Colorectal surgery with subsequent creation of colorectal anastomoses has been extensively studied throughout the years. Various procedures and several materials have been examined resulting in continuous improvements in surgical techniques. The introduction of stapling devices in the 1970s allowed lower anastomoses leading to accumulating numbers of colorectal anastomoses and improved application in laparoscopic surgery (1).

Colorectal cancer is the third most common cancer worldwide, with a persistent increasing incidence (2). In the current multidisciplinary treatment approach, surgery is the only curative treatment strategy for colon cancer. For rectal cancer however, non operative treatment is currently focus of interest. Complete pathological response in patients treated with neoadjuvant chemoradiation followed by a wait and see policy, seems to have good results without the morbidity of surgery (3,4). Not all rectal tumours react with a complete response to neoadjuvant therapy and at this moment there are no long term results. Hence, currently, surgical resection remains the cornerstone of treatment for both colon and rectal cancer. In 2013 almost 10.000 colorectal cancer resections were performed in the Netherlands (5). Colorectal resections however, are not only performed for a malignancy, but also for benign indications, resulting in a significant higher nationwide total amount of annual colorectal surgical procedures.

Following colorectal resection, there are three surgical options, consisting of creation of bowel continuity by means of a primary anastomosis, an anastomosis with a temporary defunctioning stoma or the omission of bowel continuity by construction of a terminal ileo- or colostomy. Each of these three surgical options is associated with their specific advantages and disadvantages and corresponding outcome.

PRIMARY ANASTOMOSIS

Restoration of bowel continuity with a primary anastomosis is the first choice treatment for patients undergoing an uncomplicated resection. An anastomosis however, bears the risk of anastomotic leakage, one of the most common surgical complications after colorectal resection. Anastomotic leakage, leads to high rates of morbidity, re-interventions, longer hospital stay and mortality (6-8), and possibly a worse oncological outcome (9,10). The overall anastomotic leakage incidence varies widely in the literature, ranging from 4 to 20% in colorectal anastomoses (7,11-13) and 3 to 6.5% in colonic anastomoses (14-16). In the Netherlands 11% of the patients operated on for rectal cancer developed anastomotic leakage and 7.2% of patients undergoing...
**GENERAL INTRODUCTION AND OUTLINE OF THESIS**

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**PRIMARY ANASTOMOSIS**

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colon cancer resection (17). Variations in the definition of anastomotic leakage may in part account for this difference, but patient selection and clinical practice may as well account to it.

The pathogenesis of the occurrence of anastomotic leakage is still not fully understood. It is generally advised that a well-fashioned anastomosis should be made in an adequately vascularized bowel in the absence of contamination. Tension on the anastomosis can result in insufficient circulation leading to ischemia and inadequate anastomotic healing. Tension can also lead to traction and a mechanical rupture of the anastomosis, especially when no defunctioning stoma is made and (mass)peristalsis plays a role (18). Also intraoperative contamination results in worse healing (16,19). Even though there are known risk factors including patient factors as comorbidity, American Society of Anesthesiologist classification (19,20), tumour factors as stage of disease, tumour localization (15,21) and treatment factors including emergency surgery (20,21), and construction of a defunctioning stoma (7,13), it is still difficult to predict the anastomotic leakage risk for the individual patient.

Improvements in surgical techniques as staple-line reinforcements (22), transanal stents (23) and applications of intraluminal devices (24-27), aimed to diminish anastomotic leakage rates. Despite these promising perspectives, clinical anastomotic leakage rates remain unaltered.

**DEFUNCTIONING STOMA**

In order to prevent the occurrence of anastomotic leakage and diminish its clinical consequences, a temporary defunctioning stoma, could be made (7,13). Results of a Swedish randomized clinical trial, randomizing rectal cancer patients undergoing low anterior resection between a defunctioning stoma or a primary anastomosis, showed significant more anastomotic leakage in patients without a defunctioning stoma, 28% vs 10.3% respectively (13). Despite the high overall anastomotic leakage percentage in the control group, the outcome of this trial initiated a defensive surgical strategy, translating in high defunctioning stoma rates. In the Netherlands a defunctioning stoma is made in 70% of the patients with a colorectal anastomosis (5,17,28). Leakage rates after rectal cancer surgery were significantly lower for patients with a defunctioning stoma, compared to patients without a stoma, 10 and 13% respectively. The leakage incidence after colonic anastomoses did not significantly differ, respectively 6% in patients with a defunctioning stoma and 7% in patients without a stoma (17).

Even though a defunctioning stoma may result in lower leakage rates, anastomotic leakage still occurs. Furthermore, stomas have their own drawbacks. The creation of a defunctioning stoma is associated with more postoperative complications, stoma problems and higher hospital re-admission rates (29-31). Also, patients with a defunctioning stoma need another operation to
reverse the stoma with subsequent associated postoperative complications, and in addition, these patients still bear the risk for anastomotic leakage after stoma reversal (32,33). A high proportion of temporary defunctioning stomas is not reversed at all and becomes permanent (34).

**END-COLOSTOMY**

Avoidance of an anastomosis after colorectal resection is often considered in high-risk patients. In these patients an end-colostomy is constructed with closure of the rectal stump. This surgical option protects against anastomotic leakage and its sequelae, and it also leads to better functional results in patients with a low anastomosis (35). Further, patients with permanent stomas are described to have a better quality of life than patients with temporary stomas (36). There is no difference in quality of life between patients with a permanent end-colostomy compared to patients without a permanent end-colostomy after rectal cancer resection (37). Construction of an end-colostomy seems to be a good solution in high risk patients avoiding the sequelae of anastomotic leakage, however, also creation of an end-colostomy has its disadvantages. Construction of and end-colostomy is associated with stoma complications, more intra-abdominal and pre-sacral abscesses due to stump necrosis, more re-interventions and a higher hospital re-admission rate (38,39).

Although creation of defunctioning stomas reduces the anastomotic leakage rate, and end-colostomies even prevent leakage, the drawbacks of stomas, both temporary defunctioning stomas and end-colostomies, should be taken into account, prior to surgical resection. Outcome of these three surgical options, together with the patient’s preference, should be considered for good pre-operative clinical shared decision-making.

**DUTCH SURGICAL COLORECTAL AUDIT**

All aforementioned considerations of different surgical options and corresponding outcome, together with existing scientific evidence, emphasize the importance of careful decision making in anastomosis and stoma construction following colorectal resection. There is no uniform policy concerning anastomosis and stoma creation. This decision process varies per country, per hospital, per surgeon and per patient.

Currently, when quality indicators are a major topic in healthcare, there is increasing interest in surgical outcome. The Dutch Surgical Colorectal Audit is a quality institution in which all Dutch Hospitals participate. This audit is established in 2009 to monitor and improve surgical outcome for patients with colorectal cancer. National audits provide insight in surgeries and their...
corresponding outcome and can be useful in order to achieve improvements. Outcome of national data has the benefit that it is less biased than outcome of clinical trials, often excluding subpopulations as elderly, emergency patients and patients with metastatic disease. In the future these results might contribute to establish a uniform policy according anastomosis and stoma construction in colorectal surgery and possibly even custom made for groups or for the individual patient.
Introduction

**OUTLINE OF THESIS**

This thesis aims to describe surgical outcome of colorectal anastomoses and prevention of anastomotic leakage. The majority of scientific clinical results are based on the combined outcome of both colon and rectal surgical resections. The present thesis attempted to obtain better insight in surgical outcome by differentiating between both colon and rectal surgery. The first part focuses on surgical outcome of colorectal cancer resection in the Netherlands, using population-based data from the Dutch Surgical Colorectal Audit. The second part of the thesis is centered on the prevention of anastomotic leakage and its sequelae after colorectal resection.

Chapter 2 identifies risk factors for anastomotic leakage and mortality following anastomotic leakage in patients undergoing colon cancer resection. In Chapter 3 postoperative outcome of non-elective colon cancer resections is focus of interest. Chapter 4 shows results of mid and high rectal cancer resections, in which differences in outcome between primary anastomoses, defunctioning stomas and end-colostomies were analyzed. Chapter 5 describes one-year surgical outcome after low anterior resection for rectal cancer differentiating between the aforementioned three surgical treatment strategies.

Chapter 6 reveals the study protocol of the C-seal trial. The C-seal is designed to prevent anastomotic leakage. It is an intraluminal biodegradable drain, which is fixed proximal to the anastomosis with a circular stapler. This randomized clinical trial examined the influence of the C-seal on the occurrence of clinical anastomotic leakage after colorectal resection. The results of the C-seal trial are presented in Chapter 7. Chapter 8 focuses on techniques used in Dutch colorectal anastomoses after colorectal resection.
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PART I

SURGICAL OUTCOME OF COLORECTAL CANCER RESECTION IN THE NETHERLANDS