Original article

Impact of radiotherapy on local recurrence of rectal cancer in Norway

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Background: **The purpose of this study was to analyse the impact of radiotherapy on local recurrence of rectal cancer in Norway after the national implementation of total mesorectal excision (TME).**
Methods: **This was a prospective national cohort study of 4113 patients undergoing major resection of rectal carcinoma between November 1993 and December 2001.**
Results: **The proportion of patients who had radiotherapy before or after operation increased from 4·6 per cent in 1994 to 23·0 per cent in 2001. The cumulative 5-year local recurrence rate decreased from 16·2 to 10·7 per cent. Multivariable analysis showed that preoperative radiotherapy significantly reduced local recurrence (hazard ratio 0·59 (95 per cent confidence interval 0·39 to 0·87)). The use of preoperative radiotherapy in patients from a local hospital offering radiotherapy was 50 per cent higher than that for patients from a hospital without such services ($P = 0{\cdot}003$); cumulative 5-year local recurrence rates for these patients were 10·6 and 15·8 per cent respectively ($P < 0{\cdot}001$).**
Conclusion: **Following national implementation of TME for rectal cancer, increased use of preoperative radiotherapy appeared to reduce recurrence rates further.**

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Introduction

Reducing the local recurrence rate is a major challenge in rectal cancer treatment. The Norwegian Rectal Cancer Project, initiated in 1993, aimed at improving the outcome of patients with rectal cancer by nationwide implementation of total mesorectal excision (TME) as the standard resection technique[1]. Support for this strategy came from a study by Heald and Ryall[2], who reported a 4 per cent local recurrence rate after surgery alone. Similar results were also demonstrated in Norway by Bjerkeset and Edna[3].

In contrast to practice in other Scandinavian[4] and European[5] countries, there were no national guidelines for adjuvant radiotherapy in Norway until the mid-1990s. The intention of the registry study was to confirm that TME was the only treatment necessary to minimize local recurrence rates. Some centres even reduced their use of radiotherapy. In 1996 a publication from the Norwegian Gastrointestinal Cancer Group recommended combined chemotherapy and long-course preoperative radiotherapy (25 × 2 Gy) for patients with fixed, primarily irresectable rectal cancer[6]. From 1999, additional national guidelines recommended postoperative chemoradiotherapy following intraoperative perforation of the tumour or bowel wall, or when tumour growth was within 1 mm of the circumferential resection margin (CRM) for patients less than 75 years of age.

Several recent publications from the Norwegian Rectal Cancer Registry have demonstrated a reduction in local recurrence and survival benefit following the introduction of TME[1,7–9]. Although radiotherapy was included as a variable in some analyses, the group of patients who had radiotherapy in this national cohort has not yet been studied with respect to local recurrence, distant metastases and overall survival. The aim of this study was to analyse the impact of radiotherapy on local recurrence of rectal cancer in Norway.

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Patients and methods

This study was a part of the Norwegian Rectal Cancer Project, previously described in detail by Wibe *et al.*[1]. All new patients with rectal cancer have been registered prospectively in a national database, including patient, tumour and treatment characteristics.

Patient characteristics

Between November 1993 and December 2001 a total of 5888 patients with a tumour within 15 cm from the anal verge were added to the database. Patients with T1–4 tumours treated with major resection (5201 patients) and curative intent (R0 or R1 resection) (4500 patients) were selected. A total of 387 patients who did not have TME were excluded, giving a study population of 4113 patients. Major resection included: anterior resection (2612 patients, 63·5 per cent), abdominoperineal resection (APR) including 17 proctocolectomies (1226 patients, 29·8 per cent) or Hartmann's procedure (275 patients, 6·7 per cent).

During the study period, magnetic resonance imaging (MRI) was not used routinely, and the most common selection criterion for preoperative radiotherapy was clinical evaluation of tumour mobility. Computed tomography or ultrasonography was rarely used according to the registry data.

Norway has a population of 4·6 million, mainly rural, and rectal cancer surgery was performed in 50 hospitals during this interval. Six of these hospitals (university hospitals) had a radiotherapy department. The study population was divided into two groups: patients from local hospitals offering radiotherapy and the remainder from hospitals without such services. In Norway, most patients with suspected rectal cancer are referred to the local (closest) hospital, regardless of radiotherapy facilities.

The study population was analysed in annual groups according to year of operation to investigate annual variations in treatment and outcome. In the analyses of survival and metastasis, aggregated results from the first (November 1993 to December 1997) and second (January 1998 to December 2001) intervals were compared. When differences in the use of radiotherapy in high-volume hospitals were analysed, the Norwegian Radium Hospital was excluded because it is a highly specialized hospital for treatment of locally advanced tumours using high frequency of radiotherapy.

Definitions

Patient and treatment characteristics were collected from project-specific forms. Information on tumour differentiation, tumour node metastasis (TNM) stage[10] and residual tumour (R) stage were gathered from histopathology reports. R1 stage included specimens with a margin 0–1 mm from the tumour to the line of resection. A CRM of more than 1 mm was considered to be uninvolved (R0)[11].

Data on local recurrence and metastasis are monitored continuously by the Norwegian Rectal Cancer Registry. The national follow-up schedule is every 3 months for the first 2 years, then every 6 months for the next 3 years. None of the patients was lost to follow-up, which ended on 31 December 2003. The median follow-up time was 40 (range 0–123) months.

Local recurrence was defined as clinically or histopathologically verified recurrent disease in the pelvis, including the site of the bowel anastomosis and the perineal wound, and was retrieved from project-specific forms or the pathology departments' obligatory reports to the Norwegian Cancer Registry. Histopathological verification was available for more than 90 per cent of the reported recurrences. The rate of local recurrence was based on the sum of the patients who had isolated local recurrence and those with both local recurrence and distant metastasis.

Survival rates were given as overall (not cancer-specific) rates. The Norwegian Cause of Death Registry provided information on time of death. The date of operation was used as the start of follow-up, and endpoints were local recurrence or death regardless of cause.

Standard preoperative and postoperative radiotherapy treatment consisted of 25×2 Gy over 5 weeks. The interval between completion of preoperative radiotherapy and surgery was usually 4–6 weeks. A concomitant bolus of 5-fluorouracil–levamisole as a radiosensitizer was used together with postoperative radiotherapy. Chemotherapy was not part of the preoperative radiotherapy regimen, and only 19 patients received neoadjuvant chemotherapy.

Statistical analysis

Patient, tumour and treatment characteristics were described by frequency tables and compared using the Pearson χ^2 test. Local recurrence rates, distant metastases and overall survival were estimated by univariable Kaplan–Meier analyses and compared by the log rank test. Cox proportional hazards model was used to determine whether or not radiotherapy and radiotherapy service at the local hospital were independent prognostic factors. $P < 0.050$ was considered statistically significant. All analyses were performed using SPSS® version 11.5 (SPSS, Chicago, Illinois, USA).

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Results

Patient, tumour and treatment characteristics according to whether or not radiotherapy was given are shown in *Table 1* for 4113 patients, 2369 men (57·6 per cent) and 1744 women (42·4 per cent) who had a resection with curative intent. A total of 3736 patients (90·8 per cent) had no residual tumour after resection (R0 resection), whereas 377 patients (9·2 per cent) had microscopic residual tumour (R1). Preoperative radiotherapy was given to 285 patients (6·9 per cent) and postoperative radiotherapy to 229 patients (5·6 per cent). Some 45·1 per cent with advanced-stage non-metastatic rectal cancer (T4) did not undergo radiotherapy. The radiotherapy rate increased with both decreasing age and tumour level. Patients who had APR or Hartmann's procedure received radiotherapy three times more often than those who had anterior resection. The postoperative mortality rate after 30 days was 3 per cent, 3·2 per cent in non-irradiated patients and 1·4 per cent in irradiated patients ($P = 0·239$).

The total radiotherapy rate (preoperative and postoperative) increased from 4·6 per cent in 1994 to 23·0 per cent

Table 1 Patient and tumour characteristics of 4113 individuals treated with curative intent for rectal cancer within 15 cm of the anal verge according to radiotherapy use

	Preop. radiotherapy	Postop. radiotherapy	Total radiotherapy	No radiotherapy	*P*‡
No. of patients	285 (6·9)	229 (5·6)	514 (12·5)	3599 (87·5)	
Hospital caseload§					0·001
≥ 20 procedures	102 (6·3)	84 (5·2)	186 (11·5)	1428 (88·5)	
< 20 procedures	58 (2·5)	137 (5·9)	195 (8·4)	2139 (91·6)	
Age (years)					< 0·001
< 50	21 (9·4)	31 (13·8)	52 (23·2)	172 (76·8)	
50–64	90 (8·5)	75 (7·1)	165 (15·6)	891 (84·4)	
65–74	113 (8·2)	75 (5·5)	188 (13·7)	1184 (86·3)	
75–84	56 (4·5)	47 (3·7)	103 (8·2)	1151 (91·8)	
≥ 85	5 (2·4)	1 (0·5)	6 (2·9)	201 (97·1)	
Sex					0·001
M	192 (8·1)	138 (5·8)	330 (13·9)	2039 (86·1)	
F	93 (5·3)	91 (5·2)	184 (10·6)	1560 (89·4)	
Tumour stage (T)					< 0·001
1	6 (1·7)	4 (1·1)	10 (2·9)	340 (97·1)	
2	26 (2·4)	20 (1·8)	46 (4·2)	1037 (95·8)	
3	125 (5·3)	155 (6·6)	280 (11·9)	2074 (88·1)	
4	128 (39·0)	50 (15·2)	178 (54·3)	150 (45·7)	
Node status (N)					< 0·001
0	205 (7·6)	90 (3·3)	295 (10·9)	2404 (89·1)	
1	57 (5·9)	72 (7·4)	129 (13·3)	841 (86·7)	
2	23 (5·2)	67 (15·1)	90 (20·3)	354 (79·7)	
Dukes' stage					< 0·001
A	31 (2·6)	17 (1·4)	48 (4·0)	1138 (96·0)	
B	173 (11·4)	73 (4·8)	246 (16·3)	1265 (83·7)	
C	81 (5·7)	139 (9·8)	220 (15·5)	1196 (84·5)	
Tumour level (cm)*					< 0·001
12–15	31 (2·6)	43 (3·6)	74 (6·2)	1115 (93·8)	
6–11	129 (7·5)	83 (4·9)	212 (12·4)	1497 (87·6)	
0–5	125 (10·3)	103 (8·5)	228 (18·8)	987 (81·2)	
Type of resection					< 0·001
Anterior resection	101 (3·9)	94 (3·6)	195 (7·5)	2417 (92·5)	
APR	143 (11·6)	112 (9·1)	255 (20·8)	971 (79·2)	
Hartmann	41 (14·9)	23 (8·4)	64 (23·3)	211 (76·7)	
Perforation#					< 0·001
Yes	42 (11·4)	111 (30·1)	153 (41·5)	216 (58·5)	
No	195 (5·3)	115 (3·1)	310 (8·5)	3341 (91·5)	
CRM involved†					< 0·001
Yes	37 (16·5)	48 (21·4)	85 (37·9)	139 (62·1)	
No	171 (7·7)	117 (5·3)	288 (12·9)	1938 (87·1)	

Values in parentheses are percentages. *Distance from anal verge to distal margin of tumour. †Values missing for 1663 patients. APR, abdominoperineal resection; CRM, circumferential resection margin. ‡Total *versus* no radiotherapy (Pearson χ^2 test). §The Norwegian Radium Hospital was excluded in this analysis because it is a highly specialized hospital using a high frequency of radiotherapy. #Values missing for 93 patients.

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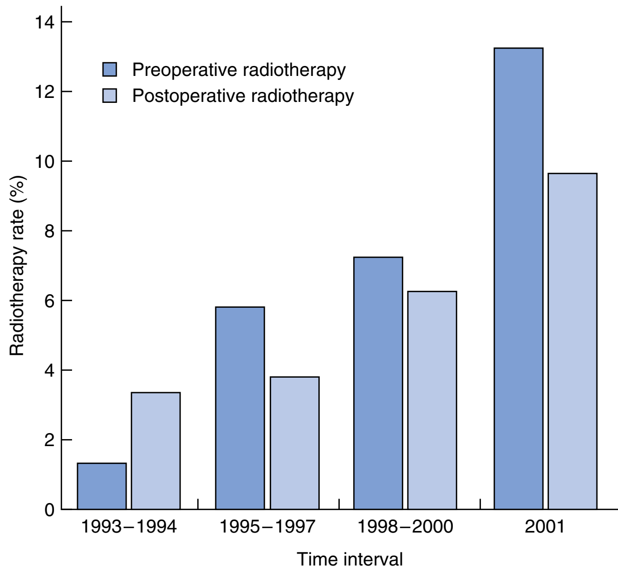

Fig. 1 Radiotherapy rate over time in 4113 patients treated with total mesorectal excision for rectal cancer

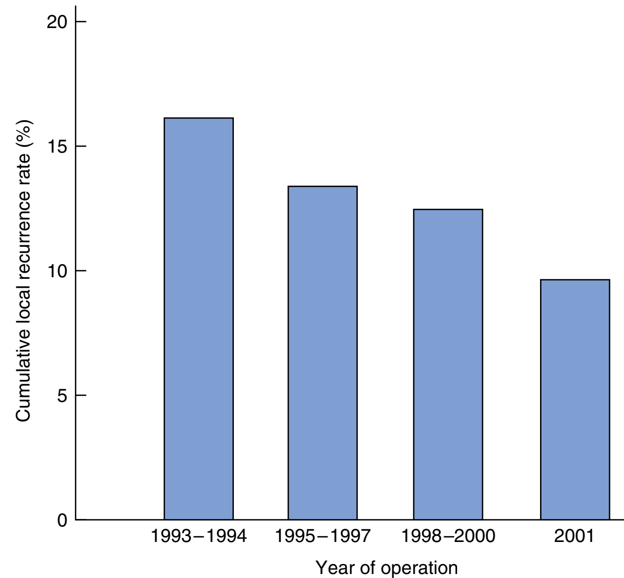

Fig. 2 Trend in 5-year cumulative recurrence rate, calculated by the Kaplan–Meier method, after total mesorectal excision in 4113 patients with rectal cancer

in 2001 (*Fig. 1*). During the same interval, the cumulative 5-year local recurrence rate decreased gradually from 16·2 to 10·7 per cent (*Fig. 2*). There was no significant difference between the early (November 1993 to December 1997) and late (January 1998 to December 2001) interval with regard to overall survival (59·9 and 62·4 per cent respectively; $P = 0{\cdot}193$), although there was a reduction in the 5-year cumulative rate of distant metastasis (26·4 *versus* 21·8 per cent; $P = 0{\cdot}007$). Preoperative radiotherapy was not a significant factor affecting this difference in multivariable analysis. The total radiotherapy rates in the early and late intervals were 8 and 16 per cent respectively.

In an analysis adjusted for age, sex, tumour level, perforation, preoperative and postoperative radiotherapy, T, N and R stage, preoperative radiotherapy significantly influenced the rate of local recurrence: hazard ratio 0·59 (95 per cent confidence interval (c.i.) 0·39 to 0·87) (3880 patients available for analysis). Multivariable analysis did not reveal any effect of postoperative radiotherapy on the rate of local recurrence: HR 0·82 (95 per cent c.i. 0·58 to 1·16).

The use of preoperative radiotherapy was higher for patients who had treatment in a local hospital with a radiotherapy department (11·6 *versus* 7·6 per cent; $P = 0{\cdot}003$). There was an independent association between treatment in a hospital with a radiotherapy unit and local recurrence rate, and this effect was significant even when adjusted for hospital caseload: HR 0·70 (95 per cent c.i. 0·56 to 0·89) (3769 patients in analysis). The cumulative local recurrence rate at 5 years was 10·6 per cent for patients with a radiotherapy unit in their local hospital compared with 15·8 per cent in the remainder ($P < 0{\cdot}001$) (*Fig. 3*).

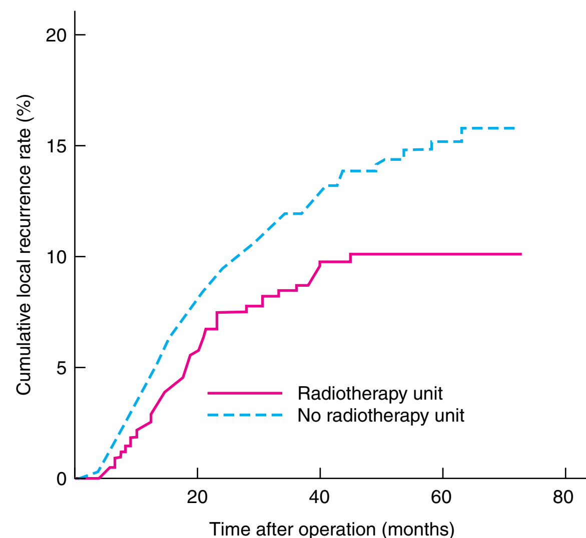

Fig. 3 Local recurrence after treatment for rectal cancer in 2184 patients according to whether the local hospital had a radiotherapy unit. $P < 0{\cdot}001$ (log rank test)

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Differences in the use of radiotherapy in high-volume institutions (seven hospitals each performing 20 or more major rectal resections per year) were also investigated. The four hospitals in this group with the lowest local recurrence rate had a higher radiation rate than the remaining three hospitals in which the recurrence rate was higher (10·4 *versus* 0·6 per cent; $P < 0{\cdot}001$). The rate of local recurrence was 8·9 and 16·7 per cent respectively in the two groups ($P < 0{\cdot}001$). The mean local recurrence rate in the high-volume hospitals was 12 per cent. Low-volume hospitals (43 hospitals that each performed fewer than 20 major rectal resections per year) used preoperative radiotherapy in 2·5 per cent of their patients and the mean local recurrence rate was 15·2 per cent.

Discussion

This study indicated that the decrease in local recurrence rates following TME for rectal cancer in Norway from 1993 to 2001 was associated with an increase in the use of preoperative radiotherapy in patients with advanced-stage disease. It also demonstrated that Norwegian patients treated in hospitals with radiotherapy services were more frequently offered radiotherapy and had lower local recurrence rates. Consequently, the previously described decrease in local recurrence rate in Norway may not be attributed entirely to improved surgical technique alone.

After the introduction of TME, the number of hospitals performing rectal cancer surgery in Norway decreased from 50 to 41. In addition, fewer surgeons perform operations for rectal cancer. These factors have contributed to the development of subspecialization in colorectal surgery in Norway. Several studies imply a beneficial outcome for patients with rectal cancer treated by specialists in colorectal surgery or surgical oncology[12–15]. Publications from Norway before introduction of the rectal cancer registry showed local recurrence rates of 21–32 per cent and a 5-year survival rate of 55 per cent[16,17].

After TME had been implemented in all hospitals performing rectal cancer surgery[9], there was a 50 per cent reduction in the local recurrence rate, and the 5-year survival rate improved from 55 to 71 per cent[9]. During these first years from 1993 to 1997, radiotherapy was seldom used, and deliberately reserved for locally advanced tumours. Only 8 per cent of the patients received preoperative or postoperative radiotherapy, so the effect of this treatment on the whole cohort in this first interval was limited. In the interval from 1998 to 2001, the use of radiotherapy doubled to 16 per cent, and the rate of local recurrence continued to decrease.

The present analysis revealed a 41 per cent reduction in the risk of local recurrence after preoperative radiotherapy, in accordance with several previous studies[17–21]. It could therefore be argued that preoperative radiotherapy contributed to the reduced risk of local recurrence following TME.

There was considerable variation in the use of adjuvant radiotherapy throughout Norway, especially before operation. The use of radiotherapy was 50 per cent higher in patients from an area served by a local hospital with a radiotherapy unit, and the local recurrence rate in these patients was significantly lower. Thus, access to treatment appeared to be of importance in prognosis. Other factors such as surgeon competence and quality of TME treatment could also have affected these results, but these data were not available. It is unlikely that surgeons in high-volume hospitals without a radiotherapy unit provided lower-quality work.

A gradual but persistent increase in the use of adjuvant radiotherapy for patients with rectal cancer was demonstrated from 1993 to 2001. However, a substantial number of patients who might have benefited from radiotherapy did not receive it. Given the variation in frequency of adjuvant radiotherapy and the change in rate over time, it is likely that this was due to preferences of individual surgeons or practice patterning from institutions.

Wibe *et al.*[7] published data showing that hospital caseload affected local recurrence and survival rates; low patient volumes were associated with increased recurrence and lower survival rates. However, some hospitals with large caseloads had high local recurrence rates, so volume on its own is no guarantee of favourable outcome.

A possible explanation why hospitals without a radiotherapy unit did not refer their patients on for radiotherapy could be concern about losing these patients. Given the variations in use of adjuvant radiotherapy by geographical location identified in this study and others[22], access to this potentially beneficial therapy could still be improved. Revised national guidelines from 2005 recommend preoperative chemoradiotherapy for patients with a CRM of 3 mm or less determined by preoperative MRI.

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