

Canadian Association of General Surgeons Evidence Based Reviews in Surgery. 5. Need for preoperative radiation in rectal cancer

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CAGS Evidence Based Reviews in Surgery

In September 2000, the Canadian Association of General Surgeons (CAGS) initiated a program entitled "CAGS Evidence Based Reviews in Surgery" (CAGS-EBRS) to help practising clinicians improve their critical appraisal skills. During the academic year, 8 clinical articles are chosen for review and discussion. Both methodologic and clinical reviews of the article are performed by experts in the relevant areas. The *Canadian Journal of Surgery* will publish 4 of these reviews each year. Each review will consist of an abstract of the selected article and a summary of the methodologic and clinical reviews. We hope that readers will find these useful and learn skills that can be used to evaluate other articles. For more information about the CAGS-EBRS or information about participating in the program, send an email to mmckenzie@mtsinaï.on.ca.

Selected article

Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, et al: **Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer.** *N Engl J Med* 2001;345(9):638-46.

Abstract

Question: Does the addition of preoperative radiotherapy increase the benefit of total mesorectal excision for rectal cancer? **Design:** A randomized controlled trial. **Setting:** A multicentre setting, which included hospitals from The Netherlands, Sweden, Canada and

other European locations. **Patients:** The study included 1861 patients who had histologically confirmed adenocarcinoma of the rectum without evidence of distant metastases and in whom the inferior margin of the tumour was located not farther than 15 cm from the anal verge and below the level of S1-2. **Intervention:** Patients were randomly assigned to treatment with preoperative radiation (5 Gy on each of 5 d) followed by total mesorectal excision ($n = 897$) or to total mesorectal excision alone ($n = 908$). **Main outcome measures:** Two main outcomes were measured: overall survival rate and local recurrence. **Results:** The table shows the results at the 2-year follow-up. **Conclu-**

Table

Results in 1861 Patients Who Underwent Mesorectal Excision, With or Without Preoperative Radiotherapy, for Rectal Cancer

| Outcome measure | Intervention | | p value |
|--------------------------|---|--|---------|
| | Preoperative radiotherapy + mesorectal excision ($n = 897$) | Mesorectal excision only ($n = 908$) | |
| Local recurrence, % | 2.4 | 8.2 | < 0.001 |
| Overall survival rate, % | 82.0 | 81.8 | 0.84 |

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sion: Preoperative radiotherapy (short course) with total mesorectal excision significantly decreases the local recurrence rate compared with surgery alone at a median follow-up of 2 years.

Commentary

The article reviewed in this issue is an important one because this is the first randomized controlled trial assessing therapy for rectal cancer in which attempts have been made to standardize the quality of surgical resection. There are multiple previously reported trials, and they have consistently shown that both preoperative and postoperative radiotherapy decrease the risk of local recurrence although there is little evidence that radiotherapy alone improves survival. Thus, adjuvant radiotherapy has become standard practice in the management of rectal cancer in Canada. However, in these previous trials, surgical technique was not standardized and the local recurrence rates in the control groups have ranged from 15%–50%. In the last 10 years, total mesorectal excision has become the standard for surgical extirpation of rectal cancer, and local recurrence rates of less than 10% without adjuvant radiotherapy have been achieved. This has made surgeons question the need for adjuvant radiotherapy when a proper surgical resection is performed. Thus, this trial addresses the following question: Is adjuvant preoperative radiotherapy beneficial when optimal surgical therapy is performed in patients with rectal cancer?

In this large, well-designed and performed trial, the main finding is that a short course of preoperative radiation (25 Gy given over 5 d) does decrease the risk of local recurrence at 2 years' follow-up for rectal cancers resected with macroscopically uninvolved margins. The rate of local recurrence was 2.4% in the radiotherapy-plus-surgery group compared with 8.2% in the surgery-only group.

The results of a clinical trial may

be presented in a variety of ways. In this study, the absolute risk reduction in local recurrence is 5.8% (8.2% – 2.4%). The absolute risk reduction is simply the difference in the risk of an event in one group compared with the risk of an event in the other group. The authors also present the data as a hazard ratio, which is 3.42. In other words, patients assigned to surgery alone had a 3.42 (95% confidence interval, 2.05–5.71) increased risk of local recurrence. This is also known as the relative risk and is calculated by dividing the risk of local recurrence in the control group by that in the treatment group (i.e., 8.2%/2.4% = 3.42). Although relative risk is often reported, there are concerns with this figure because the baseline event rate is not considered. Thus, if the baseline event rate was 0.5% and the event rate in the treatment group was 0.25%, the relative risk of developing an event in the treatment group would be 0.5. This relative risk would remain constant even if the baseline event rate was 5% and was reduced to 2.5% or was 50% and was reduced to 25%. However, the clinical significance of the treatment effect might be viewed quite differently. For example, if the local recurrence rate was 0.5% with surgery alone, the addition of radiotherapy probably would not be worthwhile if the local recurrence rate was reduced to 0.25%. On the other hand, if the local recurrence rate was 50% in the surgery alone group and adjuvant radiotherapy reduced the local recurrence rate to 25%, adjuvant radiotherapy would be considered highly worthwhile. Thus, the relative risk may not be helpful without knowing the baseline event rate.

The number needed to treat (NNT) is another way to present the data. It is calculated by taking the reciprocal of the absolute risk reduction (i.e., 1/ARR) or by dividing 100 by the ARR. The utility of the NNT is that it changes with a change in the underlying risk. It is also a concept that is easy for clinicians to

understand. Thus, in this trial, the NNT would be 1/5.8, or approximately 17 patients would have to be treated with preoperative radiotherapy to prevent 1 local recurrence. Is this worthwhile?

In determining the significance of a result, we consider both statistical and clinical significance. Statistical significance is determined by performing statistical tests. In this study, the result is highly significant ($p < 0.001$). Clinical significance is determined by the clinician using his or her clinical expertise. The following factors should be considered in making that judgement: How morbid is the event that is being prevented? What are the side effects of treatment? What is the cost of treatment? How feasible (to the patient, the physician and the system) is the treatment? There may be others factors. So, in this case, survival is not improved but local recurrence causes significant morbidity and is, in most cases, not treatable, and palliation is poor. On the other hand, there is increasing evidence that functional results are impaired by the addition of both preoperative and postoperative radiotherapy. There is great pressure on most radiotherapy facilities, and in Canada many patients may come from afar to regional cancer centres to receive radiation. However, after considering all of these factors, most clinicians would consider prevention of 1 local recurrence while giving adjuvant radiotherapy to 17 patients (16 who would not benefit) to be worthwhile.

In addition to the primary analysis, subgroup analyses revealed that preoperative radiotherapy significantly decreased local recurrence for cancers 10 cm or less from the anus (from about 10% to less than 6%) but not for cancers more than 10 cm above the anus (local recurrence rates less than 4%). Also, preoperative radiotherapy significantly decreased local recurrence for both stage 2 (6% to 1%) and stage 3 cancers (15% to 4%). Finally, this study did not show any

difference in overall survival (82% v. 81.8%). This may be due to the relatively short follow-up, but given that there is no trend at 2 years it is unlikely that a difference will be observed with longer follow-up.

One concern of short-course radiotherapy is that there may be increased morbidity and even mortality. However, there was no difference in post-operative mortality in this trial. There was a significant difference in perineal complications in those who underwent abdominoperineal resection (26% v. 18%). This number can also be expressed as the number needed to harm. This can be calculated like the NNT (i.e., $1/26\% - 18\% = 12$). Thus,

for every 12 patients treated with radiotherapy and having an abdominoperineal resection, 1 patient would suffer a perineal complication. Functional outcomes, including incontinence, were not reported. Long-term follow-up and reporting of functional data will be very important.

This study provides strong evidence that adjuvant radiotherapy is still indicated even when optimal surgery is performed. Currently, post-operative long-course radiotherapy is the standard in most centres in Canada. However, preoperative short-course radiotherapy is feasible and presents a potential cost-saving, and may relieve the pressure on ra-

diotherapy facilities making radiation more accessible to patients and decreasing waiting times. Recently, there has been a trend to using long-course preoperative chemoradiation. This appears to downstage cancers, and local recurrence rates of less than 10% have been reported in case series. To date there are no data from randomized controlled trials comparing preoperative short-course to preoperative chemoradiation. Perhaps, that is the next trial to be performed.

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