Improving colorectal cancer care: treatment and outcomes of patients with colorectal cancer

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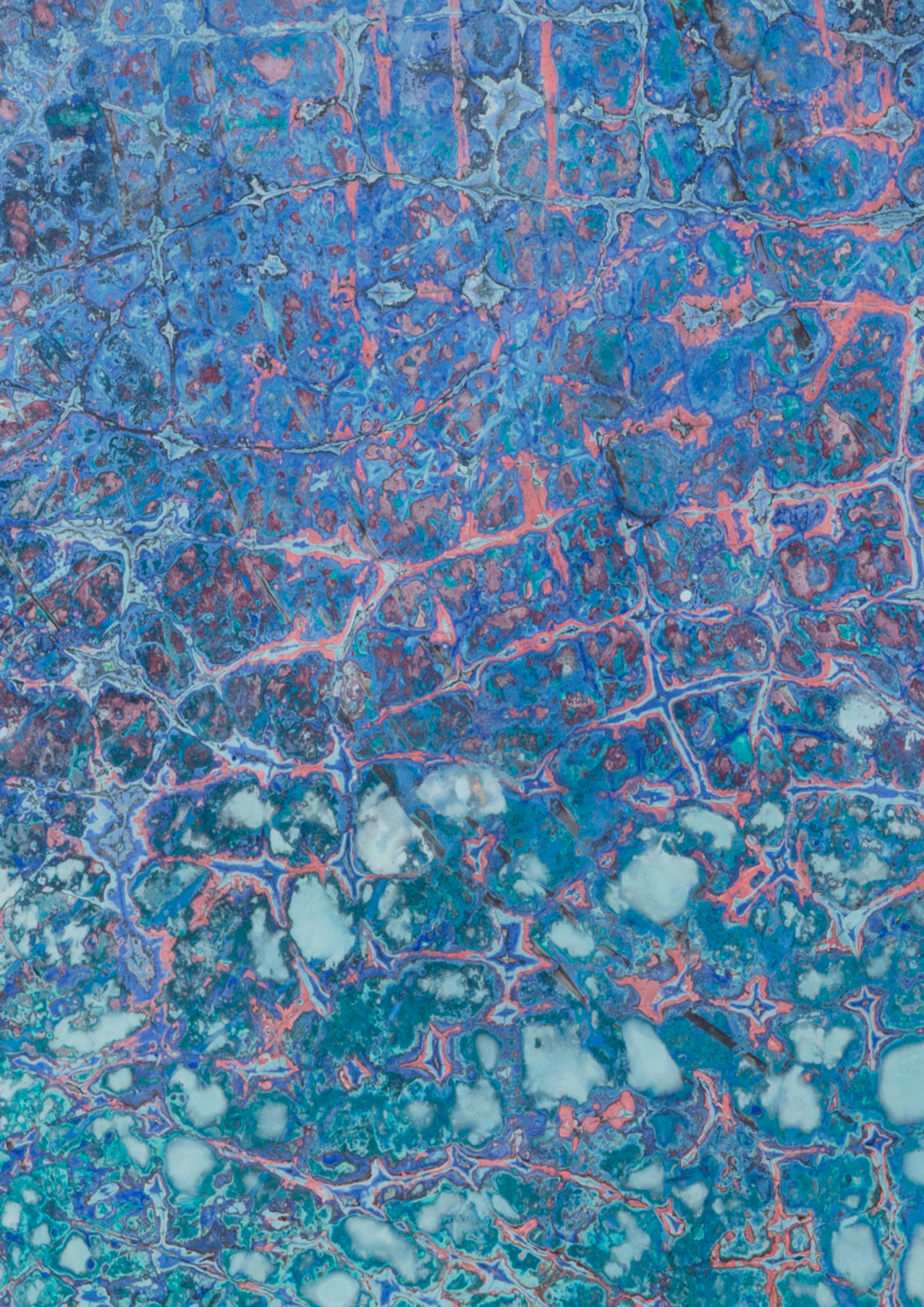
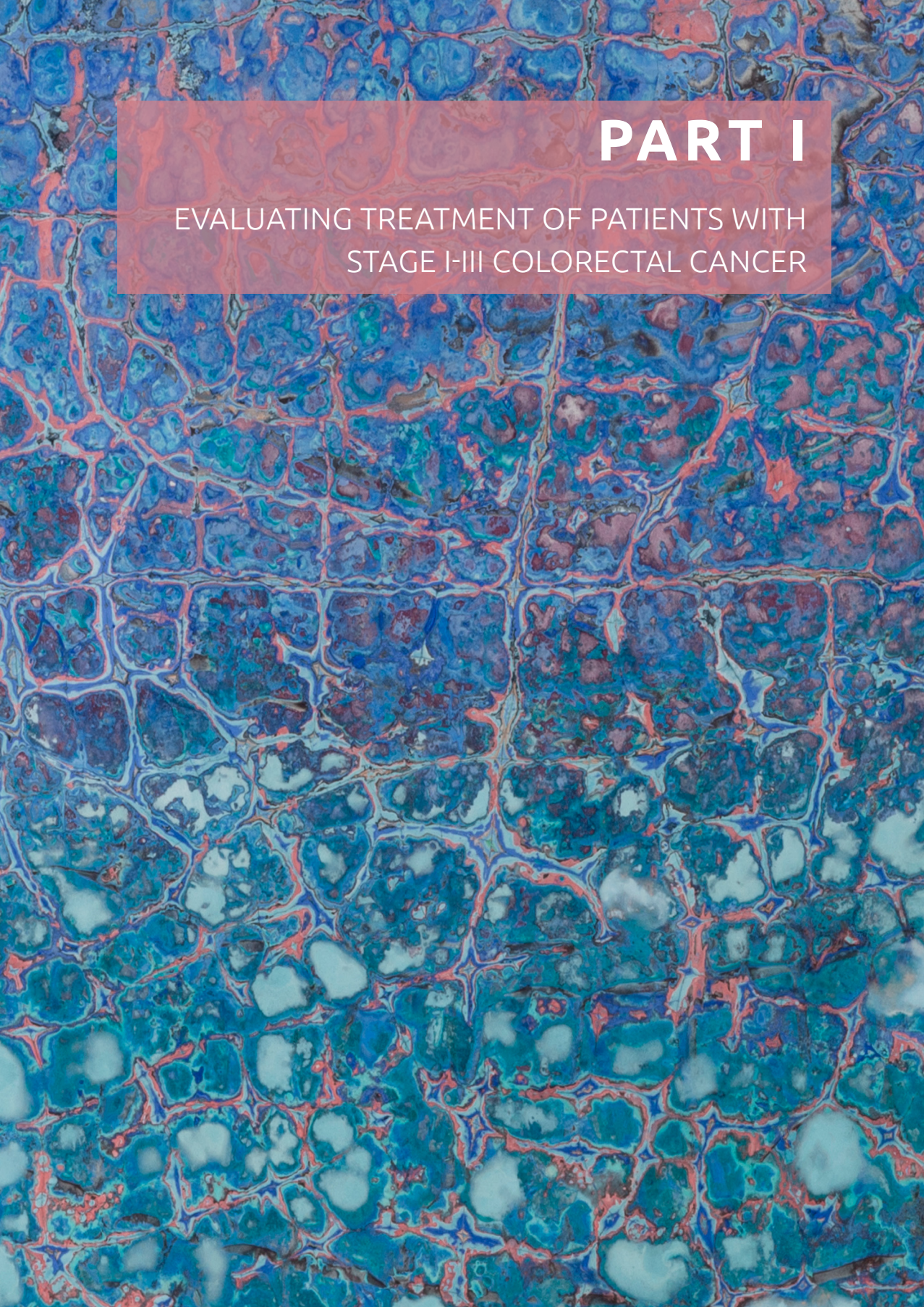
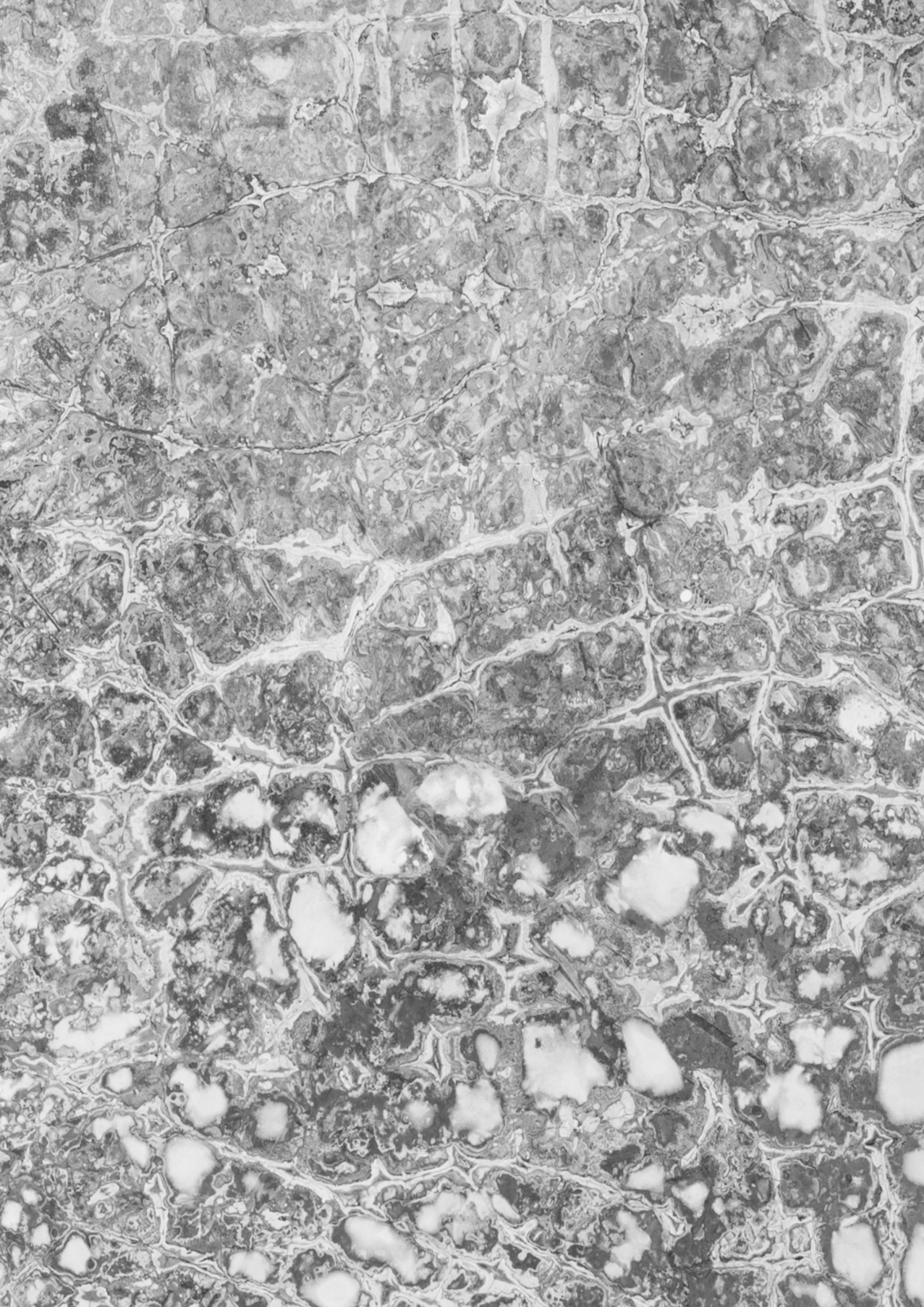




PART I

EVALUATING TREATMENT OF PATIENTS WITH STAGE I-III COLORECTAL CANCER



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Association between the most frequent complications after surgery for stage I-III colon cancer and short-term survival, long-term survival, and recurrences

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ABSTRACT

Background

The purpose of this study was to identify the ten most frequent complications after surgery for stage I-III colon cancer and to assess the association between these complications and overall survival, conditional overall survival, and recurrences.

Methods

All patients who underwent surgery for stage I-III colon cancer in five hospitals in the Western region of the Netherlands were identified. Crude and adjusted Cox proportional hazards models were used to study the association between complications and 1-year overall survival, 5-year overall survival, 5-year conditional overall survival, and 5-year disease-free period.

Results

Data from 761 patients were used for the analyses. Complications were associated with decreased 1-year overall survival (hazard ratio (HR) 2.87, 95% CI 1.82-4.51; p<0.001), 5-year overall survival (HR 1.59, 95% CI 1.25-2.04; p<0.001), and 5-year conditional overall survival (HR 1.34, 95% CI 1.06-1.69; p=0.016), whereas an increasing number of complications had no additional impact. Anastomotic leakage, excessive blood loss, and (abdominal) sepsis were associated with reduced 1-year overall survival, anastomotic leakage, delirium, abscess, and (abdominal) sepsis with reduced 5-year overall survival, and anastomotic leakage, delirium, and abscess with reduced 5-year conditional overall survival. Anastomotic leakage, electrolyte disorders, and abscess were risk factors for recurrence within five years.

Conclusions

Our results demonstrate the serious impact of the most frequent complications after surgery for colon cancer on short-term and long-term outcomes. This study confirms the prolonged impact of surgery and demonstrates that complications result not only in reduced 1-year survival, but also in reduced long-term outcomes.

INTRODUCTION

Colorectal cancer is one of the most commonly diagnosed malignancies worldwide.[1] In the Netherlands, approximately 15,000 patients were diagnosed with colorectal cancer in 2014, of which almost 70% had a tumour located in the colon.[2] Surgery is the mainstay curative treatment for non-metastasised colon cancer. Depending on stage, surgery is followed by adjuvant chemotherapy.[3-5] Still ~20% of all patients with stage I-III colon cancer will eventually develop metastatic disease within 5 years.[6] Five-year overall survival ranges from 94% for patients with stage I disease to 75% for patients with stage III disease.[2]

A considerable amount of patients will suffer from postoperative complications.[7-11] Previous studies have shown an association between the occurrence of complications and decreased overall survival, whereas the association between complications and recurrences is less clear.[12-15] Importantly, Dekker et al. showed that 30-day mortality after surgery for colon or rectal cancer underestimates 1-year mortality.[16] The 1-year excess mortality rate was more than 10% for patients who underwent surgery for colon cancer, and was even much higher for subgroups.[16,17] Several risk factors have been identified for excess mortality during the first year after surgery for colon cancer, including stage III disease, comorbidity, emergency surgery, and postoperative surgical complications.[17] Moreover, readmission within 30 days after colectomy for cancer predicts 1-year mortality.[18] These results suggest a prolonged impact of surgery on survival.

Most previous studies investigating the association between complications and outcomes after surgery for colon cancer lacked detailed information for specific complications or studied surgical complications only. The association between specific complications, directly as well as indirectly related to surgery, and survival and recurrences therefore is not yet completely unravelled.

The purpose of this study was to identify the ten most frequent complications after surgery for stage I-III colon cancer and to assess the association between these complications and 1-year overall survival, 5-year overall survival, 5-year conditional overall survival (i.e., conditional on having survived the first postoperative year), and 5-year disease-free period.

PATIENTS AND METHODS

Patients

All patients with stage I-III colon cancer (ICD-10 C18), diagnosed between January 1, 2006 and December 31, 2008, and treated with curative intent in the following hospitals:

Leiden University Medical Centre, an academic hospital, HAGA Hospital, Reinier de Graaf Gasthuis, Medical Centre Haaglanden, and Groene Hart Hospital, all teaching hospitals, were included. We started with data from the Netherlands Cancer Registry. Trained data managers collected additional data from the medical records in the hospitals. We excluded patients with unknown localisation of the tumour and missing medical records. We collected data on patient characteristics, diagnosis, surgery, TNM stage, adjuvant treatment, complications, comorbidity, recurrence, and follow-up.

Age was categorised as <65 years, 65-74 years, and ≥75 years. Comorbidity was categorised as 0, 1, 2, and ≥3 comorbidities. The information on TNM stage was based on pathological reports. If pathological data were missing, clinical TNM stage was used. Complications were defined as any complication within 30 days after surgery, as well as any long-term complication registered in the medical records. Complications included both complications directly related to surgery (e.g. anastomotic leakage), as well as indirectly related to surgery (e.g. pneumonia). We categorised complications as no and yes, and the total number of complications as 0, 1, and ≥2. Furthermore, we identified the ten most frequent complications after surgery. Anastomotic leakage included both anastomotic leakage as well as faecal peritonitis and abdominal sepsis as a result of anastomotic leakage. Complications were classified as (abdominal) sepsis if (abdominal) sepsis was registered in the medical records without identifiable cause. Type of surgery was recorded as elective or emergency surgery. Recurrence included both locoregional and distant recurrence.

Endpoints were 1-year overall survival, 5-year overall survival, 5-year conditional overall survival, and 5-year disease-free period. Five-year conditional overall survival was calculated as the proportion of patients surviving five additional years under the condition of surviving the first postoperative year. Overall survival was defined as time from surgery to death of any cause, or to end of follow-up (censored). Disease-free period was defined as time from surgery to recurrence, or as time from surgery to end of follow-up, or death in case of no recurrence. Follow-up was completed through April 1, 2013.

Statistical analyses

Median follow-up was calculated according to the reverse Kaplan-Meier method.[19] The percentages 1-year overall survival, 5-year overall survival, and 5-year disease-free period were obtained from life-tables. We used Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) to study the association between complications and overall survival (truncated at 1 and 5 years), disease-free period (truncated at 5 years), and conditional overall survival (truncated at 5 years under the condition of surviving the first postoperative year). A Kaplan-Meier curve was

constructed to compare overall survival between patients with no complications, one complication, and two or more complications.

One-year overall survival, 5-year overall survival, 5-year disease-free period, and 5-year conditional overall survival analyses were adjusted for the following potential confounders: gender, age, T-stage, N-stage, grade, emergency surgery, and comorbidity. A p-value <0.05 was considered as statistical significant.

Moreover, we described the number of complications as well as the percentage 1-year overall survival, 5-year overall survival, and 5-year disease-free period for patients with and without complications by age categories.

All analyses were done with IBM SPSS Statistics, version 20.0.

RESULTS

Between January 1, 2006 and December 31, 2008, a total of 776 patients were identified. We excluded seven patients with an unknown localisation of the tumour, and eight patients with missing medical records. Data from the remaining 761 patients were used for analyses. Table 1 shows the characteristics of the patients. Median follow-up from surgery was 5.4 years (interquartile range 4.7-6.2 years).

Table 1. Patient characteristics

Characteristics	Colon cancer (*n* =761)
Gender	
Male	360 (47.3)
Female	401 (52.7)
Age	
<65 years	206 (27.1)
65-74 years	210 (27.6)
≥ 75 years	345 (45.3)
Year of diagnosis	
2006	273 (35.9)
2007	260 (34.2)
2008	228 (30.0)
T stage	
T1-T2	185 (24.3)
T3-T4	575 (75.6)
Unknown	1 (0.1)
N stage	
N0	479 (62.9)
N1	186 (24.4)
N2	94 (12.4)
Unknown	2 (0.3)

Table 1. Continued

Characteristics	Colon cancer (*n* =761)
Stage	
I	144 (18.9)
II	335 (44.0)
III	280 (36.9)
Unknown	2 (0.3)
Grade	
I	46 (6.0)
II	499 (65.6)
III	112 (14.7)
Unknown	104 (13.7)
Comorbidity	
0	179 (23.5)
1	200 (26.3)
2	159 (20.9)
≥3	223 (29.3)
Emergency surgery	
No	656 (86.2)
Yes	105 (13.8)

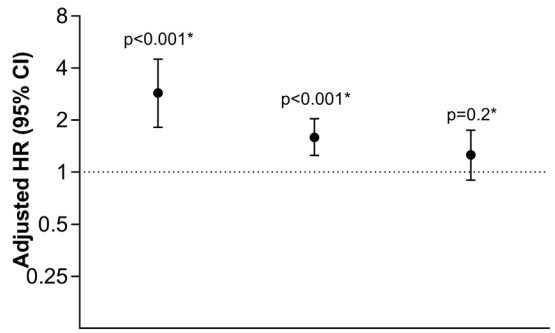
Data are presented as *n* (%)

Presence and number of complications

Complications occurred in 41.9% of the patients, of which 21,8% had one complication and 20.1% had two or more complications. More than 95% of all first complications occurred within 30 days after surgery.

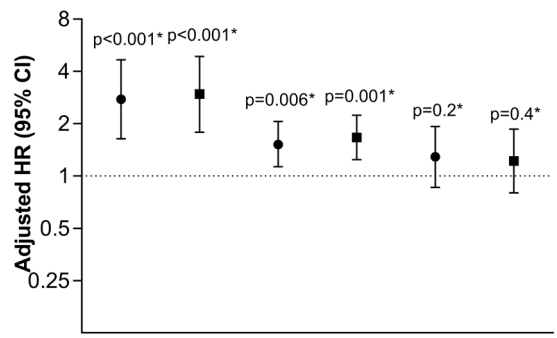
Figure 1 shows the association between complications (no and yes, as well as 0, 1, and ≥2) and survival and recurrences. Complications were associated with decreased 1- and 5-year overall survival, although an increasing number of complications had no significant additional impact on survival. One-year overall survival was 93.8% (95% CI 91.2-95.8%) for patients with no complications compared with 77.1% (95% CI 72.1-81.4%) for patients with complications (adjusted HR 2.87, 95% CI 1.82-4.51; p<0.001). For patients with one complication, 1-year overall survival was 80.1% (95% CI 73.2-85.4%) with an adjusted HR of 2.77 (95% CI 1.64-4.67; p<0.001 compared with no complications), and 73.9% (95% CI 66.1-80.1%) for patients with two or more complications (adjusted HR 2.96, 95% CI 1.79-4.89; p<0.001 compared with no complications). Five-year overall survival was 70.4% (95% CI 65.8-74.6%) for patients with no complications and 53.7% (95% CI 47.9-59.1%) for patients with complications (adjusted HR 1.59, 95% CI 1.25-2.04; p<0.001). Five-year overall survival was 57.0% (49.0-64.2%) for patients with one complication (adjusted HR 1.52, 95% CI 1.13-2.06, p=0.006 compared with no complications), and 50.0% (95% CI 41.7-57.8%) for patients with two or more complications (adjusted HR 1.67, 95% CI 1.24-2.24; p=0.001 compared with no complications). Figure 2 shows the cumulative overall survival by number of complications.

a



Complications	*n* (%)	% 1-year OS **	% 5-year OS **	% 5-year DFP **
No (ref.)	442 (58.1)	93.9%	70.4%	78.8%
● Yes	319 (41.9)	77.1%	53.7%	74.0%

b

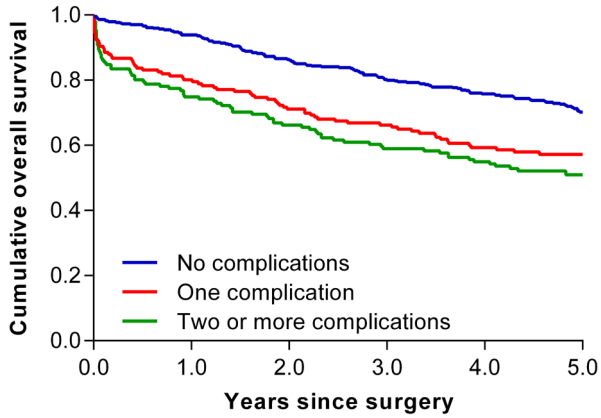


Complications	*n* (%)	% 1-year OS **	% 5-year OS **	% 5-year DFP **
No (ref.)	442 (58.1)	93.9%	70.4%	78.8%
● One	166 (21.8)	80.1%	57.0%	74.9%
■ Two or more	153 (20.1)	73.9%	50.0%	73.0%

Figure 1. Association between a. presence of complications and b. number of complications and one-year overall survival, five-year overall survival, and five-year disease-free period

* Adjusted for gender, age, T-stage, N-stage, grade, emergency surgery, and comorbidity

** Percentages obtained from life-tables



Number at risk						
No complications	442	414	379	350	321	195
One complication	166	133	118	106	92	64
Two or more complications	153	113	100	89	81	44

Figure 2. Cumulative overall survival for patients with no complications, one complication, and two or more complications

We did not detect differences in 5-year disease-free period between patients with complications (no and yes, as well as 0, 1, and ≥2) and patients without complications (Figure 1).

Supplementary table 1 describes the number of complications and the percentages 1-year overall survival, 5-year overall survival, and 5-year disease-free period for patients with and without complications by age categories.

Ten most frequent complications

Table 2 shows the association between the ten most frequent complications and survival and recurrences. The ten most frequent complications were ileus (7.0%), anastomotic leakage (5.3%), pneumonia (5.0%), excessive blood loss (5.0%), electrolyte disorders (4.1%), cardiac arrhythmia (4.1%), delirium (4.1%), abscess (3.7%), urinary tract infection (3.4%), and (abdominal) sepsis (3.3%).

In adjusted analyses, patients with anastomotic leakage (HR 3.29, 95% CI 1.83-5.91, p<0.001), excessive blood loss (HR 1.98, 95% CI 1.02-3.84; p=0.04), and (abdominal) sepsis (HR 4.09, 95% CI 2.11-7.93, p<0.001) had worse 1-year overall survival compared with patients without these specific complications.

Moreover, patients with anastomotic leakage (adjusted HR 2.74, 95% CI 1.81-4.15; p<0.001), delirium (adjusted HR 1.90, 95% CI 1.20-2.99; p=0.006), abscess (adjusted HR

1.88, 95% CI 1.11-3.17; p=0.02), and (abdominal) sepsis (adjusted HR 2.93, 95% CI 1.74-4.92; p<0.001) had reduced 5-year overall survival.

Table 2. Association between the ten most frequent complications and one-year overall survival, five-year overall survival, and five-year disease-free period

			1-year overall survival					
Complication	***n***	**(%)**	**1yr OS (%) no-yes**	**Crude**	**(95% CI)**	**p-value**	**Adjusted***	**(95% CI)**	**p-value**
Ileus	53	(7.0)	86.9-86.8	1.00	(0.47-2.16)	1.0	0.83	(0.38-1.82)	0.6
Anastomotic leakage	40	(5.3)	88.1-65.0	3.36	(1.91-5.91)	<0.001	3.29	(1.83-5.91)	<0.001
Pneumonia	38	(5.0)	87.5-73.7	2.28	(1.18-4.37)	0.01	1.30	(0.66-2.58)	0.5
Excessive blood loss	38	(5.0)	87.7-71.1	2.53	(1.35-4.73)	0.004	1.98	(1.02-3.84)	0.04
Electrolyte disorders	31	(4.1)	86.7-90.3	0.69	(0.22-2.19)	0.5	0.64	(0.20-2.03)	0.5
Cardiac arrhythmia	31	(4.1)	87.8-64.5	3.41	(1.82-6.37)	<0.001	1.83	(0.95-3.53)	0.07
Delirium	31	(4.1)	87.8-64.5	3.38	(1.81-6.33)	<0.001	1.67	(0.85-3.26)	0.1
Abscess	28	(3.7)	87.0-82.1	1.35	(0.55-3.32)	0.5	1.11	(0.44-2.84)	0.8
Urinary tract infection	26	(3.4)	86.5-96.2	0.27	(0.04-1.91)	0.2	0.24	(0.03-1.76)	0.2
(Abdominal) sepsis NOS	25	(3.3)	88.2-48.0	6.60	(3.68-11.85)	<0.001	4.09	(2.11-7.93)	<0.001
			5-year overall survival					
Complication			**5yr OS (%) no-yes**	**Crude**	**(95% CI)**	**p-value**	**Adjusted***	**(95% CI)**	**p-value**
Ileus	53	(7.0)	62.7-73.0	0.70	(0.41-1.19)	0.2	0.67	(0.39-1.15)	0.1
Anastomotic leakage	40	(5.3)	65.0-34.8	2.66	(1.77-3.99)	<0.001	2.74	(1.81-4.15)	<0.001
Pneumonia	38	(5.0)	63.8-55.0	1.48	(0.91-2.42)	0.1	1.06	(0.64-1.76)	0.8
Excessive blood loss	38	(5.0)	63.9-53.1	1.45	(0.88-2.36)	0.1	1.36	(0.82-2.24)	0.2
Electrolyte disorders	31	(4.1)	63.7-56.5	1.18	(0.68-2.06)	0.6	1.15	(0.65-2.02)	0.6
Cardiac arrhythmia	31	(4.1)	64.0-48.4	1.92	(1.16-3.19)	0.01	1.31	(0.78-2.21)	0.3
Delirium	31	(4.1)	64.9-28.4	3.00	(1.94-4.65)	<0.001	1.90	(1.20-2.99)	0.006
Abscess	28	(3.7)	64.2-40.7	2.00	(1.21-3.32)	0.007	1.88	(1.11-3.17)	0.02
Urinary tract infection	26	(3.4)	63.0-75.4	0.56	(0.25-1.25)	0.6	0.51	(0.22-1.15)	0.1
(Abdominal) sepsis NOS	25	(3.3)	64.7-25.7	3.71	(2.30-5.99)	<0.001	2.93	(1.74-4.92)	<0.001
						5-year disease-free period			
Complication			**5yr DFP (%) no-yes**	**Crude**	**(95% CI)**	**p-value**	**Adjusted***	**(95% CI)**	**p-value**
Ileus	53	(7.0)	76.9-79.1	0.89	(0.47-1.68)	0.7	0.88	(0.46-1.68)	0.7
Anastomotic leakage	40	(5.3)	78.2-51.5	2.82	(1.63-4.89)	<0.001	2.66	(1.50-4.70)	0.001
Pneumonia	38	(5.0)	76.8-81.7	0.74	(0.30-1.80)	0.5	0.65	(0.26-1.60)	0.3
Excessive blood loss	38	(5.0)	77.3-71.1	1.35	(0.69-2.64)	0.4	1.84	(0.92-3.71)	0.08
Electrolyte disorders	31	(4.1)	77.6-63.7	1.68	(0.89-3.20)	0.1	2.08	(1.08-3.97)	0.028
Cardiac arrhythmia	31	(4.1)	76.7-86.0	0.60	(0.19-1.86)	0.4	0.50	(0.16-1.60)	0.2
Delirium	31	(4.1)	77.3-63.7	1.39	(0.61-3.14)	0.4	1.17	(0.49-2.77)	0.7
Abscess	28	(3.7)	77.9-50.7	2.55	(1.38-4.71)	0.003	2.04	(1.08-3.85)	0.028
Urinary tract infection	26	(3.4)	77.0-76.7	1.00	(0.44-2.26)	1.0	1.12	(0.49-2.58)	0.8
(Abdominal) sepsis NOS	25	(3.3)	77.4-56.7	2.38	(1.05-5.40)	0.04	2.13	(0.90-5.05)	0.09

*Adjusted for gender, age, T-stage, N-stage, grade, emergency surgery, comorbidity

Patients with anastomotic leakage (adjusted HR 2.66, 95% CI 1.50-4.70; p=0.001), electrolyte disorders (adjusted HR 2.08, 95% CI 1.08-3.97; p=0.028), or an abscess (adjusted HR 2.04, 95% CI 1.08-3.85; p=0.028) more often developed recurrences within

5 years after surgery compared with patients without these complications.

Conditional survival

The association between complications and 5-year overall survival under the condition of surviving the first postoperative year is shown in Table 3. Twenty-seven patients without complications died in the first postoperative year compared with 73 patients with complications (*n*=33 with 1 complication and *n*=40 with 2 or more complications). Patients with complications who survived the first postoperative year more often died after five additional years compared with patients without complications who survived the first postoperative year (adjusted HR 1.34, 95% CI 1.06-1.69; p=0.016). The adjusted HR was 1.25 (95% CI 0.94-1.66; p=0.13) for patients with one complication, and 1.45 (95% CI 1.08-1.95; p=0.013) for patients with two or more complications, both compared with patients without complications.

Patients with anastomotic leakage, delirium, or an abscess had worse 5-year overall survival under the condition of surviving the first postoperative year compared with patients without these specific complications.

Table 3. Association between complications and conditional survival

	5-year overall survival under the condition of surviving the first postoperative year					
Presence of complications	**Crude**	**(95% CI)**	**p-value**	**Adjusted***	**(95% CI)**	**p-value**
No	1	Reference		1	Reference	
Yes	1.34	(1.00-1.79)	0.05	1.34	(1.06-1.69)	0.016
Number of complications	**Crude**	**(95% CI)**	**p-value**	**Adjusted***	**(95% CI)**	**p-value**
0	1	Reference		1	Reference	
1	1.25	(0.87-1.79)	0.23	1.25	(0.94-1.66)	0.13
≥2	1.44	(1.00-2.09)	0.05	1.45	(1.08-1.95)	0.013
Ten most frequent complications *(no vs. yes)*						
Ileus	0.49	(0.23-1.05)	0.066	0.49	(0.23-1.05)	0.067
Anastomotic leakage	2.14	(1.22-3.77)	0.008	2.47	(1.38-4.42)	0.002
Pneumonia	0.88	(0.41-1.87)	0.7	0.66	(0.30-1.43)	0.3
Excessive blood loss	0.74	(0.33-1.66)	0.5	0.71	(0.31-1.62)	0.4
Electrolyte disorders	1.54	(0.84-2.82)	0.17	2.63	(0.68-10.19)	0.16
Cardiac arrhythmia	1.07	(0.47-2.40)	0.9	0.86	(0.37-1.97)	0.7
Delirium	2.94	(1.67-5.17)	<0.001	2.32	(1.29-4.20)	0.005
Abscess	2.66	(1.48-4.77)	0.001	2.80	(1.52-5.15)	0.001
Urinary tract infection	0.64	(0.26-1.56)	0.33	0.65	(0.27-1.61)	0.35
(Abdominal) sepsis NOS	2.05	(0.91-4.63)	0.08	1.91	(0.81-4.48)	0.14

*Adjusted for gender, age, T-stage, N-stage, grade, emergency surgery, comorbidity

DISCUSSION

This study shows an association between complications after surgery for stage I-III colon cancer and decreased short-term overall survival, as well as decreased long-term overall survival - even under the condition of surviving the first postoperative year. However, an increasing number of complications had no significant additional impact on survival. Of the ten most frequent complications, anastomotic leakage, excessive blood loss, and (abdominal) sepsis were associated with reduced 1-year overall survival. Anastomotic leakage, delirium, abscess, and (abdominal) sepsis were risk factors for worse 5-year overall survival, whereas anastomotic leakage, delirium, and abscess were risk factors for 5-year conditional overall survival. Moreover, anastomotic leakage, electrolyte disorders, and abscess were risk factors for recurrence within 5 years after surgery.

More than 40% of all patients with stage I-III colon cancer in this study suffered from at least one complication. Previous studies have shown a complication rate of approximately 30-35% after surgery for colorectal cancer.[7-11] Possible explanations for the higher rate in our study could be that some studies assessed surgical complications only, whereas other studies did not record all specific complications separately. Moreover, given that all patients underwent surgery between 2006 and 2008, there could have been improvements over time in surgery and perioperative care, resulting in fewer complications.

In line with previous studies, the results of the current study show an association between complications and decreased overall survival.[12-15] A remarkable finding of our study was that no significant differences in overall survival were found between patients with one complication and patients with two or more complications, although this might be related to sample size. Possibly, the first registered complication is the most serious complication mainly affecting survival, whereas subsequent complications are less serious or might be related to the first complication.

Several studies have shown that the impact of colorectal cancer surgery and postoperative complications goes beyond thirty-day postoperative mortality.[16,17,20-22] Importantly, up to 25% of all colorectal cancer deaths in the first postoperative year are attributed to postoperative complications.[23] Moreover, anastomotic leakage is known to be a serious complication in colorectal surgery, causing a significant increase in short-term mortality, as well as long-term mortality and recurrences[24,25] Furthermore, a recent study by Odermatt et al. shows that major postoperative complications negatively impacted long-term survival, although no association with recurrences was demonstrated.[13] The results of our study are in accordance with these results. Our study adds important information about the association between specific complications and

survival and recurrences. Moreover, we showed that there still is an association between complications and surviving five additional years after surviving the first postoperative year (5-year conditional overall survival). This finding underlines the long-term effect of complications on overall survival, and shows that the long-term overall survival is not only determined by the short-term survival.

In the present study, it was demonstrated that anastomotic leakage, excessive blood loss, and (abdominal) sepsis were risk factors for dying in the first postoperative year. These serious complications directly impact important functions to survive. Both anastomotic leakage and (abdominal) sepsis were also associated with reduced 5-year overall survival, showing the prolonged impact of complications on survival.

Furthermore, abscess and delirium were associated with decreased 5-year overall survival. Previous studies have shown that postoperative delirium is associated with prolonged hospital stay and poor functional recovery.[26] The most important risk factors for postoperative delirium known from literature are advanced age, preoperative cognitive performance, and comorbidity.[27] This implies that patients who develop delirium are more frail, as also suggested by Raats et al.[28], which could be a possible explanation for worse long-term survival.

In a retrospective analysis by Law et al, postoperative complications were found to be adversely affected with recurrences.[12] By contrast, Odermatt et al. did not demonstrate this association.[13] Although we also found no association between the presence or the number of complications and recurrences, we did demonstrate that patients with anastomotic leakage, electrolyte disorders, or abscess more often had recurrences within 5 years after surgery compared with their counterparts. The exact mechanism of the association between complications and recurrences has not been elucidated yet. It has been shown that severe postoperative surgical complications in patients with stage III colon cancer were associated with less use or discontinuation of adjuvant chemotherapy.[10] This might partly explain the association between the specific complications and recurrences for patients with high-risk stage II disease or stage III disease, although we did not demonstrate an association between the presence or number of complications and recurrences. Moreover, it is suggested that extended immunosuppression and/or angiogenic stimulation due to postoperative infectious complications could play a role in proliferation of metastatic tumour cells.[12,13,29] The finding that anastomotic leakage and abscess were associated with recurrences supports this theory. However, we could not explain the association between electrolyte disorders and recurrences.

This study has some limitations. Although we adjusted the analyses for potential confounders, there might have been residual confounding. Since not only complications

within 30 days after surgery, but also long-term complications were included, immortal time bias might have been introduced. However, we consider the risk of immortal time bias to be very low given that over 95% of all first complications occurred within 30 days after surgery. Unfortunately, we had no information on the severity of complications. However, the main strength of this study is its detailed information regarding complications. Furthermore, this study is, to our knowledge, unique in providing a comprehensive insight into the association between the most frequent complications after surgery for stage I-III colon cancer and short-term as well as long-term outcomes. Moreover, our study covered patients from several hospitals, including both university and teaching hospitals.

CONCLUSIONS

Complications are associated with decreased short-term and long-term overall survival, although an increasing number of complications had no significant additional impact on survival. Of the ten most frequent complications, anastomotic leakage, excessive blood loss, and (abdominal) sepsis were associated with reduced 1-year overall survival. Anastomotic leakage, abscess, delirium, and (abdominal) sepsis were associated with decreased 5-year overall survival, while anastomotic leakage, delirium, and abscess were associated with decreased 5-year conditional overall survival. Furthermore, anastomotic leakage, electrolyte disorders, and abscess were associated with recurrences at 5 years. This study confirms the prolonged impact of surgery and demonstrates that complications result not only in reduced 1-year survival, but also in reduced long-term outcomes.

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SUPPLEMENTARY DATA

Supplementary table 1. Number of complications and percentages one-year overall survival, five-year overall survival, and five-year disease-free period for patients with and without complications by age categories.

	<65 years	65 – 74 years	≥75 years
Complications			
No	149 (72.3%)	129 (61.4%)	164 (47.5%)
Yes	57 (27.7%)	81 (38.6%)	181 (52.5%)
One-year overall survival			
No complications	99.3%	91.5%	90.9%
Complications	85.9%	90.1%	68.5%
Five-year overall survival			
No complications	81.5%	73.5%	58.0%
Complications	67.9%	66.3%	43.5%
Five-year disease-free period			
No complications	79.0%	80.2%	77.3%
Complications	62.8%	65.2%	84.1%