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Clinical Predictors for Reduced Long-Term Survival and Cause of Death after Curative Resection for Rectal Cancer

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Abstract

Purpose: To identify clinical predictors for reduced long-term survival and describe the cause of death after surgical treatment for rectal cancer. **Methods:** A retrospective follow-up study of 442 consecutive, unselected patients treated for rectal cancer at a tertiary centre from 1990 until 2000 and followed for 17 years or until death. Predictors for death were assessed by Cox regression analysis. The cause of death was obtained from the Norwegian Cause of Death Registry. **Results:** 254 men and 188 women with a median age of 71 years (21 - 95 years) were resected for rectal cancer with low anterior resection (n = 266), abdominoperineal resection (n = 125), Hartmann's procedure (n = 19) or diverting stoma only (n = 32). Median follow-up was 5 years (0 - 17 years). The relative five-year survival rates for stages I, II, III and IV was 83.9%, 65.2%, 41.1% and 9.3%, respectively. The proportion of deaths due to recurrence from colorectal cancer in stages I, II, III and IV was 23.5%, 55.8%, 72.3% and 98.0%, respectively. Heart, lung and cerebrovascular disease and other malignancies were the cause of death in the other patients. Higher age, abdominoperineal resection compared to low anterior resection, lack of lymph node dissection compared to total mesorectal excision (TME), postoperative reoperations, TNM stages II and III compared to stage I and residual tumours after surgery were all significant independent predictors of reduced survival in the adjusted Cox regression model. **Conclusions:** Age, tumour stage, type of surgery, lymph node dissection, residual tumour after surgery and reoperations are predictors for survival after surgery for rectal can-

cer. In the patients who died, the cause of death was due to a condition other than colorectal cancer recurrence in 32.3% of the patients. The five-year relative survival rate was related to tumour stage.

Keywords

Rectal Cancer, Predictors, Survival, Recurrence, Reoperation, Complication, Cause of Death

1. Introduction

Surgical resection is the cornerstone of rectal cancer treatment. Cancer recurrence occurs in about 30% of patients after curative resections [1] [2]. The tumour stage at surgery is the main predictor of long-term survival. Previous studies have identified several other factors associated with cancer recurrence and unfavourable outcomes. Patient factors such as cigarette smoking after surgery [3]; tumour factors like differentiation and vein, nerve and lymphatic ingrowth [4]; and molecular factors [5] have been shown to increase cancer recurrence rates and reduce life expectancy. Adjuvant oncological treatment is considered for these patients.

The present study was designed to determine the effect on survival of certain clinical factors obtained during the hospital stay—the effect of emergency resection, tumour perforation, blood transfusions, type of surgery, lymph node dissection and reoperation on survival—and examine their independent roles as predictors for long-term survival. So far, few studies have evaluated which of these potential factors are the best predictors of survival. Advances in preoperative evaluation, surgical techniques with laparoscopy and robots, individualised use of neo-adjuvant radio/chemotherapy, and better treatment of metastases have improved long-term results in recent years [6] [7] and [8]. The present study was performed in the time period 1990-2000, with standardised open surgery and little use of radiotherapy or chemotherapy. Thus, we could investigate the influence of clinical factors without the need to correct for a number of different treatment modalities.

We also aimed to determine life expectancy of the patients compared with the normal population and identify the cause of death of these patients. This information was provided by the Norwegian Cause of Death Registry [9], which is a registry of the cause of death of Norwegian citizens based on information from the doctor present at death who signed the death certificate, autopsies, information from the police or officials, and/or the Norwegian Cancer Registry [10].

2. Patients and Methods

A retrospective observation study of 442 consecutive patients surgically treated for rectal cancer was carried out at one tertiary centre from January 1990 until

January 2000, with a median follow-up time of 5 years (ranging from 0 - 17). Data were collected from patient records. Patients below 70 years of age were followed up at the hospital for five years with clinical evaluations, blood samples, chest x-rays, ultrasonography of the liver and/or CT scans of the thorax and abdomen according to Norwegian guidelines. In patients living more than five years after treatment, the cause of death was extracted from hospital files where the death was reported and from the Norwegian Cause of Death registry. The surgical procedure for all patients was open midline laparotomy in general anaesthesia. The surgical technique of tumour-resection, with precise dissection in the avascular "holy plane", including the mesorectum, was adopted during this period with a personal demonstration by Dr. Heald [11]. The operations were thus classified as a "no mesorectal excision" before the introduction or a "proximal (PME) or total (TME) mesorectal excision" after introduction of this technique. The use of preoperative radiotherapy (6.1%) and postoperative chemotherapy (5.6%) was limited, which implies an excellent opportunity to study the effects of surgery. Normal life expectancy for each year from 1990-2000 was determined using the Norwegian Statistical Agency [12]. From these data, a relative survival stratified by tumour stage was calculated and compared to relative death rates for rectal cancer published in reports from the national cancer registry. The study was approved by the Norwegian Ethics Committee.

Statistics

Baseline demographic and clinical characteristics of patients were presented as means and standard deviations (SD), medians (minimum-maximum), or as frequencies and percentages, as appropriate. Continuous and categorical variables for the whole dataset of the 442 patients were compared between those alive and dead at the end of the observation period using the Independent samples t-test and the χ^2-test, respectively. Kaplan-Meyer survival plots and log rank test were used to compare the cumulative survival rate between the patient groups. Unadjusted and adjusted Cox proportional hazard regression models were estimated to assess predictors of unfavourable long-term outcome death. Cases where the tumour was not removed and cases with at least one missing value on considered predictors were excluded from the regression analyses, leaving 373 cases. Proportional hazard assumption and multicollinearity were assessed by standard statistical tests. For regression analyses, all types of reoperations were coded as Yes or No to obtain a sufficient number of cases.

All tests were two-sided, and the results with p-values below 0.05 were considered statistically significant. The analyses were performed in SPSS v26.

3. Results

The demographic and clinical characteristics of all 442 patients are shown in Table 1. 182 (41.2%) patients had no comorbidity, whereas the others suffered from cardiovascular (n = 165 (37.3%)), pulmonary (n = 16 (3.6%)), both (n = 6

(1.4%)) or other (n = 73 (16.5%)) diseases. Emergency surgery was performed in 31 patients (7%) due to obstruction or perforation. In 52 patients, the technique was unknown and deemed non-conformant to department standards. Perforation of tumour occurred in 35 (7.9%) patients, preoperative in 20 patients (4.5%) and perioperative in 15 (3.4%) patients. The number of surgeons performing the operations was 35, seven of whom executed more than 20 resections. These surgeons performed 314 (71%) of the operations. Operation time was 145 minutes (18 - 440 minutes), with bleeding of 500 ml (0 - 6000 ml), preoperative blood transfusion of 0 units (0 - 27 units), perioperative fluid transfusions of 6300 ml (500 - 16,415 ml) and a body temperature of 35.8˚C (33.5˚C - 38.6˚C) at the end of the operation. 41 (9.3%) patients needed reoperations. Anastomotic leakage after low anterior resections occurred in 20 (7.5%) of 266 patients. The other 21 reoperations were due to wound rupture in four (0.9%), bowel obstruction in four (0.9%), bleeding in seven (1.6%), intra-abdominal abscess in two (0.5%) and stoma revision in four (0.9%) patients.

Tumour characteristics are shown in Table 2. The cancers were staged by the 7th edition of the American Joint Committee on Cancer (AJCC). Pre- and per-operative metastases were found in 70 (15.8%) patients: 41 (9.3%) in the liver, 4 (0.9%) in the lung, 9 (2.0%) in the peritoneum, 14 (3.2%) in a combination of organs and 2 (0.4%) in other categories. Metastases were not resected during surgery for rectal cancer, leaving residual tumours in these patients. Surgery for metastases, either present at surgery or recurrence detected by follow-up, was performed in 58 patients: liver (n = 28), lung (n = 10), peritoneum (n = 3), lymph nodes (axilla, supraclavicular fossa) (n = 2), ovary (n = 1), local recurrence (n = 10) and anastomotic recurrence (n = 5).

Table 1. Baseline characteristics of 442 patients surgically treated for rectal cancer.

	All	Alive at the end of observation	p[1]
Age (years)			<0.001[2]
Mean (SD)	68.7 (11.6)	64.3 (11.9)	
Median (min-max)	71 (21 - 95)	66 (31 - 87)	
Gender			0.065
Male	254 (57.5)	76 (29.9)	
Female	188 (42.5)	72 (38.3)	
Comorbidity			0.064
No	182 (41.2)	70 (38.5)	
Yes	260 (58.8)	78 (30.0)	
Mode of presentation			0.004
Emergency	31 (7)	3 (9.7)	
Elective	411 (93)	145 (35.3)	

Continued

Tumour location in the rectum			0.152
Upper 1/3	163 (36.9)	60 (36.8)	
Middle 1/3	158 (35.7)	56 (35.4)	
Lower 1/3	121 (27.4)	32 (26.4)	
Type of surgery			<0.001
Hartmann's procedure	19 (4.3)	5 (26.3)	
Low anterior resection	266 (60.2)	111 (41.7)	
Abdominoperineal resection	125 (28.3)	32 (25.6)	
Deviating stoma only	32 (7.2)	0 0	
Tumour fixated to surroundings			<0.001
No	369 (83.5)	138 (37.4)	
Yes	73 (16.5)	10 (13.7)	
Lymph node dissection			<0.001
No mesorectal excision	134 (30.3)	33 (24.6)	
Proximal mesorectal excision (PME)	69 (15.6)	26 (37.6)	
Total mesorectal excision (TME)	155 (35.1)	71 (45.8)	
Not specified	52 (11.8)	18 (34.6)	
Tumour not removed	32 (7.2)	0 0	
Tumour perforation			0.004
No perforation	407 (92.1)	144 (35.4)	
Pre/perioperative	35 (7.9)	4 (11.4)	
Radicality			0.000
No residual tumor	355 (80.3)	144 (40.6)	
Residual tumor/metastases	87 (19.7)	4 (4.6)	
Blood transfusion			<0.001
No	279 (64.1)	111 (39.8)	
Yes	156 (35.9)	35 (22.4)	
Reoperation			0.019
No	401 (90.7)	141 (35.2)	
Yes	41 (9.3)	7 (17.1)	
Results at discharge from hospital			
Alive	430 (97.3)		
Dead	12 (2.7)		

Values are frequencies and percentages unless otherwise indicated. [1]p-value comparing alive and dead at the end of observation for χ^2-test unless otherwise indicated; [2]p-value for Independent samples t-test.

Table 2. Tumour characteristics of 442 patients surgically treated for rectal cancer.

	All	Alive at the end of observation	p[1]
Tumour type			0.038
Ulcerative	245 (55.4)	78(31.8)	
Vegetative	107 (24.2)	44 (41.1)	
Mixed	43 (9.7)	18 (41.9)	
Stricture	23 (5.2)	4 (17.4)	
Unknown	24 (5.4)	4 (16.7)	
Tumour stage			<0.001
Stage I	83 (18.8)	49 (59.0)	
Stage II	160 (36.2)	65 (40.6)	
Stage III	113 (25.6)	30 (26.5)	
Stage IV	54 (12.2)	4 (7.4)	
Tumour not removed	32 (7.2)	0 (0)	
Serosal ingrowth			0.050
No	276 (62.4)	104 (37.7)	
Ingrowth	140 (31.7)	38 (27.1)	
Unknown	26 (5.9)	6 (23.1)	

Values are frequencies and percentages. [1]p-value comparing alive and dead at the end of observation for χ^2-test.

The median distance from the tumour to the anal verge was 9 cm (2 - 16 cm). Median resection margins were 8 mm (0 - 100 mm). The median tumour diameter was 45 mm (10 - 170 mm), the number of lymph nodes measured was 5 (0 - 22), the number of lymph nodes with metastases was 0 (0 - 17) and the percentage of lymph nodes with metastases was 0 (0% - 100%). The tumour differentiation was classified as high in 69 patients (15.6%), medium in 258 (58.4), low in 20 (4.5%) and unknown in 76 (17.2%).

The impact of tumour stage and postoperative reoperations on survival is illustrated in **Figure 1** and **Figure 2**, respectively. The results of the Cox multiple regression analyses in the 373 patents are shown in **Table 3**. Higher age, emergency surgery, abdominoperineal resection compared to low anterior resection, fixated tumour, lack of lymph node dissection compared to TME, perforation, stage, serosal involvement, presence of residual tumour, reoperation and blood transfusion were all significant for unfavourable outcomes in the unadjusted analyses. In the adjusted model, higher age, abdominoperineal compared to low anterior resection, lack of lymph node dissection compared to TME, tumour stages II and III compared to stage I and residual tumour remained significant predictors of death.

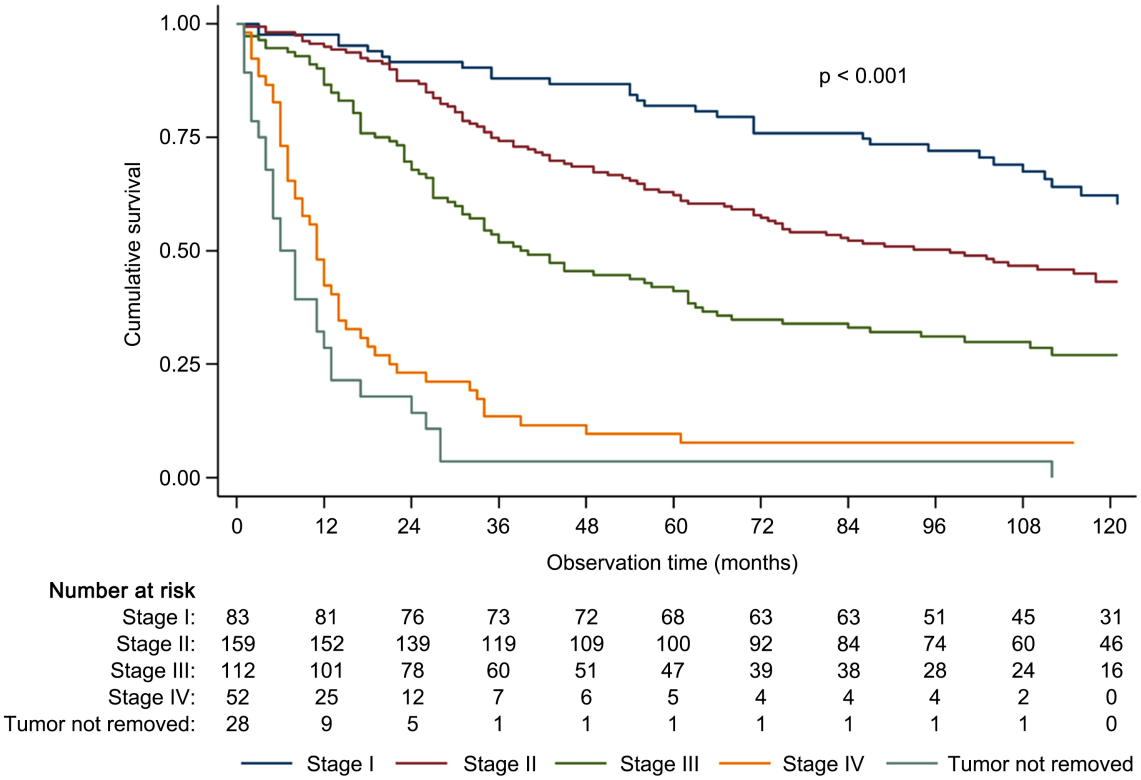

Figure 1. Impact of tumour stage on survival after surgical treatment of rectal cancer.

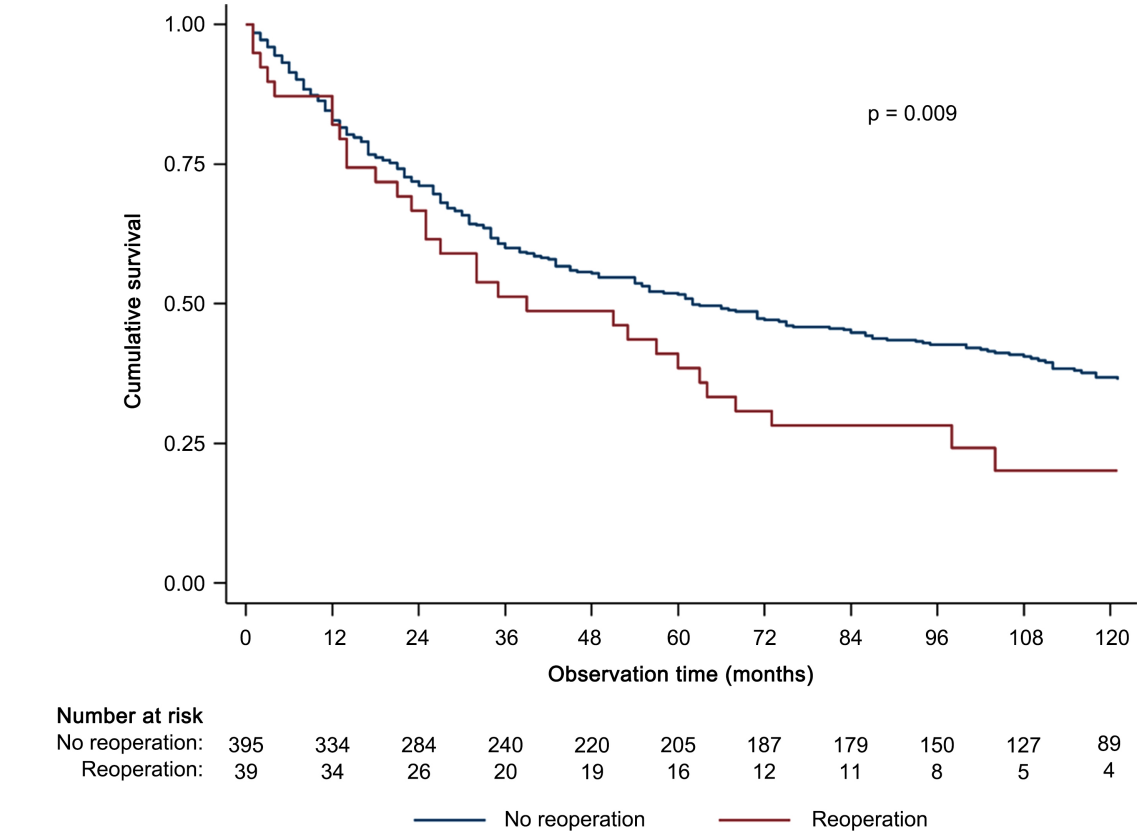

Figure 2. Impact of reoperations on survival after surgical treatment of rectal cancer.

Table 3. Results of Cox regression analyses of survival in patients surgically treated for rectal cancer (n = 373).

Covariate	Unadjusted model		Adjusted model	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.03 (1.02; 1.05)	**<0.001**	1.04 (1.03; 1.06)	**<0.001**
Gender				
Male-ref.	1		1	
Female	0.78 (0.60; 1.01)	0.058	0.87 (0.66; 1.15)	0.321
Comorbidity				
No-ref.	1		1	
Yes	1.29 (0.99; 1.68)	0.062	1.16 (0.86; 1.55)	0.332
Mode of presentation				
Emergency	2.18 (1.19; 3.99)	**0.012**	1.62 (0.83; 3.17)	0.161
Planned-ref.	1		1	
Type of surgery				
Hartmann	1.05 (0.59; 1.88)	0.870	0.58 (0.30; 1.14)	0.112
Low Anterior Resection	0.71 (0.54; 0.93)	**0.013**	0.65 (0.47; 0.91)	**0.011**
Abdominoperineal res.-ref.	1		1	
Tumour fixation				
No-ref.	1		1	
Yes	1.55 (1.04; 2.32)	**0.032**	1.20 (0.74; 1.92)	0.462
Lymph node dissection				
No mesorectal excision-ref.	1		1	
PME	0.84 (0.58; 1.22)	0.356	0.92 (0.61; 1.41)	0.714
TME	0.64 (0.47; 0.87)	**0.004**	0.69 (0.50; 0.95)	**0.024**
Unknown	0.82 (0.54; 1.26)	0.369	0.91 (0.58; 1.44)	0.685
Perforation				
No perforation	1		1	
Pre/perioperative perforation	1.96 (1.27; 3.01)	**0.002**	1.22 (0.76; 1.96)	0.407
TNM-stage				
Stage I-ref.	1		1	
Stage II	1.69 (1.13; 2.52)	**0.010**	1.55 (1.00; 2.40)	**0.049**
Stage III	2.91 (1.93; 4.40)	**<0.001**	2.95 (1.87; 4.67)	**<0.001**
Stage IV	9.19 (5.76; 14.67)	**<0.001**	1.23 (0.14; 10.77)	0.851

Continued

Tumour type				
Ulcerative	1		1	
Vegetative	0.85 (0.63; 1.15)	0.292	0.88 (0.64; 1.23)	0.462
Mixed	0.87 (0.56; 1.35)	0.542	0.97 (0.61; 1.53)	0.886
Stricture	1.02 (0.50; 2.07)	0.967	1.22 (0.56; 2.64)	0.621
Serosal involvement				
No-ref.	1		1	
Yes	1.42 (1.09; 1.85)	**0.011**	0.90 (0.66; 1.22)	0.498
Radicality				
No residual tumor-ref.	1		1	
Residual tumor	5.22 (3.71; 7.35)	**<0.001**	12.30 (1.48; 102.61)	**0.020**
Reoperation				
No-ref.	1		1	
Reoperation	1.77 (1.21; 2.60)	**0.004**	1.70 (1.12; 2.57)	**0.013**
Perioperative blood transfusion				
No-ref.	1		1	
Yes	1.63 (1.26; 2.11)	**<0.001**	1.31 (0.96; 1.78)	0.088

The cause of death during the observation period stratified according to stage is shown in Table 4. 294 of the 442 patients died during the observation period. In 95 (32.3%) patients, the cause of death was due to a condition other than colorectal cancer and highly dependent on tumour stage. In lower stages, more patients died from other causes than recurrence from colorectal cancer. Details concerning the cause of death in the other malignancy and others categories presented in Table 4 are the following:

Malignancy other than colorectal cancer (other malignancy): Stage I: pancreas (n = 1), stomach (n = 1), breast (n = 1), prostate (n = 3), kidney (n = 1), urinary bladder (n = 2), leukaemia (n = 1). Stage II lung (n = 1), melanoma (n = 1), breast (n = 1), prostate (n = 2), urinary bladder (n = 2). Stage III: stomach (n = 1), anal (n = 1), bone (n = 1), breast (n = 1), leukaemia (n = 1). Stage IV: brain (n = 1). Not removed: leukaemia (n = 1), bowel disease not specified (n = 1).

Others: Stage I: sarcoidosis (n = 1), acute cholecystitis (n = 1), aortic dissection (n = 1), bone fracture (n = 1). Stage II: diabetic coma (n = 1), mors subita (n = 1), liver cirrhosis (n = 1), unknown (n = 4). Stage III: sepsis (n = 1), arteriosclerosis (n = 1), ruptured aortic aneurysm (n = 1), renal failure. (n = 1), unknown (n = 1). Stage IV: Not removed: pneumonia (n = 1)

The relative one- and five-year survival rates stratified by stage are presented in Table 5.

Table 4. The cause of death in 442 patients surgically treated for rectal cancer according to stage.

	Stage I n = 83	Stage II n = 160	Stage III n = 113	Stage IV n = 54	Tumour not removed n = 32
Colorectal cancer	8 (23.5)	53 (55.8)	60 (72.3)	49 (98.0)	29 (90.1)
Other malignancy	10 (29.4)	7 (7.4)	5 (6.0)	1 (2.0)	2 (6.2)
Heart disease	9 (26.5)	8 (8.4)	6 (7.2)	0 (0)	0 (0)
Cerebral disease	2 (5.9)	12 (12.6)	4 (4.8)	0 (0)	0 (0)
Lung disease	1 (2.9)	8 (8.4)	3 (3.6)	0 (0)	1 (3.1)
Others	4 (11.8)	7 (7.4)	5 (6.0)	0 (0)	0 (0)
All deaths	34 (100)	95 (100)	83 (100)	50 (100)	32 (100)

Values are frequencies and percentages.

Table 5. One- and five-year relative survival rates of 410* patients surgically treated for rectal cancer stratified on stage and gender.

	1-year relative survival rates			5-year relative survival rates		
	Male	Female	All	Male	Female	All
Stage I	98.1	96.8	97.6	79.9	90.3	83.9
Stage II	92.2	97.1	94.4	65.9	64.3	65.2
Stage III	83.6	88.5	85.8	34.4	49.0	41.1
Stage IV	47.1	30.0	40.7	11.8	5.0	9.3
All			85.6			54.7

*Patients with irresectable tumours were excluded (TNM staging not possible).

4. Discussion

In the present study, we identified four independent predictors for unfavourable outcomes after rectal cancer surgery corrected for age, gender and stage. These predictors are type of surgery (abdominoperineal vs. low anterior resections), lymph node dissections (lack of dissection vs TME), residual tumours after surgery and reoperations.

The importance of surgical method, which also depends on the preference and expertise of the surgeon, is in line with other studies from this period, where abdominoperineal resection was associated with up to a 50% higher probability of local recurrence and unfavourable outcomes compared to anterior resections [13]. Results of abdominoperineal resections have improved since then, and studies have now shown comparable results between these techniques, with low recurrence rates and similar life expectancy [14].

The importance of correct dissection of the mesorectum and, thereby, lymph node dissection was introduced during these years [11] [15]; it is now considered

to be the gold standard in rectal cancer surgery [16]. The present study supports the superiority of this technique. Total mesorectal resection (TME) is used for tumours in the lower rectum to decrease local recurrence rates [11] [17]. In tumours in the upper third of the rectum, division of the mesorectum with proximal mesorectal excision (PME) may be performed with the same favourable results as TME [18].

The presence of residual tumours and/or metastases after surgery predicted an unfavourable outcome. Oncological and surgical treatments were seldom used during this period. This has changed markedly during the last decades, improving outcomes for these patients.

The impact on oncological outcomes of reoperations after rectal surgery is under discussion. In the present study, reoperation was identified as an independent predictor of reduced overall survival. The reoperation rate of 9.3% was similar to other studies, reporting reoperation rates of 5% - 10% after rectal cancer surgery and leak rates in colorectal and colo-anal anastomoses of 5% - 19% [19] [20]. In a previous study, reoperation after surgery for colorectal cancer was associated with increased frequency of cancer recurrence [21]. This is also supported by studies from Kulu *et al.* and Ptok *et al.*, reporting an increase in recurrence rate and reduced survival rate in patients with anastomotic leaks after curative resection for rectal cancer [22] [23]. A meta-analysis of 11,353 patients also supports this view, reporting increased local recurrence rates and reduced overall and cancer-specific survival rates but not an increase in distant metastases [24]. These findings should not, however, discourage the surgeon to perform a reoperation if indicated. Prevention of complication is the key factor, by optimal preparation of the patient before surgery, and meticulous performance by experienced surgeons during surgery. Furthermore, Sabrina et al. did not find any unfavourable oncological effect from anastomotic leaks in a study on rectal cancer operations with an 11% leak rate [25]. A study by a Spanish rectal cancer project supports this view, concluding that anastomotic leaks do not affect oncological outcomes [26].

Several other factors of interest did not significantly influence long-term survival. Comorbidity, emergency surgery, tumour fixation, perforation, tumour type, serosal involvement and blood transfusion were not deemed to be independent predictors of reduced long-term survival. While our finding regarding comorbidity is surprising, it is supported by a study of 621 rectal cancer patients over 65 years, where comorbidity was not a significant predictor of survival [27].

Emergency surgery due to obstruction, perforation or bleeding has been shown to give inferior oncological results and life expectancy compared to planned surgery [28]. A contributing factor for this is that emergency surgery is often performed during afternoon/night shifts or weekends and by a high number of different surgeons, which has been shown to give inferior results [29]. The present study did not support this finding. Despite a high number of different surgeons and the likelihood of working night shifts on a regular basis, emergency surgery

was not followed by an increased risk of death in the present study.

Perforation of the bowel during rectal cancer resection has been shown to increase the local recurrence rates and decrease life expectancy [30] [31]. Serosal involvement has also been shown to predict pelvic recurrences and inferior prognosis [32] [33]. However, our study did not support these findings.

Reports on the effect of perioperative blood transfusions on oncological outcomes and survival are conflicting. The need for blood transfusions varies from 25% - 50% in different studies [34] [35]. In one study with 24,230 patients, 29% of whom received blood transfusions, perioperative blood transfusions were associated with lower survival rates after colon cancer resections [34]. In a tertiary centre, 21.4% of 1423 patients resected for colonic cancer received blood transfusions. In this study, blood transfusions were associated with comorbidity and serious illness but not recurrence rates [36]. In another single-centre study on 309 patients with stage III colon cancers, 47.9% received blood transfusions, which did not significantly reduce the rate of survival. The authors concluded that the clinical circumstances, not the blood transfusions, reduced the chances for survival [35]. This is supported by other studies [37] and in line with our study. In our study, 35.9% of the patients received blood transfusions, which did not increase the risk of death.

The relative survival rates obtained in the present study are similar to the national relative survival rates published by the Norwegian Cancer Registry for this period [10]. However, results are improving. In a study of 885 patients operated for rectal cancer from 2002-2011, 10 years after our cohort, patients with stage I rectal cancer were curable, exhibiting the same life expectancy as the normal population. The authors also stated that the cause of death was due to a condition other than recurrence from colorectal cancer in about half of the patients who died [38]. This is supported by our study, as the cause of death was not colorectal cancer in 32.3% of the patients, though strongly dependent on stage.

5. Strengths and Weaknesses

The present study consists of a complete patient sample of ten years from one tertiary centre, with long-term follow-up by the same investigators. We also present reliable data of cause of death retrieved from the Norwegian Cause of Death Registry.

The weaknesses of the study are the retrospective method. This is a limitation concerning performance of lymph-node dissection. Lymphadenectomy is performed depending on the clinical situation, which is not apparent from the clinical records. There are also some missing values.

6. Conclusion

Age, tumour stage, type of surgery, lymph node dissection, residual tumour after surgery and reoperations are significant predictors for survival after surgery for rectal cancer. The five-year relative survival rate is closely related to tumour

stage. In 32.3% of the patients, the cause of death was due to a condition other than colorectal cancer recurrence.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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