Advances in colorectal surgery
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General introduction and outline of the thesis
General Introduction

Laparoscopy and fast track perioperative care programmes

Two major developments in colorectal surgery since the nineties have been the introduction of laparoscopic surgery and the implementation of multimodal fast track perioperative care programmes. Both focus on an enhanced recovery after surgery, reduced morbidity and a shorter hospital stay as compared to open surgery in a traditional perioperative care setting.

Laparoscopic segmental colectomy was first described in 1991.1 Ever since a great deal of effort has been made to establish its feasibility and safety particularly in segmental colectomy for cancer. Several randomised trials comparing laparoscopic with open segmental colectomy have indicated that laparoscopic surgery can be applied safely for both benign and malignant diseases.2-7 Furthermore, laparoscopic surgery, in a traditional perioperative care setting, was associated with less morbidity, less postoperative pain, a faster postoperative recovery and a shorter hospital stay.2;8;9 More recently, it has been shown that short term cancer related outcomes such as cancer-free resection margins and the number of harvested lymph nodes, as well as long term cancer related outcomes such as disease free survival are comparable between laparoscopic and open surgery.2

At the same time, enthusiasm was raised for the so-called fast track perioperative care programme, also referred to as Enhanced Recovery After Surgery (ERAS®). This essentially is a modification of the programme initially developed by the Danish surgeon Henrik Kehlet.10-12 The multimodal and multidisciplinary programme, involving optimization of several aspects of the perioperative management of patients undergoing segmental colectomy, enables patients to recover faster resulting in an earlier discharge as compared to the traditional perioperative care setting. Lengths of postoperative hospital stay of two to three days after open segmental colectomy have been reported. Furthermore, postoperative morbidity might be reduced in a fast track perioperative care setting.13-18 The essence of the fast track perioperative care programme is summarized in Figure 1.10-18

Figure 1. The essential elements of the fast track perioperative care programme.
During the early implementation, there were concerns regarding the number of readmissions after fast track perioperative care programmes. Initial programmes of fast track open colonic surgery had a planned two day postoperative hospital stay. This lead to a high readmission rate (up to 20%). However, Andersen et al. reported that the readmission rate declined when the planned postoperative hospital stay was increased from two up to three days. Readmission rates decreased from 20% (period planned hospital stay of two days) to 11% (period planned hospital stay of three days). The median length of primary hospital stay was two days for the first group and three days for the second, and median total hospital stay (including the readmissions) was three days in both groups, respectively. Therefore, a reduction of hospital stay seems feasible with a lower limit of postoperative day three. Several other studies have also reported no increase in the number of readmissions after a primary hospital stay of three to four days. Nevertheless, despite the high level of evidence supporting the individual elements of the fast track perioperative care programme, there seems to be no widespread implementation of these elements. This is further demonstrated in a recent survey that investigated clinical practice around colonic operations across 295 hospitals including several European countries and the United States. Preoperative bowel clearance was still used in more than 85% of patients. A postoperative nasogastric tube was left in place in more than half of the patients, to be removed about three days postoperatively. Furthermore, it took three to four days until half of the patients first tolerated liquids and four to five days until half of patients were eating and bowel movements were present. The delay in integrating novel clinical management strategies within routine practice may be ascribed to the time required to develop guidelines, the implementation process, the target group of professionals, the patients, the cultural and social setting, and the organizational and economic environment. Clearly, the issue of effective implementation and a consequent high rate of compliance are essential in terms of problem solving, achieving uniformity of patient management and finally postoperative recovery. Although fast track perioperative care programmes have been evaluated in a variety of centres, little has been published on the degree of compliance with such protocols when they have been implemented. In a study by Maessen et al. the protocol compliance, regarding the individual fast track elements, before and during the surgical procedure was high, but it was low in the immediate postoperative phase. Also, there was a delay in the discharging of the recovered patients. Patients fulfilled predetermined recovery criteria at a median of three days after operation but were actually discharged at a median of five days after surgery. Discharge delay and the development of major complications were the main reasons for prolonged length of hospital stay. The phenomenon that the existence of a protocol is not enough to enable discharge of patients on the day of functional recovery is also described by others.

In conclusion, despite the current enthusiasm regarding fast track perioperative care programmes and laparoscopic surgery, there are only few data available that provide evidence on the optimal combination (laparoscopic or open surgery and fast track or traditional perioperative care) in terms of shorter lengths of hospital stay, number of
readmissions, reduced morbidity, quality of life and cost effectiveness. Furthermore, the implementation of the evidence based individual fast track elements seems difficult. The most effective way to implement the protocol is unclear. In addition to this, the effects of protocol compliance on the outcome of fast track perioperative care programmes remain unclear as well.

**Laparoscopy-related complications**

As mentioned before, laparoscopy has achieved broad acceptance nowadays and is a fast expanding surgical discipline due to its short term advantages with respect to open surgery. Although laparoscopy is favourable in terms of overall morbidity the implementation of this new surgical discipline also implies the introduction of a new spectrum of complications. These potential complications include those related to laparoscopy itself and those related to the surgical procedure. Most of the laparoscopy-related complications are associated with the entry into the peritoneal cavity, i.e. the creation of the pneumoperitoneum and subsequently the introduction of the surgical instrumentation. This remains a potentially dangerous first step, which is exclusively associated with the laparoscopic approach. Several studies have demonstrated that 20 to 50% of all intra-operative morbidity occurs during the creation of the pneumoperitoneum.

Several techniques to establish the pneumoperitoneum have been described. Roughly, entry techniques can be divided into two groups. The first group comprises entry techniques performed without direct visual control, the so called blind-entry techniques. The second group comprises of entry techniques performed under visual control. The latter includes the open-entry technique and closed-entry techniques with optical trocar devices. Concerning the prevention of entry related complications none of the techniques is supported by solid evidence. Until today there is an ongoing debate about the preferred technique, mainly between gynaecologists favouring the closed-entry technique, and surgeons favouring the open-entry technique. Many general surgeons suggest that the open-entry technique results in an equal amount of visceral lesions, but significantly fewer vascular lesions compared to the closed-entry technique.

**Anastomotic leakage**

A feared complication after colorectal resection with anastomosis is anastomotic insufficiency with subsequent leakage of intestinal contents into the abdominal cavity. The frequency of anastomotic leakage following large bowel resection is quoted between 0.5 and 30%. Considerable variation is seen between surgeons but a realistic clinically apparent leakage rate for experienced colorectal surgeons is likely to be between 3.4 and 6%. There seems to be no evident difference in the leak rate between laparoscopic and open colorectal surgery. Furthermore, leak rates are broadly similar for all types of bowel anastomosis proximal to the peritoneal reflection of the rectum, including small bowel anastomosis. However, for anterior resection, clinically apparent leak rates are higher, ranging between 2.9 and 15.3%. Moreover, a significant difference has been demonstrated between leak rates following high and low anterior resection.
Anastomotic insufficiency is a major cause of morbidity, including long intensive care admittance, sepsis and several abdominal wall complications due to reinterventions and wound infections. Apart from its immediate clinical consequences, anastomotic leakage also has an independent negative association with survival after resections for colorectal cancer. Postoperative mortality due to anastomotic leakage is considerable, ranging between 6.0 and 39.3%. Moreover, the main cause of postoperative mortality after elective segmental colorectal resections is anastomotic leakage. Several risk factors for anastomotic insufficiency have been identified, such as malnutrition, weight-loss, long-course neo-adjuvant radiotherapy or neo-adjuvant chemo-radiotherapy, preoperative steroid use, bowel obstruction, septic conditions, intra-operative blood loss and intra-operative adverse events. Nevertheless, the most consistent factor to predict leakage is low rectal anastomosis.

In the traditional perioperative care setting it has been suggested that some elements might reduce the leak rate. However, there is no evidence showing that preoperative bowel preparation reduces the rate and consequences of leaks or any supporting the use of drains when an anastomosis has been made outside the pelvis, though there is evidence showing pelvic drainage may be important after anterior resection. The use of covering stomas has not been shown to reduce leak rate but does mitigate the clinical effects of leaks.

Despite the identification of several potential risk factors the actual cause or contributing factor(s) to anastomotic insufficiency is not always clear. With known risk factors aside, surgical instruments used, in particular stapling and cutting devices, could also contribute to anastomotic insufficiency if they malfunction or are used inappropriately.

Management of massive anastomotic leakage with peritonitis generally requires resuscitation of the patient followed by prompt (re)laparotomy. However, with increasing numbers of bowel resections being undertaken laparoscopically and the fact that over the past years abdominal emergencies have been increasingly managed by laparoscopy, including those patients with peritonitis the question arises whether postoperative complications in primary laparoscopic operated patients should also be tackled laparoscopically. To date reintervention for anastomotic leakage is generally performed by an open approach mainly because of the fear of causing bowel injury due to distended bowel and lack of exposure for cleaning the abdominal cavity. However, after primary laparoscopic surgery the previously used trocar incisions can easily be re-used. Nevertheless, patients with an extensive ileus and those with long standing peritonitis with pus pockets and inflammatory adhesions are probably not amenable for laparoscopic treatment. Open-abdomen management might be necessary because of abdominal compartment syndrome. Moreover, closure of the abdominal wall after open reintervention might also be impossible due to extensive bowel oedema after resuscitation. Therefore, in some cases full fascial closure is precluded by the condition of the patient and open-abdomen treatment is started.

In general, there are three relatively frequent scenarios in which the operating surgeon may decide to start open-abdomen treatment with temporary abdominal closure. These are abdominal sepsis (peritonitis), intra-abdominal hypertension and following damage
control surgery. In these circumstances, the open abdomen needs to be closed temporarily until the oedema has subsided and definitive closure can be attempted. Several techniques and strategies for the temporary closure of the open abdomen are available. These include the insertion of an (absorbable) mesh (with or without fluid suction system), Bogota or intravenous bag, Velcro or zipper systems and in recent years, the abdominal Vacuum Assisted Closure (VAC®) system was introduced.

When the abdominal sepsis and visceral oedema has resolved and fascial closure of the abdomen can be planned, the edges of the fascia have frequently retracted laterally due to the continuous contraction of the oblique lateral abdominal musculature. This makes full fascial closure of the abdomen difficult. When full fascial closure during index admission is not possible, the fascial defect is left to heal by secondary intention (granulation) or an absorbable mesh is used to close the abdomen without an attempt to close the original fascia. Split thickness skin grafts are frequently used to cover the wound and these planned ventral hernias can be corrected at a later stage. However, due to the complicated course of these patients, the large defects are often associated with enterocutaneous fistula and stomas. Closure of these fistula and stomas with simultaneous closure of the large and contaminated abdominal wall defect requires major surgery that includes extensive adhesiolysis, bowel resection with reanastomosing, and closure of the abdominal wall. Ideally, a non-absorbable mesh is used to close the abdominal wall. This technique ensures durable abdominal wall prosthesis. However, application of a non-absorbable mesh is associated with an increased risk of infection, especially if used in a contaminated surgical field. The use of an absorbable mesh avoids infectious complications, but is only for temporary closure of the ventral hernia. The most logical alternative for these large contaminated abdominal wall defects is the use of autologous tissue repair, including the component separation technique, which was first described by Ramirez et al. The separation of the muscle components of the abdominal wall allows local advancement with complete continuity of the released muscle layers over a greater distance compared to mobilisation of the entire abdominal wall as a block. This enables closure of large abdominal wall defects under contaminated circumstances, avoiding mesh infection.

Prognostication after colorectal cancer resection

For any individual patient, it is essential that their survival can be accurately predicted and the likely sites of recurrence identified. The methods of prediction should be simple, widely available, sensitive, specific and reproducible in any clinical setting. Mortality and survival rates in colorectal cancer are highly influenced by the stage of the disease at diagnosis, with the five-year survival rate dropping from 95% in Dukes A (T1-2N0M0) to less than 10% in metastatic disease (Dukes D, T1-4N0-2M1). With respect to long-term outcome haematogenous and lymphatic spread are the pathways of metastasis and are therefore the most important factors associated with prognosis. Metastasis to regional lymph nodes, as determined by pathologic assessment, is one of the factors that most strongly predict outcome following surgical resection, second only
to distant metastatic disease in importance.\textsuperscript{88-90} Besides the presence or absence of lymph node metastasis \textit{per se}, lymph node staging may be further refined by the identification of different levels, the absolute number of lymph nodes with metastasis, the absolute number of negative nodes, and the lymph node ratio (i.e. the number of involved nodes over the total number of resected and identified nodes).\textsuperscript{91-94} Also, the presence of micrometastasis in lymph nodes has been identified as a prognostic factor.\textsuperscript{95,96} The prognostic value of extracapsular lymph node involvement has been studied for several malignancies, including breast, oesophageal, prostate, vulva, bladder, lung, and head and neck cancer.\textsuperscript{97-103} Extracapsular lymph node involvement is the extension of cancer cells through the nodal capsule into the perinodal fatty tissue. Patients with extracapsular lymph node involvement have a reduced overall and disease free survival in these malignancies.\textsuperscript{97-104} However, in colonic cancer the prognostic value of extracapsular lymph node involvement has not yet been established. Only two studies have been published on extracapsular in both colonic and rectal cancer suggesting prognostic significance of extracapsular lymph node involvement.\textsuperscript{105,106} As mentioned before, distant metastatic disease is the most important factor that predicts outcome following surgical resection.\textsuperscript{88-90} However, the question whether circulating tumour cells detected in peripheral blood of colorectal cancer patients represent metastatic dissemination, or are merely cancer cells that have detached from the primary tumour without metastatic potential, has been debated over half a century.\textsuperscript{107} In 1869, Ashworth was the first to describe circulating tumour cells when he discovered cells in the blood stream similar to those in the tumour at post-mortem studies.\textsuperscript{108} These circulating tumour cells could be a potential cause of disease relapse particularly after surgery, therefore, the presence or absence of circulating tumour cells has been considered by some to be an important prognostic factor preoperatively and/or postoperatively, and an indicator for the decision concerning adjuvant treatment and follow-up.\textsuperscript{109} However, this idea has been questioned by others because the majority of circulating tumour cells shed from solid tumours do not survive in the blood and only approximately 1% live long enough to potentially form distant metastasis.\textsuperscript{86,110}

\textbf{Aim of the thesis}

In this thesis, several aspects of colorectal surgery are highlighted. The aim of this thesis is to critically appraise colorectal surgery and to evaluate potential improvements in perioperative care (part I), complications (part II), and prognostication (part III).
Outline of the thesis

Part I: Fast track colorectal surgery
Fast track perioperative care programmes have been successfully introduced in several surgical procedures. In chapter 1 the application of fast track perioperative care in colonic surgery is described. Furthermore, the individual elements of the programme are reviewed. In chapter 2 the effect of the fast track perioperative care programme on the outcome of, especially open colorectal surgery is systematically reviewed. In chapter 3 differences between open and laparoscopic surgery, both within a fast track perioperative care programme are systematically reviewed. To investigate if the demonstrated benefits of such a programme also apply to our own patient population, a pilot study was initiated, which is described in chapter 4. Both the number of successfully applied pre-defined fast track elements per patient (protocol compliance), as well as the combined effect of these fast track perioperative care elements on postoperative recovery, are evaluated. The results are compared to the results obtained in patients treated in a traditional perioperative care setting. In chapter 5 a randomised controlled multi-centre trial is proposed to determine whether laparoscopic surgery, fast track perioperative care, or a combination of both, is to be preferred over open surgery with standard care in patients having segmental colectomy for malignant disease.

Part II: Complications in colorectal surgery
The creation of the pneumoperitoneum and subsequently the introduction of the surgical instrumentation remains a potentially dangerous first step, which is exclusively associated with the laparoscopic approach. In chapter 6 several techniques for the establishment of the pneumoperitoneum are described including the equipment that is used and the potential complications that can occur. In chapter 7 the number of entry related complications that provoked medical liability insurance claims for laparoscopic surgery was assessed at the largest medical liability mutual insurance company for institutions in health care in the Netherlands. Furthermore, the used entry technique (i.e. open vs. closed), distribution of injured organs, and predictive factors for litigation are described. With the ongoing implementation of laparoscopy and the fact that over the past years abdominal emergencies have been increasingly managed by laparoscopy, including those patients with peritonitis, the question arises whether postoperative complications could be tackled laparoscopically. The study described in chapter 8 evaluates whether a laparoscopic reintervention for anastomotic leakage after primary laparoscopic surgery is technically feasible and safe. Postoperative morbidity and recovery is assessed, and compared with patients that had primary open surgery and subsequently open reintervention for anastomotic leakage in the same period.
In chapter 9 potential usage concerns regarding linear cutters are described. An incomplete linear staple line discovered during the stapling of an ileal pouch presented as a case report in this chapter indicated that malfunctioning might occur when using linear cutters.
Severe intra-abdominal sepsis may implicate repeated reinterventions and open-abdomen management to control the sepsis. Moreover, closure of the abdominal wall might also be impossible due to extensive bowel oedema after resuscitation. In chapter 10 different strategies for open-abdomen treatment in terms of full fascial closure of the abdomen are systematically reviewed. After open-abdomen management when full fascial closure during index admission is not possible, the fascial defect can be left to heal by secondary intention or an absorbable mesh can be used to close the abdomen. These planned ventral hernias are often associated with enterocutaneous fistula and stomas. Closure of enterocutaneous fistula and/or stomas in the presence of large abdominal wall defects is a challenging problem. Simultaneous management of a large abdominal defect is an accompanying problem making the combined procedure more difficult. In chapter 11 the results of closure of enterocutaneous fistula and/or stomas and simultaneous abdominal wall repair using the components separation technique are described.

Part III: Prognostication in colorectal cancer
The impact of extracapsular lymph node involvement has been studied for several malignancies, including gastrointestinal malignancies. In chapter 12 the current evidence on extracapsular lymph node involvement in gastrointestinal malignancies is systematically reviewed in order to assess the incidence and extent of extracapsular lymph node involvement. Furthermore, the relation between extracapsular lymph node involvement and clinico-pathological factors, its prognostic value, its effect on the type of recurrence and long term survival are evaluated. Since the prognostic significance of extracapsular lymph node involvement is not yet established in colonic cancer, a retrospective study was undertaken which is described in chapter 13.
Finally, in chapter 14 the presence and amount of circulating epithelial cells is assessed focussing on differences in peripheral and portal blood. Furthermore, the role of laparoscopy on the amount of circulating epithelial cells is also assessed.

Reference List


19 Chapter 4

General introduction and outline of the thesis


