Swedish Rectal Cancer Trial: Long Lasting Benefits From Radiotherapy on Survival and Local Recurrence Rate

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ABSTRACT

Purpose
To evaluate the long-term effects on survival and recurrence rates of preoperative radiotherapy in the treatment of curatively operated rectal cancer patients.

Patients and Methods
Of 1,168 randomly assigned patients in the Swedish Rectal Cancer Trial between 1987 and 1990, 908 had curative surgery; 454 of these patients had surgery alone, and 454 were administered preoperative radiotherapy (25 Gy in 5 days) followed by surgery within 1 week. Follow-up was performed by matching against three Swedish nationwide registries (the Swedish Cancer Register, the Hospital Discharge Register, and the Cause of Death Register).

Results
Median follow-up time was 13 years (range, 3 to 15 years). The overall survival rate in the irradiated group was 38% v 30% in the nonirradiated group (P/H11005 .008). The cancer-specific survival rate in the irradiated group was 72% v 62% in the nonirradiated group (P/H11005 .03), and the local recurrence rate was 9% v 26% (P/H11021 .001), respectively. The reduction of local recurrence rates was observed at all tumor heights, although it was not statistically significant for tumors greater than 10 cm from the anal verge.

Conclusion
Preoperative radiotherapy with 25 Gy in 1 week before curative surgery for rectal cancer is beneficial for overall and cancer-specific survival and local recurrence rates after long-term follow-up.

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INTRODUCTION

Colorectal cancer is the third most common malignant tumor throughout the Western world. Rectal cancer comprises approximately one third of the cases. In Sweden, with a population of 9 million,1 approximately 1,500 new patients with adenocarcinomas of the rectum are annually diagnosed. During the last few decades, improvements in survival and reduced local recurrence rates have been observed, probably because of changes in treatment strategies,2-5 surgical technique,6-10 and centralization to specialized units.11,12 In Sweden, the first shift of paradigm was the introduction of preoperative radiotherapy. Beneficial effects in terms of reduced local recurrence rates and enhanced survival have been seen in several randomized trials and summarized in systematic overviews.3,13,14 Rectal cancer is uncommon in people under the age of 50 years, but later in life, it is one of the most significant diseases in terms of morbidity and mortality. As longevity continues to increase, an increasing proportion of elderly patients will live for a long time after a curative treatment of rectal cancer. Today, in Sweden, a 50-year-old man can expect to live for another 29.8 years, whereas
the corresponding figure for a woman is 33.7 years.\textsuperscript{15} Therefore, the long-term results of therapy, not just the 5-year results, are of interest. The aim of the present study is to describe, in curatively treated rectal cancer patients, the long-term effects of preoperative radiation on survival, local recurrence rate, and distant metastasis in a large randomized trial.

### PATIENTS AND METHODS

The Swedish Rectal Cancer Trial (SRCT) was run between March 1987 and February 1990. Eleven hundred sixty-eight patients from 70 hospitals in Sweden, who were younger than 80 years of age and had resectable rectal cancer, were included in the trial. Random assignment was to either preoperative radiotherapy ($5 \times 5$ Gy delivered in 1 week) followed by surgery within a week or surgery alone. Of the 1,168 patients, 908 patients (454 in each group) were judged to have had a curative treatment based on the absence of distant metastases and R0 surgery (ie, both the histopathologic report and the surgeon stated radical surgery). Of the remaining 260 randomly assigned patients who had no radicular surgery, 245 (94\%) were dead at the time of the long-term follow-up. Details of the study cohort are listed in Table 1. Follow-up was performed by matching all curatively treated patients in the SRCT database against the Swedish Cancer Register, the National Hospital Discharge Register, and the Cause of Death Register until December 31, 2001. The clinical records of all patients in two of the participating regions, Stockholm and Uppsala ($n = 353$; 30\%), were checked for validity of the outcome of the register investigation by manual control. In these 353 patients, two patients had distant metastasis, and one patient had a local recurrence that was not recorded earlier in any of the registries.

Statistic calculations were made using StatSoft, Inc (2001) Statistica software, version 6 (StatSoft, Tulsa, OK). Survival and cumulative incidence of local recurrence were calculated by actuarial methods. Differences between groups were analyzed using the log-rank test. Differences in proportions were analyzed using the $\chi^2$ test. The Mann-Whitney $U$ test was used to compare medians between groups. $P < .05$ was considered statistically significant.

### RESULTS

Of the 908 curatively treated patients, 542 (60\%) were men, and 366 (40\%) were women, which corresponded to the original proportions of the 1,168 patients included in the SRCT. The median age at inclusion was 68 years (range, 27 to 81 years), and the median follow-up time of living individuals was 13 years (range, 11.5 to 15 years), with the exception of two individuals who were censored at emigration after 3 and 7 years. A difference in the distribution of stages between the treatment groups was noted (Table 2) and already commented on in the original publication of the study.\textsuperscript{2} However, stages were evenly distributed between men and women. The rates of local radicality (89\%) were identical between the preoperative radiotherapy group and the surgery alone group.

### Survival

Overall survival in all patients and by stages I to III is presented in Figure 1, and overall and cancer-specific survival rates at median follow-up are listed in Table 3. Deaths ascribed to rectal cancer constituted 51\% of the deaths registered until December 31, 2001. Women, compared with men, had a better overall survival rate (41\% v 30\%, respectively; $P = .001$, log-rank test) and cancer-specific survival rate (74\% v 62\%, respectively; $P < .001$, log-rank test), although no differences in stage distribution were seen. Irrespective of whether radiotherapy was administered or not, women had a better overall survival rate than men (radiotherapy, 46\% v 33\%, respectively; $P = .004$, log-rank test; no radiotherapy, 35\% v 26\%, respectively; $P = .01$, log-rank test). A crude survival analysis of all 1,168 patients originally included in the study showed a persistent survival benefit in the preoperative radiotherapy group (31\% with radiotherapy v 20\% without radiotherapy; $P = .009$, log-rank test).

### Local Recurrence

Cumulative proportions of local recurrences, overall and stage by stage, are presented in Figure 2. At median follow-up, the cumulative proportion of local recurrence was 9\% in the preoperative radiotherapy group and 26\% in

### Table 1. Selection of the Study Cohort

<table>
<thead>
<tr>
<th>Patient Category</th>
<th>Radiotherapy and Surgery</th>
<th>Surgery Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized</td>
<td>583</td>
<td>585</td>
</tr>
<tr>
<td>Ineligible</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Eligible</td>
<td>573</td>
<td>574</td>
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<tr>
<td>Refused surgery</td>
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<td>0</td>
</tr>
<tr>
<td>No resection performed</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>Local resection performed</td>
<td>553</td>
<td>557</td>
</tr>
<tr>
<td>Distant metastases found</td>
<td>42</td>
<td>41</td>
</tr>
<tr>
<td>Locally noncurative surgery</td>
<td>14</td>
<td>19</td>
</tr>
<tr>
<td>Local cure uncertain</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>Curatively treated</td>
<td>454</td>
<td>454</td>
</tr>
</tbody>
</table>

### Table 2. Distribution of Stages Among Patients Who Had R0 Resections Assigned to Surgery Alone or Radiotherapy and Surgery

<table>
<thead>
<tr>
<th>Disease Stage</th>
<th>Radiotherapy and Surgery (No.)</th>
<th>Surgery Alone (No.)</th>
<th>Total Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Stage I</td>
<td>174</td>
<td>321</td>
<td>35</td>
</tr>
<tr>
<td>Stage II</td>
<td>157</td>
<td>307</td>
<td>34</td>
</tr>
<tr>
<td>Stage III</td>
<td>123</td>
<td>280</td>
<td>31</td>
</tr>
<tr>
<td>Total</td>
<td>454</td>
<td>908</td>
<td>100</td>
</tr>
</tbody>
</table>

*$\chi^2$ test.
the surgery-alone group ($P < .001$, log-rank test). In stage I patients, the cumulative recurrence rates were 4.5% and 14% ($P = .009$, log-rank test) for the preoperative radiotherapy and surgery-alone groups, respectively; in stage II and III patients, these proportions were 6% and 22% ($P < .001$, log-rank test) and 23% and 46% ($P < .001$, log-rank test), respectively. A lower local recurrence rate was seen at all distances from the anal verge, as measured by a straight rectoscope, although it was not statistically significant for tumors originating from greater than 10 cm from the anal verge (Table 4). Sex did not influence the rates of local recurrence. Four of the five patients with a local recurrence detected later than 5 years after surgery were in the nonirradiated group. Local recurrences were found up to 12 years after surgery. Time to death from the occurrence of a local recurrence differed significantly ($P < .001$, Mann-Whitney $U$ test) between the irradiated group (median, 295 days; range, 18 to 1,818 days; $n = 40$) and the surgery-alone group (median, 398 days; range, 28 to 1,590 days; $n = 104$).

**Distant Metastases**

In the analysis of local failure and distant metastasis, the data represent failure rates at any time. However, of 66 patients who had both local recurrence and distant metastasis, only one patient had distant metastases as first site of failure. All adenocarcinomas diagnosed after resection of the rectal cancer, without a diagnosis of a new primary adenocarcinoma, were regarded as recurrences. Recurrences not located in the pelvis (ie, outside the radiation target) were considered distant metastases. Distant metastases were also found as late as 12 years after surgery. At median follow-up, 34% of patients had developed distant metastases irrespective of whether preoperative radiother-

![Fig 1. Overall survival analysis. (A) All curatively treated patients ($n = 908$, $P = .008$); (B) stage I patients ($n = 321$, $P = .31$); (C) stage II patients ($n = 307$, $P = .27$); and (D) stage III patients ($n = 280$, $P = .18$, log-rank test). RT+, preoperative radiotherapy; RT−, surgery alone.](image-url)
apy was administered or not. No significant differences between the irradiated and nonirradiated groups were found in the stage-by-stage analyses (stage I, 14% v 13%, respectively; \( P = .5 \); stage II, 29% v 36%, respectively; \( P = .5 \); and stage III, 55% v 57%, respectively; \( P = .9 \)). The incidence of distant metastases was not influenced by sex. No significant difference (\( P = .8 \), Mann-Whitney \( U \)) in time to distant metastasis from occurrence of local recurrence was found between the two groups (median, 114 days for nonirradiated patients v 164 days for irradiated patients).

**DISCUSSION**

Our findings reveal an overall long-term survival benefit for the entire group of preoperatively irradiated patients, but for the separate stages, the differences did not reach statistical significance when comparing the irradiated and the nonirradiated groups. The improved survival can be explained by a marked reduction in the risk of local recurrence after radiotherapy, whereas the rate of distant metastases was not influenced. The magnitudes in the gains in cancer-specific survival and overall survival remained the same throughout the follow-up period, indicating that there is no excessive lethal toxicity, either immediately postoperatively or later in the course of the disease, from the radiotherapy.

The lack of statistically significant differences in overall and cancer-specific survival (with the exception of stage I patients) in the stage-by-stage analyses can likely be explained by the fact that these analyses are biased because of the downstaging seen in the radiotherapy group; although,
potentially, a lack of power because of reduced numbers may have contributed. The risk of distant metastases is likely predominately influenced by stage at diagnosis, before radiotherapy is administered, rather than by the stage 8 to 14 days later. In contrast, the risk of local failure may mainly be influenced by the stage at surgery, although the stage before the radiation therapy can also be of importance in predicting the risk of metastases in the lateral lymph nodes, which are never removed during surgery. Thus, it is logical that there is a clear difference in local failure rates according to stage but a less clear and frequently statistically insignificant difference in the biased stage-by-stage analyses of survival. It is also logical that any difference in survival is clearer for stage I patients, including the isolated statistical significance for cancer-specific survival, than for stage II patients and, particularly, stage III patients because the relative importance of distant metastases, which is predicted mainly by stage at diagnosis, for the number of deaths is highest for the advanced stages.

The clear benefit from radiotherapy in stage I is somewhat contradictory to the prevailing opinion of not offering radiotherapy to patients with this stage of disease. There may be several reasons for this result, one of which is that the SRCT was undertaken during a period in which most hospitals had not adopted the total mesorectal excision (TME) technique, thereby performing less radical surgery. Furthermore, pathology reports were not up to present standards, which involve routinely examining the circumferential margin and a sufficient number of lymph nodes, which are never removed during surgery. Thus, it is known that lymph nodes are more difficult to find after preoperative radiotherapy. Another factor that we now know predicts not only local recurrence rates but also survival is the circumferential margin, which was not routinely reported at the time of the study. With modern staging, including preoperative magnetic resonance imaging and/or ultrasound, adequate surgery, and a complete pathology report according to Quirke et al and Quirke and Dixon, fewer patients with stage I disease would likely have been observed.

In the analysis of local recurrences, the effect of radiotherapy is clear both in the overall and the stage-by-stage analyses. Actually, the relative decrease in the risk of local failure is highest in stage I patients (80%), intermediate in stage II patients (73%) and lowest but still definitive in stage III patients (50%). This is also a logical result because the less cancer cells there are, the higher the relative cell kill effect of radiation is. A striking result is the high recurrence rates in the nonirradiated groups, which, again, are probably a result of surgery not considering the anatomic planes. These high numbers are not reached when TME is adopted, but the effect of preoperative radiotherapy is still evident in all stages. Also, in the TME trial, there was a higher relative efficacy of radiation seen in the stages having a statistically lower risk of tumor cells left after TME. On the basis of the results of the present trial, the TME trial, and the meta-analysis, the relative efficacy of a preoperative treatment, such as the 5 × 5 Gy schedule, means a 30% to 50% reduction in local failure rates if the surgical margins are close (eg, circumferential resection margin ≤ 1 mm) or if extensive lymph node metastases are present and a 70% to 90% reduction if the resection margins are wider or no lymph node metastases are present. Because the number of events is much smaller when the surgical margins are wider, the absolute reduction in local failures will be smaller, and consequently, overtreatment will be higher. This intricate balance is not always clear. Recently, the benefits of radiotherapy using the 5 × 5 Gy schedule in the treatment of low rectal cancers has been questioned because a clear and statistically significant reduction in local failure rates was not observed in the updated report from the TME trial. In this randomized trial, however, preoperative radiotherapy particularly diminished the risk of developing a local recurrence for the low-lying (0 to 5 cm) tumors. A possible explanation for a smaller benefit in the TME trial is that the dissection, in modern surgery, is almost always driven to the pelvic floor even if an abdominoperineal resection is planned. This dissection will cause a coning effect, with a risk of entering the tumor and, consequently, a higher risk of a later local recurrence in both nonirradiated and irradiated patients. To avoid this for low-lying tumors, it is necessary to stop the mesorectal dissection in time and do a more extensive perineal dissection.

Better pretreatment staging and selecting the most appropriate preoperative treatment and surgical technique are required to achieve low local recurrence rates for the entire rectal cancer population. The late recurrences occurred predominantly in the nonirradiated groups, possibly because of growth from micrometastases, which, in the irradiated group, would have been eradicated. A delay in the occurrence of local recurrence as a result of radiotherapy has been hypothesized. However, this follow-up shows that such a postponement is unlikely because the difference between the treatment groups persists over time.

Distant metastasis of rectal cancer may occur late, but the risk is low, and only a few patients developed distant metastasis after the 5-year follow-up. Because the frequency of distant metastases, irrespective of stage, was independent of whether preoperative radiotherapy was administered or not, the origin of the metastases was likely from the primary tumor and not secondary to a local failure. Otherwise, a lower rate of late-occurring distant metastases would have been seen in the irradiated group.

It is well known that radiotherapy may cause both acute and late effects related to the total radiation dose and the normal tissue volumes irradiated. At a given dose, higher fraction doses cause potentially more problems. However, because the total dose in rectal cancer radiotherapy has been reduced to 20 to 25 Gy using 5-Gy fractions,
compared with total doses of 40 to 50 Gy using 1.8- to 2.0-Gy fractions, the reported toxicities do not fundamentally differ between these two schedules, with the exception of acute neurogenic pain, which is observed in more patients treated with 5-Gy fractions.\textsuperscript{14,27} The acute morbidity to the 5 × 5 Gy schedule administered with multiple beams, as in the SRCT and the TME trials, has usually been limited to delayed wound healing after an abdominoperineal resection.\textsuperscript{2,8,28,29} Increased postoperative mortality has only been seen when large tissue volumes were irradiated, as, for example, in the Stockholm I trial.\textsuperscript{30} A slight excess of non-colorectal cancer death during the first postoperative year, but not later, was seen when all randomized trials were analyzed together; however, this was largely driven by the Stockholm I trial. Of even greater concern than acute toxicity is late toxicity from radiation therapy. When the Uppsala trial (three beams) was analyzed after 10 years, it was not possible to detect any increase in late toxicity from preoperative radiotherapy (5 × 5 Gy) compared with surgery alone.\textsuperscript{31} In the SRCT, no increase in hospital admissions could be detected after a minimum of 8 years of follow-up.\textsuperscript{32} An update after 13 years is presently ongoing, revealing that, besides more admissions during the first 6 months as a result of the acute and subacute toxicities, there is no significant increase in late admissions, although a trend for this is seen for some abdominal diseases starting after approximately 8 years. There is also an almost two-fold increase in secondary malignancies (Birgisson et al, manuscript submitted for publication) seen both within/adjacent to the radiation beams and at distant sites. Impaired anal function has also been reported after 5 years from the SRCT, although this was considered of limited importance in light of the gains.\textsuperscript{33} Similar results have recently been found from the TME trial.\textsuperscript{34} In contrast to the limited late toxicity from 5 × 5 Gy seen when three or four beams were used, more late toxicity was reported from the Stockholm group using two beams and large tissue volumes.\textsuperscript{34}

We do not yet have a complete picture of the late consequences from pre- or postoperative radiotherapy in rectal cancer patients partly because follow-up times are not long enough. Furthermore, the knowledge we presently have is from treatments administered 10 to 15 years ago, as in the SRCT, and thus, techniques that are presently considered suboptimal were used. The knowledge from the 5 × 5 Gy schedule, as used in the SRCT, is that the adverse effects after a follow-up of up to 15 years do not counterbalance the beneficial gains, with long-term survival gains of approximately 10% and a lowering of the local recurrence rate from approximately 30% to approximately 10%. With improved staging and surgery, groups of patients with less advanced disease are at such a low risk of local failure without the additional radiotherapy that radiotherapy should not be administered, whereas groups of patients with locally more advanced disease will likely continue to have sufficient gains.

In the follow-up of the SRCT, we decided to analyze the outcome for the curatively treated patients only. Long-term results for this group, who were randomly assigned either to preoperative adjuvant radiotherapy or no radiotherapy, have been poorly described in the literature. The fairly large randomized study of the SRCT and the Swedish system with population-based health registries made it possible to follow-up the patients from the aspects of survival, local recurrence, and distant metastasis. Studies based on matching of several registers can always be questioned regarding reliability.\textsuperscript{35} Many possibilities of errors may accumulate in the process of establishing registries and also when extracting data from the registries.\textsuperscript{36,37} However, in this study, we used validated registries with an almost complete coverage of the Swedish population for follow-up. A validation of 30% of the medical records confirmed the usefulness of health registries in patients with a severe main diagnosis.\textsuperscript{36,37} In conclusion, preoperative adjuvant radiotherapy with 25 Gy in 1 week before curative surgery for rectal cancer has positive effects on overall and cancer-specific survival and on local recurrence rates after long-term follow-up, when the risk of further local recurrences in practice has disappeared.

**References**


