Chapter 1:

META-ANALYSIS OF THE RISK FOR ANASTOMOTIC LEAKAGE, THE POSTOPERATIVE MORTALITY CAUSED BY LEAKAGE IN RELATION TO THE OVERALL POSTOPERATIVE MORTALITY.

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Abstract

Introduction: Availability of anastomotic leakage rates and mortality rates following anastomotic leakage is essential when informing patients with rectal cancer preoperatively. We performed a meta-analysis of studies describing anastomotic leakage and the subsequent postoperative mortality in relation to the overall postoperative mortality after low anterior resection for rectal cancer.

Methods: A systematic search was performed of the published literature. Data on the definition and incidence rate of AL, postoperative mortality caused by AL, and overall postoperative mortality were extracted. Data were pooled and a meta-analysis was performed.

Results: Twenty-two studies with 10343 patients in total were analyzed. Meta-analysis of the data showed an average AL rate of 9%, postoperative mortality caused by leakage of 0.7% and overall postoperative mortality of 2%. The studies showed variation in incidence, definition and measurement of all outcomes.

Conclusion: We found a considerable overall AL rate and a large contribution of AL to the overall postoperative mortality. The variability of definitions and measurement of AL, postoperative mortality caused by leakage and overall postoperative mortality may hinder providing reliable risk information. Large-scale audit programs may provide accurate and valid risk information which can be used for preoperative decision making.

Introduction

When discussing treatment options for rectal cancer with patients preoperatively, difficult considerations can be encountered. Besides tumour and patient related factors, both doctors and patients' preferences play a role in the decisions about treatment options. This is particularly the case in surgical treatment for rectal cancer, when deciding between constructing an anastomosis and/or creating a stoma. Both patients and doctors have a strong preference to avoid a stoma, under the assumption that it will have negative consequences on quality of life.[1]

On the other hand, an anastomosis may not be beneficial to all patients, as a considerable proportion of patients with rectal cancer report defecation problems following a low anastomosis, such as fecal incontinence and urgency.[2] Even more important is considering the risk of anastomotic leakage (AL) following the construction of an anastomosis. AL is the most frequent major complication after surgery for rectal cancer, causing re-operations, prolonged hospital stay, morbidity, mortality and possibly a worse oncological outcome.[3] Recent advances in surgical techniques have increased options for sphincter preservation in rectal cancer. The increasing use of sphincter preserving procedures subsequently exposes more patients to the risk of anastomotic leakage.[4] In order to inform and involve patients in clinical decision-making, clinicians need reliable and accurate information on AL rates and mortality rates following AL. Previous studies have shown that patients with rectal cancer prefer to be involved in the decision making process and to be informed on risks of different treatment options[5].

The aim of this study was to perform a systematic review of studies describing anastomotic leakage and the associated mortality in comparison to the overall postoperative mortality after low anterior resection (LAR) for rectal cancer. Regarding the difference in impact and consequences for a patient, it is important to distinguish clinically

relevant anastomotic leakage from radiologic leakage.[1] In this review we assessed clinical anastomotic leakage.

Methods

Literature search

Relevant studies published between January 1990 and August 2011 were identified by searching Medline, Embase and The Cochrane Library databases. The following search terms were used: AL, dehiscence, mortality, anterior resection, mesorectal excision. Both free text search and MeSH search for keywords were employed. Two investigators (HS and BB) independently performed the literature search. To increase the sensitivity of the search strategy, the 'related article' function was used, and reference lists of relevant articles were searched for additional relevant studies. The search was restricted to publications in English.

Study selection and data extraction

All randomized controlled, multi-center and single-center, prospective and retrospective studies describing surgical therapy for rectal cancer were considered for inclusion. Studies were included when describing patients undergoing elective LAR for rectal cancer. The articles had to contain at least data on 1) AL rates 2) mortality following AL and 3) overall mortality. Only articles describing all three outcomes were included. Only original articles were included in order to maintain adequate details on patient selection, study design, methods and outcome, allowing for accurate comparison of the study results. Studies were excluded from analysis when they also described patients that underwent emergency resections, high anterior resections, abdominoperineal resections, procedures other than for rectal cancer and experimental surgical techniques such as robot-assisted surgery. We extracted data on the definition and incidence rate of AL, postoperative mortality caused by AL and overall postoperative

mortality. No rating of these studies was performed; al studies were accepted or rejected based on the criteria noted above. Data were extracted independently by two different researchers and compared. Any discrepancies were resolved by discussion.

Statistical analysis

The percentages of AL, postoperative mortality following leakage and overall postoperative mortality were meta-analyzed with a random effects model. Because the numbers were small in most studies, we applied the method of Hamza et al.[6] The standard deviations of the random effect was zero, therefore data could be pooled. The overall percentages of the outcomes were therefore the number of events over studies divided by the total number of patients over studies.
Statistical analyses were carried out in PASW Statistics, Rel. 18.0.2009 (SPSS inc., Chicago, Il, USA) and R 2-14 (The R Project for Statistical Computing and The Comprehensive R Archive Network; http://cran.r-project.org/).

Results

Included studies

We identified 188 studies of which 22 were included.[3,7-26] One hundred and sixty six studies did not meet the inclusion criteria and were excluded from further analysis. The most common reason for exclusion was that the study described also other types of surgery without providing specific data on the outcomes of LAR alone (n=69). Twenty-eight studies were excluded because they did not mention all three outcome measures. Reasons for exclusion are shown in *table 1*.
The included studies had a total population of 10343 patients. Sample sizes of studies varied from 38 to 2726 patients. There were two randomized controlled trials investigating the effect of a defunctioning stoma on AL rates. The other studies were non-randomized (*table 2*).

Anastomotic leakage: incidence and definition.

For the meta-analysis we used the number of ALs as defined in the study. The overall AL rate was 9% (974 out of 10343 patients). There was a large variation in AL rates; the highest reported AL rate was 28% and the lowest reported rate was 3% (*figure 1*).

AL was described in 19 of 22 studies. Three studies gave no definition of AL, fourteen studies gave a detailed description of the definition of AL and the remaining studies gave only a limited definition. Most definitions of AL consisted of a clinical suspicion based on the patient's symptoms. The reported symptoms comprised the signs of localized or generalized peritonitis (10 studies), fecal discharge from the wound and/or drain (9 studies), abscess (10 studies), recto-vaginal fistulas (6 studies), purulent discharge from drain, wound and leukocytosis (1 studies). The need for active intervention was used in some studies to define a clinically relevant AL, whereas others accepted signs of leakage without further intervention. None of the authors provided a grading system to classify the severity of AL (*table 3*).

Overall mortality: incidence and definition

For the meta-analysis we used the number of postoperative deaths as was described in the study. The mean overall postoperative mortality rate was 2% and varied from 0 to 8% (*figure 2*).

The definition of postoperative mortality differed. Two studies specified postoperative mortality as death within 30 days after operation, both in-hospital and after discharge. One study considered all in-hospital deaths as postoperative mortality. Five studies reported postoperative mortality as all patients who died within 30 days after surgery and gave no further specification of the location (in-hospital or after discharge). Three studies included all in-hospital deaths in the postoperative mortality rate, without specification of timing. Nine studies described postoperative mortality without specification of location (in-hospital or after discharge) or timing. Two studies did not specify their definition of mortality.

Postoperative mortality caused by AL: incidence and definition.

For the meta-analysis we used the number of postoperative mortality caused by ALs as defined in the study. In total, 71 out of 10343 patients died as a direct consequence of AL (0.7%), ranging from 0 to 5%. One third of the overall mortality was caused by AL. This ratio ranged from 0 to 100% (*figure 2*).

Nine studies defined postoperative mortality caused by AL as 'death of septic complications secondary to AL'. Five studies defined postoperative mortality caused by AL as 'all deaths after anastomotic leakage'. No study reported details on how causes of death were determined, for example autopsy findings. The remaining studies reported no postoperative deaths in patients with AL (*table 3*).

Discussion

In this thorough overview of studies describing anastomotic leakage and subsequent mortality after low anterior resection for rectal cancer we found that patients have a considerable risk for AL (9%). We found that AL considerably contributed to mortality after rectal cancer surgery, accounting for one third of all postoperative mortality. This finding is supported by, and could well be compared with, the results of a nationwide population based study assessing exclusively patients who died following anterior resection of the rectum[28]. The study describes 140 patients that died following rectal excision with anastomosis, of whom 42% had anastomotic leakage, a result very similar our findings.

The information of the present study may very well be used for counseling patients preoperatively. However, we also found that the definitions of AL and postoperative mortality varied widely. The twenty-two included studies used twelve different definitions to describe AL. The lack of universally accepted definitions for AL has already been described in 2001 by Bruce et al[29]. They described 29 separate definitions for AL after lower gastrointestinal surgery. The author plead

for the use of a standard definition that could distinguish between clinical minor and major leaks.

We also found six different definitions of overall postoperative mortality. The timing (30-days or 90-days) or location of death (in-hospital mortality or death after discharge) varied. Recent evidence shows that mortality almost doubles by 90 days when compared with the rate at 30 days in patients undergoing colorectal surgery[30]. This clarifies the importance of a uniform agreement on measurement of postoperative mortality.

Average rates of AL, postoperative mortality and mortality as a result of AL all showed a wide range between the different publications. This may be a reflection of differences in definition, as well as actual differences in performance.

Surgical treatment for rectal cancer is embedded with difficult decision, often subject to both doctors and patients' preferences. The variability of definitions and variance in outcome rates between studies may hinder providing patients with reliable risk information preoperatively.

Obviously, AL and its subsequent mortality will never occur if an anastomosis is avoided, e.g. when a permanent end colostomy is constructed. In the case of choosing the anastomosis there is today strong evidence for adding a defunctioning stoma in order to reduce the risk for clinical leakage.[31] The benefits of preventing or minimizing AL should always be balanced against the disadvantages of the alternatives. A defunctioning stoma itself carries a substantial risk of becoming permanent either as a loop stoma[32] or as a permanent loop ileostomy or a permanent end colostomy.[33,34] Also, different studies report that stomal complications are prevalent, as they are seen in 25 to 50% of patients with a stoma after 8-10 years of follow-up.[35,36] Furthermore, the morbidity and mortality of closure of a defunctioning stoma should be taken into account.[37] On the other hand, if AL occurs in patients without a deviating stoma, it often requires re-operation, and also creation of a

secondary stoma. Last, the effect of a treatment on quality of life should be considered. Opposed to the negative influence of a stoma on quality of life, patients with (low) anastomoses also have a risk for functional derangements, incontinence, sexual and bladder functions. All these factors should be balanced against each other and taken into account in the final decision.

This decision would be easier if we could select those patients with a higher risk for AL and subsequent mortality. Predicting AL enhances the possibility to take precautions to prevent it, or diminish its consequences. The percentage of patients developing AL depends on multiple factors. Several patient-, tumour-, and therapy-related parameters have been identified as risk factors for AL in a large amount of studies. A disturbed microcirculation, as seen in nicotine abuse or diabetes mellitus patients, has been said to increase the risk for AL[38,39] Also, height of the anastomosis, preoperative radiation, a malnourished status, steroid use, male gender and peri-operative bleeding are previously described potential risk factors.[40] Unfortunately, despite the vast body of evidence on the potential risk factors, AL remains difficult to predict in an individual patient. As the selection process of high-risk patients remains imperfect, we emphasize that every single patient should be counseled preoperatively on the risk of AL, the consequences including mortality and the possibility of stoma formation.

The available literature however, is insufficient to inform patients on AL and subsequent mortality and make the trade-off between an anastomosis (with or without defunctioning stoma) or a permanent end colostomy.

Ideally, to support clinical decision making in current surgical practice, this meta-analysis would also provide information on AL and the subsequent mortality risk in subgroups of patients, such as patients treated with preoperative radio- or chemotherapy or patients with a defunctioning stoma. However, an important inclusion criterion in our analysis was the availability of data on AL, mortality due to AL and overall mortality. Most articles did not stratify all these three outcomes

for individual subgroups; therefore meta-analysis within these subgroups was not possible. The lack of availability of this data further emphasizes the limitation of current evidence on anastomotic leakage rates for the use in daily clinical decision making.

Therefore, more research is needed, one of the most important things being uniformity of definitions. Recent growing public interest in quality and outcome of medical and surgical care has led to the development of audit programs. These guarantee uniformity of definition and measurement of basic outcome parameters such as AL, subsequent postoperative mortality and overall postoperative mortality. Frequent feedback of these outcomes may support clinicians when informing patients about risks of different treatment options and facilitates the decision making process.

Table 1: Studies excluded from the meta-analyses.

Reason for exclusion	***Number of studies (n)***
Other types of surgery included	69
Not all three outcome criteria mentioned	28
Surgical procedures other then for rectal cancer included	14
Only abstract available	13
Review of the literature	13
Described also non-curative resection	6
Also emergency situations included	5
Described new surgical technique to avoid leakage	8
Other	9
Total	**165**

Table 2: Characteristics of the included studies.

Author	***Year***	***Patients (n)***	***Study design***
Swellengrebel et al	2011	47	Prospective single centre
Shiomi et al	2010	329	Retrospective single centre
Fouda	2010	56	Prospective single centre
Den Dulk et al	2009	2726	Retrospective multi centre
Bertelsen et al	2009	1494	Retrospective multi centre
Tsikitis et al	2009	237	Retrospective single centre
Eberl et al	2009	472	Retrospective single centre
Kuroyanagi et al	2008	159	Retrospective single centre
Asteria et al	2008	520	Retrospective single centre
Pugliese et al	2008	157	Retrospective single centre
Matthiessen et al	2007	134	Randomized controlled trial
Lefebure et al	2007	132	Retrospective single centre
Krushewski et al	2007	276	Retrospective single centre
Dulucq et al	2005	218	Retrospective single centre
Eriksen et al	2004	1958	Retrospective single centre
Chaudry et al	2000	69	Retrospective single centre
Poon et al	1999	148	Retrospective single centre
Machado et al	1999	161	Retrospective single centre
Pakkastie et al	1997	38	Randomized controlled trial
Enker et al	1999	681	Retrospective single centre
Memon et al	1996	154	Retrospective single centre
Grabham et al	1995	77	Retrospective single centre
Fick et al	1990	39	Retrospective single centre

Table 3: Definition of AL, overall postoperative mortality and postoperative mortality caused by AL.

Author	***Definition of anastomotic leakage***	***Definition of postoperative mortality caused by anastomotic leakage***	***Definition of overall postoperative mortality***
Swellengrebel et al	Not specified	Not specified	30-day mortality
Shiomi et al	Clinically by the presence of the following: discharge of gas, pus or feces from the drain or wound; discharge of pus per rectum; or rectovaginal fistula	Mortality caused by leakage	Not specified
Fouda et al	Clinically as gas, pus or fecal discharge from the drain, operative wound, pelvic abcess, peritonitis and rectovaginal fistula	Mortality caused by leakage	Not specified
Den Dulk et al	Faecal discharge from pelvic drain or abdominal wound, or radiologically, endoscopically or surgically proven anastomotic leakage in symptomatic patients such as those with peritonitis	All deaths after leakage	30-day mortality
Bertelsen et al	Symptomatic anastomotic leakage defined as peritonitis and a defect in the anastomosis, or discharge of pus from the rectum, or rectovaginal fistula, or the passage of faeces or gas from an abdominal drain	All deaths after leakage	30-day mortality
Tsikitis et al	Pelvic abscess included	Not specified	Postoperative mortality
Eberl et al	Gas, pus or fecal discharge from the pelvic drain, peritonitis, signs of rectovaginal fistula, fever, or leukocytosis	Mortality caused by leakage	30-day mortality or during hospital stay
Kuroyanagi et al	Not specified	Not specified	In-hospital mortality
Asteria et al	Small adjacent absces, adjacent unilocular, abscess, failure of half or more of the circumference of an anastomosis, multilocular abscess or peritonitis	All deaths after leakage	30-day mortality

Pugliese et al	Not specified	Mortality caused by leakage	Postoperative mortality
Matthiessen et al	Peritonitis caused by leakage from any staple line, rectovaginal fistula, and pelvic abscess without radiologically proven leakage mechanism were included	Not specified	30-day mortality
Lefebure et al	Pus or fecal discharge from the drain, pelvic abscess, peritonitis, or discharge of pus per rectum	All deaths after leakage	30 days of operation, both in-hospital and death after discharge
Krushewski et al	Clinically manifest anastomotic leakage: fecal discharge from the drain, surgical wound or vagina or by CT detection	Mortality caused by leakage	Postoperative mortality
Dulucq et al	Leakage requiring operative management with a diverting stoma or treated conservatively with TPN and percutaneous drainage when needed	Not specified	Postoperative mortality
Eriksen et al	Pelvic abscess, faecal discharge from wound, septicaemia, peritonitis, with or without radiologically confirmed leakage.	All deaths after leakage	30 days of operation, both in-hospital and death after discharge
Chaudry et al	Asymptomatic leakage, abcess requiring drainage or reintervention.	Not specified	Postoperative mortality
Poon et al	Clinical anastomotic leakage	Not specified	Postoperative mortality
Machado et al	Pelvic sepsis, which included clinical staple line leaks,infectious collections in the pelvis with or without a proven staple line leak, and enterovaginal fistulas	Mortality caused by leakage	30-day mortality or during hospital stay
Enker et al	Clinically or radiologically apparent leakage, pelvic abscess	Mortality caused by leakage	In-hospital mortality
Memon et al	Clinical anastomotic leakage	Mortality caused by leakage	Operative deaths
Grabham et al	Clinical anastomotic leakage	Not specified	Perioperative deaths
Pakkastie et al	Feacal discharge from the wound or drain, pelvic sepsis, postoperative fever or septicaemia	Mortality caused by leakage	Postoperative mortality

Figure 1. AL rates reported by the included studies ranked by volume.

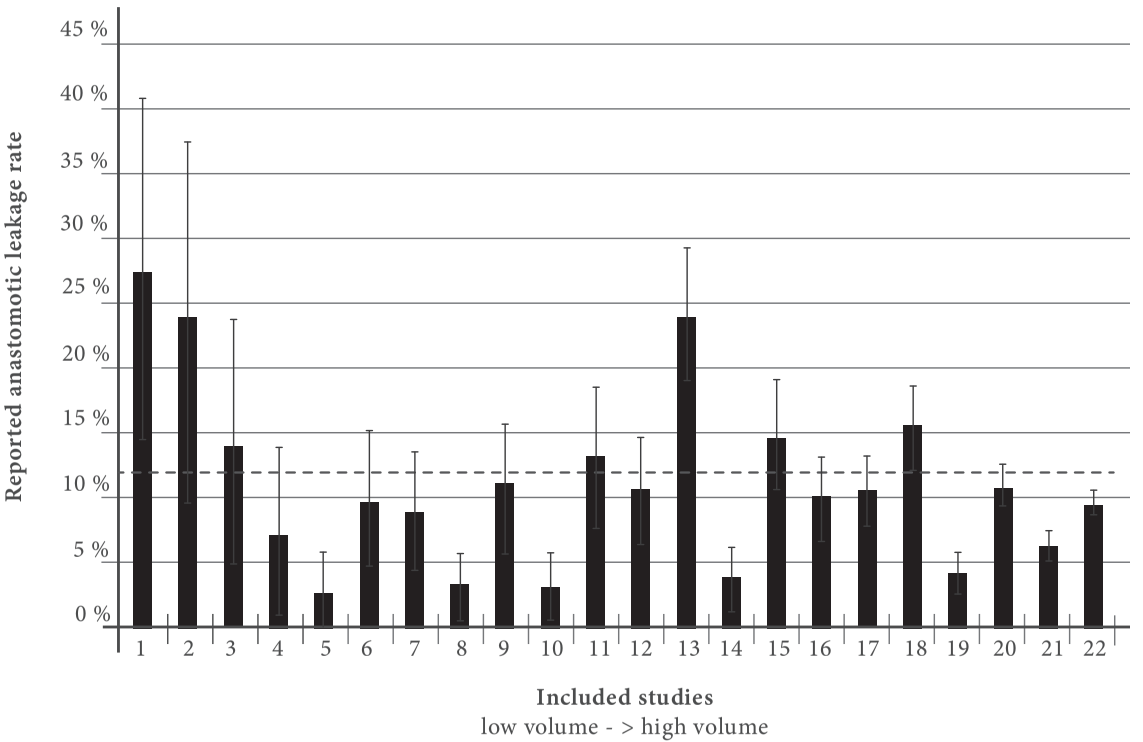
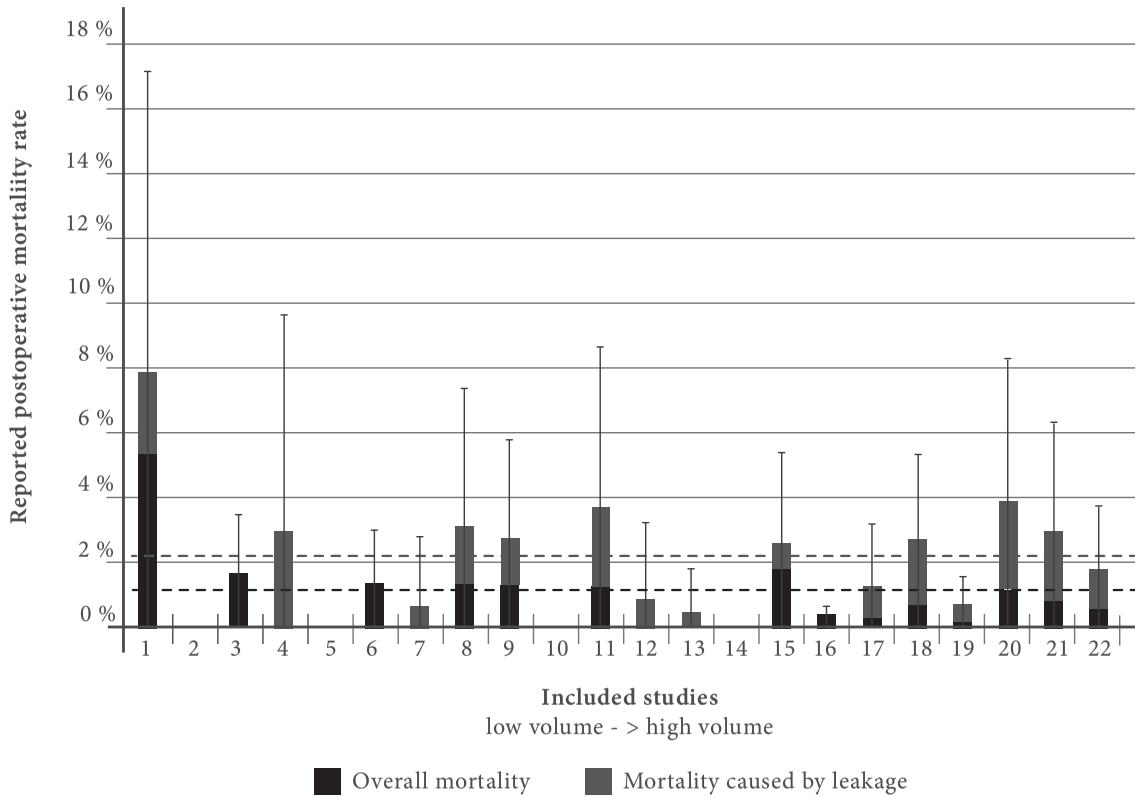


Figure 2. Overall postoperative mortality rates and postoperative mortality caused by AL reported by the included studies. Studies are ranked by volume.



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