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Cause of Death and Clinical Predictors of Survival after Curative Resection for Colon Cancer

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Abstract

Background: Clinical predictors of death and survival in surgical treatment of colon cancer are easily confounded by the modern adjuvant and neo-adjuvant chemotherapy. This study focuses on lethality and survival during implementation of ultra-radical surgery for colonic cancer prior to multimodal therapy. **Methods:** Retrospective observational follow-up study of 824 consecutive, unselected patients resected for Stage I, II, III and IV colon cancer from 1990 until 2000 at one tertiary centre, with a median follow-up of 45 months (0 - 202 months). Predictors for death were assessed by Cox regression analyses and log-rank test. The cause of death was obtained from the Norwegian Cause of Death Registry. **Results:** The relative survival rates were 86.3%, 71.9%, 50.3% and 6.6% in Stage I, II, III and IV, respectively. In 28.7% of the patients, the cause of death was other than colorectal cancer recurrence. The adjusted Cox regression model showed that higher age (1.04 (95% CI: 1.03; 1.05)), male gender (1.37 (1.14; 1.66)), emergency surgery (1.52 (1.21; 1.93)), left vs. right hemicolectomy (1.39 (1.03; 1.87)), and perioperative blood transfusion (1.25 (1.01; 1.55)) were predictors of reduced survival. Health without known comorbidity (0.71 (0.58; 0.88)), D2 versus D1 lymph node dissection (0.66 (0.53; 0.83)) and tumour Stage I, II, III versus Stage IV 0.10 (0.06; 0.16), 0.14 (0.11; 0.19), 0.23 (0.18; 0.30) were associated with prolonged survival. **Conclusions:** In 28.7% of the patients, the cause of death was other than colorectal cancer recurrence. Age, sex, comorbidity, emergency resection, lack of lymph node dissection, tumour stage, and preoperative blood trans-

fusions are all significant predictors for reduced survival after surgery for colon cancer.

Keywords

Colon Cancer, Predictors for Survival, Emergency Surgery, Lymph Node Dissection, Blood Transfusion

1. Introduction

Colonic cancer is the third most common cancer in Norway and is diagnosed at a median age of 73 years. Incidence rates have been increasing for the last 50 years and have reached 54.5 (males) and 50.7 (females) per 100,000 person-years. Screening programs have been advocated to reduce the incidence rates. The mortality rates per 100,000 person-years are 23.9 and 19.5 for males and females, respectively [1]. Cancer recurrence is the main cause of death after curative treatment of colon cancer. Tumour stage at surgery is the main prognostic factor for survival. Previous studies have described a number of additional factors identified during the hospital stay that influence survival. Factors such as smoking and alcohol abuse reduce life expectancy [2]. General health at the time of surgery, the expertise and technique of the surgeon [3], and biologic [4] and molecular characteristics [5] of the cancer have been shown to influence life expectancy after surgery. These studies often focus on one factor of interest only. The aim of the present study was to examine whether the following parameters assessed simultaneously were independent predictors of survival: emergency resection, tumour perforation, type of resection, lymph node dissection, tumour fixation to local organs, blood transfusions, serosa involvement and postoperative complications in need of reoperation. So far, few studies have evaluated which of these parameters are independent predictors for survival. The study was performed during a 10-year period from 1990 till 2000, in which open surgery was performed on all patients, with limited use of adjuvant or palliative chemotherapy. Therefore, analyses are well suited to assess the effect of surgery alone since there is no need for adjustment for different regimes of chemotherapy or novel surgical techniques. The cause of death was obtained from the Norwegian Cause of Death Registry [6].

2. Patients and Methods

This series of 824 consecutive patients represents all patients operated for colonic cancer over a 10-year period between January 1990 and January 2000 at a tertiary referral centre in Norway. During this period, total mesocolic resection was introduced as a method for resection of colonic cancer. However, all surgeons did not adhere to this principle. Systematic adjuvant chemotherapy was not implemented in this period. Patients were registered prospectively in the

hospital's patient information and management systems and in the operations registration system. Both systems were searched with separate and combined queries for diagnosis and surgical procedures. Patient records of all identified patients were reviewed, and those diagnosed or operated on for cancer in the ascending, transverse, descending and sigmoid colon were included. The patient's records were reviewed systematically. Demographic information and information on comorbidity, stage of disease, surgical risk stratification, operation reports and postoperative course, as well as time and location of recurrences, were registered. Patients were followed until closure of the study or time of death. The data were entered into different predefined systematic schemes. The importance of lymph node dissection was realized during this time period, and complete D2-lymph node dissection was adopted. D3-lymph node dissection was not performed. Operation reports were reviewed several times and independently by two of the surgeons according to predefined criteria. The procedures were deemed with a complete D2-lymph node dissection when all D2 stations were removed as proven by entering into the D3-lymph node regions of the different resections (right, left, and sigmoid resections). Cases with insufficient information in the operation reports for definitive classification were classified as "unknown".

The patients were followed up according to the Norwegian guidelines, with regular blood-samples (carcinoembryonic antigen/CEA), chest x-rays, ultrasound and/ or CT scans and coloscopy for five years or until death in patients below 70 years old. Thereafter, a final follow-up with regard to survival was performed in 2006. Thus, all living patients had a minimal observation time of five years. The median observation time for all patients was 45 months (0 - 202 months). Surgery was performed under general anaesthesia by open technique through a midline incision in all patients, either as planned daytime surgery or emergency surgery by surgeons on call during nightshifts or weekends. Ileocecal resection was performed in some patients with a tumour located in the cecum. Otherwise, cancers in the cecum, right colon and right 2/3 part of the transverse colon were treated with right/extended hemicolectomy. In some cases, according to the surgeon's preference, transverse resection was performed in cancers located in the transverse colon. In cancers in the left colon and sigmoid colon, left hemicolectomy and resection of colon sigmoid was performed, respectively. Hartmann's procedure was performed in some emergency situations as well as in patients with comorbidity with increased risk of anastomotic leakage. Subtotal colectomy was performed in patients with left-sided colon obstruction, where the circulation of the dilated proximal colon was judged insufficient.

In patients where the tumour was adherent to surrounding organs, the surgeon decided whether the adherence was caused by benign inflammation or malignant tumour invasion. Inflammatory adherences were dissected, whereas in locally advanced tumours, the adherent organs were either partly or completely resected to achieve R0-resection, or the tumour was not removed and an internal

bypass or deviating stoma was performed. The colon cancers were classified according to the American Joint Committee on Cancer (AJCC, 7th edition). Blood transfusions were given as packed red blood cells of 250 ml (one unit).

In this time period, adjuvant or palliative chemotherapy was used in 56 (8.6%) patients; 53 of them received 5-fluorouracil and leukovorin, two received Campto, and one was unknown. The cause of death was obtained from the Norwegian Cause of Death Registry. Survival rates for the normal Norwegian population were obtained from the Central Bureau of Statistics, Norway [7]; thus, relative one- and five-year survival rates could be calculated.

3. Statistics

Demographic and clinical characteristics of patients at baseline were presented as means and standard deviations (SD), medians (minimum-maximum), or as frequencies and percentages, as appropriate. Independent samples t-test and χ^2-test were used to compare continuous and categorical variables, respectively, between those alive and those dead at the end of the observation period. Kaplan-Meyer survival plots and log-rank test were used, respectively, to illustrate and compare the cumulative survival between the patient groups. Unadjusted and adjusted Cox proportional-hazards regression models were estimated to assess predictors of unfavourable long-term outcome and death. Cases where the tumour was not removed (n = 39) and cases with at least one missing value (n = 64) on considered predictors were excluded from the regression analyses, leaving 721 cases for regression analysis. Proportional-hazard assumption and possible multicollinearity issues were assessed by standard statistical tests. All types of reoperations and perforations were coded "Yes" or "No" for regression analyses 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.

4. Results

A total of 824 patients were identified and included in the study. Demographic and surgical characteristics are presented in Table 1. Of the patients, 505 (61.3%) patients with comorbidity suffered from cardiovascular (n = 330/40.0%), pulmonary (n = 37/4.5%), renal (n = 5/0.6%), combinations of these (n = 13/1.6%) and other (n = 120/14.6%) diseases. Emergency surgery was performed in 229/27.8%) of the patients due to obstruction, perforation or bleeding from the tumour. The tumours were located in the cecum (n = 163/19.8%), right colon (n = 226/27.4%), transverse colon (n = 76/9.2%), left colon (n = 94/11.4%) and sigmoid colon (n = 265/32.2%).

In 150 (18.2%) patients, the tumour was adherent to the neighbouring organ. In 80 (9.7%) of these, malignant invasion into a neighbouring organ was diagnosed, and resection of small bowel (n = 33/4.0%), ovary (n = 14/1.7%), part of duodenal wall (n = 7/0.8%), urinary bladder wall (n = 5/0.6%), tail of pancreas

Table 1. Demographic and surgical characteristics of 824 patients surgically treated for colon cancer.

	All n = 824	Alive at the end of observation n = 277	p-value[1]
Age mean ± SD	71.3 ± 11.6	67.1 ± 11.3	<0.001[2]
Gender			
Male	377 (45.8)	109 (28.9)	0.009
Female	447 (54.2)	168 (37.6)	
Comorbidity			
None	310 (37.6)	132 (42.6)	<0.001
Disease	505 (61.3)	145 (28.7)	
Unknown	9 (1.1)	0	
Indication			
Planned	595 (72.2)	230 (38.7)	<0.001
Emergency	229 (27.8)	47 (20.5)	
Type of surgery			
Ileocecal resection	12 (1.5)	2 (16.7)	
Right hemicolectomy	406 (49.3)	154 (37.9)	
Transversum resection	25 (3.0)	6 (24.0)	
Left hemicolectomy	106 (12.9)	40 (37.7)	<0.001
Sigmoid resection	187 (22.8)	57 (30.5)	
Hartmann's procedure	25 (3.0)	5 (20.0)	
Subtotal colectomy	24 (2.8)	13 (54.1)	
Internal bypass/ diverting stoma	39 (4.7)	0	
Tumour adherent to surroundings			
No	674 (81.8)	242 (35.9)	0.003
Yes	150 (18.2)	35 (23.3)	
Lymph node dissection			
D1-resection	350 (42.5)	83 (23.7)	
D2-resection	330 (40.0)	150 (45.5)	<0.001
Unknown	105 (12.7)	44 (41.9)	
Tumour not removed	39 (4.7)	0	
Perforation tumour			
No	743 (90.2)	255 (34.3)	0.196
Perforation	81 (9.8)	22 (28.9)	
Blood transfusion			
No	608 (73.8)	220 (36.2)	0.015
Yes	195 (23.7)	52 (26.7)	
Unknown	21 (3.5)	5 (23.8)	
Reoperation			
No	763 (92.6)	264 (34.6)	0.034
Reoperation	61 (7.4)	13 (21.3)	

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.

(n = 4/0.5%), spleen (n = 4/0.5%), part of stomach (n = 2/0.2%), liver (n = 2/0.2%), diaphragm (n = 2/0.2%), left kidney (n = 1/0.1%), gall bladder (n = 1/0.1%), uterus (n = 1/0.1%), abdominal wall (n = 1/0.1%), and ureter (n = 1 /0.1%) were included in the colon resection to obtain a R0-resection. 350 (42.5%) patients were resected without attention to central lymph node removal and were termed D1 dissection. In 330 (40.0%) patients, a dissection and removal of the central lymph nodes was performed as a D2-resection. In 105 (12.7%) patients, lymph node dissection was not possible to classify. Perforation of colon occurred

in 81 (9.8%) patients, pre- and peroperatively in 76 (94%) and 5 (6%) cases, respectively. One hundred ninety-five (23.7%) patients received blood transfusions during surgery. In resected patients, 176 (21.4%) had metastases located in the liver (n = 130/15.8%)), lung (n = 16/(1.9%), peritoneum (63/7.6%), adrenal gland (n = 1/0.1%), bone (n = 2/0.2%) and ovary (n = 1/0.1%). Surgery for metastases was performed in 28 patients (16.0%), only 18 (10.0%) with an R0-resection on liver (n = 16), lung (n = 1) and small bowel (n = 1).

Postoperative complications occurred in 247 patients (30.0%). The most frequent were infection (n = 130/15.8%) (pneumonia, urinary infection, wound infection, intra-abdominal abscess, septicaemia), cardiovascular complications (n = 25/3.0%), thrombo-embolism (n = 9/1.1%). 62 (7.5%) of the patients needed reoperation after surgery. Reoperation due to anastomotic leak was performed in 19/744 (2.6%) patients with anastomosis, which occurred in five (1.2%) patients after right colectomy, one (1.4%) after transverse resection, five (4.7%) after left colectomy, seven (3.3%) after sigmoid resection and one (4.2%) after subtotal colectomy and ileo-sigmoidostomy. Other causes for reoperation were wound rupture (n = 16 /1.9%), bowel obstruction (n = 11/1.3%) and bleeding (n = 6/0.7%). Ten other patients (1%) were reoperated for gauze pads left behind during surgery, intra-abdominal abscess, colonic necrosis, pressure wound, arterial embolus in a leg, synchronous cancer detected, revision of colostomy, second look due to suspicion of anastomotic leak (no leak detected), reposition of a hip prosthesis luxation and revision of colostomy with splenectomy.

Tumour stage and serosa involvement are shown in Table 2. There were few early cancers in this series of patients. Stage II dominated, with a number of patients similar to the cumulative number of Stage III and Stage IV cancers. In 39 (4.7%) patients, the tumour was not removed, and classification was not possible. In patients where the tumour was removed and TNM-classification was possible; the stage was classified as either Stage I (55 (6.7%)), Stage II (364 (44.2%)), Stage III (190 (23.1%)) or Stage IV (176 (21.4%)). Hospital stay was nine days (1 - 119 days), hospital mortality was 43 (5.2%), 30-day mortality was 36 (4.4%) and 90-day mortality was 81 (9.8%).

Table 2. Tumour characteristics in 824 patients operated for colon cancer.

	All n = 824	Alive at the end of observation n = 277	p-value[1]
Serosal involvement			
No	434 (52.7)	161 (37.1)	0.170
Yes	337 (40.9)	109 (32.3)	
Unknown	53 (6.4)	7 (13.2)	
Tumour stage			
Stage I	55 (6.7)	33 (60.0)	<0.001
Stage II	364 (44.2)	173 (47.5)	
Stage III	190 (23.1)	65 (34.2)	
Stage IV	176 (21.4)	6 (3.4)	
Tumour not removed	39 (4.7)	0	

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

Factors expected to affect long-term survival were analysed in a Cox model (Table 3). Patient factors all associated with increased risk of death included higher age (RR: 1.04, 95% CI: 1.03 - 1.05), male sex (1.37, 1.14 - 1.66), a clinical situation requiring emergency surgery (1.52, 1.21 - 1.93) and a higher stage. Absence of comorbidity (0.71, 0.58 - 0.88) was the only beneficial asset. Figure 1 illustrates the stunning results of emergency versus planned surgical treatment on long-term survival, which is well-noticed even 10 years later.

Table 3. Results from regression analyses, Cox model in 721 patients.

Covariate	Unadjusted model		Adjusted model	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.03 (1.02; 1.04)	**<0.001**	1.04 (1.03; 1.05)	**<0.001**
Gender				
Male	1.32 (1.10; 1.59)	**0.003**	1.37 (1.14; 1.66)	**0.001**
Female-ref.	1		1	
Comorbidity				
None	0.70 (0.57; 0.85)	**<0.001**	0.71 (0.58; 0.88)	**0.002**
Comorbidity	1		1	
Indication				
Emergency	1.71 (1.40; 2.09)	**<0.001**	1.52 (1.21; 1.93)	**<0.001**
Planned-ref.	1		1	
Type of surgery				
Right hemicolectomy-ref.	1		1	
Ileocecal resection	2.55 (1.31; 4.97)	**0.006**	1.45 (0.73; 2.89)	0.288
Transversum resection	1.89 (1.18; 3.02)	**0.008**	1.43 (0.87; 2.36)	0.156
Left hemicolectomy	0.96 (0.72; 1.28)	0.781	1.39 (1.03; 1.87)	**0.031**
Sigmoid resection	1.14 (0.91; 1.43)	0.263	1.17 (0.92; 1.48)	0.201
Hartmann's procedure	1.84 (1.11; 3.06)	**0.018**	1.39 (0.80; 2.42)	0.242
Subtotal colectomy	0.70 (0.36; 1.35)	0.284	0.76 (0.38; 1.52)	0.438
Tumour adherence				
No-ref.	1		1	
Yes	1.29 (0.996; 1.66)	0.054	1.30 (0.98; 1.74)	0.070
Lymph node dissection				
D1-ref.	1		1	
D2	0.48 (0.40; 0.59)	**<0.001**	0.66 (0.53; 0.83)	**<0.001**
Unknown	0.51 (0.37; 0.69)	**<0.001**	0.78 (0.56; 1.07)	0.124
TNM-stage				
Stage I-ref.	0.11 (0.07; 0.17)	**<0.001**	0.10 (0.06; 0.16)	**<0.001**
Stage II	0.15 (0.12; 0.19)	**<0.001**	0.14 (0.11; 0.19)	**<0.001**
Stage III	0.23 (0.17; 0.29)	**<0.001**	0.23 (0.18; 0.30)	**<0.001**
Stage IV	1		1	
Tumour perforation				
No perforation-ref.	1		1	
Pre/per-op perforation	1.10 (0.79; 1.52)	0.586	0.81 (0.55; 1.19)	0.277
Blood transfusion				
No-ref.	1		1	
Yes	1.48 (1.20; 1.82)	**<0.011**	1.25 (1.01; 1.55)	**0.044**
Serosal involvement				
No-ref.	1		1	
Yes	1.19 (0.99; 1.43)	0.069	1.03 (0.82; 1.29)	0.802
Reoperation				
No-ref.	1		1	
Reoperation	1.81 (1.32; 2.48)	**<0.001**	1.35 (0.96; 1.89)	0.081

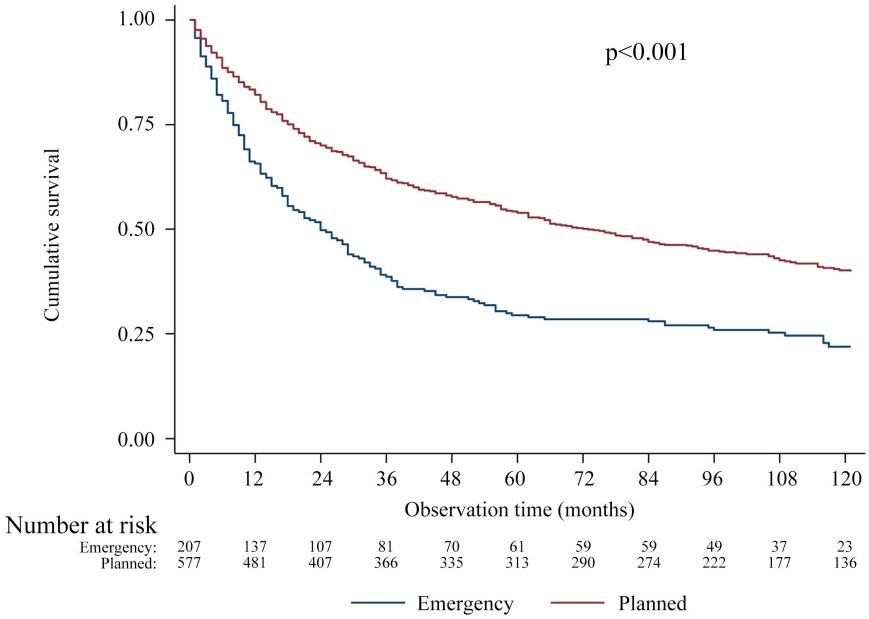

Figure 1. Effect of emergency versus planned surgical treatment on long-term survival after surgical resection for colon cancer in 824 patients.

Among treatment factors, extended lymph node dissection (RR: 0.66, 95% CI: 0.53 - 0.83) improved significantly long-term survival. When lymph node dissection was deemed unknown, survival data took on an intermediate position between D2 and limited lymph node dissection (**Figure 2**). The observed difference was also noticed in the unadjusted Cox model (RR 0.51, 0.37; 0.69) but not in the adjusted model (**Table 3**).

Interventions that required blood transfusion (1.25, 1.01 - 1.55) reduced survival of colonic cancer. This effect is pronounced and remains a lasting issue for years to come (**Figure 3**).

Limited resections of the ileocecal area (2.55, 1.31 - 4.97), transverse colon (1.89, 1.18 - 3.02), and the Hartman type of resections (1.84, 1.11 - 3.06), as well as procedures necessitating a reoperation (1.81, 1.32 - 2.48) were all significantly associated with reduced overall survival in the unadjusted model. However, only left hemicolectomy (1.39, 1.03 - 1.87) was significantly associated with reduced survival in the adjusted model.

Death was strongly associated with stage of disease as demonstrated in **Figure 4**. Most patients died within a year and very few survived more than two years if the tumour could not be removed, and approximately 75% of patients with a Stage IV disease died within two years of surgery in this time period.

Of the 547 patients who died during the observation period, 157 (28.7%) died from causes other than colon cancer recurrence (**Table 4**). These rates were strongly associated with stage. The cause of death other than colorectal cancer in Stage I, Stage II, Stage III, Stage IV and in patients where the tumour was not removed was 72.7%, 55.0%, 24.8%, 1.2% and 7.3%, respectively. In Stages I and II, the deaths from other causes outnumbered colon cancer deaths. Details of the

category "other malignancy" include Stage I: malignant melanoma (n = 1); Stage II: cancer in stomach (n = 1), pancreas (n = 1), lung (n = 1), breast (n = 3), prostate gland (n = 6), urinary bladder (n = 1), brain (n = 1), B-cell-lymphoma (n = 1); Stage III: cancer in urinary bladder (n = 1), prostate (n = 1). Details of others include Stage I: sudden death (n = 1), gram-negative septicaemia (n = 1), liver cirrhosis (n = 1), unknown (n = 4); Stage II: myelodysplastic syndrome (n = 1), amyotrophic lateral sclerosis (ALS) (n = 1), epilepsy (n = 1), acute peritonitis (n = 1), found dead (n = 5), sequela tuberculosis (n = 2), non-specific infection (n = 1), diabetes mellitus (n = 2), amyloidosis (n = 1), dehydration (n = 1), polyneuropathy (n = 2), diverticulitis (n = 1), arterial hypertension (n = 1), lymphedema (n = 2), renal failure (n = 3), sudden death (n = 3), unknown (n = 2), bone fracture (n = 1), trauma (n = 1); Stage III: urinary septicaemia (n = 2), diabetes mellitus (n = 1), dementia (n = 1), found dead (n = 1), unknown (n = 2), bone fracture (n = 1).

The one- and five-year overall relative survival rates were 77.4% and 53.1%, respectively, and were also strongly dependent on stage (Table 5).

5. Discussion

This study was set out to find which prognostic factors that independently influenced the long term outcome after surgical treatment of colon cancer, during a time period where surgery was standardized, and the only treatment option. The main findings were that higher age, male sex, comorbidity, emergency surgery, left hemicolectomy, and perioperative blood transfusions were independent predictors for reduced long term survival. As in all malignant diseases, tumour stage is a main prognostic factor for survival. D2 lymphnode dissection predicted better long term survival compared to D1-resections.

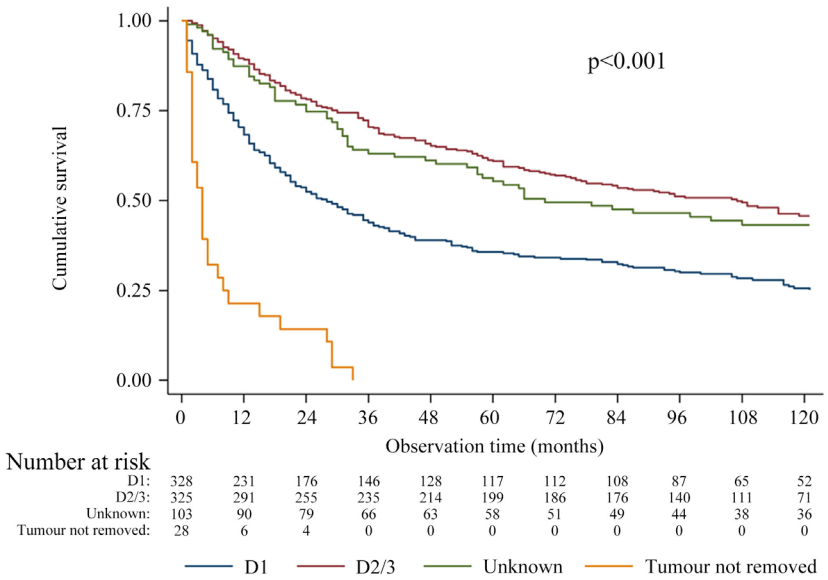

Figure 2. Effect of lymph node dissection during surgical treatment for long-term survival after surgical resection for colon cancer in 824 patients.

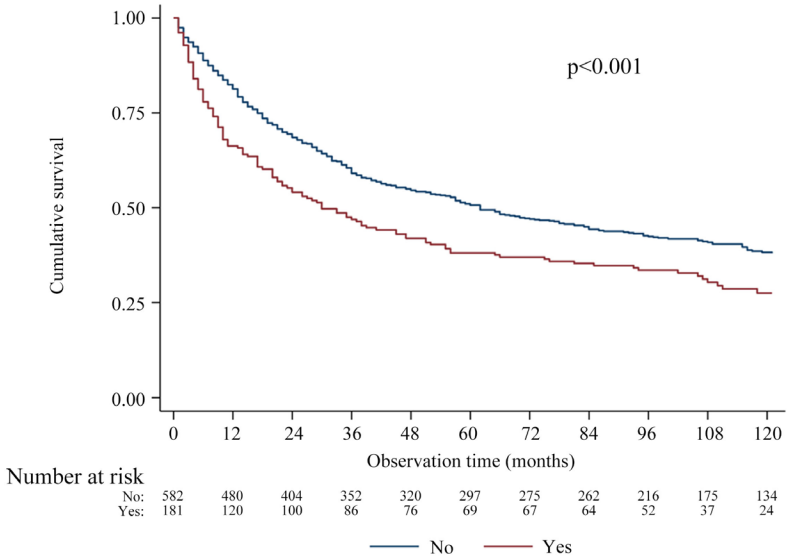

Figure 3. Effect of blood transfusion during surgical treatment for long-term survival after surgical resection for colon cancer in 824 patients.

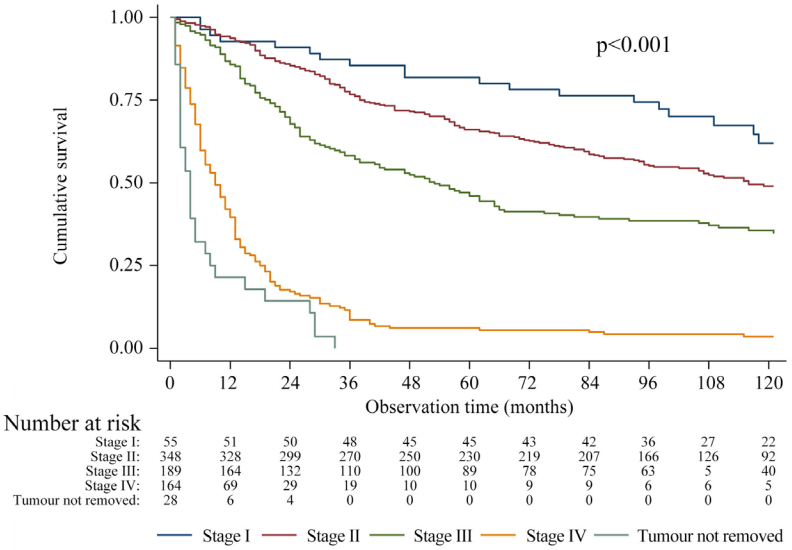

Figure 4. Effect of tumour stage on long-term survival after surgical resection for colon cancer in 824 patients.

Table 4. Cause of death during long-term follow-up after surgery for colon cancer according to tumour stage (n = 824).

	Stage I n = 55	Stage II n = 364	Stage III n = 190	Stage IV n = 176	Tumour not removed n = 39
Colon cancer	6 (27.3)	86 (45.0)	94 (75.2)	168 (98.8)	36 (92.3)
Other malignancy	1 (4.5)	15 (7.9)	2 (1.6)	0	0
Cardiovascular	3 (13.6)	34 (17.8)	9 (7.2)	2 (1.2)	1 (2.6)
Cerebral disease	5 (22.7)	16 (8.4)	5 (4.0)	0	1 (2.6)
Lung disease	0	8 (4.1)	7 (5.6)	0	1 (2.6)
Others	7 (31.9)	32 (16.8)	8 (6.4)	0	0
All deaths	22 (100)	191 (100)	125 (100)	170 (100)	39 (100)

Values are frequencies and percentages unless otherwise indicated.

Table 5. One- and five-year relative survival rates after surgery for colon cancer stratified for stage and gender.

	1-year relative survival rates			5-year relative survival rates		
	Male	Female	Total	Male	Female	Total
Stage I	86.2	100.0	92.6	74.1	100.0	86.3
Stage II	86.8	90.8	89.1	70.6	72.8	71.9
Stage III	82.4	90.3	86.8	48.5	51.6	50.3
Stage IV	34.2	41.5	37.9	2.7	10.2	6.6
All			77.4			53.1

Patients with higher age or comorbidity may thus present a dilemma with regard to active surgical or oncological treatment. The question is whether active treatment will give any overall benefit to the patient, as life expectancy at an advanced age is low, and many die from causes other than colon cancer [8]. These considerations may lead to selective treatment. Hayes *et al.* showed that age is a major factor in treatment decisions in their hospital, and many patients are not offered surgery due to old age [9]. As a consequence, geriatric evaluations of older patients should be performed, to evaluate their fitness for surgery. Patient groups called "frail" and "non-frail" older patients have been defined, and studies have shown that fragility is as important as tumour stage for one- and five-year survival: 80% versus 92% and 24% versus 66% in frail- and non-frail older patients, respectively [10]. Quality of life in the remaining years should also be considered. In a study of patients above 80 years operated on for colon cancer, quality of life at three months was improved after surgery in the surviving patients and the frail patients [11]. Some kind of selection of geriatric patients for active treatment seems reasonable, as well as preoperative prehabilitation.

Male sex was associated with inferior long-term survival compared with females, which is in accordance with the Cancer Registry of Norway [1]. In a prospective register study with a hypothesis of different biology and treatment of males and females, Gaitonde *et al.* described more right-side and earlier T-stage cancers in females than males. This did not, however, translate into better recurrence-free or overall survival rates [12]. Most patients resected for Stages I and II colon cancer are cured, and the difference in life expectancy in these patients will be similar to the normal Norwegian population, where females have a longer life expectancy than males regardless of age [7].

Emergency surgery was associated with reduced long-term survival. Previous studies have also shown a 10% - 15% increase in perioperative morbidity and mortality rates after emergency surgery compared to planned treatment [13] [14]. In the emergency situation, the patient's preoperative state is generally worse compared to patients with planned surgery. During emergency surgery, the main focus is on saving the patient's life and having a short time in general anaesthesia, and there is less focus on, for example, extended lymph node dissection. More procedures are performed on nightshifts and weekends, which is associated with higher mortality and more severe complications [15]. During this

period, emergency surgery in our institution was performed by many general surgeons, and even residents, not specialized in colorectal surgery, which has been shown to increase the rate of distant recurrences [16]. Increased specialization in recent years has been shown to improve survival of colorectal cancer [17].

In the present study, left hemicolectomy showed inferior results in the adjusted regression analyses. This is not in agreement with other studies that have shown similar results comparing right-sided and left-sided colectomy on early outcomes [18]. In a study comparing curative resections of right- and left-sided colon cancers, resections of left-sided colon cancers showed better survival [19]. This is supported by a study of Lee *et al.*, who found a worse oncological outcome after resections for right-sided cancers compared to left-sided [20]. A possible explanation due to the number of lymph nodes harvested is also presented. In a register study of 504,958 patients, those patients resected for right-sided colon cancer/right hemicolectomy, in whom more than 22 lymph nodes were harvested by central vascular ligation/dissection, showed improved survival compared to patients with fewer lymph nodes harvested. This makes a D3-resection/complete mesolectal excision in right hemicolectomy reasonable [20]. This finding is supported by Benedix *et al.*, who, in a review of 17,641 patients, found that right- and left-sided cancers differed, with a worse prognosis for right-sided cancers, suggesting higher age, more women and genetic differences as possible causes. Due to the high number of patients in this register study (n = 17,641), even marginal differences reached statistical significance, and care should be taken to translate this into clinical relevance [21]. Embryologic differences in origin between right and left colon, which translates into differences in cancer morphology and prognosis, is one of the hypotheses.

Lymph node dissection D2 versus D1 showed improved long-term survival in the present study. D2-dissection during colon surgery has been incorporated into the national guidelines for resections of colon cancers, and no controversy exists regarding the recommendation of D2-resections as the procedure of choice. An expansion of lymph node dissection to include more central lymph nodes (whole mesocolon/D3 lymph node dissection) is now under discussion. Multicentre studies comparing D2- and D3-resection for colonic cancer is under way [22] [23]. These studies may resolve the discussion.

Blood transfusions were associated with reduced survival. This result supports the findings of other studies, where per-operative blood transfusion are associated with shorter survival after colon resections, independent of sepsis [24] [25]. Sepsis and blood transfusions have an additive effect and are associated with even worse survival [25]. In contrast, in a study of Stage III colonic cancers, where 47.9% of the patients received blood transfusions, Tarantino *et al.* concluded that blood transfusions did not increase the risk of five-year mortality, which is supported by other studies [26] [27]. Surgical techniques are evolving, with more attention to meticulous, precise surgery, with open and even more so

with laparoscopic and robot-assisted surgery. Blood loss during surgery is decreasing, as is the need for blood transfusions. Consequently, a decreasing number of patients are exposed to blood transfusions and their negative side effects.

Tumour adherence to surrounding organs, serosa ingrowth, colon perforation and reoperation due to postoperative complications had no independent influence on outcome. Tumour adherent to surroundings was not a significant independent factor in the present study. However, the colon cancer in several patients was irresectable, leaving the patients to a dismal prognosis, which were very significant for them. In a study of 121 locally advanced colon cancers, actual tumour cell invasion was found in 63.6% of the specimens, whereas 36.4% were caused by inflammation. R0-resections were obtained in 92.6% of the patients [28]. Some authors suggest that optimizing preoperative radiological investigations, considering neo-adjuvant chemotherapy, would further improve the results [29].

Tumour perforation was not an independent risk factor in this study. Previous reports have shown high perioperative mortality rates in cases with tumour perforation, partly dependent on the perforation site. Some studies show reduced long-term survival, whereas others show no influence, as discussed in a review by Otani *et al.* [30]. Due to blow-out perforation, proximal perforations with faecal peritonitis have been thought to be more serious than tumour perforations, which leads to localized inflammation. After the postoperative period, however, there is no difference between the two situations. Moreover, the long-term prognosis is entirely dependent on tumour stage, and not perforation. Curative treatment during surgery rather than palliative treatment is therefore recommended.

Serosa ingrowth is considered important for peritoneal spread and prognosis [31] but was not an independent prognostic factor in the present study.

Reoperation predicted reduced survival in the unadjusted analyses, but not when adjusted for the other variables. This finding is in contrast to other studies. Khoury *et al.* studied patients reoperated in the early postoperative period and reported lower long-term overall and disease-free survival than matched controls without reoperations [32]. Inferior oncological result and reduced life expectancy after reoperations have also been reported by others [32] [33]. In a study of 5667 patients resected for colon cancer, Bakker *et al.* described an anastomotic leakage rate of 7.5%. The overall mortality rate was 4.1%, which increased to 16.4% after leakage [34]. Prevention of such complications should therefore be mandatory. Several studies have identified risk factors of importance for leakage [35]. Adopting preoperative strategies such as prehabilitation programs addressing these risk factors may reduce the risk of reoperation and improve oncological outcomes in addition to the short-term advantages [32] [33].

In 28.7% of the patients, the cause of death was other than colorectal cancer recurrence. This fact is important when reading cancer statistics. Not all deaths are due to cancer recurrence. The rates were strongly dependent on stage. The cause of death other than colorectal cancer in Stage I, Stage II, Stage III, Stage IV

and in patients where the tumour was not removed was 72.7%, 55.0%, 24.8%, 1.2% and 7.3%, respectively.

The one- and five-year overall survival rates were 77.4% and 53.1%, respectively, also strongly dependent on stage. These survival rates are similar to the national survival rates at that time. Survival rates have since improved by 20%, with relative overall five-year survival rates of 70% in the period of 2015-2019 in Norway.

Strengths of the study: 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 on cause of death retrieved from the Norwegian Cause of Death Registry. Weakness of the study: Retrospective registration of medical records, with some missing data.

6. Conclusion

Age, sex, comorbidity, indication, lack of lymph node dissection, tumour stage, and preoperative blood transfusions are significant predictors for survival after surgery for colon cancer. A total of 28.7% of the patients died from causes other than recurrence of colon cancer.

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Ethics Approval

The study was approved by the Norwegian Ethical Committee.

Conflicts of Interest

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

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