Complete Summary

GUIDELINE TITLE

The use of preoperative radiotherapy in the management of patients with clinically resectable rectal cancer.

BIBLIOGRAPHIC SOURCE(S)

Figueredo A, Zuraw L, Wong RK, Agboola O, Rumble RB, Tandan V. 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. PubMed

Gastrointestinal Cancer Disease Site Group. Figueredo A, Zuraw L, Wong RK, Agboola O, Rumble RB, Tandan V. The use of preoperative radiotherapy in the management of patients with clinically resectable rectal cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2004 Jan [online update]. 29 p. (Practice guideline report; no. 2-13). [52 references]

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SCOPE

DISEASE/CONDITION(S)

Resectable rectal cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Gastroenterology
Oncology

Radiation Oncology
Surgery

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

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

TARGET POPULATION

Adult patients with clinically resectable rectal cancer

Note: 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.

INTERVENTIONS AND PRACTICES CONSIDERED

1. Preoperative radiotherapy
2. Surgery alone
3. Postoperative adjuvant radiotherapy
4. Preoperative radiotherapy plus chemotherapy
5. Preoperative radiotherapy with surgery
6. Alternative preoperative radiotherapy regimens

MAJOR OUTCOMES CONSIDERED

- Survival/mortality rates
- Local failure rates
- 30-day postoperative mortality
- Tumour resectability
- Tumour downstaging
- Adverse effects

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Original Guideline: December 2002

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.

January 2004 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 American Society of Clinical Oncology and American Society for Therapeutic Radiology and Oncology abstracts were also searched for relevant trial reports. Additionally, the Physician Data Query database was also searched for relevant on-going and recently closed clinical trials.

Inclusion Criteria

Trials of preoperative radiotherapy (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 detailed many of the pitfalls that marred early trials, including deficiencies in trial design, eligibility criteria, treatment standardization, and reporting of results. The guideline developers 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 comorbidity 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).

January 2004 Update

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

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 comorbidity by clinical and imaging procedures and were assessed as surgically resectable for cure.

NUMBER OF SOURCE DOCUMENTS

Original Guideline: December 2002

Twenty-four trials and two meta-analyses were identified.

January 2004 Update

The updated literature search identified five additional reports.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Original Guideline: December 2002

Trials of preoperative radiotherapy (RT) versus surgery alone were pooled using the software package Metaanalyst$^{0.998}$ (J. 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. 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. 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 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 radiotherapy 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. 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.

January 2004 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 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, alpha/beta=10 for tumour effect and acute reactions and alpha/beta=3 for late reactions, gamma/alpha = repair rate set at 0.6 Gy/day and T = total treatment time and Tk = initial delay time set at 7 days.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Original Guideline: December 2002

The discussion of the Gastrointestinal Cancer Disease Site Group (DSG) focused on results from recent trials of preoperative radiotherapy (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 chemotherapy.

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 to smaller volumes and multiple fields, instead of the past practice of two

fields, has been shown to decrease both early postoperative morbidity and mortality. The exclusion of patients with poor performance status and those with ischemic changes in the electrocardiogram reduced both mortality and morbidity in the first two months. More difficult to predict is the long-term anorectal dysfunction, which restricts the social life of one third of survivors in some series following both pre- and postoperative adjuvant RT. 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, particularly if there is downstaging of the disease. The postoperative pathological staging is very important to determine the need for adjuvant chemotherapy, which improves survival and reduces local recurrence.

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 radiotherapy plus chemotherapy. This combined treatment has been demonstrated to significantly reduce local failure by 50% (95% confidence interval [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. 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. Preoperative RT alone, when compared to surgery, has been shown to decrease local failure by approximately 50% and to improve survival by approximately 15%. The improvement in local recurrence occurs even after optimal surgery with total meso-rectal excision (TME). In a single trial, preoperative short-course RT has detected less local recurrence (11% versus 22%, p=0.02) and less morbidity than conventional postoperative RT alone. From these results it can be inferred that preoperative RT is a better treatment choice than postoperative RT plus chemotherapy with less local failures and less morbidity. A comparison of preoperative RT followed by postoperative chemotherapy versus combined postoperative RT plus chemotherapy 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 the guideline developers confirm their recommendation for combined postoperative RT plus chemotherapy for resected patients with stage II and III rectal cancer, based on the evidence from the Swedish and Dutch trials, preoperative RT (followed by chemotherapy 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.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

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 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 Disease Site Group (DSG) reviewed the results of the survey.

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

The revised version of the guideline was circulated to 11 members of the Practice Guidelines Coordinating Committee. 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.

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

MAJOR 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.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized trials and meta-analyses.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- 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 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.

POTENTIAL HARMS

- Preoperative radiotherapy (RT) did not significantly increase 30-day postoperative mortality compared with surgery alone (relative risk [RR], 1.33; 95% confidence interval [CI], 0.87 to 2.05; $p=0.19$). These results showed significant heterogeneity of trial results ($X^2=23.29$; $p<0.05$). 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 ($X^2=62.74$; $p<0.001$). Results were not different for patients receiving high or low dose radiotherapy or delay to surgery of <7 or >8 days.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- 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.
- Results of trials comparing preoperative radiotherapy to the commonly used postoperative radiotherapy plus chemotherapy are not available for review at this time.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Figueredo A, Zuraw L, Wong RK, Agboola O, Rumble RB, Tandan V. 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. PubMed

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ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2002 Dec (revised 2004 Jan)

GUIDELINE DEVELOPER(S)

Practice Guidelines Initiative - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Gastrointestinal Cancer Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please visit the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

The FULL REPORT, initially the full original Guideline or Evidence Summary, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

GUIDELINE AVAILABILITY

Electronic copies: Available from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- The use of preoperative radiotherapy in the management of patients with clinically resectable rectal cancer. Summary. Toronto (ON): Cancer Care Ontario (CCO), 2004 Jan. Electronic copies: Available from the Cancer Care Ontario Web site.
- 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 Feb;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on May 14, 2004. The information was verified by the guideline developer on June 2, 2004.

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