THE SAHLGRENSKA ACADEMY

Degree Project

Incidence of Anastomotic Leakage After Colorectal Cancer Surgery with Primary Anastomosis at Norra Älvsborgs Länssjukhus, Trollhättan, Sweden 2014-2018.

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Abstract

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Background: Colorectal cancer (CRC) is one of the most common and deadliest cancer forms in the world. Surgery plays a key role as part of the curative treatment plan. As with all surgery, complications can arise and one of the most dreaded and serious complications is anastomotic leakage (AL) after colorectal surgery. This complication has been shown to be underreported to the Swedish Colorectal Cancer Registry (SCRCR).

Objectives: How many patients suffer from anastomotic leakage after colorectal cancer surgery at NÄL? Is there an underreporting of anastomotic leakage after colorectal cancer surgery in the existing quality register, SCRCR? Do factors such as anastomotic technique (hand sewn or stapled), surgical method (open or laparoscopic) and acute or elective surgery increase the risk of developing anastomotic leakage?

Methods: This study included a cohort of 653 patients from SCRCR that underwent colorectal cancer surgery with primary anastomoses between years 2014-2018 at NÄL. Medical records were reviewed manually. Data regarding demographics, hospital stay, performed surgery, presence and severity of anastomotic leakage was collected.

Results: Of 653 registrations, a total of 52 AL (8%) were identified during manual chart review, whereas only 20 registrations were reported in the SCRCR. This revealing that there is a significant ($P < 0.0001$) underreporting to the SCRCR regarding anastomotic leakage at NÄL.

Conclusion: This study found a significant underreporting of AL to the SCRCR. Further improvements and standardization should be considered regarding chart documentation and reporting routines to minimize the risk of underreporting leakages. At the same time, extending the period of registration may increase the number of leakages found.

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List of abbreviations

AL – Anastomotic leakage

CRP – C-reactive protein

CRC – Colorectal cancer

CIs – Confidence intervals

Hb – Hemoglobin

IC – Intermediate care

ICU – Intensive care unit

ISREC – International study group of Rectal Cancer

NÄL – Norra Älvsborgs Länssjukhus

OR – Odds Ratio

POD – Postoperative day

SCRCR – Swedish Colorectal Cancer Registry

SRCR – Swedish Rectal Cancer registry

TIA – Transient ischemic attacks

Introduction

Colorectal cancer

Colorectal cancer (CRC) is globally the third most common type of cancer, following lung- and breast cancer. It is also considered to have one of the highest mortality rates. In 2020, CRC was responsible for approximately 2 million cases worldwide. (1) The incidence rate in Sweden for CRC is a total of 7000 new cases annually, in which colon cancer is just under 5000 and just under 2000 for rectal cancer. (2) Annually, 880 000 individuals are estimated to die due to CRC, which corresponds to roughly 9% of all cancer-caused deaths and makes it the second leading cause of cancer death in the world and the fourth in Sweden. (3)

Etiology

In most cases, CRC arises from adenomatous polyps (neoplastic epithelial polyps). The prevalence of adenoma is unknown, however a large prevalence study from Germany that included 3.6 million participants undergoing screening colonoscopy program estimated the prevalence of regular adenomas to be 16% in men and 9.6 % in women (ages ranging from 55-59 years old). For patients with ages between 75 to 79 years old, the prevalence was estimated to 18,2 % in men and 12.8% in women. (4) The lifetime risk to develop colorectal cancer in Sweden is 5% and is therefore significantly lower than the estimated prevalence of adenomas (3).

Risk factors'

Studies have shown several risk factors that might increase a person's chance of developing CRC. These factors can be divided into modifiable factors such as lifestyle-related factors and non-modifiable such as age or genetic predisposition. Hereditary factors are known to cause 20-25 % of all CRC. This includes disorders such as Lynch's syndrome and familial adenomatoses polyposis (FAP). Examples of lifestyle-related factors include consumption of red and processed meat, physical inactivity, excess body weight, inflammatory bowel diseases (in particular ulcerative colitis), alcohol consumption and smoking. (3)

Surgical treatment of Colorectal Cancer

There are different surgical procedures performed for CRC depending on the location and characteristics of the tumor. The types of surgical procedures performed for colon cancer

include right-sided hemicolectomy, left-sided hemicolectomy, transverse resection, sigmoid resection and colectomy (subtotal or total). Right-sided hemicolectomy includes resection of the right colon including the flexure and the distal parts of ileum. Left-sided hemicolectomy refers to resection of the left flexure, descending and sigmoid colon and anastomosis between colon transversum and rectum. The general procedure performed for tumors located in transverse colon includes an extended right-sided hemicolectomy with anastomosis between ileum and the left side of the transverse or proximal descending colon.(3)

The types of surgeries performed for rectal cancer include anterior resection, which is the standard treatment. Anterior resection is performed in tumors located in the middle and upper third part of rectum. During this surgery, patients can temporarily get a loop-ileostomy. This is when a loop is made from the ileum and then brought out through the abdomen, as a stoma bag. The loop-ileostomy is used to divert stool through the small bowls out to the stoma bag, to protect the distal anastomoses made and can in some cases be reversed. (5) Other surgical procedures performed for rectal cancer are abdominoperineal resection (tumor located in the lower rectum) and Hartmann's surgery (tumor located in left colon/upper rectum). (3)

Open vs laparoscopic surgery

Research indicates that the long-term survival (5-year follow up study) and oncological outcomes are the same for both laparoscopic surgery and open surgery.(6, 7) The evidence is high for colon cancer, and moderate for rectal cancer. Results have shown that laparoscopic surgery compared to open surgery contributes to faster recovery, fewer hospitalization hours, fewer overall complications and less post-operative pain resulting in less needs of analgesics. (7)

In terms of anastomotic leakage (AL), most studies (8) have demonstrated that there are no significant differences in the incidence rate of AL in laparoscopic surgery versus open surgery, (9) meanwhile some research indicate that laparoscopic surgery is associated with a reduced risk of developing AL following colorectal surgery compared to open surgery. (10)

Stapled vs hand-sewn

There are different techniques used to form the anastomosis, such as hand-sewn and stapled techniques. The most classic method is hand-sewn anastomosis which is primarily used in

open surgery. The development of stapled anastomosis began in the 1990s and has quickly become the most used anastomotic technique. Anastomotic leakage is the most critical postoperative complication. When comparing the incidence of AL between hand-sewn anastomosis to stapled anastomosis, early research has demonstrated significantly higher rates of leakage for the stapled technique. (11) However, more recent studies and a Cochrane review from 2012 have shown similar incidence rates of AL for both techniques in colorectal surgery. (12, 13)

A multicenter study examined whether the incidence rate of AL after right-sided hemicolectomy was influenced by the anastomotic technique (handsewn vs stapled) and found that no significant differences were observed in AL between the two techniques. (14) Meanwhile, a Cochrane analysis from 2011 compared the outcome of ileocolic anastomosis, which is commonly performed for right-sided colon cancer, with handsewn and stapling technique in a small, randomized trial. This report concluded that the stapling technique had a lower leakage rate in regards to ileocolic anastomosis. (15) A Swedish population-based study from 2015 has however demonstrated that hand-sewn anastomosis has a lower leakage rate compared to stapled anastomosis. (16)

Surgical complications and classification

Anastomotic Leakage

Anastomotic leakage is a dreaded complication to CRC surgery and is associated with high rates of morbidity and mortality. Several definitions for anastomotic leakage exist in literature. The definition proposed by the international study group of rectal cancer is the following “a defect of the intestinal wall at the anastomotic site leading to a communication between the intra-and extraluminal compartments”. (17)

The lack of consensual standard definition of AL factor can partly explain the variations in reported cases of AL. (18) The etiology of AL is described as multifactorial. The highest risk factor for AL is the distance of the anastomosis from the anal verge, with a lower distance (<6 cm) increasing the risk of fistula/leakage. (8)

Anastomotic leakage occurs in 10-15% of patients completing anterior resection. Accordingly, the incidence of AL varies depending on the anatomical site of the anastomosis.

If the anastomosis is located in distal parts of colorectal, coloanal and ileoanal sites, the incidence of AL ranges from 1% to 20%. Meanwhile, colocolonic anastomosis has an AL incidence of 0% to 2 % and ileocolonic anastomosis has an AL rate ranging from 0.02% to 4%. Resection of distal rectal cancer has been demonstrated to have a nearly five-times increased risk of AL compared to resection for colon cancer. (19) Examples of general risk factors for AL include male sex, malnutrition, diabetes, immunosuppression, non-steroidal anti-inflammatory drug (NSAID) use, emergency surgery, chronic steroid therapy, and radiation therapy. (20, 21) Preoperative risk factors as low rectal anastomosis, male gender and preoperative radiotherapy have also been identified as possible risk factors for colorectal anastomotic leakage.(22) Seeing as the severity and clinical symptoms of AL may vary all from abdominal pain to organ failure, the intervention used to correct the complication may also differ, which is why classifications are needed to rank surgical complications based on severity and need for intervention.

Clavien- Dindo Classification

In 2004 an updated version of the Clavien-Dindo Classification was issued which currently consists of a total of 7 grades, including 2 subgroups for grade 3 and 4. The principle behind the classification is to be used to rank a surgical complication based on the type of therapy needed to correct a specific complication. The definition of each grade is cited in Table 1. (23)

Table 1. Clavien-Dindo definition and classification of Surgical Complications.

Clavien-Dindo Classification	
Grade	**Definition**
I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens including: drugs as antiemetics, antipyretics, analgesics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
III	Requiring surgical, endoscopic, or radiological intervention
a	Intervention not under general anesthesia

	b	Intervention under general anesthesia
IV		Life-threatening complications (including CNS complications) * requiring IC/ICU-management
	a	Single organ dysfunction (including dialysis)
	b	Multiorgan dysfunction
V		Death of patient

***Brain hemorrhage, ischemic stroke, subarachnoid bleeding, but excluding TIA; Intensive care (IC); Intensive care unit (ICU).**

International study group of rectal cancer

In 2010 members of the International Study Group of Rectal Cancer (ISREC) sought to find a definition and severity grading of AL after anterior rectal resection. After reviewing several studies, a consensus definition was established, one that grades the severity of the AL based on the impact on clinical management and is only validated for rectal cancer. The grading system is divided into 3 groups and is cited in Table 2. (17)

Table 2. Definition of severity grade and typical clinical characteristics of AL after anterior resection of the rectum.

	ISREC Classification		
	Grade A	**Grade B**	**Grade C**
Definition	AL requiring no active therapeutic intervention	AL requiring active therapeutic intervention but is manageable without re-laparotomy	AL requiring re-laparotomy
Clinical condition	Good	Mild/moderate discomfort	Severely impaired
Clinical symptoms	No	Yes • Abdominal/pelvic pain • May have fever • Purulent/fecal vaginal discharge (rectovaginal fistula) • Turbid/purulent rectal discharge	Yes • Peritonitis • Septicemia/sepsis
Contents from the drain (if present)	Serous fluid • May have turbid or feculent contents	Turbid/purulent (fecal) content	Fecal (purulent) content

	from the drain		
Laboratory tests	Normal	Leukocytosis CRP elevation	Leukocytosis CRP elevation • May have changes owing to sepsis (e.g., Leukopenia)
Radiologic evaluation	Small, contained AL	AL • May have local complications (e.g., pelvic abscess)	AL • May have generalized complications (e.g., peritonitis)
Specific treatment	No	Yes • Antibiotics • Interventional drainage • Transanal lavage/drainage	Yes • Re-laparotomy with control of septic focus

The Swedish Colorectal Cancer registry

SCRCR registers and collects data from all new CRC cases in Sweden. It consists of 2 registers, one for rectal cancer that started 1995 and another for colon cancer that began 2007. The main goal of the SCRCR is to assess the quality and results of treatment methods and to thereby improve treatment options and survival rates for CRC in Sweden.(3)

Norra Älvsborgs Länssjukhus years 2014-2018

Colon cancer

Based on data from the SCRCR years 2014-2018, a total of 734 patients (and 781 tumours, including synchronous tumours) were diagnosed with colon cancer at NÄL. Out of those patients, 78,4% underwent tumour removing surgery, 3 % had other forms of surgery, 2,4% had polypectomy and 16,2 % did not receive any surgery. The post-operative complication rate after tumour removing colon cancer surgery is categorized into mild complication which is defined as Clavien-Dindo grade 2 and 3a, whereas severe complication is defined as grade 3b or higher, see Table 3. (24-28)

Table 3. Post-operative complication rate (%) after tumour(s) removing colon cancer surgery NÄL, years 2014-2018. Based on data from SCRCR.

Colon cancer			
Year	**Mild complications (%)**	**Severe complications (%)**	**No complications (%)**
2014	19,1	3,6	76,4 (0,9% Missing)
2015	9,4	9,4	81,1
2016	13,5	7,9	78,6
2017	11,8	8,4	79,8
2018	14,9	9,1	76,0

Rectal cancer

Based on data from SCRCR years 2014-2018, a total of 344 patients (and 347 tumours including synchronous tumours) were diagnosed with rectal cancer at NÄL. Out of those patients, 69,6% underwent tumour removing, 3,5% underwent other surgeries, 3,8% had polypectomy and 23,1% did not receive any surgery. The post-operative complication rate after tumour removing rectal cancer surgery is categorized into mild complication which is defined as Clavien-Dindo grade 2 and 3a, whereas severe complication is defined as grade 3b or higher, see Table 4. (29-34)

Table 4. Post-operative complication rate (%) after tumour removing rectal cancer surgery NÄL, years 2014-2018, based on data from SCRCR.

Rectal cancer			
Year	**Mild complications (%)**	**Severe complications (%)**	**No complications (%)**
2014	26,9	9,6	63,5
2015	39,6	17,0	43,4
2016	27,3	13,6	59,1
2017	28,6	18,4	51,0 (2 % Missing)
2018	47,5	5,0	47,5

Anastomotic Leakage at Norra Älvsborgs Länssjukhus

Based on data from SCRCR, a total of 13 AL were reported within 30 days of the primary operation for colon cancer between the years 2014-2018 at NÄL.(24) Moreover, a total of 8 AL were reported during the same period for rectal cancer making it a total of 21 reported AL to SCRCR between the years 2014-2018. (29)

Underreporting of Anastomotic leakage to the SCRCR

A retrospective cohort study was conducted and investigated at patients with rectal cancer who underwent anterior resection at 15 different Swedish hospitals, between the years 2013-2017. The study was based on SCRCR which then found that there was a significant under-reporting of AL after anterior resection in the first 30 postoperative days. The false-negative rate was between 29%-41%. (35) Further, one master thesis paper performed at Södra Älvsborgs hospital (36) reported an underreporting of AL to the SCRCR. Additionally, another study report at Skaraborg hospital reported a significant underreporting of AL, with 28% cases were failed to be reported in the SCRCR. (37)

Aim

This study seeks to determine the frequency of the complication, AL after colorectal cancer surgery at NÄL, between years 2014-2018. In addition to this, examine potential factors that may increase the risk of developing AL, as well as comparing the incidence of AL reported in SCRCR with the amount found during manual chart review in NÄL.

Specific objectives

How many patients suffer from anastomotic leakage after colorectal cancer surgery at NÄL?

Is there an underreporting of anastomotic leakage after colorectal cancer surgery in the existing quality register, SCRCR?

Do factors such as anastomotic technique (hand sewn or stapled), surgical method (open or laparoscopic) and acute or elective surgery increase the risk of developing anastomotic leakage?

Material and methods

Study design

For this retrospective cohort study, patient records were retrieved from SCRCR registry data. The cohort includes patients registered in SCRCR from 1 January 2014 to 31 December 2018 in NÄL, with the following ICD diagnoses: C18 (malignant neoplasm of colon), C19 (malignant neoplasm of rectosigmoid junction) and C20 (malignant neoplasm of rectum).

The sample size consisted of 924 registrations, including doublet registrations due to multiple tumors found in the same patient. Doublet registrations that resulted in two or more anastomoses were registered separately, considering the risk of AL from two different sites. Moreover, doublet registrations that resulted in one anastomosis answered to one patient. Patients who underwent surgery without anastomosis were excluded from the study. Hence, a total of 653 patients were operated with an anastomosis and met the inclusion criteria. Patients were then assigned an identification number to be de-identified prior to data collection and compilation.

Data collection procedures

Prior to data collection a protocol in Excel was made by the research team. The patients' sex was based of their Swedish personal identification number and the age at which they were diagnosed was entered into a de-identified Excel document. Electronical medical records were collected from medical record system, Melior, SIEview and Orbit.

Medical records were perused to firstly note type of operation and if an anastomosis was constructed or not. In addition, it was noted whether the type of operation in the registry was registered correctly or not. For patients where an anastomosis was constructed, data was collected regarding date of surgery, length of stay (days), anastomosis technique (stapled or hand-sewn), highest value of CRP (mg/L) during hospital stay, lowest value of albumin (g/L) during hospital stay of the surgery, latest recorded albumin-level preoperatively (g/L) recorded at least a calendar day before surgery, lowest value of Hb (g/L) during hospital stay of the surgery, latest pre-surgery recorded Hb (g/L) recorded at least a calendar day before surgery, surgical method (open or laparoscopic) and if the surgery was performed acute or elective.

Patient cases that showed signs of complications, such as longer periods of care and or readmissions, were subjects to an in-depth review of the medical records. This to confirm whether AL was present or not, which was determined by either the presence of diagnosis of AL in the medical records, endoscopic finding supporting the diagnosis, reoperation, or radiological signs of AL. For these patients the following information was collected: postoperative days (POD) in which the AL was detected, grading of the leakage based on both Clavien-Dindo and ISREC and if the AL occurred post loop-closure of the primary anastomosis after an anterior resection. It should be noted that the ISREC-classification used for AL is as previously mentioned only validated for rectal cancer. In this study, the classification was applied to all patients, with colon and rectal cancer that developed AL.

Statistical analysis

All statistical analysis were performed by SPSS (IBM SPSS Statistics Version 29). McNemar's test (paired proportions) was used to test the difference between the amount of registered AL in SCRCR and the amount of AL found during manual chart review. Before running McNemar's test, a primary assumption was made that a difference between the two proportions should not be higher than 10%. Logistic regression was performed to evaluate associations to the factors presented in Table 5, where the presence of AL is used as the dependent variable. Firstly, logistic regression was done by using the surgeries that were mostly performed, which in this study were right-sided hemicolectomies, anterior resection and sigmoidectomy (Type of surgery 1). Thereafter, another comparison was made using surgeries that hade a free choice regarding the anastomotic technique used during surgery, in this case right-sided hemicolectomies, left-sided hemicolectomies and sigmoidectomy (Type of surgery 2). Odds ratios (OR) and 95% confidence intervals (CIs) were estimated and P-value < 0.05 was considered statistically significant.

Table 5. Variables used for simple logistic regression with the presence of AL as the dependent variable.

Factor	Definition
Anastomotic technique	Hand-sewn or stapled
Type of Surgery 1	Right-sided hemicolectomy or anterior resection and sigmoidectomy
Type of Surgery 2	Right-sided hemicolectomy or left-sided hemicolectomy and sigmoidectomy
Surgical method	Open or laparoscopic surgery
Surgery	Acute or elective surgery

Student's contribution

At the start of the study, patient records were retrieved and prepared from SCRCR registry. Data was collected from medical records of patients who had undergone surgery at NÄL with the diagnoses C18, C19 or C20 during 2014-2018. Additionally, data compilation and analysis were done by the student whilst writing the report.

Ethics

This study had previously been approved by the Swedish Ethical Review Authority in 2021, registration number 2020-06593, as it serves as a complementary one to a larger project " Incidensen av anastomosinsufficiens efter kolorektalcancerkirurgi med primär anastomos I Västra Götalandsregionen år 2014-2018- en retrospektiv kohortstudie". Regarding data collection and reviewal of medical records, approval was given by head of the Department of surgery at NÄL.

Since the reviewal of medical records was done retrospectively, the study's outcome did not affect patients included in this study. To protect patient integrity, all data was pseudonymized.

Results

Study participants

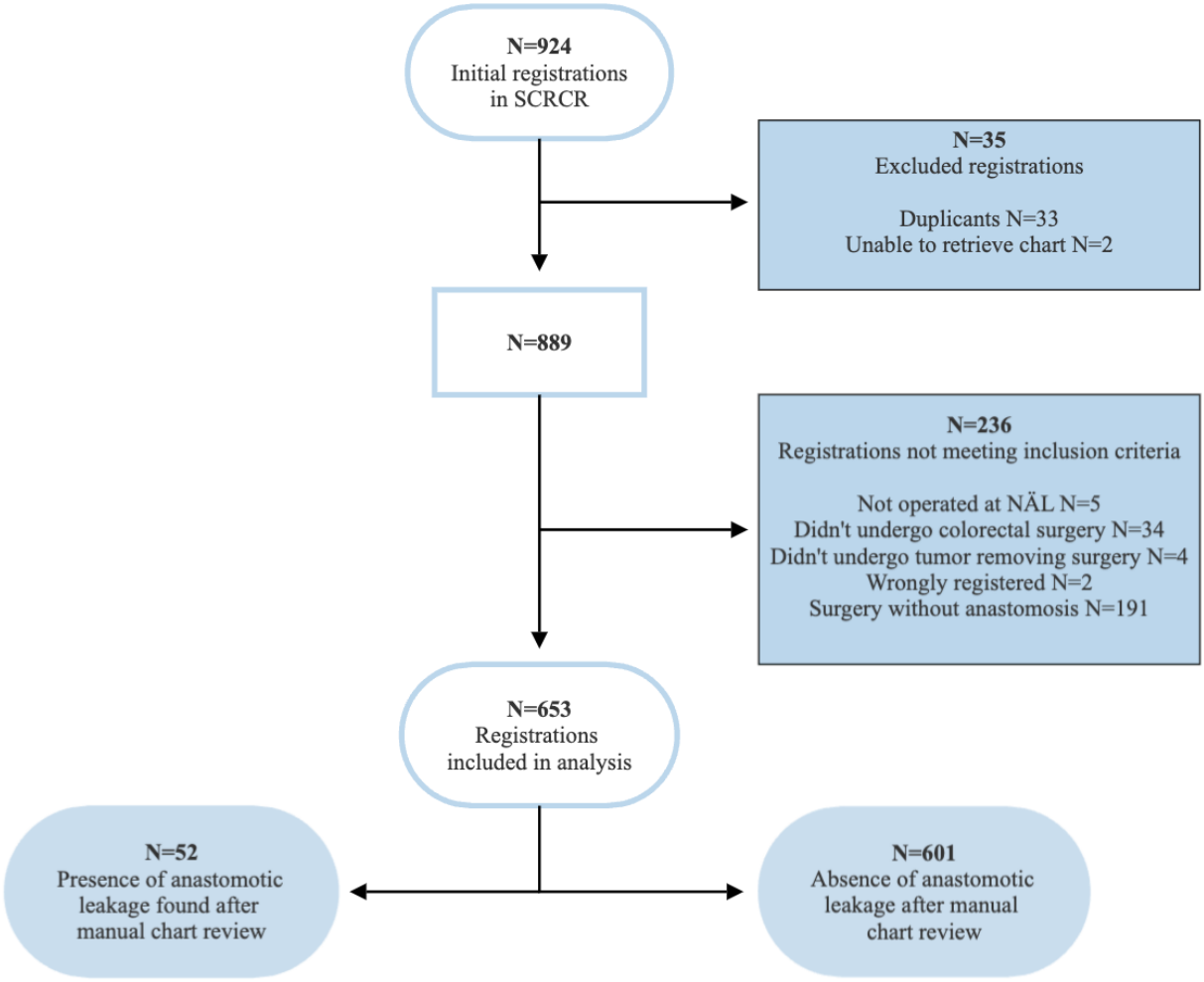

Figure 1. Flow chart of cohort from initial registrations in SCRCR to cohort included in analysis.

Figure 1 presents a total of 924 registrations that were initially found in SCRCR. 33 registrations were duplicates, meaning that there were multiple tumors present, but that only one or no anastomoses was constructed, and were therefor excluded. In this study, patients did not obtain more than one anastomoses after resection surgery. 2 registrations were excluded as charts could not be retrieved for manual review, thus leaving us with 889 registrations eligible for manual chart review.

A total of 236 patients were excluded considering 5 registrations were not operated in NÄL, 34 registrations did not undergo colorectal surgery, 4 registrations did not undergo tumor removing surgery, 2 were wrongly registered and were diagnosed with small-intestinal cancer

and 191 registrations underwent surgery without anastomosis. In total leaving us with 653 registrations (including 2 Hartmann operations that were later reversed with an anastomoses) that met the inclusion criteria and that were included in the analysis.

Table 6 below depicts descriptive statistics of the demographics of the participants included in the study and is based on the presence or absence of AL. Of the initial 653 patients, 52.1% were females and 47.9% were male. In this study, 69.7% of the surgeries were performed open and 91.6% of the surgeries were performed elective. The majority of anastomosis were hand sewn, 68.8%. Table 6B shows that the majority of the surgeries performed were right hemicolectomies (N=317) followed by anterior resections (N=144) and sigmoidectomy (N=97). The majority of AL were found after anterior resection (61.5%).

Table 6A. Demographic table the presents the distribution of the patients included in the study based on the presence or absence of AL.

	No anastomotic leakage	**Anastomotic leakage**
	Median (range)	Median (range)
Age	74 (38-95)	69 (42-87)
	N (%)	**N (%)**
Sex		
Male	278 (88.8)	35 (11.2)
Female	323 (95)	17 (5)
Anastomosis technique		
Hand sewn	432 (96.2)	17 (3.8)
Stapled	169 (83)	35 (17.2)
Surgical method		
Open surgery	420 (92.3)	35 (7.7)
Laparoscopic surgery	181 (91.4)	17 (8.6)
Elective or acute surgery		
Elective	550 (92)	48 (8)
Acute	51 (93)	4 (7.3)

Table 6B. Demographic table the presents the distribution types of surgeries performed, based on the presence or absence of AL.

	No anastomotic leakage	Anastomotic leakage
	N (%)	N (%)
Type of surgery		
Right hemicolectomy	308 (51.2)	9 (17.3)
Left hemicolectomy	64 (10.6)	4 (7.7)
Sigmoidectomy	93 (15.5)	4 (7.7)
Anterior resection	112 (18.6)	32 (61.5)
Transverse colectomy	13 (2.2)	1 (1.9)
Colectomy	8 (1.3)	2 (3.8)
Laparotomy without resection	1 (0.2)	0 (0)
Closure of Hartmann's procedure	2 (0.3)	0 (0)
Total:	99.9	99.9

Incidence of Anastomotic Leakage

The 24 registrations of AL that were reported in SCRCR were found during the manual chart review. Two of these cases were registered twice in the SCRCR because they had two synchronous tumors, one was not operated in NÄL and one did not undergo tumor removing surgery, resulting in 4 false positive registrations in the SCRCR. Therefore, only 20 cases of AL that were reported in SCRCR were used when comparing to the cases of AL found during manual chart review.

A total of 52 AL were identified during manual chart review, 41 (79%) were found within 30 POD and the remaining 11 (21%) cases occurred after 30 POD which would not be registered in SCRCR. One AL that occurred more than 30 days POD was classed as a Clavien-Dindo 1, which would not be noted in SCRCR considering they only register complications classed as Clavien-Dindo 2 or higher. Accounting for the 20 registrations that were already reported, there is a total of 21 missing AL registrations, that took place within 30 POD. The median POD for detection of AL was day 14, ranging from POD 1 to POD 461. The mean of POD at which the presence of AL was detected was 40.92 days.

Analysis was made between cases of AL registered in SCRCR and cases of AL found during manual chart review. Binomial calculations of CI for frequency of AL in manual chart review was 6.3% (95% CI, 4.56–8.45) and for the frequency of AL in SCRCR was 3.1% (95% CI, 1.91–4.73). Comparing the two proportions with McNemar's test a difference of 3,2% (95% CI, 1.86-4.57%) is given which shows that the difference between the two methods is statistically significant ($P < 0.0001$).

Table 6A shows that the presence of AL was mostly found in the anastomosis that were stapled. Table 7 presents the different types of surgery and the frequency of the two used anastomosis techniques, stapled and hand sewn. The majority of right hemicolectomies, left hemicolectomies and transverse colectomies were hand-sewn, whilst the anastomosis for all anterior resections were stapled. Table 7 also presents the incidence of AL for each surgery and shows that the majority of AL occurred after anterior resection.

Table 7. Distribution of anastomotic technique, stapled and hand sewn for the different types of surgery and the incidence of AL for the individual surgeries.

Type of surgery	**Anastomotic technique**		**Total**	**N of AL**	**Incidence of AL (%)**
	Stapled	**Handsewn**			
Right hemicolectomy	6	311	317	9	2.8
Left hemicolectomy Including sigmoidectomy	55	110	165	8	4.8
Anterior resection	144	0	144	32	22.2
Transverse colectomy	0	14	14	1	7.1
Colectomy	1	9	10	2	20
Laparotomy without resection	1	0	1	0	0
Closure of Hartmann's procedure	2	0	2	0	0
Total	**209**	**444**	**653**	**52**	**8**

Severity of Anastomotic Leakage

SCRCR uses the Clavien-Dindo classification to grade the complication AL. Table 8 presents the frequency of each classification for the 52 cases of AL that were found during the manual chart review. Of the 8 patients that were classified as Clavien-Dindo 2, 4 of them were found

within 30 POD and the other 4 were found after 30 POD. 4 were rectal cancers and the remaining 4 were colon cancers.

Table 8. Classification of the severity of AL according to Clavien-Dindo and ISREC-classification found during manual chart review and reported to the SCRCR.

Clavien-Dindo	Frequency in chart review N (%)	Frequency in SCRCR N (%)
I	1 (1.9)	-
II	8 (15.4)	-
IIIa	15 (28.8)	3 (15)
IIIb	16 (30.8)	15 (75)
IVa	7 (13.5)	2 (10)
IVb	3 (5.8)	-
V	2 (3.8)	-
ISREC	**Frequency in chart review N (%)**	
A	2 (3.8)	
B	27 (51.9)	
C	23 (44.2)	

A total of 9 AL cases were found to have differing registered Clavien-Dindo classification in the registry than the one found during manual chart review. All cases occurred before 30 POD. Four cases were registered as 3b but received intensive unit care due to single organ dysfunction and should have been registered as 4a. Two cases were registered as 3b but received intensive unit care due to multiorgan dysfunction and should therefore have been registered as 4b. Two of the AL cases were registered as 3b but passed away due to the AL and should have therefor been registered as Clavien-Dindo 5. One patient was registered as 4a but should have been registered as 4b due to multi organ dysfunction. See Table. 9.

Table 9. Presentation of 9 AL cases that were registered in the SCRCR with a differing Clavien-Dindo classification than the one found during manual chart review.

Case	Gender	Age of diagnosis of tumor	POD of AL	Operation type	Clavien-Dindo reported in SCRCR	Clavien-Dindo found during manual chart review
1	Male	74	8	Right hemicolectomy	3b	4a
2	Female	65	4	Anterior resection	3b	4a
3	Male	66	1	Anterior resection	3b	4a
4	Male	76	5	Sigmoidectomy	3b	4a

5	Male	46	1	Anterior resection	3b	4b
6	Male	85	9	Anterior resection	3b	4b
7	Male	77	4	Anterior resection	3b	5
8	Female	75	4	Left hemicolectomy	3b	5
9	Male	70	5	Colectomy	4a	4b

Risk factors of Anastomotic Leakage

Univariate analyses was used to evaluate the association between the factors presented in Table 10 and the risk of developing AL. The definition of each factor is presented in Table 5. For the logistic regression, the surgeries that were mostly performed (Type of surgery 1): right-sided hemicolectomy, anterior resection and sigmoidectomy were first compared for the risk of developing AL. Later, surgeries such as right-sided hemicolectomy, left-sided hemicolectomy and sigmoidectomy were compared for the risk of developing AL in a separate comparison, seeing as the choice of anastomotic technique is not free during rectal surgery. Factors such as surgical method, if the surgery was performed elective or acute and if it was a right-sided hemicolectomy or left-sided hemicolectomy and sigmoidectomy (type of surgery 2) did not correlate significantly with AL. The odds ratio (OR) for anastomotic technique had a value below 1 demonstrating a lower risk of AL for hand sewn anastomosis, also P-value < 0.001 correlating significantly with the risk of AL. Analysis demonstrated a higher risk of AL for anterior resection and sigmoidectomy (type of surgery 1), with a P-value < 0.001. Multiple logistic regression was performed for the two factors that hade a P-value < 0.05 from the univariate analysis, see table 10. Significance was found for the anastomotic technique (P-value=0.043) but not for the type of surgery 1 performed.

Table 10. Factors analyzed using logistic regression, where the presence of AL is used as the dependent variable.

Univariate analysis, simple logistic regression				
Factor	**OR**	**P-value**	**95% CIs**	
Surgical method	0.887	0.698	0.484	1.625
Elective or acute	1.113	0.843	0.386	3.210
Anastomotic technique	0.198	< 0.001	0.108	0.363
Type of Surgery 1	6.010	< 0.001	2.835	12.742
Type of Surgery 2	1.738	0.265	0.658	4.592
Multivariate analysis, multiple logistic regression				
Anastomotic technique	0.289	0.043	0.087	0.963
Type of Surgery 1	2.127	0.250	0.588	7.691

Discussion

This study assessed the frequency of anastomotic leakage and possible risk factors that may increase the risk of developing anastomotic leakage in a retrospective cohort of patients that underwent colorectal cancer surgery with primary anastomosis at NÄL. Our findings present a total of 52 patients that developed anastomotic leakage, of which only 20 were reported in the SCRCR. This study found a considerable underreporting of anastomotic leakage to the SCRCR. In regards to the risk of developing AL, statistical analysis demonstrated that there is significant difference in risk of developing AL between hand-sewn and stapling technique.

Incidence and severity of Anastomotic Leakage at NÄL

In the patient cohort, 52 out of 653 (8%) were found to have an anastomotic leakage. Leakages were mostly found in rectal cancer surgery and among male patients. This is in line with previous research that argue that the closer the distance of the anastomosis is to the anal verge, the higher the risk of leakage (8).

One interesting finding was that 9 out of the 42 anastomotic leakages that occurred before 30 POD had been reported to the SCRCR with a Clavien-Dindo classification lower than the one found during chart review. For patients that were registered as 3b, but received intensive care were graded as 4a or 4b during chart review. One possible explanation behind this is human error, seeing as the person in charge of registering the AL did not take the ICU note into account. Further, the two patients that passed away because of the anastomosis were according to SCRCR classed as Clavien-Dindo 3b. This differing classification is also prone to human error, seeing as it is an interpretive question if the death was in fact caused by the anastomotic leakage or if there were other factors that might have been the cause of death.

Risk factors for Anastomotic Leakage at NÄL

Factors such as surgical method and whether the performed surgery was elective or acute did not in the univariate analysis correlate with the increased risk of developing AL. Meanwhile, the anastomotic technique and the type of surgery 1 showed significant risk of developing AL in the univariate analysis, but when combined in the multiple logistic regression only the anastomotic technique proved to be significant. This was interpreted as the risk of AL being higher when using the stapling technique. On the other hand, a factor that needs to be taken into consideration is that the choice of anastomotic technique is not free for all surgeries and

was used as an independent variable in the analysis. For instance, the surgeon in charge can choose between hand sewn or stapled anastomosis for right hemicolectomies and left hemicolectomies. However, low anastomosis in the rectum, can only be constructed with the stapling technique and is therefore not and "independent" variable. For this reason, univariate analysis was run to see if there was a significant correlation between anastomotic leakage and if the surgery performed was a right hemicolectomy or left hemicolectomy and sigmoidectomy, which showed no statistical significance. Therefore, if cancer in the rectum is disregarded, there is still not a significant correlation between the risk of developing AL and the type of surgery performed, but that there is still a significant correlation between the risk of developing AL and the anastomotic technique used.

The results from our study demonstrated a significant correlation between the anastomosis technique used in colorectal surgery and the risk of AL, with the hand-sewn technique resulting in a significantly lower incidence of AL compared to the stapled technique. Previous research has shown different results when comparing both anastomosis techniques. As previously mentioned, a Swedish population-based study (16) evaluated whether the incidence of AL in a cohort of 3428 participants, that received ileocolic anastomosis were associated with the anastomosis technique (hand-sewn vs stapled). Most of the anastomoses were hand sewn and the stapling technique was more common among emergency cases. The results indicated a higher incidence of leakage when performed with the stapled technique compared to the hand sewn. These results are in line with the results found in our study. However, in the population-based story, the stapled technique was mostly used in acute cases. Although the results in our study did not indicate a higher risk for AL in acute surgeries versus elective, some studies suggest that AL occur more frequently in acute cases (20). This may explain why the stapling technique was associated with a higher leakage rate.

In contrast to the findings from our study, a multicenter study from Germany (14) that evaluated the incidence of AL after open right hemicolectomy, demonstrated no significant difference in the incidence of AL between the two anastomosis techniques. Unlike the current study, the German study did not include patients that underwent anterior resection. All anterior resections performed in our study used the stapled technique. Furthermore, the current study demonstrated that the majority of AL occurred after anterior resection, supporting the evidence that a lower distance from the anal verge increases the risk for AL. (8) Hence, the significance demonstrated in our study, favouring hand-sewn anastomosis over

the stapled technique might be due to the fact that all of the anterior resections were performed with the staple technique. This can further explain the discrepancy in our results compared to the German study. Nevertheless, these findings are interesting, but additional studies are recommended to further study the possible risk factors of anastomotic leakage.

Underreporting of Anastomotic Leakage to the SCRCR

Out of all the anastomotic leakages found during chart review, 32 out of 52 cases (62%) were not reported in the registry. A possible explanation for this number of underreporting is that the SCRCR does not register anastomotic leakages found after 30 POD. However, taking those leaks into account there are still 51.2% missing reports, which is a significant underreporting regarding anastomotic leakages within 30 POD in the SCRCR. Another explanation for this underreporting is that 8 of the anastomotic leakages found in this study were classified as Clavien-Dindo 2 but were not registered as leakages in SCRCR. These are cases of anastomotic leakage that can be questioned amongst clinicians. These patients encountered problems during the hospital stay which led to an extended stay at the hospital and were found on the CT to have debris close to the anastomosis, which we classed as AL in this study. In addition, 4 of the 8 anastomotic leakages were found after anterior resection and should according to ISREC be classified as anastomotic leakages. Further, clinicians may not interpret these 8 cases as anastomotic leakages seeing as they were not obvious cases, which may be true. However, omitting to the cases that were classed as Clavien-Dindo 2 and that occurred within 30 POD, a 46% underreporting is still seen and if all the 8 cases were rectal cancers they would have been classified as anastomotic leakages according to ISREC.

As previously mentioned, a consensual definition of anastomotic leakage does not exist among clinicians which can factor as a possible reason for the underreporting found in this study.(18) Although most of the leakages found were obvious during chart review, the risk of human error regarding registration procedures can also be seen as a possible reason for the underreporting. Moreover, there is no standardized registration procedure in the hospital and the experience of the registrar can vary considerably increasing the risk of human error.

Previous studies have assessed the validity of registry data from the SCRCR. (38, 39) One study assessed a total of 14 variable from the Swedish Rectal Cancer registry between years 1995-1997 and found that the registry held a high validity rate. (38) Further, a more recent

study showed that the completeness of the registry data from SCRCR was 98.5% for colon cancer and 98.8% for rectal cancer between the years 2008-2015. However, the study did not specifically validate registry data regarding anastomotic leakage, but an overall validation of the registry.(39) Nevertheless, recent studies within the same overarching project as this study have shown a significant underreporting of anastomotic leakages in the SCRCR and that a certain amount of these arise after 30 POD.(35-37)

Strengths and weaknesses

A limitation to this study is that it is retrospective and is therefore limited to registry routines used during the years 2014-2018. Thus, reporting routines throughout the years may vary and develop more with time. Another limitation to this study is that a large portion regarding laboratory tests were missing from the patient cohort. Thus, making it impossible to draw any conclusion regarding other risk factor that may increase the incidence of AL, such as Hb and Albumin levels which was intended at the start of the study.

One strength of this study is that medical charts were reviewed and examined by one investigator, thus minimizing the risk for interpretation discrepancies. However, this can also be seen as a limitation to the study seeing as the risk of human error still exists. By reviewing all suspected AL alongside primary supervisor, head physician in General surgery and secondary supervisor, resident in General surgery, clinical expertise was given to strengthen the reliability of the results.

Another strength of this study is the sample size of 653 patients which is in the higher range compared to similar studies who had sample sizes of 420 and 511 patients. As such, strengthening the statistical power of this study.

Conclusion and Implications

This study reveals that there is a significant underreporting to the SCRCR regarding anastomotic leakage at NÄL. Therefore, extending the POD to more than 30 days could increase the number of leakages found. Moreover, reporting routines should be improved amongst the different hospitals in Sweden not only for anastomotic leakage but also the Clavien-Dindo classification. Further improvements and standardization should be

considered regarding chart documentation to minimize the risk of underreporting leakages. Seeing as similar studies have shown an underreporting of AL at two other hospitals and that the SCRCR is used nationwide, further research should be conducted in other Swedish hospitals for a better understanding of the degree of underreporting regarding this complication.

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