

Improved Survival and Reduction in Local Failure Rates After Preoperative Radiotherapy

Evidence for the Generalizability of the Results of Swedish Rectal Cancer Trial

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Objective

The Swedish Rectal Cancer Trial (SRCT) demonstrated that a short-term regimen of high-dose preoperative radiotherapy (5×5 Gy) not only reduced the local recurrence rates but also improved the overall survival rate. This compelling evidence will have a significant impact on the primary treatment of rectal cancer. The authors' aim was to explore the representativeness of the study.

Summary Background Data

Until the SRCT was presented in 1997, no major trial had established that radiotherapy has a positive effect on the overall survival rate.

Methods

A review of all rectal cancer cases reported to the Swedish Cancer Registry during the same period that the SRCT accrued patients (1987 to 1990) was performed at 57 of 68 participating hospitals. At these 57 hospitals, there were 2366 patients with invasive rectal cancer, with 1664 of these patients fulfilling the criteria for inclusion in the SRCT.

The use of irradiation in addition to surgery for patients with resectable rectal cancer has been extensively studied in trials exploring both preoperative¹⁻⁶ and postoperative⁷⁻¹⁰ radiotherapy. A reduction in local recurrence rates has been seen in most of these trials and has been particularly pronounced with the use of preoperative irradiation. In a randomized trial in the Uppsala region of Sweden, preoperative irradiation was found to be more effective than postopera-

Results

Fifty-two percent (866/1664) of eligible patients were included in the SRCT. The patients not included, of whom 8% (67/798) received adjuvant radiotherapy, had an overall 5-year survival rate of 48%, which was identical to the overall survival rate in the SRCT surgery-alone group (48%) but was inferior to the SRCT radiotherapy group (58%). The cancer-specific 5-year survival rates were 65% and 66% among the patients not included and the surgery-alone group, respectively. The local recurrence rates reached 27% in both groups. The results were still comparable when stratifying for curative surgery, tumor stage, and surgical procedure.

Conclusions

The achieved inclusion level of 52% in a randomized multicenter trial is comparatively high. Because the population in the SRCT was representative, it was concluded that the study results are reliable.

tive radiotherapy.¹¹ However, until the results of the Swedish Rectal Cancer Trial (SRCT) were presented in 1997,¹² no other major trial had yet shown that radiotherapy plus surgery significantly improves the overall survival rate. The SRCT demonstrated a 21% relative survival benefit, which corresponds to an increase in 5-year survival from 48% to 58% and a reduced local failure rate from 27% to 11%.¹² In the trial, which included 1168 patients, a short-term regimen of high-dose preoperative radiotherapy (5×5 Gy) with a three- or four-beam technique was followed by surgery within 1 week. The preoperative treatment did not increase the postoperative mortality rate. Improved disease-free survival rates were found in three other trials.^{1,2,4}

Supported by the Swedish Cancer Society (grant no. 1921-B98-15XCC).
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Accepted for publication December 2, 1998.

The SRCT was a large, prospectively randomized clinical trial that included most Swedish hospitals. For these reasons, it can be argued that the trial results possess sufficient validity. It is also likely that the results of the study have had a considerable impact on the primary treatment of resectable rectal cancer. However, because every trial has defined inclusion and exclusion criteria, and because not all eligible patients are included in the trial, the representative nature of the trial results on a population level is still unclear. Therefore, the aim of this study was to explore whether the trial results are representative of the Swedish population by reviewing all rectal cancer cases reported to the Swedish Cancer Registry during the same period that the SRCT was accruing patients.

PATIENTS AND METHODS

From 68 Swedish hospitals, 1168 patients with resectable rectal carcinoma during the period March 1987 to February 1990 were recruited into the SRCT.¹³ A retrospective review of all rectal cancer cases reported to the Swedish Cancer Registry during the same period that the SRCT recruited patients was performed at 57 of the 68 participating hospitals. Ten hospitals, all of which were from the same health care region, did not accept the audit because of hospital policy, and one hospital rejected the audit, referring to patient integrity. The patient characteristics and the treatment results of the 302 patients from these hospitals in the SRCT did not differ from the rest of the participating hospitals (data not shown). From the 57 hospitals, 2444 cases of invasive rectal cancer were reported to the Swedish Cancer Registry.¹⁴ Of these, medical records were missing for 64 patients, 14 patients were diagnosed at autopsy, and 460 did not undergo resection, resulting in a final sample of 1906 resected invasive rectal carcinomas. The reasons patients did not undergo resection were advanced metastatic disease in 263 cases and advanced local disease in 83 cases. A total of 104 patients did not undergo surgery because of high age and/or deteriorated physical status, and 10 patients refused surgery. In the case of missing data, an inquiry was made to the National Population Registry and, in the case of death, further inquiry was directed to the National Causes of Death Registry. At the 57 hospitals, 866 of the patients who underwent resection were randomized in the SRCT, leaving 1040 patients who underwent resection excluded from the study. Of these, 798 were eligible for the SRCT. Those patients who did not meet the inclusion criteria included 16 patients with primarily nonresectable tumors, 35 with local procedures, and 191 older than 79 years of age.¹³ The median follow-up time for living patients included in the SRCT was 75 months¹²; for those not included, it was 108 (range 85 to 126) months.

Surgery and Histopathology

Standard surgical procedures determined by the surgeon were used. A surgical procedure was considered locally

curative if both the surgeon and the histopathologist reported free margins. The locally curative nature of surgery was defined as uncertain when either the surgeon or pathologist reported a questionable margin. In all other cases, the treatment was considered not locally curative. Tumor stage refers to the local extent of the tumor, irrespective of whether distant metastases were present.

Adjuvant Therapy

Sixty-seven (8%) eligible, but not randomized, patients received radiotherapy, either before or after surgery. None of the patients in the surgery-alone group included in the SRCT received adjuvant radiotherapy (Table 1). No patients were treated with adjuvant chemotherapy.

Statistical Analyses

Differences in proportions were calculated using the chi square test. The differences were considered significant at $p < 0.05$. Survival and local recurrence rates were analyzed using the log-rank test. Analyses of postoperative mortality, overall local recurrence, and overall survival rates were based on all patients who underwent resection. All comparisons were made between the surgery-alone group in the SRCT and the eligible-but-not-included group.

RESULTS

Fifty-two percent (866/1664) of eligible patients were included in the SRCT. Patients not included but eligible were matched with the surgery-alone group in the SRCT regarding tumor stage and age, but the fraction of men was somewhat higher in the SRCT (see Table 1). The tumor height from the anal verge was also greater, and consequently the fraction of anterior resections was greater in the nonrandomized group. The characteristics of the noneligible patients are listed in Table 1. In-hospital mortality rates did not differ between the groups (see Table 1).

There were no differences in overall local recurrence rates between the eligible-but-nonrandomized patients and the surgery-alone group in the SRCT. The comparability between these two groups was maintained when stratifying for curative surgery, tumor stage (Tables 2 and 3), and surgical procedure (Table 4). The local recurrence rate for all noneligible patients was 24% (57/242). Among the 48 noneligible patients younger than 80 years of age, of whom 32 (66%) had a local procedure performed, the local failure rate was 35% (17/48).

The overall 5-year survival rates for the eligible-but-nonrandomized group and the surgery-alone group were 47% (95% confidence interval [CI], 44% to 50%) and 48% (95% CI, 44% to 52%), respectively. The cancer-specific survival rates for curatively operated patients were 65% (95% CI, 61% to 69%) and 66% (95% CI, 61% to 71%), respectively (Fig. 1).

Table 1. PATIENT CHARACTERISTICS IN AUDIT AND IN SURGERY-ALONE GROUP OF THE SRCT

	Not Eligible		Eligible		p Value*
	Age < 80 (48)	Age ≥ 80 (194)	Not Randomized for SRCT (798)	SRCT Surgery-Along Group (557)	
Gender (male/female)	23/25 (48/52)	107/87 (55/45)	448/366 (55/45)	336/221 (60/40)	p = 0.02
Age, years (median [range])	70 (37–79)	82 (80–94)	69 (32–79)	67 (31–79)	NS
Dukes					
A†	30 (62)	53 (27)	174 (22)	154 (27)	
B	11 (23)	78 (40)	308 (39)	173 (31)	NS
C	7 (15)	63 (33)	309 (39)	230 (41)	
Tumor height, cm (median [range])	5 (1–15)	10 (0–20)	10 (0–22)	8 (0–18)	p < 0.001
Surgical procedure					
Anterior resection	8 (17)	83 (43)	464 (58)	227 (40)	
Abdominoperineal excision	8 (17)	86 (44)	304 (38)	322 (58)	p < 0.001
Other	0	9 (5)	30 (4)	8 (2)	
Local procedure	32 (66)	16 (8)	—	—	
Adjuvant radiotherapy, preop/postop	18/2 (38/4)	3/0	46/21 (6/3)	0/0	
In-hospital deaths	2 (4)	13 (7)	23 (3)	15 (3)	NS

SRCT = Swedish Rectal Cancer Trial. Figures are number of patients and (percentages) unless otherwise indicated.

* p-value, chi square test, or Mann-Whitney test in comparison between the surgery-alone group of the SRCT and those eligible but not randomized for the SRCT.

† Dukes stage refers to local stage only.

Among eligible patients, there were no significant differences in the treatment results as a function of gender. The local recurrence rates were 27% (118/437) in men and 28% (100/361) in women; the 5-year overall survival rates were 45% and 48% in men and women, respectively.

DISCUSSION

In Sweden, rectal cancer surgery was performed in the majority of surgical departments in the late 1980s using mostly standard surgical techniques. Under these circumstances, the SRCT has unequivocally demonstrated that a short-term regimen of high-dose preoperative radiotherapy (5 × 5 Gy) reduces the local recurrence rates and improves

the overall survival rates. A reduction of 60% (from 27% to 11%) in the relative local recurrence rate and an overall 5-year relative survival benefit of 21% (from 48% to 58%) were observed.¹² The implication is that 15 of 100 patients will not have a painful local recurrence and that 10 of 100 patients will survive because of the additional radiotherapy. Lower rates of local recurrence have also been shown in virtually all of the previous trials evaluating adjuvant radiotherapy,^{1–10} particularly in trials employing preoperative irradiation^{1–6}; however, no statistically significant effects on the overall survival rate have been noted. A metaanalysis of all controlled trials of adjuvant radiotherapy published before 1986 found a marginally positive effect of radiother-

Table 2. LOCAL RECURRENCE RATES ACCORDING TO DUKES STAGE AMONG PATIENTS WITH RESECTED TUMORS IN SRCT SURGERY-ALONE GROUP AND THOSE ELIGIBLE FOR SRCT BUT NOT RANDOMIZED

	Surgery-Along Group in SRCT				Eligible for SRCT but Not Randomized			
	Dukes Stage A	Dukes Stage B	Dukes Stage C	Total	Dukes Stage A	Dukes Stage B	Dukes Stage C	Total
Distant metastasis	1/4	3/12 (25)	8/25 (32)	12/41 (29)	1/3	6/22 (27)	23/74 (31)	30/100 (30)
Locally noncurative surgery	0/3	5/16 (31)	27/43 (63)	32/62 (52)	0/2	20/25 (80)	11/18 (61)	31/46 (67)
Curative surgery	17/147 (12)	31/145 (21)	58/162 (36)	106/454 (23)	15/169 (9)	61/261 (23)	81/217 (37)	157/652 (24)
Total	18/154 (12)	39/173 (23)	93/230 (40)	150/557 (27)	16/174 (9)	87/308 (28)	115/309 (37)	218/798 (27)

SRCT = Swedish Rectal Cancer Trial. Number with recurrence/total number (percent).

Table 3. LOCAL RECURRENCE RATES ACCORDING TO DUKES STAGE AMONG PATIENTS WITH RESECTED TUMORS ASSIGNED TO RADIOTHERAPY PLUS SURGERY WITHIN SRCT AND THOSE NOT ELIGIBLE FOR SRCT

	Radiotherapy Group in SRCT				Noneligible for SRCT			
	Dukes Stage A	Dukes Stage B	Dukes Stage C	Total	Dukes Stage A	Dukes Stage B	Dukes Stage C	Total
Distant metastasis	0/5	0/11	5/26 (19)	5/42 (12)	—	4/13 (31)	2/13 (15)	6/26 (23)
Locally noncurative surgery	0/2	9/19 (47)	8/36 (22)	17/57 (29)	2/5 (40)	1/3 (33)	2/7 (29)	5/15 (33)
Curative surgery	8/174 (5)	11/165 (7)	22/115 (19)	41/454 (9)	14/78 (18)	15/73 (21)	17/50 (34)	46/201 (23)
Total	8/181 (4)	20/195 (10)	35/177 (20)	63/553 (11)	16/83 (19)	20/89 (22)	21/70 (30)	57/242 (24)

SRCT = Swedish Rectal Cancer Trial. Number with recurrence/total number (percent).

apy on survival.¹⁵ It has further been shown that preoperative radiotherapy is more “dose-effective” than postoperative radiotherapy.¹⁶ Nevertheless, chiefly because of a lack of documented improved survival and because in some trials it has been linked with an increased postoperative mortality rate, preoperative irradiation has not been routinely recommended. However, we strongly believe that the results of the SRCT will alter the general recommendation of radiotherapy in rectal cancer toward an increased use of the short-term, high-dose preoperative regimen. The present study’s clear confirmation of the SRCT results supports this view.

The patients in the eligible-but-not-randomized group were comparable with the surgery-alone group in the SRCT, except for a larger proportion of women and a larger proportion of anterior resections because of higher tumor height among the nonrandomized patients. In the audit, all cases of rectal carcinomas reported to the Swedish Cancer Registry at the same time as the SRCT accrued patients were reviewed. Thus, some rectosigmoid tumors that would not have been randomized in the SRCT were included. Retrospectively, it was not always possible to identify this group to comply with the inclusion criteria¹³ (*i.e.*, including only those tumors situated below the sacral promontory as shown on a side projection on barium enema). There was no

significant difference, however, in the treatment results for gender, and prognostically the upper tumors are the most favorable group of rectal tumors. Thus, this incomparability should not be detrimental to the conclusions of the SRCT or to the present validation.

For completeness, the patient characteristics and the treatment results of the noneligible patients are specified briefly. The noneligible group had a higher median age, a higher in-hospital mortality rate, and an earlier tumor stage relative to the other two groups. This finding is anticipated in that age older than 79 years and local resection (chiefly small and polypoid tumors) were both criteria for exclusion. An unexpectedly high local failure rate was found among the noneligible patients younger than age 80, raising questions about how accurately patients on a routine basis at a number of hospitals were selected for a local surgical procedure. Beyond this, it is not possible to extract any implications from the treatment results of this group.

A controversy involving the SRCT is that the patients included in the SRCT did not undergo “optimized surgery,” as popularized by Heald and others.^{17,18} With this refined technique, it may be that adjuvant radiotherapy is superfluous. However, whether Heald and Karanjia’s¹⁹ excellent figure of 7% overall local recurrence rate can be repeated by other surgeons is still to be established. This particular

Table 4. LOCAL RECURRENCE RATES ACCORDING TO SURGICAL PROCEDURE AMONG PATIENTS IN SRCT SURGERY-ALONE GROUP AND AMONG PATIENTS ELIGIBLE FOR TRIAL BUT NOT RANDOMIZED

	SRCT Surgery-Alone Group			Eligible for SRCT but Not Randomized		
	Anterior Resection	Abdominoperineal Excision	Other	Anterior Resection	Abdominoperineal Excision	Other
Noncurative surgery	11/33 (33)	32/66 (48)	2/4 (50)	21/59 (36)	29/72 (40)	11/15 (73)
Curative surgery	41/194 (21)	65/256 (25)	1/4 (25)	92/405 (23)	61/232 (26)	4/15 (27)
Total	52/227 (23)	97/322 (30)	3/8 (38)	113/464 (24)	90/304 (30)	15/30 (50)

SRCT = Swedish Rectal Cancer Trial. Number with recurrence/total number (percent).

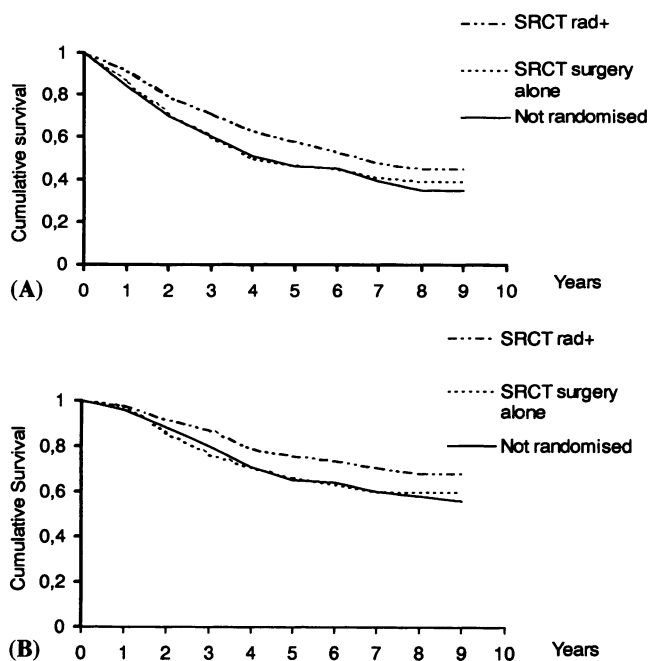


Figure 1. Cumulative overall (A) and cancer-specific (B) survival rates in the surgery-alone group in the SRCT and in the eligible-but-not-randomized patients. For comparison, the irradiation group of the SRCT (SRCT rad +) is included.

question is being addressed in a Dutch randomized trial in which patients are randomly allocated either to undergo preoperative radiotherapy (5×5 Gy) followed in 1 week by total mesorectal excision or to have total mesorectal excision alone; several Swedish departments have participated in the Dutch trial.

In conclusion, this study has shown that the SRCT data are representative of the entire Swedish population. The local recurrence rate, 27%, and the survival figures after 5 years of follow-up are identical between the surgery-alone group in the SRCT and the patients eligible but not included in the trial. The local recurrence rates are also similar to the findings in other controlled trials on this topic, in which the local recurrence rates average 28%.^{1,2,4-10,21,22} This is unacceptably high, and until a randomized study can document that optimized surgery, such as total mesorectal excision, will yield lower rates of local recurrence, preoperative radiotherapy should be considered an integral part of the routine primary care of patients with rectal cancer. It is possible, although not proven in a randomized trial, that postoperative radiochemotherapy^{7,9,20} may be as efficient as preoperative irradiation. However, in light of cost constraints, radiochemotherapy demands considerably more resources, even if given only to those at a high risk for failure.²³

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