Scientific Research Publishing

Journal of Cancer Therapy, 2017, 8, 1107-1124
http://www.scirp.org/journal/jct
ISSN Online: 2151-1942
ISSN Print: 2151-1934

Clinical Predictors for Recurrence after Curative Resection for Colorectal Cancer

Ola Røkke[1,2*], Thomas Heggelund[1], Jurate Saltyte Benth[3], Marianne Steffensen Røkke[4], Kjell Kåre Øvrebø[5]

[1]Department of Digestive Surgery, Akershus University Hospital, Lørenskog, Norway
[2]Institute of Clinical Medicine, Campus Ahus, University of Oslo, Oslo, Norway
[3]Institute of Clinical Medicine, Campus Ahus, University of Oslo, Health Services Research Unit, Akershus University Hospital, Lørenskog, Norway
[4]Department of Head and Neck Surgery, Akershus University Hospital, Lørenskog, Norway
[5]Department of Digestive Surgery, Haukeland University Hospital, Bergen, Norway
Email: *ola.rokke@medisin.uio.no, Thomas.Heggelund@ahus.no, jurate.saltyte-benth@medisin.uio.no, rokk@ahus.no, kjell.kare.ovrebo@helse-bergen.no

How to cite this paper: Røkke, O., Heggelund, T., Benth, J.S., Røkke, M.S. and Øvrebø, K.K. (2017) Clinical Predictors for Recurrence after Curative Resection for Colorectal Cancer. *Journal of Cancer Therapy*, **8**, 1107-1124.
https://doi.org/10.4236/jct.2017.812095

Received: November 1, 2017
Accepted: December 4, 2017
Published: December 7, 2017

Abstract

Purpose: To identify clinical predictors of recurrence of colorectal cancer after curative surgical treatment. **Methods:** Retrospective follow-up-study of 925 consecutive patients treated with R0-resection for colorectal cancer Stage I, II and III from 1990 until 2000 with a mean follow-up of 60 ± 37 months. Predictors for cancer recurrence were identified in a pilot-sample of these patients, followed by analyses of the rest of the patients (test-sample), and finally with a concluding analyses of the entire patient group. Data were analyzed with Pearson Chi-square test (χ^2), Cox regression analyses and log rank test. **Results:** Tumor stage (Stage I: HR 0.10 (0.05; 0.19), Stage II: HR 0.31 (0.24; 0.41)) and postoperative reoperations due to complications due to other causes than anastomotic leakage (HR 2.02 (1.21; 3.36)) were significant predictors of cancer recurrence in the multivariate Cox regression model. The association between reoperations and recurrence was strongest for the patients with the best prognosis: Stage I and Stage II-cancers. Long duration of surgery, strongly associated with blood-loss and infusions of liquid and blood-products, reoperation due to anastomotic leakage as well as right colon/transversum localization were significant at a trend-level (10%). **Conclusions:** Tumor stage and reoperations due to postoperative complications other than anastomotic leakage are significant predictors for recurrence after curative surgery for colorectal cancer.

Keywords

Cancer, Colon, Rectum, Metastases, Predictors, Recurrence, Reoperation,

Complication

1. Introduction

Cancer recurrence occurs in about 30% of patients after curative resection for colorectal cancer [1]. The main predictor for recurrence and survival is the tumor stage at the time of surgery. Previous studies have identified several possible additional factors associated with recurrence. Patient factors, like intake of coffee and alcohol, smoking, weight-loss and Glascow Prognostic score [2] [3] [4] [5] [6], treatment factors like surgical experience and technique [7] [8], tumor factors like location, differentiation, vein-, nerve- and lymphatic ingrowth [9] [10] and molecular factors [11] [12] [13] [14] have been shown to influence cancer recurrence, and adjuvant oncological therapy is often recommended. In the present study, we have taken interest in what consequences repeated or aggravated inflammatory stress will inflict on the patient and influence the risk of recurrence after potential curative resection of colorectal cancer.

We have selected clinical parameters related to repeated or exaggerated inflammatory stress, which are available at all institutions. Previous case reports have suggested that sites of inflammation and traumatized tissue are more susceptible for cancer cell deposits and growth than other sites; a phenomenon named "inflammatory oncotaxis" [15] [16] [17]. The aim of the present study was to define the independent predictive value of each of these parameters: emergency resection due to bowel obstruction, tumor perforation, exaggerated blood loss/transfusions and postoperative complications in need of reoperation. So far few studies evaluated which of these potential parameters is the most predictive.

In this time period, adjuvant chemotherapy for stage III colonic cancers and preoperative radiotherapy for rectal cancers with tumors near the circumferential margin for resection was not routinely used, and very few patients (<5%) received these treatment modalities in our study. Thus, we have the opportunity to investigate the influence of clinical factors without the need to correct for these treatment modalities. The hypothesis in the present paper is that exaggerated or repeated inflammatory stress will promote cancer recurrence.

2. Materials and Methods

1285 consecutive unselected patients admitted with colorectal cancer at Haukeland University Hospital, Norway, from January 1990 until January 2000, were included in the present retrospective observational study. To obtain a group of patients with verified R-0-resection, patients with stage IV-tumor, non-resected patients, patients who died in hospital, R1- or R-2-resceced patients, and patients lost to follow-up were excluded, leaving 925 patients for the study (**Figure 1**). The patients were routinely followed-up for five years with ultrasonography

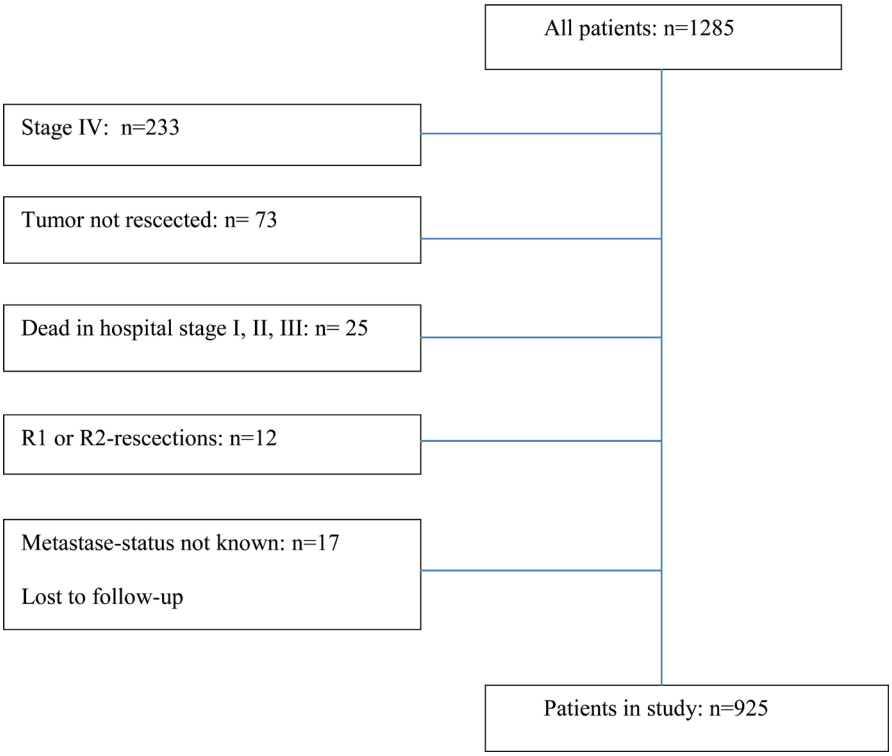


Figure 1. Patients included in the study: Consort Diagram.

of liver, plain x-ray of thorax, measurement of level of Carcinoembryonic antigen (CEA), rectoscopy after rectal cancer surgery and clinical examination three, six, twelve, eighteen, twenty-four, thirty-six, forty-eight and sixty months (coloscopy at sixty months) after surgery, and thereafter admitted to the hospital on demand. Mean follow-up time was 60 months. The criteria for diagnosis of recurrence or distant metastases included histological confirmation, palpable disease or disease revealed by radiological studies with subsequent clinical progression and supportive biochemical data, especially rise in Carcinoembryonic antigen (CEA). Local recurrence was defined as any tumor recurrence in the field of resection, most commonly pelvis or perineum. Distant metastases were defined as any tumor recurrence outside the localization of the previous tumor, including metastases to the liver, lung, brain bone and abdominal cavity.

Clinical factors of interest were gender, age, localization of tumor, indication for surgery (acute or planned operation), surgeon's experience, perforation of tumor (pre-or per-operative), duration of surgery, blood loss, infusion of blood and fluids, tumor-stage (TNM), postoperative complications and reoperations. Two categories of reoperations were defined: reoperations due to anastomotic leak (n = 22/2.4%), and reoperations due to other causes(n = 41/4.4%): wound deschise (n = 12), bowel obstruction (n = 8), bleeding (n = 7), intraabdominal abscess (n = 3), deviating stoma (n = 3), revision of colostomy (n = 2), removal of packing (n = 2), splenectomy (n = 1), bowel-resection (n = 1), revision of pressure wound (n = 1), embolectomy in the lower limb (n = 1). We did not include specific biochemical parameters or tumor characteristics in the present

Table 1. Association between duration of surgery, peroperative bleeding, and volume of liquids- and blood-infusions.

Spermans's rho		2	3	4
Duration of surgery	1	0.529*	0.349*	0.482*
Bleeding	2		0.636*	0.402*
Peroperative blood transfusions	3			0.281*
Peroperative fluid infusion	4			

*$p < 0.01$ (two tailed).

multivariate analyses, but some tumor characteristics are presented for the sake of comparison with other studies. Perioperative blood-loss, blood-transfusions, and intravenous fluid transfusions were not included as specific factors in the multivariate model, as they were all highly correlated with duration of surgery, which was selected as an indicator for all these factors (Table 1).

Statistical Analyses

Demographic and clinical characteristics are presented as mean and standard deviation (SD) or frequencies and percentages. Student's t-test or Pearson's Chi-square test (χ^2) were used as appropriate for comparison of groups of patients. The association between cancer recurrence and a number of potential predictors and confounders was assessed by Cox regression analysis. As there were several surgeons performing the operations, intra-surgeon correlations were assessed by intra-class correlation coefficient, however no such correlations were found and thus no adjustments were needed.

When assessing predictors, a data splitting approach was applied to avoid hypothesis fishing in the dataset [18]. According to this approach, the data were split into two parts. The first part (Pilot) was used to search for significant predictors in a univariate model, and then construct a multivariate Cox regression model containing only significant and/or clinically important predictors. A formal hypothesis testing was then performed in the second part of the data set (Test). A 5% level of significance was used and only the results with p-values below this limit were accepted as significant, regardless of significance level in the pilot part. Finally, analyzes were performed on the entire data set. Proportional hazards assumption was assessed by the correlations between the ranking of individual time of metastases and Schoenfeld's residuals generated from a multivariate Cox regression model for each covariate. The results were presented as hazard ratios (HR) with the corresponding 95% confidence intervals (CI) and p-values. The effect of tumor stage and reoperations on cancer recurrence was tested by a log-rank test and illustrated using Kaplan-Meyer-plots.

3. Results

There were 455 men (49.2%), 470 women (50.8%), mean age 70.2 years (±11.6 years). 348 patients (37.6%) had no previous medical history, whereas 62.4% had

either cardiovascular disease (39.4%), pulmonary disease (4.4%), renal disease (0.3%), others (15.5%) or combination of these (1.5%). A planned operation was performed in 787 patients (85.1%), whereas 138 patients (14.9%) needed acute surgery for bowel obstruction, perforation or bleeding. Tumor perforation was diagnosed in 68 patients (7.4%), 14 of these (1.5%) occurred during surgery. The tumor was located in colon in 574 patients (62.1%), whereas 351 patients (37.9%) had rectal cancer (Table 2). Table 3 shows tumor characteristics and

Table 2. Patient characteristics, N = 925.

Parameter	No metastases	Metastases	*p*-value
Age mean (SD)	70.9 (11.4)	68.1 (11.9)	0.001
Sex n (%)			0.413
Male	327 (71.9)	128 (28.1)	
Female	349 (74.3)	121 (25.7)	
Comorbidity n (%)*			0.143
None	234 (68.4)	110 (31.6)	
Cardiovascular	277 (76.1)	87 (23.9)	
Pulmonary	30 (73.2)	11 (26.8)	
Renal	2 (66.7)	1 (33.3)	
Combinations	10 (71.4)	4 (28.6)	
Others	113 (79.0)	30 (21.0)	
Indication n (%)			0.002
Acute surgery	86 (62.3)	52 (37.7)	
Planned surgery	590 (75.0)	197 (25.0)	
Perforation of tumor n (%)			0.029
No	635 (74.1)	222 (25.9)	
Pre-operative	34 (63.0)	20 (37.0)	
Per-operative	7 (50.0)	7 (50.0)	
Operation time mean (SD)**	133.9 (54.0)	148.0 (48.2)	<0.001
Location n (%)***			
Colon			0.532
Coekum	80 (72.7)	30 (27.3)	
Ascendens	126 (77.8)	36 (22.2)	
Transversum	42 (80.8)	10 (19.2)	
Descendens	52 (75.4)	17 (24.6)	
Sigmoid	124 (71.3)	50 (28.7)	
Rectum			0.130
Upper 1/3	101 (76.5)	31 (23.7)	
Middle 1/3	77 (68.1)	36 (31.9)	
Lower 1/3	69 (65.1)	37 (34,9)	
Surgeon n (%)			0.799
Resident	123 (71.1)	50 (28.9)	
Fellow	291 (73.3)	106 (26.7)	
Consultant	262 (73.8)	93 (26.2)	

*13 missing; **17 missing; ***10 missing: tumours in both colon and rectum.

Table 3. Tumor characteristics, N = 925.

Parameter	No metastases	Metastases	*p*-value
Tumor type* n (%)			0.021
Ulcerative	350 (70.5)	142 (29.5)	
Vegetative	175 (81.0)	41 (19.0)	
Strictur	73 (67.0)	23 (24.0)	
Mixed	62 (68.9)	28 (31.1)	
Tumor differentiation** n (%)			0.274
Highly	132 (75.4)	43 (24.6)	
Medium	397 (73.2)	145 (26.8)	
Low	42 (64.6)	23 (35.4)	
Not defined	89 (77.4)	26 (22.6)	
Tumor stage n (%)			0.001
Stage I	128 (92.8)	10 (7.2)	
Stage II	398 (80.4)	97 (19.6)	
Stage IIA	382 (82.2)	83 (17.8)	
Stage IIB	6 (66.7)	3 (33.3)	
Stage IIC	10 (47.6)	11 (52.4)	
Stage III	150 (51.4)	142 (48.6)	
Stage IIIA	5 (71.4)	2 (28.6)	
Stage IIIB	134 (53.6)	116 (46.4)	
Stage IIIC	11 (31.4)	24 (68.6)	

*41 missing; **28 missing.

stage. The tumor showed ulcerative growth in 482 patients (52.1%), vegetative growth in 216 (23.4%) and stricturing growth in 90 patients (9.7%). 175 patients (18.9%) had a highly differentiated tumor, 542 patients had a medium differentiated tumor, whereas 65 patients (7.0%) had a low differentiated tumor. In 138 patients (14.9%), the disease was classified as stage I. 495 patients (53.5%) were classified as stage II, and 292 patients (31.6%) as stage III. The postoperative complications are presented in Table 4. 633 patients (68.4%) recovered without complications, whereas mild complications defined as Clavien Dindo score I, II and IIIa, occurred in 228 patients (24.7%). 64 patients (6.9%) (Clavien Dindo score IIIb, IV) experienced severe complications. 63 patients (6.8%) were reoperated, 22 of them (2.4%) due to anastomotic leak. In this table, several infrequent complications are grouped together as "others": urinary retention (n = 11), surgical packing left behind during surgery (n = 1), stoma necrosis (n = 2), pressure wound (n = 2), hyperosmolarity syndrome (n = 1), anaphylactic shock (n = 1), worsening of asthma (n = 1), psychosis (n = 3), ventral hernia (n = 1), perianal sinus (n = 1), pneumothorax during central venous catheter insertion (n = 1). In the univariate model, cancer recurrence occurred significantly more frequent in younger patients, after emergency surgery, in patients with tumor perforation, in patients with longer duration of surgery, and in patients with postoperative complications and reoperations (Table 2 and Table 4). Tumor type and stage

were also significant as univariate predictors.

The location of cancer recurrence(s) according to location of the primary tumor is shown in Table 5. The liver was the most frequent organ for cancer recurrence, accounting for 42% of all recurrence. Left sided colonic cancers did have higher rates of liver metastases, right sided colonic cancers did have higher rates of lung metastases, whereas rectal cancers had higher rates of local recurrences.

Table 4. Postoperative complications, N = 925.

Parameter	No metastases	Metastases	*p*-value
Clavien Dindo score n (%)			0.007
0: No complication	477 (75.4)	156 (26.4)	
I: Mild complications	31 (64.6)	17 (35.4)	
II: Complications medicines	128 (73.6)	46 (26.4)	
IIIa: Intervention without anesth	4 (66.7)	2 (33.3)	
IIIb: Intervention with anesth	33 (54.1)	28 (45.9)	
IVa: Single organ failure	3 (100)	0	
Postoperative complications n (%)			0.001
No complications	477 (75.4)	156 (24.6)	
Anastomotic leaks	10 (45.5)	12 (54.5)	
Intra-abdominal abscess	5 (83.3)	1 (16.7)	
Other infections	132 (71.7)	52 (28.3)	
Cardiovascular	16 (72.7)	6 (27.3)	
Thrombus-emboli	7 (70.0)	3 (30.0)	
Ileus	5 (100)	0	
Wound dechise	3 (50.0)	3 (50.0)	
Rectovaginal fistula	4 (80.0)	1 (20.0)	
Bleeding	1 (25.0)	3 (75.0)	
Single organ failure	3 (100)	0	
Others	13 (52.0)	12 (48.0)	
Reoperation n (%)			0.001
No reoperation	642 (74.5)	220 (25.5)	
Anastomotic leak	10 (45.5)	12 (54.5)	
Others	24 (58.5)	17 (41.5)	
Wound dechise	5 (41.7)	7 (58.3)	
Bowel obstruction	7 (87.5)	1 (12.5)	
Bleeding	3 (42.9)	4 (57.1)	
Intraabdominal abscess	2 (66.7)	1 (33.3)	
Deviating stoma	3 (100)	0	
Stoma revision	1 (50)	1 (50)	
Removal of packing	1 (50)	1 (50)	
Splenectomy	0	1 (100)	
Bowel resection	0	1 (100)	
Revision of pressure wound	1 (100)	0	
Embolectomy of lower limb	1 (100)	0	

Table 5. Distributions of cancer recurrence.

Location Number of patients % patients with recurrence Number of recurrences	Coekum n = 30 27.2 n (%)	Ascendens n = 36 22.2 n (%)	Transversum n = 10 19.2 n (%)	Descendens n = 17 24.6 n (%)	Sigmoid n = 50 28.7 n (%)	Rectum n = 103 29.6 n (%)	All relaps N = 246* 26.6 n (%)
Liver	13(43)	11 (31)	5 (50)	11 (65)	24 (48)	37 (36)	101 (42)
Lung	1 (3)	10 (28)	3 (30)	2 (12)	9 (18)	20 (19)	45 (19)
Peritoneum	6 (20)	2 (6)	2 (20)	1 (6)	6 (12)	4 (4)	21 (9)
Local recurrence	5 (17)	3 (8)	0	4 (24)	11 (22)	34 (33)	57 (24)
Anastomotic recurrene	3 (10)	4 (11)	3 (30)	1 (6)	4 (8)	11 (11)	26 (11)
Bone		1			1	3	5
Brain	2	3				3	8
Anus						1	1
Adrenal gland					1		1
Lymph nodes fossa supraclav	2						2
Abdominal incision						1	1
Reteroperitoneal lymph nodes	1	1					2
Axillar lymph nodes						1	1
Wall of vagina						1	1
Umbilicus		1					1

*27 patients had recurrence in more than one location, three patients had tumors in more than one location, and are omitted.

The pilot dataset was employed to generate hypothesis regarding significant predictors of recurrence. In the multivariate model, age, indication for surgery (acute/planned), TNM-stage, reoperations for other causes than anastomotic leak and tumor location in the left colon were significant independent predictors (Table 6).

The test data set was used to test the hypothesis generated in the pilot set. In the multivariate model estimated on the test sample, age, gender and surgeon type were included as confounders. Indication for surgery (acute/planned) was not significant a predictor, whereas duration of surgery and tumor location (right colon/transversum) were significant on trend-level (10%) only (Table 7). Also, pre-operative and not per-operative tumor-perforation and postoperative reoperation due to other reasons than anastomotic leakage were significant predictors. Tumor stage remained highly significant.

In the final analyses, the entire data-set was assessed, as presented in Table 8. Indication for surgery (acute/planned), duration of surgery, TNM-stage, reoperation for complications other than anastomotic leakage and location of tumor were all significant in the multivariate model, whereas tumor perforation was not. However, the overall interpretation of the results using this methodological approach is as follows:

"Indication (acute/planned)" was significant in pilot part, but non-significant

in test part and thus non-significant predictor in the entire data set even though $p = 0.013$ in Table 8. "Tumor-perforation" was non-significant in pilot part, but left in the model as potential predictor. It became significant in test part, but with an opposite "direction" in HR. However, it was not a significant predictor in the entire data set. "TNM-stage" is clearly a significant predictor (Table 8), also illustrated in Figure 2. "Duration of surgery" was not significant predictor in pilot part, but was left in the model as important predictor. It was only significant on trend level in test part. Even though it is highly significant in the entire data set, we can only conclude the significance at trend level (10%), as was localization in colon. "Postoperative reoperation due to other causes than anastomotic leak was significant in both pilot and test sets. In the entire data-set,

Table 6. Results of Cox regression analysis in the pilot part, N = 307.

Variable	Bivariate model-PILOT		Multivariate model-PILOT	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Indication				
Acute	1.52 (0.89; 2.58)	0.127	2.30 (1.22; 4.34)	0.010
Planned-ref.	1		1	-
Tumor perforation				
No-ref.	1	-	1	-
Pre-operative perforation	0.95 (0.35; 2.60)	0.924	0.53 (0.17; 1.61)	0.260
Per-operative perforation	3.46 (1.09; 10.98)	0.035	1.72 (0.42; 7.01)	0.453
Duration of surgery	1.004 (1.001; 1.007)	0.008	1.004 (0.999; 1.01)	0.095
TNM-stage				
Stage I	0.03 (0.004; 0.21)	<0.001	0.03 (0.004;0.22)	0.001
Stage II	0.31 (0.20; 0.48)	<0.001	0.28 (0.17; 0.45)	<0.001
Stage III-ref.	1	-	-	-
Reoperation				
No-ref.	1	-	1	-
Anastomotic leakage	2.49 (1.004; 6.15)	0.049	2.34 (0.83; 6.59)	0.108
Other	1.96 (0.85; 4.51)	0.113	2.48 (1.03; 5.97)	0.042
Localisation				
Right colon + transversum	0.78 (0.48; 1.27)	0.319	0.75 (0.40; 1.40)	0.365
Left colon	0.52 (0.30; 0.92)	0.024	0.45 (0.23; 0.87)	0.018
Rectum-ref.	1		1	-
Surgeon				
Resident	1.02 (0.54; 1.93)	0.957	1.16 (0.57; 2.33)	0.688
Fellow	0.94 (0.58; 1.53)	0.811	1.05 (0.63; 1.75)	0.853
Consultant-ref.	1	-	1	-
Age	0.98 (0.96; 0.99)	0.005	0.98 (0.96; 0.998)	0.033
Sex				
Male-ref.	1	-	1	-
Woman	1.11 (0.72; 1.70)	0.644	1.27 (0.79; 2.02)	0.325

Table 7. Results of multivariate Cox regression analysis in the test part, N = 591.

Variable	Multivariate model-TEST	
	HR (95% CI)	*p*-value
Indication		
Acute	1.38 (0.88; 2.18)	0.163
Planned-ref.	1	-
Tumor perforation		
No-ref.	1	-
Pre-operative perforation	2.01 (1.13; 3.59)	0.018
Per-operative perforation	1.18 (0.39; 3.03)	0.882
Duration of surgery	1.003 (0.999; 1.006)	0.098
TNM-stage		
Stage I	0.13 (0.06; 9.26)	<0.001
Stage II	0.29 (0.21; 0.41)	<0.001
Stage III-ref.	1	-
Reoperation		
No-ref.	1	-
Anastomotic leakage	1.50 (0.68; 3.28)	0.315
Other	1.88 (0.99; 3.58)	0.027
Localisation		
Right colon + transversum	0.85 (0.42; 1.03)	0.052
Left colon	1.19 (0.78; 1.82)	0.422
Rectum-ref.	1	-
Surgeon		
Resident	1.24 (0.81; 1.90)	0.326
Fellow	1.01 (0.70; 1.44)	0.978
Consultant-ref.	1	-
Age	0.99 (0.98; 1.01)	0.426
Sex		
Male-ref.	1	-
Woman	0.71 (0.52; 0.98)	0.038

reoperation due to other causes than anastomotic leak was a highly significant predictor for cancer recurrence. Reoperation due to anastomotic leakage was not a significant predictor in the pilot and test sets, and only significant at a trend-level (10%) in the entire dataset. The effect of postoperative reoperations on cancer recurrence is also shown for all patients (**Figure 3(a)**) and for patients with tumor stage I (**Figure 3(b)**), stage II (**Figure 3(c)**) and stage III (**Figure 3(f)**). The analyses shows that the negative influence of reoperation is most pronounced in the patient groups with the assumed best prognosis: Stage I and II.

4. Discussion

Previous studies have shown that postoperative complications like anastomotic

Table 8. Results of Cox regression analysis performed on the entire data set (N = 898).

Variable	Bivariate analyses		Multivariate model[1]	
	HR (95% CI)	p-verdi	HR (95% CI)	p-verdi
Indication				
Acute	1.72 (1.26; 2.36)	0.001	1.59 (1.10; 2.30)	0.013
Planned-ref.	1	-	1	-
Tumor perforation				
No-ref.	1	-	1	-
Pre-operative perforation	1.54 (0.97; 2.47)	0.070	1.34 (0.80; 2.25)	0.262
Per-operative perforation	2.14 (1.01; 4.54)	0.048	1.34 (0.61; 2.94)	0.466
Duration of surgery	1.003 (1.001; 1.005)	0.001	1.003 (1.001; 1.006)[2]	0.006
TNM-stage				
Stage I-ref.	1	-	1	1
Stage II	2.81 (1.46; 5.39)	0.002	3.24 (1.67; 6.28)	0.001
Stage III	9.26 (4.87; 17.60)	<0.001	10.34 (5.39; 19.85)	<0.001
Reoperation				
No-ref.	1		1	-
Anastomotic leakage	2.26 (1.26; 4.04)	0.006	1.73 (0.95; 3.13)	0.071
Other	1.89 (1.15; 3.09)	0.012	2.00 (1.20; 3.33)	0.008
Localisation				
Colon	0.83 (0.64; 1.07)	0.144	0.75 (0.55; 1.02)	0.062
Rectum-ref.	1	-	1	-

[1]Controlled for age, gender and type of surgeon. [2]HR reported for every 1-minute difference in duration. For every 30-minutes change HR = 1.11 (1.04; 1.18), for every 60-minutes change HR = 1.23 (1.09; 1.39), for every 90-minutes change HR = 1.36 (1.13; 1.63).

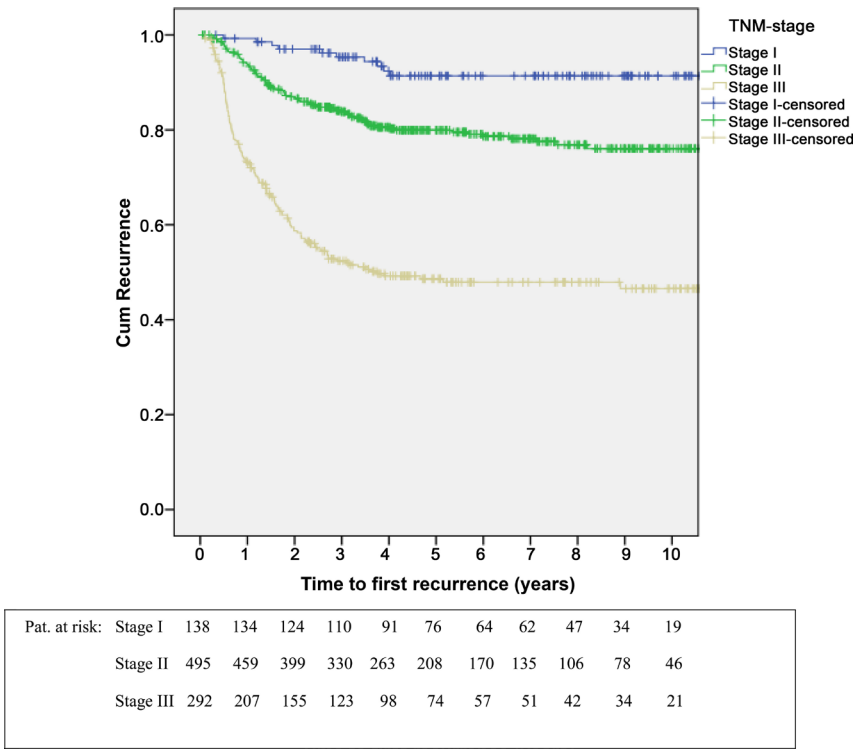
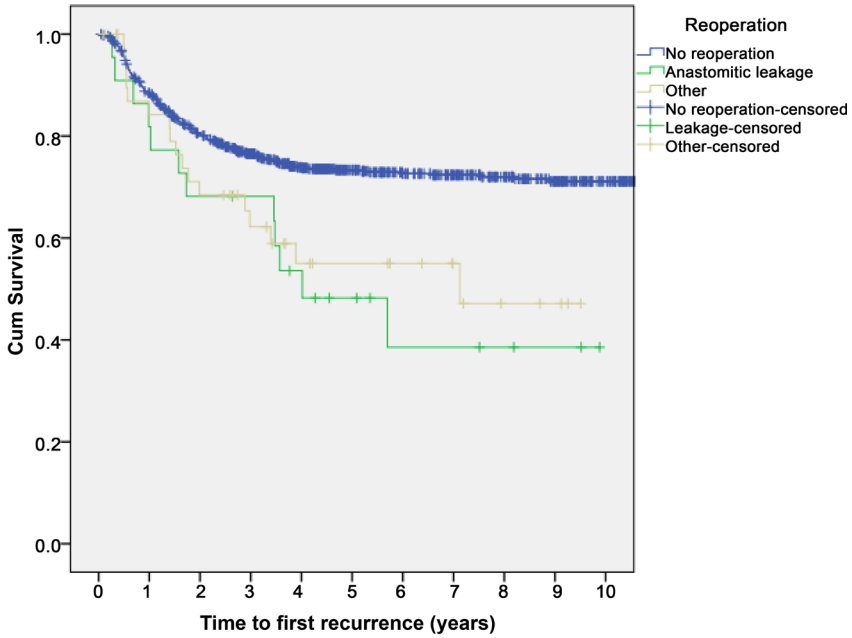
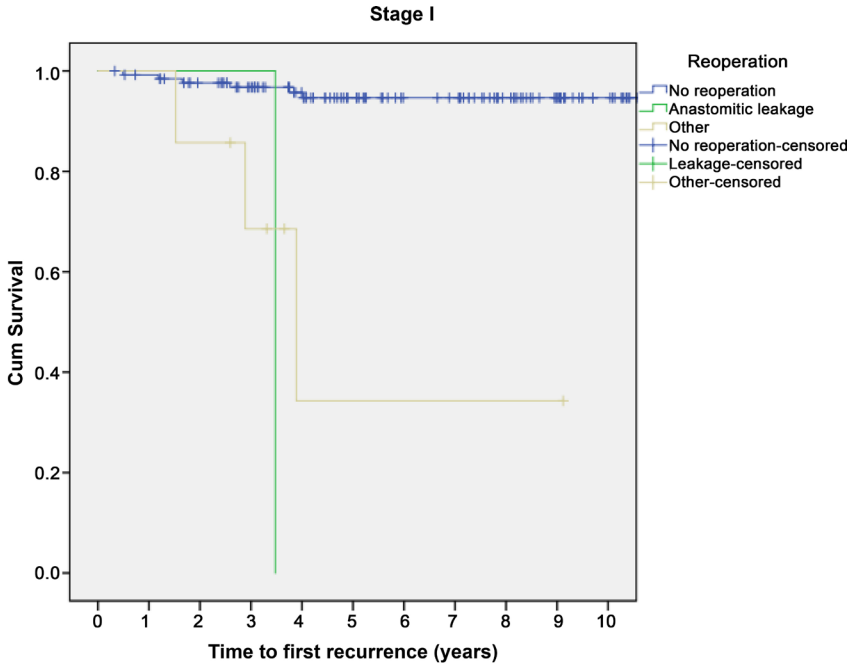


Figure 2. Time to first cancer recurrence according to tumor stage (log rank: $p < 0.001$).



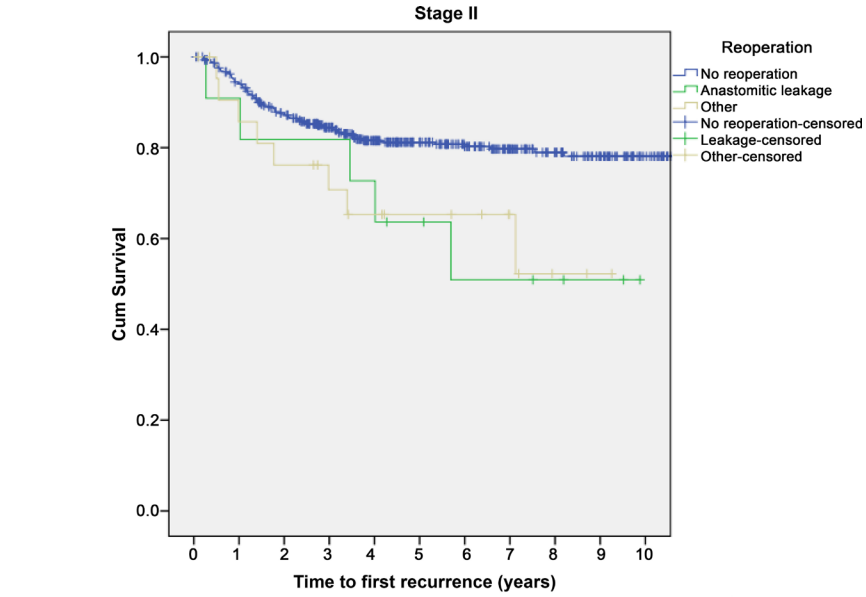
Pat at risk: leakage :	22	18	15	14	10	7	4	4	3	2	0
other:	41	32	26	20	14	12	10	7	4	3	0
No reoperation:	862	741	637	529	428	339	277	237	188	141	86

(a)

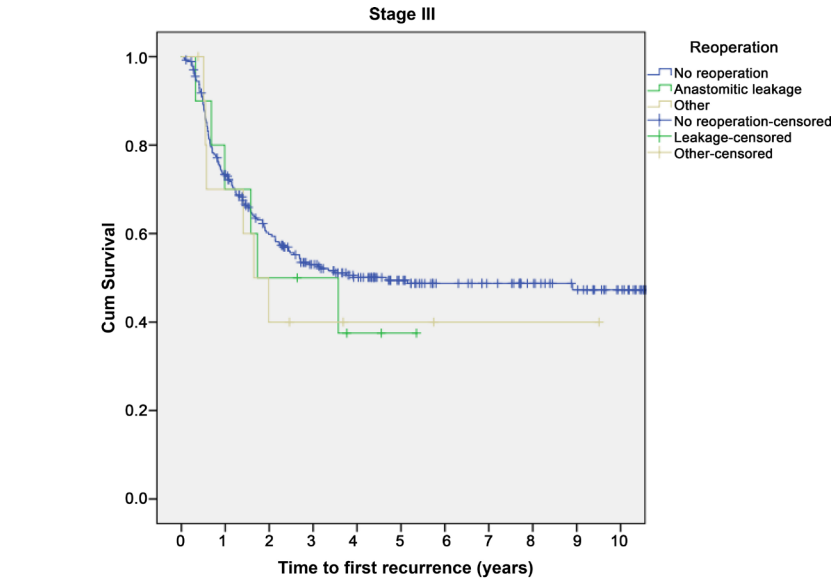


Pat at risk: leakage :	1	1	1	1	0	0	0	0	0	0	0
other:	7	7	6	4	1	1	1	1	1	1	0
No reoperation:	130	126	117	105	90	75	63	61	46	33	18

(b)



(c)



(d)

Figure 3. (a) Time to first cancer recurrence according postoperative reoperation (log rank: $p = 0.002$); (b) Time to first cancer recurrence according postoperative reoperation and tumor stage I (log rank: $p = 0.001$); (c) Time to first cancer recurrence according postoperative reoperation and tumor stage II (log rank: $p = 0.019$); (d) Time to first cancer recurrence according postoperative reoperation and tumor stage III (log rank: $p = 0.717$).

leakage after colorectal resection for cancer will increase the local and systemic recurrence rates and reduces survival [19]-[26]. Few reports have studied the effect of reoperations due to other causes. We therefore decided to separate this group from the group of patients reoperated for anastomotic leaks in the Cox model. The results showed an association between reoperation for anastomotic leaks and cancer recurrence only on trend-level (10%), which may be explained from the small number of patients in this group, and lack of statistical power. The association between reoperation for other causes than anastomotic leaks and cancer recurrence was highly significant, which is the most interesting finding in this study. The negative effect of reoperations was most pronounced in patients with the best chances of cure according to stage: stage I and stage II.

Emergency surgery, location of the tumor, duration of surgery and tumor perforation was not significant independent predictors of recurrence. This is in contrast with previous studies, which have identified emergency surgery [27], perioperative bleeding and transfusions of blood as risk factors for recurrence [27] [28] [29] [30] [31]. In one study, blood transfusions > 3 units erythrocytes increased the recurrence rates, probably through T-lymphocytes, NK-cells, CD4+/CD8+ ratio [31]. The main discussion has been whether it is the bleeding itself, or the transfusion of blood that is the main cause of recurrence. However, some studies do not show negative effects of blood transfusions after colorectal surgery [32]. Blood transfusions will also not influence recurrence rates after gastric cancer surgery [33]. The effect of blood transfusions is thus still not settled.

Previous studies have shown that surgery for bowel obstruction and tumor perforation during surgery is a risk factor for recurrence and reduced 5 year survival [2] [10] [34] [35] [36], possibly due to performance of inadequate surgery in a life-threatening situation, or spillage of cancer cells to the abdominal cavity. Cancer cells with the ability to grow have been demonstrated after colorectal cancer resections from luminal mucosa, rectal stump, serosal surface washings and post-dissection lavage tumor bed [37]. This was not supported in the present multivariate model.

We did not find any significant overall difference in recurrence rates between colon and rectal cancers, which is in contrast to a pervious Dutch study [9]. There was also no difference in time to cancer recurrence or location of cancer recurrences in patients with or without reoperations for postoperative complications (data not shown). However, left sided colonic cancers did have higher rates of liver metastases, right sided colonic cancers did have higher rates of lung metastases, whereas rectal cancers had higher rates of local recurrences. This is in accordance with a study on 10.398 colorectal cancer survivors by Augestad *et al.* [38].

The statistical study design of a pilot-test-sequence instead of analyzing the whole sample was chosen to eliminate the chance of bias in selecting predictors, which is strength of the study. However, the same design also did reduce the

power in the two sub-analyses (pilot and test), and have increased the risk of a type II-error, which is a weakness. This may explain why both emergency surgery and duration of surgery were significant in the overall multivariate analyses, but were interpreted as non-significant.

The retrospective method may be a limitation of the study. Seventeen patients were lost to follow-up, which may be another limitation. Other investigators have also taken interest in the importance of clinical factors on recurrence, as is discussed in the text.

The purpose of the present study was to evaluate the impact of several clinical parameters reflecting inflammatory stress on cancer recurrence simultaneously, and identify the factors of independent importance. We could demonstrate that surgical complications in need of reoperation due to other causes than anastomotic leak, was followed by higher recurrence rates, especially in the patients with the best prognosis (stage I and stage II). This is a strong argument for meticulous preoperative conditioning of the patient, and meticulous surgical technique.

5. Conclusion

Tumor stage and postoperative reoperations due to complications are significant predictors for recurrence after curative surgery for colorectal cancer.

Disclosure of Potential Conflict of Interest

We report no conflict of interest.

References

[1] Bridget, N. and Fahy, M.D. (2014) Follow-Up after Curative Resection of Colorectal Cancer. *Annals of Surgical Oncology,* **21**, 738-746. https://doi.org/10.1245/s10434-013-3255-4

[2] Roxburgh, C., Salmond, J. and McKee, R. (2011) Adjuvant Chemotherapy for Resected Colon Cancer: Comparison of the Prognostic Value of Tumor and Patient Related Factors. *International Journal of Colorectal Disease*, **26**, 483-492. https://doi.org/10.1007/s00384-010-1120-5

[3] Guercio, B.J., Sato, K., Niedzwiecki, D., Ye, X., Saltz, L.B., Mayer, R.J., Mowat, R.B., Whittom, R., Hantel, A., Benson, A., Atienza, D., Messino, M., Kindler, H., Venook, A., Hu, FB., Ogino, S., Wu, K., Willett, W.C., Giovannucci, E.L., Meyerhardt, J.A. and Fuchs, C.S. (2015) Coffe Intake, Recurrence, and Mortality in Stage III Colon Cancer: Results from CALCB 89803 (Alliance). *Journal of Clinical Oncology,* **33**, 3598-3607. https://doi.org/10.1200/JCO.2015.61.5062

[4] Walter, V., Jansen, L., Hoffmeister, M., Ulrich, A., Roth, W., Bläker, H., Chang-Claude, J. and Brenner, H. (2016) Prognostic Relevance of Prediagnostic Weitht Loss and Overweight at Diagnosis in Patients with Colorectal Cancer. *The American Journal of Clinical Nutrition,* **104**, 1110-1120. https://doi.org/10.3945/ajcn.116.136531

[5] Walter, V., Jansen, L., Ulrich, A., Roth, W., Bläker, H., Chang-Claude, J., Hoffmeister, M. and Brenner, H. (2016) Alcohol Consumption and Survival of Colorectal Cancer Patients: A Population-Based Study from Germany. *The American Jour-*

nal of Clinical Nutrition, **103**, 1497-1506. https://doi.org/10.3945/ajcn.115.127092

[6] Walter, V., Jansen, L., Hoffmeister, M., Ulrich, A., Chang-Claude, J. and Brenner, H. (2015) Smoking and Survival of Colorectal Cancer Patients: Population-Based Study from Germany. *International Journal of Cancer,* **137**, 1433-1445. https://doi.org/10.1002/ijc.29511

[7] Heald, R.J. and Ryall, R.D.H. (1986) Recurrence and Survival after Total Mesorectal Excision for Rectal Cancer. *Lancet*, **28**, 1479-1482.

[8] Hohenberger, W., Weber, K., Matzel, K., Papadopoulos, T. and Merkel, S. (2008) Standardized Surgery for Colonic Cancer: Complete Mesocolic Excision and Central Ligation-Technical Notes and Outcome. *Colorectal Disease,* **11**, 354-365. https://doi.org/10.1111/j.1463-1318.2008.01735.x

[9] Van der Sijp, M.P., Bastiaannet, E., Mesker, W.E., van der Geest, L.G., Breugom, A.J., Steup, W.H., Marinelli, A.W., Tseng, L.N., Tollenaar, R.A., van de Velde, C.J. and Dekker, J.W. (2016) Differences between Colon and Rectal Cancer in Complications, Short-Term Survival and Recurrences. *International Journal of Colorectal Disease,* **31**, 1683-1691. https://doi.org/10.1007/s00384-016-2633-3

[10] Nikberg, M., Chabok, A., Letocha, H., Kindler, C., Glimelius, B. and Smetdh, K. (2016) Lymphovascular and Perineural Invasion in Stage II Rectal Cancer: A Report from the Swedish Colorectal Cancer Registry. *Acta Oncologica*, **55**, 1418-1424. https://doi.org/10.1080/0284186X.2016.1230274

[11] Erstad, D.J., Tumusiime, G. and Cusack, J.C. Jr. (2015) Prognostic and Predictive Biomarkers in Colorectal Cancer: Implications for the Clinical Surgeon. *Annals of Surgical Oncology*, **22**, 3433-3450. https://doi.org/10.1245/s10434-015-4706-x

[12] Tie, J., Wang, Y., Tomasetti, C., Li, L., Springer, S., Kinde, I., Silliman, N., Tacey, M., Wong, H.L., Christie, M., Kosmider, S., Skinner, I., Wong, R., Steel, M., Tran, B., Desai, J., Jones, I., Haydon, A., Hayes, T., Price, T.J., Strausberg, R.L., Diaz, L.A., Papadopoulos, N., Kinzler, K.W., Vogelstein, B. and Gibbs, P. (2016) Circulating tumor DNA Analysis Detects Minimal Residual Disease and Predicts Recurrence in Patients with Stage II Colon Cancer. *Science Translational Medicine*, **8**, 346ra92.

[13] Matikas, A., Voutsina, A., Trypaki, M. and Georgoulias, V. (2016) Role of Circulating Free DNA in Colorectal Cancer. *World Journal of Gastrointestinal Oncology*, **8**, 810-818. https://doi.org/10.4251/wjgo.v8.i12.810

[14] Erstad, D.J., Tumusiime, G. and Cusack, J.C. (2015) Prognostic and Predictive Biomarkers in Colorectal Cancer: Implications for the Clinical Surgeon. *Annals of Surgical Oncology*, **22**, 3433-3450. https://doi.org/10.1245/s10434-015-4706-x

[15] Jones, F.S. and Rous, P. (1914) On the Cause of the Localization of Secondary Tumors at Points of Injury. *The Journal of Experimental Medicine*, **20**, 404-412. https://doi.org/10.1084/jem.20.4.404

[16] Walter, N.D., Rice, P.L., Redente, E.F., Kauvar, E.F., Lemond, L., Aly, T., Wanebo, K. and Chan, E.D. (2011) Wound Healing after Trauma May Predispose to Lung Cancer Metastasis. *American Journal of Respiratory Cell and Molecular Biology*, **44**, 591-596. https://doi.org/10.1165/rcmb.2010-0187RT

[17] Shine, T. and Wallack, M.K. (1981) Inflammatory Oncotaxis after Testing the Skin of the Cancer Patient. *Cancer*, **47**, 1325-1328. https://doi.org/10.1002/1097-0142(19810315)47:6<1325::AID-CNCR2820470615>3.0.CO;2-B

[18] Dahl, F.A., Grotle, M., Saltyte Benth, J. and Natvig, B. (2008) Data Splitting as a Countermeasure against Hypothesis Fishing: With a Case Study of Predictors for Low Back Pain. *European Journal of Epidemiology*, **23**, 237-242.

https://doi.org/10.1007/s10654-008-9230-x

[19] Park, E.J., Baik, S.H., Kang, J., Hur, H., Min, B.S., Lee, K.Y. and Kim, N.K. (2016) The Impact of Postoperative Complications on Long-term Oncologic Outcomes After Laparoscopic Low Anterior Resection for Rectal Cancer. *Medicine* (*Baltimore*), **95**, e3271. https://doi.org/10.1097/MD.0000000000003271

[20] Kang, J., Choi, G.S., Oh, J.H., Kim, N.K., Park, J.S., Kim, M.J., Lee, K.Y. and Baik, S.H. (2015) Multicenter Analysis of Long-Term Oncologic Impact of Anastomotic Leakage after Laparoscopic Total Mesorectal Excision: The Korean Laparoscopic Colorectal Surgery Study Group. *Medicine* (*Baltimore*), **94**, e1202. https://doi.org/10.1097/MD.0000000000001202

[21] Bell, S.W., Walker, K.G., Rickard, M.J., Sinclair, G., Dent, O.F., Chapuis, P.H. and Bokey, E.L. (2003) Anastomotic Leakage after Curative Anterior Resection Results in a Higher Prevalence of Local Recurrence. *British Journal of Surgery*, **90**, 1261-1266.

[22] Lu, Z.R., Ranendran, N., Lynch, A.C., Heriot, A.G. and Warrier, S.K. (2016) Anastomotic Leaks after Restorative Resections for Rectal Cancer Compromise Cancer Outcomes and Survival. *Diseases of the Colon & Rectum*, **59**, 236-244. https://doi.org/10.1097/DCR.0000000000000554

[23] Krarup, P.-M., Nordholm-Carstensen, A., Jorgensen, L.N. and Harling, H. (2014) Anastomotic Leak Increases Distant Recurrence and Long-Term Mortality after Curative Resection for Colonic Cancer. *Annals of Surgery*, **259**, 930-938. https://doi.org/10.1097/SLA.0b013e3182a6f2fc

[24] Katoh, H., Yamashita, K., Wang, G., Sato, T., Nakamura, T. and Watanabe, M. (2011) Anastomotic Leakage Contributes to the Risk for Systemic Recurrence in Stage II Colorectal Cancer. *Journal of Gastrointestinal Surgery*, **15**, 120-129. https://doi.org/10.1007/s11605-010-1379-4

[25] Walker, K.G., Bell, S.W., Rickard, M.J.F.X., Mehanna, D., Dent, O.F., Chapuis, P.H. and Bokey, E.L. (2004) Anastomotic Leakage Is Predictive of Diminished Survival after Potentially Curative Resection for Colorectal Cancer. *Annals of Surgery*, **240**, 255-259. https://doi.org/10.1097/01.sla.0000133186.81222.08

[26] Park, E.J., Baik, S.H., Kang, J., Hur, H., Min, B.S., Lee, K.Y. and Kim, N.K. (2016) The Impact of Postoperative Complications on Long-Term Oncologic Outcomes after Laparoscopic Low Anterior Resection for Rectal Cancer. *Medicine* (*Baltimore*), **95**, e3271. https://doi.org/10.1097/MD.0000000000003271

[27] Atsushi, I., Mitsuyoshi, O., Kazuya, Y., Syuhei, K., Noriyuki, K., Masashi, M., Akira, W., Kentaro, S., Nobuyuki, K., Natsuko, S., Jun, W., Yasushi, I., Chikara, K. and Itaru, E. (2016) Long-Term Outcomes and Prognostic Factors of Patients with Obstructive Colorectal Cancer: A Multicenter Retrospective Cohort Study. *World Journal of Gastroenterology*, **22**, 5237-5245. https://doi.org/10.3748/wjg.v22.i22.5237

[28] Velásquez, J.F. and Cata, J.P. (2015) Transfusions of Blood Products and Cancer Outcomes. *Revista Española de Anestesiología y Reanimación*, **62**, 461-467. https://doi.org/10.1016/j.redar.2015.02.013

[29] Talukder, Y., Stillwell, A.P., Siu, S.K. and Ho, Y.H. (2014) Comparing Survival and Recurrence in Curative Stage I to III Colorectal Cancer in Transfused and Non-transfused Patients. *International Surgery*, **99**, 8-16. https://doi.org/10.9738/INTSURG-D-13-00141.1

[30] Acheson, A.G., Brookes, M.J. and Spahn, D.R. (2012) Effects of Allogeneic Red Blood Cell Transfusions on Clinical Outcomes in Patients Undergoing Colorectal

Cancer Surgery: A Systematic Review and Meta-Analysis. *Annals of Surgery*, **256**, 235-244. https://doi.org/10.1097/SLA.0b013e31825b35d5

[31] Qiu, L., Wang, D.R., Zhang, X.Y., Gao, S., Li, X.X., Sun, G.P. and Lu, X.B. (2016) Impact of Perioperative Blood Transfusion on Immune Function and Prognosis in Colorectal Cancer Patients. *Transfusion and Apheresis Science*, **54**, 235-241. https://doi.org/10.1016/j.transci.2015.07.004

[32] Donohue, J.H., Williams, S., Cha, S., Windschit, H.E., Witzig, T.E., Nelson, H., Fitzgibbons, R.J., Wieand, S. and Moerte, C.G. (1995) Peroperative Blood Transfusions Do Not Affect Disease Recurrence of Patients Undergoing Surgery for Colorectal Carcinoma: A Mayo/North Central Cancer Treatment Group Study. *Journal of Clinical Oncology*, **13**, 1671-1678. https://doi.org/10.1200/JCO.1995.13.7.1671

[33] Cui, J., Deng, J., Ding, X., Zhang, L., Zhang, R., Wu, W., Hao, X. and Liang, H. (2016) Blood Transfusion Does Not Affect Survival of Gastric Cancer Patients. *Journal of Surgical Research*, **200**, 98-104. https://doi.org/10.1016/j.jss.2015.07.019

[34] Slanetz, C.A. (1984) The Effect of Inadvertent Intraoperative Perforation on Survival and Recurrence in Colorectal Cancer. *Diseases of the Colon & Rectum*, **27**, 792-797. https://doi.org/10.1007/BF02553942

[35] Asano, H., Kojima, K., Ogino, N., Fukano, H., Ohara, Y. and Shinozuka, N. (2016) Postoperative Recurrence and Risk Factors of Colorectal Cancer Perforation. *International Journal of Colorectal Disease*, **32**, 419-424. https://doi.org/10.1007/s00384-016-2694-3

[36] Liska, D., Stocchi, L., Karagkounis, G., Elagili, F., Dietz, D.W., Kalady, M.K., Kessler, H., Remzi, F.H. and Church, J. (2016) Incidence, Patterns, and Predictors of Locoregional Recurrence in Colon Cancer. *Annals of Surgical Oncology*, **24**, 1093-1099. https://doi.org/10.1245/s10434-016-5643-z

[37] Skipper, D., Cooper, A.J., Marston, J.E. and Taylor, I. (1987) Exfoliated Cells and *in Vitro* Growth of Colorectal Cancer. *British Journal of Surgery*, **74**, 1049-1052. https://doi.org/10.1002/bjs.1800741130

[38] Augestad, K.M., Bakaki, P.M., Rose, J., Crawshaw, B.P., Lindsetmo, R.O., Dørum, L.M., Koroukian, S.M. and Delaney, C.P. (2015) Metastatic Spread Pattern after Curative Colorectal Cancer Surgery. A Retrospective, Longitudinal Analysis. *Cancer Epidemiology*, **39**, 734-744. https://doi.org/10.1016/j.canep.2015.07.009