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Citation for published version (APA):

Ramphal, W., Boeding, J. R. E., Gobardhan, P. D., Rutten, H. J. T., de Winter, L. J. M. B., Crolla, R. M. P. H., & Schreinemakers, J. M. J. (2018). Oncologic outcome and recurrence rate following anastomotic leakage after curative resection for colorectal cancer. *Surgical Oncology*, *27*(4), 730-736. https://doi.org/10.1016/j.suronc.2018.10.003

Document status and date:
Published: 01/12/2018

DOI:
10.1016/j.suronc.2018.10.003

Document Version:
Publisher's PDF, also known as Version of record

Document license:
Taverne

Please check the document version of this publication:

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Surgical Oncology 27 (2018) 730–736

Contents lists available at ScienceDirect

Surgical Oncology

journal homepage: www.elsevier.com/locate/suronc

Oncologic outcome and recurrence rate following anastomotic leakage after curative resection for colorectal cancer

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ARTICLE INFO

Keywords:
Colorectal cancer
Anastomotic leakage
Cancer recurrence

ABSTRACT

Introduction: Anastomotic leakage is one of the most severe early complications after colorectal surgery, and it is associated with a high reoperation rate-, and increased in short-term morbidity and mortality rates. It remains unclear whether anastomotic leakage is associated with poor oncologic outcomes. The aim of this study was to determine the impacts of anastomotic leakage on long-term oncologic outcomes, disease-free survival and overall mortality in patients who underwent curative surgery for colorectal cancer.

Methods: This single-centre, retrospective, observational cohort study included patients who underwent curative surgery for colorectal cancer between 2005 and 2015 and who had a primary anastomosis. Survival- and multivariate cox regression analyses were performed to adjust for confounding.

Results: A total of 1984 patients had a primary anastomosis after surgery. The overall incidence of anastomotic leakage was 7.5%; 19 patients were excluded because they were lost to follow-up. Of the remaining 1965 patients, 41 (2.1%) developed local recurrence associated with anastomotic leakage [adjusted hazard ratio (HR) = 2.25; 95% confidence interval (CI) 1.14–5.29; P = 0.03]. Distant recurrence developed in 291(14.8%) patients with no association with anastomotic leakage [adjusted HR = 1.30 (95% CI: 0.85–1.97) P = 0.23]. Anastomotic leakage was associated with increased long-term mortality [adjusted HR = 1.69 (95% CI 1.32–2.18) P < 0.01]. Five year disease-free survival was significantly decreased in patients with anastomotic leakage, (log rank test P < 0.01).

Conclusion: Anastomotic leakage was significantly associated with increased rates of local recurrence, disease free-survival and overall mortality. Associations of anastomotic leakage with distant recurrence was not found.

1. Introduction

Anastomotic leakage (AL) is one of the most severe early complications after colorectal surgery. AL is associated with a high reoperation rate, increases in the severity of short-term morbidity and mortality rates, poor functional outcomes and higher healthcare costs [1–7]. Incidence rates of AL vary from 0.5 to 34% but are dependent on several factors, such as tumour location (colon or rectum), type of operation, and patient characteristics [4,8–10]. Another explanation for the broad range of reported cases of AL is the wide variability in the definition of AL. Some articles only included patients with symptomatic AL, whereas other authors also included asymptomatic AL, the diagnosis of which was based on radiologic findings. Because of the recent increase in sphincter preserving surgery for rectal cancer, the likelihood of AL will increase as well, and patients with a low anastomosis have a higher risk of leakage [11–14]. In general, AL is related to poor prognosis. In the literature, there have been conflicting studies of the oncologic outcomes and long-term mortality in patients with AL after curative surgery for colorectal carcinoma (CRC). Several studies have reported increased rates of local tumour recurrence [15–23], while other studies have not [24–30]. The relation with the occurrence of distant metastases has also been studied. In these studies, contradictory results have been found [9,21,22,30–32]. It remains unclear whether AL is associated with poor oncologic outcomes. The aim of this study was to determine the impact of AL on local recurrence and distant recurrence rates, -disease-free survival and overall mortality in patients who underwent curative

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https://doi.org/10.1016/j.suronc.2018.10.003
Received 10 May 2018; Received in revised form 31 August 2018; Accepted 1 October 2018
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surgery for CRC.

2. Materials and methods

2.1. Database and definitions

This was a single-centre retrospective observational study with data on eleven years of colorectal surgeries. We retrospectively reviewed all of the patients who were treated between January 2005 and December 2015. Data regarding patients between 2005 and 2010 were prospectively collected by the surgical team. Data from patients who underwent surgery in our hospital because of colorectal cancer between 2011 and 2015 were retrieved at the National Cancer Registration centre (Integraal Kanker Centrum Nederland, IKNL). Medical and demographic data were ascertained from medical charts. Data regarding surgery included the location of the tumour within the colon and/or rectum, type of resection that was performed and surgical approach (open or laparoscopic surgery). Laparoscopic surgery also included robotic surgery. Pathology results were classified according to The TNM classification, 5th edition [33]. Postoperative data consisted of surgical complications, including anastomotic leakage, oncologic outcomes and postoperative mortality. Anastomotic leakage was defined as communication between the intra- and extraluminal compartments, determined by clinical evidence and/or confirmed by radiologic imaging. Clinical evidence was based on symptomatic anastomotic leaks, defined by the presence of peritonitis or fever (temperature greater than 38.5 °C), or the discharge of pus or faeces from the abdominal drain. Clinical and/or biochemical suspicion (increased leucocytes and C-reactive protein (CRP)) of anastomotic leakage led to early CT assessment. Additionally, anastomotic dehiscences with leakage into the peritoneum or pelvic cavity, leakage from the efferent or afferent limb and anastomotic abscesses were also considered as anastomotic leakage. Asymptomatic anastomotic leakage was considered when leakage was assessed on CT-scan, without any relevant clinical symptoms or laboratory examination findings during the postoperative course. The oncological outcome measures were local recurrence, distant recurrence, disease free survival and overall survival. All patients with recurrent disease were confirmed histologically whenever possible, or otherwise by diagnostic imaging or surgery. Local recurrence was defined as recurrent tumour growth intraabdominally or within the pelvic cavity. Other tumour recurrence events were categorized as distant recurrence, including peritoneal metastasis/carcinomatosis. Disease-free survival was defined as the period from the date of curative surgery to the date of detection of local recurrence and/or distant recurrence, date of last follow-up or death. Overall survival was defined as the time from the date of curative surgery to the date of death or last follow-up. Date of death was confirmed using the social security numbers of patients in the Dutch Municipal Personal Records Database (Gemeentelijkebasisadministratie persoonsgegevens, GBA with their software program CompeT&TEindhoven). The follow-up strategies for patients with and without anastomotic leakage were identical. Most of the patients had a follow-up interval by the surgeon of three months during the first year and every six months thereafter. Each follow-up visit included a physical examination, measurement of the serum carcinoembryonic antigen (CEA), ultrasound of the abdomen and chest X-ray. Chest CT, abdominopelvic CT, or positron emission tomography (PET) were performed when there was high suspicion of recurrence of disease on routine imaging studies with or without increased CEA levels.

2.2. Inclusion and exclusion criteria

Patients were included if they underwent colorectal surgery for a colorectal tumour between 2005 and 2015. Patients with appendix carcinomas or pseudomyxoma peritonei (PMP) were excluded. Patients who underwent palliative surgical procedures were also excluded. Surgical procedures with permanent colostomy or no primary anastomosis were excluded as well (Hartmann procedure, abdominoperineal resection (APR) or transanal endoscopic microsurgery (TEM)).

2.3. Ethical approval

For ethical approval, we consulted the national institutional review board Medical Research Ethics Committees United (MEC-U). Referring to this study (reference number W17.073) confirmation was received that the Medical Research Involving Human Subject Act (WMO) does not apply; therefore, official approval of this study by the MEC-U was not required under the WMO. We also consulted the institutional review board of the Amphia Hospital (AMOA) and it confirmed that no formal written waiver for the need of ethics approval was required, because of the retrospective design of the study.

2.4. Statistics

The Kolmogorov-Smirnov test was used to define whether data was normally distributed. Data are reported as means and SDs for normally distributed data and medians and interquartile ranges (IQRs) for non normally distributed data. We used the $\chi 2$ test to compare dichotomous variables. Overall survival and disease free survival analyses were performed with Kaplan-Meier curves between anastomotic leakage and no anastomotic leakage. The log-rank test was used to test outcomes between these two groups. Cox proportional hazard models were used to estimate the independent effects of covariates on oncologic outcomes and overall mortality measured by the adjusted hazard ratio (HR) with a 95% confidence interval (CI). Variables that were statistically significant in the univariate Cox regression and/or had clinical relevance were included in the multivariate analysis. A two sided P-value less than 0.05 was used to indicate statistical significance. All of the data analyses were performed with the IBM SPSS statistics software program, version 24.

3. Results

A total of 2703 patients underwent surgery for CRC between 2005 and 2015 in this cohort.After exclusion, 1984 patients were eligible (73.4%) (Fig. 1). The overall incidence of AL was 148 out of 1984 patients (7.5%). Nineteen patients were lost to follow-up because of emigration orfollow-up in another hospital. A total of 1965 patients were included for the analysis. The median age was 70.0 years old (IQR 62–77), and the median follow-up time was 4.1 years (IQR 2.0–6.4) years). The patient and clinical characteristics are shown in Table 1.

3.1. Disease recurrence

The overall local recurrence rate was 2.1% (41 of 1965) and the overall distant recurrence ratewas 14.8% (291 of 1965). The incidence of local recurrence at the end of follow-up was significantly higher in the AL group compared to the no AL group (4.7% vs. 1.9%, P = 0.019). However, there was no significant difference in the incidence of distant recurrence at the end of follow-up in the AL group (17.6% vs. 14.6%, P = 0.326, Table 2). Local and distant recurrences were diagnosed in twenty patients (1.0%), three patients in the AL group and seventeen patients in the no AL group. The median time to diagnosis of local recurrence was 1.1 years (IQR 0.7–2.1 years). The median time to diagnosis of distant recurrence was 1.1 year (IQR 0.6–2.2 years). No significant difference was found in the median time to local recurrence in the anastomotic leakage group compared to the group without anastomotic leakage (1.1 years (IQR 0.7–1.8) vs. 1.0 year (IQR -0.7–2.3), P = 0.86). Likewise, no significant difference was found in the median time to distant recurrence in the anastomotic leakage group compared to the group without anastomotic leakage (0.5 year (IQR 0–1.1) vs. 0.4 year (IQR 0–1.4) P = 0.73). In the univariate analyses, Al was

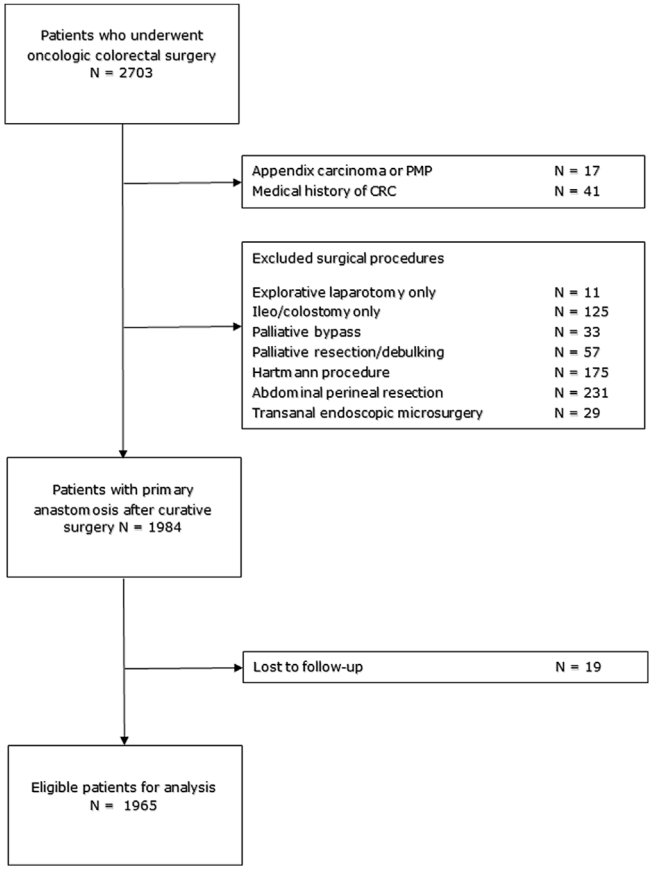


Fig. 1. Flow-chart of included patients.

associated with local recurrence [HR = 2.93 (95% CI: 1.30–6.60) P = 0.01](Fig. 2A), as confirmed in the multivariate analysis [HR = 2.25 (95% CI:1.14–5.29) P = 0.03]. The only other covariate that was a significant hazard for local recurrence was more advanced tumour stage (Table 3). A total of 14 patients (9.5%) were defined as asymptomatic and 134 patients developed symptomatic anastomotic leakage (90.5%). One patient developed local recurrence in the asymptomatic leakage group and six patients in the symptomatic anastomotic leakage group (7.1% vs 4.5%). However no significant difference was found regarding the development of local recurrences between patients with asymptomatic and symptomatic anastomotic leakage (P = 0.51). In contrast to local recurrence, no significant association between AL and distant recurrence was found in either the univariate [HR = 1.40 (95% CI: 0.94–2.10) P = 0.10](Fig. 2B)or multivariate analysis [HR = 1.30 (95% CI: 0.85–1.97) P = 0.23]. The covariates with significant influences on distant recurrence were age, tumour stage and bowel obstruction (Table 3). For patients with rectal cancer, receiving neoadjuvant therapy was associated with significant reduction in local recurrence rates in both the univariate analyses [HR = 0.44 (95% CI: 0.21–0.85) P < 0.01], and the multivariate analyses [HR = 0.62 (95% CI: 0.41–0.92) P = 0.02].

3.2. Disease-free survival and overall survival

Five-year overall survival was significantly decreased in patients with AL after surgery, compared to patients without AL (57.4% vs. 72.0% respectively P < 0.01(Fig. 3). The 30-day mortality was significant higher in the anastomotic leakage group compared to the group without anastomotic leakage (8.8% vs 2.5% P < 0.001). This significant difference even increases when the 60-day mortality was investigated (17.6% vs. 2.8% P < 0.00001). Similarly, the five year disease-free survival rate was significantly lower in patients with AL (48.0% vs 64.1% P < 0.01, (Fig. 4)). AL was significantly associated with increased overall mortality [HR = 1.69 (95% CI: 1.32–2.18) P < 0.01]. Covariates that also reached statistical significance were age, ASA-classification, type of surgical procedure, surgical approach, tumour stage and bowel obstruction (Table 3). Local recurrence [HR = 1.93 (95% CI: 1.11–3.36) P = 0.02], distant recurrence [HR = 2.53 (95% CI: 1.52–4.21) P < 0.01], and both local and distant recurrence [HR = 2.91 (95% CI 2.39–3.53) P < 0.01] after anastomotic leakage were significantly associated with impaired overall mortality in the multivariate analyses compared to patients without any type of disease recurrence (Fig. 5).

Table 1
Patient and clinical characteristics of colorectal cancer patients who underwent surgery.

	Anastomotic leakage	No anastomotic leakage
N = 1965	148 (7.5%)	1817 (92.5%)
Gender		
Male	96 (64.9%)	1005 (55.3%)
Female	52 (35.1%)	812 (44.7%)
Median age in years (IQR)	69 (63–77)	70 (62–77)
Co-morbidity		
ASA-I	12 (8.1%)	212 (11.7%)
ASA-II	82 (55.4%)	966 (53.1%)
ASA-III	52 (35.2%)	607 (33.4%)
ASA-IV	2 (1.3%)	32 (1.8%)
Tumour stadium (UICC)		
Stage I	25 (16.9%)	398 (21.9%)
Stage II	58 (39.2%)	659 (36.3%)
Stage III	43 (29.1%)	559 (30.8%)
Stage IV	19 (12.8%)	172 (9.4%)
Missing	3 (2.0%)	29 (1.6%)
Tumour location		
Colon	114 (77%)	1341 (73.8%)
Rectum	34 (23%)	476 (26.2%)
Surgical procedure		
Ileocaecal resection	2 (1.4%)	34 (1.9%)
Right hemicolectomy	46 (31.1%)	669 (36.8%)
Left hemicolectomy	19 (12.8%)	148 (8.1%)
Transverse colectomy	7 (4.7%)	54 (3.0%)
Sigmoidal resection	32 (21.6%)	309 (17.0%)
Low anterior resection	36 (24.3%)	572 (31.5%)
(Sub)total colectomy	6 (4.1%)	31 (1.7%)
Bowel obstruction		
Yes	16 (10.8%)	170 (9.4%)
No	132 (89.2%)	1647 (90.6%)
Surgical approach		
Open surgery	88 (59.5%)	952 (52.4%)
Laparoscopic surgery	52 (35.1%)	762 (41.9%)
Conversion	8 (5.4%)	103 (5.7%)
Additional therapy		
Neoadjuvant therapy	28 (19.9%)	344 (18.9%)
Adjuvant chemotherapy	39 (26.4%)	464 (25.5%)

ASA: American society of anesthesiologists.
UICC: Union for International Cancer Control.

Table 2
Numbers of patients with local recurrence and distant metastases.

	Anastomotic leakage	No anastomotic leakage	P-value
N = 1965	148 (7.5%)	1817 (92.5%)	
Local recurrence			
Present	7 (4.7%)	34 (1.9%)	0.019
Absent	141 (95.3%)	1783 (98.1%)	
Systemic recurrence			
Synchronous metastasis	18 (12.2%)	192 (10.6%)	
Present after surgery for CRC	26 (17.6%)	265 (14.6%)	0.326
Absent	104 (70.2%)	1360 (74.8%)	

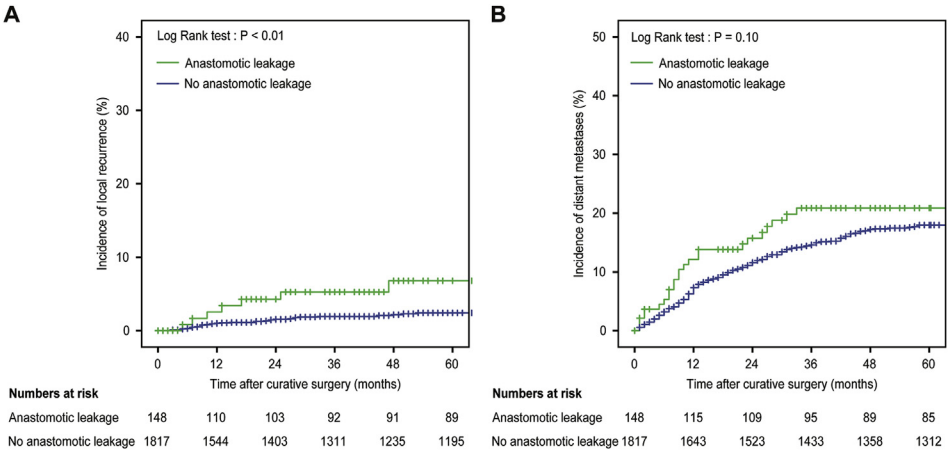


Fig. 2. Kaplan Meier plots illustrating the association between AL and the rates of local recurrence (A. log rank test: P < 0.01) and distant recurrence (B. log rank test: P = 0.10) in patients after curative surgery for CRC. (Green line: AL group, Blue line: no AL group).

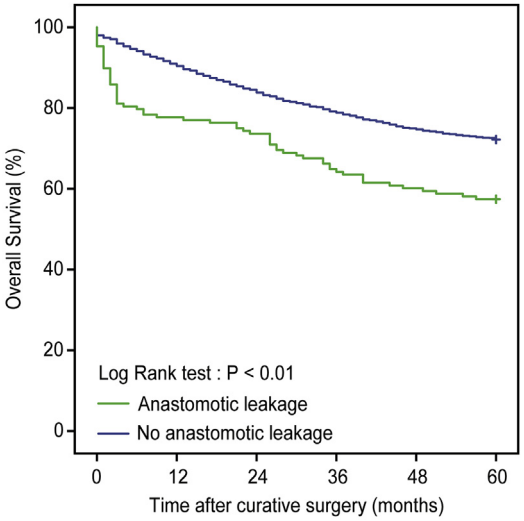
Table 3
Multivariate Cox Regression analyses of local recurrence, distant recurrence and overall mortality na: not applicalbe Comorbidity scale: American Society of Anesthesiologists (ASA) Tumour stadium scale: Union for International Cancer Control.

	Local recurrence			Distant recurrence			Overall mortality		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Anastomotic Leakage			0.03			0.23			< 0.01
No	1.00			1.00			1.00		
Yes	2.25	1.14 – 5.29		1.30	0.85 – 1.97		1.69	1.32 – 2.18	
Sex			0.54			0.41			0.12
Female	1.00			1.00			1.00		
Male	0.82	0.43 – 1.57		0.90	0.71 – 1.15		0.88	0.75 – 1.03	
Age group (years)			0.89			0.03			< 0.01
≤ 70	1.00			1.00			1.00		
71-79	0.84	0.40 – 1.77	0.64	0.67	0.52 – 0.92	0.01	1.55	1.29 – 1.87	< 0.01
≥ 80	0.97	0.36 – 2.58	0.95	0.74	0.50 – 1.10	0.14	2.76	2.23 – 3.42	< 0.01
Comorbidity			0.46			0.18			< 0.01
ASA I	1.00			1.00			1.00		
ASA II	2.15	0.50 – 9.32	0.31	1.28	0.86 – 1.91	0.22	1.49	1.06 – 2.08	0.02
ASA III	3.10	0.68 – 14.04	0.14	1.40	0.91 – 2.17	0.13	2.56	1.81 – 3.62	< 0.01
ASA IV	na			2.80	1.05 – 7.46	0.04	4.81	2.86 – 8.01	< 0.01
Tumour location			0.85			0.11			0.64
Colon	1.00			1.00			1.00		
Rectal	1.12	0.37 – 3.32		1.40	0.93 – 2.12		1.07	0.80 – 1.43	
Surgical procedure			0.63			0.15			< 0.01
Left hemicolectomy	1.00			1.00			1.00		
Ileocecal resection	2.79	0.46 – 17.03	0.27	2.11	0.98 – 4.53	0.06	1.56	0.95 – 2.56	0.08
Right hemicolectomy	1.54	0.44 – 5.36	0.50	1.51	0.94 – 2.43	0.09	1.70	1.25 – 2.32	< 0.01
Transverse resection	0.75	0.08 – 7.42	0.81	0.50	0.15 – 1.68	0.26	0.91	0.54 – 1.52	0.71
Sigmoidal resection	1.35	0.34 – 5.34	0.67	1.27	0.75 – 2.13	0.37	1.26	0.89 – 1.79	0.19
Low anterior resection (Sub)total colectomy	1.14	0.24 – 5.48	0.87	1.23	0.68 – 2.22	0.48	1.43	0.96 – 2.13	0.08
	3.49	0.65 – 18.6	0.14	1.90	0.87 – 4.13	0.11	1.40	0.76 – 2.58	0.28
Surgical approach			0.19			0.22			< 0.01
Open	1.00			1.00			1.00		
Minimally invasive	0.47	0.21 – 1.08	0.07	0.83	0.63 – 1.10	0.18	0.73	0.61 – 0.89	< 0.01
Converted	0.64	0.15 – 2.76	0.55	1.20	0.76 – 1.89	0.44	1.15	0.84 – 1.59	0.38
Tumour stage (UICC)			< 0.01			< 0.01			< 0.01
Stage I	1.00			1.00			1.00		
Stage II	4.82	0.61 – 38.39	0.14	2.28	1.43 – 3.65	< 0.01	1.47	1.14 – 1.89	< 0.01
Stage III	6.49	1.97 – 10.02	< 0.01	6.27	4.04 – 9.72	< 0.01	2.08	1.62 – 2.67	< 0.01
Stage IV	8.47	3.13 – 14.76	< 0.01	*			6.09	4.59 – 8.09	< 0.01
Bowel obstruction			0.64			< 0.01			< 0.01
No	1.00			1.00			1.00		
Yes	1.24	0.50 – 3.08		1.79	1.26 – 2.55		1.79	1.44 – 2.27	

* no analysis was performed for patients with distant metastases at the time of surgery for colorectal cancer (M1).

4. Discussion

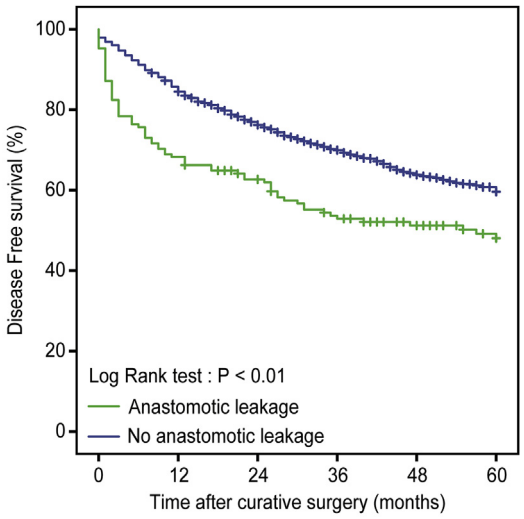
In this single-centre observational study, we determined the impact of anastomotic leakage on localand distant recurrence and overall survival in patients who underwent surgery for CRC. The principal finding was that anastomotic leakage was associated with an increased rate of local recurrence. However statistical significance was not found between AL and an increased rate of distant metastases. Local recurrence, distant metastasis and patients with both local recurrence and distant recurrence had an inferior impact on overall survival. That AL



Numbers at risk

Anastomotic leakage	148	115	109	95	89	85
No anastomotic leakage	1817	1643	1523	1433	1358	1312

Fig. 3. Overall survival in patients with (green line) and without AL (blue line) after curative surgery for CRC (log rank test: P < 0.01).

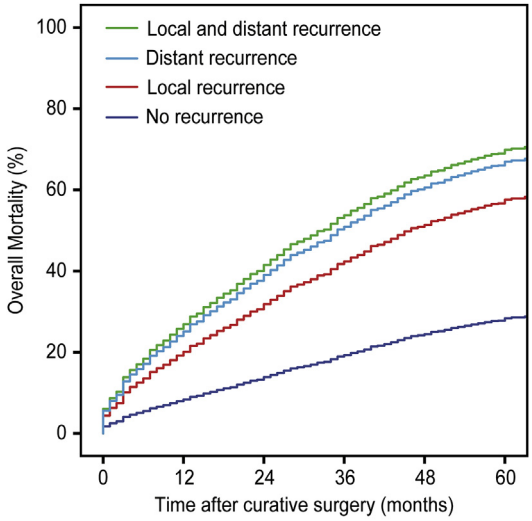


Numbers at risk

Anastomotic leakage	148	101	93	78	75	71
No anastomotic leakage	1817	1534	1391	1298	1221	1177

Fig. 4. 5 Year disease free survival in patients with AL (green line) and without AL (blue line) after curative surgery for CRC (log rank test: P < 0.01).

after curative surgery for CRC was associated with increased rates of local recurrence and the lack of association between AL and distant recurrence, are in agreement with three recently published meta-analyses [9,22,34]. However, Lu et al. only included articles on AL after rectal carcinoma, while Ha et al. and Mirnezami et al. included articles on both colonic and rectal cancer. However, Mirnezami et al. distinguished between colon and rectal anastomosis, and both were associated with increased rates of local recurrence. Ha et al. provided a comprehensive updated literature review of local and distant recurrence rates and survival after AL in these patients. They found reduced overall and disease-free survival, similar to our survival results. They performed additional subgroup analyses to assess oncological outcomes. Differences in oncological outcomes were identified in patients who received colon or rectal anastomoses, a distinction we did not



Numbers at risk

No recurrence	1654	1478	1402	1341	1288	1256
Local recurrence	21	18	12	10	9	7
Distant recurrence	270	245	204	166	140	129
Local and distant recurrence	20	17	14	11	10	4

Fig. 5. Kaplan-Meier plots illustrating overall mortality in patients after curative surgery for colorectal cancer. Mortality was increased in patients with local recurrence, distant metastases and patients with both local recurrence and distant metastases (P < 0.01).

make. Concerning distant metastases after AL,a difference was found but was not significant. Nevertheless, the analyses did demonstrate a non-significant trend towards an increased rate of distant metastases after AL. A large Danish multi-centre study with data merged from three different population-based national registers did find a significantly increased rate of distant metastases after AL [HR = 1.42 (95% CI: 1.13–1.78 P = 0.003)] [30]. Interestingly, they found no significant association between AL and increased local recurrence, which was completely the opposite of our results and the three forementioned meta-analyses. This study by Krarup et al. was one of the limited studies, which only evaluated AL after surgery for colonic carcinoma. Based on the results of Krarup et al., it is understandable to suspect there is an association between AL and developing distant metastasis. The Danish study had a larger study population than our cohort study and therefore more power to attain statistical significance. This could be precedent for a multicentre Dutch cohort study with sufficient patients to attain this power and possibly the same outcomes. Another subtle dissimilarity between our results and to those of Krarup et al. could lie in the definition of recurrence. In our cohort, patients with both local and distant recurrence were included in both the local recurrence and distant recurrence groups. In agreement with the classification of Goto et al. The Danish cohort of 8589 included patients defined patients with both local and distant recurrence as distant recurrence, leading to an underestimation of the local recurrence rate. The pathophysiology of developing local and distant recurrence after AL for CRC remains unclear, but several mechanisms have been reported. Microperforation before or during surgery could occur, which has been associated with significant higher local recurrence rates [35,36]. Vital malignant cells have been detected intraluminally and on staple and suture lines during surgery. In vitro and experimental animal studies have shown growth of these cells and their ability to metastasize [37–41]. These findings combined might explain cellular levels caused to AL leading to extra-luminal infiltration of exfoliated malignant cells from intraluminally. Moreover, after AL has occurred, it will slow the healing process of the mucosa which is a gateway for intraluminally

viable tumour cells to implant in the peritoneum or pelvis, with a higher risk for developing local recurrence [42,43]. Another and related explanation of the pathway from AL to cancer recurrence is the role of inflammation. Abdominal sepsis extends the inflammatory response from acute to chronic, leading to continued exposure of proinflammatory biomarkers associated with tumour proliferation and evolution to distant metastasis [44–48]. Two studies have even proved that extensive systemic inflammatory responses with significant elevated C-reactive protein (CRP) and other stress markers are independent predictors of higher recurrence rates and impaired disease-free survival in patients with CRC [49,50]. In mouse models, Bohle et al. proved that postoperative intra-abdominal bacterial infection stimulates Neoangiogenesis, resulting in a higher likelihood of disease recurrence [51]. In contrast to rectal cancer, colon cancer is known for lower local recurrence rates, which might be explained by colon cancer remaining undiagnosed until symptomatic systemic metastases develop [52]. A more surgery related explanation could be that margins for resection of colonic cancer are more radical than the margins for rectal cancer. Vital tumour cells located elsewhere in the lumen of the bowel than the actual tumour might have been removed with the tumour specimens [42]. The chance of local recurrence in patients having surgery for colonic cancer is therefore lower than for patient who had surgery for rectal cancer. Clearly, there were several limitations of the present study. First and foremost was the retrospective design of this cohort study, although we strived to reduce this bias with a multivariate Cox regression analysis. Second, we did not make a distinction of AL between patients with colon and rectal cancer.In the current literature opposing results could have been reported because of inconsistencies in the use of the definitions of anastomotic leakage, which could explain these discrepancies. Like Hain et al. we distinguished asymptomatic from symptomatic anastomotic leakage. However, in contrast to the study of Hain et al. no significant difference in local recurrence was found. The dissimilarity between the results may be caused by the fact that they only included patients with rectal cancer and we included both colon and rectal cancer. Another explanation could be the high incidence of anastomotic leakage in the French study (28%) [53]. A few studies have distinguished between the severity in levels of anastomotic leakage. The International Study Group of Rectal Cancer used a grading system based on clinical management methods: no change in management (grade A); active therapeutic intervention without re-laparotomy (grade B); and re-laparotomy required (grade C) [54]. The only drawback of this classification Is that it is only usable after management has been completed. Lim et al. introduced an anastomotic leakage classification according to its clinical presentation: generalized peritonitis (type I); localized peritonitis (type II); and fistula of the chronic sinus (type III) [23]. Unfortunately, this classification has some overlap in definitions between the several grades rendering it unreliable for drawing conclusions. The initiative of the categorization of different types of anastomotic leakage is certainly necessary for the differentiation in the severity of this major complication and its oncological outcomes. The literature has shown that there is evidence for increased local recurrence rates in patients with anastomotic leakage after surgery for CRC [HR = 2.9 (95%CI: 1.78–4.71 P < 0.001)], [HR = 1.3 (95%CI: 1.04–1.62 P < 0.05)] and [HR = 1.9 (95%CI: 1.48–2.44 I^2 = 78%)], as summarized in the three aforementioned meta-analyses [9,22,34]. In our study we showed that this finding was accompanied by significantly impaired overall survival. Patients who survive abdominal sepsis in the acute phase after anastomotic leakage are exposed to a significant hazard of developing local recurrence. A logical possible next step in acknowledging this problem would be to deliberate over therapeutic options after anastomotic leakage to reduce this hazard. Treating patients with adjuvant chemotherapy or radiation after anastomotic leakage will raise many questions, especially on ethical grounds, indicating that even patients with tumour stage I or II are potential candidates for adjuvant therapy after anastomotic leakage, while such therapy is initially not indicated in their pTNM stages. This fact might be an incentive for the required future studies. However, before this proposal could be investigated, there must be consensus and recognition first of the increased hazard for local recurrence after anastomotic leakage.

In conclusion, this study provided evidence that AL in patients after surgery for CRC is associated with increased local recurrence rates. Therefore, it will be crucial to strictly follow these patients. Further research is required for minimize anastomotic leakage rates and guidelines to treat and follow-up patients after anastomotic leakage to improve oncologic outcomes. An association between anastomotic leakage and distant recurrence was not found.

Disclosure

The authors have no financial or institutional interest to declare in relation to the content of this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.suronc.2018.10.003.

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