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ORIGINAL REPORT

Occurrence of Second Cancers in Patients Treated With Radiotherapy for Rectal Cancer

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ABSTRACT

Purpose
To analyze the occurrence of second cancers in patients with rectal cancer treated with external radiotherapy (RT) in addition to surgery.

Patients and Methods
The analyses were based on the Uppsala Trial (completed in 1985), with patients randomly assigned to preoperative RT to all stages or postoperative RT for stage II and III cancers, and the Swedish Rectal Cancer Trial (completed in 1990), with patients randomly assigned to preoperative RT or surgery alone. Patients from the trials were matched against the Swedish Cancer Registry.

Results
A total of 115 (7%) of the 1,599 patients developed 122 second cancers. More patients treated with RT developed a second cancer (relative risk [RR], 1.85; 95% CI, 1.23 to 2.78). A significant increased risk for second cancers in the RT group was seen in organs within or adjacent to the irradiated volume (RR, 2.04; 95% CI, 1.10 to 3.79) but not outside the irradiated volume (RR, 1.78; 95% CI, 0.97 to 3.27). For the Swedish Rectal Cancer Trial, 20.3% of the RT patients got either a local recurrence or a second cancer, compared with 30.7% of the non-RT patients (RR, 0.55; 95% CI, 0.44 to 0.70).

Conclusion
An increased risk of second cancers was found in patients treated with RT in addition to surgery for a rectal cancer, which was mainly explained by an increase in the risk of second cancers in organs within or adjacent to the irradiated volume. However, a favorable effect of radiation seemed to dominate, as shown by the reduced risk of the sum of local recurrences and second cancers.

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INTRODUCTION

Radiotherapy (RT) in addition to surgery for rectal cancer, as first described in 1959,[1] is beneficial in terms of a decreased incidence of local recurrences and improved survival, as based on several randomized trials performed mainly during the 1980s and summarized in systematic overviews.[2-5] Because of this evidence, RT is now considered a gold standard for treatment of many patients with rectal cancer. Additional studies have shown that preoperative administration of RT has a better effect on the local recurrence rate than postoperative RT.[4-7]

Although there is convincing evidence of the benefits of RT, they should be balanced against the adverse effects. Such adverse effects may be manifested during or immediately after the administration of RT (acute and subacute toxicity), but some may not appear until after several years (late toxicity). The acute and subacute toxicity is well described in the literature and includes skin, gastrointestinal, hematologic, and neurologic complaints. Late adverse effects of RT, on the other hand, are less well reported in

the literature, although such effects on urinary tract, skin, and gastrointestinal, vascular, and skeletal systems have been described.[6,8-10]

An important late adverse effect of RT is the occurrence of second cancers. Because an estimation of the risk for second cancers necessitates observation over a period of several decades, we have as yet only rudimentary knowledge about the risks after RT in addition to surgery for rectal cancer.[11] However, evaluations of results of RT given for other pelvic malignancies such as cancer of the prostate, testes, cervix, and uterus have supported the idea of an increased risk of second cancers among patients receiving RT.[12-17]

Two randomized trials from the 1980s, the Uppsala Trial[6] and the Swedish Rectal Cancer Trial (SRCT),[2] were analyzed with the aim to estimate the risk of second cancers. The primary hypothesis was that RT, given in addition to surgery for rectal cancer, increases the risk for second cancers in organs within or adjacent to the irradiated volume.

PATIENTS AND METHODS

In the Uppsala Trial, running from 1980 to 1985, 471 patients with operable rectal cancer were assigned randomly to preoperative RT 5 × 5 Gy to all stages or postoperative RT 30 × 2 Gy for stage II or III cancers (no postoperative RT for stage I). A three-portal technique was used to cover the entire dorsal pelvic cavity. Anteriorly, the beam limits included the dorsal parts of the urinary bladder and the prostate or the uterus and vagina. The upper beam limits were between L3 and L4, and the lower limits were below the anus, except in patients with high rectal cancer (> 10 cm from the anal verge), for which the limit was 4 cm above the anal verge.[18] The SRCT ran from 1987 to 1990 and comprises 1,147 patients with operable rectal cancer who were assigned randomly to preoperative RT 5 × 5 Gy or surgery alone. Three- or four-portal techniques were used, with the upper beam limits at mid-L4 and the lower limits below the anus.[19] Chemotherapy was not used in either of the two trials.

Data from the two trials were matched against the Swedish Cancer Register to obtain information about any new malignant tumor registered after the occurrence of the rectal cancer. The register has an almost 100% completeness for malignant tumors, and the unique Swedish personal identification number was used for the matching procedure.[20]

A second cancer was defined as any new cancer, other than rectal cancer, detected > 6 months after the day of surgery for the rectal cancer. Patients with a new cancer diagnosis within the first 6 months after inclusion in the trials were classified as having a synchronous cancer. Four patients were lost to follow-up and were censored at the date of the last clinical check-up.

The analyses were restricted to invasive carcinomas. Discrimination between a malignant and a benign neoplasm was based on the histological type documented in the cancer register.[21]

To prevent confounding with rectal cancer recurrence, patients in whom an adenocarcinoma developed, within 5 years from the diagnosis of the primary rectal cancer, in an organ known to be a common site of recurrence or metastasis (lungs and liver) but who were not previously registered as having recurrence were classified as having metastasis. If the origin and type of tumor were unclear during this selection procedure, the pathology report was re-evaluated.

In the analyses concerning development of second cancers from organs within or outside the irradiated volumes, small bowel and colon cancers were excluded. First, the small bowel and colon were both within and outside the irradiated volumes, and second, there is a well documented increased risk for synchronous as well as metachronous colon cancers after the occurrence of a rectal cancer.[22] The precise location of each skin and connective tissue cancer was ascertained to judge whether it had arisen within or adjacent to the irradiated volumes.

Seventeen patients in the SRCT and two patients in the Uppsala Trial who were assigned randomly to receive preoperative RT but did not receive this treatment were excluded from the analyses. Thus 1,130 patients in the SRCT and 469 in the Uppsala Trial remained for the present analyses. In the Uppsala Trial, patients randomly assigned to, but who did not receive, postoperative RT (stage I) were analyzed as nonirradiated. Irradiated patients in the Uppsala Trial were combined into one group.

A comparison of the total effect of RT on the increased risk of second cancer and the decreased risk of local recurrence was done for the SRCT. The Uppsala Trial was not analyzed in the same way, because there were only stadium I cancers in the nonirradiated group, and complete data on recurrence were only available after 5 years of follow-up.

The Ethics Committee of Uppsala University approved the study.

All analyses were calculated with Statistica software (Statsoft, Tulsa, OK). Actuarial life-table procedures were used to calculate person-years at risk, number of second cancers, and the cumulative proportion of second cancers in each group, whereas the log-rank method was used for tests of significance. Because overall survival differed between the groups, a competing risk analysis was done[23]; however, because this did not significantly modify the relations in the risk estimates between RT and non-RT patients, the results are not presented. Relative risks (RRs) were calculated with 95% CIs.[24] The stratified risk from both trials were calculated according to the Mantel-Haenszel estimation.[25]

RESULTS

After matching of the study population against the Swedish Cancer Registry, 156 patients were found to have a tumor diagnosis other than rectal cancer. Forty one of these patients were excluded: six patients diagnosed with synchronous cancer, 30 with benign or in situ tumors, three with distant metastases, one with local recurrence, and one with an unspecified gastrointestinal cancer without pathological verification. Thus, 115 patients with 122 new invasive cancer diagnoses were included in the analyses. The most common second cancers were cancers of the prostate, colon, and urinary bladder; the specific types and subgroups of second cancers are listed in Table 1.

The median age at diagnosis of the primary rectal cancer was 69 years, independent of the type of second cancer. Thirty seven (7.9%) of the 469 patients in the Uppsala Trial developed a second cancer, and the corresponding number

Table 1. Second Cancers Diagnosed in Patients With Rectal Cancer From the Uppsala Trial and the Swedish Rectal Cancer Trial Combined

Region	No.*
Head and neck region	5
Brain	2
Oral cavity	1
Thyroid	1
Eye	1
Upper gastrointestinal	14
Esophagus	3
Stomach	6
Duodenum	1
Liver	3
Pancreas	1
Small bowel	1
Colon	17
Lung	9
Skin and connective tissue	11
Within/adjacent to RT volume	1
Outside RT volume	10
Breast	9
Gynecological	8
Cervix	2
Uterus	6
Kidney	6
Prostate	21
Urinary bladder and ureter	12
Hematological	9
Acute myeloid leukemia	1
Chronic lymphocytic leukemia	1
Chronic myeloid leukemia	1
Essential thrombocytosis	1
Non-Hodgkin's lymphoma	3
Multiple myeloma	2

Abbreviation: RT, radiotherapy.
*Numbers refer to the numbers of second cancers.

for the 1,130 patients in the SRCT was 78 (6.9%) (RR, 0.88; 95% CI, 0.60 to 1.31). In the SRCT, five patients developed two second cancers, and one developed three. When all patients were compared, patients with more than one second cancer were only counted once. However, when the subgroups of second cancers were compared, all second cancers were taken into account. This was done to minimize the risk of underestimating the number of second cancers in each group.

When plotting the cumulative proportion of patients developing second cancers for each treatment arm, more second cancers occurred in the RT group in the SRCT ($P = .009$), with the difference starting after 7 to 8 years from the treatment of the primary cancer (Fig 1). For the Uppsala Trial the curves seem to diverge after 15 years, but this difference was not significant ($P = .2$; Fig 1). No difference in the cumulative proportion of second cancers was detected between patients irradiated preoperatively and postoperatively in the Uppsala Trial. Because of that and the few cases of second cancer in each group, all irradiated patients in the Uppsala Trial were combined into one group.

The overall RR of developing second cancers in irradiated patients was similar for both trials (1.87 for the Uppsala Trial and 1.84 for SRCT), but the increase was significant only for the SRCT (95% CI, 1.15 to 2.97), not for the Uppsala Trial (95% CI, 0.86 to 4.10). This resulted in an overall stratified risk of 1.85 (95% CI, 1.23 to 2.78; Table 2). Colon cancers in the SRCT was the only subgroup of second cancers that had a significant increase in the RR; however, there was a nonsignificantly reduced RR for colon cancers in RT patients in the Uppsala Trial, causing stratified results of nonsignificantly increased RR. One case of soft tissue sarcoma was identified; the patient received RT, but the tumor was located in the thorax region, outside of the irradiated target.

When the Uppsala Trial and the SRCT were studied separately, nonsignificant increases in RR for second cancers were seen when analyzing organs within or adjacent to and outside of irradiated volumes (Table 2). However, stratified analyses of the results from both trials showed significantly increased risk for second cancers in the irradiated patients occurring within or adjacent to irradiated volumes (RR, 2.04; 95% CI, 1.10 to 3.79) but only a trend for an increased risk outside the irradiated volumes (RR, 1.78; 95% CI, 0.97 to 3.27; Table 2).

There were no differences in the RR of a second cancer between TNM stages; however, when each TNM stage was analyzed separately, an increased risk of developing second cancers in irradiated patients was observed in patients with stage I tumors, a tendency in stage II, and no difference in stage III (Table 3).

The median interval between inclusion in the trials and diagnosis of the second cancer was 6.5 (range, 1 to 18) years. When the results were stratified by latency period, a significantly increased RR of second cancer in the RT groups was seen only in the time period of 5 to 10 years from the primary treatment (Table 3). The type of secondary cancers diagnosed did not differ between latency periods.

After 14 years of follow-up of the SRCT, local recurrence developed in 60 (10.8%) of 555 RT patients and in 152 (26.4%) of 575 patients in the surgery-only group (RR, 0.34; 95% CI, 0.25 to 0.46). A second cancer occurred in 53 (9.5%) RT patients and 25 (4.3%) non-RT patients. Hence, 20.3% of the RT patients got either a local recurrence or a second cancer, compared with 30.7% of the non-RT patients (RR, 0.55; 95% CI, 0.44 to 0.70).

DISCUSSION

In this analysis of the occurrence of second cancers in patients treated for rectal cancer, the risk of developing second cancers was almost doubled in patients treated with RT

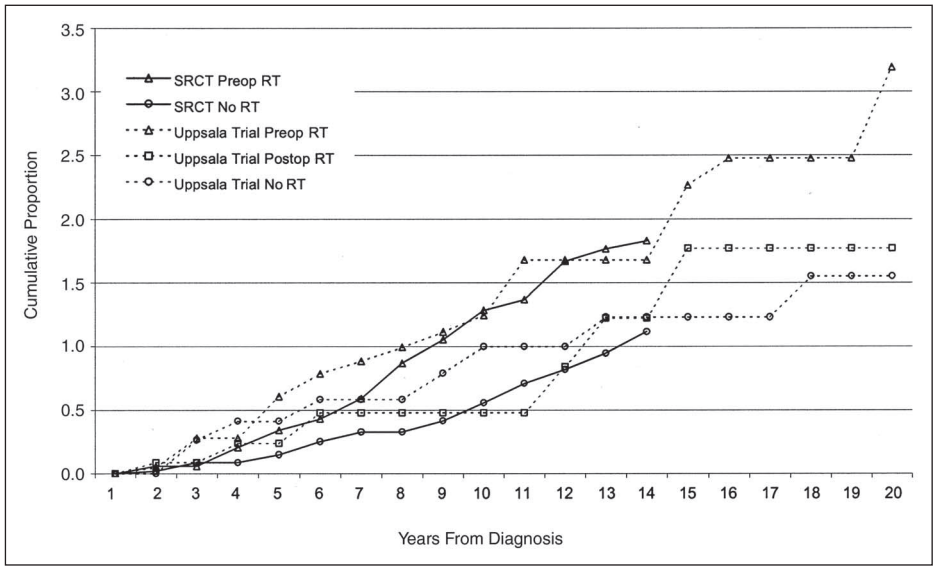

Fig 1. Cumulative proportion of patients treated for rectal cancer developing second cancers. Comparison between the radiotherapy (RT) groups of the Uppsala Trial and the Swedish Rectal Cancer Trial (SRCT) is shown. Abbreviations: Preop, preoperative; Postop, postoperative.

compared with those receiving no RT. This was mainly because of an increased risk for second cancers in organs within or adjacent to the irradiated volume, which was our a priori hypothesis, although a nonsignificantly increased risk of almost the same magnitude was seen also for second cancers in organs outside the irradiated volume.

To the best of our knowledge, this is the first study to address the question of the relationship between RT for rectal cancer and the development of second cancer. Patients with rectal cancer are generally much older than those with malignancies of the types previously investigated (eg, Hodgkin's lymphoma and testicular cancers[15,26]). Improved survival in rectal cancer during the past decades[27] and the addition of treatments other than surgery have made it important to analyze the occurrence of second cancers also in the rectal cancer group.

The increased risk for development of second cancers after RT has been known for many decades, with the first

Table 2. Relative Risks of Second Cancers in Patients Treated for Rectal Cancer in the Uppsala Trial and Swedish Rectal Cancer Trial: A Comparison Between Radiotherapy and No-Radiotherapy Groups

Subgroup of Second Cancer	Uppsala Trial				Swedish Rectal Cancer Trial				Stratified Risk	
	RT (pre/post), No.	No RT, No.	RR	95% CI	RT, No.	No RT, No.	RR	95% CI	RR	95% CI
Lung	3 (2:1)	0*			5	1	4.36	0.51 to 37.33		
Breast†	2 (2:0)	1	1.03	0.09 to 11.41	4	2	1.76	0.32 to 9.58		
Gynecologic†	0*	1			6	1	5.27	0.63 to 43.75		
Hematological	5 (5:0)	1	2.59	0.30 to 22.13	2	1	1.74	0.16 to 19.24		
Skin within RT volume	0*	0*			1	0*				
Skin outside RT volume	1 (0:1)	0*			4	5	0.70	0.19 to 2.59		
Head and neck	3 (2:1)	0*			1	1	0.89	0.05 to 13.95		
Kidney	1 (0:1)	0*			3	2	1.31	0.22 to 7.81		
Prostate‡	5 (5:0)	1	2.45	0.29 to 20.95	10	5	1.75	0.60 to 5.11		
Urinary bladder and ureter	2 (2:0)	0*			6	4	1.31	0.37 to 4.64		
Upper gastrointestinal	4 (3:1)	0*			6	4	1.31	0.37 to 4.64		
Small bowel	1 (1:0)	0*			0*	0*				
Colon	2 (1:1)	4	0.26	0.05 to 1.41	10	1	8.72	1.12 to 68.14	1.68	0.64 to 4.41
Overall	29 (23:6)	8	1.87	0.86 to 4.10	53	25	1.84	1.15 to 2.97	1.85	1.23 to 2.78
Within/adjacent to the RT volume§	13 (13:0)	3	2.24	0.64 to 7.86	25	11	1.98	0.97 to 4.02	2.04	1.10 to 3.79
Outside RT volume#	14 (9:5)	1	7.24	0.95 to 55.05	23	15	1.33	0.70 to 2.56	1.78	0.97 to 3.27

Abbreviations: RT, radiotherapy; No., number of second cancers; pre, preoperatively; post, postoperatively; RR, relative risk.
*RR was not calculated when no cases were present.
†Only females.
‡Only males.
§Gynecological, hematological, prostate, urinary bladder, ureteric cancer, and skin within RT volume.
#Lung, breast, head and neck, kidney, upper GI, and skin outside RT volume.

Table 3. Relative Risk of Second Cancers in Radiotherapy Versus No-Radiotherapy Patients With Rectal Cancer From the Uppsala Trial and Swedish Rectal Cancer Trial Combined

	No. of Second Cancers, RT:No RT	Person-Years at Risk, RT:No RT	RR	95% CI
Stage I	35:15	14,848:14,940	2.35	1.28 to 4.30
Stage II	31:9	14,126:7,836	1.91	0.91 to 4.01
Stage III	16:9	7,906:4,638	1.04	0.46 to 2.36
Years from primary treatment				
< 5	31:13	8,249:6,101	1.76	0.92 to 3.37
5-10	33:12	5,107:3,810	2.05	1.06 to 3.97
> 10	18:8	3,104:2,243	1.63	0.71 to 3.74

Note. Comparisons are made according to tumor stage and latency periods.
Abbreviations: RT, radiotherapy; RR, relative risk.

report in 1956 in patients treated with RT for benign gynecological diseases.[28] According to Travis,[26] second cancers account for approximately 15% of all cancers registered, including second cancers likely to be caused by radio- or chemotherapy. It is known that combined chemotherapy and RT has an additive effect on the occurrence of second cancers.[29] At the time of the present trials, chemotherapy had not been introduced as postoperative treatment for rectal cancer; however, palliative chemotherapy was used extensively. The results of this study are unlikely biased by chemotherapy, because the survival after noncurative surgery or after the diagnosis of a recurrence is generally short.

Studies on second cancers caused by RT for other pelvic malignancies than rectal cancer have been carried out. An increased risk for various types of second cancers has been found, such as acute myelogenic leukemia, malignant melanoma and cancer of the lung, genital organs, urinary bladder, connective tissue, stomach, colon, and rectum.[13,16,17] The present study confirms these results, because the increase in second cancers among those receiving RT could not be attributed to one or a few specific types of cancers. Although there was a significant increase only for second cancers in organs within or adjacent to the irradiated target, a clear trend for increased RR for second cancers in organs outside of the irradiated target in RT patients was seen. The explanation for this is not obvious, because the organs affected get quite low irradiation doses compared to the doses received by irradiated organs. Conceivably, radiobiological mechanisms underlying irradiation-induced second cancers are direct effects of the radiation beams traversing through normal tissues, or of intermediary radiation products, causing deletion, induction, or transcription of genes in cells that may later develop to a cancer.[11] Etiologic factors such as smoking, alcohol, and occupation may be of some relevance and can be part of the lifestyle or the environment.[26] The time interval from administration of RT to the occurrence of second cancers is thought to range from 4 to 15 or more years.[12] In a study of Hodgkin's lymphoma survivors, an apparent downturn in RRs was seen after 25 years.[30] However, an increased risk for second cancers has been observed > 30 years after RT in a study of patients with cervical cancer.[13] In this study, RT patients had the highest probability of developing a second cancer in the 5- to 10-year time period after treatment of the primary cancer.

The magnitude of the increased risk for second cancers, being close to 2, was similar to that seen in studies of irradiation to other cancer types.[15,16,29] The comparability of short-term RT with higher fraction doses (5 to 5.1 Gy), used in the present rectal cancer trials, to conventional RT with lower fractions doses (1.8 to 2.0 Gy) is not known. In the present study, the cumulative proportion of second cancers tended to be lower for the group receiving postoperative RT in the Uppsala Trial compared with those receiving preoperative RT, but the numbers at risk were small, and the patient groups were not comparable according to stage of disease; thus, it is difficult to make definitive conclusions.

The particularly increased risk in second cancers in RT patients with stage I disease is difficult to explain, but in a study on second cancers after RT for cervical cancer, patients with in situ cancer had a higher risk of developing second cancers than those with invasive cancers.[13] If the present results are true, it stresses the importance of selecting patients with rectal cancer for RT, weighting the benefits of reduced local recurrence against the increased risk of severe adverse effects such as second cancers. This is now done in most parts of Sweden, excluding patients with T1 and T2 tumors > 6 to 10 cm from the anal verge, because these tumors have a low risk of local recurrence after curative surgery with total mesorectal excision.

Although second cancers were more common in the RT group, the favorable effect of RT seemed to dominate, as shown by the reduced risk of local recurrences and second cancers together in the SRCT. Using the results of the present study to initiate a specific follow-up program for screening for second cancers is not yet recommended, because the absolute risk is still comparably low compared with the risk for local or distant recurrences, which should be the primary focus of the follow-up, at least during the first 5 to 8 years.

We conclude that RT increases the risk for second cancers in patients treated for cancer of the rectum and that awareness of the possibility of second cancers of all types should be heightened.

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Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following author or immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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