-FU is more effective than bolus injection.

Appendix III. Quality of study design and analysis.

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The quality of the 14 eligible randomized trials of preoperative RT in operable rectal cancer were scored independently by five assessors using the Detsky instrument, which addresses five domains of study quality: randomization process, outcomes measure, patient eligibility, treatment description and statistical procedures. Each of the 14 questions on the Detsky instrument can be answered "adequate", "inadequate" or "partial" and scored 1, 0 or 0.5, respectively. The final score is a ratio of the observed points divided by the total number of questions answered. We considered trials with quality scores greater than 0.50 to be high quality. The results from the five assessors were averaged for a final score. According to this score, the trials were ranked as follows:

Trial (Reference)	Score	Rank
Stockholm-II (28)	0.88	1
MRC-II (25)	0.83	2
Sweden (27)	0.82	3
Norway (19)	0.80	4
Stockholm-I (24)	0.74	5
VASOG-II (18)	0.70	6
EORTC (20)	0.67	7
MRC-I (17)	0.66	8
ICRF (23)	0.64	9
NW-UK (26)	0.57	10
Toronto (16)	0.55	11
Brazil (21)	0.48	12
Hungary (22)	0.44	13
Yale (15)	0.29	14