European Colorectal Congress

29 November – 2 December 2020, St.Gallen, Switzerland

Sunday, 29 November 2020

MASTERCLASS

Introduction & course objectives
Michel Adamina, Winterthur, CH

Myths and facts about oral antibiotics, bowel preparation, and timing of iv antibiotics to reduce surgical site infection
Frédéric Ris, Geneva, CH

Management of colorectal GIST – all you should know from diagnosis to handling recurrences
Paris Tekkis, London, UK

Do and don't in taTME surgery – a decade of experience explaned
Roel Hompes, Amsterdam, NL

What your pathologist can do for you: from standard margins recommendations to molecular pathology, liquid biopsies, and the microbiome
Phil Quirke, Leeds, UK

Prehabilitation, patient blood management, frailty index – welcome addition or resource wasting
Des Winter, Dublin, IE

Selective use of neoadjuvant and adjuvant radiotherapy for rectal cancer
Chris Cunningham, Oxford, UK

Handling large rectal adenoma and malignant polyps
Willem Bemelman, Amsterdam, NL

All techniques to avoid staple line intersections in colorectal surgery
Antonino Spinelli, Milano, IT

Management of pelvic sepsis after colorectal / coloanal anastomosis and oncological outcomes of the GRECCAR 5 trial
Quentin Denost, Bordeaux, FR

Best practices in colostomy construction and repair of parastomal hernia
Eva Angenete, Göteborg, SE

The EBSQ Coloproctology Examination
Michel Adamina, Winterthur, CH

Wrap-up
Michel Adamina, Winterthur, CH

Sunday, 29 November 2020

COURSE OF PROCTOLOGY

Introduction & course objectives
Bruno Roche, Geneva, CH

Complex pelvic fistula revisited: established wisdom and innovative approaches
Alexander Herold, Mannheim, DE

Obstretrical trauma: assessment, timing and options to repair
Patrick Hohlfeld, Lausanne, FR

The painful bottom – Proctalgia beyond the classical abscess, fissures, and hemorrhoids
Bruno Roche, Geneva, CH

Sexually transmitted diseases in proctology
Karel Skala, Geneva, CH

Anorectal trauma and foreign bodies
Richard Cohen, London, UK

Pilonidal sinus – strategies and outcomes
Frédéric Ris, Geneva, CH

Fecal incontinence: investigations and conservative treatment
Beatrice Salvioli, Milano, IT

Fecal incontinence: neuromodulation and interventional options
Joan Robert-Yap, Geneva, CH

The pelvic floor revealed: transperineal / transvaginal / transanal repairs explained
Bruno Roche, Geneva, CH

The pelvic floor revealed: investigations and pelvic floor therapy
Jacqueline de Jong, Bern, CH

Obstructed defecation and IBS: investigations, differential diagnosis, and treatment strategies
Daniel Pohl, Zurich, CH

Obstructed defecation: surgical options
André d'Hoore, Leuven, BE

Wrap-up
Alexander Herold, Mannheim, DE

Monday, 30 November 2020

SCIENTIFIC PROGRAMME

Opening and welcome
Jochen Lange, St. Gallen, CH

Is cancer an infectious disease: role of the microbiome
Philip Quirke, Leeds, UK

Ethical considerations in crisis – lessons from Covid-19
Omar Faiz, London, UK

SATELLITE SYMPOSIUM
Medtronic

Prophylactic mesh in colorectal surgery
René H. Fortelny, Wien, AT

Lars Pahlman lecture: Extending the limits of liver surgery
Markus Büchler, Heidelberg, DE

Multimodal approaches to colorectal liver metastases
Mohammed Abu Hilal Brescia, IT

SATELLITE SYMPOSIUM
Ethicon

Urogenital dysfunction in patients treated for rectal cancer – what do we know and what can we do?
Eva Angenete, Göteborg, SE

Hemorrhoids – new options and time-tested solutions
Alexander Herold, Mannheim, DE

Anal pain and emergency proctology: what every surgeon should know & do
Richard Cohen, London, UK

All you need to know about anorectal fistula
Bruno Roche, Genève, CH

Strategies and outcomes for obstructive cancers of the colon and rectum
Willem Bemelman, Amsterdam, NL

Tuesday, 1 December 2020

BREAKFAST SYMPOSIUM
Karl Storz

Lessons learned along the robotic learning curve: a video guide for colorectal surgeons
Jim Khan, Portsmouth, UK

EAES presidential lecture: Strategies for lifelong learning and implementation of new technologies
Andrea Pietrabissa, Pavia, IT

SATELLITE SYMPOSIUM
Intuitive

A journey in global surgery – why getting out of the comfort zone
Raffaele Rosso, Lugano, CH

Enhanced recovery pathwaysreloaded – a practical guide to success
Roberto Persiani, Roma, IT

Cancer at the extremes of age: are there any differences in handling youngsters and seniors
Des Winter, Dublin, IE

Management pearls for early rectal cancer
Roel Hompes, Amsterdam, NL

Ventral rectopexy: indications, tricks of the trade, and long-term results
Chris Cunningham, Oxford, UK

SATELLITE SYMPOSIUM
BBraun

Total neoadjuvant therapy for colon and rectum cancers
Ronan O'Connell, Dublin, IE

Randomized trial evaluating chemotherapy followed by pelvic reirradiation vs chemotherapy alone as preoperative treatment for locally recurrent rectal cancer (GRECCAR 15)
Quentin Denost, Bordeaux, FR

Timeline of surgery following neoadjuvant radiotherapy – balancing morbidity and efficacy
Torbjörn Holm, Stockholm, SE

Poster award
Michel Adamina, Winterthur, CH

Wednesday, 2 December

Place and outcome of total colectomy in the surgical armentarium
Neil Mortensen, Oxford, UK

Kono S anastomosis and over the valve stricturoplasties: hope for better outcomes
André D'Hoore, Leuven, BE

New drugs, old fears: state of the art management of IBD patients
Gerhard Rogler, Zurich, CH

SATELLITE SYMPOSIUM
Takeda

Do resection of the mesentery in Crohn's & appendectomy in ulcerative colitis alter the course of disease
Christianne Buskens, Amsterdam, NL

The septic abdomen: getting out of misery and closing the case
Marja Boermeester, Amsterdam, NL

Management strategies for patients with advanced colorectal cancers
Paris Tekkis, London, UK

Anastomotic leak in colorectal surgery: insights, perspectives, and practical strategies
Antonino Spinelli, Milano, IT

Closing words
Michel Adamina, Winterthur, CH

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Original article

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Anastomotic leak after surgery for colon cancer and effect on long-term survival

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Abstract

Aim An anastomotic leak after surgery for colon cancer is a recognized complication but how it may adversely affect long-term survival is less clear because data are scarce. The aim of the study was to investigate the long-term impact of Grade C anastomotic leak in a large, population-based cohort.

Method Data on patients undergoing resection for Stage I–III colon cancer between 2008 and 2012 were collected from the Swedish, Norwegian and Danish Colorectal Cancer Registries. Overall relative survival and conditional 5-year relative survival, under the condition of surviving 1 year, were calculated for all patients and stratified by stage of disease.

Results A total of 22 985 patients were analysed. Anastomotic leak occurred in 849 patients (3.7%). Five-year relative survival in patients with anastomotic leak was 64.7% compared with 87.0% for patients with no leak ($P < 0.001$). Five-year relative survival among the patients who survived the first year was 88.6% *vs* 81.3% ($P = 0.003$). Stratification by cancer stage showed that anastomotic leak was significantly associated with decreased relative survival in patients with Stage III disease ($P = 0.001$), but not in patients with Stage I or II ($P = 0.950$ and 0.247, respectively).

Conclusion Anastomotic leak after surgery for Stage III colon cancer was associated with significantly decreased long-term relative survival.

Keywords Colon cancer, anastomotic leak, relative survival, surgery, colorectal cancer registries

What does this paper add to the literature?
Cancer-specific survival after surgery for colon cancer is not well addressed in the literature. Cancer-specific survival is expressed by national cancer registries using relative survival as the default approach. This study shows that anastomotic leak is associated with significantly reduced long-term relative survival in patients with Stage III colon cancer.

Introduction

The aim of surgery in the management of colon cancer is to cure the disease without the need for a permanent stoma. Most will undergo a restorative procedure with an ileo-colonic or colo-colonic anastomosis but with an inherent risk of anastomotic leak which not only may harm the patient in the short term but also may affect outcomes over time [1–4]. Long-term survival is considered a key indicator for monitoring the effectiveness of cancer treatment as well as health services in general [5,6].

Anastomotic leak has specifically been reported to increase short- and long-term morbidity and mortality [3,4,7–10]. There are fewer data on the impact of anastomotic leak on long-term oncologic outcome. A recent review and meta-analysis concluded that there are only a limited number of publications which address colon cancer surgery, most studies investigated rectal cancer and colorectal cancer combined [11]. Only four out of

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31 studies on anastomotic leak dealt with colon cancer. None reported cancer-specific survival, considered as a crucial measure of the effect of cancer treatment for cure. Moreover, there is little information on the impact of anastomotic leak applied to the different stages of colon cancer.

The incidence of anastomotic leak after colonic resection is reported to be between 3% and 5% [12]. As a consequence, large patient cohorts are required to provide data with sufficient statistical power in the long-term analysis of outcomes [9]. This is particularly true for subgroup analyses such as stage of disease. Large population-based studies may contribute to a better understanding.

In Sweden, Norway and Denmark, public healthcare systems are organized according to the common principle of free and equal healthcare services to all citizens regardless of social status and income. The Scandinavian national guidelines for diagnosis and treatment of colon cancer (preoperative studies, the obligatory use of multidisciplinary team meetings and adjuvant treatment for Stage III disease) are highly comparable. The Colorectal Cancer Registries of the Scandinavian countries continuously collect high-quality data on patient characteristics, treatments and outcomes, and provide data for events with low frequency on a larger scale compared to more limited data at an institutional level. As national cancer registries do not provide follow-up data of individual patients, they report relative survival outcomes as a well-accepted measure of cancer-specific survival [13].

The aim of this study was to investigate the impact of anastomotic leak Grade C on long-term colon-cancer-specific survival, expressed by relative survival, in patients according to stage of disease.

Methods

Ethics

The Regional Ethical Review Board at Karolinska Institutet approved this study in Sweden (2016/146-31). In Norway, the study was conducted under the regulations of the Cancer Registry of Norway; in Denmark, the study was classified as a quality assurance project using anonymous data, and so not under the mandate of the Regional Ethics Committee in Norway or the Danish Data Protective Agency.

Data were reported and collected according to the governmental regulations for the Colorectal Cancer Registries of Sweden, Norway and Denmark. All patient records were assembled without any person-identifying information, excluding the possibility of backward identification.

Study design and data collection

The present study used data from the dedicated Colorectal Cancer Registries of Sweden, Norway and Denmark to investigate anastomotic leak rates and the impact on relative survival. A unique personal identification number assigned to all residents in these countries facilitated effective and reliable identifying and tracking of patients, record linkage and exclusion of duplicates across registries.

All patients with a first-time diagnosis of Union for International Cancer Control (UICC) Stage I–III colon cancer who underwent surgical resection with primary anastomosis between 1 January 2008 and 31 December 2012 were included. Patients who had undergone a protective proximal loop-stoma or a terminal stoma or those with incomplete data on cancer stage or unknown surgical approach were excluded. The study is reported according to the STROBE guidelines [14].

The Scandinavian cancer registries

The cancer registries of Sweden, Norway and Denmark were established in 1958, 1953 and 1943, respectively, and dedicated national quality registries for colorectal cancer were established between 1995 and 2007. These quality registries record detailed data on diagnosis and treatment and have resulted in numerous scientific studies as well as annual governmental reports on national quality measures for cancer treatment [15–17]. Reporting to the colorectal cancer registries is compulsory in Scandinavia. All patients with a first-time diagnosis of colorectal cancer are registered, ensuring high data quality and reliability, in addition to a patient completeness above 95%, as previously documented [18–20]. Complete follow-up is secured by a unique personal number for all inhabitants of the Scandinavian countries (10-digit in Denmark and Sweden, 11-digit in Norway).

Outcome measures

Primary outcome was 5-year relative survival and conditional relative survival, conditional on surviving the first year, stratified by stage of disease. In order to capture the impact of anastomotic leak, survival was estimated from the day of surgery until the end of follow-up at 5 years.

Relative survival was estimated up to 5 years after surgery and defined as the ratio between survival in patients included in the study and the survival expected in a general population with the same age, sex, year of

birth and nationality distribution as the patient cohort. Accordingly, relative survival estimates the mortality that is related to the diagnosis and treatment of colon cancer. To further evaluate the long-term impact of anastomotic leak, relative survival, conditional on surviving the first year, was also assessed. This approach limits relative survival analysis to those patients who had survived the first year post-surgery, thus eliminating the influence of early mortality during the first year [21,22]. Data on survival for the general Swedish, Norwegian and Danish populations were collected from population life tables in the Human Mortality Database [23].

Anastomotic leak was defined as a communication between the intraluminal and extraluminal compartments through the anastomotic line confirmed by reoperation under general anaesthesia, corresponding to a Grade C leak as recommended by the International Study Group of Rectal Cancer and to Clavien–Dindo complication Grade IIIb or higher [24,25]. Currently, no specific recommendations for the grading of anastomotic leak after colon resections exist, and the assumption was made that this classification applies equivalently for colon and rectal resections.

Patients, staging and variable definitions

Patient demographics, tumour characteristics and treatment factors were consecutively recorded in the national colorectal cancer registries and merged with data on patient survival or death. By using the same predefined definitions for each variable and variable value, inherent national differences were minimized.

Patients were subdivided into three groups by age: < 65 years, 65–79 years and ≥ 80 years. Comorbidity was addressed using the American Society of Anesthesiologists (ASA) score [26], categorized as I–II, III and IV–V. The Norwegian and Danish patient data were linked to each country's national patient registry to calculate the Charlson Comorbidity Index (CCI), categorized as scores of 0, 1–2 and> 2 [27]. Such coupling was not performed for Swedish patients, so the CCI was not available for the Swedish cohort.

Cancer stage was classified according to the 7th UICC TNM classification, based on findings of preoperative CT scan of the chest and abdomen and pathological examinations of the surgical resection specimens [28]. T stage was categorized as T1–2, T3 and T4. Histologically verified lymph node metastases were defined as N+. The colon was defined as such anatomically from the appendix to 15 cm above the anal verge. Surgical procedures were defined as right hemicolectomy, transverse colectomy, left hemicolectomy and sigmoid colectomy. Surgical approach was defined according to the intention-to-treat principle: any laparoscopic procedures converted to open surgery were defined as a laparoscopic approach. Surgical priority was defined as elective or emergency due to obstruction or perforation of the colon.

Statistical analysis

The distribution of the duration of follow-up was calculated using the reverse Kaplan–Meier approach. The chi-squared test was used to compare categorical variables between patient groups. Univariable and multivariable logistic regression analyses were used to investigate factors associated with anastomotic leak. In these analyses Hosmer and Lemeshow's purposeful variable selection method was used, including testing for potential interaction effects [29]. As the CCI was unavailable in the Swedish cohort, it was excluded in analyses that included all countries. Because of a large proportion of missing values for ASA scores in the Norwegian cohort, multiple imputation was used to verify the results of analyses including the ASA score.

Given the large sample size and to partially address for multiple testing problems with a large number of tests conducted, a two-tailed P value ≤ 0.010 was considered to imply a statistically significant effect.

Statistical analyses were done by IBM SPSS Statistics (IBM Corporation, Armonk, New York, USA) version 23 and R version 3.5.2 [30]. The R-package 'relsurv' version 2.2-3 was used for the relative survival calculations, using the maximum likelihood method for parameter estimation [31].

Results

A total of 41 981 patients with a first-time diagnosis of colon cancer were identified, of whom 22 985 (54.8%) were included according to the eligibility criteria (Fig. 1). Overall median follow-up was 62.8 months (interquartile range 46.9–78.4 months). The data completeness was high, except for missing ASA scores in 3855 patients (16.8%), mostly from the Norwegian cohort (40.2%, Table S1).

Patient characteristics

Patient characteristics are shown for the entire patient cohort and by stages (Table 1). Some variations in distribution of age, burden of comorbidity, tumour site, tumour stage, proportion of patients treated as an emergency, and rate of laparoscopic treatment between countries were seen (Table S1).

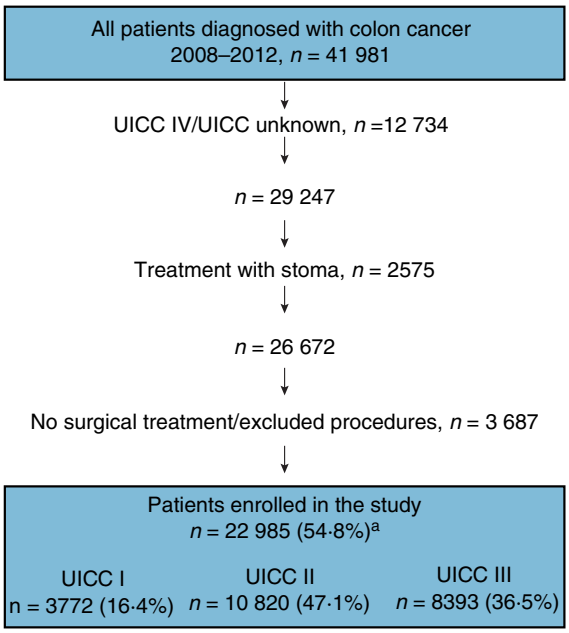


Figure 1 Flowchart of patients with colon cancer registered at the Colorectal Cancer Registries in Sweden, Norway and Denmark during the years 2008–2012. Patients who underwent resection for colon cancer Stage I–III were included in the analysis. Detailed figures for each country are shown in Table S1. [a]Percentage of all patients.

Characteristic of anastomotic leaks

A total of 849 (3.7%) patients developed an anastomotic leak (Table 1). This was significantly more frequent in the Danish cohort (5.3%) compared with the Norwegian (3.0%, $P < 0.001$) or the Swedish cohort (3.1%, $P < 0.001$) (Table S1). Factors associated with increased risk of anastomotic leak are shown in Table 2. Multivariable analysis revealed that male gender, Stage II disease, higher ASA score and resections beyond the right flexure were significantly associated with anastomotic leak. Resections in octagenarians and nonagenarians were associated with lower risk of anastomotic leak. These results were confirmed by multiple imputation accounting for the missing data on the ASA score (Table S1).

Relative survival

Overall, 5-year relative survival was 87.0%, and differed significantly between stages (Stage I, 99.9%; Stage II, 94.1%; Stage III, 72.2%; $P < 0.001$). Anastomotic leak was associated with a lower 5-year relative survival in the entire cohort (64.7%; $P < 0.001$; Fig. 2). During the first year after surgery, mortality was highest, and relative survival was 77.8%, similar in all stages (Stage I, 83.4%; Stage II, 77.6%; Stage III, 75.4%; $P = 0.373$).

Conditional relative survival

Conditional relative survival after 5 years, conditional on surviving the first year after surgery, was 89.9 % in all patients (90.1 % in those without leak and 82.1 % in patients with anastomotic leak) (Table 3; $P = 0.003$). Conditional relative survival stratified by stage showed that patients with Stage III disease and anastomotic leak had a significantly lower survival after 5 years than those who had not experienced anastomotic leak (63.5% and 79.0%, $P = 0.001$, Table 3, Fig. 2). Anastomotic leak in patients with Stage I and II disease was not associated with reduced conditional relative 5-year survival (Table 3, Fig. 2). Stratification for age groups, i.e. 75 or 80 years, showed similar results.

Discussion

Anastomotic leak is one of the most serious complications following colon resections and has a grave impact on patients' physical and mental health [32,33]. This study found a total of 849 anastomotic leaks (3.7%) in 22 985 patients resected for colon cancer Stage I–III. This was associated with a reduced 5-year relative survival in patients with Stage III colon cancer. The cohort is double the size reported in a recent meta-analysis dealing with long-term outcomes after anastomotic leak following colorectal resections which concluded that data on long-term cancer-specific survival for colon cancer patients with anastomotic leak are lacking [11].

This study uses a high-quality dataset with complete follow-up, secured by unique national personal identification numbers and official death statistics. Anastomotic leak was associated with highly significant short-term mortality up to 1 year after treatment. In other studies, short-term mortality is usually reported as 90-day mortality since most patients who are ill after anastomotic leak are successfully treated and survive far beyond 30 days post-surgery. It is important to recognize that anastomotic leak mortality occurs beyond the first 3 months and throughout the first year (Fig. 2).

More importantly, the study reveals a strong negative impact on long-term relative survival following anastomotic leak after curative resection for colon cancer. In contrast to overall survival, relative survival reflects the survival related to a diagnosis and treatment of a given disease compared to the survival estimates of a matched background population [34]. Relative survival is a useful statistical tool for assessment of differences in survival and for adjustment of the different expected survival rates in respective general populations and relates closely to cancer-specific survival [35]. Other large registries have used this measurement as the equivalent of cancer-

Table 1 Characteristics of 22 895 patients surgically resected for colon cancer Stage I–III.

	Stage I		Stage II		Stage III		All stages		
	n	%	*n*	%	*n*	%	*n*	%	*P*
Total	3772	16.4	10 820	47.1	8393	36.5	22 985	100.0	
AL									
Leak	107	2.8	445	4.1	297	3.5	849	3.7	0.0011
No leak	3665	97.2	10 375	95.6	8096	96.5	22 136	96.3	
Sex									
Female	2007	53.2	5739	53.0	4483	53.4	12 229	53.2	0.8763
Male	1765	46.8	5081	47.0	3910	46.6	10 756	46.8	
Age									
< 65	779	20.7	2223	20.5	2186	26.0	5188	22.6	< 0.0001
65–79	1903	50.5	5276	48.8	4041	48.1	11220	48.8	
> 79	1090	28.9	3321	30.7	2166	25.8	6577	28.6	
Country									
Sweden	1777	47.1	4611	42.6	3961	47.1	10 349	45.0	< 0.0001
Norway	973	25.8	2875	26.6	2019	24.1	5867	25.5	
Denmark	1022	27.8	3334	30.8	2413	28.8	6769	29.4	
ASA score									
I–II	2233	70.9	6089	68.4	5111	72.2	13 433	58.4	< 0.0001
III	852	27.1	2593	29.1	1825	25.8	5270	22.9	
IV–V	63	2.0	217	2.4	147	2.1	427	1.9	
Missing							3855	16.8	
Charlson									
0	1155	58.4	3774	61.0	2766	62.7	7695	33.5	0.0109
1–2	632	32.0	1829	29.6	1287	29.2	3748	16.3	
> 2	190	9.6	583	9.4	362	8.2	1135	4.9	
Missing							10 407	45.3	
Procedure									
Right	2021	53.9	6531	60.4	5027	59.9	13 579	59.1	< 0.0001
Transverse	73	1.9	258	2.4	174	2.1	505	2.2	
Left	376	10.0	1324	12.2	1003	12.0	2703	11.8	
Sigmoid	1302	34.5	2707	25.0	2189	26.1	6198	27.0	
Approach									
Open	2424	64.5	7.951	73.6	6344	75.8	16 719	72.7	< 0.0001
Laparoscopic	1337	35.5	2.845	26.4	2030	24.2	6212	27.0	
Missing							54	0.2	
Priority									
Elective	3541	96.4	9.363	88.8	6883	84.2	19 787	86.1	< 0.0001
Emergency	133	3.6	1.186	11.2	1288	15.8	2607	11.3	
Missing							591	2.6	

AL, anastomotic leak; ASA, American Society of Anesthesiologists.
P value of the Pearson chi-squared test of differences between stages.

specific survival, since this approach eliminates mortality from other causes [36,37]. The use of conditional 1-year relative survival analysis eliminates the mortality due to anastomotic leak during the first year [21,22]. This approach describes the mortality during the remaining 4 years of the total 5-year follow-up, and depicts the true long-term mortality related to Grade C anastomotic leak. The results of our study show that conditional 1-year relative survival was significantly reduced compared with patients who did not develop an anastomotic leak. This increased late mortality was statistically significant for patients with Stage III disease compared to Stage I or II (Table 3, Fig. 2).

The reasons for impaired long-term survival among Stage III patients with anastomotic leak are unclear. The event of anastomotic leak may possibly enforce the adverse impact of Stage III disease on the biological course of the cancer disease, lymph node involvement

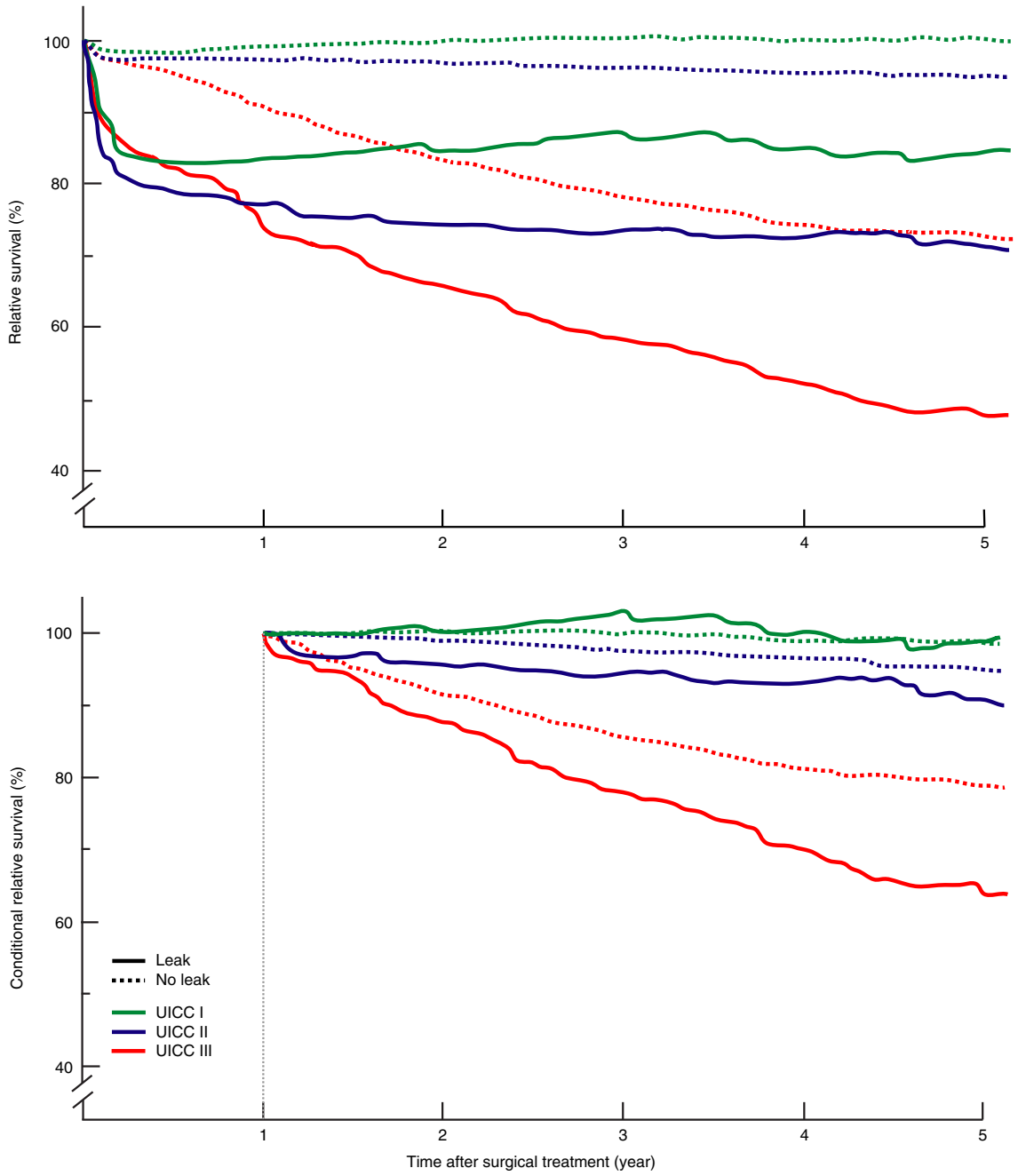
Table 2 Multiple logistic regression of possible independent factors influencing the occurrence of anastomotic leak after surgery for colon cancer Stages I–III.

	Univariable			Multivariable		
	OR	*P*	CI	OR	*P*	CI
Gender						
Female	Ref.			Ref.		
Male	1.76	< 0.001	1.47–2.12	1.50	< 0.001	1.23–1.84
Age					< 0.001	
<65	Ref.	0.002		Ref.		
65–79	0.92	0.323	0.74–1.14	0.85	0.088	0.67–1.09
>79	0.72	0.001	0.55–0.93	0.64	< 0.001	0.47–0.86
T stage						
T1	Ref.	0.002				
T2	0.82	0.324	0.82–1.37			
T3	1.23	0.226	0.80–1.90			
T4	1.36	0.090	0.85–2.19			
N stage						
N0	Ref.					
N+	0.93	0.310	0.77–1.21			
UICC					< 0.001	
I	Ref.	0.032		Ref.		
II	1.32	0.011	1.11–2.31	1.59	< 0.001	1.17–2.17
III	1.57	0.017	1.09–2.27	1.31	0.034	0.94–1.81
Charlson Comorbidity Index						
0	Ref.	0.973				
1–2	0.97	0.835	0.65–1.45			
> 2	0.98	0.913	0.64–1.51			
ASA score					< 0.001	
I–II	Ref.	< 0.001		Ref.		
III	1.44	< 0.001	1.17–1.77	1.61	< 0.001	1.29–2.01
IV–V	1.95	0.001	1.15–3.30	2.29	< 0.001	1.33–3.91
Priority						
Elective	Ref.					
Emergency	1.11	0.340	0.84–1.45			
Approach						
Open	Ref.					
Laparoscopic	1.08	0.334	0.88–1.32			
Procedure					< 0.001	
Right	Ref.	< 0.001		Ref.		
Transverse	2.35	< 0.001	1.45–3.81	2.32	< 0.001	1.34–4.00
Left	1.84	< 0.001	1.42–2.38	1.91	< 0.001	1.45–2.52
Sigmoid	1.62	< 0.001	1.32–1.98	1.66	< 0.001	1.32–2.08

ASA, American Society of Anesthesiologists; UICC, Union for International Cancer Control. Method forward (WALD).
Patients included 19 033; patients with missing ASA score excluded. Charlson Comorbidity Index not included for analysis. Goodness-of-fit $P = 0.875$ in step 5 (by Homer and Lemeshow test). Variables excluded in final analysis: T stage $P = 0.145$, N stage $P = 0.343$, priority $P = 0.302$ and approach $P = 0.206$. No significant interactions were found.

being one of the strongest negative prognostic factors for patients with potentially curable colon cancer [38,39]. Other new concepts like the role of the microbiome in the bowel on this tumour–host relationship may give important clues to a better understanding of the impact of anastomotic leak on treatment outcomes [40].

The health consequences of a Grade C anastomotic leak may mean that the patient is unfit for adjuvant chemotherapy and, even if given, that its efficacy may be reduced [1,3,4,9]. According to a recent study, in 44% of the patients who started adjuvant chemotherapy, planned doses and/or duration had to be changed due



Number at risk	20 888	18 743	15 405	12 394	8470
UICC I	3580	3315	2 809	2317	1596
UICC II	9991	9167	7 592	6104	4172
UICC III	7317	6261	5 004	3972	2702
Number censored (died)	2098 (2091)	4242 (3559)	7580 (4737)	10 591 (5689)	14 515 (6346)
UICC I	193 (192)	457 (322)	963 (457)	1454 (596)	2176 (692)
UICC II	829 (824)	1653 (1324)	3228 (1 805)	4716 (2 220)	6648 (2546)
UICC III	1076 (1075)	2132 (1 913)	3389 (2 475)	4421 (2 873)	5691 (3108)

Figure 2 Relative 5-year survival (above) and conditional relative survival (below), conditional on having survived the first year after surgery, of patients resected for colon cancer with regard to anastomotic leak and stratified by Stage I, II or III. Conditional relative survival of patients with anastomotic leak was significantly lower compared to those without leak in Stage III ($P < 0.001$), but not in patients with Stage I or II (Table 3).

Table 3 Long-term relative survival and relative conditional survival (conditional on having survived 1 year after surgery) at different time intervals (years), with regard to anastomotic leak.

	Relative survival					Conditional relative survival				
	1 years	2 years	3 years	5 years		1 years	2 years	3 years	5 years	
UICC I										
Leak	83.4	84.8	87.0	84.5	0.005		100.1	102.5	99.0	0.950
No leak	99.2	99.9	100.4	100.3			100.1	100.0	98.7	
Overall	98.8	98.8	100.0	100.0			100.1	100.0	98.7	
UICC II										
Leak	77.6	74.7	73.8	94.1	<0.001		95.8	94.6	90.4	0.247
No leak	97.2	96.8	96.0	95.0			99.1	97.7	95.2	
Overall	96.4	95.9	95.1	71.5			99.0	97.6	95.1	
UICC III										
Leak	75.4	66.0	58.8	48.2	<0.001		87.5	77.8	63.5	0.001
No leak	90.9	83.5	78.5	73.1			91.5	85.8	79.0	
Overall	90.3	82.8	77.8	72.2			91.4	85.5	78.6	
UICC I–III										
Leak	77.8	73.0	70.2	64.7	<0.001		93.6	90.0	82.1	0.003
No leak	95.2	92.4	90.3	87.9			96.6	93.9	90.1	
Overall	94.6	91.7	89.6	87.0			96.5	93.8	89.9	

UICC, Union for International Cancer Control.

to various adverse events, which render the adjuvants less effective [41]. The possible relationship between adjuvant chemotherapy and impaired survival in Stage III after anastomotic leak is a very complex issue. Based on the recommendation of adjuvant chemotherapy for patients with Stage III disease up to 75 years, and eventually 80 years, conditional relative survival analysis stratified by stage was also performed as a sensitivity analysis with regard to age below or above 75 and 80 years as a proxy for the use of chemotherapy. These analyses did not reveal any differences to the dataset with all patients (data not shown). Highly granular data on type of drug, duration, dose adjustments or other factors do not exist in the registries for the study period. Moreover, these data are complex and do not allow simple dichotomization of treatment given into adjuvant treatment given or not. This topic poses methodological challenges that cannot be met by large national datasets but need appropriately designed prospective studies. Serious complications including anastomotic leak after surgery have recently been identified as a significant predictor for delayed return to work and this observation underlines the serious impact of anastomotic leak on the individual patient [42].

Only 3%–4% of patients develop an anastomotic leak after colonic resection. This usually represents a low number of patients in any series and it is therefore difficult to corroborate the association between anastomotic leak and impaired long-term outcomes. A recent single centre study found only one recurrence among 12 of 445 patients with anastomotic leak, while Hüttner *et al.* reported 26 patients with anastomotic leak in a series of 628, thus underlining the need for large-scale population-based analyses [10,43]. Impaired overall survival was demonstrated in a Japanese cohort of 4919 patients and suggested an increased risk of local recurrence associated with anastomotic leak, but in contrast to a Danish study there was no association with distant metastases in the Japanese cohort [3,9]. In their meta-analysis, Mirnezami *et al.* showed increased rates of local recurrences after anastomotic leak following resections for rectal cancer but inconclusive for colon cancer and similarly for the risk of distant spread [4].

The present analysis of 22 985 patients, based on national data from three countries covering a population of 18 million, reports on 849 patients with anastomotic leak, enabling reliable outcomes due to high-quality national registries with clear definitions of variables and complete follow-up based on unique personal identifiers. The observations of inferior long-term outcome after anastomotic leak associated with the subgroup of patients with Stage III disease are founded on large numbers, strongly supporting the idea of an unfavourable relation between anastomotic leak and patients with metastatic lymph nodes. National cancer registries notoriously do not provide detailed data on recurrent disease, something more achievable in institutional series. However, the observation of impaired long-term

relative survival after Grade C anastomotic leak in Stage III patients translates into impaired long-term cancer-specific survival. Further studies are needed to elaborate this association and should include novel concepts on the molecular or microbiome level.

The present study has a number of limitations. Population-based registry analyses intend to identify associations but do not aim to reveal causal relationships between variables. Despite the high accuracy of national registry data, some variables had considerable missing values, such as ASA classification or the CCI. While the former was missing for about 40% of the Norwegian dataset, CCI was not possible to establish for Swedish data, limiting analysis to Norway and Denmark. Imputation analyses confirmed the results for analyses including ASA score, and introduction of a bias was considered unlikely. Potential differences in definition, detection and treatment of anastomotic leak might represent a further limitation [44].

Only patients surgically treated for anastomotic leak, i.e. Clavien–Dindo Grade IIIb complication, were included in the present cohort. This enables a robust analysis. Valid data indicating conservative treatment or minimally invasive procedures, e.g. percutaneous drainage, are difficult to obtain and were not registered. Consequently, this analysis may underestimate the total incidence of anastomotic leak. However, the definition of Grade C anastomotic leak secures unequivocal data on anastomotic leak and contributes to better comparability with other studies, and our results apply for this patient group.

One might argue that an anastomotic leak requiring reoperation could have a stronger impact on long-term outcomes. These patients represent the core population to experience this potentially lethal complication with strongest impact on physiology and the need for rapid reoperation. This is expressed by Grade IIIb or higher on the Clavien-Dindo complication scale compared to patients with a subclinical course of anastomotic leak (Grade A) or who are treated with percutaneous drainage of an abscess related to the anastomosis with minimal leak (Grade B). The definition of subclinical anastomotic leak is challenging within a large dataset such as ours and has been described as divergent [11].

In conclusion, relative survival analysis showed a strong negative impact of anastomotic leak on long-term outcomes in patients resected for colon cancer and translates into impaired cancer-specific survival. The results of this study highlight the detrimental impact of anastomotic leak after surgery for colon cancer in particular on patients with Stage III disease. Further efforts are needed to better understand the development and prevention of this serious complication.

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Conflicts of interest

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Characteristics of patients displayed by country. *P* value of the Pearson chi-squared test of differences between countries.

