Advances in colorectal surgery
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Advances in colorectal surgery
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Advances in colorectal surgery

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Faculteit der Geneeskunde
“It is not the strongest of the species that survives, nor the most intelligent that survives. It is the one that is the most adaptable to change”

Charles Darwin (1809-1882)
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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 led to a high readmission rate (up to 20%).\textsuperscript{17} However, Andersen \textit{et al.} reported that the readmission rate declined when the planned postoperative hospital stay was increased from two up to three days.\textsuperscript{19} 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.\textsuperscript{20,21}

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.\textsuperscript{22} 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.\textsuperscript{23,24} 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 \textit{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.\textsuperscript{25} 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.\textsuperscript{26}

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.\textsuperscript{21,27-31} 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.\textsuperscript{8,9,32} 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.\textsuperscript{33} 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.\textsuperscript{34-36} 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.\textsuperscript{37,38} 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.\textsuperscript{36,39} 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.\textsuperscript{35,39}

**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\%.\textsuperscript{40-44} Considerable variation is seen between surgeons but a realistic clinically apparent leak rate for experienced colorectal surgeons is likely to be between 3.4 and 6\%.\textsuperscript{40-43} 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.\textsuperscript{40,43,45} However, for anterior resection, clinically apparent leak rates are higher, ranging between 2.9 and 15.3\%.\textsuperscript{40,46,47} Moreover, a significant difference has been demonstrated between leak rates following high and low anterior resection.\textsuperscript{40,48-50}
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...
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 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 bloodstream 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}

\section*{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


Part 1

Fast track colorectal surgery
Fast track perioperative care programmes in colonic surgery

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On behalf of the LAFA and ERAS study group

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Abstract

Fast track perioperative care programmes are intensive multimodal programmes, combining a number of perioperative care elements with the goal to preserve normal preoperative body composition, organ functions, and to actively enhance postoperative recovery. Fast track perioperative care programmes have been introduced into the perioperative protocol of several surgical procedures. This article reviews the use of fast track perioperative care in colonic surgery. The essence of fast track perioperative care in colonic surgery consists of extensive preoperative counselling, no preoperative fasting but adequate nutrition, reducing surgical trauma, abstaining routine use of drains and nasogastric tubes, tailored anaesthesiology encompassing thoracic epidural, early and enhanced postoperative feeding and mobilisation, and medicinal support with prokinetics and laxatives. A systematic review demonstrates that fast track perioperative care programmes, in colonic surgery, enhance recovery, and shorten primary and overall hospital stay.
Introduction

In the previous decades, there has been a tendency to aim for a shorter hospital stay following several surgical procedures, including colorectal surgery. There are many reasons for this; firstly, increasing knowledge has improved the understanding of how the postoperative convalescence of a patient can be accelerated. Secondly, the aim to reduce hospital stay is based on economic efficiency. Furthermore, several technical developments play an important role, including the introduction of minimally invasive (laparoscopic) surgery, and the introduction of fast track perioperative care programmes also referred to as Enhanced Recovery After Surgery (ERAS®). Fast track programmes combine a number of perioperative elements (Figure 1), in order to preserve normal preoperative body composition and organ functions, and to actively enhance postoperative recovery. This results in a faster recovery, less morbidity and a shorter hospital stay.1-11

Figure 1. The essential elements of the fast track perioperative care programme.

Kehlet et al. developed a multimodal fast track perioperative care programme specifically for elective large bowel surgery. This programme is aimed to enhance postoperative recovery and to avoid common reasons that interfere with early hospital discharge, such as the need for parenteral analgesics or fluids, inadequate oral intake, delayed patient mobilisation, complications, and lack of home care.1-6 The essence of Kehlet’s and other fast track programmes in colonic surgery, comprises of extensive preoperative counselling, adequate preoperative nutrition including no preoperative fasting but carbohydrate loaded liquids until two hours prior to surgery, no bowel preparation, and no sedative pre-medication. Furthermore, the fast track programme includes tailored anaesthesiology
encompassing thoracic epidural anaesthesia and short acting anaesthetics, non-opioid pain management, avoiding perioperative fluid overload, minimal invasive surgery, no routine use of drains and nasogastric tubes, early removal of bladder catheters, standard laxatives and prokinetics, and early and enhanced postoperative feeding and mobilisation. A reduction in hospital stay of up to two or three days after elective open segmental colectomy has been reported, in a fast track care programme.\textsuperscript{1-6}

Although many surgeons currently apply some of the fast track elements which are not incorporated in a complete fast track perioperative care programme, such as the omission of oral bowel preparation and drains, and early removal of the nasogastric tube, considerable variation still exists throughout Europe in the degree into which these elements are applied into daily practice.\textsuperscript{12-15}

Apart from elective large bowel surgery, fast track programmes have been successfully applied in several fields of elective surgery, e.g., for aortic aneurysm repair, pulmonary lobectomy, and laparoscopic gastro-oesophageal reflux surgery.\textsuperscript{16-18}

In this paper, the individual elements of fast track perioperative care will be discussed, followed by a systematic review of prospective clinical controlled trials that have been published on fast track perioperative care programmes used in elective segmental colorectal resections.

**Fast track perioperative care elements**

**Preoperative fast track care elements**

In fast track perioperative care, preoperative counselling is more extensive compared to traditional care. Patients are informed on the important elements of fast track perioperative care, such as the importance of early mobilisation and diet resumption to reduce starvation and muscle loss, which is facilitated by tailored locoregional analgesia and medicinal support. Furthermore, at this first meeting, the patient is informed on his/her active role with specific tasks in the early postoperative period. These tasks include targets for oral intake and mobilisation. It is also important to discuss when discharge can be expected.\textsuperscript{19-22}

Patients included in the fast track programme do not receive oral bowel preparation. Patients only receive two enemas before surgery (evening before and preoperatively). In recent meta-analyses on bowel preparation it has been shown that there are no advantages of oral bowel preparation in colonic surgery.\textsuperscript{23-25} On the contrary, it is suggested that after bowel preparation more anastomotic leaks might occur and there is also a trend towards more wound infections, peritonitis and mortality. Other drawbacks of oral bowel preparation include longer preoperative hospitalisation, induction of stress-response, and disturbence of the physiological bowel motility and bacterial flora. Furthermore, bowel preparation can result in dehydration and electrolyte abnormalities.

Besides the patients’ own medication, patients who are treated in a fast track perioperative
care programme do not receive sedative pre-medication. Pre-medication, most often consisting of benzodiazepines, might result in a somnolent/sedated patient both pre- and postoperatively. As a consequence, provided information is not interpreted adequately and active mobilisation is reduced.26 As the patient starts with oral intake and mobilisation directly after surgery, sedation is undesirable.

The Dutch Anaesthesia Society states that intake of clear fluids up to 2-4 hours before initiation of anaesthesia is safe. However, in daily practice this implies that a patient has to fast from the evening before the operation. This is unnecessary because clear liquids or carbohydrate loaded beverages are out of the stomach within 90 minutes and thereafter there is no increased risk of aspiration.15;27-29 Another advantage of offering clear carbohydrate loaded beverages two hours before surgery is that it reduces preoperative thirst, hunger, anxiety, and glycogen depletion. Finally, postoperatively insulin resistance is reduced with less risk of hyperglycaemia.15;29

**Perioperative fast track care elements**

An important element of anaesthesiologic care in the fast track programme is thoracic epidural analgesia which is commenced preoperatively and continued until two days postoperatively. This thoracic epidural catheter provides optimal pain relief, with the preservation of the patients’ normal capability of mobilisation (i.e. no motor function loss of the legs). Furthermore, the use of epidural analgesia results in a reduction of systemic opioid usage. Finally, afferent nerves from the surgical field are blocked (sympathetic block) resulting in a reduced stress-response, less gut paralysis, and a decreased risk of pulmonary complications.15;30-32

General anaesthesia is accomplished by agents with short pharmaco-dynamic duration resulting in a shorter stay in the recovery department. As a result pro-active recovery is possible on the day of surgery. Postoperative nausea and vomiting are treated with a combination of anti-emetic drugs.15;32;33

The surgical “access trauma” is reduced by using small incisions resulting in a reduction of the inflammatory- and neuro-endocrine stressresponse.14;34-36 A further reduction might be accomplished with a laparoscopic approach. In a meta-analysis on the safety and effectiveness of elective laparoscopic segmental colorectal resections for malignancy it has been demonstrated that laparoscopy, within a traditional care setting, is associated with less morbidity, an enhanced recovery of gastro-intestinal motility, and a shorter hospital stay.37 However, others have shown no differences between laparoscopic and open surgery within a fast track perioperative care programme.38

Surgical incisions are infiltrated with a local anaesthetic agent which results in less wound pain. Infiltration of the operative field prior to the incision, results in a better pain control when compared to infiltration during wound closure.39;40

During (prolonged) operative procedures there is a risk of hypothermia. During re-warming of the patient, catecholamines and cortisol are released which enhance the stress-response. Prevention of hypothermia with upper-body forced-air heating covers (Bair Hugger®) and infusion of warmed fluids, is important for the reduction of the stress-response,
complications, and organ dysfunction.\textsuperscript{14} It has been shown that active hypothermia prevention reduces the risk of wound infection, blood loss, cardiac complications and discomfort.\textsuperscript{41,42}

Recent literature has demonstrated that restriction of perioperative i.v. fluids (1500-3000 ml) reduces postoperative morbidity and shortens postoperative ileus.\textsuperscript{32,43,44} Furthermore, patients treated according to fast track perioperative care principles have a reduced need for i.v. fluids because of the omission of oral bowel preparation and an increased oral intake perioperatively. Patients with an epidural may experience vasodilatation leading to hypotension. Judicious use of vasopressors in the treatment of this hypotension can avoid excessive fluid administration.\textsuperscript{45}

In two meta-analyses it has been demonstrated that routine nasogastric decompression should be avoided after elective colorectal surgery.\textsuperscript{46,47} A nasogastric tube is very unpleasant for the patient, hinders oral intake and prolongs (artificially) postoperative ileus. Early removal of the nasogastric tube is not accompanied by an increased number of complications. Moreover, the incidence of postoperative fever, atelectasis, and pneumonia might be reduced. Therefore, in daily practice the nasogastric tube is removed during extubation. If a patient develops nausea and vomiting postoperatively, treatment should be started with a combination of anti-emetics and not directly by nasogastric tube insertion.

Postoperative fast track care elements
Postoperative bed rest results in an increased insulin resistance, muscle loss with decreased strength, decreased pulmonary function and tissue oxygenation, and an increased risk of thrombo-embolic complications.\textsuperscript{3,14,15}

The presence of an abdominal drain represents a significant burden during early mobilisation. It has never been demonstrated that the use of drains after colonic surgery beneficially influences the occurrence of anastomotic leakage and morbidity.\textsuperscript{48,49} Therefore, the use of abdominal drains should be minimized.

Also, urinary drainage holds patients back during mobilisation. For this reason, it is recommended to use urinary bladder drainage only for the duration of epidural analgesia.\textsuperscript{15}

Since the day of surgery must be considered as the first day of recovery, patients are mobilised directly after surgery. The aim is to have patients out of bed for two hours on the day of surgery and at least six hours per day thereafter, until discharge. The early mobilisation is facilitated by adequate pain relief with thoracic epidural analgesia and encouragement to achieve the daily targets. The early mobilisation reduces the risk of thrombo-embolic and pulmonary complications, decreases the amount of muscle loss and increases muscle strength, and postoperative insulin resistance is also reduced.\textsuperscript{3,14,15}

Early introduction of oral intake postoperatively is well tolerated by most patients. Early feeding might increase bowel motility resulting in a shorter postoperative ileus and a shorter hospital stay.\textsuperscript{50} A meta-analysis on early enteral or oral feeding versus “nil by mouth” demonstrated that early feeding reduced both the risk of infectious complications and hospital stay. Furthermore, there was a trend towards less anastomotic leakages.
However, early feeding was associated with some gastro-intestinal symptoms, especially vomiting.51
To further enhance oral intake, it is important to prevent postoperative gut dysfunction.
Postoperative ileus is partly caused by an inhibitory reflex from the surgical field. A thoracic epidural, in contrast to a lumbar epidural, blocks this reflex and therefore might have a positive effect on the prevention of paralytic ileus. Another important issue regarding postoperative analgesia is opioid sparing and thereby avoiding opioid-related side effects such as sedation and a negative effect on gut motility. For this reason, patients additionally receive paracetamol and after discontinuation of the epidural a non steroidal anti-inflammatory drug (NSAID) is started.14;15
Furthermore, it is important to avoid fluid overload (i.v. fluids) and medicinal support is started such as oral magnesium oxide and pro-kinetic drugs.14;15;30;32

The implementation of the programme into daily practice

The relative contribution of each of the single elements in the fast track programme remains uncertain. For some elements there is solid evidence that its implementation as a single modality within a traditional care setting results in less morbidity and/or a faster recovery, i.e. the omission of bowel preparation, removal of the nasogastric tube at the time of extubation, and optimal pre- and postoperative nutritional care.23-28 For other elements the evidence is less robust, and the implementation into the fast track programme is in those cases either based on “common sense” or on consensus interpretation of accumulating evidence.15
The effect of a fast track perioperative care programme might be, for an important part, caused by working according to a clearly defined evidence-based protocol. Both patient and care takers are well informed which targets have to be reached at a certain point in the recovery of a patient.
In the fast track care programme it is important to discharge patients “under supervision”. Once at home, patients are contacted by phone within 24-48 hours after discharge to ensure that there are no questions or complications. Patients should be discharged according to predefined discharge criteria. These discharge criteria include adequate pain control with oral analgesics, absence of nausea, ability to take solid foods, passage of flatus and/or stool, mobilisation and self support as compared to the preoperative level, and finally acceptance of discharge by the patient.
When the postoperative course of a patient is uncomplicated, discharge can normally be expected between the third and sixth postoperative day.2;7;8;52;53 Facilities should be created to rapidly deal with complications that occur after discharge. Readmission in itself does not always imply an overnight stay. Often patients can re-attend the hospital as an out-patient, receive treatment (e.g. anti-emetics/fluids) and be discharged the same day.
Nevertheless, it is essential that there is a clear pathway for the prompt and safe readmission of patients who experience major complications (e.g. anastomotic leakage).\textsuperscript{15}

Most likely, fast track perioperative care programmes are not associated with an increased workload of the first line home care takers (e.g. district nurse or general practitioner). This is because patients are discharged in the same condition as formerly in a traditional care setting. Moreover, the patient is instructed to contact the hospital if any questions or complications may arise. First line home care takers should be involved earlier because the discharge process has already started at the preadmission counselling session. Problems regarding the patients’ social environment or special needs are addressed in this session and if necessary first line care takers are contacted at this stage.\textsuperscript{15}

There are no absolute contra-indications for fast track perioperative care itself. However, there may be certain contra-indications for individual protocol elements. For example, in patients with coagulation disorders the application of an epidural catheter is not possible. In those circumstances only the contra-indicated elements are omitted, the other elements are applied normally. It has been shown that fast track perioperative care is safe, feasible, and associated with positive results in an older population or for patients with significant co-morbidity.\textsuperscript{9,54} However, for this patient population it might be difficult to achieve certain targets, such as the amount of postoperative mobilisation. In those cases targets are set at the highest level possible.

It is important that the outcome is documented and evaluated during the introduction of a fast track perioperative care programme. This not only ensures that morbidity and mortality are optimal but also that feedback is provided on the protocol compliance to the individual elements and to identify aspects of the programme that may need further development of infrastructure and staff education.\textsuperscript{15}

### Table 1. Patient characteristics, quality assessment, and results of the included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>Age (yr)</th>
<th>% ASA I&amp;II</th>
<th>PHS (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson et al.</td>
<td>RCT</td>
<td>14 / 11</td>
<td>64 / 68</td>
<td>93 / 91</td>
<td>4 (3) / 7 (7) ‡</td>
</tr>
<tr>
<td>BJS 2003</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delaney et al.</td>
<td>RCT</td>
<td>31 / 33</td>
<td>51 / 42</td>
<td>61 / 79</td>
<td>5.2 / 5.8</td>
</tr>
<tr>
<td>DCR 2003</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raue et al.</td>
<td>CTT</td>
<td>23 / 29</td>
<td>63 / 65</td>
<td>52 / 72</td>
<td>(4) / (7) ‡</td>
</tr>
<tr>
<td>Surg Endosc 2004</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradshaw et al.</td>
<td>CTT</td>
<td>36 / 36</td>
<td>63 / 60</td>
<td>No ASA IV</td>
<td>4.9 / 6 ‡</td>
</tr>
<tr>
<td>Basse et al.</td>
<td>CTT</td>
<td>130 / 130 †</td>
<td>72 / 74</td>
<td>60 / 77 ‡</td>
<td>3.3 (2) / 10 (8) ‡</td>
</tr>
<tr>
<td>DCR 2004</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Continued data (age, PHS and OHS): mean (median); FT: Fast Track perioperative care; TC: Traditional Care; PHS: Primary Hospital Stay; OHS: Overall Hospital Stay (including readmissions within 30 days); RCT: Randomised Clinical Trial; CCT: Clinical Controlled Trial; ASA: American Society of Anaesthesiologists; ‡ p<0.05; †Traditional Care group retrospectively collected in another hospital; *Quality assessment: score ranging from 0 (worst)-5 (best) based on the cumulative score on the items randomisation, consecutivity, adequate follow-up (>30 days), independent collection of data and similarity of the groups.
Chapter 1

Fast track perioperative care programmes in colonic surgery

Systematic review; what can be accomplished with the implementation of a fast track perioperative care programme in colonic surgery?

The Medline, EMBASE, and Cochrane Library databases were searched for all randomised or controlled clinical trials with a prospective intervention group comparing a multimodal fast track perioperative care programme with traditional care in patients undergoing elective segmental colonic resection. Two investigators (JW, SP) independently performed the literature search, data-extraction and quality assessment of the included studies. The search identified 39 publications, of which 34 were excluded due to insufficient details, a completely retrospective, uncontrolled study design or because the data had been used in other selected publications. Five studies were included in the final analysis comprising two randomised and three controlled clinical trials. The studies were published between 1998 and 2004. In Table 1 the patient characteristics and quality assessment is shown.

The application of the predefined fast track perioperative care elements varied widely between the studies. The programmes that were reported on in the five studies contained an average of 7.6 (range 4-10) fast track perioperative care elements. Accelerated mobilisation and early postoperative feeding were present in all studies, while other elements, such as omission of sedative pre-medication, the use of preoperative carbohydrate loaded liquids, omission of bowel preparation, and perioperative restriction of i.v. fluids, were less effectively applied. Particularly the preoperative care elements were less implemented.

The primary hospital stay (PHS) and overall hospital stay (OHS), including the readmissions within 30 days are shown in Table 1. PHS was significantly shorter after fast track perioperative care in four of the five studies. OHS was reported in three studies, all of which reported a significantly shorter OHS in the fast track perioperative care group as compared to the traditional care group. It has been suggested that a reduction of PHS might increase the number of readmissions. However, in the included studies there were no significant differences in the number of readmissions between the fast track perioperative care and traditional care groups. Readmission rates were 0-21% and 0-18%
respectively. The morbidity and mortality rates are shown in Table 1. With the exception of one study that reported significant less morbidity in the fast track perioperative care group, there were no further differences.  

**Conclusion**

Fast track perioperative care programmes are intensive multimodal and multidisciplinary programmes with the goal to reduce loss of functional capacity and to enhance postoperative recovery, resulting in a shorter hospital stay and an earlier return to normal life.

Concerning cost-effectiveness, costs are reduced for the health care insurers and society on the one hand. This is due to a reduction in hospital stay and an earlier resumption of work. On the other hand, the costs for the hospital are increased because the hospital invests in a multimodal and multidisciplinary programme which results in a shorter hospital stay and correspondingly a smaller reimbursement by the health care insurer. To compensate for this, an adjusted reimbursement should be introduced for procedures performed within a fast track perioperative care programme.

When hospital stay is reduced, it is important to assure that patients are discharged in the same condition as would have been the case in a traditional care situation: ‘an earlier discharge is possible because the patient has recovered earlier’. This, in part, can be achieved by applying strict discharge criteria. In addition to this, patients should be able to easily contact the hospital for questions. Also, readmission procedures should be simplified to assure that there is no delay in admission and to provide the necessary treatment.

Finally, the question remains how to implement such evidence based perioperative care programmes on a broader basis in the Netherlands. Future studies should investigate the added benefit of laparoscopic surgery within a fast track perioperative care programme.  

**Reference List**


Chapter 1

Fast track perioperative care programmes in colonic surgery


(22) Disbrow EA, Bennett HL, Owings JT. Effect of preoperative suggestion on postoperative gastrointestinal motility. West J Med 1993;158:488-492


Systematic review of enhanced recovery after surgery (‘Fast Track’) programmes in colonic surgery

J Wind
SW Polle
PHP Fung Kon Jin
CHC Dejong
MF von Meyenfeldt
DT Ubbink
DJ Gouma
WA Bemelman

On behalf of the LAFA study and ERAS group

British Journal of Surgery 2006;93:800–809
Abstract

Introduction
Fast track programmes optimise perioperative care in an attempt to accelerate recovery, reduce morbidity and shorten hospital stay. Aim of this systematic review is to assess the current evidence of fast track for elective segmental colonic resections.

Methods
A systematic review was performed of all randomised controlled trials (RCTs) and controlled clinical trials (CCTs) on fast track colonic surgery. Main endpoints were number of applied fast track elements, hospital stay, readmission rate, morbidity and mortality. Quality assessment and data extraction were performed independently by three observers.

Results
Six papers were eligible for analysis (3 RCTs and 3 CCTs), comprising 512 patients. The fast track programmes contained an average of nine (range 4-12) of the 17 fast track elements as defined in the literature. Primary hospital stay (weighted mean difference: -1.56, 95%-confidence interval [CI]: -2.61 to -0.50) and morbidity (relative risk 0.54, 95% CI: 0.42 to 0.69) were significantly lower in favour of fast track. Readmission rates were not significantly different (relative risk 1.17, 95% CI: 0.73 to 1.86). No increase in mortality was found.

Conclusions
Based on limited evidence, fast track appears safe and shortens hospital stay after elective colorectal surgery. However, since the evidence is currently limited, a multi-centre randomised trial seems justified.
Chapter 2

Systematic review of fast track programmes

Introduction

A recent development in elective large bowel surgery is the introduction and implementation of fast track perioperative care, also referred to as Enhanced Recovery After Surgery (ERAS®). Fast track perioperative care combines a number of perioperative elements with the purpose to actively enhance recovery and to reduce the profound stress response seen after surgery. This has been proposed to affect metabolic, neural, and other organ functions beneficially, resulting in a reduction of morbidity, a faster recovery and a shorter hospital stay. Kehlet et al. developed a multimodal fast track recovery programme for elective large bowel surgery to enhance postoperative recovery and to avoid common reasons that interfere with early hospital discharge, such as the need for parenteral analgesics or fluids, delayed patient mobilisation, complications and the lack of home care. Main elements of Kehlet’s, and similar fast track programmes, in colonic surgery are extensive preoperative counselling, no bowel preparation, no pre-medication, the administration of synbiotics preoperatively, no preoperative fasting but carbohydrate loaded liquids until two hours prior to surgery, tailored anaesthesiology encompassing thoracic epidural anaesthesia and short acting anaesthetics, perioperative high inspired O₂ concentrations, avoiding perioperative fluid overload, short incisions, non-opioid pain management, no routine use of drains and nasogastric tubes, early removal of bladder catheters, standard laxatives and prokinetics, and early and enhanced postoperative feeding and mobilisation.

Apart from elective large bowel surgery, fast track programmes have been applied in various other fields of elective surgery, e.g. for aortic aneurysm and lobectomy, reducing hospital stay to three and two days respectively. Furthermore, laparoscopic gastro-oesophageal reflux surgery has been reported to be successful in an ambulatory setting using fast track programmes. The aim of this systematic review is to assess the current evidence on fast track perioperative care in segmental colonic resections as compared with traditional care.

Methods

Data search

The Medline database (from January 1966 to December 2005), EMBASE database and the Cochrane Library (both from January 1980 to December 2005) were searched using the following keywords; colon, colonic, colorectal, rectum, rectal, sigmoid, and sigmoidal, in combination with fast, fast track, fast tract, enhanced, recovery, accelerated, rehabilitation, convalescence, multimodal, rapid, perioperative care and ambulation. Three investigators (JW, PFKJ, SP) independently performed the literature search. Electronic links to related articles and references of selected articles were hand-searched as well. Leading investigators in the field were contacted to inquire whether studies were missed or
publications were recently submitted. A hand search of relevant journals and conference proceedings was not performed. The search was restricted to publications in the English, Dutch or German language.

**Study selection and data extraction**

From the potentially eligible studies randomised or controlled clinical trials with a prospective intervention group comparing a multimodal fast track perioperative care programme with traditional care in patients undergoing elective segmental colonic resection for malignant and benign diseases were selected. In case of disagreement, full papers were obtained for final judgement. Each of the selected trials was critically appraised by all three investigators, using a critical review checklist for study validity as proposed by the Dutch Cochrane Collaboration. Data were extracted from original articles only. Trials were selected if they presented the following data: age, gender, ASA or POSSUM score, type of resection, primary (PHS) and/or overall hospital stay (OHS), readmission rate, morbidity, mortality, and at least four fast track elements were used in a fast track protocol. We identified 17 fast track elements, 15 as proposed by Kehlet et al. and the Enhanced Recovery After Surgery (ERAS®) study group with the addition of perioperative high inspired O\(_2\) concentrations, and the administration of synbiotics preoperatively. The arbitrary number of four fast track elements was chosen because of the fact that less elements might represent “modern” traditional care. Duplicate publications and papers that reported on (parts of) the same study population were excluded. In that situation only the largest or the most recent publication was included. Final inclusion was done after consensus was reached. Discrepancies in judgement, if any, were resolved by discussion.

**Analysis and presentation of data**

Hospital stay is expressed in days in hospital after surgery, where OHS represents PHS including the hospitalisation period of patients readmitted within 30 days after surgery.

**Table 1. Quality assessment and study design**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>N (FT vs TC)</th>
<th>Consecutive series</th>
<th>Allocation concealment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson et al.(^9)</td>
<td>RCT</td>
<td>14 vs 11</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Delaney et al.(^10)</td>
<td>RCT</td>
<td>31 vs 33</td>
<td>Unclear</td>
<td>No</td>
</tr>
<tr>
<td>Gatt et al.(^13)</td>
<td>RCT</td>
<td>19 vs 20</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Basse et al.(^4)</td>
<td>CCT</td>
<td>130 vs 130</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Raue et al.(^19)</td>
<td>CCT, prospective intervention group (hospital 1) vs. Retrospective control group (hospital 2)</td>
<td>23 vs 29</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Bradshaw et al.(^20)</td>
<td>CCT</td>
<td>36 vs 36</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

FT: Fast Track; TC: Traditional Care; RCT: Randomised Controlled Trial; CCT: Controlled Clinical Trial
Results

Included studies
The search identified 44 publications, of which 35 were excluded due to insufficient details or a completely retrospective or uncontrolled study design. Furthermore, after contacting the principal investigator, three studies were excluded because either part or all of the data had been used in other selected publications. Six studies were taken into account in the final analysis comprising three randomised and three controlled clinical trials. These studies were published between 1998 and 2005 and reported on a total of 512 patients, with a range of 25 to 260 patients per study. In Table 1 the overall quality assessment and study designs are presented. Table 2 shows the patient characteristics and results of the included studies.

<table>
<thead>
<tr>
<th>Blinding and data collection</th>
<th>Similar groups</th>
<th>Follow up</th>
<th>Similar non-trial treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not blinded</td>
<td>Yes</td>
<td>30 days</td>
<td>Yes</td>
</tr>
<tr>
<td>(Data collection by 2 individuals)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not blinded</td>
<td>Yes</td>
<td>30 days</td>
<td>Yes</td>
</tr>
<tr>
<td>Not blinded</td>
<td>Yes</td>
<td>30 days</td>
<td>Yes</td>
</tr>
<tr>
<td>Institution bias</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not blinded</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
</tr>
<tr>
<td>Operator bias</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not blinded</td>
<td>Yes</td>
<td>Unclear</td>
<td>Not completely</td>
</tr>
</tbody>
</table>

Readmissions, morbidity and mortality are presented as a percentage of all included patients. We defined morbidity as the reported morbidity in the included studies. Quantitative data, if available were entered into Cochrane Review Manager 4.2 software and analysed using RevMan Analyses 1.0.2 (The Cochrane Collaboration, Oxford, UK). Summary estimates of treatment effects, including 95% confidence intervals (CI), were calculated for each comparison. For continuous outcome data (hospital stay), means and standard deviations were used to calculate a weighted mean difference (WMD) in the meta-analysis. For dichotomous outcomes (readmissions, morbidity, mortality), the relative risk (RR) was calculated. Statistical heterogeneity was tested using Chi-square and I-square statistics. Data were pooled using a fixed effect model if heterogeneity was limited; the random effect model was used in case of moderate heterogeneity.
The included studies had several limitations. It concerned single-centred, small studies, and the studies were possibly insufficiently powered to detect important outcomes such as quality of life and patient satisfaction. Only a few studies applied well-defined discharge criteria, which is of major importance with hospital stay as one of the outcome parameters. In the three randomised studies, randomisation was performed using sealed envelopes. This may have threatened the concealment of allocation. In general, losses to follow-up were not reported. Only Delaney et al. described an intention to treat principle.\textsuperscript{10} Blinding of the medical staff and patients was not possible owing to the nature of fast track perioperative care. Data collection was not done by independent individuals. Only Anderson et al. described data collection done by two separate individuals.\textsuperscript{9} In the study by Basse et al. there was an institution bias because the intervention and control groups were from two different hospitals.\textsuperscript{4} In the study by Bradshaw et al. and Basse et al. the control group was retrospectively collected.\textsuperscript{4,20}

**Number of included fast track items**

The application of the 17 predefined fast track elements varied widely between the studies (Table 3). The fast track programmes that were reported upon in the six studies contained an average of nine (range 4-12) of the 17 fast track elements as defined in the literature. Accelerated mobilisation and postoperative feeding were present in all studies, while other elements, such as no use of premedication and active prevention of hypothermia with warmed i.v. fluids and upper body air-warming were less frequently reported.

**Primary and overall hospital stay**

All six studies reported on PHS and this was significantly shorter after fast track perioperative care in five of the six studies (Table 2). Only the study by Delaney et al. showed no significant difference in PHS, although patients younger than 70 years and patients treated by a surgeon experienced with the fast track programme had a

---

**Table 2. Demographics, patient characteristics, and results of the included studies**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age (years) FT / TC</th>
<th>% ASA I&amp;II FT / TC</th>
<th>Type of surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson et al.</td>
<td>64 / 68</td>
<td>93 / 91</td>
<td>LH, RH. All LT</td>
</tr>
<tr>
<td>Delaney et al.</td>
<td>51 / 42*</td>
<td>61 / 79</td>
<td>Segmental intestinal resections. All LT</td>
</tr>
<tr>
<td>Gatt et al.</td>
<td>67 / 67</td>
<td>Med. ASA II in both groups</td>
<td>RH, LH, SR, HM, AR, SC, PC, APR</td>
</tr>
<tr>
<td>Basse et al.</td>
<td>72 / 74</td>
<td>60 / 77*</td>
<td>Elective RH, LH, TR, SR, RS. All LT</td>
</tr>
<tr>
<td>Raue et al.</td>
<td>63 / 65</td>
<td>52 / 72</td>
<td>Elective SR. All LS</td>
</tr>
<tr>
<td>Bradshaw et al.</td>
<td>63 / 60</td>
<td>No ASA IV</td>
<td>SR, RH, LH, SC, LA</td>
</tr>
</tbody>
</table>

FT: Fast Track; TC: Traditional Care; PHS: Primary Hospital Stay; OHS: Overall Hospital Stay; ASA: American Society of Anaesthesiologists; LH: Left Hemicolecotomy; RH: Right Hemicolecotomy; SC: Subtotal Colectomy; SR: Sigmoid Resection; RS: RectoSigmoid resection; LA: Low Anterior resection; TR: Transverse colon Resection; HM: Hartmann’s procedure; AR: Anterior Resection; PC: ProctoColectomy; APR: AbdominoPerineal Resection; LT: Laparotomy; LS: Laparoscopic; * p<0.05; NR: Not Reported; Continuous data: mean (median)
significantly shorter PHS. Also traditional care patients had a shorter PHS when they were treated by a surgeon experienced with the fast track programme.\textsuperscript{10}

After pooling available data, PHS in the fast track group was significantly lower than in the group treated traditionally (WMD -1.56 days, 95% CI: -2.61 to -0.50 days, Figure 1).

OHS was reported in three studies, all of which reported a significantly shorter OHS in the fast track group as compared to the traditional care group (Table 2).\textsuperscript{4,9,10} In the study by Delaney et al., the significant shorter OHS was partly due to fewer readmissions in the fast track group. Pooling could not be performed because only a few studies reported on this outcome and because standard deviations were missing.

### Readmission rate

Readmission rates were reported in all studies and varied from 0 to 21% after fast track care and from 0 to 20% after traditional care (Table 2). After pooling all available studies, there was no significant difference in readmission rate between the fast track and traditional care group (RR 1.17, 95% CI: 0.73 to 1.86, Figure 2). There was a trend to more readmissions after fast track perioperative care in the non-RCTs due to the study of Basse et al., the only study reporting more readmissions after fast track care.\textsuperscript{4} However, the pooled data of the RCTs showed a trend to more readmissions after traditional care.

### Table 2: Systematic review of fast track programmes

<table>
<thead>
<tr>
<th>Study or subcategory</th>
<th>N</th>
<th>Fast track Mean (SD)</th>
<th>Traditional Mean (SD)</th>
<th>WMD (random) 95% CI</th>
<th>Weight %</th>
<th>WMD (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 RCTs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anderson</td>
<td>14</td>
<td>4.00(1.80)</td>
<td>7.00(2.10)</td>
<td>23.81</td>
<td>-3.00</td>
<td>-4.56, -1.44</td>
</tr>
<tr>
<td>Delaney</td>
<td>31</td>
<td>5.20(2.50)</td>
<td>5.80(3.05)</td>
<td>27.38</td>
<td>-0.60</td>
<td>-1.95, 0.75</td>
</tr>
<tr>
<td>Gatt</td>
<td>19</td>
<td>6.60(4.40)</td>
<td>9.00(4.60)</td>
<td>10.86</td>
<td>-2.40</td>
<td>-5.32, 0.42</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>64</td>
<td></td>
<td></td>
<td>62.04</td>
<td>-1.89</td>
<td>-3.61, -0.18</td>
</tr>
<tr>
<td>Test for heterogeneity: Chi(^2) = 5.46, df = 2 (P = 0.07), (I^2) = 63.4%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.16 (P = 0.03)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>02 Non-RCTs</th>
<th>N</th>
<th>Fast track Mean (SD)</th>
<th>Traditional Mean (SD)</th>
<th>WMD (random) 95% CI</th>
<th>Weight %</th>
<th>WMD (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basse</td>
<td>130</td>
<td>3.30(0.00)</td>
<td>10.00(0.00)</td>
<td>37.96</td>
<td>-1.10</td>
<td>-1.49, -0.72</td>
</tr>
<tr>
<td>Bradshaw</td>
<td>36</td>
<td>4.90(1.90)</td>
<td>6.00(1.70)</td>
<td>37.96</td>
<td>-1.10</td>
<td>-1.93, -0.27</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>166</td>
<td></td>
<td></td>
<td>100.00</td>
<td>-1.56</td>
<td>-2.61, -0.50</td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect: Z = 2.59 (P = 0.010)</td>
<td></td>
<td></td>
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</tbody>
</table>

**Figure 1** Weighted mean difference (WMD) for primary hospital stay (PHS) in days

**RCTs:** Randomised Controlled Trials

**Non-RCTs:** Non Randomised Controlled Trials
### Table 3. Summary of outcomes and fast track items presented in the selected trials

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type</th>
<th>N</th>
<th>Mortality</th>
<th>Morbidity</th>
<th>Readmissions</th>
<th>Primary Hospital Stay</th>
<th>Total Hospital Stay</th>
<th>Minimum of 30 days follow-up</th>
<th>Preoperative counselling</th>
<th>Preoperative feeding</th>
<th>Symbiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson et al. 9</td>
<td>RCT</td>
<td>25</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Delaney et al. 10</td>
<td>RCT</td>
<td>64</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Gatt et al. 13</td>
<td>RCT</td>
<td>39</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Basse et al. 4</td>
<td>CCT</td>
<td>260</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Raue et al. 19</td>
<td>CCT</td>
<td>52</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<td>✓</td>
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<tr>
<td>Bradshaw et al. 20</td>
<td>CCT</td>
<td>72</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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</tr>
</tbody>
</table>

NG: Nasogastric; RCT: Randomised Controlled Trial; CCT: Controlled Clinical Trial; ✓: Adequately described/Present; -: Not Present/Not studied; ~: Not adequately described/partially present.

### Figure 2 Relative Risk (RR) for readmission rates

<table>
<thead>
<tr>
<th>Study or subcategory</th>
<th>Fast track</th>
<th>Traditional</th>
<th>RR (Fixed) 95% CI</th>
<th>Weight %</th>
<th>RR (Fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 RCTs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anderson</td>
<td>0/14</td>
<td>0/11</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Delaney</td>
<td>3/31</td>
<td>6/33</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gatt</td>
<td>1/19</td>
<td>4/20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events: 4 (fast track), 10 (Traditional) Test for heterogeneity: $\chi^2 = 0.32$, df = 1 ($p = 0.57$), $I^2 = 0%$ Test for overall effect: $Z = 1.54$ ($p = 0.12$)</td>
<td></td>
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<tr>
<td>02 Non-RCTs</td>
<td></td>
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<tr>
<td>Basse</td>
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<td>15/130</td>
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<td></td>
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<tr>
<td>Bradshaw</td>
<td>1/36</td>
<td>1/36</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Raue</td>
<td>1/23</td>
<td>2/29</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events: 29 (fast track), 19 (Traditional) Test for heterogeneity: $\chi^2 = 0.75$, df = 2 ($p = 0.69$), $I^2 = 0%$ Test for overall effect: $Z = 1.60$ ($p = 0.11$)</td>
<td></td>
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<tr>
<td>Total (95% CI)</td>
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<td>259</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Total events: 33 (fast track), 29 (Traditional) Test for heterogeneity: $\chi^2 = 5.24$, df = 4 ($p = 0.26$), $I^2 = 23.6%$ Test for overall effect: $Z = 0.65$ ($p = 0.25$)</td>
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</table>

RRTs: Randomised Controlled Trials
Non-RCTs: Non Randomised Controlled Trials
# Fast Track Items

<table>
<thead>
<tr>
<th>No bowel preparation</th>
<th>No premedication</th>
<th>Fluid restriction</th>
<th>Perioperative high O₂ concentrations</th>
<th>Active prevention of hypothermia</th>
<th>Epidural analgesia</th>
<th>Minimal invasive/transverse incisions</th>
<th>No routine use of NG tubes</th>
<th>No use of drains</th>
<th>Enforced postoperative mobilization</th>
<th>Enforced postoperative oral feeding</th>
<th>No systemic morphine use</th>
<th>Standard laxatives</th>
<th>Early removal of bladder catheter</th>
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<tbody>
<tr>
<td>✓</td>
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<td>✘</td>
<td>✘</td>
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</tr>
</tbody>
</table>

## Morbidity and mortality

Morbidity rates were reported in all included studies and ranged between 8% and 47% in the fast track group and between 11% and 75% in the traditional care group (Table 2). Basse et al. reported significantly less morbidity in their fast track group, especially cardiovascular and pulmonary (pneumonia) complications.\(^4\) Also the other studies reported less morbidity in the fast track group, however not significantly different (Table 2).

The pooled data including all six studies showed significantly less morbidity in the fast track group (RR 0.54, 95% CI: 0.42 to 0.69, Figure 3). The pooled data of the three RCTs, showed only a trend towards reduced morbidity in the fast track group. The absolute risk reduction of the pooled data was -0.15 (95% CI: -0.28 to -0.02). This means that the number needed to treat is 6.7, \(i.e.\) for every seven patients receiving fast track perioperative care, morbidity is avoided in one patient as compared with traditional care.

A feared complication after colonic surgery is anastomotic leakage. Only in the study by Basse et al. were anastomotic leakages reported (3.8% in both groups).\(^4\) Four out of the five patients with a leakage in the fast track group were readmitted with an anastomotic leakage. The readmission was done promptly without mortality. Mortality was reported in four of the included publications and ranged from 0 to 5% and from 0 to 9% in the fast track and traditional care groups, respectively (Table 2).\(^4\); \(^9\); \(^13\); \(^19\)
Clinical outcome parameters

Gut function
Postoperative ileus, in terms of the necessity for reinsertion of a nasogastric decompression tube, time until first defecation, or the number of days required postoperatively to attain tolerance of solid food, was reduced in the fast track group (Table 4).

Pulmonary function
Raue et al. assessed pulmonary function by measuring forced vital capacity (FVC). FVC was significantly better in the fast track group on the first postoperative day, but thereafter no further differences were detected. In the studies by Anderson et al. and Gatt et al., pulmonary function expressed as forced expiratory volume in one second (FEV₁) was not different at any time point between the two groups.

Pain, fatigue, and quality of life.
In the study by Anderson et al., pain and fatigue, as measured using the visual analogue scale (VAS-score), were a significantly more prominent feature in the traditional care group. Delaney et al. found no difference in pain scores, measured using the VAS-score and McGill pain score questionnaire (MGPS), and quality of life, measured using the SF-36 and the Cleveland Clinic Global Quality of Life (CGQL) questionnaire, between traditional care and fast track care groups. Raue et al. found no difference in pain scores, but fatigue was increased in the traditional care group on the first two postoperative days. In
Chapter 2

Systematic review of fast track programmes

This study both outcomes were measured using the VAS-score. Gatt et al. also used the VAS-score to evaluate fatigue and pain and found no significant differences.

Discussion

The results of this systematic review suggest that fast track multimodal perioperative care programmes result in an enhanced recovery after surgery, reducing morbidity rates, primary- and overall hospital stay. However, this systematic review demonstrates that the evidence on fast track colonic surgery to date is scarce, and further research is warranted.

Fast track programmes in colonic surgery have been introduced more than a decade ago with favourable early results. Many elements of these fast track programmes are based on solid evidence derived from randomised trials or meta-analyses. However, it is quite surprising, that implementation in daily practice has so far stayed behind. This can partly, be explained by the necessity to break with long-standing traditions, such as preoperative fasting, slow postoperative advancement of oral feeding, and delayed mobilisation.

Nowadays, some of the fast track elements, such as omission of bowel preparation and drains, early removal of nasogastric tubes, and early feeding and mobilisation have already been incorporated in “modern” traditional care, although considerable variation still exists throughout Europe. This modernisation of traditional care has been initiated, at least to some extent, by the development of laparoscopic surgery.

The relative contribution of each of the single elements in the fast track programme remains uncertain. For some elements there is solid evidence that its implementation results in less morbidity and/or a faster recovery, i.e. removal of the nasogastric tube at the time of extubation and no bowel preparation. For other elements the evidence is less robust, and the implementation into the fast track programme is in those cases either based on “common sense” or on consensus interpretation of accumulating evidence.

However, in all cases this evidence is derived from traditional care settings. To distinguish the critical elements in a fast track programme, further studies are needed that asses the

<table>
<thead>
<tr>
<th>Reference</th>
<th>% of reinserted NG tubes FT / TC</th>
<th>First bowel movement FT / TC</th>
<th>Tolerance of normal diet FT / TC</th>
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</thead>
<tbody>
<tr>
<td>Anderson et al</td>
<td>NR</td>
<td>NR</td>
<td>2 / 3*</td>
</tr>
<tr>
<td>Delaney et al</td>
<td>6 / 9</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Gatt et al</td>
<td>NR</td>
<td>NR</td>
<td>2 / 3.8*</td>
</tr>
<tr>
<td>Basse et al</td>
<td>2 / 15*</td>
<td>2 / 4.5*</td>
<td>NR</td>
</tr>
<tr>
<td>Raue et al</td>
<td>13 / 21</td>
<td>2 / 3*</td>
<td>1 / 2*</td>
</tr>
<tr>
<td>Bradshaw et al</td>
<td>NR</td>
<td>(2.5) / (3.7)*</td>
<td>(1) / (2.9)*§</td>
</tr>
</tbody>
</table>

FT: Fast Track; TC: Traditional Care; *: p<0.05, Continuous data: median (mean); §: tolerance of fluid diet; NR: Not Reported; NG: Naso-Gastric
protocol compliance to each element. With this data the critical fast track elements might be identified for example by using a regression model.

A drawback of the term fast track is the suggestion that the ultimate and main goal is to discharge the patient earlier. This in fact is not the case; fast track programmes aim at improving patient recovery postoperatively and reduce morbidity. In doing so, such programmes enable the patient to go home earlier, if this is agreeable to the patient.

A fast track programme requires a dedicated and motivated team consisting of an anaesthesiologist, surgeon, dietician, physiotherapist, social worker, and nursing team. This is nicely illustrated in the paper by Basse et al., indicating that in the absence of the research team (i.e. holidays), patients were not included in the fast track regimen. Experience with the programme is another important factor for success. Delaney et al. reported that fast track patients treated by an experienced fast track surgeon spent significantly less time in the hospital compared with the fast track patients that were treated by a surgeon less experienced with the programme. Also younger patients had more benefit of the fast track programme compared with older patients. On the contrary in the study by Basse et al. the ASA-classification of the fast track group was significantly higher. Others have confirmed the safety, feasibility, and positive results of fast track in an older population or for patients with significant co-morbidity. This is a confirmation of the view that particularly the old and the frail patient will benefit from the application of fast track programmes.

One of the major concerns regarding fast track programmes is that reduction of the PHS might result in an increased readmission rate. In this review there was no significant difference in readmission rate. On the contrary, there was a trend to less readmissions in the fast track group when only the randomised controlled studies are considered. The trend to an increased readmission rate after fast track recovery, seen in the pooled result of only the non-randomised studies is caused by the largest study by Basse et al., reporting the largest reduction in PHS but also an increased readmission rate in the fast track group. The other included studies reported a reduction in PHS also, albeit less pronounced, but without an increased readmission rate. In other words there seemed to be a turning point after which reducing the PHS further, the readmission rate would increase. This, in part, can be prevented by applying strict discharge criteria. Only in this way, it is assured that patients are discharged in the same condition as would have been the case in a traditional care situation. This review shows that not all studies used such discharge criteria. In the studies by Anderson et al., Delaney et al., and Gatt et al., discharge criteria had been defined for both the fast track and traditional care patients. These discharge criteria comprised the ability to tolerate solid food, full mobilisation, and pain medication limited to oral analgesics. Delaney et al. defined additional discharge criteria concerning passage of flatus or stool and agreement of the patient with the scheduled discharge. Bradshaw et al. used three discharge criteria for the fast track patients including normal body temperature, return of gastrointestinal function and the tolerance of oral nutrition. In the other studies there were no properly defined or described discharge criteria. Secondly a higher readmission rate makes it necessary to simplify the readmission procedure to assure that there is no delay in admission and treatment if necessary.
In this meta-analysis the PHS was reduced by 1.6 days. The study by Basse et al. was excluded in the calculation of the weighted mean difference because a standard deviation was not given. In this, relatively large, study the difference in mean PHS between fast track and traditional care was 6.7 days in favour of fast track.\footnote{If this study would be taken into account, the difference would probably have been considerably greater than 1.6 days.} The reduction in PHS was partly facilitated by the prevention or reduction of postoperative ileus and decreased morbidity, however, when only the randomised controlled studies were considered in the morbidity analysis, the results were less pronounced, and no longer significant. This may be explained by the remarkably great difference between the fast track group and traditional care group in the large study by Basse et al.\footnote{Furthermore, this traditional care group was collected retrospectively from another institution.} Gatt et al. reported high morbidity rates in both the traditional care group and the fast track group. This can partly be explained by the fact that minor morbidity such as vomiting and diarrhoea were also taken into account.

This systematic review has many limitations; the overall quality of the included studies was moderate with several sources of bias. Possibly, there also could be a publication bias because all studies reported positive results in favour of fast track. The number of applied fast track elements varied widely, in general only half of the pre-defined elements were used. To partly deal with the heterogeneous nature of studies, a distinction was made between the randomised and the non-randomised studies.

In conclusion, based on six comparative single centre studies, fast track programmes were found to reduce the time spent in the hospital, and were found to be safe in major abdominal surgery. Shortening hospital stay and morbidity reduction are attractive, since both increase the availability of beds and might reduce the overall cost of hospital stay. However, despite the current enthusiasm and implementation into daily practice this systematic review shows that to date, there are few data available. The positive results, e.g. shorter hospital stay, and reduced morbidity, should therefore encourage further studies on fast track colonic surgery and not be used as a justification for broader implementation into daily practice. Thus, multi-centre prospective randomised trials are needed to confirm the broader applicability and favourable results of fast track programmes in colonic surgery.

Reference List


(17) Therapy checklist (Dutch extended version) of the Dutch Cochrane Centre.


Implementation of a fast track perioperative care programme; what are the difficulties?

SW Polle
J Wind
JW Fuhring
J Hofland
DJ Gouma
WA Bemelman

Digestive Surgery 2007;24:441-449
Abstract

Introduction
The aim of the present study was to evaluate the feasibility of a fast track programme and its effect on postoperative recovery.

Methods
All patients, scheduled for elective segmental colorectal resection were treated in a fast track programme. Data were compared to a control-group operated for elective colorectal resections and treated in a traditional care programme. Data from the fast track group were collected prospectively, data from the traditional care group retrospectively. Outcome-parameters included the number of successfully applied fast track modalities, patient-satisfaction, morbidity rate, reoperation rate, primary (PHS) and total hospital stay (THS), and readmission rate.

Results
One-hundred-and-seven patients were included (55 fast track group vs. 52 traditional care group). The groups were comparable for patient-characteristics as age and cr-POSSUM-score (p=0.22 and p=0.40). An average of 7.4 out of 13 predefined fast track modalities were successfully achieved per patient. Patient-satisfaction was comparable (p=0.84). Seven versus five patients required a reoperation in the fast track and traditional care group, respectively (p=0.52). Morbidity rate was comparable (n=16 vs. n=15, p=0.83). Median PHS was 4.0 vs. 6.0 days and median THS was 4.0 vs. 6.5 days in the fast track group and traditional care group (p<0.01 and p<0.03, respectively). Six versus three patients were readmitted in the fast track and traditional care group, respectively (p=0.49).

Conclusion
Implementation of all fast track modalities was difficult since a rather low number of pre-defined fast track modalities were effectively realized. Despite incomplete implementation, PHS and THS were shorter in the fast track group without affecting patient-satisfaction.
Introduction

Fast track programmes, also referred to as Enhanced Recovery After Surgery (ERAS®), are supposed to reduce morbidity, accelerate recovery and consequently shorten hospital stay of surgical patients. Kehlet and co-workers achieved a reduction in hospital stay from 10 to 3.3 days for patients undergoing segmental colonic resection. To a lesser degree, others have also reported a reduction in hospital stay after the implementation of a fast track programme. Although the number of studies reporting on advantages of fast track care programmes are growing, the evidence is still rather limited; only three small randomized controlled trials (RCTs), encompassing a total number of 64 patients treated in a fast track perioperative care programme, have been published. Most of the available non-randomised studies have a retrospective design or are case-series without adequate control groups and without reporting on patient satisfaction with such a programme. Although the combination of laparoscopic surgery and fast track care might be the optimal strategy, only two RCTs have compared laparoscopic to open surgery within a fast track programme. The conflicting results of these reports justify further study.

While most authors have meticulously described the fast track modalities included in their protocols (e.g. omission of bowel preparation and pre-medication, use of thoracic epidural anesthesia for perioperative analgesia management, early post-operative mobilisation and feeding), none of them actually described the degree of compliance with each of the single fast track modalities as defined in their protocols. For this reason, the exact influence of the number of and type of fast track modalities within a fast track programme remains unknown. Moreover, most authors publishing on their results after introduction of a fast track programme probably report on their results after an initial period of pilot testing with such a programme. No data are available with respect to the encountered early difficulties with the introduction of such a programme.

The objective of this study was therefore to describe our results from the start of introduction of a fast track programme by evaluating both the number of successfully applied pre-defined fast track modalities per patient as well as the combined effect of these fast track modalities on postoperative recovery. These results were compared to results of patients treated in a traditional care programme. The faced bottlenecks with the introduction of the programme will be commented on.

Methods

In the Academic Medical Centre in Amsterdam two separate gastro-intestinal surgery units are available. A fast track perioperative care programme was introduced in one of the two gastrointestinal surgery units in August 2004. Patients scheduled for elective abdominal segmental colorectal resection including ileo-colic (re-) resection in the period August 2004 to July 2005, and admitted on the fast track unit, were treated according
to the fast track programme (fast track group). The allocation of patients to the unit with fast track or the unit without fast track in this period, depended on the availability of hospital beds on both units, the availability of a fast track nurse and the fast track surgeon who initiated this project. A consecutive series of patients, scheduled for elective segmental colorectal resection in the period June 2003 to January 2004 and admitted on both gastrointestinal surgery units, was treated in a traditional care programme and served as a control group (traditional care group). Only patients with American Society of Anaesthesiologists (ASA) classification I or II were included in this study. In both study groups, patients with prior segmental colorectal resections were included as were both open and laparoscopic procedures. Patients requiring a palliative resection or an abdomino-perineal resection (APR) for colorectal cancer were excluded. Outcome data of the fast track group were recorded prospectively; outcome data of the traditional care group were collected retrospectively from patients’ records. All data were analyzed according to an intention-to-treat principle meaning that patients who were unable to fulfil (parts of) the fast track programme were analyzed in the fast track group. Since each single modality as applied in our fast track programme is an accepted form of treatment in daily care, no ethics approval from our Ethic Committee was requested. Each patient was however informed about the combination of these accepted and evidence based single modalities applied in the fast track protocol.

Primary outcome parameters were the number of successfully applied fast track modalities per patient and patient satisfaction. Secondary outcome parameters were overall morbidity rate, reoperation rate, primary hospital stay, total hospital stay, readmission rate, and mortality rate.

A total of 13 fast track modalities were identified (Table 1). For each patient each modality was evaluated for successful implementation (e.g. if bowel preparation was omitted it was scored as successful implementation, if it was not omitted it was considered unsuccessful).

Table 1. Evaluated fast track modalities

| Omission of bowel preparation |
| Prevention of hypothermia |
| Pre-operative counselling by fast track nurse |
| Intake of 4 CHL drinks on day before surgery |
| Epidural anaesthesia |
| Prophylactic PONV medication |
| Intake of 2 CHL drinks 2 hours before surgery |
| Suprapubic catheter |
| Omission of evening medication |
| Omission of pre-medication |
| Intake of 2 CHL drinks on evening after surgery |
| Early extension of oral liquids |
| Early mobilisation |

CHL: carbohydrate loaded drink (Nutridrink®)
In this manner all successfully applied items per patient were scored. Also the average number of successfully applied items of all patients was calculated. Overall morbidity was defined as any complication requiring an unplanned intervention within 30 days after the operation. A major complication was considered any complication requiring a surgical reintervention or resulting in permanent adverse sequel (such as myocardial infarction). Total hospital stay was defined as primary hospital stay plus the hospitalisation period of patients that were readmitted within 30 days after surgery.

**Fast track vs. traditional care protocol**

Details of the fast track perioperative and traditional care protocols are summarized in Table 2. Discharge criteria were similar for both groups consisting of 1) adequate pain control with oral medication, 2) absence of nausea, 3) passage of first flatus and/or stool, 4) ability to tolerate solid food, 5) mobilisation and self support as preoperative and finally 6) acceptance of discharge by the patient. Within 24 - 48 h after discharge, fast track patients were contacted by telephone by a specially trained fast track senior nurse (JWF) to check for complications. During this contact, patients were provided to ask questions about

<table>
<thead>
<tr>
<th>Table 2. Differences between fast-track and traditional care protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-operative phase</strong></td>
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<td></td>
</tr>
<tr>
<td>Outpatient department of anaesthesiology</td>
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<td></td>
</tr>
<tr>
<td>Pre-admission guided tour on surgical ward</td>
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<tr>
<td><strong>Day of admission</strong></td>
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<td>Pre-operative fasting</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Pre-anaesthetic medication</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
### Day of Surgery

#### Anaesthetic management
- Placement of thoracic epidural catheter (T6-T10, depending on the surgical resection); test-dose (bupivacaine 0.25% with adrenaline 1:200,000), top-up dose (bupivacaine 0.25% ± 10 ml) with sufentanil 25 μg, followed by continuous infusion (bupivacaine 0.125% with fentanyl 2.5 μg.ml-1) until day 2 postoperative
- IV morphine loading (0.1 mg.kg-1) followed by continuous IV morphine infusion or PCA-morphine, OR placement of epidural catheter (T10-L1, test dose, top-up dose and continuous infusion in the same way as for fast track) when an open surgical procedure will be performed
- IV morphine loading (0.05-0.1 mg.kg-1) followed by PCA-morphine or continuous IV morphine infusion when a laparoscopic surgical procedure is performed
- Combined with balanced general anaesthesia
- Restricted per-operative fluid infusion regime (Ringers lactate 20 ml.kg-1 in the 1st h followed by RL 6 ml.kg-1.h-1)
- Use of extra fluid challenge as 1st choice for management of mean blood pressure drop > 20% below baseline
- Forced body heating (Bair hugger system and warmed IV fluids)
- Naso-gastric tube remain until day 1 after surgery
- Use of odansetron, dexamethason or droperidol for PONV management according to attending anaesthesiologist
- Combined with balanced general anaesthesia
- Standard per-operative fluid infusion regime (Ringers lactate 20 ml.kg-1 in the 1st h followed by RL 10-12 ml.kg-1.h-1)
- Use of extra fluid challenge as 1st choice for management of mean blood pressure drop > 20% below baseline
- Forced body heating (Bair hugger system and warmed IV fluids)
- Naso-gastric tube remain until day 1 after surgery
- Use of odansetron, dexamethason or droperidol for PONV management according to attending anaesthesiologist

#### Surgical Management
- Minimal invasive incisions
- Supra-pubic urine catheter
- Infiltration of surgical wounds with bupivacaine
- Median laparotomy approach
- Urine catheter according to attending surgeon
- No infiltration of surgical wounds with local anaesthetic drugs
- Standard use of abdominal drains
- Continuous IV morphine infusion or PCA-morphine OR use of epidural catheter as mentioned before to which paracetamol 4 x 1 g.d-1 and/or diclofenac 3 x 50 mg.d-1 are added
- Small amount of water orally + IV infusion of RL 2.5 l.d-1
- Bed rest

#### Early post-operative management
- No standard use of abdominal drains
- Use of epidural catheter as mentioned before to which paracetamol 4 x 1 g.d-1 is added
- First oral drinks at 2 h post-surgery + IV infusion of RL 1.5 l.d-1
- Mobilisation in the evening (>2 h out of bed)
- First semi-solid food intake in the evening
- No infiltration of surgical wounds with local anaesthetic drugs
- Standard use of abdominal drains
- Continuous IV morphine infusion or PCA-morphine OR use of epidural catheter as mentioned before to which paracetamol 4 x 1 g.d-1 and/or diclofenac 3 x 50 mg.d-1 are added
- Small amount of water orally + IV infusion of RL 2.5 l.d-1
- Bed rest
Chapter 3

Implementation of a fast track programme

<table>
<thead>
<tr>
<th>Day 1 after Surgery</th>
<th>Oral intake &gt; 2 l (including 4 units CHL drinks), offer solid food</th>
<th>Diet increased on daily basis when normal bowel sounds are examined</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stop IV fluid administration (leave canulla)</td>
<td>IV fluid administration (2.5 l.d-1) is continued till adequate oral fluid intake</td>
</tr>
<tr>
<td></td>
<td>Start laxative (MgO, 2 x 1 g.d-1)</td>
<td>Start laxative (MgO, 2 x 1 g.d-1)</td>
</tr>
<tr>
<td></td>
<td>Close supra-pubic urine catheter and remove when residue &lt; 50 ml</td>
<td>Close supra-pubic urine catheter and remove when residue &lt; 50 ml</td>
</tr>
<tr>
<td></td>
<td>Expand mobilisation (&gt; 6 h out of bed)</td>
<td></td>
</tr>
</tbody>
</table>

Day 2 after surgery
- Offer solid food
- Expand mobilisation (> 8 hours)
- Plan discharge

Day 3 after surgery
- Remove epidural catheter
- Continue Paracetamol 4x 1000 mg
- Add NSAID
- Remove IV cannula
- Expand mobilisation (> 8 hours)
- Evaluating discharge criteria; discharge if fulfilled

Day 4 after surgery
- Continue as on day 3 until discharge criteria are fulfilled
- Continue as on day 1 until discharge criteria are fulfilled

FT: Fast-track; TC: Traditional care; CHL: carbohydrate loaded drink (Nutridrink®)

their recovery and reassured when necessary. All patients (both traditional care and fast track) were seen at the outpatient department at a minimum of 30 days postoperatively. Complications in the period after discharge, if any, were recorded.

Analysis of outcome parameters
To evaluate a possible learning effect with the implementation of the fast track protocol, a comparison was made between the first and second half of patients treated since the introduction of the fast track care programme (period I: 08-2004 to 12-2004 and period II: 01-2005 to 07-2005).
To assess patient satisfaction with the hospitalisation, a self-report questionnaire consisting of 16 modalities, was sent to all fast track patients within 30 days after discharge. This questionnaire is routinely used in our hospital and includes questions concerning intake on the surgical ward, degree of personal attention from the surgeon and nurse, transfer of information of medical results, arrangement of discharge and questions concerning aftercare. Patients were asked to rate their satisfaction with each single modality on a Likert scale ranging from one (dissatisfied) to five (very satisfied). The scores of each question are combined to form a total patient satisfaction score ranging from 16 (lowest patient satisfaction) to 80 (highest patient satisfaction). The same questionnaire was used previously to monitor patient satisfaction in the year 2003. Patient satisfaction of fast track patients was compared to that of patients from the traditional care group.

Also a comparison was made between patients who underwent open resection with those
who underwent a laparoscopic resection, according to the type of perioperative care. So, a subanalysis of four subgroups was performed: 1) open resection and fast track care (Open-fast track group), 2) laparoscopic resection and fast track care (Lap-fast track group), 3) open resection and traditional care (Open-traditional care group) and 4) laparoscopic resection and traditional care (Lap-traditional care group).

**Statistical analysis**
Data are presented as median values with ranges for continuous and discrete data, unless otherwise specified. Categorical data are presented as frequencies or percentages. Differences between groups were tested using Kruskal Wallis test or Mann-Whitney U test for continuous data, depending on the number of groups compared. The Fisher’s exact test or Chi-square test when appropriate were used to test for differences between groups in case of categorical data. A p-value <0.05 was considered statistically significant for all tests. Statistical analysis was done using the SPSS v.12.0 package (SPSS, Chicago, Illinois, USA).

**Results**
A total of 107 patients were included in this study: 55 in the fast track group and 52 in the traditional care group. None of the patients eligible for the fast track programme refused participation in the study. Patient characteristics of the fast track and traditional care patients are shown at Table 3. The fast track and traditional care group were comparable for all patient characteristics although there were more open procedures and a trend to more stomas in the traditional care compared to the fast track group. Within the fast track group, patient characteristics of patients treated in the first and second fast track period were comparable (data not shown). Patient characteristics of the four subgroups (data not shown) were comparable except for a higher number of primary diverting stomas in the open traditional care group compared to the laparoscopic fast track group (p<0.01).

**Protocol compliance**
An average of 7.4 out of a potential of 13 evaluated fast track modalities were successfully applied per patient. Results of the degree of protocol compliance per fast track modality are given at Table 4, ranging from 13% (intake of two CHL drinks the evening after surgery) to 100% (prevention of hypothermia and omission of bowel preparation). There were no differences in protocol compliance between the first and the second fast track period in any of the evaluated variables, although a small improvement in the number of patients receiving epidural analgesia in the second fast track period could be observed (period II vs. period II: 58% vs. 81%, respectively; p=0.08).
Chapter 3
Implementation of a fast track programme

Table 3. Patient characteristics and type of resection according to care protocol

<table>
<thead>
<tr>
<th></th>
<th>TC N=52</th>
<th>FT N=55</th>
<th>p†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-median (range)</td>
<td>47 (18-89)</td>
<td>49 (20-79)</td>
<td>0.224‡</td>
</tr>
<tr>
<td>ASA n (%)</td>
<td></td>
<td></td>
<td>0.402</td>
</tr>
<tr>
<td>-1</td>
<td>25.0</td>
<td>32.7</td>
<td></td>
</tr>
<tr>
<td>-2</td>
<td>75.0</td>
<td>67.3</td>
<td></td>
</tr>
<tr>
<td>Gender ratio (M:F) n</td>
<td>21:31</td>
<td>13:42</td>
<td>0.096</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-median (range)</td>
<td>24.0(15.2-37.7)</td>
<td>23.5(15.7-39.3)</td>
<td>0.803‡</td>
</tr>
<tr>
<td>CR-POSSUM operative severity score</td>
<td></td>
<td></td>
<td>0.395‡</td>
</tr>
<tr>
<td>-median (range)</td>
<td>7.0 (7-11)</td>
<td>7.0 (7-13)</td>
<td>0.804§</td>
</tr>
<tr>
<td>Type of operation n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-ileocolic (re-) resection</td>
<td>15 (28.8)</td>
<td>19 (34.5)</td>
<td></td>
</tr>
<tr>
<td>-right hemicolecctomy</td>
<td>10 (19.2)</td>
<td>6 (10.9)</td>
<td></td>
</tr>
<tr>
<td>-sigmoid resection</td>
<td>12 (23.1)</td>
<td>17 (30.9)</td>
<td></td>
</tr>
<tr>
<td>-rectal resection (anteriore + low anterior)</td>
<td>10 (19.2)</td>
<td>10 (18.2)</td>
<td></td>
</tr>
<tr>
<td>-subtotal / total resection</td>
<td>3 (5.8)</td>
<td>2 (3.6)</td>
<td></td>
</tr>
<tr>
<td>-other partial colonic resection</td>
<td>2 (3.8)</td>
<td>1 (1.8)</td>
<td></td>
</tr>
<tr>
<td>Indication for resection n (%)</td>
<td></td>
<td></td>
<td>0.695</td>
</tr>
<tr>
<td>-malignant disease</td>
<td>21 (40.4)</td>
<td>20 (36.4)</td>
<td></td>
</tr>
<tr>
<td>-benign disease</td>
<td>31 (59.6)</td>
<td>35 (63.6)</td>
<td></td>
</tr>
<tr>
<td>Laparoscopic operation n (%)</td>
<td>17 (32.7)</td>
<td>29 (52.7)</td>
<td>0.051</td>
</tr>
<tr>
<td>Primary (temporary) stoma n (%)</td>
<td>13 (25.0)</td>
<td>7 (12.7)</td>
<td>0.138</td>
</tr>
</tbody>
</table>

†Fisher’s exact test unless otherwise specified; ‡Mann Whitney U test; §Chi square test; TC: Traditional care; FT: Fast track care; CR-Possum: Colorectal Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity

**Patient’s satisfaction**

The response rate of the patient’s satisfaction questionnaire was 78% and 81% in the fast track and traditional care group respectively. Total patients satisfaction score was comparable in both groups (50.4 and 49.8 out of a potential 80 points in the fast track and traditional care group respectively, p=0.84). The intake at the surgical ward was evaluated more positively in the fast track group (mean score 3.8 and 3.3 in the fast track and traditional care group respectively, P=0.02). Satisfaction between the two groups with all of the other single modalities was comparable.

**Outcome after fast track vs. traditional care (Table 5)**

Overall morbidity and number of major and minor complications of the fast track and traditional care groups were comparable. However, it seemed that more patients in the fast track group had an anastomotic leakage (n=6 (11%) vs. n=2 (4%), p=0.27). Reoperation rate was comparable and median primary hospital stay was reduced by two days (p<0.01). Despite an increase in the number of readmissions in the fast track group, total hospital
Table 4. Degree of protocol compliance in fast track patients per evaluated modality

<table>
<thead>
<tr>
<th>Evaluated modality</th>
<th>Degree of compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omission of bowel preparation n (%)</td>
<td>55 (100)</td>
</tr>
<tr>
<td>-yes</td>
<td></td>
</tr>
<tr>
<td>-no</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Prevention of hypothermia n (%)</td>
<td>55 (100)</td>
</tr>
<tr>
<td>-yes</td>
<td></td>
</tr>
<tr>
<td>-no</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pre-operative counselling by FT nurse n (%)</td>
<td>48 (87.3)</td>
</tr>
<tr>
<td>-yes</td>
<td></td>
</tr>
<tr>
<td>-no</td>
<td>7 (12.7)</td>
</tr>
<tr>
<td>Intake of 4 CHL drinks on day before surgery n (%)</td>
<td>46 (83.6)</td>
</tr>
<tr>
<td>-yes</td>
<td></td>
</tr>
<tr>
<td>-no</td>
<td>8 (26.4)</td>
</tr>
<tr>
<td>Epidural anaesthesia n (%)</td>
<td>39 (70.9)</td>
</tr>
<tr>
<td>-yes</td>
<td></td>
</tr>
<tr>
<td>-T7-T10 level</td>
<td>-22 (40.0)</td>
</tr>
<tr>
<td>-below T10 level</td>
<td>-17 (30.9)</td>
</tr>
<tr>
<td>-no</td>
<td>16 (29.1)</td>
</tr>
<tr>
<td>Prophylactic PONV medication n (%)</td>
<td>37 (67.3)</td>
</tr>
<tr>
<td>-yes</td>
<td></td>
</tr>
<tr>
<td>-no</td>
<td>18 (32.7)</td>
</tr>
<tr>
<td>Intake of 2 CHL drinks 2 hours before surgery n (%)</td>
<td>37 (67.3)</td>
</tr>
<tr>
<td>-yes</td>
<td></td>
</tr>
<tr>
<td>-no</td>
<td>18 (32.7)</td>
</tr>
<tr>
<td>Suprapubic catheter n (%)</td>
<td>26 (47.3)</td>
</tr>
<tr>
<td>-yes</td>
<td></td>
</tr>
<tr>
<td>-no</td>
<td>29 (52.7)</td>
</tr>
<tr>
<td>Omission of evening medication n (%)</td>
<td>22 (40.0)</td>
</tr>
<tr>
<td>-yes</td>
<td></td>
</tr>
<tr>
<td>-no</td>
<td>33 (60.0)</td>
</tr>
<tr>
<td>Omission of pre-medication n (%)</td>
<td>17 (30.9)</td>
</tr>
<tr>
<td>-yes</td>
<td></td>
</tr>
<tr>
<td>-no</td>
<td>38 (69.1)</td>
</tr>
<tr>
<td>Intake of 2 CHL drinks on evening after surgery n (%)</td>
<td>7 (12.7)</td>
</tr>
<tr>
<td>-yes</td>
<td></td>
</tr>
<tr>
<td>-no</td>
<td>48 (87.3)</td>
</tr>
<tr>
<td>Total oral daily intake of fluids after operation (ml)</td>
<td></td>
</tr>
<tr>
<td>-POD 1 (first day after surgery)</td>
<td>944</td>
</tr>
<tr>
<td>-POD 2</td>
<td>1313</td>
</tr>
<tr>
<td>-POD 3</td>
<td>1622</td>
</tr>
<tr>
<td>Total duration of daily mobilisation after operation (min)</td>
<td></td>
</tr>
<tr>
<td>-POD 0 (day of surgery)</td>
<td>29</td>
</tr>
<tr>
<td>-POD 1</td>
<td>110</td>
</tr>
<tr>
<td>-POD 2</td>
<td>178</td>
</tr>
<tr>
<td>-POD 3</td>
<td>339</td>
</tr>
</tbody>
</table>

FT: Fast-track; POD0: day of surgery; POD1: first day after surgery; POD2: Second Day after surgery; POD3: Third day after surgery; CHL: carbohydrate loaded drink; PONV: post-operative nausea or vomiting prophylaxis
stay was reduced with 2.5 days (p=0.03). There was no mortality within 30 days after surgery in either group.

Outcome after first fast track period compared to second fast track period
Overall morbidity rate seemed to decrease in the second compared to the first fast track period (Period I: n=10 vs. Period II: n=5, p=0.07) as was the case for the number of major complications (Period I: n=6 vs. Period II: n=2, p=0.07). Primary hospital stay was 4.0 days in both periods and total hospital stay was 4.5 days in the first fast track period compared to 4.0 days in the second fast track period (p=0.43). All other evaluated outcome parameters for both periods were comparable as well (data not shown).

Outcome differences of fast track vs. traditional care according to type of surgery (Table 6)
Within the laparoscopic groups, there was no significant difference in primary and total hospital stay (p=0.13 and p=0.44, respectively). There also was no difference in overall morbidity (p=0.49). Major complications and reoperations occurred more frequent in the fast track group (n=0 and n=5 for both major complication rate and reoperation rate in the

<table>
<thead>
<tr>
<th>Table 5. Postoperative results according to care protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TC</strong></td>
</tr>
<tr>
<td>N=52</td>
</tr>
<tr>
<td>---------------------------------------------------------</td>
</tr>
<tr>
<td>Overall morbidity &lt;30 days n (%)</td>
</tr>
<tr>
<td>Major complications n (%)</td>
</tr>
<tr>
<td>- anastomotic leakage</td>
</tr>
<tr>
<td>- abdominal bleeding</td>
</tr>
<tr>
<td>- abdominal abscess</td>
</tr>
<tr>
<td>- myocardial ischemia</td>
</tr>
<tr>
<td>- persistent ileus requiring re-operation</td>
</tr>
<tr>
<td>- iatrogenic perforation requiring re-operation</td>
</tr>
<tr>
<td>Minor complications n (%)</td>
</tr>
<tr>
<td>- urinary tract infection</td>
</tr>
<tr>
<td>- wound infection</td>
</tr>
<tr>
<td>- supraventricular arrhythmia</td>
</tr>
<tr>
<td>- NSAID gastritis</td>
</tr>
<tr>
<td>- high output stoma with dehydration</td>
</tr>
<tr>
<td>- persistent ileus treated conservatively</td>
</tr>
<tr>
<td>Re-operation n (%)</td>
</tr>
<tr>
<td>PHS (days)</td>
</tr>
<tr>
<td>- median (range)</td>
</tr>
<tr>
<td>THS (days)</td>
</tr>
<tr>
<td>- median (range)</td>
</tr>
<tr>
<td>Readmissions &lt;30 days (%)</td>
</tr>
<tr>
<td>Mortality &lt;30 days (n)</td>
</tr>
</tbody>
</table>

†TC vs. FT; PHS: primary hospital stay; THS: total hospital stay; TC: Traditional care; FT: Fast track care
Table 6. Subanalysis of postoperative results according to care protocol and type of surgery

<table>
<thead>
<tr>
<th></th>
<th>Lap-TC N=17</th>
<th>Lap-FT N=29</th>
<th>Open-TC N=35</th>
<th>Open-FT N=26</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall morbidity &lt;30 days n (%)</td>
<td>3 (17.6)</td>
<td>9 (31.0)</td>
<td>13 (37.2)</td>
<td>6 (23.1)</td>
<td>0.441</td>
</tr>
<tr>
<td>Major complications n (%)</td>
<td>0 (0.0)</td>
<td>5 (17.2)</td>
<td>8 (22.9)</td>
<td>3 (11.5)</td>
<td>0.167</td>
</tr>
<tr>
<td>Minor complications n (%)</td>
<td>3 (17.6)</td>
<td>4 (13.8)</td>
<td>5 (14.3)</td>
<td>3 (11.5)</td>
<td>0.907</td>
</tr>
<tr>
<td>Re-operation n (%)</td>
<td>0 (0.0)</td>
<td>5 (17.2)</td>
<td>5 (14.3)</td>
<td>2 (7.7)</td>
<td>0.243*</td>
</tr>
<tr>
<td>PHS (days)</td>
<td>-median (range) 5.0 (3-18)</td>
<td>4.0 (2-33)</td>
<td>8.0 (2-36)</td>
<td>4.5 (2-19)</td>
<td>0.000**</td>
</tr>
<tr>
<td>THS (days)</td>
<td>-median (range) 5.0 (3-18)</td>
<td>4.0 (2-33)</td>
<td>8.0 (2-36)</td>
<td>5.0 (2-23)</td>
<td>0.002***</td>
</tr>
<tr>
<td>Readmissions &lt;30 days n (%)</td>
<td>0 (0.0)</td>
<td>3 (10.3)</td>
<td>3 (8.6)</td>
<td>3 (11.5)</td>
<td>0.566</td>
</tr>
<tr>
<td>Mortality &lt;30 days n (%)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>-</td>
</tr>
</tbody>
</table>

\(\text{§Lap-TC vs. Lap-FT vs. Open TC vs. Open FT; PHS: primary hospital stay; THS: total hospital stay; TC: Traditional care; FT: Fast track care}\)

\* Re-operation rate:

<table>
<thead>
<tr>
<th></th>
<th>Lap TC vs Lap FT:</th>
<th>Lap FT vs Open TC:</th>
<th>Lap TC vs Open TC:</th>
<th>Lap FT vs Open FT:</th>
<th>Lap TC vs Open FT:</th>
<th>Open TC vs Open FT:</th>
</tr>
</thead>
<tbody>
<tr>
<td>(P)</td>
<td>0.073</td>
<td>0.557</td>
<td>0.105</td>
<td>0.232</td>
<td>0.247</td>
<td>0.428</td>
</tr>
</tbody>
</table>

\** PHS:**

<table>
<thead>
<tr>
<th></th>
<th>Lap TC vs Lap FT:</th>
<th>Lap FT vs Open TC:</th>
<th>Lap TC vs Open TC:</th>
<th>Lap FT vs Open FT:</th>
<th>Lap TC vs Open FT:</th>
<th>Open TC vs Open FT:</th>
</tr>
</thead>
<tbody>
<tr>
<td>(P)</td>
<td>0.131</td>
<td>0.000</td>
<td>0.003</td>
<td>0.077</td>
<td>0.762</td>
<td>0.017</td>
</tr>
</tbody>
</table>

\***THS:**

<table>
<thead>
<tr>
<th></th>
<th>Lap TC vs Lap FT:</th>
<th>Lap FT vs Open TC:</th>
<th>Lap TC vs Open TC:</th>
<th>Lap FT vs Open FT:</th>
<th>Lap TC vs Open FT:</th>
<th>Open TC vs Open FT:</th>
</tr>
</thead>
<tbody>
<tr>
<td>(P)</td>
<td>0.437</td>
<td>0.001</td>
<td>0.001</td>
<td>0.069</td>
<td>0.314</td>
<td>0.083</td>
</tr>
</tbody>
</table>

FT: Fast-track group; TC: Traditional care group; Lap-TC: group of patients operated laparoscopically and treated in a traditional care programme; Lap-FT: group of patients operated laparoscopically and treated in a fast track programme; Open-TC: group of patients operated by an open approach and treated in a traditional care programme; Open-FT: group of patients operated by an open approach and treated in a fast track programme; PHS: Primary hospital stay; THS: Total hospital stay.

Lap-traditional care and Lap-fast track group respectively; \(p=0.07\).

Within the open groups there was a significant reduction in primary hospital stay in the fast track compared to the traditional care group (8 vs. 4.5 days, \(p=0.02\)). Total hospital...
stay was shorter as well, although not significantly (8 vs. 5 days, p=0.08). There were no significant differences in overall morbidity, reoperation and major and minor complication rates (Table 6).

**Outcome differences of laparoscopic vs. open surgery according to type of perioperative care (Table 6)**

Within the fast track groups, both primary and total hospital stay seemed shorter in the laparoscopic group (Table 6, reduction 0.5 and 1 day for primary hospital stay and total hospital stay respectively, p=0.08 and p=0.07 respectively). There were no differences in overall morbidity, and the number of major and minor complications between the open and laparoscopic group (p=0.56, p=0.71, and p=0.70 respectively).

Within the traditional care groups, a reduction of three days of both primary and total hospital stay was found in the laparoscopic compared to the open group (Table 4, p<0.01 and p<0.01, respectively). Overall morbidity rate and reoperation rate were higher in the open group because of a significant higher rate of major complications in this group (Table 6, p=0.04).

**Discussion**

The present study showed that full implementation of a fast track care programme for patients undergoing an elective segmental colorectal resection is troublesome, since overall 7.4 out of the predefined items were achieved. However despite a relatively low protocol compliance, hospital stay is reduced without affecting overall morbidity and without affecting patient satisfaction. It further indicates that the combination of laparoscopy and fast track care might have an amplifying effect.

The implementation of a fast track care programme for colorectal surgery requires a dedicated and motivated team of which the surgeon, anaesthesiologist and nursing team are the mainsprings. The 180 degrees reversal in policy affecting current practice of three different disciplines appeared difficult to apply in daily clinical practice. The change of a delayed mobilisation into early mobilisation, the change of pre-operative fasting into pre-operative feeding and the introduction of epidural analgesia in laparoscopic surgery were important bottlenecks in the present study. The involved personnel need to be trained, and probably the training must be repeated to maintain a high compliance. The efforts to incorporate such an intensive and multidisciplinary programme in a hospital should therefore not be underestimated.

Nonetheless, some of the fast track components are already implemented in a modern traditional care programme; omission of bowel preparation, restrictive use of abdominal drains and naso-gastric tubes, early mobilisation and advancement of oral diet, are common practice in many hospitals. Those changes in daily practice are partly instigated by the implementation of laparoscopic surgery.
Despite strenuous efforts of the study coordinators of the involved disciplines to comply with all modalities of the fast track protocol, compliance with each of the single modalities was relatively low; only a mean of 7.4 out of a potential 13 evaluated fast track modalities per patient were achieved. In contrast to what could be expected, protocol compliance did not improve significantly with increasing experience with the programme. Only, a non-significant improvement in protocol compliance with the number of patients receiving epidural analgesia in the second fast track period was observed. Possibly a much longer period of training is necessary to break with the longstanding traditions in traditional care. Still, despite the relatively low compliance, a significant reduction in primary and total hospital stay was observed. This finding seems to suggest that it is rather the protocolised way of perioperative treatment that enhances recovery, than it is the combined effect of each of the single fast track modalities. Working according to the fast track protocol, there is no argue about removal of i.v. drips, epidural catheters, urine catheters, advancement of diet and mobilisation. Another important explanation could be the fact that by inviting patients to participate in a “fast-track” programme, both the patient and the surgeon are committed to work together striving for an enhanced recovery. The clear goals for the patient to reach every day and possibly also the expectations that are being raised by the term “fast” may have contributed to the reduced hospital stay as well.

In the present study, overall morbidity between the fast track and traditional care group was comparable. This is in accordance with data from a meta-analysis comparing fast track and traditional care in patients requiring segmental colonic resection. Although the number of readmitted patients seemed higher in the fast track compared to the traditional care group, total hospital stay was shorter in the fast track group. A feared complication of fast track care programmes is an increased incidence of anastomotic leakages, supposed to be caused by the early start of oral feeding. In the present study, more patients with an anastomotic leakage were found in the fast track compared to the traditional care group. This probably represents an unfortunate coincidence, since all leakages occurred in the first fast track period and none occurred in the second fast track period. In literature there is no association of anastomotic leakage with the absence of bowel preparation or early feeding.

Several randomised trials have demonstrated that a laparoscopic approach reduces hospital stay after segmental colorectal resection for cancer and inflammatory bowel disease in a traditional care programme. Theoretically, the combination of fast track care with laparoscopy might be the most optimal combination. In this way the minimal invasive incisions are combined with the advantages of the optimization package of the fast track programme. Because the numbers of patients in each subgroup were too small, no robust conclusions can be drawn from the comparison between the four subgroups in which open and laparoscopic surgery as well as traditional care and fast track care were compared. Nonetheless, a reduction in primary and total hospital stay in the open fast track compared to the open traditional care group was found. This might be attributed to the implementation of the fast track care programme. By combining laparoscopic
surgery and fast track care, a further decrease in primary and total hospital stay might be achieved. Despite the relatively small number of patients in this pilot study, the findings of the present study justify these findings to be tested in a randomised controlled trial. At present such a study is being conducted in a multi-centre randomised setting. In this trial the cost-effectiveness of the fast track programme compared to laparoscopy alone or in combination with laparoscopy should be evaluated as well. ASA III patients, who were not included in the present study are included in this multicentre trial as well. The reason that only ASA I and ASA II patients were included in the present study was because it was the authors expectation that ASA I and ASA II patients would optimally benefit from the fast track protocol. Recent studies however have shown that ASA III patients may also benefit from a fast track treatment protocol. This was unknown at the time the authors started the study.

In conclusion, successful implementation of a fast track programme appeared difficult. Despite a relatively low compliance, a reduction of 2.5 days of hospital stay was achieved, indicating that it is rather the combination of the protocolised way of perioperative treatment and patients expectations that enhances recovery. The role and necessity of each single modality as well as the place of laparoscopy both within and compared to such a programme remain to be determined.

Reference List


Systematic review of laparoscopic versus open colonic resection within a fast track perioperative care programme

MS Vlug
J Wind
DT Ubbink
HA Cense
E van der Zaag
WA Bemelman

Submitted
Abstract

Introduction
Fast track perioperative care programmes accelerate recovery, reduce morbidity and shorten hospital stay. It is unclear what the effects are of laparoscopic and open surgery within a fast track perioperative care programme. Aim of this systematic review was to review the existing evidence.

Methods
A systematic review was performed of all randomised (RCTs) and controlled clinical trials (CCTs) on laparoscopic and open surgery within a fast track perioperative care programme. Main endpoints were primary and overall hospital stay, readmission rate, morbidity and mortality. Study selection, quality assessment and data extraction were performed independently by two observers.

Results
Only two RCTs and three CCTs were eligible for final analysis, which reported on 400 patients. Data could not be pooled because of clinical heterogeneity. Two studies stated a shorter primary hospital stay in the laparoscopic group of two and three days. In one study the readmission rate was lower in the laparoscopic group, the absolute risk reduction was 21.4% (95% confidence interval [CI]: 6% to 42.3%) and a “number needed to treat” (NNT) of 4.7 patients. One study showed a 23 % difference in favour of the laparoscopic group with regard to morbidity (95% CI: 6.3% to 39.1%), i.e. a NNT of 4.4 patients. There were no significant differences in mortality rates.

Conclusion
Due to the present lack of data, no robust conclusions can be made. A large randomised controlled trial is required to compare laparoscopic with open surgery within a fast track perioperative care setting.
Introduction

A recent development in elective large bowel surgery is the introduction of enhanced recovery programmes after surgery (ERAS®)1,2, also referred to as fast track perioperative care. It combines a number of elements aiming at a faster recovery after surgery and to reduce the surgical stress response.3-12 This multidisciplinary protocol is developed by Kehlet et al. for all patients undergoing elective segmental colectomy enabling a faster recovery resulting in an earlier discharge as compared to traditional care.4-6;9-11 Furthermore, postoperative morbidity might be reduced in a fast track perioperative care setting.5-7;9;13;14 The essence of fast track perioperative care consists of extensive preoperative counselling, no bowel preparation, no sedative premedication, carbohydrate loaded liquids until two hours before surgery, thoracic epidural anaesthesia, short acting anaesthetics, perioperative intravenous fluid restriction, small incisions, and no routine use of drains and nasogastric tubes. Postoperative care includes non-opioid pain management, early oral feeding, enforced mobilisation, early removal of bladder catheter and standard laxative.1-12;15

Laparoscopic surgery was first described in 1991 and is still increasingly popular.16 Advantages of laparoscopic surgery are a reduced hospital stay of about four to eight days17-22, less morbidity and less postoperative pain.17;21-26 After open colorectal surgery postoperative hospital stay is about six to 11 days.17-22 It is unclear what the difference is in hospital stay and clinical endpoints between laparoscopic and open surgery in a fast track perioperative care programme. The aim of this systematic review was to appreciate the existing high-level evidence on these differences.

Methods

Data search
Medline database (from January 1950 to August 2007), EMBASE and the Cochrane Library (both from January 1980 to August 2007) were searched for randomised controlled trials (RCTs) or controlled clinical trials (CCTs) with a prospective intervention group comparing laparoscopic surgery with open surgery within an enhanced recovery programme, using the following MeSH (Medical Subject Headings) terms and free text words; fast track, enhanced recovery, ERAS, laparoscopy, laparoscopic, minimally invasive, surgery, laparotomy, open, colon, colonic, colorectal or rectal.

Electronic links to related articles and references of selected articles were hand-searched as well. Leading investigators in the field were contacted to inquire whether studies were ongoing or publications were recently submitted. A hand-search of relevant journals and conference proceedings was not performed. No language restriction was applied.
Study selection, quality assessment and data extraction

From the potentially eligible studies, two investigators (JW, MSV) independently selected suitable studies on the basis of their titles and abstracts. Studies were included if they reported the following primary endpoints: age, gender, American Society of Anaesthesiologists (ASA) classification, type of resection, primary (PHS) and/or overall hospital stay (OHS), readmission rate, morbidity, mortality, and whether at least four fast track elements were used in a standardised protocol. If an eligible study did not specify at least one of these endpoints, it was excluded. The arbitrary number of four fast track elements was chosen because fewer elements might represent ‘modern’ traditional care. Secondary endpoints were: quality of life, gastrointestinal function, and the use of pain medication.

In case of disagreement, full papers were obtained for final judgement. Discrepancies were resolved by discussion. Final inclusion was done after consensus was reached. The remaining trials were critically appraised using the standard checklist from the Dutch Cochrane Collaboration. Subsequently, study data on the predefined endpoints were extracted, again independently by the two investigators.

Data analysis

Primary hospital stay (PHS) is expressed as a median value and inter-quartile range (IQR) or range for each surgical treatment group, calculated from the date of operation to the date of discharge. Overall hospital stay (OHS) was defined as PHS including the hospitalisation period of patients readmitted within 30 days of surgery. Readmission rate, morbidity and mortality are presented as a percentage of the included patients in each surgical treatment group. Morbidity was defined as the reported major and/or minor morbidity rates within 30 days after surgery. The authors of the papers included, were asked to send the median, inter-quartile range, and range of their PHS and OHS for proper statistical analysis. For dichotomous outcomes (readmission, morbidity, and mortality) the Absolute Risk Reduction (ARR), Number Needed to Treat (NNT) and 95% confidence intervals (CIs) were calculated. In the absence of clinical heterogeneity a meta-analysis was attempted.

Results

Included studies

The search identified 178 publications of which 171 were excluded, because those studies did not match the criteria for inclusion. From the seven selected studies, two studies were excluded because all data was used in one of the other selected studies. Of the three studies reporting on the same data, the study by Junghans et al. was included in the final analysis, because both other studies reported on smaller sample sizes. Five studies remained for final analysis, comprising of two RCTs and three CCTs. The selection process of the studies included is summarised in Figure 1.
The included studies were published between 2004 and 2008 and reported on a total of 400 patients, ranging from 55 to 147 patients per study. In Table 1 overall quality assessment is presented. Patient characteristics and results of the included studies are shown in Table 2. The individual data could not be pooled because of clinical heterogeneity among the studies, for instance different inclusion criteria and different surgical procedures. Hence, only individual study results are presented.

**Methodological quality of the studies**

Two studies, by Basse *et al.*[^28] and King *et al.*[^30], were RCTs. The others by Mackay *et al.*[^31], Junghans *et al.*[^29] and Polle *et al.*[^32] were CCTs. The five studies had several limitations.[^28-32] All had relatively small sample sizes. One of the two RCTs did not describe how randomisation was performed.[^28] Hence, allocation concealment was unclear. Only the study by Basse *et al.* was double-blinded, *i.e.* for both patients and data assessors.[^28] The included patients had an opaque dressing covering their whole abdomen, which was applied after surgery and was not removed until the decision about discharge had been taken. In the other studies the non-blinded study design and data collection may have caused observer bias, which theoretically could have been in favour of the laparoscopic group. In the study by Basse *et al.* the non-trial treatment differed between the groups.[^28] Patients in the open group received an additional epidural dose of morphine. Only three studies applied well-defined discharge criteria, which is of major importance as hospital stay is one of |

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[^28]: Basse et al.
[^29]: Junghans et al.
[^30]: King et al.
[^31]: Mackay et al.
[^32]: Polle et al.
the outcome parameters. The analysis of Polle et al.\textsuperscript{32} was a subgroup analysis. In this study patients were included who underwent an elective open or laparoscopic segmental colorectal resection within an enhanced recovery programme or traditional care setting. The investigators mainly focused on the difficulties implementing fast track surgery.

Table 1. Quality assessment

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Study design</th>
<th>Concealment of allocation</th>
<th>Intention to treat</th>
<th>Blinding and data collection</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCTs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basse et al.\textsuperscript{28}</td>
<td>2005</td>
<td>RCT</td>
<td>Unclear</td>
<td>Yes</td>
<td>Patient: yes, Physician: no, Observer: yes</td>
</tr>
<tr>
<td>King et al.\textsuperscript{30}</td>
<td>2005</td>
<td>RCT</td>
<td>Yes</td>
<td>Yes</td>
<td>Not blinded</td>
</tr>
<tr>
<td>CCTs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MacKay et al.\textsuperscript{31}</td>
<td>2006</td>
<td>CCT Both groups prospective</td>
<td>No</td>
<td>Yes</td>
<td>Not blinded</td>
</tr>
<tr>
<td>Junghans et al.\textsuperscript{29}</td>
<td>2006</td>
<td>CCT Both groups prospective</td>
<td>No</td>
<td>Yes</td>
<td>Not blinded</td>
</tr>
<tr>
<td>Polle et al.\textsuperscript{32}</td>
<td>2008</td>
<td>CCT Both groups prospective</td>
<td>No</td>
<td>Yes</td>
<td>Not blinded</td>
</tr>
</tbody>
</table>

Open: Open surgery; Lap: Laparoscopic surgery; RCT: Randomised Controlled Trial; CCT: Controlled Clinical Trial

Table 2. Demographics, patient characteristics, and results of the included studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>N Lap / Open</th>
<th>Age (years) Lap / Open</th>
<th>% ASA I&amp;II Lap / Open</th>
<th>Type of surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCTs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basse et al.\textsuperscript{28}</td>
<td>30 / 30</td>
<td>75.5 / 75</td>
<td>83 / 63</td>
<td>RH, SR</td>
</tr>
<tr>
<td>King et al.\textsuperscript{30}</td>
<td>41 / 19</td>
<td>72.3 / 70.4 (mean)</td>
<td>78 / 84</td>
<td>LH, RH, SR, AR, APR</td>
</tr>
<tr>
<td>CCTs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MacKay et al.\textsuperscript{31}</td>
<td>21 / 57</td>
<td>72.0 / 73.2</td>
<td>77 / 74</td>
<td>LH, RH, AR, HC</td>
</tr>
<tr>
<td>Junghans et al.\textsuperscript{29}</td>
<td>100 / 47</td>
<td>65 / 67</td>
<td>67 / 51.1</td>
<td>SR, RR</td>
</tr>
<tr>
<td>Polle et al.\textsuperscript{32}</td>
<td>29 / 26</td>
<td>46.4 / 50.4</td>
<td>100 / 100</td>
<td>SC, IR</td>
</tr>
</tbody>
</table>

* p<0.05; NR: Not Reported; Continuous data: median (IQR or range); LH: Left Hemicolectomy; RH: Right Hemicolectomy; SC: Subtotal Colectomy; SR: Sigmoid Resection; RR Rectal Resection; IR: Ileocolic Resection; AR: Anterior Resection; APR: AbdominoPerineal Resection; HC: Hartmann Closure; ASA: American Society of Anaesthesiologists
### Comparability at baseline

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Complete follow-up</th>
<th>Similar non-trial treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>30 days</td>
<td>100 %</td>
</tr>
<tr>
<td>Yes</td>
<td>3 months</td>
<td>100 %</td>
</tr>
<tr>
<td>Yes</td>
<td>3 months</td>
<td>88 %</td>
</tr>
<tr>
<td>Yes</td>
<td>30 days</td>
<td>100 %</td>
</tr>
<tr>
<td>Yes</td>
<td>30 days</td>
<td>100 %</td>
</tr>
</tbody>
</table>

### Table

<table>
<thead>
<tr>
<th>PHS (days)</th>
<th>OHS (days)</th>
<th>Readmissions % (n)</th>
<th>Morbidity % (n)</th>
<th>Mortality % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lap / Open</td>
<td>Lap / Open</td>
<td>Lap / Open</td>
<td>Lap / Open</td>
<td>Lap / Open</td>
</tr>
<tr>
<td>2 (range 2-20) / 2 (range 2-5)</td>
<td>2 (NR) / 2 (NR)</td>
<td>20 (6) / 26.6 (8)</td>
<td>26.6 (8) / 20 (6)</td>
<td>0 / 10 (3)</td>
</tr>
<tr>
<td>5 (IQR 3-6) / 8 (IQR 5-9.25)*</td>
<td>6 (IQR 3-11) / 8.5 (IQR 6-12.5)*</td>
<td>4.6 (2) / 26.3 (5)*</td>
<td>14.9 (6) / 26.3 (5)</td>
<td>2.4 (1) / 5.3 (1)</td>
</tr>
<tr>
<td>6 (IQR 5-9) / 6 (IQR 5-10)</td>
<td>NR</td>
<td>0 / 3.4(2)</td>
<td>27.2 (6) / 22.4 (13)</td>
<td>4.5 (1) / 1.7 (1)</td>
</tr>
<tr>
<td>4 (range 3-123) / 6 (range 3-79)*</td>
<td>NR</td>
<td>NR</td>
<td>22 (22) / 44.7 (21)*</td>
<td>0 / 0</td>
</tr>
<tr>
<td>4 (IQR 3-5.5) / 4.5 (IQR 4-8.25)</td>
<td>4 (IQR 3-6.5) / 5 (IQR 4-10.25)</td>
<td>10.3 (3) / 11.5 (3)</td>
<td>31.0 (9) / 23.1 (6)</td>
<td>0 / 0</td>
</tr>
</tbody>
</table>
Primary outcome parameters

Primary and overall hospital stay
All five studies reported on PHS.28-32 One RCT30 and one CCT29 reported a shorter PHS after laparoscopy. The randomised trial of King et al. showed a significant difference in PHS of three days. The PHS was five (IQR 3-6) days in the laparoscopic surgery group versus eight (IQR 5-9.25) days in the open surgery group (Table 2).30 In the study by Junghans et al. the authors reported a PHS of four (range 3-123) days in the laparoscopic group versus six (range 3-79) days in the open group.29 Overall the PHS varied widely between the studies. The largest difference was seen between the RCT of Basse et al.28 and the CCT of MacKay et al.31 Basse et al. reported a PHS of two (range 2-20) days in the laparoscopic group and two (range 2-5) days in the open group.28 MacKay et al. reported a PHS of six (IQR 5-9) days in the laparoscopic group and six (IQR 5-10) days in the open group.31 Overall hospital stay was reported in three studies.28;30;32 Only the RCT of King et al. showed a significant shorter OHS in the laparoscopic group; six (IQR 3-11) days versus 8.5 (IQR 6-12.5) days.30

Readmission rate
Readmission rates were reported in four studies.28;30-32 A large variation was observed in readmission rates among the studies (Table 2). Concerning the laparoscopic surgery group, the highest readmission rate of 20% was reported by Basse et al.28 and the lowest (0%) was reported by MacKay et al.31 With respect to the open surgery group the same two studies reported the highest (26.6%) and lowest (3.4%) readmission rates, respectively. MacKay et al. who readmitted the lowest number of patients reported the longest PHS; six days in both treatment groups.31 In the study by King et al. the readmission rate was significantly lower in the laparoscopic group; ARR of 21% (95% CI: 0.6% to 42.3%), resulting in a NNT of 4.7 patients.30 The other studies did not show a significant difference in readmission rates between the two surgical techniques.

Morbidity and mortality
Morbidity rates were reported in all studies. Only in the study by Junghans et al. a 23% difference in favour of the laparoscopic group was shown (95% CI: 6.3% to 39.1%), i.e. a NNT of 4.4 patients.29 In the included studies, there were no significant differences between the treatment groups with regard to mortality (Table 3).

Number of fast track items
The application of the 17 fast track perioperative care elements varied among the studies (Table 4). The median number of fast track elements that was applied in the five studies was 13 (IQR 11.5-14.5). Preoperative counselling, fluid restriction, no routine use of nasogastric tubes, enforced postoperative oral feeding/mobilisation, and early removal of the bladder...
catheter was required by protocol in all studies. Other fast track care elements, such as the omission of bowel preparation and no premedication, were less frequently executed.

Table 3. Numbers needed to treat (NNT) and absolute reduced risk (ARR) with corresponding 95% confidence intervals

<table>
<thead>
<tr>
<th>Reference</th>
<th>Readmissions</th>
<th>Morbidity</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RCTs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basse et al.</td>
<td>NNT 15.0</td>
<td>NNT -15.0</td>
<td>NNT 10</td>
</tr>
<tr>
<td></td>
<td>ARR 0.067 (-0.147 - 0.280)</td>
<td>ARR -0.067 (-0.280 - 0.147)</td>
<td>ARR 0.100 (-0.007 - 0.207)</td>
</tr>
<tr>
<td>King et al.</td>
<td>NNT 4.7</td>
<td>NNT 8.5</td>
<td>NNT 35.5</td>
</tr>
<tr>
<td></td>
<td>ARR 0.214 (0.006 - 0.423)</td>
<td>ARR 0.117 (-0.109 - 0.342)</td>
<td>ARR 0.028 (-0.083 - 0.139)</td>
</tr>
<tr>
<td><strong>CCTs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MacKay et al.</td>
<td>NNT 28.5</td>
<td>NNT -17.3</td>
<td>NNT -33.2</td>
</tr>
<tr>
<td></td>
<td>ARR 0.035 (-0.013 - 0.083)</td>
<td>ARR -0.058 (-0.279 - 0.164)</td>
<td>ARR -0.030 (-0.127 - 0.067)</td>
</tr>
<tr>
<td>Junghans et al.</td>
<td>NR</td>
<td>NNT 4.4</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>ARR 0.227 (0.063 - 0.391)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polle et al.</td>
<td>NNT 84.0</td>
<td>NNT -12.5</td>
<td>NP</td>
</tr>
<tr>
<td></td>
<td>ARR 0.012 (-0.153 - 0.177)</td>
<td>ARR -0.080 (-0.313 - 0.154)</td>
<td></td>
</tr>
</tbody>
</table>

NP: not possible to calculate due to lack of data or zero in both groups; NR: not reported

**Secondary outcome parameters**

**Quality of life**
In the study by King et al.\(^\text{30}\) and MacKay et al.\(^\text{31}\) quality of life after surgery was evaluated. Neither of these studies showed a statistical difference between the treatment groups. King et al. did report that quality of life in both groups deteriorated two weeks after surgery, but improved in both groups after six weeks. \(^\text{30}\)

**Gastrointestinal function**
Three studies reported on gastrointestinal function.\(^\text{28,29,31}\) Basse et al.\(^\text{28}\) and MacKay et al.\(^\text{31}\) did not find any significant difference between the treatment groups regarding nausea scores. Median time to first defecation was two days in both groups in the study of Basse et al.\(^\text{28}\) In the study of Junghans et al. the median time to first defecation was one (range 0-6) day postoperatively in the laparoscopic group versus two (range 0-6) days in the open group.\(^\text{29}\) This difference was reported as significant. In the study by MacKay et al. median times to first flatus and first defecation were similar between the treatment groups.\(^\text{31}\)
Table 4. Summary of outcomes and fast track items presented in the included trials

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Mortality</th>
<th>Morbidity</th>
<th>Readmissions</th>
<th>Preoperative counselling</th>
<th>Total Hospital Stay</th>
<th>Minimum of 30 days follow-up</th>
<th>Preoperative feeding</th>
<th>No bowel preparation</th>
<th>Fluid restriction</th>
<th>Active prevention of hypothermia</th>
<th>Epidural analgesia</th>
<th>Minimal invasive / transverse incisions</th>
<th>No routine use of NG tubes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basse et al.</td>
<td>60</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
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<td>√</td>
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</tr>
<tr>
<td>King et al.</td>
<td>62</td>
<td>√</td>
<td>√</td>
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<td>√</td>
<td>√</td>
<td>√</td>
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<td>MacKay et al.</td>
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<td>Junghans et al.</td>
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<td>Polle et al.</td>
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√: Adequately described/Present; -: Not Present/ Not studied; ∼: Not adequately described/ partially present

**Pain medication**

In the study by King et al., significantly more patients required additional opioid analgesics in the open group; ARR of 52% (95% CI: 28.2% to 75.2%) and NNT of 1.9 patients. There were no significant differences reported in use of morphine, paracetamol and tramadol between the groups in the study by MacKay et al.

**Discussion**

This review might suggest a minimal superiority of laparoscopic surgery within a fast track perioperative care setting with respect to hospital stay, readmission rates, and morbidity. However, the available evidence is scarce due to a lack of good quality trials. Of the two RCTs included in this review, only one showed a significantly lower primary and overall postoperative hospital stay in the laparoscopic group. The differences
between the two included RCTs in PHS and OHS were considerable.\(^{28,30}\) There are several possible explanations. In the study of King \textit{et al.} only patients with diagnosed colorectal carcinoma were included.\(^{30}\) Basse \textit{et al.} included patients with benign as well as malignant conditions.\(^{28}\) The condition of the patients in the study of King \textit{et al.}\(^{30}\) could therefore be worse resulting in a longer postoperative recovery period. Furthermore, patients requiring a rectal resection or not living independently were excluded in the study of Basse \textit{et al.}\(^{28}\), but were included by King \textit{et al.}\(^{30}\) In the university hospital of Basse \textit{et al.} fast track surgery has been developed. Therefore, the results of their programme are likely to be most favourable.\(^{28}\) Basse \textit{et al.} demonstrated that a postoperative hospital stay of two to three days after colonic surgery can be achieved both after laparoscopic and open colectomy if performed in a fast track perioperative care setting. However, these results were achieved at the expense of readmission rates up to 26.6%.\(^{28}\) Basse \textit{et al.} showed a remarkable high mortality rate in the open group of 10%. This can be explained by the higher ASA scores in that group.\(^{28}\) The study of King \textit{et al.} was not blinded.\(^{30}\) It is unclear how this affects hospital stay. On the one hand an observer bias favouring the laparoscopic group, could have influenced the
results of the study of King et al. reporting a significantly worse PHS, OHS, and readmission rate in the open group. On the other hand, blinding with large bandages might give the patient the impression they had open surgery hampering recovery and discharge.

In the three CCTs included in the present review, one study demonstrated a significantly shorter PHS in the laparoscopic group. However, in this study almost half of the patients in the open group had an ASA score of III or IV and more patients in this group were operated because of a carcinoma. In the laparoscopic group, 33% of the patients had an ASA score of III or IV and only 41% had a carcinoma. This might be an explanation for the longer PHS and higher morbidity in the open group. In the study by Polle et al. only patients with an ASA score of I and II were included.

Morbidity was around 20 to 30% in four studies. Junghans et al. reported a 23% reduction in morbidity in the laparoscopic group, but their morbidity of 44.7% in the open group is very high. However, it was not clear whether patients with more than one complication were counted twice resulting in this high morbidity rate. A readmission rate of 0% in the laparoscopic group and 3.4% in the open group in the study by MacKay et al. suggests that a longer hospital stay, reduces the number of readmissions. Recently, Kehlet’s group confirmed this relation between hospital stay and readmissions. They achieved lower readmission rates when hospital stay was prolonged with one day. The longer hospital stay in the study of MacKay et al. may be caused by their use of patient-controlled analgesia instead of epidural analgesia.

Allocation bias could have influenced the results in favour of laparoscopic surgery in the three CCTs by MacKay et al., Polle et al. and Junghans et al., because the surgeon decided which patient would undergo laparoscopic or open surgery.

This systematic review was limited by a low number of studies. All studies had small sample sizes and only one study used a proper sample size calculation. Overall quality of the selected studies was found to be moderate. Of the five included studies, three studies were CCTs, which increases the probability that bias occurs. Due to clinical heterogeneity the data could not be pooled. Mean differences and 95% CIs could not be calculated as data were not normally distributed.

Fast track perioperative care programmes in colonic surgery have been introduced more than ten years ago. In the included studies the number of applied fast track elements in the protocol were reported, but only one study, Polle et al. reported the number of elements actually achieved. In this study 15 fast track elements were applied and 13 elements were evaluated. An average of 7.4 of the elevated elements were successfully achieved per patient. Nevertheless, despite this relatively low protocol compliance a significantly faster recovery of the fast track group resulted in a shorter hospital stay. It is clear that a full implementation of all fast track perioperative care elements encompassing the fast track protocol requires a learning curve and a dedicated multidisciplinary functioning team. Although there is evidence about most elements of the programme, it seems hard to implement all different elements of fast track care as every discipline has to break with long-standing traditions.

In conclusion, the presently available evidence does not allow a robust conclusion on
the outcomes of laparoscopic versus open surgery within a fast track perioperative care setting. Only five studies were available for analysis. So, the question remains whether fast track or modern traditional care, laparoscopic or open surgery, or a combination of both is the preferred strategy. This research question is the objective of the LAFA study, compromising over 400 patients, that will hopefully provide the answer to this question in the middle of 2009.36

Reference List


Perioperative strategy in colonic surgery; LAparoscopy and/or FAst track multimodal management versus standard care (LAFA trial)
- design and rationale of a randomised controlled multicentre trial -

J Wind
WA Bemelman
On behalf of the LAFA study group

BMC Surgery 2006 29;6:16
Abstract

Introduction
Recent developments in large bowel surgery are the introduction of laparoscopic surgery and the implementation of multimodal fast track recovery programmes. Both focus on a faster recovery and shorter hospital stay. The randomised controlled multicentre LAFA-trial (LAparoscopy and/or FAst track multimodal management versus standard care) was conceived 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.

Methods
The LAFA-trial is a double blinded, multicentre trial with a two by two balanced factorial design. Patients eligible for segmental colectomy for malignant colorectal disease i.e. right and left colectomy and anterior resection will be randomised to either open or laparoscopic colectomy, and to either standard care or the fast track perioperative care programme. This factorial design produces four treatment groups; open colectomy with standard care (a), open colectomy with the fast track programme (b), laparoscopic colectomy with standard care (c), and laparoscopic surgery with the fast track programme (d). Primary outcome parameter is postoperative hospital length of stay including readmission within 30 days. Secondary outcome parameters are quality of life two and four weeks after surgery, overall hospital costs, morbidity, patient satisfaction and readmission rate.

Based on a mean postoperative hospital stay of 9 +/- 2.5 days a group size of 400 patients (100 each arm) can reliably detect a minimum difference of one day between the four arms (alfa = 0.95, beta = 0.8). With 100 patients in each arm a difference of 10% in subscales of the Short Form 36 (SF-36) questionnaire and social functioning can be detected.

Conclusions
The LAFA-trial is a randomised controlled multicentre trial that will provide evidence on the merits of fast track perioperative care and laparoscopic colorectal surgery in patients having segmental colectomy for malignant disease (ISRCTN:79588422).
Introduction

Recent developments in large bowel surgery are the introduction of laparoscopic surgery and the implementation of multimodal fast track perioperative care programmes. Both focus on enhanced recovery and shorter hospital stay as compared to open surgery and traditional care. Laparoscopic colectomy was first described in 1991. Since then a lot of effort has been made to establish its feasibility and safety particularly in laparoscopic colectomy for cancer. Recently, several randomised trials comparing laparoscopic with open colectomy indicated that laparoscopic surgery can be applied safely both for malignant and benign diseases. Several systematic reviews that assessed the evidence on the laparoscopic approach for colorectal cancer reported that laparoscopic surgery, in a traditional perioperative care setting was associated with less morbidity, less postoperative pain, earlier recovery and shorter hospital stay. Furthermore, 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 were comparable between laparoscopic and open surgery. These results stimulated many surgeons in the Netherlands to set up a laparoscopic colorectal programme.

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®), which essentially is a modification of the programme initially developed by the Danish surgeon Henrik Kehlet. This multimodal programme, involving optimisation of several aspects of the perioperative management of patients undergoing colectomy, enables patients to recover earlier and therefore go home as early as three days after open colectomy. Furthermore, postoperative morbidity was reduced. The essence of a fast track perioperative care programme consists of extensive preoperative counselling, no bowel preparation, no sedative premedication, no preoperative fasting but carbohydrate loaded liquids until two hours prior to surgery, tailored anaesthesiology encompassing thoracic epidural anaesthesia and short acting anaesthetics, perioperative intravenous fluid restriction, minimally invasive surgery (i.e. through small incisions or laparoscopy), non-opioid pain management, no routine use of drains and nasogastric tubes, early removal of bladder catheter, standard laxatives and prokinetics, and early and enhanced postoperative feeding and mobilisation.

As these new developments have been introduced in clinical practice, time has come to evaluate their feasibility, safety, and cost-effectiveness in large bowel surgery in a randomised controlled setting. It can be hypothesized that fast track and/or laparoscopy are associated with less attenuation of the patient’s condition after surgery resulting in a shorter postoperative hospital stay, a faster recovery to full activity at home, and a better quality of life.

Since it has not been established which combination of perioperative management and surgical approach i.e. standard care, fast track care, laparoscopic surgery or open surgery is best in terms of postoperative hospital stay, quality of life, postoperative morbidity,
Methods

Study objectives
The objective of this study is 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 undergoing segmental colectomy for malignant disease. The objective is subdivided in three research questions; first, how laparoscopic surgery compares to open surgery in terms of hospital stay, quality of life and costs? Second, how fast track perioperative care compares to standard care in terms of hospital stay, quality of life, and costs? Finally, what is the added benefit of the fast track perioperative care programme in laparoscopic surgery in terms of hospital stay, quality of life and costs?

Study design
The LAFA-trial is a randomised multicentre trial, designed as a two by two balanced factorial design. Patients are blinded for the type of intervention i.e. laparoscopic or open surgery. Patients eligible for segmental colectomy, for malignant colorectal disease i.e. right and left colectomy and anterior resection will be randomised to either open or laparoscopic colectomy, and to either standard care or the fast track programme. This factorial design results in four treatment groups; open colectomy with standard care (a), open colectomy with fast track perioperative care (b), laparoscopic colectomy with standard care (c), and laparoscopic surgery with fast track perioperative care (d) (see Figure 1). Randomisation is performed by an Internet randomisation module. Block-randomisation is used and the randomisation is stratified for the randomising centres.

Primary and secondary endpoints
The primary endpoint of the LAFA-study is total postoperative hospital stay in days, including hospital stay of patients who are readmitted within 30 days after surgery. Secondary endpoints are quality of life at two and four weeks after surgery. Quality of life will be measured by two validated questionnaires; Short Form 36 (SF-36) and the Gastro-Intestinal Quality of Life Index (GIQLI). Further secondary endpoints are; medical and non medical costs, morbidity, and mortality within 30 days after surgery, patient satisfaction measured by standardised questionnaires, and readmission rate.

Participating centres
Nine Dutch hospitals of the LAFA-study group, including three academic centres and four non-academic centres, will enroll patients.
Study population
The study population consists of patients eligible for segmental colectomy for malignant colorectal disease, i.e. right and left colectomy and anterior resection. Inclusion criteria are; age between 40 and 80 years, colorectal cancer including colon and recto-sigmoid cancers, ASA I-III, and informed consent. Exclusion criteria are; prior midline laparotomy, ASA IV, laparoscopic surgeon not available, emergency surgery and a planned stoma.
Ethics
This study is conducted in accordance with the principles of the Declaration of Helsinki
and ‘good clinical practice’ guidelines. The independent medical ethics committees of the
participating hospitals have approved the study protocol. Prior to randomisation, written
informed consent will be obtained from all patients.

Study outline
Informed consent will be obtained at the outpatient department if the patient fulfils the
inclusion and exclusion criteria. Randomisation is performed instantly through the study
website.

The randomisation produces four treatment groups; open colectomy with standard care (a),
open colectomy with fast track perioperative care (b), laparoscopic colectomy with standard
care (c), and laparoscopic surgery with fast track perioperative care (d) (see Figure 1).
Patients that are randomised to fast track perioperative care will be informed by a
“fast track” trial nurse and by the anaesthesiologist about the essence of the fast track
programme. Appointments for these consultations will be made after consulting the
surgeon and randomisation has been done. All patients randomised to have a fast track
perioperative treatment will be admitted to a separate “fast track” ward, where the nurses
and medical staff are trained in fast track perioperative management.
Patients who will receive standard treatment are not counselled by the fast track nurse
and will have a standard preassessment by the anaesthesiologist.
Patient and medical staff will be blinded for the surgical approach until the day of discharge
by applying a covering abdominal bandage.

Surgery
Both open and laparoscopic surgery is done according to the technique applied by the
local surgeon. Antibiotic prophylaxis is done according to hospital protocol. All patients
will have two enemas before surgery (evening before and morning before). After surgery
the surgical wounds are covered with an abdominal dressing in order to blind the medical
staff for the type of approach. A requirement for the participating laparoscopic surgeons
to perform laparoscopic colectomy for cancer is a minimum of 20 laparoscopic colectomies
for benign disease as indicated by the proclamation of the American Society of the Colon
and Rectum Surgeons in 2004.20,21

Fast track and standard care
Comparison of the different strategies is only possible when a fast track programme
is running sufficiently and patients are nursed separately depending on the results of
randomisation either on a standard care or fast track ward in order to avoid a bias towards
fast track treatment by the nursing and medical staff. Patients that have standard care
cannot be nursed by nurses that have experience with fast track care. Fast track multimodal
management is done according to the protocol summarized in Table 1.
Table 1. Differences between fast-track and traditional care protocol

<table>
<thead>
<tr>
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<th>Fast-track Care</th>
<th>Traditional Care</th>
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<tbody>
<tr>
<td><strong>Pre-operative phase</strong></td>
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</table>
| Outpatient department of Surgery | - Scheduling of operation  
- Information about FT  
- Informed consent | - Scheduling of operation  
- Pre-assessment for risk adjustment |
| Outpatient department of anaesthesiology | - Pre-assessment for risk adjustment  
- Discussion focusing on placement of thoracic epidural catheter for management of perioperative analgesia | - Open discussion about different possibilities for management of perioperative analgesia (i.e. placement of epidural catheter on any level, patient controlled analgesia with morphine (PCA-morphine) or continuous IV morphine infusion |
| Pre-admission guided tour on surgical ward | - Yes  
- No tour |                                                                                  |
| **Day of admission** |                                                                                  |                                                                                  |
| Pre-operative fasting | - Last meal 6 h before operation  
- Last clear drink (CHL) 2h before operation | - Last meal until midnight  
- No oral intake at the day of surgery |
| Pre-anaesthetic medication | - Lorazepam, 1 mg the evening before operation if necessary  
- No sedative medication at the day of operation | - Lorazepam, 1 mg or temazepam 10 or 20 mg the evening before operation  
- Lorazepam 1mg, temazepam 10 or 20 mg, or midazolam 7.5 mg at the day of operation |
| **Day of Surgery** |                                                                                  |                                                                                  |
| Anaesthetic management | - Placement of thoracic epidural catheter (T6-T10, depending on the surgical resection); test-dose (bupivacaine 0.25% with adrenaline 1:200,000), top-up dose (bupivacaine 0.25% [±10 ml] with sufentanil 25 μg, followed by continuous infusion (bupivacaine 0.125% with fentanyl 2.5 μg.ml-1) until day 2 postoperative  
- Combined with balanced general anaesthesia  
- Restricted per-operative fluid infusion regime (Ringers lactate 20 ml.kg-1 in the 1st h followed by RL 6 ml.kg-1.h-1)  
- Use of vasopressor drugs as 1st choice for management of mean blood pressure drop > 20% of baseline | - IV morphine loading (0.1 mg.kg-1) followed by continuous IV morphine infusion or PCA-morphine, OR placement of epidural catheter (T10-L1, test dose, top-up dose and continuous infusion in the same way as for fast track) when an open surgical procedure will be performed  
- IV morphine loading (0.05-0.1 mg.kg-1) followed by PCA-morphine or continuous IV morphine infusion when a laparoscopic surgical procedure is performed  
- Combined with balanced general anaesthesia  
- Standard per-operative fluid infusion regime (Ringers lactate 20 ml.kg-1 in the 1st h followed by RL 10-12 ml.kg-1.h-1)  
- Use of extra fluid challenge as 1st choice for management of mean blood pressure drop > 20% below baseline |
<table>
<thead>
<tr>
<th>Surgical Management</th>
<th>Early post-operative management</th>
<th>Day 1 after Surgery</th>
<th>Day 2 after surgery</th>
<th>Day 3 after surgery</th>
<th>Day 4 after surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Forced body heating (Bair hugger system and warmed IV fluids)</td>
<td>- Minimal invasive incisions</td>
<td>- Oral intake &gt; 2 l (including 4 units CHL drinks), offer solid food</td>
<td>- Offer solid food</td>
<td>- Remove epidural catheter</td>
<td>- Continue as on day 3 until discharge criteria are fulfilled</td>
</tr>
<tr>
<td>- Forced body heating (Bair hugger system and warmed IV fluids)</td>
<td>- Supra-pubic urine catheter</td>
<td>- Stop IV fluid administration (leave cannula)</td>
<td>- Expand mobilisation (&gt; 8 hours)</td>
<td>- Continue Paracetamol 4x 1000 mg</td>
<td>- Continue as on day 1 until discharge criteria are fulfilled</td>
</tr>
<tr>
<td>- Removal of naso-gastric tube before extubation</td>
<td>- Infiltration of surgical wounds with bupivacaine</td>
<td>- Start laxative (MgO, 2 x 1g.d-1)</td>
<td>- Plan discharge</td>
<td>- NSAID</td>
<td>- Continue as on day 1 until discharge criteria are fulfilled</td>
</tr>
<tr>
<td>- Prophylactic use of odansetron (4 mg) to prevent PONV</td>
<td>- First oral drinks at 2 h post-surgery + IV infusion of RL 1.5 l.d-1</td>
<td>- Close supra-pubic urine catheter and remove when residue &lt; 50 ml</td>
<td>- Expand mobilisation (&gt; 6 h out of bed)</td>
<td>- Remove IV cannula</td>
<td>Continue as on day 1 until discharge criteria are fulfilled</td>
</tr>
<tr>
<td>- Naso-gastric tube remain until day 1 after surgery</td>
<td>- Mobilisation in the evening (&gt;2 h out of bed)</td>
<td>- Close supra-pubic urine catheter</td>
<td>- First semi-solid food intake in the evening</td>
<td>- Expand mobilisation (&gt; 8 hours)</td>
<td>Continue as on day 1 until discharge criteria are fulfilled</td>
</tr>
<tr>
<td>- Use of odansetron, dexamethasone or droperidol for PONV management according to attending anaesthesiologist</td>
<td>- Continuous IV morphine infusion or PCA-morphine OR use of epidural catheter as mentioned before to which paracetamol 4 x 1 g.d-1 and/or diclofenac 3 x 50 mg.d-1 are added</td>
<td>- Start laxative (MgO, 2 x 1 g.d-1)</td>
<td>- Evaluating discharge criteria; discharge if fulfilled</td>
<td>- Remove epidural catheter</td>
<td>Continue as on day 1 until discharge criteria are fulfilled</td>
</tr>
<tr>
<td>- Median laparotomy approach</td>
<td>- Standard use of abdominal drains</td>
<td>- Small amount of water orally + IV infusion of RL 2.5 l.d-1</td>
<td>- Diet increased on daily basis when normal bowel sounds are examined</td>
<td>- Continue Paracetamol 4x 1000 mg</td>
<td>- Continue as on day 3 until discharge criteria are fulfilled</td>
</tr>
<tr>
<td>- Urine catheter according to attending surgeon</td>
<td>- Continuous IV morphine infusion or PCA-morphine OR use of epidural catheter as mentioned before to which paracetamol 4 x 1 g.d-1 and/or diclofenac 3 x 50 mg.d-1 are added</td>
<td>- Bed rest</td>
<td>- IV fluid administration (2.5 l.d-1) is continued till adequate oral fluid intake</td>
<td>- Remove IV cannula</td>
<td>- Continue as on day 1 until discharge criteria are fulfilled</td>
</tr>
<tr>
<td>- No infiltration of surgical wounds with local anaesthetic drugs</td>
<td>- No infiltration of surgical wounds with local anaesthetic drugs</td>
<td>- Start laxative (MgO, 2 x 1 g.d-1)</td>
<td>- Start laxative (MgO, 2 x 1 g.d-1)</td>
<td>- Expand mobilisation (&gt; 8 hours)</td>
<td>- Continue as on day 1 until discharge criteria are fulfilled</td>
</tr>
<tr>
<td>FT: Fast-track; TC: Traditional care; CHL: carbohydrate loaded drink (Nutridrink®)</td>
<td>- Small amount of water orally + IV infusion of RL 2.5 l.d-1</td>
<td>- Close supra-pubic urine catheter and remove when residue &lt; 50 ml</td>
<td>- Expand mobilisation (&gt; 6 h out of bed)</td>
<td>- Evaluate discharge criteria; discharge if fulfilled</td>
<td>- Continue as on day 3 until discharge criteria are fulfilled</td>
</tr>
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</table>
**Discharge criteria**

Since hospital stay is a primary efficacy parameter, the discharge criteria are defined. Every postoperative day will be noted whether the discharge criteria are met, and other reasons of prolonged hospital stay e.g. social environment or patient inacceptance. The discharge criteria include adequate pain control with oral analgesics, no nausea, ability to take solid foods, passage of flatus and/or stool, mobilisation and self support as compared to the preoperative level, and acceptance by the patient.

**Statistical analysis**

*Intention to treat*

The analysis will be performed in accordance with the intention to treat principle.

*Sample size calculation*

Since both, fast track care and laparoscopy focus on earlier recovery resulting in a reduction of hospital stay, the latter is used as primary efficacy parameter. The mean postoperative hospital stay for segmental bowel resection with standard care is nine days with a standard deviation of 2.5 days in the Academic Medical Centre Amsterdam. Using a 5% significance level, a total sample size of 400 would have a power of >95% to detect a minimum reduction of one day in hospital stay between laparoscopic surgery and open surgery, a one day reduction in hospital stay between fast track care and standard care, and a power of 80% to detect the same difference between the combination of fast track care with laparoscopic surgery and current treatment.

A much larger difference can be expected between the other treatment groups, for instance open surgery and standard care compared to fast track perioperative care and laparoscopic surgery. In order to obtain results with adequate precision we have calculated group size using a difference of one day rather than the expected 2-4 days. With a group size of one hundred patients per arm it is possible to find a significant difference (alfa=0.05, beta=0.1) of at least 10% in subscales of the SF-36, a validated quality of life questionnaire, at two weeks after surgery.\(^{22-24}\) Liem et al. demonstrated 20-30% differences in subscales of the SF-36 between laparoscopic versus open hernia repair one week after surgery.\(^{24}\) Maartense et al. found a 10% difference in physical and social function two weeks after surgery comparing laparoscopic versus open ileocolic resection in a randomised study from our institution.\(^{25}\)

*Economic evaluation*

The marginal direct medical, non-medical and time cost differences will be calculated for the four treatment strategies. These will include the additional costs of laparoscopy, of fast track care, as well as the differences due to complications and readmissions.
Data collection and monitoring

Data are collected via a secured internet module which is specially designed for the LAFA-study. Data are collected daily until the day of discharge. Preoperatively, and at two and four weeks postoperatively the questionnaires (SF-36 and GIQLI) are filled in by the patient. One month postoperatively, the general practitioner is contacted to inform whether he/she was contacted by the patient for problems related to the operation. There will be regular contact between the study coordinators and the participating centres. One research fellow will monitor the included data of every patient.

Discussion

Fast track programmes in colonic surgery have been introduced more than a decade ago with favourable early results. Many elements of these fast track programmes are based on solid evidence derived from randomised trials and systematic reviews. However, it is quite surprising, that implementation in daily practice has so far stayed behind.26-28 This can partly be explained by the necessity to break with long-standing traditions, such as preoperative fasting, slow postoperative advancement of oral feeding, and delayed mobilisation. In a recent systematic review including six comparative single centre studies, fast track programmes were found to reduce the time spent in the hospital and were found to be safe in major abdominal surgery. However, this systematic review demonstrated that the evidence on fast track colonic surgery was scarce.29 Both, laparoscopic surgery and fast track programmes are costly and require extensive expertise. Laparoscopic surgery is costly due to expensive disposables and additional operating time. Furthermore, a considerable learning curve must be mastered. Only 5-8% of the colectomies are therefore done laparoscopically in the Netherlands. Fast track multimodal perioperative care requires additional personnel trained in several aspects of the fast track programme to make the programme work. It is clear that both, laparoscopic surgery and fast track programmes enhance recovery and thereby reduce hospital stay.2,8,29-32 Shortening hospital stay and reduction of morbidity are attractive, since both increase the availability of beds and might reduce the overall cost of hospital stay. However, despite the current enthusiasm and implementation into daily practice of fast track care and laparoscopic surgery, there are few data available that provide evidence on the optimal combination (laparoscopic or open surgery and fast track or standard care) in terms of shorter hospital stay, reduced morbidity and cost effectiveness. The largest reduction in hospital stay can probably be achieved by a combination of fast track programmes and laparoscopic surgery. However, it is not known what the additional costs of laparoscopic surgery or fast track programmes are compared to the reduction in hospital stay that can be achieved with these programmes. Since the average postoperative hospital stay after segmental colectomy is still considerable in the Netherlands as well as throughout Europe, an enormous improvement can be expected applying fast track
programmes and/or laparoscopy. The relative contribution to the reduction in hospital stay of both methods is unknown. This must be assessed in a setting where patients are blinded for the approach of surgery. The randomised controlled LAFA-trial was conceived 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 undergoing segmental colectomy for malignant disease.

Reference List


Part 2

Complications in colorectal surgery
Chapter 6

Installation of the pneumoperitoneum; technique and complications

J Wind
WA Bemelman

Adapted from:
Handboek Endoscopische Chirurgie, Bohn Stafleu van Loghum, in press
Nederlands Tijdschrift voor Heelkunde 2007;16:429-432
Abstract

A variety of techniques to establish a pneumoperitoneum have been described. Roughly, techniques for the installation of the pneumoperitoneum can be divided in two groups. The first group comprises of introductions performed without direct visual control, the so-called blind-entry techniques. These blind-entries are performed by using a Veress needle to establish the pneumoperitoneum followed by trocar insertion, or less frequently used, direct trocar insertion without previously establishing a pneumoperitoneum. The other group comprises of entry techniques performed with visual control, including the open-entry technique and the closed-entry techniques with optical trocar devices.

For all the entry techniques there is a wide variety of reusable and disposable trocars, and Veress needles designed and marketed with its individual advantages and disadvantages. With respect to complications, approximately one half of all intra-operative laparoscopic complications are caused during the establishment of the pneumoperitoneum and introduction of the trocars. The reported incidence of vascular and bowel injuries varies and is between 0.05 and 0.5 complication per 100 laparoscopic procedures. In literature, it is suggested that the open-entry technique is the safest introduction technique because an overshoot of the introduction, especially those resulting in retroperitoneal vascular injury, can be avoided. However, an open-entry does not preclude bowel injury. In patients who had no history of abdominal surgery the installation of the pneumoperitoneum by using the reusable TrocDoc® trocar (“half open”) might be an effective and less expensive alternative for the traditional open-entry technique according to Hasson. In obese patients an open-entry technique can be technically difficult. For these patients the blind-entry technique with the Veress needle remains a good alternative. Finally, the identification of patients with an increased risk of an entry-related injury is essential for a safe installation of the pneumoperitoneum to prevent injuries.
Introduction

Several randomised controlled trials and meta-analyses have demonstrated that laparoscopic surgery is superior to conventional open surgery in terms of morbidity, postoperative recovery, and hospital stay.\textsuperscript{1-3} Due to these short term advantages, laparoscopic surgery has achieved broad acceptance nowadays and is a fast expanding surgical discipline. However, the initiation of laparoscopic surgery, \textit{i.e.} the creation of a pneumoperitoneum and subsequently the introduction of the surgical instrumentation, 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 during laparoscopic surgery occurs during the installation of the pneumoperitoneum.\textsuperscript{4-6}

Several techniques to establish the pneumoperitoneum have been described. Roughly, entry techniques can be divided in two groups (\textit{Table 1}). The first group comprises of introductions performed without (direct) visual control, the so-called blind-entry techniques, which are performed by using a Veress needle to establish the pneumoperitoneum followed by primary trocar insertion or, less frequently used, direct trocar insertion without previously establishing a pneumoperitoneum. The other group comprises of entry techniques which are performed with visual control. This group includes the open-entry technique and the closed-entry techniques with optical trocar devices. The open-entry technique is performed through a small laparotomy. Successively, skin, rectus fascia, and peritoneum are incised under direct vision, followed by blunt (Hasson's) trocar insertion. Subsequently, the pneumoperitoneum is created. This technique was firstly described by the gynaecologist Harrith Hasson in 1971.\textsuperscript{7} Alternative techniques for the open placement technique are closed-entry techniques with optical trocar devices. The transparent tip of the optical trocar allows a controlled passage of the individual tissue layers of the abdominal wall.\textsuperscript{8}

\textit{Table 1. Overview of entry techniques}

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<tr>
<th>Visually controlled entry techniques</th>
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<td>1.</td>
<td>Open-laparoscopy</td>
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<tr>
<td>2.</td>
<td>Hasson's technique</td>
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<td>3.</td>
<td>TroDoc\textsuperscript{®}</td>
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<td>2.</td>
<td>Closed-entry techniques</td>
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<td>3.</td>
<td>Optiview\textsuperscript{®} (Ethicon)</td>
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<td>4.</td>
<td>Endotip\textsuperscript{®} (Karl Storz)</td>
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<td>5.</td>
<td>Visiport\textsuperscript{®} (Auto-Suture)</td>
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<tr>
<th>Blind-entry techniques</th>
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<tr>
<td>1.</td>
<td>Direct trocar insertion</td>
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<td>2.</td>
<td>Veress needle</td>
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<td>3.</td>
<td>normal pressure (12-15 mmHg)</td>
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<td>4.</td>
<td>high pressure (25-30 mmHg)</td>
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<td>5.</td>
<td>optical Veress needle</td>
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With respect to the prevention of entry-related injuries none of the above mentioned techniques is supported by solid evidence and until today there is an ongoing debate, mainly between gynaecologists favouring the closed-entry technique, and surgeons favouring the open-entry technique, which technique is to be preferred. Many general surgeons suggest that the open-entry technique results in an equal amount of visceral lesions compared to the closed-entry technique, but significantly fewer (retroperitoneal) vascular lesions.

In this chapter several techniques for the establishment of the pneumoperitoneum are described including the instrumentation that is used and the potential complications that can occur.

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Instrumentation

The Veress needle
The pneumonologist Janos Veress introduced a needle for the establishment of a pneumoperitoneum in 1938. This so-called Veress needle has two working parts; an outer needle with a sharp bevelled edge, and an inner, spring-loaded, retractable blunt shaft that extends beyond the end of the needle point. During insertion, the blunt inner part of the needle is pushed inwards resulting in a sharp tipped instrument. As soon as the peritoneum is penetrated, the blunt shaft is propelled forward beyond the sharp tip by the spring-loaded mechanism, thus making the instrument blunt. Theoretically, this mechanism prevents that the sharp tip of the needle reaches the intra-abdominal organs and blood vessels.

Standard lengths of the Veress needle are 10, 12, and 15 centimetres. Veress needles are available in both disposable and reusable systems. Besides the standard Veress needle, optical needles are also available. The outer shaft of the optical Veress needle has a diameter of 2.1 millimetres and a length of 10.5 centimetres. After correct placement of the needle a mini-laparoscope with a diameter of 1.2 millimetre is introduced through the outer shaft. The optical Veress needle can be used in patients with an increased risk of peri-umbilical adhesions. The optical system offers an intra-abdominal visual control during the placement of the primary trocar. A panoramic view on the abdominal cavity and subsequent visualisation of adhesions around the umbilical area can be established after placement of the optical Veress needle at Palmer’s point (left upper quadrant). When adhesions are absent the primary trocar can still be placed at the umbilicus.

Trocars
Trocars are an essential part of the laparoscopic instrumentation. The word “trocar” is originated from the French word “trois quarts”, which is the original name for a knife with three cutting edges. All trocars share the common aim of allowing the passage of surgical instruments into the peritoneal cavity, whilst simultaneously preventing gas leakage. The latter is in general by means of a flapper-valve or rubber membrane mechanism. A wide
variety of reusable and disposable trocars have been designed and marketed for the use of laparoscopic surgery.

Disposable trocars are constructed predominantly of plastic materials. Many disposable trocars have a built-in mechanism guarding their sharp tips; these are the so-called shielded trocars. They usually rely on one of three basic designs; either a retractable external shield, a retractable central blunt point, or an internal shield which protects the sharp outer sleeve of the trocar. The shields are either retracted prior to placement of the trocar in the wound or automatically retract during the placement. Once the sharp tip of the trocar penetrates the abdominal wall and enters the abdominal cavity, the spring-loaded safety shield automatically deploys, covering the cutting edges of the tip and locking in place. Both the retractable spike and the internal shield may provide more effective protection than the external shields, which can be retracted during the passage of the abdominal wall by the surrounding tissues. Also, most reusable trocars do not have a guarded design.

When assessing the costs per instrument used, disposables initially appear more expensive due to the obvious higher purchase price. However, cleaning and sterilisation costs for reusable trocars must also be taken into account.

In general, reusable trocars are less sharp compared to disposable trocars. Therefore, during the insertion of a sharper disposable trocar less force is required. When performing a blind-entry technique using the Veress needle, it might be advantageous to use a sharper disposable trocar because “overshoot” of the introduction might be prevented due to the fact that less force is required during insertion.

Besides threaded cannulas that do not require a trocar for entry and optical trocars, trocars are created with a tip based on several designs including blunt, conical, round, bladed, and pyramidal tipped trocars. Blunt trocars, such as the widely known Hasson trocar, are used during the open-entry technique. Conical trocars, however, have a round sharp tip and dilate the fascial and muscular tissue after a small opening is made. Each side of pyramidal trocars forms a knife-like surface that slices open the tissue encountered. Less force is used during the insertion of these pyramidal trocars as compared to conical trocars.

Optical trocar systems allow for placement of the laparoscope in the trocar during the insertion, enabling the operating surgeon to continuously visualise the layers of the abdominal wall throughout the insertion process.

**Entry techniques**

The patient is positioned supine on the table, without rotation or a head down or modified Trendelenburg position. Because in these alternative positions, the relationships of the great vessels and other gastro-intestinal structures to the abdominal landmarks such as the umbilicus may be altered increasing the likelihood of injury. Verification of the position of several important anatomical structures is vital. Localising the aortic bifurcation,
palpation of the promontorium and crista iliaca provide a contribution to the virtual image of the abdominal cavity. Furthermore, organomegaly or intra-abdominal tumours should be ruled out via palpation or percussion. An empty bladder is important to avoid bladder injury and to provide more range of vision and working space. Bladder drainage can be achieved by inserting a urine catheter or once-only catheterisation. A nasogastric tube prevents gastric distension which reduces the risk of injury to the stomach and transverse colon. Drainage of the bladder and stomach are especially important when performing a blind-entry technique. Finally, the instrumentation to perform a laparotomy should be close at hand in case of serious vascular injury caused by the introduction of the Veress needle or trocar.

The open-entry technique

During the open-entry technique according to Hasson, a small laparotomy is performed of 1-2.5 centimetres. Successively, skin, rectus fascia, and peritoneum are incised under direct vision, followed by the insertion of a blunt trocar (Hasson trocar). During the incision of the several layers, the abdominal wall should be lifted, for example with towel clips or clamps. The introduction of the primary trocar is performed completely under direct visual control. After the blunt trocar is inserted and its correct position is confirmed, the gas insufflation can be initiated directly through the cannula with the obturator (inner removable part) still in place. After the pneumoperitoneum has been established, the trocar is fixated with two sutures. Modified Hasson trocars are manufactured with an inflatable balloon for a gas tight fixation of the trocar. At the termination of the laparoscopic procedure the trocar is removed with the laparoscope in it, followed by fascial closure. With the exception of the blunt primary trocar and the instruments necessary for the mini-laparotomy, the remaining instrumentation is identical to the other entry techniques. It is assumed that the open-entry technique reduces retroperitoneal vascular injuries to a minimum. However, the open-entry technique is less frequently used as compared to the blind-entry technique with the Veress needle. Reasons for this are the assumed larger incision (scar) that has to be made with the open-entry technique and the fact that more manipulations are needed with the open-introduction technique. Furthermore, the occurrence of gas leakage at the primary trocar site might be higher with the open-entry technique. Nevertheless, several studies have demonstrated that the open-entry technique is faster and cheaper as compared to entries with the Veress needle. Besides the traditional Hasson trocar, several disposable and reusable blunt trocars have been designed and marketed. One of these is the blunt TrocDoc® trocar which was derived from a sharp tipped trocar. The tip of a 10/11-mm trocar was loosened from its shaft and replaced by a longer blunt tip, which was 10 mm at the connection with the shaft tapering to 5 mm at the tip. The peritoneal cavity is reached through an incision large enough to facilitate the passage of the 5-mm blunt tip of the TrocDoc®. Due to the gradual increase in diameter from 5 to 10 mm, the trocar can be pushed in gently by stretching the abdominal fascia, providing a tight fit without gas leakage. This introduction technique provides visual control and needs no fixing sutures as with the Hasson trocar.
Closed-entry techniques with optical trocar devices

Optical trocars (Optiview®, Visiport®) allow a visually controlled passage of the individual tissue layers of the abdominal wall. The transparent trocar and the laparoscope are inserted together. The layers of the abdominal wall can be visualized individually, at which the peritoneal cavity depicts dark. In contrast, adhesive bowel and omentum depicts more lighter. Furthermore, in the event of an injury it can be noticed directly.

Another instrument that allows a visually controlled insertion, is the so-called endoscopic screw (Endotip®). The insertion of the endoscopic screw is performed without a prior pneumoperitoneum. After a small incision is made in the fascia the endoscopic screw, with the laparoscope in it, is ‘screwed’ in the fascia with a rotary motion. During the insertion the tissue is pushed away instead of being divided. It must be stressed that the recognition of the successive layers of the abdominal wall is not easy applying these closed-entries using optical trocar devices.

Blind-entry technique with the Veress needle

Before using the Veress needle, the sharpness and the spring-loaded tip mechanism must always be checked if it functions properly. Subsequently, after a small incision is made and the abdominal wall is lifted, the needle is introduced at an angle to the abdominal wall; normally this angle is approximately 30-45 degrees with respect to the vertical axis. The slantwise introduction of the needle is because of the fact that the needle must be introduced perpendicular with respect to the abdomen wall. When the abdomen wall is lifted, an angle is then created with the horizontal axis. Lifting the abdominal wall is mainly for fixation, otherwise the abdomen wall would be pushed inwards and the distance to the retroperitoneal structures would be reduced. It should be noted that the distance between the abdominal wall and the underlying structures is not increased during lifting as long as there is no pneumoperitoneum because the intra-abdominal structures are still situated against the abdomen wall (i.e. intra-abdominal vacuum). When the tip of the needle reaches the abdominal cavity, a double click is heard or felt which is caused by retraction of the blunt inner part of the needle after the penetration of the fascia and peritoneum. Furthermore, a hissing sound caused by passing air into the peritoneal cavity due to the negative intra-abdominal pressure can be heard. The correct position of the Veress needle can be verified with several tests such as the “drip-test”. The test involves a drip of NaCl which is placed on top of the closed Veress needle. When the needle is opened the drip of NaCl is sucked into the needle, especially when the abdominal wall is lifted. Another test to confirm proper needle placement is Palmer’s aspiration test. Here, a syringe filled with NaCl is connected to the Veress needle. Next, the NaCl is “injected” intra-abdominally through the Veress needle. The NaCl should be inserted without any resistance. Subsequently, with the same syringe an attempt is made to aspirate and during this manoeuvre the aspiration of blood or bowel contents is abnormal. Other tests include the disappearance of liver dullness during percussion, symmetrical distension of the abdomen during insufflation, and confirmation of the negative intra-abdominal pressure after connection with the insufflator during lifting of the abdominal wall. If the correct
position of the needle is verified, insufflation can be performed up to a pressure of 12-15 mmHg. Insufflation of CO₂ gas with a flow of 2-3 l/min with a low counter pressure (< 5 mmHg) also indicates correct position of the needle.

Following the insertion of the needle and insufflation, the primary trocar is inserted at the same place as the needle was positioned. Before the insertion of the primary trocar, it is important to ensure that the skin incision is large enough. Resistance during the insertion of the trocar is in general caused at skin level where the incision is not large enough and not during the passage of the fascia. If the Veress needle cannot be placed correctly, another one or two attempts might be undertaken. Thereafter, an open-entry should be performed.

The so-called radial distension trocar (Step®) is made up of a Veress needle with a polymeric sleeve, both are inserted simultaneously. After the correct position of the needle is checked and the abdomen is insufflated, the needle is retracted from the sleeve. Subsequently, the sleeve is dilated with a blunt obturator. With this technique the layers of the abdominal wall are pushed away instead of being perforated or incised. The advantage of this technique is that the needle with the sleeve is the only sharp instrument that is blindly inserted. Furthermore, stability of the trocar, less gas leakage, less tissue damage, less postoperative pain, and a decreased risk of postoperative hernia are reported as advantages as well.

With the hyperinsufflation technique, a higher abdominal pressure is applied during the entry of the first trocar to prevent injury, especially injury of the large retroperitoneal vessels. After the insertion of the Veress needle and confirmation of its correct position a pneumoperitoneum is established with high pressures of 25-30 mmHg. Subsequently, at the umbilical entry site, the primary trocar is inserted. After entrance of the abdominal cavity with the trocar, the intra-abdominal pressure is decreased. The higher intra-abdominal pressure increases the distance between the abdominal wall and the retroperitoneal vessels. Furthermore, the high pressure gives more counter pressure during the insertion of the trocar. The high pressure is maintained only for a short period, therefore the risk of deep venous thrombosis, gas emboli, and subcutaneous emphysema is minimal. This technique is applied mostly in young and healthy patients. In these patients the influence of the high intra-abdominal pressure on the cardiovascular system and pulmonary functions is limited. However, in the elderly and in patients with severe comorbidity the increased intra-abdominal pressure might result in cardiovascular or pulmonary complications. Therefore, this technique is only suitable in young and healthy patients.

Direct trocar insertion

Direct insertion of the first trocar without previously establishing a pneumoperitoneum can be applied in a selected group of patients with a mobile ventral abdominal wall and without a history of abdominal surgery or infections. Sufficient muscle relaxation, a skin incision large enough to facilitate the trocar without resistance, sharp trocars, and knowledge of the position of important anatomical structures, such as the aortic bifurcation, are essential when applying this technique. The advantage of this technique
is that injuries caused by the introduction of the Veress needle are avoided. However, the insertion of the primary trocar is still performed without any visual control and with the risk of an overshoot of the introduction.

**Secondary trocar placement**
Injury to the epigastric vessels during placement of secondary trocar(s) form a substantial part of all vascular injuries.5 The secondary trocar should be placed in a well-controlled manner and with direct visualisation to prevent injuries. The laparoscope is used to identify the deep inferior epigastric vessels (typically located underneath the rectus muscles) and transillumination is used to identify the superficial vessels.

**Entry sites**
The usual site for the primary introduction is the lower border of the umbilicus, where the abdominal wall is at its thinnest and the skin is in direct contact with the fascia despite the presence of adiposity. It is important not to damage the intra-abdominal structures during the incision of the skin and fascia since there are reports of severe vascular injuries made with a scalpel during the skin incision. When there is a deformity of the umbilicus or when the risk of intra-abdominal adhesions is increased, an introduction at the umbilicus might be undesirable. Alternative introduction places include a point halfway the umbilicus and the pubic symphysis, directly above the umbilicus, left or right at McBurney’s point or between the seventh and eight costa in the midaxillary line on the left side. Another alternative, specially when adhesions at the umbilicus are expected or with bariatric surgery, is Palmer’s point, which is located three centimetres caudal of the lowest costa in the mid-clavicular line on the left.

**Removal of the trocars**
Removal of the trocars should be performed under direct visual control. The last trocar is removed with the laparoscope in the trocar. This allows identification of vascular injuries which remained unnoticed because the bleeding was temporarily stopped due to the pressure of the pneumoperitoneum or plugging by the trocar. Furthermore, bowel injury and the occurrence of herniation can also be identified during the trocar removal. Fascial defects created by 10-mm or larger trocars should be closed to prevent hernia formation.22 All layers of the abdominal wall should be closed meticulously under direct vision including the peritoneum.22-24 When active manipulation through a 5-mm port has occurred during prolonged procedures or stretching the port side for retrieval, the fascia should also be closed to prevent complications.22,25,26
**Complications**

It has been calculated that approximately one half of all intra-operative laparoscopic complications is caused during the installation of the pneumoperitoneum and the subsequent introduction of the trocars.\(^4,6,27\) Entry related injuries can be divided in two different groups. The first group comprises of injuries to blood vessels and organs within their normal anatomical position. The second group comprises of injuries to structures which are located at an abnormal position, such as bowel or omentum which is adhesive to the anterior abdominal wall. Besides direct injury to intra-abdominal structures during the entry phase, the pneumoperitoneum itself influences the cardiovascular system due to the increased intra-abdominal pressure. The cardiovascular effects of the pneumoperitoneum occur mainly during its initiation. This should be considered when the intra-abdominal pressure is initially increased for the introduction of access devices.\(^27,30\) In young and healthy patients (ASA I and II) the hemodynamic and circulatory effects of a 15 mmHg pneumoperitoneum are generally not clinically relevant. Care has too be taken when establishing the pneumoperitoneum in the elderly and patients with severe co-morbidity (ASA III and IV).\(^27,29-31\) Invasive measurement of blood pressure or circulating volume should be considered. These patients should also receive adequate preoperative volume loading and beta-blockers.\(^27,32,33\) If technically feasible, gasless or low pressure laparoscopy might be an alternative for patients with limited cardiac function.\(^27-29\)

**Incidence**

Entry-related injuries mostly involve bowel and blood vessel injuries. The reported incidence of vascular and bowel injuries varies and is between 0.05 and 0.5 complications per 100 laparoscopic procedures.\(^9,34-36\) This is most likely an under-estimation as in the majority of cases, most injuries are not reported. The result of major vascular and unrecognized bowel injuries is serious, often leading to severe morbidity and even mortality. The overall mortality rate is reported to be about 4%, increasing to 21% for unrecognized bowel injury.\(^34,36-40\)

The incidence of clinically relevant gas embolism is very rare (0.002-0.02%), but if it occurs it can be a fatal complication.\(^27,41\) Gas embolism usually occurs during the installation of the pneumoperitoneum using the Veress needle or less frequently a sharp trocar. The usual cause of gas embolism is the accidental placement of a needle or trocar into a blood vessel. Similarly, any injury to veins or parenchymal organs can result in direct gas inflow into the systemic circulation, especially during liver surgery.\(^27\)

The incidence of extraperitoneal insufflation is between approximately 0.4 and 3.5%. Extensive preperitoneal insufflation can result in an altered outline of the abdominal cavity which can severely hamper the exposure of the laparoscopic procedure. Furthermore, extensive preperitoneal insufflation can result in serious complications such as a pneumothorax, pneumomediastinum, or pneumopericardium.\(^27\)
Complications during open and blind-entries

Historically, gynaecologists have been trained in the blind-entry technique with the Veress needle. Although the technique of open-laparoscopy was first described by the gynaecologist Hasson in 1971, only a few gynaecologists apply the open-entry technique. Some have reported comparable or even higher complication rates when applying the open-entry technique in gynaecological case series. However, in these studies the participating gynaecologists did not frequently use the open-entry technique and if used, this was mainly in selected patients who had prior abdominal surgery. Consequently, these patients already were at a higher risk for entry related complications. This explains why in a systematic review by Merlin et al. the risk of major complications initially appeared to be higher for the open-entry technique. When only prospective series were taken into account the opposite was shown; a relative risk of 0.30 (95% CI 0.09-1.03) was found in favour of the open-entry technique. It was noted that retrospective studies compared a high-risk with a low-risk patient population, while the prospective studies investigated an unselected patient population.

Recently, a review was performed concerning entry-related complications which included all malpractice claims filed at the largest medical liability mutual insurance company for hospitals in health care in the Netherlands. From January 1993 to December 2005, 229 laparoscopy-related claims were filed of which 41 (18%) claims were identified as entry-related complications. Most were young (median age 35 years) female patients who had routine, non-advanced laparoscopic procedures planned as short-stay or day-care procedures. In these patients, a total of 51 structures were injured. There were 18 vascular structure injuries, mainly retroperitoneal arteries. Furthermore, there were 30 bowel injuries, in two patients the uterus was injured and one injury involved extensive preperitoneal insufflation. An open-entry technique was used in only two (5%) of the 41 included patients. Both patients had a history of previous abdominal surgery and the injured structure was bowel. In the remainder, a blind (Veress) entry technique had been applied. Vascular injury was exclusively associated with the blind-entry technique. In only 19 (46%) patients the entry-related complication was diagnosed peroperatively. In the remaining patients, the entry-related injury was diagnosed postoperatively, median on day two (range 0-5).

In a recent survey of the U.S. Food and Drug Administration (FDA) by Fuller et al. reviewing all reports in a period from January 1997 to June 2002, 31 fatal and 1353 nonfatal trocar injuries were identified. Most fatalities involved vascular injuries. It was remarkable that almost all the vascular injuries were caused with the Veress needle or trocar during blind-entries. Bowel injury was reported in both the blind and open-entries. Furthermore, many injuries were caused by disposable shielded trocars and optical trocars. Although, the exact perspective concerning these FDA data is unclear because it is unknown how many open and blind-entries are being performed and how many shielded and optical trocars are used, it could carefully be concluded that neither shielded nor optical trocars can guarantee a safe installation of the pneumoperitoneum. Furthermore, retroperitoneal vascular injury seems to be associated with the blind-entry technique due to an “overshoot” of the introduction of the Veress needle or trocar. This injury mechanism is not present.
with the open-entry technique. However, an open-entry does not preclude bowel injury, just as a formal laparotomy could be complicated by bowel injury.

**Discussion**

The European Association for Endoscopic Surgery (E.A.E.S; www.eaes-eur.org) practical clinical guideline on the pneumoperitoneum does not state which of the entry techniques is the preferred one. In literature, it is suggested that the open-entry technique is the most safe entry technique because an overshoot of the introduction, especially those resulting in retroperitoneal vascular injury, can be avoided. However, an open-entry does not preclude bowel injury. Hashizume et al. reported in a retrospective study (1991-1995) that during the study period 96.6% of the Japanese surgeons changed their method of establishing a pneumoperitoneum from the closed technique to the open technique in order to increase patient safety. The rate of complications related to needle and/or trocar insertion subsequently decreased as the surgeon’s experience performing laparoscopic surgery using the open-entry technique increased.5

In patients without abdominal surgery in their history, an entry with the reusable TrocDoc® trocar (“half open”) might be an effective and less expensive alternative for the open-introduction according to Hasson.14 With respect to obese patients the open-entry technique can be technically difficult. For these patients, the blind-entry technique with the Veress needle remains a good alternative. The presence of peritonitis is not an absolute contra-indication for a laparoscopic approach. However, distended bowel poses a risk for bowel injury during the installation of the pneumoperitoneum. Therefore, a well controlled open-entry is in those circumstances the safest option.

In children and relatively thin adult patients the distance between the abdominal wall and retroperitoneal structures is reduced. Therefore, in those patients the open-entry technique might be the safest. Also, in pregnant females and in patients with ascites an open-entry is preferred.27

Nevertheless, identification of patients who have an increased risk of an entry-related injury is essential to prevent such injuries. Prior abdominal surgery, especially midline laparotomy, is associated with a considerable increased risk of adhesions of bowel with the anterior abdominal wall. After a Pfannenstiel incision in 31% of the patients adhesions are present and in 10% of the patients these adhesions are extensive. After a midline laparotomy, this is 51% and 30% respectively.45 Furthermore, a history of inflammatory bowel disease, peritonitis, and radiotherapy is associated with intra-abdominal adhesions and anatomical changes.

During physical examination it is important to search for abdominal wall herniations to prevent that the installation of the pneumoperitoneum is performed at these sites. Furthermore, the abdomen should be palpated to exclude organomegaly.

In conclusion, the installation of the pneumoperitoneum is exclusively associated with the laparoscopic approach and remains a potentially dangerous first step. Moreover,
approximately one half of all intra-operative laparoscopic complications are caused during the establishment of the pneumoperitoneum and introduction of the trocars. Although the incidence of entry-related injuries is very low for both the open and blind-entry techniques, retroperitoneal vascular injury ("overshoot of the introduction") might be prevented by the open-entry technique. Based on available and reviewed literature, the open-entry technique seems to be the most safe entry technique and is to be preferred in most cases.

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Chapter 6

Installation of the pneumoperitoneum: technique and complications


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Chapter 7

Medical liability insurance claims on entry-related complications in laparoscopy

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Abstract

Introduction
Installation of the pneumoperitoneum is an essential part of laparoscopic surgery. Creation can be performed by either the open or a closed technique. The aim of this study was to assess the number of, and contributing factors to entry-related complications in medical liability insurance claims in the Netherlands.

Methods
A retrospective chart review was performed including all malpractice claims filed at MediRisk, which is presently the largest medical liability mutual insurance company for institutions, mainly hospitals in health care in the Netherlands.

Results
From January 1993 to December 2005, 41 claims were identified as entry-related complications which comprised 18% of all laparoscopy-related complications leading to claims. Most were young (median age 35 years) female patients who had routine, non-advanced laparoscopic procedures planned as short-stay or day-care procedures. The claims were equally divided between general surgery (n=20) and gynaecology (n=21). A total of 51 structures were injured. There were 18 vascular structure injuries, 30 bowel injuries and three other injuries. An open-entry technique was used in only two (5%) patients. Vascular injury was exclusively associated with the closed-entry technique. In only 19 (46%) patients the entry-related complication was diagnosed peroperatively, consisting of 70% of the vascular and 25% of the bowel injuries. Twenty-six patients (64%) were admitted to the Intensive Care Unit for a median of five days. There was no mortality. Besides conversion, the majority of the patients filed a claim to compensate for a longer hospital stay and related costs. A payment was made in 17 (57%) of the 30 settled claims.

Conclusion
Medical liability claims concerning laparoscopic entry-related complications comprised one fifth of all laparoscopy-related claims. Claims concerning entry-related complications occurred in young patients who had routine, non-advanced procedures. In the investigated cases most claims involved the closed-entry technique.
Introduction

Despite the ongoing technological advances in laparoscopic surgery, the creation of a pneumoperitoneum and the additional introduction of surgical instruments remains a potential dangerous first step that can result in serious injuries to the viscera and major intra- and retroperitoneal vessels. The reported incidence of vascular and bowel injuries varies and is between approximately 0.05–0.5 complications per 100 laparoscopic procedures.\textsuperscript{1-4} Although the incidence of entry-related complications is rare, the result of major vascular and unrecognized bowel injuries is serious, often leading to severe morbidity and even mortality. The overall mortality rate is reported to be about 4% increasing to 21% for unrecognized bowel injury.\textsuperscript{5-7} In several reports the fatalities result from about 75% vascular injuries and the remaining 25% from unrecognized bowel injuries.\textsuperscript{4;5;8} Furthermore, it has been calculated that one half of all laparoscopic complications can be blamed on the entry technique.\textsuperscript{9-11}

In general, there are two techniques to establish the pneumoperitoneum and to enter the abdominal cavity. The first is the closed (blind) entry, which is performed by using a Veress needle to establish the pneumoperitoneum followed by trocar insertion or, less frequently, direct trocar insertion without previously establishing a pneumoperitoneum. The second method is the open technique, in which a small laparotomy is performed. Successively, skin, rectus fascia, and peritoneum are incised under direct vision, followed by blunt (Hasson’s) trocar insertion. Subsequently the pneumoperitoneum is created.\textsuperscript{1;12} With respect to the prevention of entry-related complications, neither of these two techniques is supported by solid evidence and there is an ongoing debate, mainly between gynaecologists who favour the closed-entry technique, and surgeons who favour the open-entry technique, about which technique is better.\textsuperscript{1;10} Many general surgeons suggest that the open-entry technique results in the same number of visceral lesions as does the closed-entry technique, but significantly fewer vascular lesions.\textsuperscript{1;13} Furthermore, it could be hypothesized that another advantage of the open-entry is that at least part of the bowel injuries is immediately seen under direct vision. Because of the lack of evidence, the European Association for Endoscopic Surgery (E.A.E.S.) practical clinical guideline on the pneumoperitoneum could not state which of the entry techniques is preferred.\textsuperscript{9}

To answer this questions with a high level of evidence a randomised comparison of the open and closed access techniques with a sample size of over 200,000 patients would be required to detect a reduction of major complications from one per 1000 to 0.5 per 1000.\textsuperscript{14} Therefore, it is important to continue to report on this topic because one has to rely on accumulating evidence of a lower level. In this study medical liability data sources were used to provide evidence on entry-related injuries.

The aim of this study was to assess the number of entry-related complications that provoked medical liability insurance claims for laparoscopic surgery at the largest medical liability mutual insurance company for institutions in health care in the Netherlands. Furthermore, the used entry technique (\textit{i.e.} open vs. closed), distribution of injured organs, and predictive factors for litigation were assessed.
Methods

Data source
A retrospective chart review was performed which included all malpractice claims filed at MediRisk concerning entry-related complications in the period January 1993 to December 2005. MediRisk was founded in 1993 and is presently the largest medical liability mutual insurance company for institutions, mainly hospitals in the healthcare industry in the Netherlands. In 1993 MediRisk insured 21 hospitals. At the end of 2005 the number of insured hospitals included 80 of the 101 Dutch hospitals (Figure 1). The insured institutes are broadly representative of the Dutch teaching and non-teaching hospitals, with the exception of all eight academic hospitals in the Netherlands, none of which are insured at MediRisk.

Figure 1. The number of hospitals insured and the amount of claims that were filed between 1993 and 2005

Definitions and inclusion and exclusion criteria
An entry-related complication was defined as a direct injury related to the insertion of either the Veress needle or the first trocar, including preperitoneal insufflations and injuries to epigastric vessels, intraperitoneal viscera and vessels, and retroperitoneal viscera and vessels. Port-site hernias were excluded from this analysis. Claims, in which the aetiology of the injury was not clear and other causes than insertion (e.g. coagulation injury or other procedure-related complications) could not be ruled out, based on operative reports and/or histological examination, were excluded. Furthermore, injuries caused by second-trocar insertion were also excluded.

Claim characteristics
All included claims were reviewed and the following data were extracted using a preformatted sheet; age, gender, co-morbidity, prior abdominal surgery and/or
previous intra-abdominal infectious events, body mass index (BMI, kg/m²), specialty (i.e. gynaecology or general surgery), urgency, experience (i.e. resident or consultant), informed consent, indication for surgery, entry technique (i.e. open or closed), type of entry-related complication, moment of diagnosis of the entry-related complication, postoperative recovery including data such as reoperations, Intensive Care Unit (ICU) admission, postoperative morbidity and mortality. The entry-related complications were classified as ‘bowel’, ‘vascular’ or ‘other’. The gastrointestinal tract was divided into three parts: stomach, small intestine and large intestine. Vascular injuries were divided into retroperitoneal, intraperitoneal, and abdominal wall (epigastric vessels). Furthermore, the vascular injuries were subdivided into arterial, venous, or vascular not specified.

**Statistics**

Data were calculated as median values with ranges for continuous and discrete data, unless otherwise specified. Categorical data are presented as frequencies or percentages. Analysis was done using the SPSS v.12.0 package (SPSS, Chicago, Illinois, USA).

**Results**

**Filed claims concerning laparoscopic procedures and entry-related complications**

In the study period, a total of 10552 claims were filed at MediRisk (Figure 1) of which 229 (2%) involved gynaecological and surgical laparoscopic procedures. Of these 229

![Figure 2. The relation between laparoscopy-related claims in total and entry-related injuries between 1993 and 2005](image-url)
claims, 50 were identified as an entry-related complication. Subsequently, seven claims were excluded because the aetiology of the injury was not clear and causes other than Veress needle or trocar insertion could not be ruled out. Furthermore, two claims were excluded because the injury was caused by insertion of the second-trocar. The final analysis comprised 41 claims, which is 18% of all laparoscopy-related claims filed at MediRisk. Figure 2 shows the relationship between all laparoscopy-related claims and the number of entry-related complications. The yearly number of filed claims concerning entry-related complications remained stable during the study period.

Characteristics of the entry-related complications
The median age of the 41 patients included in this study was 35 years (range 14-81). Median BMI was 24.0 kg/m$^2$ (range 18.6-55.9 kg/m$^2$). Sixteen (39%) patients had a high (> 25.0 kg/m$^2$), and six (15%) had a low (< 20 kg/m$^2$) BMI. Twenty-one patients (51%) had a history of prior abdominal surgery (range 1-3 procedures). The ratio between general surgery and gynaecology was 20:21. The surgical patients consisted of 17 (85%) females and three (15%) males. Residents were involved in six (15%) claims. In both surgical and gynaecological patients the planned procedures were routine and non-advanced and in 37 (90%) patients they were elective (Table 1).

Table 1. Planned operative procedures in the 41 patients with an entry-related complication

<table>
<thead>
<tr>
<th>Planned procedure</th>
<th>Number of patients (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gynaecology</strong></td>
<td></td>
</tr>
<tr>
<td>sterilization</td>
<td>11</td>
</tr>
<tr>
<td>diagnostic laparoscopy</td>
<td>4</td>
</tr>
<tr>
<td>ovarian cystectomy</td>
<td>2</td>
</tr>
<tr>
<td>adhesiolsis</td>
<td>2</td>
</tr>
<tr>
<td>ectopic pregnancy</td>
<td>1</td>
</tr>
<tr>
<td>adnex extirpation</td>
<td>1</td>
</tr>
<tr>
<td><strong>Surgery</strong></td>
<td></td>
</tr>
<tr>
<td>cholecystectomy</td>
<td>10†</td>
</tr>
<tr>
<td>diagnostic laparoscopy</td>
<td>3</td>
</tr>
<tr>
<td>appendectomy</td>
<td>3</td>
</tr>
<tr>
<td>hernia repair</td>
<td>2</td>
</tr>
<tr>
<td>gastric banding</td>
<td>1</td>
</tr>
<tr>
<td>gastric perforation</td>
<td>1</td>
</tr>
</tbody>
</table>

†Including two open-entry techniques; in all other patients a closed-entry technique was used

A total of 51 structures were injured (Table 2). There were 18 vascular structure injuries consisting mainly of retroperitoneal vessels (n=13, 72%) of arterial origin (n=10, 77%), 30 bowel injuries and three other injuries. Thirty-six patients had one injury, five (12%) patients had a combination of entry-related complications (range 2-3). The injured retroperitoneal arteries included the right iliac artery (n=2, 20%), the left iliac artery (n=2, 20%), and the abdominal aorta (n=3, 30%); in the remaining three (30%) cases the injured artery was not reported. The large bowel injuries comprised mainly the transverse (n=4, 40%) and left sided colon (n=4, 40%). Two (5%) patients had an open entry-related complication.
Both patients had a history of a previous laparotomy. In one patient the exact type of entry technique was not mentioned. A closed-entry technique was used in the remaining 38 (93%) patients. All vascular entry-related complications were seen after the closed-entry technique. In 15 (39%) cases in which the closed-entry technique was used it could not be determined whether the Veress needle or the primary trocar was responsible for the injury. In the remaining closed-entry cases, the Veress needle was responsible in 12 (32%) and the first trocar in 11 (29%) cases. In only five of the latter cases the design of the trocar was reported; four shielded trocars and one optical trocar.

Table 2. Type of entry-related complications (n=51) in the 41 patients included in this study

<table>
<thead>
<tr>
<th>Type of entry-related complication</th>
<th>Gynaecology (n=21)</th>
<th>Surgery (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vascular</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>epigastric vessels</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>retroperitoneal vessels</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>intraperitoneal vessels*</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>Bowel</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>stomach</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>small intestine</td>
<td>9</td>
<td>9†</td>
</tr>
<tr>
<td>large intestine</td>
<td>6</td>
<td>4†</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>uterus</td>
<td>0</td>
<td>2†</td>
</tr>
<tr>
<td>preperitoneal insufflation</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

*mesenterial artery or omental artery; †One patient was 22 weeks pregnant; ‡including one open-entry technique

Thirteen (32%) claims provided additional narrative comments by the surgeon on the cause of the injury, citing various factors that contributed to the injury. These comments included adhesions (n=4), “overshoot” with the trocar (n=2), distended intestine (n=2), very thin patient (n=2), pregnancy (n=1), post partum (n=1), obesity (n=1), and device problems during introduction (n=1).

**Time of diagnosis and postoperative course**

In 19 (46%) cases the entry-related complication was diagnosed peroperatively resulting in 16 conversions. In the remaining 22 (54%) cases the injury was diagnosed at median postoperative day two (range 0-5), resulting in one or more reoperations and a complicated postoperative course (Table 3). Eighty percent of the combined injuries and 70% of the vascular injuries were diagnosed peroperatively, the remaining vascular and combined injuries were diagnosed on the same day. Only 25% of the bowel injuries were diagnosed peroperatively, the remainder were diagnosed at median postoperative day two. Twenty-six patients (64%) were admitted to the ICU for a median of five days (range 1-60). Seventy percent of the patients with a vascular injury were admitted to the ICU for a median of two days (range 1-34). Fifty-eight percent of patients with a bowel injury were admitted to the ICU for a median of eight days (range 1-60). There were no claims for fatal injuries. Nine (22%) patients suffered permanent harm (> 1 year). The latter consisted of post
traumatic stress disorder (n=3), neuropathy (n=2), post ventilation lung damage (n=1), premature childbirth due to uterus perforation (n=1), permanent enterocutaneous fistula (n=1), and intermittent claudication (n=1).

Table 3. Time of diagnosis (no delay vs. delayed diagnosis) and postoperative course of the 41 patients included in this study

<table>
<thead>
<tr>
<th></th>
<th>No delay (n=19)</th>
<th>Delayed diagnosis (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU stay</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- number of patients (%)</td>
<td>8 (42%)</td>
<td>18 (82%)</td>
</tr>
<tr>
<td>- median days (range)</td>
<td>1 (1-18)</td>
<td>8 (1-60)</td>
</tr>
<tr>
<td>Patients with postoperative morbidity (%)</td>
<td>6 (32%)</td>
<td>17 (77%)</td>
</tr>
<tr>
<td>Permanent harm</td>
<td>5 (26%)</td>
<td>4 (18%)</td>
</tr>
</tbody>
</table>

ICU: Intensive Care Unit

From patient records only in 13 (32%) claims, informed consent was properly established, i.e. documented and understood by the patient. In the remaining claims informed consent was not documented or not given at all. In 48% of the claims complications such as bowel injury or the chance of conversion to laparotomy were discussed preoperatively. According to the records a postoperative meeting between surgeon and patient, in which the complications that occurred were discussed, had taken place in only 16 (39%) cases. The majority of the patients claimed financial compensation for the prolonged hospital stay, related costs such as travelling expenses and domestic care and the midline laparotomy scar. Thirty (73%) claims were settled at the end of the study period and a payment was made in 17 (57%) of the settled claims.

Discussion

Several randomised controlled trials and meta-analyses have demonstrated that laparoscopic surgery is superior to laparotomy in terms of morbidity, postoperative recovery, and length of hospital stay.\textsuperscript{15,16} Having achieved broad acceptance, minimally invasive surgery is a fast-expanding surgical discipline. Nevertheless, the initiation of laparoscopy, i.e. the creation of a pneumoperitoneum followed by the introduction of the surgical instruments remains a potentially dangerous first step, which is exclusively associated with the laparoscopic approach.

The present study demonstrates that medical liability claims involving entry-related injuries comprised about one fifth of all laparoscopic surgery-related claims filed at MediRisk. The claims were equally distributed between general surgery and gynaecologic procedures. However, this distribution does not implicate that the incidences of entry-related complications are comparable because the number of laparoscopic procedures of both specialities performed during the study period is not known.

In both the general surgery and gynaecology cases the planned procedure was generally a routine one and elective in nature. Furthermore, these procedures involved mostly young
female patients who planned to be operated on in a day-care setting or in short stay surgery. The consequences of an entry-related complication in these young patients who underwent a routine procedure are striking, however. The entry-related complication resulted in one or more laparotomies, stay in the ICU, and prolonged hospitalisation. Furthermore, 22% of the patients suffered from permanent harm.

Since the first reports on entry-related complications many articles have been published on this subject and trocars have been introduced with new design features, including retractable shields and optical trocars to allow direct viewing during insertion. Furthermore, to avoid entry-related complications it is important to identify patients at risk, e.g. those with adhesions from previous laparotomy and obese and very thin patients. However, despite this identification entry-related complications still occur at a constant rate. In a recent survey of the U.S. Food and Drug Administration (FDA) Fuller et al., who reviewed all reports from January 1997 to June 2002, identified 31 fatal and 1353 nonfatal trocar injuries. Most fatalities involved vascular injuries.

In our study most claims were provoked by injuries caused by the closed-entry technique, and vascular injury was exclusively caused by the closed-entry technique. However, this does not mean that the incidence of entry-related complications for the closed-entry technique is much higher compared with that of the open-entry technique because the numbers of performed closed- and open-entry techniques are unclear. However, retroperitoneal vascular injury is associated with “overshoot” of the introduction of the Veress needle or the first trocar. Theoretically, this can be avoided by using an open introduction. It is known that an open introduction might reduce the incidence of this serious complication. On the other hand, bowel injuries are not fully avoided by the open-entry technique.

Historically, gynaecologists have been trained in the closed-entry technique. Although the technique of open laparoscopy was first described by the gynaecologist Hasson in 1971, only a few gynaecologists use the open-entry technique. Some have reported comparable or even higher complication rates with the open-entry technique in gynaecologic case series. However, in these studies gynaecologists did not use the open-entry technique frequently; it was used mainly in selected patients who had prior abdominal surgery. Consequently these patients already were at a higher risk for entry-related complications. This explains why in a systematic review by Merlin et al. the risk of major complications initially appeared to be higher for the open-entry technique. When only prospective series were taken into account the opposite was shown; a relative risk of 0.30 (95% confidence interval 0.09-1.03) in favour of the open-entry technique. It was noted that retrospective studies compared a high-risk with a low-risk patient population, while the prospective studies investigated an unselected patient population. Furthermore, in a Japanese survey of laparoscopic surgeons, Hashizume et al. reported that during the study period 96.6% of the surgeons changed their method of establishing a pneumoperitoneum from the closed-entry technique to the open-entry technique to increase patient safety. The rate of complications related to needle and/or trocar insertion subsequently decreased as the surgeon’s experience performing laparoscopic surgery using the open-entry technique increased.
Our study also consists of a selected series of patients, because 51% percent of them had a history of surgery, and only 46% of the patients had a normal BMI (20-25 kg/m²). It is well recognized that the introduction of a pneumoperitoneum and trocars in obese patients is difficult because of the lack of feeling the instruments penetrate the fascia or the insertion is too deep. However, most patients at risk are lean. In these patients the distance between the abdominal wall and the underlying structures is short so that a Veress needle or trocar penetrating the abdominal fascia and peritoneum with a little too much force puts these structures at risk. Furthermore, the risk of bowel injury is increased in patients who had previous abdominal surgery because of adhesions of the small bowel to the abdominal wall. Nevertheless, in the present series of patients a closed-entry technique was used despite the increased risk of complications caused by an abnormal BMI and the risk of adhesions after previous surgery.

It is remarkable that in only one third of the claims informed consent was properly given and documented, and in only 48%, were complications discussed with the patient preoperatively. An unexpected negative outcome, that is neither discussed preoperatively nor explained postoperatively, is probably the most important trigger for litigation. A properly informed patient is less likely to file a claim. This group of patients consisted of young patients who underwent routine nonadvanced surgical procedures and both surgeon and patient did not expect such a serious complication. Another factor that may have provoked litigation is that more than half of the entry-related complications were diagnosed with a delay and that several of these patients had already been discharged. Therefore, it is important to discuss with the patient the risk of conversion to open surgery and the risk of vascular and bowel injuries in general, and to point out that not all of these injuries are diagnosed immediately. This conversation, including the informed consent of the patient, must be documented and patients at risk (e.g. lean or obese patients or those who had previous abdominal surgery) should be identified. Furthermore, it is important to keep in mind that entry-related complications still occur at a constant rate, even in routine procedures.

This study has several limitations. First, it probably represents only a part of all entry-related complications that occur. Furthermore, the study consists of a small, retrospectively collected, and selected population of patients, probably representing the most dramatic cases. During the study period a (growing) fraction of the hospitals in the Netherlands were insured at MediRisk. Because of insufficient record-keeping, we were unable to clearly identify risk factors or specific trocar devices at risk. In general, this study does not present any data on the total population who had a laparoscopic procedure by the same surgeons responsible for the claims analysed. Therefore, the definite relationship between several factors associated with entry-related injuries could not be established.

In conclusion, entry-related complications provoking litigation probably comprise one fifth of all laparoscopy-related claims. Patients that filed a claim were mostly young females with a history of abdominal surgery who were operated on in a day-care setting or had short-stay surgery with severe consequences of the entry-related complication. Most claims involved the closed-entry technique.
Reference List


Laparoscopic reintervention for anastomotic leakage after primary laparoscopic colorectal surgery; a comparative study

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MI van Berge Henegouwen
JFM Slors
DJ Gouma
WA Bemelman

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Abstract

Introduction
Anastomotic leakage is associated with high morbidity and mortality. Aim of this study was to assess potential benefits of a laparoscopic reintervention for anastomotic leakage after primary laparoscopic surgery.

Methods
From January 2003 to January 2006, patients who underwent laparoscopic colorectal resection and subsequently developed anastomotic leakage underwent a laparoscopic reintervention (laparoscopic group, n=10). Relaparotomy was performed in patients who had primary open surgery (open group, n=15).

Results
Patient characteristics in both groups were comparable, including pre- and postoperative APACHE II scores. Median length of time from first operation to reintervention was six days in both groups. There were no conversions. Intensive Care Unit (ICU) stay was shorter in the laparoscopic group (1 vs. 3 days; p=0.002). Resumption of a normal diet (3 vs. 6 days, p=0.03) and first stoma output (2 vs. 3 days, p=0.04) occurred earlier in the laparoscopic group. Postoperative 30-day morbidity was lower (40% vs. 80%, p=0.09), and hospital stay shorter (9 vs. 13 days, p=0.06) in the laparoscopic group. The incidence of incisional hernia was 0% in the laparoscopic group versus 33% in the open group (p=0.06).

Conclusions
These data suggest that a laparoscopic reintervention for anastomotic leakage after primary laparoscopic surgery is feasible and safe. It tends to be associated with less morbidity, a faster recovery and fewer abdominal wall complications as compared to relaparotomy.
Introduction

Anastomotic leakage is the most important surgical complication following colorectal resection with intestinal anastomosis. The reported clinical leakage rate after colorectal resection depends on the site of anastomosis and ranges from 2 to 21 per cent. Anastomotic leakage after colorectal surgery is associated with high morbidity and even mortality. Morbidity includes long Intensive Care Unit (ICU) admittance, sepsis and several abdominal wall complications due to reinterventions and wound infections. Furthermore, the risk of permanent stoma ranges from 10 to 100 per cent. In colorectal surgery, mortality due to anastomotic leakage is considerable. Moreover, the main cause of postoperative mortality are anastomotic complications.

Elective laparoscopic colectomy was introduced in the early nineties. Since then several randomised controlled trials have reported favourable results of laparoscopic colorectal surgery as compared to open surgery. Laparoscopic surgery offers several advantages including a faster postoperative recovery and a shorter hospital stay. Laparoscopic colorectal surgery is associated with a similar anastomotic leak rate as compared to open surgery.

Massive anastomotic leakage and peritonitis generally requires prompt reintervention by relaparotomy. Despite the short term benefits of laparoscopic colorectal resections and the high implementation rate, reintervention for suspect anastomotic leakage is generally done by an open approach. Most authors consider peritonitis to be a contraindication for laparoscopic approach due to the risk of enhanced bacteraemia by pneumoperitoneum, risk of bowel injury due to distended bowel, and presumed better visualization and irrigation possibility of the abdomen by open surgery. In theory, laparoscopic reintervention for anastomotic leakage after primary laparoscopic surgery might be beneficial when considering abdominal wall complications and postoperative recovery. However, laparoscopic reintervention in case of anastomotic leakage is not current practice yet, and comparative data does not exist in the literature. Therefore, the objective of this study was to evaluate 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 open surgery and open reintervention for anastomotic leakage in the same period.

Methods

The present study consists of a consecutive series of patients with anastomotic leakage after open or laparoscopic colorectal resection operated on in the period January 2003 to January 2006. Data were assessed in a retrospective manner. All patients who underwent laparoscopic colorectal resection and subsequently developed anastomotic leakage were reoperated laparoscopically (laparoscopic group). Relaparotomy was performed in patients who had primarily open surgery (open group). One patient underwent a laparotomy
for anastomotic leakage after primary laparoscopic surgery, this patient was excluded. Furthermore, all patients in which anatomic leakage was managed by conservative treatment were excluded. The decision to perform the initial operation laparoscopically or open was based on referral to a surgeon capable of performing laparoscopic resection and on patients’ and surgeons’ preference. Referral patterns for all surgeons were similar throughout the whole study period.

Charts of the included patients were reviewed and the following data were extracted using a preformatted sheet: age, gender, co-morbidity, previous midline laparotomy, Body Mass Index (BMI, kg/m²) measured prior to primary surgery, ASA classification, indications for the primary procedure, performed surgical procedure at the primary operation, time-span between the primary intervention and the reintervention, “Acute Physiology and Chronic Health Evaluation II” (APACHE II) scores before and 24 hours after the reintervention, abdominal cavity cultures and postoperative recovery including ICU stay, resumption of a normal diet, first stoma output, wound complications including incisional hernia, postoperative mortality, and morbidity. Outcome and complications were noted during clinical and out-patient clinic follow-up.

**Operative procedures**

In all patients the suspicion of anastomotic leakage was established on clinical examination, laboratory test and/or CT-scanning. Operative procedure consisted of inspection and exploration, followed by culturing and rinsing of the abdominal cavity. Ileoanal, coloanal and low colorectal anastomosis were diverted by creating a loop ileostomy and rinsing of the rest colon. In case of major breakdown the afferent loop was exteriorized as an end stoma. In case of anastomotic leakage after intra-abdominal resections, the anastomosis was dismantled and an end colostomy was created in case of anatomic leakage after left-sided resections. An end ileostomy was created after right-sided resections.

During laparoscopic reintervention the prior trocar wounds were used for insertion of a blunt TrocDoc® trocar establishing the pneumoperitoneum. The total reintervention was performed laparoscopically and the mini-laparotomy, which was used for specimen retrieval the first operation, was only opened when necessary. Wound closure and postoperative wound care were at the discretion of the attending surgeon. All open procedures were performed or supervised by one of the two colorectal surgeons. All laparoscopic procedures and laparoscopic reinterventions were performed by a single laparoscopic trained colorectal surgeon.

**Definitions**

The presence of anastomotic leakage was defined by clinical criteria and operative findings: laboratory abnormalities and clinical deterioration with signs of peritonitis at physical examination, with or without radiologically confirmed leakage. Operative finding had to include a collection of pus or faecal material related to an insufficient anastomosis and signs of (general) peritonitis. Furthermore, there had to be a positive culture indicating intestinal bacteria. Morbidity was defined as all complications within 30 days after the
reintervention. Incisional herniation was assessed at long term follow up during a survey in September 2006. ICU and hospital stay are given as the total number of days patients stayed at the ICU or in the hospital respectively, after the reintervention.

**Statistics**
Data are presented as median values with ranges for continuous data, unless otherwise specified. Categorical data are presented as frequencies or percentages. Differences between groups were tested using Mann-Whitney $U$ test for continuous data. The Fisher’s exact test was used to test for differences between groups in case of categorical data. A p-value <0.05 was considered statistically significant for all tests. Statistical analysis was done using the SPSS v.12.0 package (SPSS, Chicago, Illinois, USA).

**Results**

**Patient characteristics**
Between January 2003 and January 2006, 398 consecutive patients underwent colorectal resection with intestinal anastomosis and without diverting stoma. Two hundred fifty one (63%) patients underwent open resection and 147 (37%) underwent a laparoscopic resection. Subsequently, 26 (6.5%) patients were reoperated for anastomatic leakage. In 11 (7.5%) patients the anastomotic leakage developed after a prior laparoscopic colorectal resection. Ten patients were reoperated on laparoscopically and were included in the laparoscopic group. The remaining patient was excluded from the analysis because this patient underwent an open reintervention on postoperative day six after an initial laparoscopic left colectomy. In this patient the anastomosis was dismantled and a colostomy was constructed. Postoperatively, there was an episode of dyspnoea due to cardiac decompensation. On postoperative day 14 the patient was discharged. No wound or abdominal wall complications were observed. Relaparotomy for anastomotic leakage was performed in 15 (6.0%) patients who had primary open surgery (open group).

Primary operations of the 25 included patients consisted of 16 segmental colonic resections, five restorative proctocolectomies and four other procedures (*Table 1*). The number of included open and laparoscopic procedures was comparable between the first and second study period. Five patients participated in different randomised trials in which patients were randomised between open and laparoscopic surgery.

Although, previous abdominal surgery was not an absolute contraindication there was a non significant trend to more patients with a history of midline laparotomy in the open group (p=0.09). Furthermore, patients in the laparoscopic- and open group were comparable for age, gender, ASA classification, surgical indication, type of initial procedure, and preoperative APACHE II score (*Table 1*). Median length of time from the primary operation to reintervention was six days in both groups.
Table 1. Patients characteristics of the 25 patients included in this study

<table>
<thead>
<tr>
<th></th>
<th>laparoscopic group (n=10)</th>
<th>open group (n=15)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)†</td>
<td>45 (17-71)</td>
<td>45 (20-79)</td>
<td>0.78</td>
</tr>
<tr>
<td>Sex (male: female)</td>
<td>3:7</td>
<td>7:8</td>
<td>0.68</td>
</tr>
<tr>
<td>BMI (kg/m²)†</td>
<td>22.4 (16.6-28.1)</td>
<td>22.2 (16.8-32)</td>
<td>0.96</td>
</tr>
<tr>
<td>ASA I/II/III</td>
<td>5/5/0</td>
<td>6/8/1</td>
<td>0.67</td>
</tr>
<tr>
<td>Previous midline laparotomy*</td>
<td>1 (10%)</td>
<td>7 (47%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Indication for surgery</td>
<td></td>
<td></td>
<td>0.40</td>
</tr>
<tr>
<td>- Inflammatory bowel disease</td>
<td>6</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>- Malignancy</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>- Diverticulitis</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>- Other</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Initial procedure</td>
<td></td>
<td></td>
<td>0.83</td>
</tr>
<tr>
<td>- Right sided colonic resection</td>
<td>3</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>- Left sided colonic resection</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>- (Low) anterior resection</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>- Restorative proctocolectomy</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>- Other procedures</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Length to reintervention (days)†</td>
<td>6 (3-9)</td>
<td>6 (2-11)</td>
<td>0.74</td>
</tr>
<tr>
<td>APACHE II score prior to reintervention†</td>
<td>10 (7-15)</td>
<td>10 (5-17)</td>
<td>0.89</td>
</tr>
</tbody>
</table>

†Median (range); *Absolute number (percentage); ASA: American Society of Anaesthesiologists; APACHE II: Acute Physiology and Chronic Health Evaluation II; BMI: Body mass index

Reintervention
There were no conversions in the laparoscopic group. The minilaparotomy needed to be opened in two (20%) patients, both after right sided resection in order to exteriorize the afferent loop as an ileostomy and to exteriorize the efferent loop for closure or mucus fistula creation.

In the laparoscopic group no intra-operative morbidity was reported. In the open group there was one iatrogenic bowel perforation requiring an additional bowel resection. Median operation time was not significantly different in the laparoscopic group as compared to the open group (116 versus 105 minutes; p=0.52).

Four patients (27%) in the open group underwent a second reoperation compared to none in the laparoscopic group (p=0.13). In two patients the reoperation was a planned second look operation as part of a randomised trial comparing relaparotomy on demand or planned laparotomy, one patient was reoperated for a blow out of the ascending colon, and one patient was reoperated for a dehiscent fascia.

Short term outcome
Median length of ICU admission was shorter in the laparoscopic group compared to the open group. There was less postoperative morbidity within the first 30 days after reintervention in the laparoscopic group, although this difference was not statistically different (p=0.087). In the laparoscopic group four (40%) patients had one or more complications. Complications in the laparoscopic group consisted of abscesses (n=3), wound healing disorders (n=1), cardiovascular complications (n=1), psychiatric complications
(n=1), and prolonged postoperative ileus (n=1). In the open group 12 (80%) patients had one or more complications. Complications in the open group consisted of abscesses (n=5), wound healing disorders (n=3), ongoing sepsis (n=3), cardiovascular complications (n=2), and respiratory complications (n=1). First stoma output and return to a normal diet occurred significantly earlier in the laparoscopic group compared to the open group. Median hospital stay in the laparoscopic group was nine (range 6-28) days compared to 13 (range 7-38) days in the open group (p=0.06). One patient (10%) in the laparoscopic group and two (13%) patients in the open group were readmitted within 30 days (p=1.0). Furthermore, in both the laparoscopic group and open group one patient was readmitted after 30 days, respectively for abdominal abscesses and dehydration (see Table 2).

<table>
<thead>
<tr>
<th>Table 2. Operative data of the reintervention and postoperative course of the 25 patients included in this study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>laparoscopic</strong></td>
</tr>
<tr>
<td>Operation duration (minutes) †</td>
</tr>
<tr>
<td>Procedure:</td>
</tr>
<tr>
<td>- end ileostomy</td>
</tr>
<tr>
<td>- diverting ileostomy</td>
</tr>
<tr>
<td>- end colostomy</td>
</tr>
<tr>
<td>- diverting colostomy</td>
</tr>
<tr>
<td>APACHE II score postoperatively †</td>
</tr>
<tr>
<td>ICU stay (days) †</td>
</tr>
<tr>
<td>Postoperative 30 day morbidity*</td>
</tr>
<tr>
<td>Resumption normal diet (days) †</td>
</tr>
<tr>
<td>First stoma output (days) †</td>
</tr>
<tr>
<td>Hospital stay (days) †</td>
</tr>
<tr>
<td>Readmissions within 30 days*</td>
</tr>
<tr>
<td>Incisional hernia*</td>
</tr>
<tr>
<td>Stoma closure rate*</td>
</tr>
</tbody>
</table>

†Median (range); *Absolute number (percentage); APACHE II: Acute Physiology and Chronic Health Evaluation II; ICU: Intensive Care Unit

**Long term outcome**

There were less patients with incisional hernias in the laparoscopic group; zero versus five (33%), although this difference was not statistically significant (p=0.06). In eight (80%) patients in the laparoscopic group the stoma had been closed. This was done after a median of five (range 2-12) months. In nine (60%) patients in the open group the stoma had been closed. This was done after a median six (range 3-16) months (p=0.40). Two patients in the open group underwent an extensive abdominal wall reconstruction during the same procedure the stoma was closed. In the laparoscopic group one patient underwent a surgical correction of a post-stoma scar. There were no other abdominal wall reconstructions in both groups during the study period. Median follow-up was 22 (range 12-28) months in the laparoscopic group and 22 (range 10-48) months in the open group (p=0.72). None of the patients was lost to follow up.
Discussion

Laparoscopy has gained widespread acceptance in common surgical practice as a diagnostic and therapeutic tool. Over the past years abdominal emergencies have been increasingly managed by laparoscopy, including those patients with peritonitis.\textsuperscript{13,17-21} The present study showed that a laparoscopic reintervention after primary laparoscopic surgery for anastomotic leakage is feasible and may be safe in terms of conversions, intra-operative morbidity, necessity of opening the minilaparotomy, and operating time. In addition, laparoscopic reintervention may be associated with less postoperative morbidity, a faster recovery and fewer abdominal wall complications as compared to open reintervention after primary open surgery.

Reintervention for anastomotic leakage is generally done 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. After primary laparoscopic surgery the previously used trocar incisions can easily be re-used. In this series of patients the pneumoperitoneum was established through a prior trocar wound by an open entry technique using a blunt trocar.\textsuperscript{22} This technique minimizes the risk of bowel injury, even in case of distended bowel. A laparoscopic reintervention after open surgery might be appealing avoiding wound problems and incisional hernia. However, installation of the pneumoperitoneum is more difficult, because the trocars need to be inserted in open manner or blindly after using the Veress needle.

The morbidity observed in our study is comparable with the percentage reported in literature.\textsuperscript{5,6} However, in our series of patients no mortality was observed in both groups. In part, this can be explained by the fact that in our series patients were relatively young, since a great part of these patients were operated because of inflammatory bowel diseases. Nonetheless, this observation is limited due to a small sample size. APACHE II scores preoperatively and within 24 hours after surgery were moderately elevated, indicating mild peritonitis and a non delayed diagnosis and reintervention for anastomotic leakage in both the laparoscopic and the open group.

Laparoscopic reintervention after primary laparoscopic surgery can be initiated as an early diagnostic tool to confirm the anastomotic leakage or to explore and identify other causative pathology if patients do not improve as expected after laparoscopic surgery. Recovery after laparoscopic surgery is generally fast.\textsuperscript{9,10} If the patient is not able to tolerate a normal diet within a couple of days in combination with signs of infection, anastomotic leakage must be suspected. For this reason, it could be hypothesized that patients after laparoscopic surgery might have their reintervention earlier than after open surgery. This earlier reintervention might prevent severe generalized peritonitis and systemic sepsis. However, long standing peritonitis with pus pockets and inflammatory adhesions is probably not amenable for laparoscopic treatment.

Following open surgery the systemic immunological function is depressed with adverse alterations in cytokine levels and changes in the function of cellular components of the systemic immune response. Furthermore, functions of the peritoneal macrophages are
better preserved when laparotomy is avoided. Others suggests that a laparoscopic approach might be beneficial in the surgical management of intra-abdominal sepsis and results in fewer postoperative septic complications.\textsuperscript{23,24} However, further research is warranted on the effect of laparoscopy and the pneumoperitoneum on the intra-abdominal immune system in the presence of peritonitis.

Another important advantage of laparoscopic reintervention might be a reduction in wound complications such as early dehiscence and incisional herniation. However, the results of the present study must be interpreted carefully because of several limitations. First of all it comprises a small single centre retrospective study. Secondly, the surgical indications and primary procedure were variable. Although patient characteristics were comparable between both groups and considering the fact that the indication to perform the initial procedure laparoscopically was mainly based on referral pattern, selection bias could not be ruled out completely.

Furthermore, the included patients were not representative for the typical selection of laparoscopic surgery. While the majority of laparoscopic resections are currently performed for diverticular disease, adenoma and early stage cancer the majority of the laparoscopic patients in the present study were operated on for inflammatory bowel disease.

The severity of the anastomotic leakage; \textit{i.e.} the extent of peritonitis and severity of sepsis were only assessed with the APACHE II scoring system and positive cultures. Although in both groups patients had there reintervention at the same time after the first operation and the APACHE II scores before and after the reintervention were the similar, we do not have other objective data on the extent and severity of the peritonitis such as the Mannheim peritonitis index or other scoring systems for severity of disease.\textsuperscript{25,26} Furthermore, all laparoscopic procedures were performed by an experienced laparoscopic surgeon and potentially this may have influenced the outcome.

Nonetheless, these preliminary data suggest that a laparoscopic reintervention for anastomotic leakage after primarily laparoscopic surgery is probably feasible and might be safe. While no conversions and intra-operative complications were observed. Furthermore, a laparoscopic reintervention tends to be associated with less postoperative morbidity, a faster recovery and fewer abdominal wall complications.

Ideally, a prospective trial should confirm these data. To evaluate the effect of laparoscopic reintervention after primary laparoscopic surgery, it has to be part of a very large study randomising patients for a laparoscopic or open initial procedure.

**Reference List**


(6) Alberts JC, Parvaiz A, Moran BJ. Predicting risk and diminishing the consequences of anastomotic dehiscence following rectal resection. Colorectal Dis 2003;5:478-482.


Chapter 9

Staple line failure using the Proximate® 100 mm linear cutter

J Wind
F Safiruddin
MI van Berge Henegouwen
JFM Slors
WA Bemelman

Diseases of the Colon and Rectum, in press
Abstract

Introduction
An incomplete linear staple line that was discovered during the stapling of an ileal pouch alerted us to evaluate potential usage concerns with linear cutters. This study was designed to assess the integrity of the staple line of three different sizes of linear staplers.

Methods
In an animal model three different lengths of linear cutters (Proximate®, Ethicon Endo-Surgery) were used to cross-staple and transect the large bowel of one pig to check for the integrity of the proximal end of the staple line.

Results
Cross-stapling and transecting across the pig’s large bowel demonstrated that if the tissue is advanced up to the highest number on the scale of the 100 mm stapling device, insufficient overlap between the proximal end of the staple line and the proximal end of the cut line occur.

Conclusion
Although a more than 100 mm staple line is delivered, the 100 mm cutter may not produce a double-staggered row of staples at the most proximal end of the staple line if the tissue is advanced past the 9.5 cm mark. Ethicon Endo-Surgery has agreed to add indicator markers to the scale label on the instrument to provide the user with additional guidance for tissue placement.
Introduction

Several risk factors for anastomotic insufficiency have been identified.\textsuperscript{1-3} Despite the identification of these 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 contribute to anastomotic insufficiency if they malfunction or are used inappropriately. Concerning surgical stapling devices the United States Food and Drug Administration (FDA) received reports of 22,804 malfunctions, 2,180 injuries, and 112 deaths from 1992 up to July 1, 2001. These numbers include all types of linear and circular stapling devices as well as clip appliers. Most of these reports comprised device or user related errors of linear cutters and staplers. Furthermore, the majority of operations reported were gastrointestinal. Failure of stapler devices to function or be used properly, resulted in suture line separation or leak as the most commonly reported problem.\textsuperscript{4} However, when interpreting these data it should be kept in mind that besides the fact that staplers are used very frequently, the exact denominator is not known. This subscribes the importance of understanding the correct usage of the device, as well as the appropriate surgical techniques to inspect and verify staple lines and staple formation, and the techniques to employ should issues occur.\textsuperscript{5} Nevertheless, despite correct usage staple line failure might still occur.

The following case alerted us to evaluate the function of a linear cutter (Proximate\textsuperscript{®} 100 mm-TLC10, Ethicon Endo Surgery).

Case
A patient with ulcerative colitis was referred for a laparoscopic restorative proctocolectomy because of recurrent disease relapses despite extended medicinal therapy (no steroid use preoperatively).

One firing of a 100 mm linear cutter (Proximate\textsuperscript{®} TLC10, Ethicon Endo Surgery) was used to construct the (relatively) small ileal pouch extracorporally. Subsequently, the anvil of the circular stapler was placed in the base of the pouch to create a double-stapled ileoanal anastomosis. The donuts were checked for their integrity and proved to be intact. During the operation there was no significant blood loss and there were no intraoperative adverse events.

The procedure was ended by the transanal insertion of a 24 Fr Foley catheter (outside diameter 8 mm) in the pouch for temporary postoperative pouch decompression, because there was no indication for a defunctioning ileostomy. During insertion it was noticed that the drain could be pushed in much further than expected without resistance. This unexpected observation urged reinstallation of the pneumoperitoneum. Inspection showed that the drain emerged in between the mesentery of the pouch and the pouch itself suggesting a failure of the posterior linear staple line. Subsequently, the drain was pulled back and a defunctioning ileostomy was constructed. The defect in the pouch was not repaired because of its difficult approachability.
The gap in the staple line was identified at the most proximal end of the linear cutter staple line. After this incident, we investigated the proximal portion of the staple line of three different sizes of linear cutters after cross-stapling of the large bowel of a pig.

**Methods**

To investigate whether insufficiency of the proximal staple line would occur if cross-stapling of the bowel was performed according to the users’ manual three different lengths of linear cutters from the same company (Proximate® 55 mm-TLC55, 75 mm-TLC75 and 100 mm-TLC10, Ethicon Endo-Surgery) were used to cross-staple the large bowel of one pig. The pig (female, 10 weeks old, weight 30 kilograms) was sacrificed after a prior experiment which was not related to the bowel. The large bowel of a pig was chosen because this offered the same tissue characteristics as human tissue compared with artificial material (e.g. PTFE). The complete experiment was approved by the institutional animal ethics committee. Special attention was paid to the positioning of the bowel in the cutter; the tissue was not advanced further than the end marks on the cutter.

After firing the cutter, the proximal area of the two double-staggered rows of staples was photographed and visually evaluated for staple pattern and placement. Subsequently, in the presence of a gap in the staple line, the gap was measured by using a pair of pickups. The lab experiments were witnessed by representatives of the device manufacturer.

**Results**

Three different lengths of linear cutters (Proximate® 55 mm-TLC55, 75 mm-TLC75 and 100 mm-TLC10, Ethicon Endo Surgery) were used to cross-staple the large bowel of one pig. Each cutter was fired three times.

The cross-stapling of the pigs large bowel demonstrated that the 100 mm cutter did not produce a double-staggered row of staples at the most proximal end of the staple line if the tissue was advanced up to the 10 mark on the stapling device. At the proximal end of the staple line the bowel was cut but not stapled resulting in a gap ranging between three and five mm (Figure 1). The 55 and 75 mm cutters produced visually adequate staple line patterns, provided that the tissue was not squeezed or forced in beyond the five (TLC55) and seven (TLC75) marks respectively during closure of the stapler. If tissue was squeezed or forced proximal to these marks, cutting without stapling occurred. Inspection of the three sizes of linear cutters demonstrated that the 100 mm cutter does not have a staple overlap (double-staggered row) at the proximal end of the device. In Figure 2 it is shown that the two double-staggered rows of staples stop at the 9.5 mark and only a single staple is positioned proximally. Therefore, advancing the tissue to the 10 mark will cause cutting without stapling resulting in a five mm gap. If the tissue is forced into the device while closing, the gap is even longer.
Figure 1. Large bowel of a pig after stapling close to the proximal end of the 100 mm Proximate® linear cutter (TLC10, Ethicon Endo Surgery). At the proximal end of the staple line, the bowel is cut but not stapled, leaving gap of 3 mm.

Figure 2. The proximal end of the 100 mm Proximate® linear cutter (TLC100, Ethicon Endo Surgery) in detail. The two double-staggered rows of staples stop already at 95 mm and a single staple is positioned proximal. Users should not position the tissue up to the 100 mm mark because the cutter divides the tissue beyond 100 mm, resulting in a small gap of several millimetres.
Discussion

Both the presented case and animal model demonstrated that when using the 100 mm Proximate® linear cutter (TLC10, Ethicon Endo Surgery) care must be used when stapling tissue close to the proximal end of the cutter. As shown in Figure 2 the row of staples stops between the 10 and 9.5 indicators and only at the 9.5 mark a double-staggered row is present. Beyond this point there is a possibility that the intestine is cut but not stapled, leaving a gap of several millimetres.

Post market surveillance data by the manufacturer for the TLC10 device during a two-year period showed no additional serious injury reports for leaking or incomplete staple lines, which potentially could be related to the described staple pattern. The incidence of clinically significant problems associated with this stapler is low, because it probably only occurs when the 100 mm cutter is used for its full length, stapling large bowel and pouches. Since the described incident occurred, we routinely inspect the pouch after linear stapling, both anteriorly and posteriorly, by inversion of the pouch to check for insufficiency of the proximal staple line. If an insufficiency is identified, it is most commonly located both anteriorly and posteriorly, and the gap can usually accommodate at least one leg of a pair of pickups (Figure 3). On the posterior site, the hole is oversewn and at the anterior site of the pouch the hole is incorporated in the purse string of the anvil of the circular stapler. In case of a side-to-end colonic anastomosis, the proximal end of the cross-stapling line is routinely checked and oversewn if necessary.

Figure 3. Schematic drawing of the construction of a pouch using the 100 mm Proximate® linear cutter (TLC10, Ethicon Endo Surgery). A small gap of several millimetres arises when the cutter is used to its full length because of cutting without stapling (A, arrow). Both on the anterior and posterior site of the pouch, a small gap (*) is present because of cutting without stapling (B).
The observations in the animal model have been witnessed by employees of the manufacturer. The manufacturer has agreed to add indicator markers to the scale label on the instrument, to provide the user with additional guidance for tissue placement. However, no further changes to the proximal part are planned. As shown in Figure 4, an arrow has been added to the scale labels of all three lengths of cutters to be consistent and to indicate recommended tissue placement. As a result of the findings presented in this paper, the following comment was added to the instructions for use; “Tissue to be transected must be located between the arrows marked on the instrument jaw. Any tissue located outside of the arrows is out of the stapling range.” The existing warning: “After removing the instrument, examine the staple lines for haemostasis/pneumostasis and proper staple closure.” is worth noting, because it is good clinical practice to check the staple line to ensure that tissue condition, technique, and device did result into an intact staple line. Whenever there is a question regarding the sealing of a staple line, it is advisable to perform a leak test. This is routinely recommended when using the circular staplers.
Figure 4. The anvils of the 100 mm, 75 mm, and 55 mm Proximate® linear cutters (Ethicon Endo Surgery), with the added arrows to indicate the tissue stapling range for the devices, to ensure presence of a double-staggered row of staples at the point of tissue placement.

Reference List

(1) Alberts JC, Parvaiz A, Moran BJ. Predicting risk and diminishing the consequences of anastomotic dehiscence following rectal resection. Colorectal Dis 2003;5:478-482.


Temporary closure of the open abdomen; a systematic review on delayed primary fascial closure in patients with an open abdomen

P Boele van Hensbroek
J Wind
MGW Dijkgraaf
ORC Busch
JC Goslings

Submitted
Abstract

Introduction
In some severe cases of peritonitis or abdominal trauma the abdomen cannot be closed at the end of the laparotomy due to swelling of the abdominal contents or packing. This so-called “open abdomen” must then be temporarily closed. The aim of the present study was to systematically review the literature on temporary abdominal closure (TAC) of the open abdomen and to assess which TAC technique, controlled for potential confounders like age, sex, and the presence of fistulae or abscesses, is associated with the highest delayed primary fascial closure (FC) rate.

Methods
The Cochrane Register of Controlled Trials, MEDLINE and EMBASE databases were searched until December 2007. References were checked for additional studies. Search criteria included (synonyms of) “open abdomen”, “fascial closure”, “vacuum”, “re-approximation” and “ventral hernia”. Open abdomen was defined as the inability to close the abdominal fascia after laparotomy. Two reviewers independently extracted data from original articles using a predefined checklist.

Results
The search identified 154 abstracts of which 96 were considered relevant. No comparative studies were identified. After reading them, 51 articles, including 57 case series were included. The techniques described were Vacuum Assisted Closure (VAC) (8 series), Vacuum pack (15 series), Artificial burr (4 series), Mesh/sheet (16 series), Zipper (7 series), Silo (3 series), Skin closure (2 series) Dynamic Retention Sutures (DRS), and Loose packing (1 series each).  The highest FC rates were seen in the Artificial burr (90%), DRS (85%), and VAC (60%). The lowest mortality rates were seen in the Artificial burr (17%), VAC (18%), and DRS (23%).

Conclusions
These results suggest that the TAC techniques that keep permanent traction on the fascial edges (e.g. VAC, DRS, and Artificial burr) show the highest FC rates and the lowest mortality rates.
Introduction

At the end of most laparotomies, the abdominal fascia can be closed primarily at the end of the operation. However, sometimes full fascial closure is precluded by the condition of the patient or the bowel and open abdominal treatment is necessary. These patients are often severely ill and the open abdomen is therefore associated with mortality rates over 50%.

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), Abdominal Compartment Syndrome (ACS) and abdominal trauma (damage control surgery). Peritonitis is often caused by anastomotic leakage or bowel perforation. The associated severe bowel oedema opposes fascial closure. Damage control surgery in trauma patients consists of rapid assessment of the abdominal injuries and control of bleeding by direct suture/ligation or packing with gauzes to stop the bleeding before transport to the Intensive Care Unit (ICU) or angio-intervention for further resuscitation. The bowel oedema due to massive resuscitation with intravenous fluids and/or the presence of the packing gauzes may preclude full fascial closure in these patients.

ACS is characterized by an increased intra-abdominal pressure which compromises the respiratory, renal, and cardiac function of a patient. This condition is commonly caused by bowel oedema following intra-abdominal infection, abdominal trauma or massive fluid resuscitation. A ‘decompressing laparotomy’ is often indicated to relieve the intra-abdominal pressure. Due to the extended bowel and as part of the treatment, the abdomen is not closed.

In open abdomen treatment, the need arises for temporary abdominal closure (TAC). Several techniques for TAC have been described over the past years including mesh or foil insertion, sterilised IV bag insertion, Velcro or zipper closure, and skin closure with towel clips. Several articles have described the application of a fluid drainage system with drains. In recent years, the application of the Vacuum Assisted Closure (VAC®) system has been described and popularised for TAC of the open abdomen. All these techniques not only vary in the way they cover the abdominal contents, but also the amount of traction that is applied on the abdominal fascia to prevent lateral retraction, differs between the techniques. Because, during open abdominal treatment, the fascial edges tend to retract laterally due to continuous traction from the (oblique) lateral abdominal musculature which might be prevented by traction to the fascial edges. The different techniques for TAC are listed in Table 1.

Following open abdominal treatment, the abdominal fascia can be closed primarily, with a mesh or granulation tissue covered by a split skin graft. Rationales for permanent coverage of the open abdomen with a mesh or granulation tissue include persistent visceral oedema, loss of domain due to trauma, infection, lateral retraction or delayed primary fascial closure is simply not attempted at all. When delayed primary fascial closure is not possible these patients develop a ventral hernia. The extent of these so-called ‘planned ventral hernias’ varies from small and asymptomatic to very large. In case of physical or cosmetic complaints, the ventral hernia needs to be surgically corrected once the patient

Chapter 10
Temporary closure of the open abdomen
has recovered. However, recovery frequently takes several months in these patients and a ventral hernia may cause a considerable burden. Furthermore, reconstructive surgery, like every operative procedure, carries a risk of morbidity and mortality. These burdens and risks associated with (planned) ventral hernias should be taken into account when deciding on the strategy for TAC and whether or not to attempt fascial closure during the index admission. Delayed primary fascial closure avoids ventral hernias and can therefore be considered as the preferred outcome. However, no (randomised) comparative trials have been conducted evaluating the effect of different strategies on the rate of delayed primary fascial closure. Furthermore, it is unknown which other factors may influence the fascial closure rate during index admission. Therefore, the aim of the present study was

<table>
<thead>
<tr>
<th>Technique</th>
<th>Description</th>
<th>Re-approx*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vacuum Assisted Closure (VAC®)</td>
<td>A perforated sheet is placed over the abdominal contents and under the fascial edges. A sponge is cut in the correct size and sutured to the facial edges. The entire wound is then covered by a drape which is opened in the middle to allow a suction drain pass through. The suction drain is connected to a pump and fluid collection system which keeps constant negative pressure on the wound.</td>
<td>Yes</td>
</tr>
<tr>
<td>Vacuum pack</td>
<td>A perforated plastic sheet is laid over the abdominal contents and covered by damp surgical towels. A surgical drain is placed on top of the towels and the entire wound is covered by an airtight seal. The drain is then attached to two bulb suctions to keep negative pressure on the wound.</td>
<td>Yes</td>
</tr>
<tr>
<td>Artificial burr (Wittmann patch)</td>
<td>Two opposite Velcro sheets (hooks and loops, one on each side) are sutured to the facial edges. This allows for easy access and stepwise re-approximation on the fascial edges.</td>
<td>Yes</td>
</tr>
<tr>
<td>Dynamic retention sutures</td>
<td>Horizontal sutures are placed through a large-diameter bolster and through the skin and fascia on both sides. The sutures may then be tightened to allow staged re-approximation of the fascial edges.</td>
<td>Yes</td>
</tr>
<tr>
<td>Plastic silo (Bogotá bag)</td>
<td>A sterile x-ray film cassette bag or sterile 3-Litre genitourinary irrigation bag is sutured between the fascial edges and opened in the middle. This allows for easy re-entry and can be taken in to approximate the fascial edges.</td>
<td>Yes</td>
</tr>
<tr>
<td>Mesh/sheet</td>
<td>An absorbable or non-absorbable mesh or sheet is sutured between the fascial edges. The mesh or sheet can either be removed or left in place at the end of the open abdominal treatment. Examples are the Dexon mesh, Marlex mesh, and Vicryl mesh. Examples of Sheets are the Silastic or silicone sheets.</td>
<td>No</td>
</tr>
<tr>
<td>Loose packing</td>
<td>The fascial defect is covered by dressing only.</td>
<td>No</td>
</tr>
<tr>
<td>Skin approximation</td>
<td>The skin is closed over the fascial defect with either towel clips or a running suture.</td>
<td>No</td>
</tr>
<tr>
<td>Zipper</td>
<td>A mesh or sheet with a sterilized zipper is sutured between the fascial edges. This only allows for easy re-entry.</td>
<td>No</td>
</tr>
</tbody>
</table>

*Re-approx: technique aimed at re-approximation of the edges of the abdominal fascia.*
to systematically review the literature on temporary closure of the open abdomen and to assess which TAC technique, controlled for potential confounders like age, sex, and the presence of fistulae or abscesses, is associated with the highest delayed primary fascial closure rates.

Methods

Literature search
The Cochrane Database of systematic reviews, the Cochrane central register of controlled trials, and MEDLINE databases were searched using keywords related to open abdominal treatment (Table 2). The search period started in 1966 and extended until December 2007. Electronic links to related articles and references of selected articles were hand-searched as well. A manual search of relevant journals and conference proceedings was not performed. The search was not restricted to any language, however in the systematic review only studies published in English, German or Dutch were taken into account.

Table 2. Search terms, as used in the systematic review

<table>
<thead>
<tr>
<th>Search terms</th>
<th>MeSH:</th>
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<tr>
<td>MeSH:</td>
<td>Not used</td>
</tr>
<tr>
<td>Free Text words:</td>
<td>(open abdomen OR laparostomy OR open peritoneal cavity OR celiotomy OR open management abdomen OR abdominal wall defect OR open abdominal wound) AND (VAC OR V.A.C. OR vacuum OR closure OR re-approximation OR re-approximation OR fascial closure OR ventral hernia OR temporary abdominal closure OR bogota bag OR fascial dehiscence)</td>
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</table>

MeSH: medical subject headings

Study selection and data extraction
From the potentially eligible publications only studies were included that reported on open abdominal treatment and in which delayed primary fascial closure rates were reported. Series of patients of less than five and studies with a non-consecutive inclusion period were excluded. Furthermore, series that described patients with sub-costal incision, as well as series that described the use of multiple TAC techniques in the same study population were excluded. The definition of open abdominal treatment had to include the inability to close the abdominal fascia after laparotomy. Two investigators (PBvH, JW) independently extracted the following data, if reported, from the original studies using a preformatted sheet; inclusion period, number of patients, type of patients (trauma, peritonitis, pancreatitis, ACS), age, gender, Injury Severity Score (ISS), APACHE (Acute Physical And Chronic Health Evaluation) II, type of open abdominal treatment (e.g. Vacuum pack, Vacuum Assisted Closure (VAC) system, Bogota bag, Zipper, Mesh), mortality, complications (i.e. abscesses, fistulae), number of surgical interventions until final closure, duration of open abdominal
treatment, percentage of full fascial closure, additional techniques for abdominal closure, percentage of planned ventral hernias, ICU stay, length of hospital stay and length of follow-up.

Each selected study was critically appraised by the two investigators, using a modified form as proposed by the Dutch Cochrane Collaboration and assessing if a study was randomised, consecutive, prospective or retrospective, and mentioned rates of full fascial closure. In case of retrospective analysis of data collected prospectively, a study was defined as prospective. Final inclusion was done after consensus was reached. Discrepancies in judgment, if any, were resolved by discussion between the investigators. In case an article described separate series with specific patient groups (either separate underlying causes or TAC techniques) each series was assessed separately. In case of missing data the principal investigators of those publications were contacted.

Analysis and presentation of data

The characteristics of the included series were presented per technique. The delayed primary fascial closure rate was calculated by dividing the number of patients with delayed fascial closure by the total number of included patients. The mortality rate was calculated by dividing the number of deceased patients by the total number of included patients. The percentage of male patients, age, fistula rate, and abscess rate were described as the median value (and range) of the concerning series.

The examined fascial closure rate (as a proportion) was derived from the series with different TAC techniques. A random effect meta-regression approach was used to take into account the differences in sample size between studies (putting more emphasis on larger studies) and to account for remaining variability among studies beyond chance. The logit-transformed fascial closure proportion was used as the outcome variable with TAC technique as the main predictor of differences between studies, while adjusting for other univariately significant predictors of fascial closure. A backward stepwise approach was followed, starting with potential predictors with a p-value below 0.1 in the univariate analyses. Final statistical significance was set at an alpha level of 0.05 or below. All analyses were performed in SAS (Copyright © 2008 SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA).

Results

Included studies

The searches identified a total of 1493 manuscripts. Based on the title, 154 were selected. The 1339 other titles were not considered relevant. After reading the abstracts, 58 manuscripts were excluded because they did not concern open abdominal treatment, were case reports or reviews. Five of these abstracts were excluded because the articles were written in Chinese, Norwegian, French (all once), or Russian (2 articles). Ninety six abstracts were considered relevant and the complete articles were obtained. Of these, 45
articles did not meet the inclusion criteria and were therefore excluded. The remaining 51 articles were included in this review. These included articles were published between 1981 and 2007. There were no randomised controlled trials or other comparative studies. The 51 articles included a total 57 case series describing various patient groups and TAC techniques. The included case series described a total of 3169 patients. The inclusion periods ranged from six to 168 months, with a median of 48 months.

**Patient population**

Nineteen series described trauma patients only and an additional sixteen series described a mixture of trauma, vascular surgery and general surgical patients. Twenty two series described non-trauma patients of which eight with peritonitis patients only, and three with vascular patients only. The remaining 11 series described a mixture of general surgical, peritonitis, pancreatitis and vascular patients.

The gender distribution was described in 40 series (70%). The percentage of male patients ranged from 62% in the one series with Dynamic Retention Sutures to 94% in the Artificial burr series. In forty four series (77%) the mean age of the patients was reported. The median age over these series was 40.1 years (range: 29.5 to 75). Median age was the highest in the one Dynamic Retention Suture series (50 years), followed by the Zipper series (46 years) and the Silo series (44 years). Twenty one series reported on the Injury Severity Score (ISS). The median ISS ranged from 20.3 in the series that used Meshes or sheets to 30.5 in the Artificial burr series. The APACHE II score was reported in 13 series only and ranged from 17.8 in the Artificial burr series to 24.7 in the Mesh/sheet series.

**Temporary closure techniques described**

The VAC technique was applied in eight series which were published since 2003 (*Table 3a*). The Vacuum pack has been described in 15 series published since 1995 (*Table 3b*). The four series that described the application of the Artificial burr were published since 1990 (*Table 3c*). The VAC, Vacuum pack, and Artificial burr technique have all been published until 2007.

The first series that described the use of Meshes or sheets was published in 1983. The 16 other series that used Meshes or sheets were before 2005 (*Table 3d*). The first of the seven series that applied Zippers was published in 1991 and no series with Zippers have been published since 2001 (*Table 3e*). The three series in which the Silo technique was used were published between 2001 and 2007 and the two Skin only series were published in 1992 and 2001. Loose packing and Dynamic Retention Sutures were each used in one series published in 1981 and 2001 respectively (*Table 3f*).
### Table 3a. The VAC series

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<th>Prospective / retrospective</th>
<th>Group</th>
<th>Patients (n)</th>
<th>ISS</th>
<th>Technique</th>
<th>Duration of treatment (mean; days)</th>
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<th>Abscess (%)</th>
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ACS: Abdominal Compartment Syndrome; GS: General Surgery; Gs: Gastrochisis; Om: Omphalocele; NF: Necrotising Fasciitis; Pt: Peritonitis; Tr: Trauma; Retro: retrospective inclusion; Prosp: prospective inclusion; Empty boxes indicate that these data were not reported.

### Table 3b. The Vacuum pack series

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(R)AAA: (Ruptured) Abdominal Aortic Aneurysm; Bl: Bleeding; CD: Crohns Disease; GS: General Surgery; Mi: Mesenterial ischemia; Pc: Pancreatitis; Pt: Peritonitis; Va: Vascular; Tr: Trauma; VP: Vacuum pack; Retro: retrospective inclusion; Prosp: prospective inclusion; Empty boxes indicate that these data were not reported.
Table 3c. The Artificial burr series

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ACS: Abdominal Compartment Syndrome; Pt: Peritonitis; Tr: Trauma; AB: Artificial burr; Retro: retrospective inclusion; Prosp: prospective inclusion; Empty boxes indicate that these data were not reported.

Table 3d. The Mesh or sheet series

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</tr>
<tr>
<td>Mayberry</td>
<td>2004</td>
<td>Retro</td>
<td>Tr</td>
<td>140</td>
<td>M/S</td>
<td>31.2</td>
<td>18.9</td>
<td>7</td>
<td>5</td>
<td>17</td>
<td>31</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AAA: (Ruptured) Abdominal Aortic Aneurysm; ACS: Abdominal Compartment Syndrome; GS: General Surgery; Mi: Mesenterial ischemia; Pc: Pancreatitis; Pt: Peritonitis; Va: Vascular; Tr: Trauma; M/S: Mesh/Sheet; Retro: retrospective inclusion; Prosp: prospective inclusion; Empty boxes indicate that these data were not reported.
Table 3e. The zipper series

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Prospective / retrospective Group</th>
<th>Patients (n)</th>
<th>APACHE-II (mean)</th>
<th>Technique</th>
<th>Duration of treatment (mean; days)</th>
<th>Re-laparotomies (mean)</th>
<th>Fistula (%)</th>
<th>Abscess (%)</th>
<th>Mortality (%)</th>
<th>Closure (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cuesta</td>
<td>1991</td>
<td>Retro Pt</td>
<td>7</td>
<td>30.0</td>
<td>Zipper</td>
<td>5.0</td>
<td>29</td>
<td>0</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bose</td>
<td>1991</td>
<td>Retro Pt</td>
<td>5</td>
<td>Zipper</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>20</td>
<td>38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hannon</td>
<td>1992</td>
<td>Pt; Mi</td>
<td>8</td>
<td>19.9</td>
<td>Zipper</td>
<td>12.6</td>
<td>5.1</td>
<td>0</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Singh</td>
<td>1993</td>
<td>Pt</td>
<td>8</td>
<td>28.3</td>
<td>Zipper</td>
<td>10.5</td>
<td>4.6</td>
<td>5.1</td>
<td>25</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Hubens</td>
<td>1994</td>
<td>Pt; NEC; Pc</td>
<td>23</td>
<td>20.3</td>
<td>Zipper</td>
<td>3.9</td>
<td>0</td>
<td>39</td>
<td></td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Goor, van</td>
<td>1997</td>
<td>Retro Pt; Mi</td>
<td>24</td>
<td>Zipper</td>
<td>14.0</td>
<td>6.6</td>
<td>17</td>
<td>4</td>
<td>29</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>Zingales</td>
<td>2001</td>
<td>Retro Pt; Pc; IC; Pi</td>
<td>60</td>
<td>19.7</td>
<td>Zipper</td>
<td>7.7</td>
<td>13</td>
<td>38</td>
<td>20</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IC: Ischemic Colitis; Mi: Mesenterial ischemia; NEC: Necrotising Enteroclitis; Pc: Pancreatititis; Pi: Parietal Incompetence; Pt: Peritonitis; Tr: Trauma; Retro: retrospective inclusion; Prospt: prospective inclusion; Empty boxes indicate that these data were not reported.

Table 3f. The Silo, Skin, Loose packing, and Dynamic Retention Suture series

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Prospective / retrospective Group</th>
<th>Patients (n)</th>
<th>ISS (mean)</th>
<th>APACHE-II</th>
<th>Technique</th>
<th>Duration of treatment (mean; days)</th>
<th>Re-laparotomies (mean)</th>
<th>Fistula (%)</th>
<th>Abscess (%)</th>
<th>Mortality (%)</th>
<th>Closure (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doyon</td>
<td>2001</td>
<td>Retro Pt</td>
<td>17</td>
<td>19.4</td>
<td>Silo</td>
<td>15.2</td>
<td>6.5</td>
<td>0</td>
<td>6</td>
<td>18</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>Tremblay</td>
<td>2001</td>
<td>Retro Tr; Bl; Pc; Mi</td>
<td>75</td>
<td>23.6</td>
<td>Silo</td>
<td>53</td>
<td>17</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kushimoto</td>
<td>2007</td>
<td>Retro Tr; NT</td>
<td>17</td>
<td>Silo</td>
<td>17.6</td>
<td>0</td>
<td>31</td>
<td>29</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smith</td>
<td>1992</td>
<td>Tr</td>
<td>8</td>
<td>Skin</td>
<td>25</td>
<td>75</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tremblay</td>
<td>2001</td>
<td>Retro Tr; Bl; Pc; Mi</td>
<td>93</td>
<td>23.6</td>
<td>Skin</td>
<td>40</td>
<td>40</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duff</td>
<td>1981</td>
<td>Retro Tr; Pt</td>
<td>18</td>
<td>LP</td>
<td>28</td>
<td>39</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Koniaris</td>
<td>2001</td>
<td>Retro Tr; Pt; IL; AAA; CS; Pc</td>
<td>13</td>
<td>43.0</td>
<td>DRS</td>
<td>2.8</td>
<td>23</td>
<td>85</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Bl: Bleeding; Mi: Mesenterial ischemia; NT: Non-Trauma; Pc: Pancreatititis; Pt: Peritonitis; Va: Vascular; Tr: Trauma; LP: Loose packing; Skin: Skin only closure; Silo: plastic silo closure; Retro: retrospective inclusion; Empty boxes indicate that these data were not reported.

Fascial closure

As shown in Table 4, the highest pooled fascial closure rates corrected for study size (1/variance) were achieved in the techniques that applied continuous traction on the fascial edges to prevent lateral retraction. The series in which the Artificial burr was used achieved the highest pooled closure rate (90%). The second highest pooled closure rate was achieved by the one series that used the Dynamic Retention Sutures (85% closure), followed, in third place, by the series that used the VAC technique (60% closure). The
closure rates in the other techniques ranged from 11% in the one series with Skin only closure to 52% in the Vacuum pack series.

**Fistulae and abscesses**
The occurrence of fistulae as a complication of TAC was reported in 44 series (75%) and is shown in Table 4. The highest pooled fistulae rate (1/variance) was observed in the series that used Loose packing (28%). However, this was only one series with eighteen patients. The second highest fistulae rate was observed in the Zipper (13.8%) series. The lowest rates of fistulae were seen in the Silo series (0%), the Artificial burr series (2.0%), the VAC series (2.9%), and the Vacuum pack series (5.7%).
The number of abscesses was reported in 29 series (49%) and the pooled rate varied per technique (Table 4). The highest pooled abscesses rate (1/variance) was observed in the Zipper series (5.8%). However, only two of the seven Zipper series reported the abscess rate. The second highest median abscess rate (4.1%) was seen in the Artificial burr series. The lowest pooled abscess rates were observed in the Mesh/sheet series (2.1%), the VAC series (2.6%) and the Artificial burr series (3.0%).

**Mortality**
The pooled mortality rate (1/variance) over all techniques was 26% (95% CI: 24 – 27). The highest overall mortality rates were seen in the Silo series (41%), and the Skin only series (39%). The lowest overall mortality rates were observed in the Artificial burr series (17%) and the VAC series (18%). The lowest mortality rates were observed in the four techniques that showed the highest fascial closure rate (Table 4).

**Meta-regression analysis**
Based on the results above, the authors identified a set of possible predictive factors for delayed primary fascial closure (from the case series). These factors included intrinsic pre-TAC factors; the TAC technique, nature of the underlying condition, gender, age, ISS, and APACHE II. Intrinsic factors known during the TAC were duration of the treatment, mortality, duration of hospital stay, duration of ICU stay, number of surgical reinterventions, and percentage of fistulae and abscesses. Qualitative predictors which were known at the start of the TAC were the year of inclusion and the country in which the study took place.

Univariate logit-transformed meta-regression identified eight significant predictive factors. Positive predictors were the Artificial burr and VAC technique. Negative predictors were series with pancreatitis patients, the Mesh/sheet technique, number of surgical reinterventions, duration of TAC, duration of ICU stay, and mortality. Multivariate logit-transformed meta-regression analysis revealed that the Artificial burr is positively associated with delayed primary fascial closure. The Mesh/sheet technique, duration of TAC, and mortality were negative predictors for delayed primary fascial closure.
Table 4. Temporary Abdominal Closure techniques: pooled data on age, gender, complications, mortality and fascial closure

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Case series</th>
<th>Pts n</th>
<th>Males % (95% CI)</th>
<th>Age (yr) med (range)</th>
<th>Fistulae % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAC</td>
<td>8</td>
<td>251</td>
<td>68 (60 – 77)</td>
<td>41 (35 – 65)</td>
<td>2.9 (0.7 – 5.1)</td>
</tr>
<tr>
<td>Vacuum pack</td>
<td>15</td>
<td>1186</td>
<td>70 (67 – 72)</td>
<td>42.5 (32 – 62)</td>
<td>5.7 (4.3 – 7.0)</td>
</tr>
<tr>
<td>Artificial burr</td>
<td>4</td>
<td>180</td>
<td>94 (87– 100)</td>
<td>34 (30 – 43)</td>
<td>2.0 (-0.1 – 4.1)</td>
</tr>
<tr>
<td>DRS</td>
<td>1</td>
<td>13</td>
<td>62</td>
<td>50</td>
<td>NR</td>
</tr>
<tr>
<td>Silo</td>
<td>3</td>
<td>109</td>
<td>74 (65 – 83)</td>
<td>43.9 (40 – 48)</td>
<td>0</td>
</tr>
<tr>
<td>Mesh/sheet</td>
<td>16</td>
<td>1176</td>
<td>80 (78 – 83)</td>
<td>37 (31 – 75)</td>
<td>5.5 (3.6 – 6.7)</td>
</tr>
<tr>
<td>Loose packing</td>
<td>1</td>
<td>18</td>
<td>NR</td>
<td>NR</td>
<td>28</td>
</tr>
<tr>
<td>Skin only</td>
<td>2</td>
<td>101</td>
<td>90 (84 – 96)</td>
<td>36.1 (32 – 40)</td>
<td>NR</td>
</tr>
<tr>
<td>Zipper</td>
<td>7</td>
<td>135</td>
<td>72 (64 – 80)</td>
<td>46 (32 – 64)</td>
<td>13.8 (7.6 – 20.0)</td>
</tr>
</tbody>
</table>

Pts: Patients; 95% CI: 95% Confidence Interval; *Reported in one series only; **Reported in two series only

Table 5. Pre-TAC predictors for delayed primary fascial closure

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Beta</th>
<th>95% CI lower limit</th>
<th>95% CI upper limit</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artificial burr</td>
<td>1.1526</td>
<td>0.03831</td>
<td>2.2669</td>
<td>0.0426*</td>
</tr>
<tr>
<td>Vacuum Assisted Closure</td>
<td>0.4225</td>
<td>-0.3923</td>
<td>1.2374</td>
<td>0.3091</td>
</tr>
<tr>
<td>Mesh/sheet</td>
<td>-0.6466</td>
<td>-1.2576</td>
<td>-0.03551</td>
<td>0.0381*</td>
</tr>
<tr>
<td>Series with pancreatitis</td>
<td>-0.6671</td>
<td>-1.3407</td>
<td>0.006558</td>
<td>0.0523**</td>
</tr>
</tbody>
</table>

*significant at p<0.05; **strong trend at p<0.1

In order to aid decision making at the start of the TAC, the pre-TAC predictors were analysed separately (Table 5). Multivariate logit-transformed meta-regression showed that the Artificial burr (positive) and the Mesh/sheet (negative) were significant individual predictors. Furthermore, series with pancreatitis patients showed a trend towards negative prediction. Eliminating the VAC as a non-significant predictor from the multivariate analysis revealed that only the Mesh/sheet and series with pancreatitis patients remained individual significant predictors (p=0.012 and p=0.023 respectively). In this analysis, the Artificial burr showed a strong trend (p=0.066).

Discussion

In this systematic review on the treatment of the open abdomen, the highest pooled delayed primary fascial closure rates were seen in the series in which the Artificial burr or the VAC was applied. Dynamic Retention Sutures, although described in only one series, also showed a high rate of delayed primary fascial closure.

The included studies were generally retrospective chart reviews and no comparative trials were identified. The available data in these cases series varied. For example, more than
one third of the series did not report whether the patients were included prospectively or retrospectively, or whether it concerned a consecutive series of patients. Furthermore, the exact inclusion and exclusion criteria often were not reported. The decision to operate a specific patient as well as the decision of TAC was usually left to the discretion of the operating surgeon without an explanation of the rationale behind it. Scoring systems such as the Acute Physiology and Chronic Health Evaluation II (APACHE II) and the Simplified Acute Physiology II (SOFA II), both reflecting the severity of the disease, were reported infrequently. The ISS in trauma patients was reported more frequently. However, differences in severity of the patients’ conditions were still difficult to assess, because the ISS involves all injuries to the body. These facts imply that the studies suffer from considerable bias in both patient selection and treatment selection.

The fact that, over all series, three quarters of the patients were men could partly be explained by the high percentage of male patients in the series with trauma patients. However, even the series without trauma patients showed high percentages of male patients. For the purpose of this study, the results were pooled per technique. However, no standardised techniques were used in these series. By implication, even though series with multiple techniques were excluded, an unknown amount of practice variation for each technique remains.

Some techniques were used in only one series (Dynamic Retention Sutures and Loose packing) with less than 20 patients per series. Other techniques were used in two (Skin) or three series (Silo). These series, however, did include more than one hundred patients each. Hence, the reliability of the pooled estimate of fascial closure per series differs.

In contrast to the other techniques, the VAC, Vacuum pack, and Mesh/sheet techniques have been used in trauma series, mixed series as well as non-trauma patients. However, subdivision of the results per patient group and technique, resulted in small numbers of patients and heterogeneous rates of complications, mortality and fascial closure. Therefore
further subdivision of the results was omitted.

The availability and preference for the different techniques seems to have evolved over the past 30 years. The first published studies on temporary closure of the open abdomen concern mostly Mesh/sheet and Zipper techniques. Over the years, choice for temporary abdominal closure technique seems to have shifted towards techniques that more actively pursue abdominal drainage and fascial re-approximation. Furthermore, 85% of the studies that were published since 1998 use a vacuum technique (Vacuum Assisted Closure or Vacuum pack). Therefore, the surgeons preference seems to have shifted toward the vacuum based techniques. The results show that this may be a good evolution because these techniques show high closure rates and low complication rates. However, the Artificial burr is better in terms of delayed primary fascial closure rate.

The best rates of delayed primary fascial closure were seen in the Artificial burr series and the Dynamic Retention Suture series, although the latter concerned only one series. The VAC and Vacuum pack also showed high closure rates which were comparable but in favour of the VAC. The median closure rate in the Silo series is surprisingly low since this technique allows for gradual re-approximation of the fascial edges. In other techniques, this seems to result in higher fascial closure rates. After careful evaluation of these three series, no clue was found for the reason of this low closure rate.

The results suggest that a more active approach towards fascial closure of the open abdomen may result in higher fascial closure rates. The Artificial burr and the Dynamic Retention Sutures, in which the fascial edges are actively pulled medially, showed the highest closure rates.

As mentioned in the methods, the delayed primary fascial closure rate was calculated over all included patients and not the survivors. This was done simply because the in-hospital mortality often was not divided into pre-closure and post-closure mortality. However, it is likely that most patients have died in the early stage of the open abdominal treatment (i.e. before closure). Therefore, the delayed fascial closure rate of the survivors may indeed have been even higher than the rates reported in this review. This applies to all TAC techniques.

The Zipper series showed a surprisingly high median fistulae rate. Furthermore, although reported in few series, the abscess rate was also high in the Zipper series. Surprisingly, the Artificial burr series showed some of the lowest fistulae rates as well as the highest abscess rate. In contrast, the VAC also showed one of the lowest fistulae rates, however, the VAC series reported no abscesses. Of all possible complications of the open abdomen, fistulae and abscesses were reported most consistently. However, the reported rates may be underestimating the true number of fistulae and abscesses. This is because, in retrospective chart reviews, complications may not have been reported and can be difficult to identify. Especially the less grave complications which do not have therapeutic consequences may be difficult to retrieve from the medical charts.

All included studies reported on mortality. Despite the high overall mortality, two series reported a mortality rate of zero. This could partly be explained by the fact that these two series concern few patients (8 and 11). Somewhat surprising is the fact that the three
techniques with the highest fascial closure rates, also showed the lowest mortality rates. This may indicate that these techniques are indeed superior when it comes to fascial closure and mortality. However, the fact that the general ICU treatment has improved considerably over the years and that the VAC has only been used in recent years indicates that there may be some confounding factors. However, contrary to this explanation, the Artificial burr (which showed the highest closure rate as well as the lowest mortality rate) was used over a large period of time.

Interestingly, the predictors from the univariate meta-regression analysis mainly concerned TAC techniques and factors concerning hospital admission. The series with pancreatitis patients was the only case in which the underlying condition predicted the outcome. This partly contradicts the common surgeons’ phrase that delayed primary fascial closure is easier in trauma patients because of the absent abdominal infection.

Four of the eight initial predictors for delayed primary fascial closure concerned factors that are only fully known at the end of the TAC. These factors, although they predict the outcome, are not suitable for clinical decision making pre-TAC. Therefore only the factors that were known pre-TAC were further analysed.

The only two factors that remained significant were negative predictors. These results suggest that, when using a Mesh or sheet, the probability of achieving delayed primary facial closure is lower than for the other techniques described in this review. Furthermore, the overall delayed primary fascial closure rate seems to be lower if the series contains patients with pancreatitis. The former can be explained, because Meshes and sheets do not keep appropriate tension on the fascial edges and therefore are in opposition to fascial closure. It can be argued that the series with pancreatitis patients contain more severely ill patients that may spend longer periods in the hospital and intensive care unit. However, these factors, while significant in the univariate regression analysis, are not significant in the multivariate analysis. Therefore, it is suggested that there may be unreported factors that cause the decreased fascial closure in series with pancreatitis patients.

In conclusion, the results of this review suggest that temporary abdominal closure techniques that keep traction on the fascial edges result in high rates of fascial closure. Furthermore, techniques with high closure rates seem to result in low rates of fistulae, abscesses, and mortality. The results of the meta-regression suggest that, of the reported factors, Mesh/sheet use and series with pancreatitis patients negatively predict delayed primary fascial closure. Randomised controlled trials are required to indicate more clearly which technique produces higher delayed primary fascial closure rates.

Reference list


(14) Therapy checklist (Dutch extended version) of the Dutch Cochrane centre. www.cochrane.nl.


Chapter 10

Temporary closure of the open abdomen


Single-stage closure of enterocutaneous fistula and stomas in the presence of large abdominal wall defects using the components separation technique

J Wind
PJ van Koperen
JFM Slors
WA Bemelman

American Journal of Surgery, in press
Abstract

Introduction
Closure of an enterocutaneous fistula and/or stomas in the presence of large abdominal wall defects is a challenging problem. In the present study the results of the components separation technique are described.

Methods
All patients with an enterocutaneous fistula and/or stomas in the presence of large abdominal wall defects (i.e. laparostomy of ventral hernia) who underwent a single-stage repair using the components separation technique in the period from January 2000 to July 2007 were reviewed retrospectively.

Results
A total of 32 patients were included. Median operating time was 204 minutes (range 87-573). In 18 patients, additionally to the components separation, an absorbable mesh was used. Postoperatively, in 16 patients 22 complications were reported. There were nine patients with local wound problems. Median postoperative hospital stay was 12 days (range 5-74). Seven patients developed a ventral hernia. Four of them were small asymptomatic recurrences. Four out of the 15 patients with an enterocutaneous fistula developed a recurrent fistula. Median follow-up was 20 months (range 3-54).

Conclusion
Closure of enterocutaneous fistula and/or stomas and simultaneous repair of large abdominal wall defects is feasible using the components separation technique but morbidity is considerable. Early recurrence of abdominal hernia and fistula is acceptable.
Introduction

Patients surviving intra-abdominal catastrophes frequently have large abdominal wall defects. These defects are generally the result of open abdomen management for severe intra-abdominal sepsis, trauma, or other abdominal emergencies. These large defects are often associated with enterocutaneous fistula and stomas.\(^1\) Closure of enterocutaneous fistula and/or stomas and 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. Morbidity and mortality rates are high in these often malnourished patients, particularly those with high-output enterocutaneous fistula.\(^2;3\) The actual timing of the operation requires thoughtful consideration. Planning the operation too soon may result in an extremely difficult surgical procedure in an often fragile patient. Postponing the operation for too long exposes the patient unnecessarily to the deleterious metabolic effects of the fistula and catheter-related morbidity in case of parenteral nutrition.\(^2;3\)

Ideally, a non-absorbable mesh is used to close the abdominal wall because primary fascial closure is rarely possible in these patients.\(^4\) This technique ensures durable abdominal wall prosthesis. However, the application of a non-absorbable mesh is associated with an increased risk of infection, especially when used in a contaminated surgical field, for instance in the presence of enterocutaneous fistula and stomas.\(^5;6\) Furthermore, the implanted mesh might damage exposed bowel if the peritoneum or greater omentum are not interposed between the mesh and the bowel. Therefore, many surgeons are reluctant to use non-absorbable meshes in these complicated abdominal wall defects.\(^5-7\) The use of an absorbable mesh avoids infectious complications, but is only for temporary closure of the hernia.

The most logical alternative for these large and contaminated abdominal wall defects is the use of autologous tissue repair including local tissue repair, autologous grafts and pedicled or free vascularised flaps. In a recently published systematic review several techniques for autologous repair of abdominal wall defects were reviewed.\(^8\) Despite the poor quality of the included studies the components separation technique was the best documented procedure. This technique, for the repair of large ventral hernias, was first described by Ramirez et al.\(^9\) 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. Nevertheless, most of the studies included in the review concerned only clean or clean-contaminated surgical fields.\(^8\)

The aim of this study was to evaluate the results of closure of enterocutaneous fistula and/or stomas and simultaneous abdominal wall repair using the components separation technique.
Methods

The present study consists of a consecutive series of patients with enterocutaneous fistula and/or stomas in the presence of a large abdominal wall defect (i.e. laparostomy or ventral hernia). Patients had a single-stage closure of the enterocutaneous fistula and/or stomas and simultaneous repair of the abdominal wall using the components separation technique as described by Ramirez et al. All operations were performed electively in the period from January 2000 to July 2007. Data were assessed in a retrospective manner. Patients under 18 years of age, large abdominal wall defects without the presence of enterocutaneous fistula and/or stomas (i.e. surgical field contamination) and multi-staged procedures were excluded from this study. Charts of the included patients were reviewed and the following data were extracted using a preformatted sheet including age, gender, co-morbidity and surgical history, Body Mass Index (BMI, kg/m$^2$), signs of malnutrition defined as a weight reduction of more than 10% in the previous six months and a low albumin level (< 30 g/l)$^{10}$, ASA classification, reasons for surgical field contamination, operating time, concomitant surgical procedures, the use of mesh reinforcement, intra-operative morbidity, 30-day morbidity and mortality, postoperative hospital stay, readmissions and reoperations within 30 days. During long term follow-up recurrence of enterocutaneous fistula or the development of ventral hernia was assessed. Outcome and complications were noted during clinical and out-patient clinic follow-up.

Operative procedures

All patients underwent general anesthesia and received preoperative parenteral antibiotic prophylaxis (Ceforoxim 1500 mg/Clindamycine 600 mg, 30 minutes before surgery). When the procedure lasted for more than four hours the same antibiotic prophylaxis was repeated. Normal body temperature was maintained with standard bair hugger warming. Perioperative glucose levels were not checked routinely. To avoid inadvertent bowel injury, the abdomen was generally entered by dissecting the stomas when present. Otherwise the laparotomy was started at the upper border of the incisional hernia or at the midline above the laparostomy. A complete adhesiolysis was generally performed to get a clear view on the anatomy and to free the bowel from the abdominal wall. If enterocutaneous fistulas were present the segment(s) from which the fistula arose was identified and isolated followed by a limited resection and reanastomosing of the two segments. If stomas were present the bowel was reanastomosed and the fascia was closed using PDS 1 (Ethicon$^{\circledR}$) or the fascia was closed with a Vicryl mesh. Care was taken to reposition the anastomosis or sutured small bowel lesions that occurred during adhesiolysis, as far away from the abdominal wall as possible. The subsequent abdominal wall closure was performed using the components separation technique (Figure 1 and 2). The skin and subcutis were separated from the underlying abdominal musculature in lateral direction up to the anterior axillary line. Next the aponeurosis of the external oblique muscle was incised pararectally. Subsequently, the external oblique muscle was separated from the underlying internal oblique muscle by blunt dissection in a relatively avascular plane.
Figure 1. Cross-sectional view. Skin and subcutaneous tissue are separated from the underlying abdominal muscle in lateral direction up to the anterior axillary line. Next, the aponeurosis of the external oblique muscle is incised pararectally, and the external oblique muscle is separated from the underlying internal oblique muscle by blunt dissection (A and B). Additionally, the rectus muscle is separated from the posterior rectus sheath (C).
This was followed by the separation of the rectus muscle from the posterior rectus sheath. The separation of the muscle components of the abdominal wall allowed mobilisation of each unit over a greater distance with less tension. Subsequently the abdominal wall was closed using PDS 1. Sometimes a temporary reinforcement consisting of an onlay Vicryl mesh was sutured to the fascia. The skin was closed with running sutures. Two suction drains were routinely used between the mobilised skin and abdominal wall musculature to drain the death space. The skin was closed because leaving the skin open would not guarantee adequate drainage (via the suction drains) of the large subcutaneous wound surfaces. Therefore, skin closure combined with closed wound drainage (suction drains) was preferred. Postoperatively, no abdominal binders were applied routinely. In case of a wound infection the running sutures were (partly) removed for adequate drainage.

Statistics
Data are presented as median values with ranges for continuous data, unless otherwise specified. Categorical data are presented as number of patients and percentages. The Chi-square or Fisher’s exact test was used to test for differences between groups. A p-value <0.05 was considered statistically significant. Statistical analysis was done using the SPSS v.12.0 package (SPSS, Chicago, Illinois, USA).

Figure 2. Frontal view. Additionally, parasagittal relaxing incisions can be made in the internal oblique muscle.
Results

Demographics of the included patients
In the study period a total of 32 patients were identified who underwent single-staged closure of enterocutaneous fistula and/or stomas and simultaneous repair of the abdominal wall using the components separation technique. There were 10 female and 22 male patients with a median age of 43 years (range 19-78), median BMI of 21.7 kg/m² (range 16-32) and a median ASA score of two (range 1-4). In nine (28%) patients there was malnutrition (weight reduction of more than 10% in the previous six months and a low albumin level) preoperatively. All patients were survivors of intra-abdominal catastrophes. In 22 (69%) patients an intra-abdominal sepsis was managed with an open abdomen. In the remaining patients a large incisional hernia was present expanding to at least half way the upper and lower abdomen. In Table 1 the reasons for the surgical field contamination are summarized. In four (13%) patients there was one source of contamination, in the remaining patients there were several sources. There were 15 (47%) patients with an enterocutaneous fistula of which nine were high output fistulas (>500 ml/24 hours). The origin of the fistula was a small bowel segment in 12 patients and in three patients the fistula arose from the large bowel. In 21 (66%) patients a stoma was closed comprising of 15 ileostomies and six colostomies. Furthermore, 22 patients had large contaminated granulating defects (i.e. laparostomy).

Table 1. Reasons for contamination of the surgical field

<table>
<thead>
<tr>
<th>Reason for contamination</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granulating defect (laparostomy)</td>
<td>22</td>
</tr>
<tr>
<td>Osteomy closure</td>
<td>21</td>
</tr>
<tr>
<td>Enterocutaneous fistula closure</td>
<td>15</td>
</tr>
<tr>
<td>Concomitant bowel resection†</td>
<td>9</td>
</tr>
<tr>
<td>Abscess</td>
<td>2</td>
</tr>
</tbody>
</table>

†Apart from resections of bowel segments from which the fistula arose in case of enterocutaneous fistula closure.

Operative data
Median operating time was 204 minutes (range 87-573). In five patients complete fascial approximation was not possible. In all these patients a Vicryl mesh was implanted. Additionally, in 13 patients the components separation was reinforced with a Vicryl mesh. This was done as an onlay procedure.
Concomitant bowel resections, apart from resections of bowel segments from which an enterocutaneous fistula arose, were necessary in nine patients; one patient underwent small and eight underwent large bowel resection(s). Furthermore, 21 patients underwent stoma closure, 15 patients underwent closure of one or more enterocutaneous fistulas. In three patients a stoma was constructed, two patients underwent a cholecystectomy, in two patients an abscess was drained and in one patient an entero-vesico fistula was closed.
Short term outcome
There was no postoperative mortality. Postoperatively, in 16 (50%) patients 22 complications were reported within the first 30 days. There were nine patients with local wound problems; eight patients had a wound infection and one patient had a large hematoma. One of these patients underwent a surgical debridement and drainage of the wound. Furthermore, five patients had a cardiopulmonary complication, three patients had a urinary tract infection, two patients had a prolonged postoperative ileus, two patients had intra-abdominal abscesses which were drained radiologically and one patient developed an enterocutaneous fistula within the first 30 days. The local wound problems were not correlated with the type of contamination (i.e. stoma or enterocutaneous fistula), with the presence of an open abdomen or with the use of a Vicryl mesh.
Median postoperative hospital stay was 12 days (range 5-74). Three patients were readmitted within the first 30 days. Reasons for these readmissions were; a recurrent fistula, a wound infection, and dehydration due to nausea and vomiting.

Long term outcome
Four patients were lost to long term follow-up. No recurrent ventral hernia was found during their median follow-up of 3.5 months (range 1-8). Median follow-up of the remaining 28 patients was 20 months (range 3-54). Seven (25%) patients developed a recurrent ventral hernia. Of the seven patients with a recurrence four had Vicryl mesh reinforcement and in three patients the fascia could not be closed entirely during the components separation. There was no correlation between recurrence and postoperative wound infection. Two out of the eight patients with a wound infection had a recurrence compared to five out of the 24 patients without a wound infection. Four recurrences were small and asymptomatic which did not require repair. Three patients underwent an uncomplicated mesh repair. However, two of these patients developed a second recurrence and underwent a new mesh repair.
Four (27%) out of the 15 patients with an enterocutaneous fistula developed a recurrent fistula after a median of four months (range 0-15). In one of the patients with a recurrence after 15 months the fistula was due to activity of Crohn’s disease. Two patients had a reoperation for their enterocutaneous fistula. In one patient a recurrent fistula was excised without further recurrences. The second patient underwent three more operations due to recurrent fistula (last operation August 2007). A Munchausen syndrome was suspected in this patient.

Discussion
Closure of enterocutaneous fistula and/or stomas in the presence of large abdominal wall defects is a challenging problem. The primary goal of surgery is to close the enterocutaneous fistula or stoma. The presence and simultaneous management of a large abdominal defect is an accompanying problem making the combined procedure more difficult. In
the event that the abdominal reconstruction fails due to wound infection, burst abdomen or infected prosthetic material, a laparostoma reoccurs with a high likelihood of intestinal fistulisation. The results of the present study demonstrated that single-stage management using the components separation technique is a feasible method avoiding early abdominal wall dehiscence. Nevertheless, the incidence of postoperative morbidity was high mainly due to wound infection. This is not surprising considering the contaminated condition and the large wound surfaces.

Mesh repair is superior to suture repair without prosthetic material with respect to the recurrence of hernia. After primary repair, rates of recurrences are reported up to 50 percent. Repairs that include the use of a mesh have recurrence rates ranging between zero and 25 percent. The morbidity rate for mesh repair in these none contaminated incisional hernias is approximately 20 percent including major complications as enterocutaneous fistula and mesh infections.

For the reconstruction of very large abdominal wall defects the lack of sufficient tissue requires the insertion of prosthetic material or transposition of autologous material to bridge the fascial gap. In a recently published interim analysis of a randomised study, 39 patients with large clean or clean-contaminated abdominal wall defects were randomised between mesh repair (PTFE) and the components separation technique. Wound complications were found in 53 percent after components separation and in 72 percent after mesh repair. Reherniation occurred in 53 percent after components separation and in 22 percent after mesh repair. However, in 39 percent of the patients having mesh repair, the prosthesis had to be removed as a consequence of early or late infection. The authors concluded that repair of large clean or clean-contaminated abdominal wall hernias with the components separation technique compares favourably with prosthetic repair. Although the reherniation rate after components separation was relatively high, the trial was discontinued because the consequences of wound healing disturbances in the presence of PTFE prosthesis were far-reaching, often resulting in loss of the prosthesis.

The components separation technique provides midline advancement by sequential incision and release of muscle layers. Bilateral partition and sequential relaxing incisions provide approximately 10, 20, and 6 centimeters of advancement, in the upper, middle, and lower thirds of the abdomen respectively.

Data of large abdominal wall defects repair in contaminated surgical fields using the components separation technique are rare. In a study by van Geffen et al. only patients with severely contaminated abdominal wall defects were included. Twenty-six patients were treated with the components separation technique. Morbidity was reported in 46 percent of the patients with wound infection as the most frequent complication. Only eight percent of the patients developed a ventral hernia after a median follow-up of 27 months. Of the nine patients with an enterocutaneous fistula three developed a recurrent fistula. Others have found comparable results with the components separation technique in contaminated abdominal wall defects. In the present study 50 percent of the patients developed one or more complications including 28 percent of the patients
with local wound problems. The recurrence rate was 22 percent. More than half of the recurrences were small and asymptomatic. Others have also reported that the majority of the recurrences after the components separation technique were small and asymptomatic and needed no further treatment.13;15

The presence of local wound problems in several patients is not surprising as the skin and subcutaneous tissue must be mobilised laterally over a large distance in order to reach the aponeurosis of the external oblique muscle resulting in a large wound surface. The extensive mobilisation endangers the blood supply, this may lead to skin necrosis and an increased risk of infection. To reduce wound complications, modifications have been described to preserve the blood supply of the skin and subcutaneous tissue by preserving the musculocutaneous perforating arteries.18;19 Saulis et al. proposed that preserving the periumbilical rectus abdominis perforators to the abdominal skin flaps will decrease the prevalence of superficial wound complications. They maintain a cluster of vessels as a broad stalk to the overlying skin at the level of the umbilicus. In a retrospective review of 66 consecutive patients the authors described a decrease in superficial wound healing complications when this technique is used (20% versus 2%, P<0.05).18

Jernigan et al. modified the components separation technique allowing more extensive mobilisation and local advancement in order to achieve a higher rate of fascial closure in very large defects and to reduce the amount of ventral hernias. The modification starts with the standard separation of components; full-thickness skin flaps are dissected from the fascia bilaterally to approximately the midaxillary line. Next, bilaterally the external oblique component of the anterior rectus sheath is divided around one centimeter lateral to the rectus muscle and continued longitudinally approximately six to eight centimeters over the costal margin superiorly, and inferiorly to the pubis. After division of the external oblique fascia, the posterior rectus fascia is separated from the rectus muscles bilaterally. The last separation is the internal oblique component of the anterior rectus sheath. This is divided superiorly from the costal margin and extending inferiorly to the arcuate line. Reconstruction is completed by suturing the most medial portion of the posterior rectus fascia to the lateral portion of the anterior rectus fascia, bilaterally. A five percent recurrent hernia rate was reported with a follow-up interval of 24 months.20

Most surgeons are reluctant to use non-absorbable mesh in a contaminated operative field.5-7 In the present series in some of the patients the components separation was reinforced with an absorbable Vicryl mesh in case of closure under tension. The presence of the Vicryl mesh did not correlate with local wound problems. Others have reported favourable results using the components separation technique enforced with non-absorbable meshes in the presence of contamination.15;17;21;22 The role of supporting non-absorbable mesh has to be investigated in prospective studies.

The use of an acellular matrix (e.g. AlloDerm) which becomes vascularized and remodeled into autologous tissue after implantation may represent an alternative with low infectious morbidity. Patton et al. retrospectively analyzed 67 patients undergoing repair of contaminated abdominal wall defects using an acellular dermal matrix.23 They reported a complication rate of 35 percent and a recurrence rate of 18 percent after a limited
mean follow-up of 11 months. Alaedeen et al. described a subset of eight patients in whom a large contaminated abdominal wall defect was repaired with the components separation technique with acellular matrix reinforcement.\textsuperscript{16} After a median follow-up of 14 months they found no recurrences. The use of an acellular matrix appears to be feasible in contaminated surgical fields. However, to date limited evidence is available on the safety and long term outcome. Furthermore, these products are very expensive and should therefore be validated in carefully controlled studies first.\textsuperscript{16;23;24}

The results of the present study must be interpreted carefully because of several limitations. First of all it comprises a small single centre retrospective study. Second, defect size was not reported in many cases. All defects were described as large or huge defects while exact measures were missing. Third, the follow-up period of 20 months is moderate. With longer follow-up a higher rate of incisional hernia might be observed.

In conclusion, closure of enterocutaneous fistula or stomas in the presence of large abdominal wall defects is feasible using the components separation technique. This technique is one of the few options available to deal with this very difficult problem. Early recurrence of abdominal hernia and fistula is acceptable but morbidity is considerable. Suggested modifications to preserve the blood supply of the skin and subcutaneous tissue, extended antibiotic therapy and changes in mesh repair might improve outcome.

Reference List


Part 3

Prognostication in colorectal cancer
A systematic review on the significance of extracapsular lymph node involvement in gastrointestinal malignancies

J Wind
SM Lagarde
FJW ten Kate
DT Ubbink
WA Bemelman
JJB van Lanschot

European Journal of Surgical Oncology 2007;33:401-408
Abstract

Introduction
The impact of extracapsular lymph node involvement has been studied for several malignancies, including gastrointestinal malignancies. Aim of this study was to assess the current evidence on extracapsular lymph node involvement as a prognostic factor for recurrence in gastrointestinal malignancies.

Methods
The Cochrane Database of systematic reviews, the Cochrane central register of controlled trials, and MEDLINE databases were searched using a combination of keywords relating to extracapsular lymph node involvement in gastrointestinal malignancies. Primary outcome parameters were incidence of extracapsular lymph node involvement and overall five-year survival rates.

Results
Fourteen manuscripts were included, concerning seven oesophageal, three gastric, one colorectal, and three rectal cancer series with a total of 1528 node positive patients. The pooled incidence of extracapsular lymph node involvement was 57% (95% confidence interval [CI]: 53-61%) for oesophageal cancer, 41% (95% CI: 36-47%) for gastric cancer, and 35% (95% CI: 31-40%) for rectal cancer. In nine of the 14 studies a multivariate analysis was performed. In eight of these nine studies extracapsular lymph node involvement was identified as an independent risk factor for recurrence.

Conclusion
Extracapsular lymph node involvement is a common phenomenon in patients with gastrointestinal malignancies. It identifies a subgroup of patients with a significantly worse long-term survival. This systematic review highlights the importance of assessing extracapsular lymph node involvement as a valuable prognostic factor. Pathologists and clinicians should be aware of this important feature.
Chapter 12
Extracapsular lymph node involvement in gastrointestinal malignancies

Introduction

The presence and extent of lymphatic dissemination are among the most important predictors for survival in gastrointestinal malignancies.1-4 Lymph node staging may be further refined by the identification of different levels (i.e. proximate versus remote lymph node stations), the absolute number of metastatic lymph nodes and/or the lymph node ratio (i.e. the number of involved nodes over the total number of resected and identified nodes).5-7 Furthermore, micro-metastasis defined as isolated tumour cells or small clusters of cells, detected in lymph nodes, has also been identified as a prognostic factor.8 Extracapsular lymph node involvement is the extension of cancer cells through the nodal capsule into the perinodal fatty tissue. The prognostic value of extracapsular lymph node involvement has been studied for several malignancies, including breast, prostate, vulva, bladder, lung, and head/neck cancer.9-15 Patients with extracapsular lymph node involvement have a reduced overall and disease-free survival in these malignancies.9-15 However, in gastrointestinal malignancies, the prognostic value of extracapsular lymph node involvement has not yet been completely established. The ability of cancer cells not only to spread into a lymph node but also to invade through the lymph node capsule in an immunologically hostile environment, probably reflects the invasiveness and thus aggressiveness of the primary tumour.16;17

Only a limited number of small studies have been published on extracapsular lymph node involvement, mainly concerning oesophageal, gastric, and rectal cancer.5;18-22 In the majority of these studies extracapsular lymph node involvement was demonstrated to have a negative effect on local control, disease-free and overall survival.5;18-22 Nonetheless, its exact incidence is unclear. Moreover, it is as yet unknown if extracapsular lymph node involvement is an early or late event in cancer progression. It has not been established if extracapsular lymph node involvement is associated with local or haematogenous recurrences.

Detection and quantification of extracapsular lymph node involvement in the surgical resection specimen of gastrointestinal malignancies might be helpful not only for staging purposes, but also for the stratification in future clinical trials and to individualize future adjuvant strategies. Therefore, we performed a systematic review in order to assess the incidence and extent of extracapsular lymph node involvement in gastrointestinal malignancies. Furthermore, the relation between extracapsular lymph node involvement and clinico-pathological factors, its prognostic value, its effect on the type of recurrence and on long term survival were evaluated.
Methods

Literature search
The Cochrane Database of systematic reviews, the Cochrane central register of controlled trials, and MEDLINE databases were searched by using keywords related to extracapsular lymph node involvement in gastrointestinal malignancies (Table 1) in order to identify studies published up to May 2006. Two investigators (JW, SML) independently performed the literature search. Electronic links to related articles and references of selected articles were hand-searched as well. A hand search of relevant journals and conference proceedings was not performed. The search was not restricted to any language, however in the systematic review only studies published in English were taken into account.

Table 1. Search terms, as used in the systematic review

<table>
<thead>
<tr>
<th>Search terms</th>
<th>Not used</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeSH:</td>
<td>(extracapsular OR extranodal OR perilymphatic) AND (esophagus OR esophageal OR oesophagus OR oesophageal OR stomach OR gastric OR junction OR liver OR pancreas OR pancreatic OR bile OR gallbladder OR peri ampullary OR Vater OR duodenum OR duodenal OR jejunum OR jejunal OR ileum OR ileal OR ileocolic OR papil OR bowel OR colon OR colonic OR rectum OR rectal OR colorectal)</td>
</tr>
<tr>
<td>Field:</td>
<td>All Fields</td>
</tr>
<tr>
<td>Limits:</td>
<td>None</td>
</tr>
</tbody>
</table>

MeSH: medical subject headings

Study selection and data extraction
From the potentially eligible publications only studies were included if they reported on extracapsular lymph node involvement in gastrointestinal malignancies. Lympho-proliferative disorders (e.g. Hodgkin disease, MALT lymphomas) and other rare malignancies located in the gastrointestinal tract were excluded. Studies were included if they formulated a clear definition of extracapsular lymph node involvement. The definition of extracapsular lymph node involvement should include the extension of malignant cells through the nodal capsule into the perinodal fatty tissue. Studies reporting exclusively on deposits of metastatic cells without any recognizable lymph node structure were excluded.

The same two investigators independently extracted the following data, if reported, from the original studies using a preformatted sheet; incidence of extracapsular lymph node involvement, pTNM-stage, differentiation grade, radicality of resection, total number of resected and identified lymph nodes, total number of positive lymph nodes, location of positive nodes, lymphatic- and blood vessel invasion, perineural invasion, and finally disease-free and/or overall survival rates. Furthermore, if possible the type of recurrence was assessed in terms of loco-regional and/or distant (haematogenous) recurrence.

 Duplicate publications and papers that reported on (parts of) the same study population were excluded. In that situation only the largest or most recent publication was included. Each of the selected studies was critically appraised by the two investigators, using a modified form as proposed by the Dutch Cochrane Collaboration and assessed if a
Chapter 12
Extracapsular lymph node involvement in gastrointestinal malignancies

The incidence of extracapsular lymph node involvement was calculated by the number of patients with extracapsular lymph node involvement divided by the number of node positive patients. Subsequently a weighted incidence with a 95% confidence interval (CI) was calculated for each type of gastrointestinal malignancy. Survival rates were expressed as overall- and disease-free five-year survival. The prognostic value of extracapsular lymph node involvement in uni- and in multivariate analyses as reported in the original studies, were expressed as a P-value and reported as a relative risk (RR), odds ratio (OR) or hazard ratio (HR). Hazard or odds ratios and corresponding standard errors of the original studies, corrected for other possible prognostic factors, were entered into Cochrane Review Manager 4.2 software and analysed using RevMan Analyses 1.0.2 (The Cochrane Collaboration, Oxford, UK). Summary estimates of prognostic significance, including 95% CI, were calculated for the comparison of intracapsular lymph node involvement versus extracapsular lymph node involvement. A weighted HR was calculated in the meta-analysis using the inverse variance method. Statistical heterogeneity was tested using Chi-square and I-square statistics.

Results

Included studies
The searches identified 34 publications, of which 20 were excluded; six manuscripts were excluded because they did not report on extracapsular lymph node involvement.4-9 Four were excluded because of an unclear definition of extracapsular lymph node involvement10-13, seven because they reported on extranodal tumour deposits rather than on extracapsular lymph node involvement.14-20 Subsequently, three manuscripts were excluded because they were written in Japanese.21-23 In the final analysis 14 studies were included which have been published between 1963 and 2006, with a total of 1528 node positive patients, with a range of 28 to 251 node positive patients per study.5;18-22,44-51 There were seven studies reporting on oesophageal cancer20,22,44,45,47,49,51, three on gastric5,21,48, one on colorectal46, and three on rectal cancer18,19,50 (Table 2).

The included studies had several limitations (Table 2). It concerned mostly retrospective single-centre studies with generally small or moderate sample sizes. Only four studies had a prospective study design.19,21,47,51 Furthermore, in half of the included studies it was not clear if the patients were of a consecutive series.5,21,22,45,48,50,51
Table 2. Study designs of the 14 studies included in the systematic review

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>R/P</th>
<th>Consecutive</th>
<th>Inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oesophageal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lagarde(^47)</td>
<td>2006</td>
<td>P</td>
<td>yes</td>
<td>Curative surgery for adenocarcinoma of the distal oesophagus and GO-junction, node positive, including M1\textsubscript{lym} transthiatal and transthoracic.</td>
</tr>
<tr>
<td>D’Journo(^51)</td>
<td>2005</td>
<td>P</td>
<td>-</td>
<td>Transthoracic oesophagectomy for adenocarcinoma of the lower oesophagus (Siewert I/II).</td>
</tr>
<tr>
<td>Lerut(^49)</td>
<td>2003</td>
<td>R</td>
<td>yes</td>
<td>Node positive T3 adenocarcinoma of the oesophagus or GO-junction.</td>
</tr>
<tr>
<td>Tachikawa(^20)</td>
<td>1999</td>
<td>R</td>
<td>yes</td>
<td>Node positive oesophageal cancer with or without (neo) adjuvant therapy.</td>
</tr>
<tr>
<td>Nakano(^22)</td>
<td>1999</td>
<td>R</td>
<td>-</td>
<td>Node positive carcinoma of the thoracic oesophagus.</td>
</tr>
<tr>
<td>Paraf(^45)</td>
<td>1995</td>
<td>R</td>
<td>-</td>
<td>Adenocarcinoma arising in Barrett segment including patients with distant metastasis. None received radiotherapy.</td>
</tr>
<tr>
<td>Gatzinsky(^44)</td>
<td>1985</td>
<td>R</td>
<td>yes</td>
<td>Surgically treated oesophageal cancer.</td>
</tr>
<tr>
<td><strong>Gastric</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nakamura(^21)</td>
<td>2005</td>
<td>P</td>
<td>-</td>
<td>Curative gastrectomy with D2 or D3 lymphadenectomy.</td>
</tr>
<tr>
<td>Di Giorgio(^51)</td>
<td>1991</td>
<td>R</td>
<td>-</td>
<td>Elective total gastrectomy for node positive adenocarcinoma with curative intent.</td>
</tr>
<tr>
<td>Zacho(^48)</td>
<td>1963</td>
<td>R</td>
<td>-</td>
<td>Gastric cancer, also palliative resection.</td>
</tr>
<tr>
<td><strong>Rectal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heide(^18)</td>
<td>2004</td>
<td>R</td>
<td>yes</td>
<td>Stage II/III rectal, postoperative radiochemotherapy. Preoperative staging by ultrasonography/ CT scan and chest X-ray.</td>
</tr>
<tr>
<td>Lupatelli(^19)</td>
<td>2001</td>
<td>P</td>
<td>yes</td>
<td>Stage II/III radically resected rectal adenocarcinoma ≤ 15 cm from the anal verge, capable to tolerate adjuvant therapy.</td>
</tr>
<tr>
<td>Ueno(^50)</td>
<td>1998</td>
<td>R</td>
<td>-</td>
<td>Curative surgery for rectal adenocarcinoma.</td>
</tr>
<tr>
<td><strong>Colorectal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Komuta(^46)</td>
<td>2001</td>
<td>R</td>
<td>yes</td>
<td>Colorectal Dukes C carcinoma.</td>
</tr>
</tbody>
</table>

P: prospective; R: retrospective; CIS: carcinoma in situ; M1\textsubscript{lym}: distant lymph node metastasis; GO-junction: gastro-oesophageal junction; -: not reported or not clear.
<table>
<thead>
<tr>
<th>Exclusion criteria</th>
<th>Follow-up (months)</th>
<th>Definition of extracapsular LNI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct postoperative deaths, residual disease. Other cancers than adenocarcinoma</td>
<td>&gt; 12 median 58</td>
<td>Extension through capsule into perinodal tissue. Deposits without a recognizable lymph node were considered as extracapsular LNI unless associated with perineural or vessel involvement.</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>Cells breaching the lymph node capsule.</td>
</tr>
<tr>
<td>Neo-adjuvant therapy, residual disease, organ metastasis, no lymphadenectomy.</td>
<td>-</td>
<td>Tumoural expansion that outgrows the node and extends beyond the capsule, not in afferent lymphatic vessels.</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>Metastasis penetrating the capsule or accompanied by nodules such as extracapsular vessel invasion.</td>
</tr>
<tr>
<td>Residual disease, direct postoperative deaths.</td>
<td>18-166</td>
<td>Cancer cells in the perinodal soft tissue, lymphatic vessel invasion included.</td>
</tr>
<tr>
<td>Squamous cell carcinoma, CIS or dysplasia only.</td>
<td>&gt; 24 median 52</td>
<td>Invasion of the adipose tissue located beyond the nodal capsule.</td>
</tr>
<tr>
<td>-</td>
<td>24-144</td>
<td>Perinodular growth in metastatic lymph nodes.</td>
</tr>
<tr>
<td>Non curative resections, metastasis, specific types of gastric cancer.</td>
<td>&gt; 21</td>
<td>Cancer cells beyond the capsule, excluding micro dissemination or vessel invasion in the adjacent tissues without spread through the capsule.</td>
</tr>
<tr>
<td>Stage T4 and M1.</td>
<td>&gt; 10</td>
<td>Infiltration of the capsule and extension beyond it by neoplastic tissue.</td>
</tr>
<tr>
<td>Multiple metastasis, anaplastic carcinoma.</td>
<td>-</td>
<td>Penetration of the capsule and invasion of surrounding tissue.</td>
</tr>
<tr>
<td>-</td>
<td>14-104 median 47</td>
<td>Extracapsular extension of lymph node metastasis.</td>
</tr>
<tr>
<td>Contraindications for adjuvant therapy, previous chemo- or radiotherapy, other malignancies, residual disease.</td>
<td>&gt; 24 median 57</td>
<td>Cells breaching the lymph node capsule.</td>
</tr>
<tr>
<td>Direct postoperative deaths, Follow-up less than 3 years</td>
<td>&gt; 3</td>
<td>Cells breaching the capsule and spreading into the perinodal fatty tissue.</td>
</tr>
<tr>
<td>Neo-adjuvant therapy</td>
<td>36-108</td>
<td>Cancer cells invading the surrounding tissue of metastatic nodes, subdivided in less or more than five cells.</td>
</tr>
</tbody>
</table>
In only three studies the histological sections were screened for extracapsular lymph node involvement by more than one researcher or pathologist.\textsuperscript{45,46,49} In general, the studies applied variable in- and exclusion criteria with respect to the type and stage of tumours and the use of (neo-) adjuvant therapies. Concerning oesophageal cancer, D’Journo et al. applied neo-adjuvant therapy in half of the patients and Gatzinsky et al. in a few patients\textsuperscript{44,51}, while Tackikawa et al. applied both neo-adjuvant and adjuvant therapy in most patients.\textsuperscript{20} Concerning rectal cancer, Heide et al. and Lupatelli et al. gave adjuvant therapy to all patients.\textsuperscript{18,19}

Furthermore, besides the extension of malignant cells through the capsule of a metastatic lymph node, some studies included large deposits without a recognizable lymph node\textsuperscript{47}, or involvement of afferent lymphatic vessels adjacent to the lymph node\textsuperscript{20,22}, while others explicitly excluded lymphatic vessel invasion\textsuperscript{21,47,49}. Only Komuta et al. gave a quantification of the extent of extracapsular lymph node involvement (i.e. more or less than five cells invading the perinodal tissue; Table 2).\textsuperscript{46} Finally, only three studies provided some detailed information on the prognostic value of the number of lymph nodes with extracapsular lymph node involvement.\textsuperscript{20,47,49}

**Oesophageal cancer**

Both squamous cell and adenocarcinomas of the oesophagus were included in the present review. Four studies exclusively reported on adenocarcinomas\textsuperscript{45,47,49,51}, one study included both adenocarcinomas and squamous cell carcinomas\textsuperscript{44} and in two studies the histological type was not stated.\textsuperscript{20,22} Six of the seven studies on oesophageal cancer reported on the incidence of extracapsular lymph node involvement which ranged from 39\% to 66\% (Table 3).\textsuperscript{20,22,44,45,47,49} The pooled incidence for extracapsular lymph node involvement in oesophageal cancer was 57\% (95\% CI: 53-61\%).\textsuperscript{20,22,44,45,47,49} The pooled incidence for extracapsular lymph node involvement in the studies that exclusively reported on the extension of malignant cells through the capsule of a metastatic lymph node and did not include vessel invasion and isolated deposits was comparable (61\%; 95\% CI: 55-67\%).\textsuperscript{44,45,49}

Four of the seven studies related extracapsular lymph node involvement to various clinico-pathological factors.\textsuperscript{20,44,45,47,49} Extracapsular lymph node involvement was significantly related to transthoracic oesophagectomy\textsuperscript{47}, T-stage\textsuperscript{20,44,47}, N-stage\textsuperscript{20,47}, number of positive nodes\textsuperscript{20,47}, lymph node ratio\textsuperscript{47}, and degree of lymphatic\textsuperscript{20} and blood vessel invasion.\textsuperscript{45} Five of the seven studies reported on the five-year overall survival which ranged from 33\% to 53\% for node positive patients with only intracapsular lymph node involvement and from 0\% to 23\% for patients with extracapsular lymph node involvement (Table 3).\textsuperscript{20,22,45,47,49} Lerut et al. and Lagarde et al. reported that patients with only one positive node identified had a significantly worse five-year survival if extracapsular lymph node involvement was present compared to patients in whom the tumour was confined within the lymph node (33\% vs. 86\% and 20\% vs. 60\%, respectively).\textsuperscript{47,49} Furthermore, Lagarde et al. divided patients with extracapsular lymph node involvement in three subgroups; patients with only intracapsular lymph node involvement, patients with one node with extracapsular
lymph node involvement and patients with two or more nodes with extracapsular lymph node involvement. Compared to only intracapsular lymph node involvement, one node and two or more nodes with extracapsular lymph node involvement were independent prognostic factors with HR of 1.6 (95% CI: 1.1-2.4) and 3.7 (95% CI: 2.5-5.3), respectively (personal communication). Patients who had two or more lymph nodes with extracapsular lymph node involvement had a median survival of 12 months compared to 21 months in patients who had only one lymph node with extracapsular lymph node involvement. Only one of the 102 patients with two or more lymph nodes with extracapsular lymph node involvement survived for more than five years. Finally, Tachikawa et al. found a better survival, although not statistically significant, of patients with three or more positive lymph nodes with only intracapsular lymph node involvement compared to those patients with three or more positive nodes with extracapsular lymph node involvement.

Nakano et al. found that 60% of the patients with extracapsular lymph node involvement in the neck and/or upper mediastinum had a local recurrence in that region compared to 21% of the patients without extracapsular lymph node involvement. Lagarde et al. reported no difference in recurrence pattern between patients with and without extracapsular lymph node involvement. In five studies a multivariate analysis was performed. In four of these studies, extracapsular lymph node involvement was identified as an independent prognostic factor (Table 3). Pooling could not be performed because of different ways of reporting and because standard deviations or 95% CIs were missing.

Gastric cancer

Both intestinal and diffuse type carcinomas of the stomach were included in the present review. All three studies reported on the incidence of extracapsular lymph node involvement which ranged from 29% to 58% (Table 3). The pooled incidence of extracapsular lymph node involvement in gastric cancer was 41% (95% CI: 36-47%). In the study by Nakamura et al. extracapsular lymph node involvement was significantly related to N-stage and serosal invasion of the tumour. In the study by Di Giorgio et al. extracapsular lymph node involvement was significantly related to T-stage, N-stage, and number of resected lymph nodes.

The five-year overall survival ranged from 35% to 61% for node positive patients without extracapsular lymph node involvement and from 5% to 23% for patients with extracapsular lymph node involvement (Table 3). In two studies a multivariate analysis was performed, in both of which extracapsular lymph node involvement was identified as an independent prognostic factor (Table 3). Nakamura et al. reported a RR of 6.9 (95% CI: 3.1-15.2) for the comparison of node positive patients with or without extracapsular lymph node involvement. Pooling could not be performed because only a few studies reported this outcome and if reported at all they did this in different ways and with standard deviations or 95% CIs frequently missing.
Table 3. Number of node positive patients, incidence of extracapsular lymph node involvement, and the prognostic significance of extracapsular lymph node involvement in uni- and multivariate analyses in the 14 included studies in the systematic review

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of node positive patients</th>
<th>Incidence ELNI (%)</th>
<th>P-value univariate</th>
<th>Reported OR, RR or HR with 95%-CI</th>
<th>P-value multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oesophageal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lagarde47</td>
<td>251</td>
<td>66</td>
<td>&lt;0.001</td>
<td>HR 2.06 (1.45-2.93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>D’Journo51</td>
<td>28</td>
<td>-</td>
<td>0.02</td>
<td>OR 5.9 (1.0-32.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>Lerut49</td>
<td>162</td>
<td>63</td>
<td>0.0001</td>
<td>HR 3.37 (1.75-6.49)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Tachikawa40</td>
<td>46</td>
<td>39</td>
<td>&lt;0.01</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nakano52</td>
<td>159</td>
<td>41</td>
<td>0.012</td>
<td>-</td>
<td>NS</td>
</tr>
<tr>
<td>Paraf45</td>
<td>34</td>
<td>65</td>
<td>&lt;0.001</td>
<td>-</td>
<td>sign</td>
</tr>
<tr>
<td>Gatzinsky44</td>
<td>43</td>
<td>51</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Gastric</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nakamura21</td>
<td>135</td>
<td>29</td>
<td>&lt;0.0001</td>
<td>RR 6.9 (3.1-15.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Di Giorgio5</td>
<td>121</td>
<td>52</td>
<td>&lt;0.05</td>
<td>-</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Zacho48</td>
<td>47</td>
<td>58</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Rectal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heide18</td>
<td>96</td>
<td>33</td>
<td>0.041</td>
<td>RR 1.6 (1.01-2.7)†</td>
<td>0.044†</td>
</tr>
<tr>
<td>Lupatelli19</td>
<td>105</td>
<td>18</td>
<td>&lt;0.0001</td>
<td>-</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ueno50</td>
<td>217</td>
<td>45</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Colorectal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Komuta46</td>
<td>84</td>
<td>55</td>
<td>&lt;0.01</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

ELNI: extracapsular lymph node involvement; OR: odds ratio; RR: relative risk; HR: hazard ratio; 95%-CI: 95% confidence interval †: for local control; -: not reported; sign: significant, no precise p-value given

(Colo)rectal cancer
The study of Komuta et al. was the only one reporting on extracapsular lymph node involvement both in colon and in rectal cancer.46 The incidence of extracapsular lymph node involvement in that study was 55%. They reported that extracapsular lymph node involvement was seen more often in nodes that were occupied for more than 50% by cancer cells compared to nodes with less than 50% occupation. Only nodes that were occupied for more than 50% sometimes showed more than five cells invading the surrounding tissue. Overall- and disease-free survival are indicated in Table 4. In patients without extracapsular lymph node involvement, distant metastases were more frequent than local recurrence (16% vs. 8%). For patients with extracapsular lymph node involvement, the risk for local recurrence and distant metastases were comparable (35% vs. 43%).46
There were three studies reporting exclusively on rectal cancer with an incidence of extracapsular lymph node involvement ranging from 18% to 45% (Table 3).18;19;50 The pooled incidence of extracapsular lymph node involvement in rectal cancer was 35% (95% CI: 31-40%).18;19;50
In the study by Heide et al. extracapsular lymph node involvement was significantly related to a higher T- and N-stage, to the presence of lymphatic vessel involvement, and to a lower differentiation grade.18 In the study by Ueno et al. the incidence of microscopic
tumoural foci discontinuous with the primary lesion was significantly higher in patients with extracapsular lymph node involvement. Five-year overall and disease-free survival are shown in Table 4. In two studies a multivariate analysis was performed and in both studies extracapsular lymph node involvement was identified as an independent prognostic factor. In the study by Heide et al. the value of extracapsular lymph node involvement for the assessment of local failure risk was confirmed in the Cox regression model, which revealed extracapsular lymph node involvement as an independent prognostic factor (RR 1.6, 95% CI: 1.01–2.7). For distant failure, however, extracapsular lymph node involvement did not independently predict outcome. Pooling could not be performed because only a few studies reported this outcome and if reported at all, they did this in different ways and with standard deviations or 95% CIs frequently missing.

Table 4. The overall- and disease-free survival rates of node negative patients and node positive patients without and with extracapsular lymph node involvement as reported in the 14 included studies in the systematic review.

<table>
<thead>
<tr>
<th>Study</th>
<th>Node negative patients overall-/disease-free survival (5 years, %)</th>
<th>Node positive patients, no ELNI overall-/disease-free survival (5 years, %)</th>
<th>Node positive patients with ELNI overall-/disease-free survival (5 years, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oesophageal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lagarde47</td>
<td>-</td>
<td>44 / -</td>
<td>12 / -</td>
</tr>
<tr>
<td>D’Journo51</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lerut49</td>
<td>57 / -</td>
<td>40.9 / -</td>
<td>18 / -</td>
</tr>
<tr>
<td>Tachikawa20</td>
<td>-</td>
<td>53.3 / -</td>
<td>0 / -</td>
</tr>
<tr>
<td>Nakano22</td>
<td>-</td>
<td>39.4 / -</td>
<td>23.2 / -</td>
</tr>
<tr>
<td>Paraf45</td>
<td>56 / -</td>
<td>33 / -</td>
<td>0* / -</td>
</tr>
<tr>
<td>Gatzinsky44</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Gastric</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nakamura21</td>
<td>91 / -</td>
<td>61 / -</td>
<td>23 / -</td>
</tr>
<tr>
<td>Di Giorgio5</td>
<td>-</td>
<td>44.8 / -</td>
<td>17.5 / -</td>
</tr>
<tr>
<td>Zacho48</td>
<td>38 / -</td>
<td>35 / -</td>
<td>5 / -</td>
</tr>
<tr>
<td>Rectal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heide18</td>
<td>- / 83†</td>
<td>- / 87†</td>
<td>- / 58†</td>
</tr>
<tr>
<td>Lupatelli19</td>
<td>87 / 84</td>
<td>76.1 / 70.7</td>
<td>33.8 / 31.6</td>
</tr>
<tr>
<td>Ueno50</td>
<td>-</td>
<td>62 / -</td>
<td>44 / -</td>
</tr>
<tr>
<td>Colorectal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Komuta46</td>
<td>-</td>
<td>81 / 76</td>
<td>30-33† / 18-30‡</td>
</tr>
</tbody>
</table>

ELNI: extracapsular lymph node involvement; †: local control; *: no survivors at 2 years; -: not reported; ‡: more or less than five cells invading the surrounding tissue respectively
Discussion

The presence of extracapsular lymph node involvement harbours important prognostic information. The present review emphasizes that extracapsular lymph node involvement is a common phenomenon in patients with gastrointestinal malignancies. The pooled incidence for oesophageal cancer was 57%, for gastric cancer 41%, and for rectal cancer 35%. Furthermore, in all gastrointestinal malignancies, extracapsular lymph node involvement identifies a subgroup of patients with a significantly worse long-term survival. Extracapsular lymph node involvement probably is a late event in cancer progression and reflects an advanced tumour stage. In several studies there was a higher chance for extracapsular lymph node involvement with higher T-stage\(^5,18,20,21,44,47\), and with higher N-stage.\(^5,18,20,21,47\) There was also a correlation between extracapsular lymph node involvement and the number of positive nodes resected\(^5,20,47\) or lympho-vascular invasion.\(^18,20,45\) However, in spite of this correlation with other well known prognostic factors, extracapsular lymph node involvement was identified as an independent prognosticator. In eight of the nine studies in which a multivariate analysis was performed extracapsular lymph node involvement was a highly significant independent prognostic factor.\(^5,18,19,21,45,47,49,51\)

The prognostic significance is further highlighted by studies that reported comparable survival in patients without lymph node involvement and patients with only intracapsular lymph node involvement which is in contrast to the major decrease in survival observed in patients with extracapsular lymph node involvement. This suggests that lymphatic dissemination does not essentially deteriorate prognosis, provided that the lymph node capsule remains intact.\(^18,19,48,49\) Furthermore, in patients with involvement of only one single positive lymph node, extracapsular lymph node involvement was correlated with a significantly worse prognosis.\(^47,49\)

The results of this review supports the results of our earlier study on oesophageal cancer also included in this review.\(^47\) However, the precise causative factor of this worse prognosis is not yet clear. It could be hypothesized that extracapsular lymph node involvement reflects the invasiveness and aggressiveness of the primary tumour, even in an immunologically hostile environment. Another hypothesis could be that extracapsular lymph node involvement reflects an extensive lymphatic spread which can lead to lymphatic obstruction. It has been reported that lymphatic obstruction results in an aberrant flow of lymph fluid leading to lymphaticovenous communication and thus to haematogenous dissemination.\(^52-54\)

This systematic review has several limitations. First, it comprises mostly single-centre studies with generally small or moderate sample sizes, with mostly retrospective designs, and in half of the included studies it was not clear if it concerned a consecutive series of patients. In general, the studies applied different in- and exclusion criteria concerning type and stage of tumours and the use of (neo-) adjuvant therapies. For oesophageal cancer no correlation could be identified between extracapsular lymph node involvement and histological type (i.e. squamous cell carcinoma versus adenocarcinoma). Also for gastric
cancer such correlation could not be identified (i.e. intestinal type versus diffuse type). Furthermore, only a few studies reported on the recurrence pattern.

A difficulty in assessing extracapsular lymph node involvement is the presence of extranodal deposits which are discontinuous with the primary tumour. These deposits have been identified in many gastrointestinal malignancies.\(^{36-40}\) It is unclear whether these are lymph nodes that have been completely replaced by tumour tissue or manifestations of multifocal metastatic disease.\(^{39}\) Tumour cells might be released from a primary lesion and subsequently spread directly into the extranodal and extramural spaces. Alternatively, extranodal deposits might occur subsequent to lymph node involvement as the ultimate form of extracapsular lymph node involvement.\(^{40}\)

In our systematic review the definition of extracapsular lymph node involvement had to include the infiltration of cancer cells beyond the capsule of the metastatic lymph node. However, besides that there was no uniform definition; some studies included micro dissemination in adjacent tissues, while others included deposits without a recognizable lymph node or involvement of afferent lymphatic vessels adjacent to the lymph node. Nonetheless, no obvious differences were observed in the incidence and prognostic significance between those studies that exclusively reported on the extension of malignant cells through the capsule of a metastatic lymph node and those studies that included vessel invasion and isolated deposits as well. However, the number of studies was too small to be confirmative on this topic.

Furthermore, it is unclear if, and to which extent, there is an inter-observer variability of the assessment of extracapsular lymph node involvement. In only three studies the histological sections were screened for extracapsular lymph node involvement by more than one researcher.\(^{45;46;49}\) In general, extracapsular lymph node involvement is often associated with a desmoplastic reaction. Sometimes this reaction is so extensive that the presence or absence of extracapsular lymph node involvement is difficult to interpret. In cases of such difficulties an imaginary line that represents the pre-existing capsule can be drawn to facilitate the interpretation.\(^{47}\)

Detection and quantification of extracapsular lymph node involvement in the surgical resection specimen of gastrointestinal malignancies might be helpful to individualize postoperative therapeutic strategies in the adjuvant setting in patients in whom the indication for adjuvant chemotherapy is not yet already been established based on other pathological factors. To facilitate a tailored approach in the neo-adjuvant setting it would be necessary to discriminate preoperatively between positive nodes with and without extracapsular lymph node involvement. In this respect, the diagnostic accuracy of endosonography, computer tomography and magnetic resonance imaging has only been tested in small studies, without convincing results so far.\(^{49;55-57}\)

However, the effect of (neo-) adjuvant therapy on the presence of extracapsular lymph node involvement and its prognosis remains unclear because many studies did not include patients who received such therapy.

In conclusion, based on the limited evidence available it can be concluded that extracapsular lymph node involvement is a common phenomenon in patients with gastrointestinal malignancies. It identifies a subgroup of patients with a significantly worse long-term
survival. This systematic review highlights the importance of assessing extracapsular lymph node involvement as a valuable prognostic factor. Pathologists and clinicians should be aware of this important feature. Further research is, however, warranted on the correlation of extracapsular lymph node involvement with different histological types (e.g. squamous cell carcinoma versus adenocarcinoma) and other important covariates, such as the recurrence pattern and the effect of (neo-)adjuvant therapy. Possibly, in future staging systems, not only the number of positive nodes and the lymph node ratio but also the presence and number of lymph nodes with extracapsular lymph node involvement should be considered.

Reference List


Chapter 12

Extracapsular lymph node involvement in gastrointestinal malignancies


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Chapter 13

The prognostic significance of extracapsular lymph node involvement in node positive patients with colonic cancer

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FJW ten Kate
JJS Kiewiet
SM Lagarde
JFM Slors
JJB van Lanschot
WA Bemelman

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Abstract

Introduction
In colonic cancer the prognostic significance of extracapsular lymph node involvement is not established and is therefore the objective of this study.

Methods
Between January 1994 and May 2005, all patients who underwent resection for primary colonic cancer with lymph node metastasis were reviewed. All resected lymph nodes were re-examined to assess extracapsular lymph node involvement. In uni- and multivariate analysis disease free survival (DFS) was correlated with various clinicopathologic factors.

Results
One hundred eleven patients were included. In 58 patients extracapsular lymph node involvement was identified. Univariate analysis revealed that pN-stage (5-year DFS pN1 vs. pN2; 65% vs. 14%, p<0.001), extracapsular lymph node involvement (5-year DFS intracapsular lymph node involvement vs. extracapsular lymph node involvement; 69% vs. 41%, p=0.003), and lymph node ratio (5-year DFS < 0.176 vs. ≥ 0.176; 67% vs. 42%, p=0.023) were significant prognostic indicators. Among these variables pN-stage (hazard ratio 3.5, 95% confidence interval [CI]: 1.72 – 7.42) and extracapsular lymph node involvement (hazard ratio 1.98, 95% CI: 1.00 – 3.91) were independent prognostic factors. Among patients without extracapsular lymph node involvement, those receiving adjuvant chemotherapy had a significantly better survival (p=0.010). In contrast, chemotherapy did not improve DFS in patients with extracapsular lymph node involvement.

Conclusion
Together with pN2 stage, extracapsular lymph node involvement reflects a particularly aggressive behaviour and has significant prognostic potential.
Introduction

The presence and extent of lymphatic dissemination are among the most important predictors for survival in colonic cancer.\textsuperscript{1,2} For stage III colonic cancer, the 5-year survival rate is approximately 50-60\%.\textsuperscript{3-5} According to stages defined by the recently revised American Joint Committee on Cancer (AJCC, sixth edition) 5-year stage specific survivals were 83\% for stage IIIa (T1-2N1), 64\% for stage IIIb (T3-4N1), and 44\% for stage IIIc (T1-4N2).\textsuperscript{6} Adjuvant chemotherapy is standard in patients with stage III disease. Adjuvant treatment with 5-fluorouracil and leucovorin reduces the risk of recurrence and death by one third.\textsuperscript{4,7}

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/or the lymph node ratio (i.e. the number of involved nodes over the total number of resected and identified nodes).\textsuperscript{8-10} Furthermore, the presence of micro-metastasis in lymph nodes has also been identified as a prognostic factor.\textsuperscript{11,12}

Extracapsular lymph node involvement is the extension of cancer cells through the nodal capsule into the perinodal fatty tissue. 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{13-19} Patients with extracapsular lymph node involvement have a reduced overall and disease free survival (DFS) in these malignancies.\textsuperscript{13-20} However, in colonic cancer the prognostic value of extracapsular lymph node involvement has not yet been established. Only one study has been published on extracapsular lymph node involvement in colonic cancer suggesting prognostic significance of extracapsular lymph node involvement.\textsuperscript{21}

Therefore, the aim of the present study was to assess the incidence and extent of extracapsular lymph node involvement in patients with node positive colonic cancer. Furthermore, its relation to other clinicopathologic factors was studied. Finally, its prognostic significance in relation to the type of recurrence was analyzed.

Methods

Patient population

Between January 1994 and May 2005, all patients who underwent segmental colonic resection in the Academic Medical Centre in Amsterdam for primary colonic cancer (rectal cancers and (sub-)total colectomies were excluded) were reviewed. All patients with lymph node involvement (stage III) were included in the present study. Patients with distant metastases (stage IV) diagnosed during preoperative staging, were excluded. Data concerning patient characteristics and performed procedure were collected during chart review using a preformatted sheet. Surgery was generally performed or supervised by a colorectal surgeon. Operations were performed with curative intent, either via median laparotomy or via laparoscopy.
Pathological processing
Routinely, after resection the pathologist who examined the operation specimen carefully palpated the specimen and all palpable lymph nodes were collected and evaluated. Routine H&E staining was performed using a standardized protocol. No additional immunohistochemical staining techniques to detect micro-metastases were used. In general all small nodes were completely embedded and serial sections were made. Larger nodes were first laminated. Subsequently they were totally embedded and serial sections were made. The findings of the pathologist were routinely discussed in a multidisciplinary meeting to evaluate the indication for adjuvant therapy. During the whole study period 5-fluorouracil based adjuvant chemotherapy was offered to all patients with lymph node involvement younger than 75 years old.

Data assessment
In the summer of 2006 an experienced pathologist re-examined all available H&E slides of both the primary tumour and all the collected lymph nodes to assess metastases and extracapsular lymph node involvement. Furthermore, pT-stage, pN-stage (i.e. ≤3 positive nodes; pN1 vs. >3 positive nodes; pN2), differentiation grade of the tumour, the presence or absence of lymphovascular invasion, total number of resected lymph nodes, total number of positive lymph nodes, lymph node ratio and the presence or absence of tumour deposits were recorded. The evaluation was done without knowledge of the clinical outcome of the patients. Extracapsular lymph node involvement was defined as metastatic adenocarcinoma extending through the nodal capsule into the perinodal fatty tissue. Deposits of metastatic adenocarcinoma without a recognizable lymph node were not considered as extracapsular lymph node involvement but scored as separate tumour deposits and assessed as a separate pathological factor. However, the size and contour of the deposits were not taken into account in this study. Extracapsular lymph node involvement is often associated with a desmoplastic stroma reaction. Sometimes this reaction is so extensive that the presence or absence of extracapsular lymph node involvement can be difficult to interpret. In that case, an imaginary line representing the pre-existing capsule was drawn to facilitate proper interpretation.20

Follow-up
Patients’ hospital and outpatient clinic records were reviewed to assess recurrence. To complete follow-up, a telephone survey contacting the patients’ general practitioner was done in August 2006. Follow-up extended until August 2006, ensuring a minimal potential follow-up of 15 months. Recurrence was classified as haematogenous recurrence, loco-regional recurrence (including peritoneal recurrence) or both.
Statistics
Statistical calculations were performed using SPSS® version 12.0 (Statistical Package for the Social Sciences, Chicago, IL, USA). Age, tumour diameter, total number of resected lymph nodes (i.e. tumour positive and negative) and lymph node ratio were dichotomized as less or more than the corresponding median value. To compare categorical data the Chi-square or Fisher exact test was used when appropriate. The Mann-Whitney test was used to compare continuous variables. Survival rates were calculated on an actuarial basis with the Kaplan-Meier method, using the log-rank test for comparison. Multivariate Cox regression analysis was carried out to identify independent prognostic factors. All significant factors from a univariate analysis were entered in a multivariate analysis. P-values < 0.05 (two-sided) were considered statistically significant.

Results
Included patients
In the study period 398 patients underwent potentially curative segmental colonic resection for primary colonic cancer. In 114 patients lymph node metastases were present without other metastasis (stage III). Subsequently, three patients were excluded; two patients died due to postoperative complications, in one patient a metastasis of an earlier gastric carcinoma was diagnosed peroperatively.
In the final analysis 111 patients were included. There were 60 male and 51 female patients. Median age was 66 (range 31-91) years. Sixteen patients were operated on in an emergency setting, the remaining patients underwent elective surgery. There were 58 right sided colectomies, 15 left sided colectomies, and 38 sigmoid resections. In the included patients, a total number of 1586 lymph nodes had been identified by the pathologist who examined the resection specimen. A median of 12 (range 1-47) nodes per patient had been identified in the specimen. In one patient only a single node was identified. Metastases were detected in 332 lymph nodes. Tumour extension through the lymph node capsule was identified in a total of 101 lymph nodes and in 58 of 111 lymph node positive patients. Extracapsular lymph node involvement was confined to only one lymph node in 35 of these patients.

Clinicopathologic characteristics
The clinicopathologic characteristics of 53 patients with only intracapsular lymph node involvement and 58 patients with extracapsular lymph node involvement are summarized in Table 1. Extracapsular lymph node involvement was seen more often if the number of positive nodes was higher, in patients with pN2 disease, with a higher lymph node ratio, with poorer differentiated tumours and with invasion of lymphic or blood vessels.
Table 1. Clinicopathologic characteristics of 111 included patients with stage III colonic cancer. Patients are divided in groups with only intracapsular lymph node involvement (LNI) and patients with extracapsular LNI.

<table>
<thead>
<tr>
<th></th>
<th>Only intracapsular LNI (n = 53)</th>
<th>Extracapsular LNI (n = 58)</th>
<th>P-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>pT stage</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>T 1</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>T 2</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>T 3</td>
<td>50</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>T 4</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Tumour diameter (cm)‡</td>
<td>5.0 (1.3-12.0)</td>
<td>4.9 (2.0-12.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Resected nodes‡</td>
<td>11 (1-47)</td>
<td>12 (4-39)</td>
<td>NS</td>
</tr>
<tr>
<td>Positive nodes‡</td>
<td>1 (1-8)</td>
<td>3 (1-21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>pN stage</td>
<td></td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>N 1</td>
<td>48</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>N 2</td>
<td>5</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Lymph node ratio‡</td>
<td>0.11 (0.02-1.0)</td>
<td>0.24 (0.08-1.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Differentiation</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>good</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>moderate</td>
<td>48</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>poor</td>
<td>2</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Lymphovascular invasion</td>
<td></td>
<td></td>
<td>0.031</td>
</tr>
<tr>
<td>no</td>
<td>38</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>15</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Extranodal deposits</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>no</td>
<td>40</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>13</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>no</td>
<td>17</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>35</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>unknown</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

*Values are mean (SD); ‡Values are median (range); †Fisher’s exact test, Chi-square test, Mann-Whitney U test applied when appropriate; LNI: lymph node involvement; NS: not significant

Follow-up and survival analysis

The median potential follow-up period was 74 months (range 16-151). In the follow-up period 45 patients developed recurrence; 26 patients developed haematogenous recurrence, seven patients developed loco-regional recurrence and 11 patients had both haematogenous and loco-regional recurrence. In one patient the type of recurrence was unknown. The pattern of recurrence was comparable between patients with and without extracapsular lymph node involvement (p=0.893).
Five-year DFS in patients with extracapsular lymph node involvement was 41% compared to 69% for those who had only intracapsular lymph node involvement (p=0.003, Table 2, Figure 1). No difference in DFS was observed between patients (n=35) with only one lymph node with extracapsular lymph node involvement as compared to patients (n=23) with more than one lymph node with extracapsular lymph node involvement; 5-year DFS was 41% vs. 40% (p=0.784) respectively.

Table 2. Univariate analysis of prognostic factors in patients with stage III colonic cancer

<table>
<thead>
<tr>
<th></th>
<th>5 year disease free survival</th>
<th>standard error</th>
<th>P-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>pT-stage</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>T1</td>
<td>‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>54%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumour diameter (cm)</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>&lt; 5</td>
<td>58%</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>≥ 5</td>
<td>51%</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>Number of resected nodes</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>&lt; 12</td>
<td>50%</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>≥ 12</td>
<td>59%</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>pN stage</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>N 1</td>
<td>65%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>N 2</td>
<td>14%</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>Lymph node ratio</td>
<td></td>
<td></td>
<td>0.023</td>
</tr>
<tr>
<td>&lt; 0.176</td>
<td>67%</td>
<td>7%</td>
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<tr>
<td>≥ 0.176</td>
<td>42%</td>
<td>7%</td>
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<td>Extracapsular LNI</td>
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<td>7%</td>
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</tr>
<tr>
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<td>41%</td>
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<td></td>
</tr>
<tr>
<td>Differentiation</td>
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<td>good</td>
<td>27%</td>
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</tr>
<tr>
<td>poor</td>
<td>45%</td>
<td>12%</td>
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</tr>
<tr>
<td>Lymphovascular invasion</td>
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</tr>
<tr>
<td>no</td>
<td>62%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>43%</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>Extra nodal deposits</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>no</td>
<td>58%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>43%</td>
<td>10%</td>
<td></td>
</tr>
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<td></td>
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</tr>
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<td>43%</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>61%</td>
<td>6%</td>
<td></td>
</tr>
</tbody>
</table>

†Log-rank test; ‡too few patients and events; LNI: lymph node involvement
In 30 patients tumour deposits without any recognizable lymph node structure were identified besides positive nodes. To assess whether the prognostic significance of these tumour deposits was different from extracapsular lymph node involvement, the study population was divided into three groups; intracapsular lymph node involvement and tumour deposits, extracapsular lymph node involvement without deposits and extracapsular lymph node involvement with tumour deposits. No difference in recurrence was observed between the three groups; 5-year DFS was 49%, 44% and 38% respectively (p=0.644).

Univariate analysis was performed to study the relation between the various factors and DFS. Univariate analysis revealed that pN-stage (5-year DFS pN1 vs. pN2; 65% vs. 14%, p<0.001), lymph node ratio (5-year DFS <0.176 vs. ≥ 0.176; 67% vs. 42%, p=0.023), and extracapsular lymph node involvement (5-year DFS intracapsular lymph node involvement vs. extracapsular lymph node involvement; 69% vs. 41%, p=0.003) were all significant prognostic indicators for survival (Table 2). It was shown that the presence or absence of tumour deposits was not a significant factor for recurrence in contrast to extracapsular lymph node involvement. Multivariate analysis demonstrated that among these variables pN-stage (hazard ratio 3.5, 95% confidence interval [CI]: 1.72 – 7.42) and extracapsular lymph node involvement (hazard ratio 1.98, 95% CI: 1.00 – 3.91) were independent prognostic factors.

**Adjuvant chemotherapy**

Sixty-six patients received adjuvant chemotherapy, 43 patients did not, and in two patients it was unknown whether or not they had received adjuvant chemotherapy. Of the 77 patients younger than 75 years, 16 patients did not receive adjuvant chemotherapy due to...
refusal by the patient or a poor performance status. Chemotherapy that was applied mostly consisted of 5-fluorouracil and leucovorin. Patients treated with adjuvant chemotherapy were significantly younger compared to those receiving no adjuvant therapy (median age was 60 vs. 77 years respectively, p<0.001). Among the other clinico-pathological factors no significant differences were observed. Overall 5-year DFS was 61% in patients who received adjuvant therapy compared to 43% in patients who did not receive adjuvant chemotherapy (p=0.067). Subsequently, the groups were divided according to the presence or absence of extracapsular lymph node involvement (Figure 2). Among the patients without extracapsular lymph node involvement those receiving adjuvant therapy had a significantly better survival compared to those who did not receive adjuvant therapy (5-year DFS was 77% vs. 48%, respectively p=0.010). In patients with extracapsular lymph node involvement the application of chemotherapy did not influence DFS; 44% vs. 39%, respectively (p=0.934).

Discussion

Prognostic significance of extracapsular lymph node involvement

In the present study it is demonstrated that extracapsular involvement together with pN-stage are independent prognostic parameters for recurrence (both loco-regional and haematogenous) in patients with colonic cancer.

A recent systematic review on extracapsular lymph node involvement in gastrointestinal malignancies demonstrated that the presence of extracapsular lymph node involvement is
a common phenomenon in patients with gastrointestinal malignancies. Furthermore, in all these malignancies, extracapsular lymph node involvement identified a subgroup of patients with a significantly worse long-term survival.\textsuperscript{22} However, for that review only one small study concerning colorectal cancer was available,\textsuperscript{23} including a small subgroup of patients with colonic cancer and showing that patients with extracapsular lymph node involvement had significantly worse overall- and disease-free survival as compared to patients with only intracapsular lymph node involvement. However, no multivariate analysis was performed. More recently, a larger study was published showing an incidence of extracapsular lymph node involvement of 49\%. Extracapsular lymph node involvement was identified as the only independent prognosticator for recurrence in multivariate analysis (hazard ratio 3.8, 95\% CI: 1.6-8.9).\textsuperscript{21}

The present study comprised of a consecutive series of lymph node positive patients with colonic cancer. Extracapsular lymph node involvement was associated with a higher number of positive nodes, pN2 stage, a higher lymph node ratio, poorly differentiated tumours, and invasion of lymph- or blood vessels. The prognostic significance of extracapsular lymph node involvement was confirmed in multivariate analysis demonstrating that it was an independent prognostic factor (hazard ratio 1.98, 95\% CI: 1.00 – 3.91). Five-year DFS in patients with only intracapsular lymph node involvement was 69\% compared to 41\% in patients with extracapsular lymph node involvement (p=0.003).

In some of the included patients lymph node staging was not adequate with less than 12 sampled nodes. However, in uni- and multivariate analysis including only patients in whom 12 nodes or more were identified; the same variables were identified as significant prognostic indicators (data not shown). Another limitation of the present study is the retrospective study design. Since the resection specimen had been thrown away and only the available slide could be assessed. However, all the available slides of both the primary tumour and all the sampled nodes were re-assessed (prospectively).

The precise causative factor of the worse prognosis in patients with extracapsular lymph node involvement is not yet clear. It could be hypothesized that the ability of cancer cells to spread through the lymph node capsule, in an immunologically hostile environment, probably reflects the invasive aggressiveness of the tumour.\textsuperscript{24,25} Another hypothesis could be that extracapsular lymph node involvement reflects an extensive lymphatic spread inducing lymphatic obstruction. It has been reported that lymphatic obstruction results in an aberrant flow of lymph fluid leading to lympho-venous communication and thus to haematogenous dissemination.\textsuperscript{26-28} However, in this study there was no correlation between extracapsular lymph node involvement and recurrence pattern.

**Adjuvant chemotherapy**

In the present study no effect on survival of adjuvant chemotherapy was observed in patients with extracapsular lymph node involvement. It can be hypothesized that the extension through the barrier of the lymph node might reflect an aggressive behaviour and/or a biological insensitivity for chemotherapy. It should be taken into account that patients receiving no adjuvant therapy were significantly older, and therefore, part of this observation could be biased. However, a pooled analysis of seven randomised
trials demonstrated no significant interaction between age and the efficacy of adjuvant chemotherapy for resected colon cancer. The incidence of toxic effects was also not increased among the elderly (age > 70 years). Furthermore, about 20% of the patients younger than 75 years did not receive or refused adjuvant chemotherapy in the present study. Finally, the study concerns a retrospectively collected series of patients in a large period and the numbers in the subgroups were small introducing the risk of having a type-II-error. Therefore, there is a need for unequivocal data from large prospective studies to support this observation.

**Extranodal tumour deposits**

The proper assessment of extracapsular lymph node involvement can be difficult in the presence of extranodal deposits which are discontinuous with the primary tumour. These deposits have been identified in many gastrointestinal malignancies. It is unclear whether these are lymph nodes that have been completely replaced by tumour tissue or manifestations of multifocal metastatic disease. In the sixth edition of the TNM staging system these tumour deposits are classified as regional lymph node metastasis if the nodule has the shape and smooth contour of a lymph node. If the deposit has an irregular contour, it is classified as pT3. However, if a deposit represents a completely overgrown lymph node with extracapsular growth the contour will be irregular rather than a smooth round contour. In earlier editions of the TNM staging system all deposits larger than three millimetres in diameter were classified as regional lymph node metastasis. Tumour deposits up to three millimetres in diameter were considered as discontinuous extension and therefore classified as pT3. So the precise origin and prognostic implications of these deposits remains unclear. Therefore, in the present study these deposits were assessed as a separate factor. In the present study 27% of the patients showed these deposits. There was no correlation between the presence of these deposits and extracapsular lymph node involvement. Furthermore, these deposits had no significant effect on survival in univariate analysis. On the other hand the survival of patients with only deposits and patients with extracapsular lymph node involvement without deposits was comparable to survival of patients with both deposits and extracapsular lymph node involvement. This suggests that tumour deposits without a recognizable lymph node structure have a comparable influence on survival as extracapsular lymph node involvement.

**Conclusion**

In conclusion, two independent study groups (ours and Yano’s) indicated that extracapsular lymph node involvement in colonic cancer is an independent negative prognostic factor, reflecting a particularly aggressive biological behaviour. It identifies a subgroup of patients with a significantly worse DFS. Detection and quantification of extracapsular lymph node involvement in the surgical resection specimen might be helpful in the future to individualize postoperative therapeutic strategies in the adjuvant setting. Pathologists should be aware of this clinically important feature and report its presence and extent upon histological examination.
Reference List


Chapter 14

Circulating tumour cells during laparoscopic and open surgery for primary colonic cancer in portal and peripheral blood

J Wind
JB Tuynman
AGJ Tibbe
DJ Richel
MI van Berge Henegouwen
WA Bemelman

Submitted
Abstract

Introduction
The objective of this study was to detect and quantify circulating tumour cells (CTC) in peripheral and portal blood of patients who had open or laparoscopic surgery for primary colonic cancer.

Methods
Patients in the laparoscopic group were operated on in a medial to lateral approach ("vessels first"), in the open group a lateral to medial approach was applied. The enumeration of CTC was performed with the CellSearch System. Intra-operative samples were taken paired-wise (from peripheral and portal circulation) directly after entering the abdominal cavity (T1), after mobilisation of the tumour baring segment (T2), and after tumour resection (T3). Ploidy of both the CTC and tissue of the primary tumour was determined for chromosome 1, 7, 8 and 17.

Results
Thirty-one patients were included; 18 patients had open surgery, 13 patients were operated on laparoscopically. The percentage of samples with CTC at T1 was 7% in peripheral blood and 54% in portal blood (p=0.002). At T2, 4% and 31% respectively (p=0.031). And at T3, 4% and 26% respectively (p=0.125). The cumulative percentage of samples with CTC was significantly higher during open surgery as compared to the laparoscopic approach. Both the CTC and tissue of the primary tumour were diploid for chromosome 1, 7, 8 and 17.

Conclusion
The detection rate and quantity of CTC is significantly increased intra-operatively and is significantly higher in portal blood compared to peripheral blood. Significantly less CTC were detected during laparoscopic surgery probably as result of the medial to lateral approach.
Introduction

It is of great importance that survival and the most likely sites of recurrence can be predicted after surgery with curative intent. 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.\textsuperscript{1-5} Patients with unfavourable prognostic factors may benefit from adjuvant chemotherapy. However, pathologic staging systems (TNM) fails to adequately identify patients with stage II and III disease who will benefit from adjuvant chemotherapy.\textsuperscript{2-5} Detection of circulating tumour cells (CTC) during and after resection might be helpful to identify those patients who will benefit from adjuvant chemotherapy and expand our knowledge about the biology of metastasis and potential role of surgery in this process. CTC were first detected in patients with colorectal cancer more than 50 years ago.\textsuperscript{6,7}

The introduction of the CellSearch\textsuperscript{TM} system has provided a standardised method for the enumeration and characterisation of CTC that permitted the evaluation of potential clinical utilities of CTC through multi-centre prospective clinical trials.\textsuperscript{8} Prospective multi-centre studies in metastatic breast, colorectal and prostate cancer showed that the presence of CTC were associated with poor outcome and were an independent predictor of progression free survival and overall survival.\textsuperscript{9-11} In primary colorectal cancer little is known about the role of CTC although a relation with stage has been shown. The specificity of CTC detection is lower at low frequencies making the data interpretation more difficult.\textsuperscript{12}

In colorectal cancer surgery the principle of early lymphovascular ligation before manipulation of the tumour has been termed the “no-touch isolation” technique.\textsuperscript{13,14} This technique was proposed to reduce intra-operative dissemination.\textsuperscript{15} In laparoscopic colorectal surgery the no-touch principles are represented in the so-called medial to lateral approach where the supplying vessels are ligated early in the procedure. Several randomised trials comparing laparoscopic with open segmental colectomy have indicated that laparoscopic surgery can be applied safely for both benign and malignant diseases.\textsuperscript{16-21} Furthermore, 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.\textsuperscript{16} However, a potential oncological benefit of laparoscopic surgery in which a median to lateral approach is applied is still debated.

The objective of this study was to determine whether CTC could be detected in peripheral and portal blood during laparoscopic and open surgery for colonic cancer. Furthermore, differences in the amount of CTC between peripheral and portal blood were assessed. Finally, the effect of the surgical approach (i.e. open versus laparoscopic) on the presence of CTC during surgery was assessed.
Methods

Study population
The current study was performed on patients with primary colonic cancer (rectal cancers were excluded) who underwent surgery with curative intent at the Academic Medical Centre, Amsterdam between August 2005 and August 2007. All patients underwent abdominal ultrasonography and chest radiography, to identify metastatic disease preoperatively. Patients with distant metastases (stage IV) were excluded. Furthermore, patients with prior abdominal surgery, emergency surgery, age over 85 years, and American Society of Anaesthesiology (ASA) score above three were excluded. Surgery was performed or supervised by a colorectal surgeon. Operations were performed with curative intent, either via midline laparotomy or via laparoscopy. All laparoscopic operations were performed according to the “no-touch isolation” technique, i.e. a medial to lateral approach with early vessel ligation. A lateral to medial approach was performed during open resections. In laparoscopic procedures pneumoperitoneum was established with CO₂ gas with an intra-abdominal pressure of 15 mmHg or less.

The majority of the patients (24/31) also participated in a randomised trial comparing open and laparoscopic surgery (ISRCTN: 79588422). Tumour stage and grading were classified according to the sixth edition of the TNM classification of the International Union Against Cancer. Informed consent was obtained from all patients. The study protocol was approved by the local medical ethics committee.

Blood collection
Peripheral whole blood samples were collected through an intravenous cannula. In left sided colectomies, portal whole blood samples were collected by insertion of a 15 centimetres long 5.5 French catheter (Arrow-Howes™ Paediatric Multi-Lumen Central Venous Line) into the inferior mesenteric vein which was advanced about 10-15 centimetres to secure position at portal vein level. In laparoscopic procedures a 30 centimetres long catheter was used which was positioned intra-abdominally through a large infusion needle. Subsequently, a small hole was created in the inferior mesenteric vein with a pair of scissors followed by insertion of the catheter laparoscopically. The catheter was advanced 10-15 centimetres to secure position at portal vein level and fixed with a purse-string suture. In case of right sided colectomy a similar procedure was performed using a venous branch of the right branch of the middle colonic vein to insert the catheter.

Blood samples were collected at four different time points which are shown in Figure 1. The first sample was collected before surgery (only peripheral, T0). Subsequently samples were taken paired-wise (peripheral and portal) after entry into the abdominal cavity and before mobilisation of the tumour bearing segment (T1), after mobilisation of the tumour bearing segment (T2), and after tumour resection (T3).
Enumeration of CTC

Blood samples were drawn into 10 ml tubes which contained a cell preservative (CellSave Preservative Tubes, Immunicon, Huntingdon Valley, USA). Samples were maintained at room temperature and processed within 72 hours after collection. The CellSearch™ Circulating Tumour Cell Test (Veridex LLC, Warren, USA) was used for the isolation and enumeration of circulating epithelial cells. The cell detection system consists of a sample preparation and cell analysis platform that have been described elsewhere in detail. In brief, ferro-fluids coated with epithelial cell-specific EpCAM antibodies were used to immuno-magnetically enrich epithelial cells from 7.5 ml of blood. The enriched samples were stained with phycoerythrin conjugated antibodies directed against cytokeratins 8, 18, and 19, an allophycocyanin conjugated antibody to CD45 and the nuclear dye DAPI. The isolated and stained CTC were transferred to a CellTracks® Cartridge and analysed on the CellTracks® Analyser II, a four colour semi-automated fluorescence microscope (Veridex). Image frames covering the entire surface of the cartridge for four different fluorescence filter cubes were captured. From the captured images, a gallery of objects meeting pre-determined criteria was automatically presented in a web-enabled browser for interpretation by a trained operator who made the final selection of cells. The criteria for an object to be defined as a CTC included round to oval morphology, a visible nucleus (DAPI positive), positive staining for cytokeratin, and negative staining for CD45. Results of cell enumeration were expressed as the number of cells per 7.5 ml of blood. The performance of the assay system is described in detail elsewhere. In this study the presence of one or more CTC in the sample was considered CTC positive.

Fluorescence in Situ Hybridization on CTC and primary tumour tissue

To determine cytogenetics changes of the CTC and as an additional identifier, Fluorescence In Situ Hybridization (FISH) was applied to CTC containing cartridges. After the CTC were isolated and identified as described in the previous section, the CTC were labelled with fluorescent FISH probes against the centromeric region of chromosomes 1, 7, 8, and 17. The location of the previous identified tumour cells was maintained during FISH analysis.
which allows revisiting of the same cell. Fluorescence images of the FISH signals were acquired and the number of FISH spots for each of the four chromosomes was determined in each CTC. For the patients with the highest number of CTC the ploidy, on basis of the number of copies of the chromosomes 1, 7, 8, and 17, of the CTC was compared with the ploidy of the primary tumour tissue. Paraffin tissues of the primary tumour were treated and hybridized and the number of FISH spots for chromosome 1, 7, 8, and 17 were determined.

**Statistics**

Statistical calculations were performed using SPSS® version 12.0.2 (Statistical Package for the Social Sciences, Chicago, IL, USA). To compare categorical data the Chi-square was used. The Mann-Whitney test was used to compare continuous variables. The McNemar and Wilcoxon tests were used to test for differences between the detection rate in portal and peripheral blood with respect to the timing of blood collection. An unpaired non-parametric test was used to assess the influence of open and laparoscopic surgery on the detection rate of CTC.

**Results**

**Study population**

During the study period 38 patients were included. Subsequently, seven patients were excluded; in five patients the cannulation of the inferior mesenteric vein was not successful and a further two patients were excluded when histological evaluation of the resected specimen revealed adenomas containing no invasive carcinoma. Thirty-one patients remained for final analysis; 19 male and 12 female patients with a mean age of 67 (±12) years. Eighteen patients had a laparotomy (open-group); the remaining 13 patients were operated on laparoscopically (laparoscopic-group). There were 16 right-sided colectomies, seven left-sided colectomies, seven (recto-) sigmoid resections, and one subtotal colectomy (Table 1).
Table 1. Clinicopathologic characteristics of the included patients

<table>
<thead>
<tr>
<th>Clinicopathologic characteristics</th>
<th>Patients divided according to surgical approach</th>
<th>P-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>all patients (n=31)</td>
<td>open-group (n=18)</td>
</tr>
<tr>
<td>Age* (yrs)</td>
<td>67 (12)</td>
<td>70 (10)</td>
</tr>
<tr>
<td>Male:female‡</td>
<td>19 (61):12 (39)</td>
<td>1 (61):7 (39)</td>
</tr>
<tr>
<td>Preoperative CEA level*</td>
<td>2.1 (2.5)</td>
<td>1.7 (1.8)</td>
</tr>
<tr>
<td>Operative procedure‡</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>- right hemicolectomy</td>
<td>16 (51)</td>
<td>12 (67)</td>
</tr>
<tr>
<td>- left hemicolectomy</td>
<td>7 (23)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>- (recto)sigmoidectomy</td>
<td>7 (23)</td>
<td>3 (17)</td>
</tr>
<tr>
<td>- subtotal colectomy</td>
<td>1 (3)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Operating time* (min)</td>
<td>178 (55)</td>
<td>153 (39)</td>
</tr>
<tr>
<td>pT stage‡</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>- T 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- T 2</td>
<td>5 (16)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>- T 3</td>
<td>26 (84)</td>
<td>17 (95)</td>
</tr>
<tr>
<td>- T 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumour diameter* (cm)</td>
<td>4.6 (2.0)</td>
<td>5.0 (2.3)</td>
</tr>
<tr>
<td>pN stage‡</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td>- N 0</td>
<td>21 (68)</td>
<td>12 (67)</td>
</tr>
<tr>
<td>- N 1</td>
<td>5 (16)</td>
<td>4 (22)</td>
</tr>
<tr>
<td>- N 2</td>
<td>5 (16)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Differentiation‡</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>- good</td>
<td>1 (3)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>- moderate</td>
<td>24 (77)</td>
<td>12 (67)</td>
</tr>
<tr>
<td>- poor</td>
<td>6 (19)</td>
<td>5 (28)</td>
</tr>
<tr>
<td>Lymphovascular invasion‡</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>- no</td>
<td>24 (77)</td>
<td>12 (67)</td>
</tr>
<tr>
<td>- yes</td>
<td>7 (23)</td>
<td>6 (33)</td>
</tr>
</tbody>
</table>

†Chi-square test, Mann-Whitney U test applied when appropriate; *Values are mean (SD); ‡Values are absolute numbers (%)

**Clinicopathologic characteristics**

The clinicopathologic characteristics of the overall study population (n=31), the open-group (n=18), and the laparoscopic-group (n=13) are summarised in Table 1. Operating times were significantly longer in the laparoscopic-group compared to the open-group (153 vs. 224 minutes, p=0.001). Furthermore, there was a higher T-stage and more lymphovascular invasion in the open-group as compared to the laparoscopic-group, although these differences were not significant. In the laparoscopic group there was slightly more N2 disease. Finally, there were more right sided resections in the open group than in the...
laparoscopic group, although this difference was not significant. Regarding the other clinicopathologic characteristics the groups were comparable.

**Enumeration of CTC**

In *Figure 2* the average number of CTC in patients who underwent laparoscopic or open surgery at the subsequent time points is shown. Although the standard deviations were large, the number of CTC detected in portal blood was higher at all subsequent time points. In the samples taken at T1, CTC were identified in 7% of the peripheral samples and in 45% of the portal samples (*p*=0.002). With respect to the samples taken at T2, CTC were identified in 4% and in 31% respectively (*p*=0.031). Finally, at T3 the detection rate was 4% and 26% respectively (*p*=0.125). Subsequently, to assess the overall difference between peripheral and portal blood the dichotomous results on the three intra-operative time points were summed, resulting in a score ranging from zero (all samples negative) to three (all samples positive). The cumulative score was significantly higher in portal blood compared to peripheral blood (*p*=0.001, *Table 2*).

**Table 2.** Cumulative result of the enumeration of CTC in peripheral and portal blood on the three intra-operative time points (*p*< 0.001)

<table>
<thead>
<tr>
<th></th>
<th>peripheral blood</th>
<th>portal blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>All samples negative</td>
<td>83%</td>
<td>28%</td>
</tr>
<tr>
<td>One sample positive</td>
<td>17%</td>
<td>45%</td>
</tr>
<tr>
<td>Two samples positive</td>
<td>-</td>
<td>27%</td>
</tr>
<tr>
<td>All samples positive</td>
<td>-</td>
<td>7%</td>
</tr>
</tbody>
</table>

The number of CTC in portal blood of patients who underwent open surgery was higher compared to patients who underwent laparoscopic surgery. According to open vs. laparoscopic surgery the percentage of samples with CTC at T1 was 0% vs. 18% (*p*=0.076) in peripheral blood and 65% vs. 36% (*p*=0.142) in portal blood respectively. At T2, 0% vs. 8% (*p*=0.288) in peripheral blood and 44% vs. 9% (*p*=0.046) in portal blood respectively. Finally, at T3, 8% vs. 0% (*p*=0.347) in peripheral blood and 29% vs. 20% (*p*=0.590) in portal blood respectively. To assess the overall difference between open and laparoscopic surgery the dichotomous results in portal blood (as this was more sensitive compared to peripheral blood) on the three intra-operative time points were added up, resulting in a score ranging from zero (all samples negative) to three (all samples positive). The cumulative score was significantly higher in the open-group compared to the laparoscopic-group (*p*=0.039, *Table 3*).

**Table 3.** Cumulative result of the enumeration of CTC in portal blood according open or laparoscopic surgery on the three intra-operative time points (*p*=0.039)

<table>
<thead>
<tr>
<th></th>
<th>open-group</th>
<th>laparoscopic-group</th>
</tr>
</thead>
<tbody>
<tr>
<td>All samples negative</td>
<td>17%</td>
<td>45%</td>
</tr>
<tr>
<td>One sample positive</td>
<td>44%</td>
<td>45%</td>
</tr>
<tr>
<td>Two samples positive</td>
<td>28%</td>
<td>9%</td>
</tr>
<tr>
<td>All samples positive</td>
<td>11%</td>
<td>-</td>
</tr>
</tbody>
</table>
CTC in relation to other clinicopathologic characteristics

To assess potential associations between the presence or absence of CTC and certain clinicopathologic characteristics all the available intra-operative samples, both peripheral and portal, and the cumulative score (see above) of both peripheral and portal samples, were tested in an univariate analysis. The following clinicopathologic characteristics were analysed; age, gender, operative procedure, tumour diameter, tumour differentiation grade, lymphovascular invasion, presence of lymph node metastasis per se, N-stage, and T-stage (T1-T2 vs. T3-T4). Besides a non-significant trend towards a higher number of samples with CTC during right-sided resections compared to left-sided resections (71% vs. 39%, p=0.085) there were no associations.

Morphology of the detected CTC

The tumour cells detected in peripheral blood had a morphology that was similar to the morphology in other carcinoma’s described elsewhere. Different morphology was observed for CTC detected in portal blood at T1 and T2. Cells present in these samples looked frayed and appeared mostly as sheets and clumps of cellular material in which the
individual cells were difficult to discriminate. No difference in morphology between the laparoscopic and open group was observed.

**FISH**

As the morphology of the CTC in portal blood at T1 and T2 deviated, the ploidy of these cells was determined as an additional tumour cell identifier, using chromosome 1, 7, 8 and 17. The CTC all contained two copies for each of the chromosomes. Subsequently, the primary tumour tissue ploidy using chromosome 1, 7, 8 and 17, was compared to that of the CTC. For each of the tested chromosomes the tumour tissue cells displayed also two copies which was equal to the detected CTC. So, ploidy of the CTC and tissue of the primary tumour did match, however both were diploid.

**Discussion**

The present study shows that the presence of CTC was significantly increased intra-operatively and was significantly higher in portal blood (26-45%) as compared to peripheral blood (4-7%). With respect to the surgical approach, the percentage of CTC containing blood samples was significantly lower in the portal blood sample after mobilisation of the tumour bearing segment during laparoscopic surgery compared to open surgery (9% vs. 44%, p=0.046).

Others that assessed the presence of CTC intra-operatively, also found significant higher detection rates in portal blood (50-65%) compared to peripheral blood (11-49%).

Theoretically, tumour cells must pass through the liver, lungs and the microcirculation of other tissues before they pass into the systemic venous circulation. Animal studies have demonstrated that 80-100% of injected human colon carcinoma cells were trapped in the capillary bed of the first organ encountered. Furthermore, a higher prevalence in portal blood might be explained by the fact that there is some dilution in the larger blood volume of the peripheral circulation. Yamaguchi et al. found a PCR-positive (CEA, cytokeratin 20) detection rate of 31% in mesenteric blood and 15% in peripheral blood (p=0.033). The presence of CEA and cytokeratin 20 mRNA in peripheral blood was not correlated with survival. However, with respect to portal blood uni- and multivariate analysis indicated that it was the only independent prognostic factor (hazard ratio 13.6, p=0.028).

Various techniques have been described in the literature to study CTC and the large differences in the reported results bring in question whether the same events are being studied. We choose to use the CellSearch system for CTC evaluation as it has been validated and used in prospective multi-centre trials. In this study the presence of one or more CTC in the sample was considered a CTC positive sample. This low threshold was chosen because of the significant relationship between the presence of one or more CTC and poor outcome in patients with metastatic disease as shown by others. The specificity of the CellSearch system is limited by the users ability to assign an event as a tumour cell. We therefore tried to improve the specificity by investigating the ploidy of
the detected tumour cells. In the cases examined, however, both CTC and primary tumour tissue were diploid for chromosome 1, 7, 8, and 17 thus not providing a definite answer whether or not the detected CTC were true tumour cells or normal epithelial cells shed into the portal blood through surgical trauma.

Since a considerable number of patients with resectable colorectal cancer subsequently develop metastatic disease, dissemination is likely to be an early event that may happen pre- or intra-operatively and is not detected by conventional staging techniques. In metastatic breast, colorectal and prostate cancer the presence of CTC was associated with a short progression free and overall survival and predicted treatment efficacy earlier and more effectively than imaging in breast cancer and PSA in prostate cancer. Nevertheless, the presence of CTC does not necessarily predict subsequent metastatic disease as this process is very inefficient. Fidler reported that less than 0.1% of tumour cells placed into the circulation survived to produce metastatic lesions in animals. However, activation of blood coagulation and relative immune suppression due to the surgical stress might enhance the metastatic potential of these intra-operatively spilled cells. So far, several studies have demonstrated a negative effect of CTC on prognosis. Furthermore, in some studies the presence of CTC was found as the only independent prognosticator. Nevertheless, others have found no association between CTC and survival. A major difficulty in interpreting these results is the variety of detection methods, the small sample sizes of the individual studies, and the relatively short follow-up.

In the present study, less CTC were found in the laparoscopically operated patients. Both the open-group and laparoscopic-group were comparable with respect to most clinicopathologic characteristics, with the exception of a non-significant trend towards more right-sided resections, a higher T-stage, and more lymphovascular invasion in the open group, and longer operating times and more N2 disease in the laparoscopic-group. Some have found an association between the presence of CTC and a higher T-stage, lymph node involvement, poorer differentiated tumours, and lymph- and blood vessel invasion. However, in these studies it was also demonstrated that in patients with early-staged cancers the detection rates were also considerable. Moreover, in the present study it was demonstrated that the only factor influencing the detection rate, besides the location of sampling (i.e. peripheral vs. portal), was the surgical approach (i.e. laparoscopic or open surgery) and that the other analysed factors were not associated with the presence or absence of CTC.

It could be hypothesised that laparoscopic surgery with a medial to lateral approach with early lymphovascular ligation is the ultimate form of no-touch surgery. In our open-group a lateral to medial approach was applied, therefore this group could be considered as ‘conventional surgery’. The results obtained in the present study therefore support the no-touch isolation technique rather than that the results suggest an oncological benefit of laparoscopic surgery itself. In a recent review on the no-touch technique the overall conversion rates (i.e. negative preoperatively, positive intra-operatively) for studies employing the no-touch technique were 0–16%, compared to 0–80% for studies utilising conventional surgery. Comparable to the present study, Bessa et al. assessed neoplastic cell mobilisation in 50 patients who were randomly assigned to open or laparoscopic
surgery. In contrast to the present study, the no-touch isolation technique was applied in both groups. In Bessa’s study, surgical neoplastic cell mobilisation was observed in only four patients, with no difference with respect to the surgical approach. Therefore, the detection rate of CTC might be unrelated to the surgical approach (i.e. laparoscopic or open surgery) but related to the moment of lymphovascular ligation as these data suggest that there is a trend towards reduced tumour cell dissemination for the no-touch isolation method. The benefit of this in terms of improved patient survival remains to be established.

In conclusion, the detection rate and quantity of CTC is significantly increased intra-operatively and is significantly higher in portal blood compared to peripheral blood. Significantly less CTC were detected during laparoscopic surgery probably as result of the medial to lateral approach.

Acknowledgement
We would like to thank dr. J.B. Reitsma from the department of Epidemiology and Biostatistics for his statistical advise.

Reference List


(7) Engell HC. [Cancer cells in the circulating blood; a clinical study on the occurrence of cancer cells in the peripheral blood and in venous blood draining the tumour area at operation.]. Ugeskr Laeger 1955;117:822-823.


Summary and conclusions
Summary and conclusions

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

Part I: Fast track colorectal surgery

In chapter 1 the application of fast track perioperative care in colonic surgery is described. Fast track perioperative care programmes have been introduced in several surgical procedures. In colonic surgery fast track perioperative care is defined as an intensive multimodal programme combining a number of perioperative elements with the purpose to preserve preoperative body composition and organ functions and to actively enhance postoperative recovery. The essence of fast track perioperative care consists of extensive preoperative counselling, no preoperative fasting but adequate nutrition, omission of oral bowel preparation, reducing the surgical trauma, no routine use of drains and nasogastric tubes, tailored anaesthesiology encompassing thoracic epidural, early and enhanced postoperative feeding and mobilisation and medicinal support with prokinetics and laxatives. Furthermore, it is highlighted that for some elements there is solid evidence that its implementation results in less morbidity and an enhanced postoperative recovery; e.g. removal of the nasogastric tube at the time of extubation and the omission of oral bowel preparation. For other elements the evidence is less robust, and the implementation into a fast track perioperative care programme is in those cases either based on “common sense” or on consensus interpretation of accumulating evidence. However, it should be noted that concerning all the individual elements the available evidence is derived from traditional perioperative care settings.

In chapter 2 a systematic review is performed of all randomised and clinical controlled trials on fast track perioperative care in colonic surgery. The main endpoints were the number of applied fast track perioperative care elements, postoperative hospital stay, readmission rate, morbidity and mortality. After a systematically performed search in several databases, six studies (three randomised and three clinical controlled trials) were eligible for analysis, including 512 patients. The fast track perioperative care programmes that were applied in the included studies contained an average of nine of the 17 fast track elements as defined in the literature. The pooled analysis showed that fast track perioperative care significantly reduced primary hospital stay (weighted mean difference: -1.56, 95% confidence interval [CI]: -2.61 to -0.50) and morbidity (relative risk 0.54, 95% CI: 0.42 to 0.69). Readmission rates were not significantly different and there was no increase in mortality. Based on this limited evidence, fast track perioperative care appears safe and enhances postoperative recovery after elective colorectal surgery. However, as the evidence is limited, a multi-centre randomised trial seems justified.

To investigate whether the demonstrated benefits of fast track perioperative care
could also be applied on our own patient population, a pilot study was initiated at the Academic Medical Centre. The results of this study are presented in chapter 3. All 55 patients, scheduled for elective segmental colorectal resection and treated in a fast track perioperative care programme were compared to a control-group of 52 patients treated in a traditional care setting. Successful implementation of the fast track care programme demonstrated to be difficult, since only 7.4 out of 13 predefined and evaluated fast track care elements were achieved per patient. Despite incomplete implementation and a potentially higher incidence of readmissions, primary and overall hospital stay were shorter after fast track perioperative care without affecting patient-satisfaction. Median primary hospital stay was 4.0 vs. 6.0 days and median overall hospital stay was 4.0 vs. 6.5 days. No robust conclusions could be drawn from a subgroup analysis in which open and laparoscopic surgery as well as traditional care and fast track perioperative care were compared, because the numbers of patients were too small. Nonetheless, the largest reduction in primary and overall hospital stay was observed in patients who had laparoscopic surgery and fast track perioperative care.

To further assess the optimal combination, in chapter 4 a systematic review was performed of all randomised and controlled clinical trials on laparoscopic and open surgery both incorporated within a fast track perioperative care programme. Main endpoints were primary and overall hospital stay, readmission rate, morbidity, and mortality. After a systematically performed literature search only two randomised and three controlled clinical trials were eligible for final analysis, which reported on a total of 400 patients. The extracted data of the individual studies could not be pooled because of clinical heterogeneity. Two studies of the five included studies reported a shorter primary hospital stay in the laparoscopic group of two and three days. In one study the readmission rate was lower after laparoscopic surgery (absolute risk reduction 21.4%, and a “numbers needed to treat” of 4.7 patients). One study showed a 23% difference in favour of the laparoscopic group with regard to morbidity, i.e. a “numbers needed to treat” of 4.4 patients. Concerning the main endpoints in the individual studies no further significant differences between open and laparoscopic surgery within a fast track perioperative care programme were found.

Despite some reported advantages of laparoscopic surgery, based on the lack of evidence, no robust conclusions can be made. A large randomised controlled trial is required to compare laparoscopic with open surgery within a fast track perioperative care setting. In chapter 5 such a randomised controlled multi-centre trial is proposed. The LAFA-trial (LAparoscopy and/or FAst track multimodal management versus standard care) is conceived to determine whether laparoscopic surgery, fast track perioperative care or a combination of both is to be preferred over open surgery with traditional care in patients having segmental colectomy for malignant disease. The LAFA-trial is a double blinded, multicentre trial with a two by two balanced factorial design. Patients eligible for segmental colectomy for malignant colorectal disease i.e. right and left colectomy and anterior resection are randomised to either open or laparoscopic colectomy, and to either traditional care or fast track perioperative care. This factorial design produces
four treatment groups; open segmental colectomy with traditional care, open segmental colectomy with fast track perioperative care, laparoscopic segmental colectomy with traditional care, and laparoscopic surgery with fast track perioperative care. The primary outcome parameter is postoperative hospital stay including readmissions within 30 days. Secondary outcome parameters are quality of life two and four weeks after surgery, overall hospital costs, morbidity, patient satisfaction and readmission rate. The LAFA-trial has started in 2005 and will be finished in the begining of 2009. Hopefully this trial will answer the question which combination of perioperative care and type of surgery is the most optimal combination.

Part II: Complications in colorectal surgery

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. Roughly entry techniques can be divided in two groups. The first group comprises introductions performed without direct visual control, the so called blind entry techniques (e.g. introductions with a Veress needle). The other group comprises of entry techniques performed under visual control. The latter includes the open entry technique and closed entry techniques with optical trocar devices. In this chapter it is demonstrated that concerning entry-related complications approximately one half of all intra-operative laparoscopic complications is caused during the establishment of the pneumoperitoneum and introduction of the trocars. The reported incidence of vascular and bowel injuries varies and is between approximately 0.05 and 0.5 complication per 100 laparoscopic procedures. The reviewed literature in this chapter, suggests that the open-entry technique is the safest introduction technique because an overshoot of the introduction, especially those resulting in retroperitoneal vascular injury can be avoided. However, open-entry techniques do not preclude bowel injury.

Chapter 7 describes a retrospective chart review including all malpractice claims concerning entry-related injuries filed at MediRisk, which is presently the largest medical liability mutual insurance company for institutions, mainly hospitals in health care in the Netherlands. From January 1993 to December 2005, 229 laparoscopy-related claims were filed of which 41 (18%) claims were identified as entry-related complications. Therefore, medical liability claims concerning laparoscopic entry-related complications comprise one fifth of all laparoscopy-related claims. Patients that filed a claim were mostly young females with a history of abdominal surgery who were operated on in a day-care setting or had short-stay surgery with severe consequences of the entry-related complication. In the investigated cases most claims involved the closed-entry technique. Vascular injury was exclusively associated with the closed-entry technique. In more than half of the complications, the entry-related injury was diagnosed with a delay. There was no mortality. Besides conversion, the majority of the patients filed a claim to compensate for the longer hospital stay and related costs. A payment was made in 17 (57%) of the 30 settled claims.
In chapter 8 the feasibility, safety, and potential benefits of a laparoscopic reintervention for anastomotic leakage after primary laparoscopic surgery was assessed. From January 2003 to January 2006, ten consecutive patients who underwent laparoscopic colorectal resection and subsequently developed anastomotic leakage, underwent a laparoscopic reintervention. Relaparotomy was performed in fifteen consecutive patients who had primary open surgery. In this chapter a laparoscopic reintervention after primary laparoscopic surgery for anastomotic leakage appears feasible and safe in terms of conversions, intraoperative morbidity, necessity of opening the minilaparotomy, and operating time. In addition, laparoscopic reintervention was associated with less postoperative morbidity (40% vs. 80%), shorter postoperative ileus (resumption of a normal diet; three vs. six days), and a faster recovery (hospital stay; nine vs. 13 days). Furthermore, the incidence of incisional hernia was zero percent in the laparoscopic group versus 33% in the open group. Nonetheless, this are preliminary data and, ideally a prospective trial, should confirm these data. To evaluate the effect of laparoscopic reintervention after primary laparoscopic surgery, it has to be part of a very large study randomising patients for a laparoscopic or open initial procedure.

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. Subsequently, in an animal model three different lengths of linear cutters (Proximate®, Ethicon Endo-Surgery) were used to cross staple and transect the large bowel of one pig to check for the integrity of the proximal end of the staple line. The experiment demonstrated that when the tissue was advanced up to the highest number on the scale of the 100 mm stapling device an insufficient overlap between the proximal end of the staple line and the proximal end of the cut line occurred. Although a more than 100 mm staple line was delivered, the 100 mm cutter may not produce a double-staggered row of staples at the most proximal end of the staple line when the tissue is advanced past the 9.5 centimeters mark. Ethicon Endo-Surgery has agreed to add indicator markers to the scale label on the instrument to provide the user with additional guidance for tissue placement. Nevertheless, it remains important to routinely inspect the pouch after linear stapling, both anteriorly and posteriorly, by inversion of the pouch to check for insufficiency of the proximal staple line. On the posterior site, the hole is oversewn and at the anterior site of the pouch the hole is incorporated in the purse string of the anvil of the circular stapler. In case of a side-to-end colonic anastomosis, the proximal end of the cross stapling line should also be routinely checked and oversewn if necessary.

In chapter 10 literature regarding different strategies for open-abdomen treatment in terms of full fascial closure of the abdomen is systematically reviewed. The aim of this review was to investigate which temporary closure technique has the highest rate of full fascial closure. The results of this review suggest that temporary abdominal closure techniques that keep traction on the fascial edges, including Vacuum Assisted Closure (VAC®) result in high rates of fascial closure. Furthermore, techniques with high closure rates seemed to result in relatively low rates of fistula, abscesses, and mortality. 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 and simultaneous management of a large abdominal defect is a difficult procedure. In chapter 11 the results of closure of enterocutaneous fistula and/or stomas and simultaneous abdominal wall repair using the components separation technique were described. All patients with enterocutaneous fistula and/or stomas in the presence of large abdominal wall defects (i.e. laparostomy of ventral hernia) who underwent a single-stage repair using the components separation technique in the period January 2000 to July 2007 were reviewed retrospectively. The study demonstrated that closure of enterocutaneous fistula or stomas in the presence of large abdominal wall defects is feasible using the components separation technique. This technique is one of the few options available to deal with this very difficult problem. Early recurrence of abdominal hernia (7/32) and fistula (4/15) was acceptable but morbidity (16/32) was considerable. Suggested modifications to preserve the blood supply of the skin and subcutaneous tissue, extended antibiotic therapy and changes in mesh repair might improve outcome.

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 literature on extracapsular lymph node involvement in gastrointestinal malignancies is systematically reviewed in order to assess the current evidence on extracapsular lymph node involvement as a prognostic factor for recurrence in gastrointestinal malignancies. Based on the limited evidence available it can be concluded that extracapsular lymph node involvement is a common phenomenon in patients with gastrointestinal malignancies. The pooled incidence of extracapsular lymph node involvement was 57% (95% CI: 53-61%) for oesophageal cancer, 41% (95% CI: 36-47%) for gastric cancer, and 35% (95% CI: 31-40%) for rectal cancer. Furthermore, extracapsular lymph node involvement identified a subgroup of patients with a significantly worse long-term survival. This systematic review highlighted the importance of assessing extracapsular lymph node involvement as a valuable prognostic factor. Pathologists and clinicians should be aware of this important feature. Further research is, however, warranted on the correlation of extracapsular lymph node involvement with different histological types and other important covariates, such as the recurrence pattern and the effect of (neo-) adjuvant therapy. Since the prognostic significance of extracapsular lymph node involvement was not yet established in colonic cancer as demonstrated in the above mentioned systematic review, a retrospective study was undertaken which is described in chapter 13. Between January 1994 and May 2005, all patients who underwent resection for primary colonic cancer with lymph node metastasis were reviewed. In a multivariate analysis, pN-stage (hazard
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Ratio 3.50, 95% CI: 1.72–7.42) and extracapsular lymph node involvement (hazard ratio 1.98, 95% CI: 1.00–3.91) were the only significant factors, indicating that extracapsular lymph node involvement in colonic cancer is an independent negative prognostic factor, reflecting a particularly aggressive biological behaviour. Interestingly, among patients without extracapsular lymph node involvement, those receiving adjuvant chemotherapy had a significantly better survival. In contrast, chemotherapy did not improve disease free survival in patients with extracapsular lymph node involvement. Therefore, detection and quantification of extracapsular lymph node involvement in the surgical resection specimen might also be helpful in the future to individualize postoperative therapeutic strategies in the adjuvant setting.

Finally, in chapter 14 the presence and amount of circulating tumour cells was assessed in peripheral and portal blood of patients who had open or laparoscopic surgery for primary colonic cancer. Patients in the laparoscopic group were operated on in a medial to lateral approach (“vessels first”), in the open group a lateral to medial approach was applied. The enumeration of circulating tumour cells was performed with immuno-magnetic isolation and immuno-specific labelling. This technique not only counts complete cells instead of cellular fragments as done by RNA identification by Polymerase Chain Reaction (PCR) but also allows for evaluation of the morphology of the detected circulating tumour cells. It was shown that the presence of circulating tumour cells was significantly increased intra-operatively and was in general significantly higher in portal blood. Between 4-7% of the peripheral and 26-45% of the portal samples contained circulating tumour cells. Significantly less circulating tumour cells were detected during laparoscopic surgery possibly as result of the medial to lateral approach. Fluorescence In Situ Hybridization (FISH) was applied as an additional tool to determine the true signature of these cells with the different morphology. Both circulating tumour cells and primary tumour tissue were diploid. Although the primary tumour tissue and circulating tumour cells showed the same cytogenetic profile this does not provide a definite answer whether or not the detected circulating tumour cells were true tumour cells or if these were normal epithelial cells that were shed into the portal blood due to the surgical trauma.
Samenvatting en conclusies
Samenvatting en conclusies

In dit proefschrift worden verschillende aspecten van de colorectale chirurgie belicht met als doel de colorectale chirurgie kritisch te beschouwen en potentiële verbeteringen te evalueren. Dit zal gedaan worden in drie afzonderlijke onderdelen, waarbij de focus ligt op de peri-operatieve zorg (deel I), complicaties (deel II) en het voorspellen van de overleving van patiënten die wegens een colorectale maligniteit zijn geopereerd (deel III).

Deel I: Fast track colorectale chirurgie

In hoofdstuk 1 wordt fast track peri-operatieve zorg bij colon chirurgie beschreven. Fast track peri-operatieve zorg is reeds geïntroduceerd bij verschillende chirurgische ingrepen. Binnen de colon chirurgie kan fast track peri-operatieve zorg worden gedefinieerd als een intensief multidisciplinair programma waarbij diverse peri-operatieve componenten worden gecombineerd tot één protocol, met als doel het behoud van preoperatieve lichaamssamenstelling en orgaanfuncties, en het actief stimuleren van het postoperatieve herstel. In essentie komt fast track peri-operatieve zorg neer op uitgebreide preoperatieve voorlichting, adequate voeding preoperatief met het vermijden van langdurig nuchter zijn, het weglaten van orale darmvoorbereiding, minimaal invasieve chirurgie en anesthesie, het vermijden van abdominale drains en maagsondes, adequate peri-operatieve pijnstilling met behulp van ondermeer thoracale epiduraal anesthesie en analgesie, snelle mobilisatie en snelle hervatting van voedselinname en medicamenteuze ondersteuning met pro-kinetica en laxantia. Verder komt in dit hoofdstuk naar voren dat er voor een aantal componenten in het fast track programma, zoals het weglaten van orale darmvoorbereiding en de maagsonde postoperatief, gedegen wetenschappelijk bewijs bestaat waaruit blijkt dat de implementatie van deze componenten morbiditeit reduceert en het herstel bespoedigt. Voor andere componenten is er echter minder wetenschappelijk bewijs voorhanden. De implementatie van deze componenten in het fast track programma berust op consensus interpretatie van het bestaande bewijs of op basis van “common sense”. Belangrijk te vermelden is dat voor alle afzonderlijke componenten van het fast track programma het bestaande bewijs afkomstig is uit onderzoeken die zijn uitgevoerd in een traditionele zorg setting.

In hoofdstuk 2 wordt een literatuur studie beschreven waarbij alle gerandomiseerde en klinisch gecontroleerde studies naar de effecten van fast track peri-operatieve zorg bij colorectale chirurgie zijn geïncludeerd. De voornaamste eindpunten die in dit review werden beschouwd, zijn het aantal toegepaste fast track componenten, duur van het postoperatief ziekenhuis verblijf, het aantal heropnames, morbiditeit en mortaliteit. Na het systematisch doorzoeken van verschillende databestanden bleken er zes studies (drie gerandomiseerde en drie klinisch gecontroleerde studies) geschikt, waarin 512 patiënten waren geïncludeerd. De fast track programma’s die in de verschillende studies werden toegepast bestonden gemiddeld slechts uit 9 van de 17 in de literatuur gedefinieerde...
fast track componenten. De gepoolde resultaten lieten zien dat fast track peri-operatieve zorg de primaire opnameduur significant reduceerde (gemiddeld gewogen verschil: -1.56, 95% betrouwbaarheidsinterval [BI]: -2.61 tot -0.50) en de morbiditeit significant reduceerde (relatieve risico 0.54, 95% BI: 0.42 tot 0.69). Het aantal heropnames was niet significant verschillend ten opzichte van traditionele zorg en er was geen toename in mortaliteit. Gebaseerd op dit beperkte bewijs lijkt fast track peri-operatieve zorg bij colorectale chirurgie veilig te zijn en bovendien het postoperatieve herstel te bespoedigen. Omdat echter het aantal beschikbare relevante studies beperkt is, lijkt een multi-centrisch gerandomiseerd onderzoek gerechtvaardigd.

Om te onderzoeken of een dergelijk fast track programma ook voordelen biedt binnen onze eigen patiëntenpopulatie, werd een pilot-studie verricht in het Academisch Medisch Centrum in Amsterdam. De resultaten van deze studie worden weergegeven in hoofdstuk 3. Vijfenvijftig consecutieve patiënten die electief een resectie ondergingen van de dikke darm werden volgens fast track peri-operatieve zorg principes behandeld. Zij werden vergeleken met 52 consecutieve patiënten die werden behandeld in een traditioneel zorg programma. Succesvolle implementatie van het fast track programma bleek lastig; slechts 7.4 van de 13 van tevoren gedefinieerde fast track componenten werden volledig toegepast per patiënt. Echter, ondanks deze onvolledige implementatie en mogelijk een hoger aantal heropnames, waren de primaire en de totale opnameduur korter in de fast track peri-operatieve zorg groep zonder dat dit de patiënttevredenheid negatief beïnvloedde. De mediane primaire opnameduur was 4.0 ten opzichte van 6.0 dagen en de mediane totale opnameduur was 4.0 ten opzichte van 6.5 dagen. Aan de in dit hoofdstuk uitgevoerde subgroep analyse, waarin zowel open en laparoscopische chirurgie als ook fast track en traditionele zorg werden vergeleken, mogen geen harde conclusies worden ontleend omdat de patiënt aantallen in de groepen klein waren. Desalniettemin werd de grootste reductie van de primaire en totale opnameduur bereikt in de groep patiënten die laparoscopisch werden geopereerd in een fast track programma.

Om meer inzicht te verkrijgen in de optimale combinatie van de manier van opereren en peri-operatieve zorg, wordt er in hoofdstuk 4 een literatuur studie beschreven waarbij alle gerandomiseerde en klinisch gecontroleerde studies naar open en laparoscopische chirurgie, beiden in een fast track programma, werden geïncludeerd. De voornaamste eindpunten die in dit review werden beschouwd zijn de primaire en totale opnameduur, het aantal heropnames, morbiditeit en mortaliteit. Na het systematisch doorzoeken van verschillende databestanden waren er slechts twee gerandomiseerde en drie klinisch gecontroleerde studies beschikbaar waarin 400 patiënten waren geïncludeerd. De data uit de individuele studies kon niet worden gepoold op basis van klinische heterogeniteit. In twee van de vijf geïncludeerde studies werd een kortere primaire opnameduur gerapporteerd in de laparoscopische groep van 2 en 3 dagen. In één studie was het percentage heropnames significant lager na laparoscopische chirurgie (absolute risico reductie 21.4%, en “numbers needed to treat” van 4.7 patiënten). Ten aanzien van morbiditeit rapporteerde één studie een 23% verschil in het voordeel van laparoscopische chirurgie, neerkomend op een “numbers needed to treat” van 4.4 patiënten. Verder werden in de geïncludeerde studies,
met betrekking tot de voornaamste eindpunten, geen significante verschillen beschreven tussen de open en laparoscopische groep.

Ondanks enkele hierboven beschreven voordelen van laparoscopische chirurgie in een fast track programma kunnen door een gebrek aan wetenschappelijk bewijs geen harde conclusies worden getrokken. Een grote gerandomiseerde studie is daarom nodig om laparoscopie in een fast track programma te vergelijken.

In **hoofdstuk 5** wordt een dergelijk gerandomiseerd multi-centrisch onderzoek voorgesteld. Deze, zogehete LAFA-studie (LAparoscopie en/of FAst peri-operatieve zorg versus traditionele zorg), is ontworpen om te bepalen of laparoscopische chirurgie, fast track peri-operatieve zorg of een combinatie van beide te prefereren is boven open chirurgie met traditionele zorg bij patiënten die een segmentale colon resectie moeten ondergaan wegens een maligniteit. De LAFA-studie is een dubbel blind gerandomiseerd multi-centrisch onderzoek volgens een “2x2 balanced factorial design”. Patiënten die in aanmerking komen voor een segmentale colon resectie wegens een maligniteit, dat wil zeggen een rechts- of linkszijdige hemicolecction en anterieure resecties, worden gerandomiseerd voor open of laparoscopische chirurgie en voor traditionele zorg of voor fast track peri-operatieve zorg. Door deze randomisatie ontstaan er vier behandelgroepen; open chirurgie met traditionele zorg, open chirurgie met fast track peri-operatieve zorg, laparoscopische chirurgie met traditionele zorg en laparoscopische chirurgie met fast track peri-operatieve zorg. Het primaire eindpunt van deze studie is de duur van het ziekenhuisverblijf inclusief het aantal heropnames binnen 30 dagen. Secundaire eindpunten zijn kwaliteit van leven twee en vier weken postoperatief, totale ziekenhuiskosten, morbiditeit, patiënttevredenheid en het aantal heropnames. De LAFA-studie is gestart in 2005 en zal in het begin van 2009 worden afgerond. Hopelijk zal deze studie het antwoord geven op de vraag welke combinatie van peri-operatieve zorg en manier van opereren het meest optimaal is.

**Deel II: Complicaties in de colorectale chirurgie**

In **hoofdstuk 6** wordt een overzicht gegeven van de verschillende manieren om een pneumoperitoneum aan te leggen, inclusief het daarbij benodigde instrumentarium en potentiële complicaties die kunnen optreden. Grofweg zijn er twee groepen technieken te onderscheiden voor het aanleggen van het pneumoperitoneum en de introductie van de trocars. Allereerst zijn er introductie technieken die niet onder zicht plaatsvinden, de zogenaamde blinde introducties, bijvoorbeeld met de Veress naald. Daarnaast zijn er introductie technieken die plaatsvinden onder direct zicht. Tot deze laatste groep worden de open introductie volgens Hasson en de gesloten introductie technieken met optische trocar systemen gerekend. In dit hoofdstuk wordt beschreven dat ongeveer de helft van alle intra-operatieve complicaties optreedt tijdens de introductiefase, nog voor er met de daadwerkelijke ingreep is gestart. De incidentie van een darm- of vaatletsel varieert in de literatuur tussen de 0.05-0.5 complicaties per 100 laparoscopische ingrepen. De in dit hoofdstuk geregereerde literatuur suggereert, dat de open introductie techniek
de veiligste introductie biedt omdat “doorschiet” letsel, in het bijzonder letseis van de grote retroperitoneale vaten kunnen worden vermeden. Echter, een open introductie sluit darmleetsel niet uit.

In hoofdstuk 7 wordt een retrospectieve analyse beschreven van alle medische aansprakelijkheid claims betreffende aan de introductie gerelateerde complicaties die werden ingediend bij de op dit moment grootste verzekeringmaatschappij voor medische aansprakelijkheid voor Nederlandse ziekenhuizen (MediRisk). Tussen januari 1993 en december 2005 werden er 229 claims betreffende laparoscopische chirurgie ingediend bij MediRisk. In 41 (18%) claims betrof het een introductie gerelateerde complicatie. Met andere woorden, ongeveer een vijfde van alle laparoscopisch gerelateerde claims betreft een introductie leetsel. In deze studie betrof het voornamelijk jonge vrouwelijke patiënten met in hun voorgeschiedenis één of meerdere buikoperaties, die werden geopereerd in dagbehandeling of als korte opname, waarbij het introductie leetsel ernstige gevolgen had. In de onderzochte claims betrof het in bijna alle gevallen een blinde introductie techniek. Alle vaatletsels werden veroorzaakt tijdens een blinde introductie. In meer dan de helft van de introductie leetsels werd de diagnose pas later gesteld. Er was in de geïncludeerde claims geen sprake van mortaliteit. Naast het feit dat de laparoscopische procedure was geconverteerd, diende de meerderheid van de patiënten een claim in ter compensatie van een langere opnameduur en de daaruit voortvloeiende kosten. In 17 (57%) van de 30 afgehandelde claims werd er een uitbetaling gedaan.

In hoofdstuk 8 wordt de technische uitvoerbaarheid, veiligheid en het eventuele voordeel van een laparoscopische reinterventie bij een verdenking op naadlekkage na eerdere laparoscopische chirurgie geëvalueerd. In de periode januari 2003 tot januari 2006, ondergingen 10 consecutieve patiënten met een naadlekkage na een eerdere laparoscopisch uitgevoerde colorectale resectie, een laparoscopische reinterventie. Vijftien consecutieve patiënten die in dezelfde periode na een eerdere laparotomie een naadlekkage ontwikkelden ondergingen een relaparotomie. De resultaten die in dit hoofdstuk worden gepresenteerd suggereren dat een laparoscopische heroperatie wegens naadlekkage technisch uitvoerbaar en veilig is wat betreft conversies, intra-operatieve morbiditeit, de noodzaak om de mini-laparotomie te openen en operatietijd. Daarnaast ging een laparoscopische reinterventie gepaard met minder postoperatieve morbiditeit (40% versus 80%), een kortere postoperatieve ileus (toleren van een normaal dieet; 3 versus 6 dagen) en een sneller herstel (opnameduur; 9 versus 13 dagen). Tot slot was de incidentie van littekenbreuken 0% in de laparoscopische groep ten opzichte van 33% in de open groep. Echter gezien het feit dat het om een kleine retrospectieve studie gaat moeten deze data worden beschouwd als hypothesevormend. Idealiter moeten deze resultaten worden bevestigd in een prospectieve studie. Om het effect van een laparoscopische reinterventie na een eerdere laparoscopische ingreep te onderzoeken zou dit deel moeten uitmaken van een zeer grote studie waarbij patiënten voor de eerste operatie al worden gerandomiseerd voor een open of laparoscopische initiële procedure.

In hoofdstuk 9 wordt het potentieel niet goed functioneren van lineaire staplers beschreven. Een defect in een gestapelde naad tijdens het aanleggen van een pouch
van het ileum na het gebruik van een lineaire stapler, gepresenteerd als een casus in dit hoofdstuk, deed ons vermoeden dat er mogelijk een probleem zou kunnen bestaan met het functioneren van de lineaire stapler. Om dit potentiële probleem verder te evalueren werd in een dier experimenteel model het colon van een varken dwars gestapled gebruikmakend van drie verschillende lengtes lineaire staplers (Proximate®, Ethicon Endo-Surgery). In het experiment werd aangetoond dat wanneer het te stapelen weefsel wordt opgevoerd tot het einde van de schaalaanduiding van de 100 mm stapler er een incomplete overlap bestaat van de rij staples resulterend in een defect aan het proximale uiteinde. Hoewel de staple rij een lengte heeft van meer dan 100 mm, kan het gebeuren dat er geen dubbele rij staples wordt geplaatst ter plaatse van het proximale uiteinde wanneer het weefsel in de stapler wordt opgevoerd voorbij het 9.5 centimeter markeringsteken. Ethicon Endo-Surgery heeft op basis van deze bevindingen besloten om additionele markeringstekens te plaatsen op de stapler om hiermee de gebruiker hulp te geven bij het juist plaatsen van het weefsel in de stapler. Niettemin blijft het essentieel om routinematig het proximale uiteinde van de pouch-naad te controleren, zowel aan de anterieure als aan de posterieure zijde na het inverteren van de pouch. Aan de posterieure zijde wordt een eventueel aanwezig defect overhecht, aan de anterieure zijde wordt het defect gereserceerd bij het afvuren van de circulaire stapler. Ook bij het maken van een side-to-end colon anastomose dient het proximale uiteinde van het dwars afgestapelde colon routinematig te worden gecontroleerd en zonodig worden overhecht.

In hoofdstuk 10 wordt een systematische literatuur studie beschreven naar de verschillende behandelingstrategieën voor de open buik behandeling. Doel van dit review was te bepalen welke techniek voor het tijdelijk sluiten van de open buik resulteert in het hoogste percentage volledige fascie sluitingen tijdens de index opname. De resultaten die in dit hoofdstuk worden gepresenteerd suggereren dat de technieken die tractie uitoefenen op de fascie randen, zoals het Vacuum Assisted Closure (VAC®) systeem resulteren in de hoogste percentages fascie sluiting. Daarnaast lijken deze technieken te zijn geassocieerd met relatief weinig complicaties zoals fistels, abcessen en mortaliteit. Wanneer na een open buik behandeling volledige fascie sluiting niet mogelijk is, kan het defect in de fascie worden gesloten met een resorbeerbare mat of kan men het defect laten dicht granuleren. Deze zogenaamde geplande ventrale hernia’s na een vaak gecomplexied beloop zijn echter vaak geassocieerd met enterocutane fistels en de aanwezigheid van stoma’s. Het opheffen van deze stoma’s en enterocutane fistels met het gelijktijdig corrigeren van het buikwanddefect is een moeilijke procedure. In hoofdstuk 11 worden de resultaten van de Ramirez buikwandplastiek (“components separation”) beschreven voor het opheffen van stoma’s en enterocutane fistels en het gelijktijdig stuiten van het buikwanddefect. Een consecutieve serie patiënten met enterocutane fistels en/of stoma’s in de aanwezigheid van een groot buikwanddefect (laparostoma of ventrale hernia) die een correctie ondergingen in dezelfde procedure middels de Ramirez buikwandplastiek werden retrospectief geanalyseerd. De studie periode betrof de periode januari 2000 tot juli 2007. De resultaten toonden dat het opheffen van enterocutane fistels en stoma’s
en het gelijktijdig corrigeren van een groot buikwanddefect haalbaar is met de Ramirez buikwandplastiek. Deze techniek is een van de weinige opties voor de behandeling van dit moeilijke probleem. Het aantal recidief ventrale hernia’s (7/32) en enterocutane fistels (4/15) was acceptabel, de morbiditeit (16/32) was echter wel aanzienlijk. Mogelijk dat technische aanpassingen aan de procedure om de bloedvoorziening van de huid en het subcutane weefsels te behouden en uitgebreidere antibiotische behandeling de resultaten verder kunnen verbeteren.

**Deel III: Het voorspellen van de overleving bij het colorectaal carcinoom**

De prognostische betekenis van extracapsulaire uitbreiding van een lymfklier metastase is onderzocht bij diverse maligniteiten waaronder gastro-intestinale maligniteiten. In **hoofdstuk 12** wordt een systematische literatuurstudie beschreven naar de prognostische betekenis van extracapsulaire lymfklier uitbreiding bij gastro-intestinale maligniteiten. Gebaseerd op beperkt wetenschappelijk bewijs kan worden geconcludeerd dat extracapsulaire lymfklier uitbreiding een veel voorkomend fenomeen is bij gastro-intestinale maligniteit. De gepoolde incidentie van extracapsulaire lymfklier uitbreiding was 57% (95% BI: 53-61%) bij het slokdarmcarcinoom, 41% (95% BI: 36-47%) bij het maagcarcinoom en 35% (95% BI: 31-40%) bij het rectumcarcinoom. Extracapsulaire lymfklier uitbreiding was sterk geassocieerd met een significant slechtere overleving. Dit hoofdstuk benadrukt het belang van extracapsulaire lymfklier uitbreiding als een belangrijke prognostische factor. Pathologen en clinici moeten zich hier dan ook van bewust zijn. Toekomstig onderzoek is echter nodig naar de correlatie van extracapsulaire lymfklier uitbreiding en verschillende histologische type tumoren en andere belangrijke factoren zoals het metastaseringspatroon en het effect van (neo-) adjuvante behandeling.

Omdat de prognostische betekenis van extracapsulaire lymfklier uitbreiding nog niet duidelijk is voor het coloncarcinoom, zoals duidelijk is geworden in het hierboven genoemde review, wordt er in **hoofdstuk 13** een retrospectieve studie beschreven die als doel heeft dit te bestuderen. In de periode januari 1994 tot mei 2005 werden alle patiënten die een resectie hadden ondergaan voor een primair coloncarcinoom waarbij lymfklier metastasering was aangetoond retrospectief geanalyseerd. In een multivariate analyse waren het pN-stadium (hazard ratio 3.50, 95% BI: 1.72–7.42) en extracapsulaire lymfklier uitbreiding (hazard ratio 1.98, 95% BI: 1.00–3.91) de enige significante variabelen. Dit betekent dat extracapsulaire lymfklier uitbreiding bij het coloncarcinoom een onafhankelijke negatieve voorspeller is. Opmerkelijk was het feit dat patiënten met lymfklier metastasering maar zonder extracapsulaire lymfklier uitbreiding een significant betere overleving hadden na adjuvante chemotherapie terwijl chemotherapie de overleving niet verbeterde bij patiënten die wel extracapsulaire lymfklier uitbreiding hadden. Daarom zou het detecteren en kwantificeren van extracapsulaire lymfklier uitbreiding in het
resectie preparaat in de toekomst van waarde kunnen zijn bij de indicatiestelling omtrent de keuze van adjuvante behandeling.

Tenslotte wordt er in hoofdstuk 14 een studie beschreven met als doel het detecteren en kwantificeren van circulerende tumorcellen in perifeer en portaal bloed van patiënten die een open of laparoscopische operatie ondergaan wegens een primair coloncarcinoom. Patiënten in de laparoscopische groep werden geopereerd volgens een mediaal naar latere benadering (“no-touch” principe), in de open groep werd een lateraal naar mediale benadering toegepast. Het detecteren en kwantificeren van de circulerende tumorcellen werd gedaan middels immuno-magnetische isolatie en immuno-specifieke labeling. Met deze techniek worden niet alleen complete cellen geïdentificeerd, maar ook kan de morfologie van de gedetecteerde circulerende tumorcel worden geëvalueerd. Dit in tegenstelling tot de cellulaire fragmenten welke gedetecteerd worden bij conventionele bepaling van RNA middels Polymerase Chain Reaction (PCR). In deze studie kwam naar voren dat de hoeveelheid circulerende tumorcellen significant was toegenomen intraoperatief en significant hoger was in portaal bloed ten opzichte van perifeer bloed; tussen de 4-7% van de perifere en 26-45% van de portale bloed afnamen waren positief voor de aanwezigheid van circulerende tumorcellen. Significant minder circulerende tumorcellen werden gevonden tijdens laparoscopische chirurgie. Dit kan mogelijk verklaard worden door de gekozen benadering (mediaal naar lateraal). Fluorescentie in Situ Hybridisatie (FISH) werd gebruikt als extra middel om de precieze herkomst van de geïdentificeerde cellen te bepalen. Zowel de circulerende tumorcellen als de primaire tumor waren diploïd. Alhoewel zowel de primaire tumor als de circulerende tumorcellen hetzelfde cytogenetische profiel hebben, geeft dit geen definitief antwoord op de vraag of de geïdentificeerde circulerende cellen daadwerkelijk tumorcellen zijn of dat het gaat om normale epitheliale cellen die door het chirurgisch trauma in de bloedbaan zijn gekomen.
Dankwoord
Dankwoord

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Curriculum Vitae
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On the sixth of May in 1979, a sunny Sunday morning, Jan Wind was born in Hilversum, the Netherlands. He attended secondary school at the Comenius College in Hilversum, from 1991 until graduation in 1997. His medical study started in 1997 at the Free University of Amsterdam. He passed his doctoral exam in 2001 and started the same year with his internships. His medical degree was obtained in December 2003.

In January 2004 he started as a surgical resident at the Hilversum Hospital (currently Tergooiziekenhuizen), where he worked until April 2005. In May 2005 he started as a research fellow at the department of Surgery at the Academic Medical Centre in Amsterdam (supervisor Prof. dr. W.A. Bemelman). The research performed during this period resulted in the present thesis. In January 2008, he started his surgical training at the Tergooiziekenhuizen in Hilversum (supervisor Dr. J.P. Eerenberg).