LAPAROSCOPIC SURGERY FOR COLONIC CANCER

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LAPAROSCOPIC SURGERY FOR COLONIC CANCER

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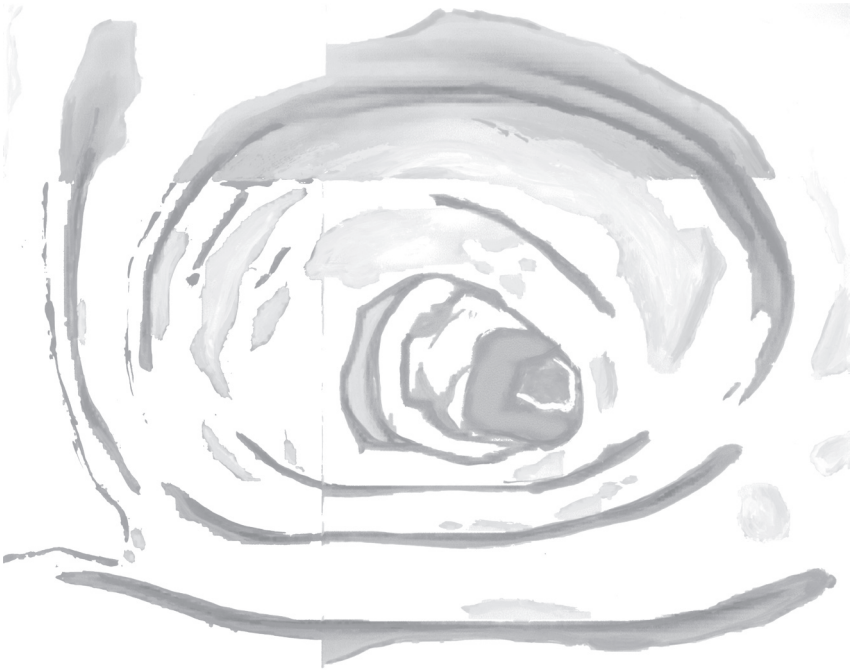
CONTENTS

'Nothing endures but change'

Heraclitus
(540BC- 480BC)

CHAPTER 1

Introduction & outline of the thesis



INTRODUCTION

Worldwide, colorectal cancer is the 3rd most common type of cancer. Yearly, 130,000 new patients are afflicted and 56,000 die of the disease in the United States alone, making it the second leading cause of cancer death in the U.S. (after lung cancer) [1]. Adjuvant therapy, such as chemotherapy and radiotherapy, can improve survival in colorectal cancer patients. However, the only treatment with curative intent is surgical resection of the tumour.

Currently, over 90% of colonic cancer is treated surgically [2]. This number includes palliative surgical resections as well as resections with curative intent. Colectomy for cancer can be performed using either a laparoscopic or an open approach. Laparoscopic surgery in the treatment of colonic cancer was already reported more than a decade ago [3]. Although the laparoscopic approach is now considered to be the preferred in patients who require colectomy for benign disease, only a minority of colectomies for cancer are performed using this approach.

For several surgical procedures, a laparoscopic approach appears to be associated with a reduction in surgical trauma and blood loss. In addition, it is presumable that some of the benefits of minimally invasive surgery, such as reduced analgesic requirements, a shorter recovery period and reduced hospital stay, are applicable to laparoscopic colectomy for cancer as well. Nevertheless, many surgeons are still reluctant to use laparoscopy in the treatment of cancer. This reluctance is partly caused by initial reports on high occurrences of port-site metastases after laparoscopic surgery for colorectal malignancies [4,5]. Even though these case series only represent a very low level of evidence, they had a major impact on the implementation of laparoscopy for colorectal malignancies in surgical practice. Since the pathogenesis of these metastases remained unclear, some surgeons feared that cancer related survival after laparoscopy might be worse than after open surgery. Furthermore, questions were raised on whether or not a proper oncologic resection and tumour staging were possible using endoscopic techniques. As a consequence, laparoscopic colectomy for malignancy has mainly been performed within the setting of randomized clinical trials. One of these trials is the COLOR trial, on which a large portion of this thesis was based. The trial was initiated in 1997 by the COLOR Study Group in order to assess the role of laparoscopy in the treatment of colonic cancer. Within the setting of a

randomized trial it was possible to perform quality control and to standardise surgical techniques.

At this time, no consensus has been reached on the value of laparoscopy in the curative treatment of colonic cancer. In this thesis, several studies are undertaken in order to determine short-term and long-term outcome after laparoscopic surgery compared to open surgery for colonic cancer. Furthermore, factors that might contribute to the results obtained after laparoscopic colectomy are analysed in an attempt to identify possible ways to improve future outcomes.

OUTLINE OF THIS THESIS

Ever since the introduction of laparoscopic colectomy, questions have been raised concerning the possible benefits and adverse effects of using minimally invasive techniques in the surgical treatment of colonic cancer. Some of the observed effects have been associated with alterations in immune responses. A possible explanation for improved clinical outcomes after laparoscopic surgery is that it is associated with less tissue trauma, which may in turn be associated with improved preservation of normal immune function.

In **Chapter 2**, we reviewed published literature on the effect of laparoscopy on immune responses to find an answer to the following question:

- Is there evidence-based support on the impact of laparoscopy on local and systemic immune responses?

Laparoscopy in general is associated with reduced morbidity, quicker recovery, less pain and an improved cosmesis. In **Chapter 3** we present the short-term results of the COLOR trial, a European multi-center randomized clinical trial comparing laparoscopic surgery and open surgery for non-metastatic colon cancer. We analysed data on 1248 patients undergoing either laparoscopic or open colectomy for cancer in order to answer the questions:

- Is laparoscopic surgery for colonic cancer safe from an oncological point of view?
- Does the manner of approach alter short-term outcome after colonic cancer surgery?

Centralisation of complex surgical procedures has been associated with improved clinical outcome. In **Chapter 4** we present the results of a study on the effect of hospital case volume on short-term outcome after laparoscopic colectomy for cancer. In this analysis, data on patients who underwent laparoscopic surgery within the framework of the COLOR trial were analysed in order to answer the question:

- Is hospital case volume associated with short-term outcome after laparoscopic colectomy for cancer?

Converting a laparoscopic procedure is associated with increased morbidity rates compared to planned open procedures. Careful preoperative patient selection is therefore of utmost importance. In **Chapter 5**, the results of a study on converted procedures within the framework of the COLOR trial are presented. With this analysis we tried to answer the question:

- Can we identify predictive factors of conversion, enabling a better patient selection?

When evaluating the value of a treatment for cancer, the main outcome measures should of course be cancer-related and overall survival. In order to compare survival of patients undergoing either laparoscopic or open surgery for colonic cancer, a meta-analysis of large randomized clinical trials was performed. In **Chapter 6** the results of this meta-analysis are presented. The main question we aimed for was:

- Is cancer-free and overall survival comparable between patients undergoing laparoscopic surgery and open surgery for colonic cancer?

Chapter 7 provides an extensive review on the current status of laparoscopic colectomy for cancer. Survival, short-term outcome, costs and learning curves associated with laparoscopic colectomy for cancer are discussed.

Chapter 8 summarises the findings, answers and recommendations presented in this thesis and **Chapter 9** contains a Dutch version of the summary.

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CHAPTER 2

Effect of laparoscopy on the immune system

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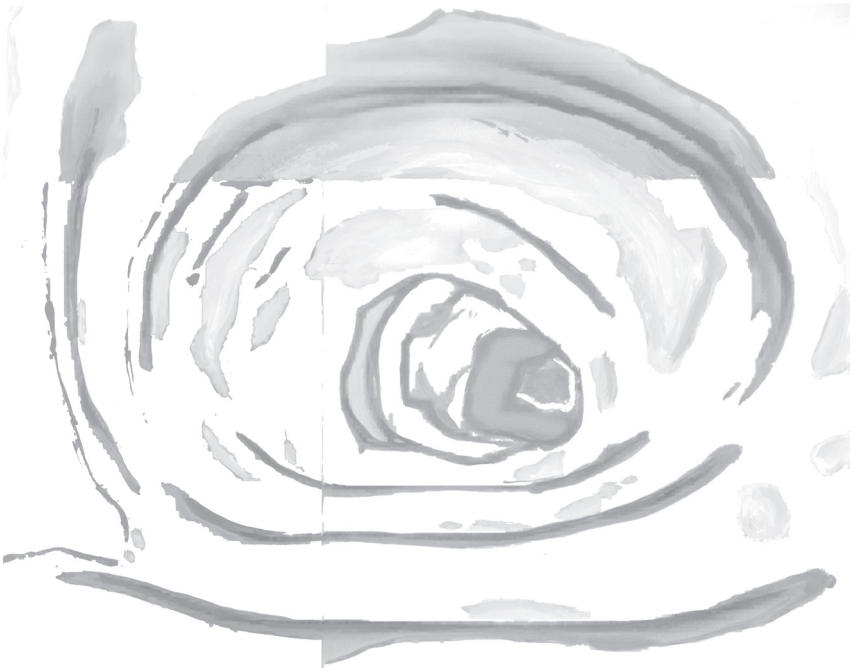

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ABSTRACT

Surgery induces alterations in local and systemic immune responses. These changes appear to be associated with an increase in postoperative morbidity. Minimally invasive techniques are considered to improve the preservation of normal immune function compared with open surgery and may therefore be beneficial for patient recovery. As laparoscopic techniques are increasingly used in abdominal surgery, more research has focused on the immunological consequences of these techniques. Nevertheless, the changes that occur in response to trauma are still not completely understood. Immunological benefits of laparoscopic surgery are found for minor surgical procedures such as cholecystectomy and antireflux surgery. For more complex procedures such as colorectal surgery for cancer, benefits are not immediately obvious. Although laparoscopic surgery for colorectal malignancies may be associated with higher survival rates and lower recurrence rates because of improved immune functions, it has also been related to high incidences of port-site metastases. Reviews in the literature have now shown that incidences of port-site metastases are comparable to incidences of wound metastases after open surgery. However, it will be necessary to wait for the long-term results of randomized, clinical trials to provide further clarification of how the immune function is altered after laparoscopic and open surgery for colorectal cancer.

INTRODUCTION

Laparoscopic techniques have greatly altered abdominal surgery in the past 10 years. The endoscopic approach has become the preferred procedure for patients who require anti-reflux surgery, cholecystectomy, or colectomy for benign diseases. Furthermore, the feasibility of a wide range of procedures in intra-abdominal surgery, including surgery for colorectal malignancies, has been demonstrated [1-7].

Currently, indications for laparoscopic surgery are continuing to expand, despite some drawbacks such as technical complexity, increased operating time, and high in-hospital costs.

The improved short-term results of laparoscopy compared with conventional open surgery seem to outweigh these disadvantages by a considerable margin. In the treatment of cholecystolithiasis for example, the purported advantages of the laparoscopic approach include less postoperative pain, a shorter recovery period, an earlier return to daily activities and work, improved cosmetic results, and greater patient satisfaction [8-11]. The same benefits are also likely to apply to other laparoscopic procedures.

One possible explanation for improved clinical outcomes after laparoscopic surgery is that this type of surgery is minimally invasive and therefore causes less operative trauma and blood loss. Tissue injury induces alterations in systemic immune responses, which in turn influence postoperative morbidity [12-16]. A reduction in trauma through the use of minimally invasive techniques appears to be related to improved preservation of normal immune function [17,18].

All traumas, whether controlled or accidental, cause the acute phase response, which is an acute metabolic and inflammatory response that prevents further tissue damage and activates repair mechanisms. Surgery, a form of controlled trauma, induces this acute stress reaction.

The extent and duration of the acute phase response is proportional to the severity of the trauma [19-21]. Although the acute phase response is a normal reaction to trauma, an extensive response, or a response at a noninflammatory site, can be harmful. A reduction of this response might therefore be beneficial for patient recovery [12].

Surgery is also associated with a transient depression of cellular immune function. Improved preservation of cellular immunity has been related to a lower incidence of

infectious complications, local recurrences, and distant tumor metastases [12-16]. Maintaining a sufficient immune response may therefore be of particular interest to patients who are surgically treated for malignant diseases.

In recent years, a great deal of research has focused on immune responses to surgery; however, this phenomenon is still incompletely understood. Most studies investigate changes in immunologic parameters during and after surgery but fail to relate these changes to clinical outcome [22]. Furthermore, the results of various studies do not always correspond thus making it difficult to draw reliable conclusions.

The objective in this article, therefore, is to assess the immunologic consequences of laparoscopic surgery with a focus on the immunologic changes that are due to laparoscopic surgery for colorectal malignancies. As laparoscopic techniques are used in the treatment of these tumors, it is of great importance to investigate the possible relationships between laparoscopy and local and systemic immune responses that play a role in the defence against cancer recurrence after surgical resection. Manipulating the immune response to prevent such a recurrence may, in future, become a new option in the treatment of colorectal cancer.

PERITONEAL IMMUNE RESPONSE

The peritoneum is of crucial importance to the local defence mechanism of the abdominal cavity [23]. It promotes the proliferation and differentiation of cells contained in the peritoneal cavity, such as monocytes, macrophages, natural killer cells and T-lymphocytes.

The first line of defence within the abdominal cavity is formed by macrophages, which are the predominant cells in the peritoneal fluid [24,25]. They are of vital importance in defending the body against foreign invaders. They do so by initiating and directing the specific and nonspecific immune responses as well as the systemic acute phase response. Furthermore, they defend local homeostasis by ingesting and subsequently killing foreign material.

Macrophages reside in different body tissues and derive from monocytes, which circulate throughout the human body. In response to stress, monocytes shift from the circulation into the affected tissues, where they differentiate into macrophages. Macrophages, monocytes, peritoneal mesothelial cells, fibroblasts and leukocytes are all

capable of producing large numbers of cytokines, such as Interleukine (IL)-1, IL-6 and tumor necrosis factor (TNF)-α [26]. These molecules are major regulators of the local and systemic immune response. The secretion of proinflammatory cytokines mainly takes place in the peritoneum [27,28]. A transient increase in the peritoneal production of interleukins occurs after surgery [27-29]. Most studies concur that, compared with laparoscopy, the increase of serum interleukin levels is more pronounced after laparotomy [27,29].

Several studies have reported on the impact of the pneumoperitoneum on immunologic parameters in the abdominal cavity. The types of insufflation gas used and intra-abdominal pressure have both been related to changes in peritoneal immune function [30-34]. West et al studied in vitro murine macrophage function after exposure to carbon dioxide, helium, and room air. Macrophages incubated in carbon dioxide produced significantly less TNF and IL-1 compared with macrophages exposed to other kinds of insufflation gases [30].

In an animal study by Watson et al, a significant increase was observed in the release of TNF after laparoscopy with air insufflation compared with carbon dioxide insufflation [31]. Hajri et al associated long-lasting exposure to a carbon dioxide pneumoperitoneum with reduced macrophage function in rats [32].

Carbon dioxide insufflation is associated with a decrease in intracellular pH of macrophages [30]. This might be the cause of impaired macrophage function after laparoscopy with carbon dioxide. Kuntz et al found a decreased pH after raising the intra-abdominal pressure in rats [33]. The observed effect may have been due to increased absorption of carbon dioxide during a high-pressure pneumoperitoneum. According to Puttick et al, warming the insufflation gas is associated with reduced cytokine production in the human abdominal cavity [34]. To date, most published animal studies show a relationship between a carbon dioxide pneumoperitoneum and decreased peritoneal macrophage function. Human studies on the same subject have not been as readily available, thereby making it difficult to draw any meaningful conclusions.

SYSTEMIC RESPONSES TO TRAUMA

Alterations of systemic immune response in reaction to trauma have been thoroughly investigated. Two major changes occur in reaction to tissue injury. First, the acute phase response is initiated. Subsequently, a gradual suppression of the systemic immune system occurs that is characterized by a decrease in peripheral blood lymphocyte levels. Changes of systemic immunity have been related to clinical outcome after surgery [12-16].

ACUTE PHASE RESPONSE

Infections, tissue injuries, bone fractures, and tumor growth can disturb homeostasis and result in the acute phase response, a complex series of reactions. This rapid, nonspecific response occurs as a reaction to the stress that results from all types of trauma, whether controlled, such as in surgery, or accidental. The function of this response is to restore the body's natural balance through metabolic, hormonal, and inflammatory reactions. During the acute phase response, changes occur in protein, lipid, and carbohydrate metabolisms.

In response to tissue injury, several reactions are initiated: First, a local response that stimulates wound healing occurs at the site of the lesion. In addition, alterations in gluconeogenesis, protein catabolism, and lipid metabolisms occur. Another characteristic feature of the response is the production of several proteins known as the acute phase proteins [35], such as C-reactive protein (CRP), lactoferrin, and amyloid, that are mainly generated in the liver in reaction to stress. Many retrospective and prospective studies have compared acute phase proteins in laparoscopic and open surgery.

Pro-inflammatory cytokines (IL-1, IL-6 and TNF-α) are important mediators of the acute-phase response. IL-6 mainly contributes to the hepatic manifestations of the response by triggering changes in the synthesis of acute phase proteins in the liver. IL-1 and TNF-α regulate nonhepatic manifestations, such as fever, leukocytosis, and tachycardia. Since proinflammatory cytokines are crucial in initiating and regulating responses to tissue injury, they are often used to monitor the impact of surgical trauma. In addition to its correlation with the severity of injury, the synthesis of IL-6

has been related to the duration of surgical intervention [20,36] and the occurrence of major postoperative complications [19].

Most published, randomized trials that have compared acute responses after laparoscopic with open cholecystectomy have concluded that the laparoscopic approach is associated with a diminished acute phase response [37-41]. This finding supports the theory that laparoscopy is associated with less tissue trauma compared with open surgery. Trials that have reported acute responses after endoscopic or open Nissen fundoplication and bilateral inguinal hernia repair have shown similar results [42,43].

Nevertheless, comparisons of the acute phase response after open and laparoscopic procedures for colorectal cancer are ambiguous. Only a few randomized studies on the acute phase response and cytokine production after colorectal cancer surgery have been published [18,29,44-46]:

- Schwenk et al studied inflammatory responses in 60 patients who were randomized to undergo either laparoscopic or open resection for colorectal cancer. IL-6 and CRP plasma levels were lower after laparoscopic colorectal surgery. The authors suggested this indicated that laparoscopy was associated with less surgical trauma compared with conventional surgery [18].
- Ordemann et al observed significantly lower cytokine plasma levels in 40 patients after they received laparoscopic surgery for colorectal malignancies [45].
- In a study by Leung et al, laparoscopic surgery was associated with a decrease in the systemic cytokine response, indicating reduced tissue trauma [29].
- Hewitt et al, in a similar study, found no significant differences in serum IL-6 levels between patients undergoing laparoscopic or open surgery for colorectal cancer [44].
- In the study by Stage et al, patients who received a laparoscopic procedure had higher IL-6 and CRP peak levels compared with patients who received open surgery [46].

Most studies that have compared laparoscopic and open surgery for gallbladder stones, reflux disease, and inguinal hernia indicate that laparoscopic surgery is associated with a reduced acute phase response. This is probably due to a decrease in tissue injury.

The results from studies that have compared acute responses after major laparoscopic surgery are ambiguous and often conflicting. A possible reason for these results being less distinct after major surgery is that the difference in tissue trauma between laparoscopic and open surgery may not be as pronounced after major surgical procedures.

CELLULAR IMMUNITY

Cellular immunity can be divided into a natural, non-specific immune response and an acquired, specific immune response. The first response is caused by cells that are able to phagocytose microorganisms: the polymorfonuclear neutrophil leukocytes and the monocyte-macrophage system. These phagocytes destroy foreign material after ingestion. Some phagocytes can also kill cells or parasites through cytotoxicity. The second response is antigen-specific and primarily represented by T-lymphocytes. Lymphocytes are produced in bone marrow, and their activity and production is mainly regulated by cytokines. Some T-lymphocytes have a regulatory function in cell-mediated immunity. Others are involved in delayed types of hypersensitivity reactions or in the destruction of bacteria that reside inside cells. Natural killer cells, a particular population of lymphocytes, also have the ability to kill cells through cytotoxicity. They have an important role in the defence against virus-infected cells; and furthermore, they may be of significance in the defence against malignancies by destroying certain types of tumor cells.

Most studies on cholecystectomy and Nissen fundoplication conclude that laparoscopy is associated with the improved preservation of the systemic immune response compared with laparotomy [47-49]. Preservation of cellular immunity may explain the excellent short-term results after laparoscopic surgery in these cases.

The differences in the systemic immune response after laparoscopic and open colectomy are less obvious. Animal studies have shown improved preservation of cellular immunity after laparoscopy [50]. Most human studies have not shown significant differences in cellular response between laparoscopic and conventional colectomy:

- Wu et al measured acute phase and cell-mediated response in 26 patients after laparoscopic or open resection for colonic cancer. No difference was observed in cellular response between the two approaches [27].

- Hewitt et al concluded that significant changes of systemic immune function occurred after surgery. However, there was no difference in changes between patients who received laparoscopic or open surgery [44].
- Whelan et al studied delayed-type hypersensitivity response in 35 patients undergoing laparoscopic or open colorectal surgery. The study concluded that, compared with open surgery, the preservation of cell-mediated immunity had improved after laparoscopic surgery [51].
- In a study by Braga et al, 269 patients with colorectal diseases were randomized into either a laparoscopic or an open procedure. The preservation of cellular immunity had improved in the laparoscopic arm of the trial [52].

Preservation of systemic immune function seems to be improved after minor surgery by the laparoscopic approach compared with the open approach. After major surgical procedures, differences in systemic immune function are less obvious. Further research on the subject may potentially lead to a more definite conclusion regarding changes in immune function in these cases.

PORT-SITE METASTASES AND THE IMMUNE SYSTEM

Although several authors have shown that minimally invasive techniques in colorectal surgery are safe and associated with less blood loss and a reduced morbidity compared with open surgery [52-54], use of the laparoscopic approach in the treatment of malignancies remains debatable. The main contributors to the controversy are several case-reports describing port-site metastases that provoked major concern among surgeons [55-57]. Initially, these recurrences seemed to occur more frequently after laparoscopic surgery compared with open surgery.

However, only a few reports on abdominal wall recurrences after conventional open surgery for colorectal malignancies have been published. The articles in question refer to incidences of 0.6% to 1.5% [58-61]. Incidences of port-site metastases after laparoscopic surgery for colorectal malignancies, mentioned in the literature, range from 0% to 21% [62-67]. Only two of these studies have reported exceptionally high numbers of port-site metastases after laparoscopic colectomy for cancer [62,67]. However, the level of evidence presented in these studies is very low, since both are mainly based

on case reports and represent a very small number of patients. Other studies report incidences that are comparable with rates for open surgery [63-66].

The pathogenesis of abdominal wall metastases after laparoscopic surgery remains unclear. During the past few years, extensive experimental research on the subject has been performed. One explanation for the occurrence of port-site metastases is the leakage of gas from the trocars, the "chimney effect", which enhances tumor take by increasing the number of free-floating tumor cells at the port-site [68,69]. Contamination of the wound by instruments and trocars that have been in direct contact with the tumor could also be important [70,71]. Another possible reason is the implantation of tumor cells in the trocar wound during the extraction of the tumor [67]. However, port-site metastases have also been reported at trocar sites that have not been used for specimen extraction, indicating other contributing factors.

Tissue trauma in general is associated with an increase in the local production of growth factors, which in turn enhances tumor growth. Furthermore, tumor growth in wounds is increased by a higher cellular proliferation. Failing host defences, the presence of TNF, and the suppression of the systemic immune system are all factors that could influence tumor take after surgery. When blood transfusions are needed, the chance of tumor recurrence seems to be greater, which is probably related to the size of the trauma [72].

One factor that could affect tumor take at trocar sites is the effect of the pneumoperitoneum on the local immune system. Intra-abdominal pressure, temperature, and type of insufflation gas used have been related to tumor growth [73-80]. Animal studies that compare the effect of elevated intra-abdominal pressure on tumor growth have had conflicting results. Some studies relate increased abdominal pressure to the promotion of tumor growth [73]. This may be associated with depressed local immune function. Others conclude that elevated pressure is associated with a decrease of tumor growth, which may be due to direct damage to the tumor cells [74]. The temperature of insufflation gases has also been related to alterations in tumor growth. In a study by Nduka et al, prevention of hypothermia during laparoscopy slowed down tumor growth in rats [75]. Most studies, however, have focused on the type of gas used in laparoscopy. In vitro, carbon dioxide seems to stimulate tumor growth [76,77]. In many animal studies, carbon dioxide insufflation resulted in enhanced tumor growth compared with gasless laparoscopy or helium insufflation [75,78-80]. One study of

patients undergoing elective gastrointestinal laparoscopic surgery showed similar results [81]. However, it is important to stress that the increase of tumor growth is less compared with the increase in tumor growth after open surgery [79,82].

Increased tumor growth after carbon dioxide insufflation can be explained by the interference of carbon dioxide with the function of peritoneal macrophages. Cellular acidification induced by carbon dioxide insufflation may alter the ability of macrophages to release cytokines and thus contribute to the depression of the local peritoneal immune response by alterations in the ability of macrophages to release cytokines [30,83]. Locally produced cytokines, including TNF, play an important role in the defence against tumor cells. Consequently, by decreasing this defence, carbon dioxide may be promoting tumor spread.

LAPAROSCOPY AND ONCOLOGIC OUTCOME

Surgery enhances tumor growth, perhaps due to the manipulation of the tumor during surgery or as a result of postoperative immune suppression. In animal studies, tumor growth after laparoscopy is less than after laparotomy [84]. However, similar results have not been achieved in human studies. To date, long-term results after laparoscopic surgery for colorectal malignancies have not been established. Only one randomized clinical trial, the Barcelona trial, has reported data on cancer-related survival and recurrences after laparoscopic versus open surgery for colonic cancer [85]. This study observed an increase in cancer-related survival after laparoscopic resection. This benefit was mainly attributable to differences in survival between laparoscopic and open surgery in patients with stage III tumors. In these patients, laparoscopic surgery was associated with an improvement of overall survival rates and a reduction in the tumor recurrence rate. However, it should be noted that this is the outcome of a single-surgeon, single-centre trial. The results of large, randomized, multi-center trials will have to be awaited.

CONCLUSIONS

Surgery alters local and systemic immune response. A better preservation of normal immune function has been related to improved postoperative outcome. Minor laparo-

scopic surgery is associated with improved preservation of systemic immune function compared to open surgery. For major surgical procedures such as colorectal surgery for malignancies, the immunologic benefits of laparoscopy are not immediately obvious. The surgical approach possibly influences the long-term outcome of cancer surgery. Higher survival rates may be obtained after laparoscopy through decreased tumor manipulation and by improved preservation of the normal immunologic responses.

The effect of the pneumoperitoneum on tumor growth and the occurrence of metastases in trocar wounds is not completely understood. However, incidences of port-site metastases after laparoscopic surgery for colorectal malignancies seem to be comparable to incidences of wound metastases after open surgery. Long-term survival data on laparoscopic versus open colectomy for cancer are not readily available. A definitive answer to how immune function changes after laparoscopic and open surgery for colorectal cancer awaits evidence from the results of large randomized clinical trials.

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CHAPTER 3

Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial

COLOR study group

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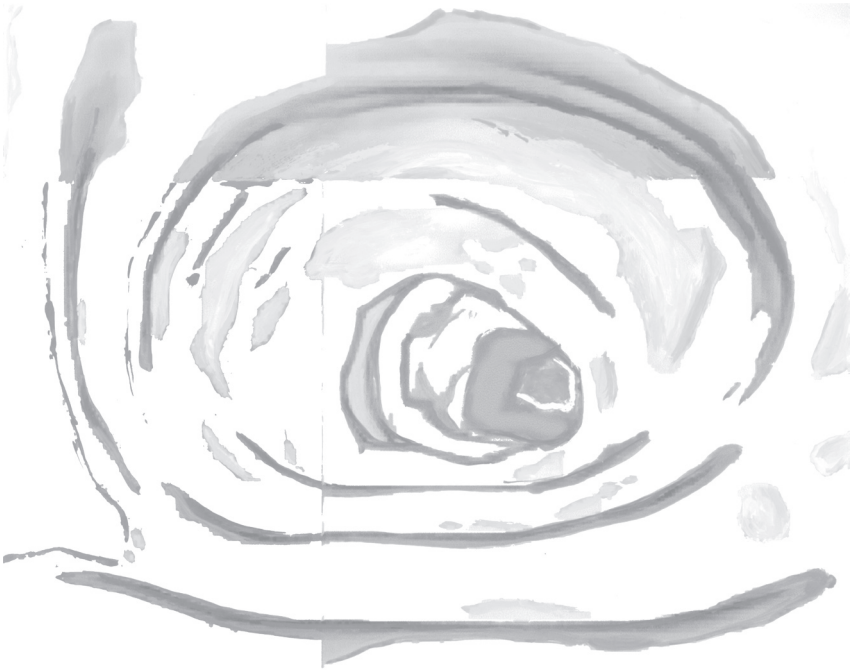

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ABSTRACT

Background: The safety and short-term benefits of laparoscopic colectomy for cancer remain debatable. The multi-centre COLOR (COlon cancer Laparoscopic or Open resection) trial was done to assess the safety and benefit of laparoscopic resection compared with open resection for curative treatment of patients with cancer of the right or left colon.

Methods: 627 patients were randomly assigned to laparoscopic surgery and 621 to open surgery. The primary endpoint was cancer-free survival at three years after surgery. Secondary outcomes were short-term morbidity and mortality, number of positive resection margins, local recurrence, port-site or wound-site recurrence, metastasis, overall survival, and blood loss during surgery. Analysis was by intention to treat. Here, clinical characteristics, operative findings and postoperative outcome are reported.

Findings: Patients assigned laparoscopic resection had less blood loss compared with those assigned open resection (median 100 mL [range 0-2700] vs 175 mL [0-2000], $p<0.0001$), although laparoscopic surgery lasted 30 minutes longer than did open surgery ($p<0.0001$). Conversion to open surgery was needed for 19% of the patients undergoing the laparoscopic procedure. Radicality of resection as assessed by number of removed lymph nodes and length of resected oral and aboral bowel did no differ between groups. Laparoscopic colectomy was associated with earlier recovery of bowel function ($p<0.0001$), need for fewer analgesics, and with a shorter hospital stay ($p<0.0001$) compared with open colectomy. Morbidity and mortality 28 days after colectomy did not differ between groups.

Interpretation: Laparoscopic surgery can be used for safe and radical resection of cancer in the right, left, and sigmoid colon.

INTRODUCTION

Minimally invasive surgery reduces surgical trauma. Laparoscopic surgery restricts the extent of abdominal incisions, avoids manual traction and manipulation of abdominal tissue, and prevents undue blood loss, thus diminishing immune activation and catabolism as a response to surgery [1,2]. Fifteen years after Muehe first did laparoscopic cholecystectomy, minimally invasive surgery has become the preferred approach for treatment of symptomatic cholecystolithiasis, gastro-esophageal reflux, and morbid obesity [3-6]. Although Jacobs and Verdeja [7] reported a case series on laparoscopic segmental colectomy in patients with sigmoid cancer in 1991, laparoscopic colectomy for cancer has not been readily accepted: the safety of the procedure has been questioned because of early reports of port-site metastases. Despite reduced morbidity and improved convalescence after laparoscopic operations for benign disorders such as gallbladder stones and reflux oesophagitis, surgeons have been skeptical about similar advantages of laparoscopic colectomy for cancer.

The European, multi-centre COLOR (COlon cancer Laparoscopic or Open Resection) trial aimed to assess laparoscopic surgery as curative treatment for colon cancer by analysis of short-term outcome and of cancer-free survival 3 years after laparoscopic surgery or open surgery for colon cancer. Data for cancer-free survival will be reported later. Here, the short-term results of clinical characteristics, operative findings, and post-operative outcome are reported.

METHODS

Patients

Between March 7, 1997 and March 6, 2003, all patients with colon cancer who presented to the 29 participating hospitals were screened for inclusion into the trial. Patients with one adenocarcinoma, localised in the caecum, ascending colon, descending colon or sigmoid colon above the peritoneal deflection who were aged 18 years or older and who gave written informed consent were eligible. The number of eligible patients who were not randomised was not recorded. Exclusion criteria were: body-mass index (BMI) of more than 30; adenocarcinoma of the transverse colon or splenic flexure; metastases in the liver or lungs; acute intestinal obstruction; multiple

primary tumours of the colon; scheduled need for synchronous intra-abdominal surgery; pre-operative evidence of invasion of adjacent structures, as assessed by CT, MRI, or ultrasonography; previous ipsilateral colon surgery; previous malignant disease (except those who had had curative treatment for basocellular carcinoma of the skin or in-situ carcinoma of the cervix); absolute contraindications to general anesthesia; and a long-term pneumoperitoneum.

627 patients were randomly assigned to laparoscopic resection and 621 to open resection by use of computer-generated random numbers; randomisation was stratified according to participating centre and type of resection (ie, right hemicolectomy, left hemicolectomy, or sigmoidectomy). Patients were randomised by the trial coordinator (RV, who was succeeded by EK) at the Erasmus University Medical Center, Rotterdam, The Netherlands, and allocation was done by telephone or fax. Patients were not blinded to the procedure they were allocated because covering all possible open and laparoscopic incisions was thought too cumbersome.

Patients were excluded after randomization only if metastasis was detected during surgery, microscopic examination of the resected sample showed no signs of malignant disease, other primary malignant disease was discovered before or during surgery, patients needed emergency surgery, or if patients withdrew consent. The trial coordinator supervised data gathering and provided progress data to the protocol committee and the monitoring committee. The ethics committee of every participating centre gave ethics approval for the trial.

Diagnosis of colon cancer was confirmed by barium-enema radiography or colonoscopy. Biopsy samples were taken for polyps, but not for macroscopically evident carcinomas. All patients underwent radiographic imaging of the liver and chest to exclude distant metastases. In patients with rectosigmoid carcinoma, lateral barium-enema radiograph was done to determine the exact location of the tumour. Bowel preparation, prophylaxis with antibiotics, and prophylactic treatment for thrombosis were done in accordance with standards at the participating institution.

Open surgery and laparoscopic surgery had similar protocols; extent of resection was much the same for both procedures. Right hemicolectomy involved resection of the caecum, ascending colon, and hepatic flexure with preservation of the main and left branches of the middle colic artery. Left hemicolectomy involved resection of at least 5 cm above and 5 cm below the lesion. For sigmoidectomy, resection of

the sigmoid 5 cm above and 5 cm below the lesion was done. During laparoscopic surgery, either the tumour and adjacent tissue or the extraction site was protected during removal of the affected bowel. For laparoscopy, all surgical teams had done at least 20 laparoscopically assisted colectomies. An unedited videotape of a laparoscopic colectomy was submitted before centre participated in the trial to assess safe and thorough techniques. All open colectomies were done by surgical teams who had at least one staff member with credentials in colon surgery. The resected tumour was presented unfixed to a pathologist, who recorded the size of the tumour, involvement of circumferential and longitudinal margins, number of resected lymph nodes, number of positive lymph nodes, and TNM classification in accordance with standardised techniques [8]; pathologist were not informed of the mode of resection.

Patients allocated laparoscopic surgery were converted to open surgery before the first incision when the laparoscopic equipment malfunctioned or when the laparoscopic team was absent. Analysis was by intention to treat- ie, patients who had preoperative conversion remained in the laparoscopic group for analysis. Case-record forms were collected by the coordinating centre in Rotterdam, The Netherlands. Short-term morbidity and mortality was defined as 28-day or in-hospital morbidity and mortality.

Interim analyses were done by the data monitoring committee after the report of every 50th recurrence in the whole study population. The trial was to be stopped if there was a convincing difference ($p<0.001$) in recurrence between groups.

Postoperative care, including use of narcotics for the first three days after surgery, was done in accordance with standard practice of the surgeons at the participating centre. Adjuvant therapy before and after surgery was allowed at the physician's discretion.

Primary & secondary outcomes

The primary outcome of the trial was cancer-free survival at 3 years after surgery, and will be reported elsewhere. Secondary outcomes were short-term morbidity and mortality, number of positive resection margins, local recurrence, port-site and wound-site recurrence, metastasis, overall survival, and blood loss during surgery. Blood loss, operating time, conversions, radicality of resections, morbidity, mortality, and hospital stay are the outcomes reported here. Cost analyses [9] and quality-of-life assessments

(not yet reported) have been done separately for every country because health-care costs and measurement of quality of life vary widely among European countries.

Statistical analysis

At the design of the trial, power calculations were done to exclude a difference of 7.4% or more in 3-year disease-free survival with 95% confidence. Thus, 1200 patients were needed to obtain a 80% power.

Percentage differences between groups were compared with the X^2 test or Fisher's exact test; comparison of continuous data was done by use of the Mann-Whitney test. Assessment of the effects of centre on operation time, blood loss, hospital stay, and number of lymph nodes was done with ANOVA after logarithmic transformation of these outcomes to obtain approximate normal distributions, and interaction terms were used to assess whether treatment effect differed between centres. Treatment effects are therefore expressed as ratios of geometric means. Centres with fewer than 30 patients were grouped. Further exploratory analyses, allowing for random centre effects, were done to investigate whether the volume of patients included per centre affected outcomes; only centres that accrued at least ten patients were included in this analysis. The effects of procedure and study centre on the odds of positive against negative resection margins were analysed by use of exact logistic regression. Statistical analyses were done with SPSS version 5.11. p=0.05 (two-sided) was the limit of significance in all analyses.

Role of the funding source

The sponsor of the trial had role in the study design; collection, analysis or interpretation of data; or the writing of the report. The corresponding author had full access to all data in the study and had final responsibility to submit the paper for publication.

RESULTS

Figure 1 shows the trial profile. The trial was not stopped early. 11 patients allocated laparoscopic surgery underwent open surgery because of malfunctioning laparoscopic equipment (eight patients) or absence of a skilled laparoscopic surgeon (three patients). Table 1 shows baseline characteristics of participants.

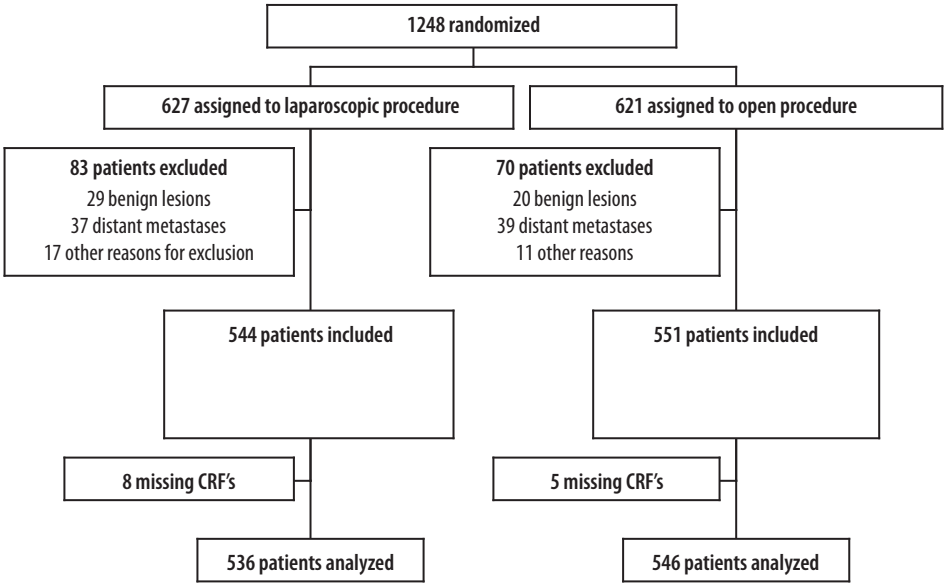

Figure 1: Trial profile

Malignant disease was confirmed preoperatively by a biopsy sample in 827 (76%) of 1082 patients. To diagnose the tumour, 876 (81%) of 1082 patients had colonoscopy and 432 (40%) had barium-enema radiography. Imaging of the primary tumour with CT was done for 48 (4%) of 1082 patients, and colonoscopic tattooing of the tumour for 37 (3%). In the laparoscopic group 21 tumours were tattooed: 15 in stage I disease, three in stage II, and three in stage III, of which four were in the right colon, five in the descending colon, and 12 in the sigmoid colon. In the open-surgery group, 16 tumours were tattooed: eight in stage I disease, six in stage II, and two in stage III, of which four were in the right colon, three in the descending colon, and nine in the sigmoid colon.

Screening for liver metastases before surgery was done by use of ultrasonography in 869 (80%) of 1082 patients, CT in 75 (7%), ultrasonography and CT in 123 (11%), and MRI combined with ultrasonography or with CT in four patients; 11 (<1%) patients did not have any such procedure and were assumed to have no liver metastases. Screening for pulmonary metastases before surgery was done with plain radiography of the chest in 1046 (97%) of 1082 patients, radiography and CT of the chest in 12 (1%), and chest CT in nine (1%); 15 (1%) patients had no procedure and were assumed to have no pulmonary metastasis. Use of imaging techniques did not differ between the

Table I: Baseline characteristics.

Characteristics		Laparoscopic colectomy (n=627)	Open colectomy (n=621)
Age (yrs)		71 (27-92)	71 (31-95)
Sex			
Men		326 (52%)	336 (54%)
ASA group	**I**	164 (26%)	166 (27%)
	II	353 (56%)	318 (51%)
	III	92 (15%)	112 (18%)
	IV	4 (1%)	5 (1%)
	Missing data	14 (2%)	20 (3%)
Body Mass Index (kg/m2)		24.5 (12.2-37.1)	24.9 (14.5-40.5)
Previous abdominal surgery*			
	No	386 (62%)	384 (62%)
	1 time	167 (27%)	163 (26%)
	2 times	41 (7%)	49 (8%)
	3 or more times	13 (2%)	9 (1%)
	Missing data	20 (3%)	16 (3%)

*Does not total 100% because of rounding.

groups. The median time between randomisation and surgery was longer in the laparoscopic group than in the open group (6 days [range 1-85] vs 5 days [1-63]; p=0.02). Table II shows operative findings.

Duration of surgery was longer for patients assigned laparoscopic resection than for those assigned open resection. ANOVA showed that the centre-adjusted ratio (laparoscopic/open) of geometric mean duration of surgery was 1.39 (95% CI 1.32-1.49), but this effect differed significantly between centres. Random-effects regression analysis showed that the difference in duration of surgery between groups decreased with increasing numbers of patients per centre, an effect that was significant for the laparoscopic group (p=0.027) but not for the open resection group (figure 2). Furthermore, time spent in the operating theatre was shorter for patients assigned open surgery than for those assigned laparoscopic surgery (table 2).

By use of ANOVA, the centre adjusted ratio (laparoscopic/open) of geometric mean time spent in theatre was 1.27 (1.22-1.32, p<0.001), which differed significantly between centres (data not shown). Random-effects regression analysis showed that mean time spent in theatre for patients assigned laparoscopic resection dropped with increased number of patients per centre (p<0.032), whereas no such association was noted for those assigned open colectomy.

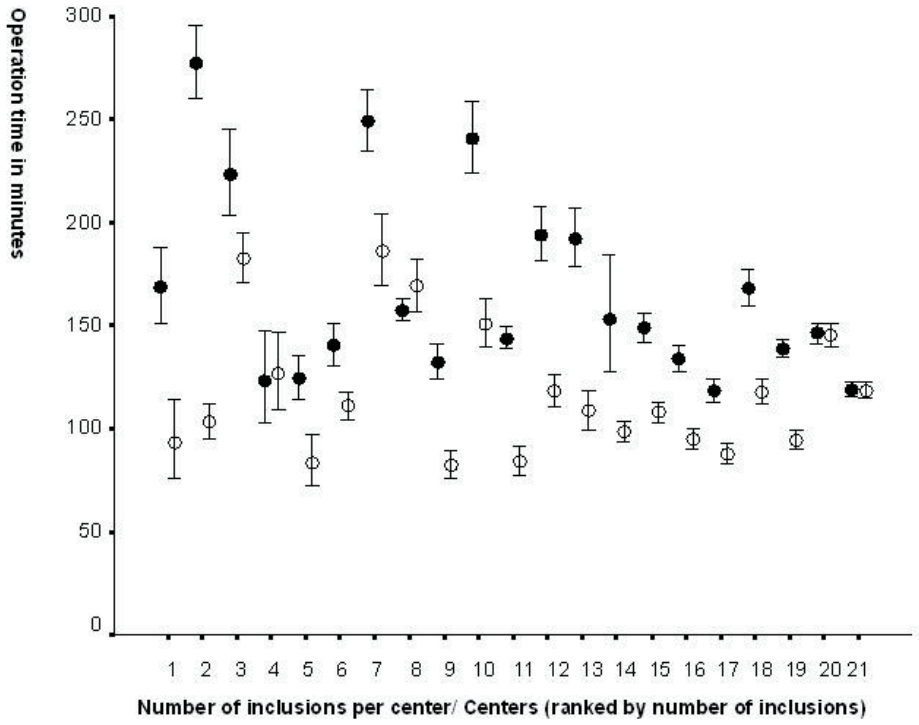

Figure 2: Mean operating time by centre.
The 21 centres are ranked according to number per centre. Vertical bars are SE.

Table 2: Operative data.

	Laparoscopic colectomy (n=536)	Open colectomy (n=546)	P
Intervention:			
Right hemicolectomy	259 (48%)	253 (46%)	0.87
Left hemicolectomy	57 (11%)	56(10%)	
Sigmoid resection	199 (37%)	212 (39%)	
Other	21 (4%)	25 (5%)	
Time in theatre (min)*			
Median (range)	202 (50-540)	170 (45-580)	<0.0001
Duration of surgery (skin to skin, min)†			
Median (range)	145 (45-520)	115 (40-335)	<0.0001
Blood loss (mL)‡			
Median (range)	100 (0-2700)	175 (0-2000)	<0.0001

*Data missing for 99 patients. †Time from first incision to skin closure: data missing for 68 patients. ‡ Data missing for 69 patients.

Blood loss during laparoscopic colectomy was significantly less than that during open colectomy (table 2). ANOVA showed a centre-adjusted ratio (open/laparoscopic) of geometric mean blood loss of 1.66 (1.37-2.00)-a treatment effect that did not differ significantly between centres (data not shown). During laparoscopic colectomy, adhesions were more frequently classified as problematic than during open colectomy (26 patients [5%] vs 11 patients [2%], p=0.02).

During surgery, 91 (17%) patients who were undergoing laparoscopic colectomy were converted to open surgery because of: fixation to, or invasion of, adjacent structures by the tumour (n=31); size of the tumour (n=8); extensive adhesions (n=8); inability to localise the tumour (n=8); bleeding (n=7); tumour in transverse colon or below promontory (n=5); bad vision (n=5); length of procedure (n=3); anatomical difficulties (n=3), macroscopic suspicious lymph nodes needing extensive resection (n=3); ischaemia of the distal colon (n=1); intra-abdominal abscess (n=1); urethral injury (n=1); two synchronous tumours (n=1); gaseous distention of the bowels after colonoscopy during surgery (n=1); resection of leiomyoma of the adnex (n=1); and unknown reasons (n=2).

Postoperative microscopic examination showed no differences between laparoscopically resected and openly resected samples. Stage distribution, size of the tumour, and histological type were much the same for both groups (table 3). Furthermore, groups did not differ in the number of positive resection margins (table 3), and centre did not modify this effect (data not shown). The common odds ratio for positive against negative resection margins was 1.01 (0.36-.68, p=1.0). In patients assigned laparoscopic resection, positive margins were recorded in four patients with T3 tumours and in six patients with T4 tumours. In patients assigned open resection, four patients with positive margins had T3 tumours and six had T4 tumours. Groups did not differ in the number of lymph nodes harvested during surgery (table 3). ANOVA showed a centre-adjusted ratio (open/laparoscopic) of geometric mean number of lymph nodes of 1.08 (0.98-1.17, p=0.106), which did not differ significantly between centres (data not shown).

After laparoscopic colectomy, patients tolerated an oral fluid intake of more than 1 L 1 day earlier than did patients assigned open surgery, and time to first bowel movement was shorter after laparoscopic surgery than after open surgery (table 4). Moreover, laparoscopic colectomy was associated with a lower need for opioid analgesics

Table 3: Details of pathology report.

	Laparoscopic colectomy (n=536)	Open colectomy (n=546)	P
Tumour size (cm)*			
Median (range)	4.0 (0.4-17)	4.5 (0.8-17)	0.09
Resection margins†			
Positive	10 of 526 (2%)	10 of 538 (2%)	1.0
Aboral	1	1	
Oral	0	1	
Circumferential	9	8	
Negative	516 of 526 (98%)	528 of 538 (98%)	
Clinical T stage‡			0.95
T1	41 of 528 (8%)	39 of 537 (7%)	
T2	107 of 528 (20%)	105 of 537 (20%)	
T3	350 of 528 (66%)	359 of 537 (67%)	
T4	30 of 528 (6%)	34 of 537 (6%)	
Clinical N stage∫¶			0.44
N0	347 of 528 (66%)	364 of 539 (68%)	
N1	125 of 528 (24%)	122 of 539 (23%)	
N2	45 of 528 (9%)	48 of 539 (9%)	
N3	11 of 528 (2%)	5 off 539 (1%)	
Tumour stage∫¶			0.60
I	129 of 528 (24%)	125 of 539 (23%)	
II	218 of 528 (41%)	239 of 539 (44%)	
III	181 of 528 (34%)	175 of 539 (33%)	
Histology∫¶			0.89
Well differentiated		86 of 538 (16%)	
Well to moderately differentiated		32 of 538 (6%)	
Moderately differentiated		315 of 538 (59%)	
Moderately to poorly differentiated		15 of 538 (3%)	
Poorly differentiated or undifferentiated		55 of 538 (10%)	
Not specified		35 of 538 (7%)	
Number of positive lymph nodes in resected sample||			0.35
Median (range)	10 (0-41)	10 (0-42)	

*Data missing for 11 patients. †Data missing for 18 patients. ‡Data missing for 17 patients. ∫Data missing for 15 patients. ¶Might not add to 100% because of rounding. ||Data missing for 36 patients.

on days 2 and 3 after surgery, and for non-opioids on the first day after surgery than was open resection. Epidural analgesics were used less frequently in the laparoscopic group compared with the open-resection group for the first 3 days after surgery (table 4). Overall morbidity was much the same after laparoscopic surgery and open surgery (table 4). Groups did not differ in the occurrence of pulmonary or cardiac events, anastomotic failure, wound or urinary-tract infections, bowel obstruction for more than 3 days after surgery, or postoperative bleeding. The number of deaths were similar after surgery for both groups (table 4).

Table 4: Postoperative recovery, morbidity, and mortality

	Laparoscopic colectomy (n=536)	Open colectomy (n=546)	Mean difference between groups (95% CI)	P
Fluid intake > 1L (days)*				
Mean (SD)	2.9 (1.9)	3.8 (3.4)	0.9 (0.6 to 1.2)	<0.0001
First bowel movement (days)†				
Mean (SD)	3.6 (1.7)	4.6 (3.0)	1.0 (0.7 to 1.3)	<0.0001
Hospital stay (days)‡				
Mean (SD)	8.2 (6.6)	9.3(7.3)	1.1 (0.2 to 1.9)	<0.0001
Analgesic use				
Day 1				
Opiates	292 of 516 (57%)	313 of 526 (60%)	3 (-3 to 9)	0.37
Non-opiates	366 of 517 (71%)	335 of 526 (64%)	-7 (-13 to –1)	0.02
Epidural	111 of 517 (22%)	190 of 526 (36%)	14 (9 to 20)	<0.0001
Day 2				
Opiates	208 of 514 (41%)	256 of 524 (49%)	8 (2 to 14)	0.008
Non-opiates	421 of 514 (82%)	443 of 524 (85%)	3 (-2 to 7)	0.29
Epidural	95 of 514 (18%)	164 of 523 (31%)	13 (8 to 18)	<0.0001
Day 3				
Opiates	132 of 513 (26%)	191 of 524 (37%)	11 (5 to 6)	<0.0001
Non-opiates	343 of 513 (67%)	368 of 526 (70%)	3 (-2 to 9)	0.27
Epidural	42 of 513 (8%)	83 of 524 (16%)	8 (4 to 12)	<0.0001
Complications §				
Overall	111 of 535 (21%)	110 of 545 (20%)	-1 (-5 to 4)	0.88
Wound infection	20 of 535 (4%)	16 of 545 (3%)	-1 (-3 to 1)	0.57
Wound dehiscence	2 of 534 (<1%)	7 of 544 (1%)	0.6 (-0.2 to 2)	0.18
Pulmonary	8 of 535 (2%)	13 of 545 (2%)	0.9 (-1 to 3)	0.40
Cardiac	4 of 535 (1%)	9 of 545 (2%)	1 (-0.5 to 2)	0.18
Bleeding	13 of 534 (2%)	8 of 544 (2%)	-0.9 (-3 to 1)	0.36
Urinary tract inf.	12 of 535 (2%)	13 of 545 (2%)	0.2 (-2 to 2)	1.00
Anastomotic failure	15 of 535 (3%)	10 of 545 (2%)	-1 (-3 to 1)	0.39
Bowel obstruction > 3 days	10 of 534 (2%)	15 of 544 (3%)	0.9 (-1 to 3)	0.45
Other	45 of 534 (8%)	40 of 544 (7%)	-1 (-4 to 2)	0.59
Reintervention	37 of 535 (7%)	25 of 545 (5%)	-2 (-5 to 0.4)	0.13
Death	6 of 535 (1%)	10 of 545 (2%)	0.7 (-0.7 to 2.2)	0.45

*Data missing for 64 patients. †Data missing for 54 patients. ‡Data missing for 11 patients. §Some patients had more than one complication.

Groups did not differ in the numbers of reinterventions done 28 days after surgery (table 4). In the laparoscopic group, 18 reinterventions were needed for anastomotic leakage and abdominal sepsis, five for wound infections and dehiscence, four for bowel obstruction lasting more than 3 days, five for bleeding, one for a ruptured inflammatory aneurysm, two for a perforated gastric ulcer, one for explorative laparotomy, and one for removal of a rectal adenoma. In the open-resection group, eight reinterventions were needed for anastomotic leakage, nine for wound infections and

dehiscence, four for bowel obstruction lasting more than 3 days, three for bleeding, and one for an ischaemic bowel.

Postoperative hospital stay was 1 day shorter in the laparoscopic group than in the open-resection group (table 4). By use of ANOVA, the centre-adjusted ratio (open/laparoscopic) of geometric mean hospital stay was 1.16 (1.08-1.23), and this treatment effect did not differ significantly between centres.

DISCUSSION

The short-term outcomes of the COLOR trial show that although duration of surgery for laparoscopic colectomy for colon cancer was longer than that of open colectomy, patients who underwent the laparoscopic procedure had less blood loss during surgery. Moreover, tumours resected by laparoscopy or by open surgery did not differ in stage, distribution, size, histology, number of positive resection margins, and number of positive lymph nodes. After surgery, patients allocated laparoscopic colectomy tolerated fluid intake and had a first bowel movement, earlier than did those allocated open colectomy. Patients assigned laparoscopic colectomy had a lower need for analgesics and epidurals in the 3 days after surgery than did those assigned open colectomy.

29 university hospitals and community hospitals in seven European countries participated in this trial, and the outcomes thus give an insight into laparoscopic colon surgery as done in Europe. Importantly, however, this trial was started in 1997 when the technique of segmental colectomy was changing. In the past 8 years, new ways of vessel sealing, such as bipolar and ultrasonic forceps, have been introduced. These devices allow faster and more secure haemostasis than do conventional laparoscopic techniques such as clips and unipolar diathermia. Furthermore, a shortcoming of this trial is that patients were not blinded as to the procedure they were allocated, which could have affected subjective outcomes. Missing data for 13 of 1248 patients seems acceptable, given that the trial was multicentre.

In this trial, patients who underwent laparoscopic colectomy spent longer undergoing surgery than did those who had open colectomy, but needed fewer opioids on the second and third postoperative day than did those who had open surgery. By contrast, Joels and colleagues [10] associated use of opioids after open colectomy

with operative time as a result of more extensive tissue manipulation and protracted incision of the abdominal wall. The findings reported here suggest that manipulation of tissues is a more important determinant of postoperative pain than is operative time, and are consistent with Weeks and co-workers trial [11], which reported shorter postoperative use of parenteral analgesics after laparoscopic colectomy than after open colectomy ($p<0.001$).

Bowel obstruction after colectomy, as defined by postoperative day of first fluid intake of more than 1 L and postoperative day of first bowel movement, was 1 day shorter in patients who had laparoscopic surgery than in those who had open surgery in the COLOR trial. Braga and colleagues [12] noted first bowel movement 1 day earlier after laparoscopic colectomy than after open colectomy, and animal studies [13] have shown that laparoscopic colectomy reduces postoperative atony of the small bowel, as measured by electromyographic activity, compared with open colectomy. Clinical manometric recordings [14] of motility at the splenic flexure of the colon have shown that colonic motility recovers earlier after laparoscopic colectomy than after open colectomy. Rapid rehabilitation protocols involving thoracic epidural local anaesthetic blockade, early mobilisation of the patient, and solid food on the first postoperative day have reduced bowel obstruction to 1-2 days [15].

Findings reported here show that hospital stay after laparoscopic colectomy was 1 day shorter than with open colectomy, and are consistent with the findings of Lacy and colleagues [16] and the Clinical Outcomes of Surgical Therapy (COST) Study Group [17] However, Basse and co-workers showed substantial reduction of hospital stay after open colectomy by use of transverse incisions combined with accelerated multimodal rehabilitation programmes. Further assessment of the effect of such rehabilitation programmes on the outcome of laparoscopic and open colectomy are needed.

Conversion of laparoscopic procedures to open surgery was necessary in 19 % of patients, mainly due to the presence of a large and invasive cancer. Size and infiltration of adjacent tissues by a tumour cannot be assessed accurately by either colonoscopy or barium enema. However, these imaging modalities are regarded as the standard of care in Europe. Only 5 % of patients had a CT scan to image the primary tumour, and use of CT or MRI in patients with colon cancer may identify patients with bulky or

invasive lesions, or lesions at the flexures or transverse colon, which are less amenable to laparoscopic removal.

Operating time varies with surgical experience, and gaining experience with laparoscopic colectomy can reduce the operating time to that with open colectomy. Although in this trial, laparoscopic colectomies lasted longer than did open procedures, operating times varied substantially between centres. Although total open surgical procedures done per centre was not recorded, the presence of a skilled colorectal surgeon during all open colectomies ensured appropriate and timely procedures. Reluctance to implement laparoscopic colectomy in surgical practice because of restraints on operating time therefore seems unsubstained.

Blood loss during laparoscopic colectomy was less than that during open colectomy in this study. Kiran and colleagues [19] assessed use of blood products (ie, packed cell or transfused red cells) in a case-matched study of patients undergoing laparoscopic colectomy or open colectomy, and reported that demand for blood transfusions during and after surgery was less in the laparoscopic group compared with the open-surgery group. Furthermore, the safety and effectiveness of laparoscopic surgery can be measured by the degree of resection and disease-free survival. In the COLOR trial, the extent of resection of colon and mesocolon was much the same for both groups. These findings are consistent with other prospective trials [20,21] of laparoscopic resection versus open resection for colon cancer, and by a consensus conference [22]. Moreover, a median number of 10 lymph nodes were removed during surgery in both groups. It has been suggested that at least 12 lymph nodes should be removed to ensure radical resection. However, the number of lymph nodes recorded by the pathologist is a function of the scrutiny of the detection method. In this study, pathologists were not urged to do a more thorough search for lymph nodes than is done in practice. A consensus conference [22] that documented available data for laparoscopic versus open colectomy showed that both procedures commonly yield ten lymph nodes. Assessment of 5-year survival after laparoscopic colectomy for tumours in the left and right colon by Jacob and Salky [24] showed that the mean harvest of ten lymph nodes was much the same as that with open colectomy.

Patients with a BMI of more than 30 were excluded from the COLOR trial because at the time of trial design obesity was regarded as a technical challenge to laparoscopic colectomy. Delaney and co-worker [25] studied patients with a BMI of more than 30

who had either laparoscopic or open colectomy. The researchers found that operating times and morbidity did not differ between groups and that hospital stay was 2 days shorter after laparoscopic surgery than after open surgery. However, the conversion rate from laparoscopic surgery to open surgery was 30 %. Leroy and colleagues [26] assessed outcome of laparoscopic colectomy in obese and non-obese patients who had diverticular disease or colon cancer, and found that groups did not differ in operating times, radicality of resection, and morbidity. Moreover, none of the 23 patients with a BMI of over 30 required conversion to open surgery in Leroy and colleagues' study [26]. Patients who are obese can thus benefit from laparoscopic surgery, and obesity should no longer be regarded as a contraindication to laparoscopic colectomy.

Elderly patients were not been excluded from the COLOR trial. Yamamoto [27] showed that surgical outcome after laparoscopic colectomy for patients 80-90 years old was much the same for those 60 years or younger. Furthermore, Sklow and co-workers [28] reported faster recovery after laparoscopic colectomy than after open colectomy in patients older than 75 years despite a longer operating time compared with open surgery.

The improved short-term outcome after laparoscopic surgery compared to open surgery may be the consequence of reduced surgical trauma. Serum concentration of interleukin 6 is a commonly used measure of surgical trauma: Ozawa and colleagues [29] recorded lower concentrations of serum interleukin 6 after laparoscopic colectomy than after open colectomy. Whelan and co-workers [30] showed that open colectomy was associated with significant suppression of the cell-mediated immune response whereas laparoscopic colectomy was not ($p<0.007$).

In conclusion, the outcomes of studies on laparoscopic resection for colon cancer reflect experience of the past decade. During this period, laparoscopic surgical techniques have improved substantially as a result of growing experience and progressing technology that allows better video imaging, and safer and more efficient tissue ablation. Procedure times have dropped and undue tissue manipulation has decreased. The practice of open colectomy is changing too, with the implementation of rapid-recovery protocols. Further studies of the current surgical approaches for colon cancer are warranted to establish the optimal procedure for the individual patient with colon cancer.

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CHAPTER 4

Impact of hospital case volume on short-term outcome after laparoscopic operation for colonic cancer

COLOR study group

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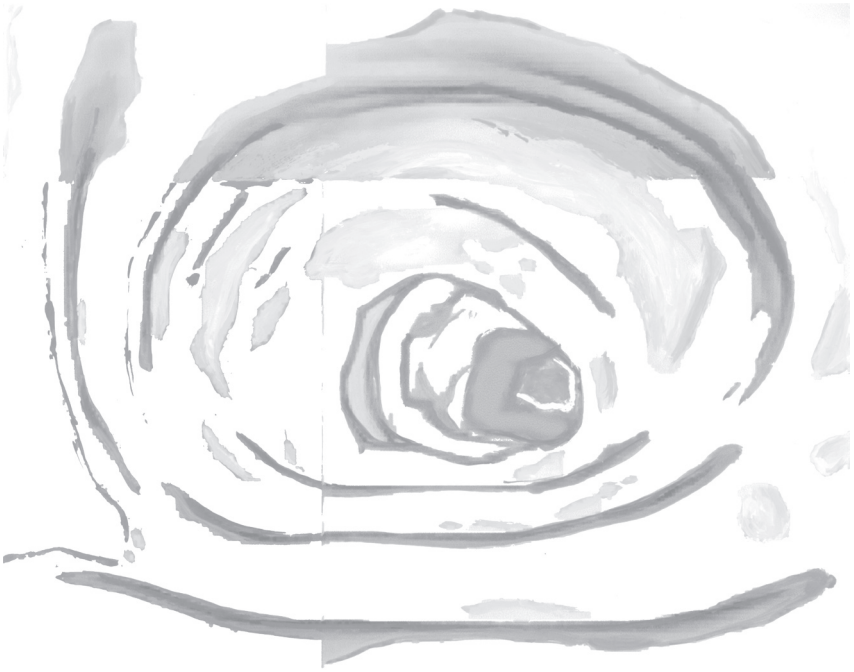

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ABSTRACT

Background High hospital case volume has been associated with improved outcome after open operation for colorectal malignancies.

Methods To assess the impact of hospital case volume on short-term outcome after laparoscopic operation for colon cancer, we conducted an analysis of patients who underwent laparoscopic colon resection within the COlon cancer Laparoscopic or Open Resection (COLOR) trial.

Results A total of 536 patients with adenocarcinoma of the colon were included in the analysis. Median operating time was 240, 210 and 188 minutes in centers with low, medium and high case volumes respectively ($P<0.001$). A significant difference in conversion rate was observed between low, medium and high case volume hospitals (24% vs. 24% vs. 9%; $p<0.001$). A higher number of lymph nodes were harvested in high case volume hospitals ($p<0.001$). After operation, fewer complications ($p=0.006$) and a shorter hospital stay ($p<0.001$) were observed in patients treated at hospitals with high caseloads.

Conclusions Laparoscopic operation for colon cancer in hospitals with high caseloads appears to be associated with improved short-term results.

INTRODUCTION

Quality of care is generally addressed by studies on efficacy and morbidity. One of the important determining factors of quality of care is caseload per hospital. High hospital case volumes have been associated with improved outcomes after complex surgical procedures, such as cardiovascular and cancer surgery [4].

The application of minimally invasive techniques to colorectal surgery has been expanding during the past decade. The feasibility of laparoscopic colorectal surgery has been demonstrated for both benign disease and cancer [14]. Laparoscopic colectomy appears to be associated with less morbidity and an earlier recovery than open colectomy [6,11]. However, laparoscopic colorectal surgery is technically demanding and therefore associated with a considerable learning curve [2,15,17].

To determine the impact of hospital case volume on short-term outcome after laparoscopic colon resection for cancer, all patients who underwent laparoscopic surgery within the framework of the COLOR (COlon cancer Laparoscopic or Open Resection) trial were analyzed. The primary endpoint of the COLOR trial, which started in 1997, was cancer-free survival 3 years after surgery.

PATIENTS AND METHODS

The COLOR trial is an international clinical trial that randomizes patients with colon cancer to undergo either laparoscopic or open operation. Patients with a solitary tumor located in the cecum, ascending colon, descending colon or sigmoid, orally to the peritoneal reflection, were included. Patients with distant metastases, signs of acute intestinal obstruction or a Body Mass Index exceeding 30 kg/m2 were not eligible. Patients with a history of malignancies or ipsilateral colon surgery and patients with absolute contraindications for general anaesthesia or a prolonged pneumoperitoneum were excluded as well. Randomizations were performed at the central co-ordinating center using a computer-generated randomization list. Randomization was done either by fax or by telephone. The trial design involved the randomization of all suitable consecutive patients with colon cancer into either a laparoscopic or an open procedure. Stratification was performed for participating center and type of resection. Analyses were conducted according to the intention-to-treat principle;

patients who did not receive the allocated procedure were analyzed in the treatment arm for which they had been assigned.

To ensure quality control, one member of the surgical team should have experience with at least 20 procedures to be qualified to perform either a laparoscopic or an open procedure within the framework of the trial. In total, 29 centers from Western Europe participated in the trial. The trial was approved by the medical ethics committee of each participating hospital. According to the guidelines of the local ethical committee, informed consent was obtained from patients prior to randomization. Data were collected centrally in the co-ordinating center in Rotterdam, The Netherlands.

To assess the impact of hospital case volume on short-term outcome after laparoscopic operation for colon cancer, hospitals were classified according to the number of laparoscopic colon resections performed. Classification was based on the rate of inclusion of patients into the COLOR trial. All participating hospitals assessed the eligibility for the COLOR trial of all patients with colon cancer referred for surgical treatment.

Hospitals were classified into three groups. Definitions of case volume were chosen in such a way that the number of surgical cases was approximately evenly distributed among the three groups. A high case volume hospital was defined as one that performed >10 laparoscopic procedures per year and >10 laparoscopic procedures during the term of the trial. Medium case volume hospitals were defined as those performing five to 10 laparoscopic procedures per year and >10 laparoscopic procedures during the term of the trial. Hospitals that performed less than five laparoscopic procedures per year or <10 laparoscopic procedures during the term of the trial were classified as low case volume hospitals.

Age, sex, number of previous abdominal operations, type of operative procedure, comorbidity and tumor stage were compared among groups to determine the potential presence of confounding factors. Assessment of the presence of comorbidity factors in patients was based on the classification of the American Society of Anesthesiologists (ASA).

Laparoscopic colonic procedures were all performed according to the same protocol. Skin-to-skin time was defined as time between first incision and closure of the skin. The total time spent in the operating theatre was called "theatre time".

After operation, an objective measurement of recovery of bowel function was obtained by recording the date of first defecation after surgery. The postoperative period was defined as the first 28 days after the operation. Tumor staging was based on the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) TNM staging criteria [8].

Short-term outcome after laparoscopic operation for colon cancer was compared among high, medium and low volume hospitals. Sex, ASA classification, tumor stage, operative procedures, inadvertent events, conversion rates, complications, and mortality were compared using the Chi-Square test. Age, number of previous operations, blood loss, skin-to-skin time, theatre time, and number of lymph nodes harvested were compared among the 3 groups using the Kruskal-Wallis test. In case of differences, the Mann-Whitney test was used to compare any two groups. To account for imbalances in ASA distribution and type of procedure, multivariate analysis (multiple regression) was used to compare hospital stay, skin-to-skin and theatre time, days until first defecation, and blood loss among the three groups. In these analyses, outcomes had to be transformed logarithmically in order to obtain approximate normal distributions. The categorical outcomes, such as postoperative complications, were evaluated multivariately using logistic regression. The limit of significance was set at $p = 0.05$ (two-sided).

The sponsor of the trial (Ethicon Endo-Surgery (Europe), Hummelsbütteler Steindam 71, Norderstedt, Germany) had no influence on the initiation and design of the study or on data collection, analysis, and interpretation.

RESULTS

From March 1997 until March 2003, 627 patients underwent operation for colon cancer within the context of the COLOR trial. Eight patients could not be analyzed due to missing data and 83 patients were excluded from the trial after randomization, leaving 536 cases for further analysis.

Reasons for postrandomization exclusion were distant metastases discovered during surgery (n=37), benign lesions (n=29), withdrawal of informed consent (n=6) or other reasons (n=11). For details regarding exclusions after randomization, see Fig. 1.

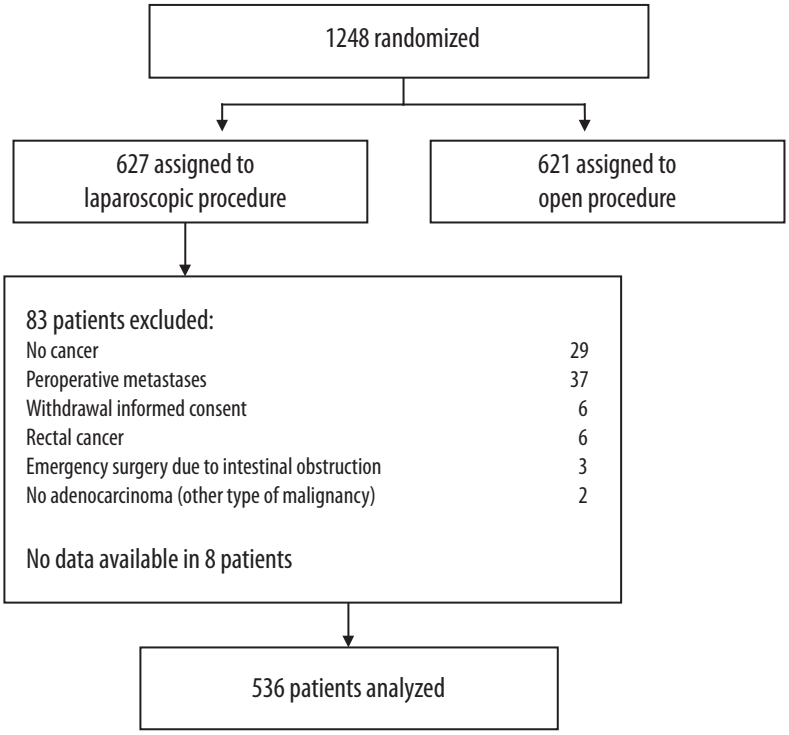

Figure 1. Randomization process

Twenty-nine centers from eight different Western European countries participated in the trial. According to our definitions, three of these centers were classified as high case volume hospitals for laparoscopic colon surgery and eight centers were classified as medium case volume hospitals. The remaining hospitals (n=18) were defined as low case volume hospitals. The average number of surgeons that reported cases was 5, 4 and 2 for high, medium and low case volume hospitals, respectively.

There were no significant differences among the three groups in terms of sex (p=0.21), age (p=0.33), or number of previous abdominal operations (p=0.30). More were there any dissimilarities in terms of tumor stage (p=0.69). A significant difference in ASA classification (p=0.02) and type of operative procedure performed (p=0.001) was present. Patients with an ASA III classification were more prevalent in high and low case volume hospitals than at medium case volume hospitals. Fewer right hemicolectomies and more left hemicolectomies were performed at high case volume hospitals. Patient, tumor and treatment characteristics are shown in Table 1.

Table 1. Patient & tumour characteristics

		Low n=161	Medium n=186	High n=189	*P*
Gender (%)	**Male**	47	51	57	NS
	Female	53	49	43	NS
Age (mean)		70.3	70.2	69.3	NS
Number of previous abd. operations (mean)		0.52	0.42	0.52	NS
Performed operative procedure (%)	**Left**	6	8	18	0.001
	Right	53	57	37	0.001
	Sigmoid	38	33	38	NS
	Other	4	3	5	NS
ASA classification (%)	**I**	24	32	23	NS
	II	58	58	56	NS
	III	18	10	21	0.019
	IV	0	0	0	-
Tumor stage (%)	**I**	24	23	26	NS
	II	41	45	38	NS
	III	35	31	36	NS

Data given are means or percentages (within volume group)

Inadvertent events occurred perioperatively in a higher number of patients undergoing colectomy at low case volume hospitals than in those treated at hospitals with medium or high caseloads (p=0.004).

These differences were mainly attributable to problems encountered when performing an anastomosis. For details on intraoperative problems, see Table 2.

Average intraoperative blood loss was 185 mL, 205 mL and 150 mL at low, medium, and high case volume hospitals, respectively (p=0.78). Median skin-to-skin time for laparoscopic colon resections was 160 minutes at low case volume hospitals, 153 minutes at medium case volume hospitals and 130 minutes at high case volume hospitals. For this reason, low and medium caseload hospitals reported significantly longer skin-to-skin times than high volume hospitals (p<0.001). Median time in the operating theatre was 240 minutes for laparoscopic colon resection at hospitals with a low case volume vs 210 minutes in medium case and 188 minutes at high case volume hospitals. All comparisons of low, medium and high case volume hospitals showed significant differences in total time spent in the operating theater (p<0.001).

Table 2. Operative findings

	Low n =161	Medium n=186	High n=189	*P*
Peroperative inadvertent advents (n)				
Hypercapnia	1	0	0	NS
Bleeding	3	8	6	NS
Fixation of the tumour	11	4	8	NS
Perforations	3	0	0	NS
Adhesions	13	7	6	NS
Problems performing an anastomosis	6	0	3	0.03
Other	9	11	10	NS
Total nr of patients with inadv. Events	36	18	26	0.004
Median (mean) blood loss (mL)	100 (185)	100 (205)	100 (150)	NS
Median skin-to-skin time (min)	160	153	130	<0.001
Median theatre time (min)	240	210	188	<0.001
Conversion rate (%)	24	24	9	<0.001
Median nr of lymph nodes harvested	9	8	12	<0.001

There was a significant difference in the conversion rate among low, medium, and high case volume hospitals (24% vs. 24% vs. 9%; $p<0.001$). At low and medium case volume hospitals, the median number of lymph nodes harvested during the surgical procedure was nine and eight respectively; whereas at high volume hospitals, the median number of harvested lymph nodes was 12 ($p<0.001$).

Six patients died during the postoperative period. Four of these patients were treated at low volume hospitals. ($p=0.14$). In two of these cases, the death was not related to surgical procedure. One patient died due to multiple organ failure (MOF) after an anastomotic leak. In another patient, necropsy revealed a large bleeding of undetermined origin. The other causes of death were: sepsis, ruptured inflammatory aneurysm, CVA and MOF with unknown cause. In the patients who died due to MOF with unknown cause or sepsis, no signs of anastomotic leakage were found at re-operation.

Complications occurred significantly less often at medium and high volume hospitals than in those with a low caseload ($p=0.006$). Table 3.

The number of re-interventions during the first 28 days after surgery showed no significant correlation with hospital caseload ($p=0.261$). There were significantly fewer

Table 3. Post-operative outcome

	low n =161	medium n=186	high n=189	*P*
Mortality (n)	4	1	1	NS
Complications (n)	48	29	34	0.006
Pulmonary	7	1	0	0.004
Cardiac	1	2	1	NS
Anastomosis related	6	3	6	NS
Urinary tract infections	6	0	6	NS
Wound infections	14	4	2	NS
Bleeding	6	2	5	NS
Ileus	4	2	4	NS
Wound dehiscence	0	1	1	NS
Other	17	16	12	NS
Re-interventions (n)	13	14	10	NS
Re-admissions (n)	9	11	1	0.011
First defecation*	3	4	3	0.004
Day of discharge*	8	7	6	<0.001

*Median number of days

readmissions to high case volume centers than to hospitals with a medium or low caseload (p=0.011).

In patients at high caseload hospitals, the first defecation was noted after an average of 3 days postoperatively, whereas at medium and low case volume hospitals the first postoperative defecation occurred after an average of 4 and 3 days, respectively (p=0.004 and p=0.78). Median time until discharge from hospital was 6, 7 and 8 days for high, medium, and low volume hospitals, respectively (p< 0.001).

Because the 3 groups differed in terms of ASA distribution and operative procedures performed, multivariate analyses were done to account for these imbalances. After adjustment for these two factors, all significant differences found in the univariate analysis still remained.

DISCUSSION

Approximately 90% of patients with colon cancer currently undergo a surgical procedure [1], and most such procedures are performed via the open approach. Although minimal-access surgery for colon cancer was introduced more than a decade ago, the

laparoscopic approach was not as readily accepted in the field of colorectal surgery as it has been in other areas of general surgery. In the early 1990, serious doubts about the role of laparoscopy in colorectal cancer surgery were raised by reports documenting high occurrences of port site metastases [3,13]. Although the level of evidence presented in these case series was very low, they alarmed many surgeons. Ever since, laparoscopic colectomy for cancer has been performed primarily within the framework of randomized trials.

Known short-term benefits of laparoscopic colectomy for cancer include a lower morbidity rate, a shorter recovery period, earlier discharge from hospital, and less postoperative pain [6,11,19]. However, whenever a treatment for cancer is evaluated, survival must be the primary endpoint. Two large randomized trials with data on survival have been published so far [5,11]. In the Barcelona trial, laparoscopic colectomy for nonmetastasized cancer was associated with an improved cancer-related survival, which was mainly attributable to a better outcome in patients with stage III colonic cancer [11]. In the multicenter Clinical Outcomes of Surgical Therapy (COST) trial, no differences in survival were observed between laparoscopically assisted and open surgery for adenocarcinoma of the colon. The Cost Study Group concluded that laparoscopic colonic resection is an acceptable alternative to the open procedure for colon cancer [5].

The COLOR trial was initiated in 1997 to compare laparoscopic and open surgery for nonmetastasized colon cancer. In the current analysis, which includes patients who underwent laparoscopic colectomy within the framework of this trial, the impact of hospital case volume on short-term outcome after laparoscopic operation for colon cancer was studied. A significant correlation was found between hospital case volume and intraoperative problems, operating time, conversion rate, number of lymph nodes harvested, recovery of bowel function, complications, and hospital stay.

To our knowledge, no studies have been conducted on the impact of caseload volume on operative and postoperative outcome with within one database of patients undergoing laparoscopic operation. However, there is some evidence that the short-term outcome of patients undergoing open colorectal operation is better at high volume hospitals is available. Most such studies comprise retrospective analyses of large cancer registries and databases, with no analysis of confounding factors.

Simons et al. analyzed 2,006 patients with rectal cancer using the Los Angeles County Cancer Surveillance Program database [18]. Patients who underwent open rectal surgery for localized disease at high case volume hospitals were more likely to have a sphincter-sparing procedure than patients treated at low case volume hospitals (69% vs. 63 %; p=0.049). Furthermore, survival was significantly better at hospitals with a high caseload ($p < 0.001$).

Similar results on the likelihood of receiving a sphincter-sparing procedure were obtained by Meyerhardt et al., who studied a cohort of patients participating in a chemotherapy trial [12]. They found significant differences in the rate of abdominoperineal resection among hospitals with low, medium, and high caseloads (46.3% vs. 41.3% vs. 31.8%, respectively; $p < 0.001$). However, they found that hospital caseload was not associated with survival or recurrence rates after open operation for rectal cancer. Kee et al. studied mortality in 3,217 patients registered in a colorectal cancer database [10]. They concluded that, although the specific surgeon had no effect on caseload, patients treated at high caseload hospitals had a slightly worse 2-year survival rate than patients treated at low case volume hospitals. They suggested that there could be factors other than surgical case volume that might be far more important in improving quality of care.

The impact of hospital caseload on short-term outcomes after colorectal operation, other than the likelihood of receiving a sphincter-sparing procedure, has not been studied in any great detail. In a retrospective cohort study by Schrag et al., modest differences in the 30-day postoperative mortality rate were observed between patients treated for colon cancer at hospitals with low vs high case volume (5.5% vs. 3.5%) [16]. In addition, they found that the long-term survival of patients treated at high case volume hospitals was better (p<0.001). Dimick et al. reported that postoperative mortality rates after open colorectal surgery for cancer were lower in patients treated at high case volume hospitals than those treated at low case volume hospitals (2.5% vs. 3.7%; p=0.006) [7]. The differences were even more pronounced in elderly patients. In a study by Harmon et al., no significant impact of hospital case volume on in-hospital mortality was observed [9]. But Zingmond et al., who used the California hospital discharge database to identify patients who had previously undergone colorectal operation for cancer [20], found a lower complication rate in patients treated at hospitals with high caseloads.

The present study has clearly shown that surgical outcome is related to case volume. This observation should provide a further stimulus to examine the efficacy of both the teaching and the performance of laparoscopic colectomy. Good results in such variables as operating time, blood loss, and conversion rates are the end product of multiple factors. To suggest that the expertise of the surgeon is the determining factor is a somewhat myopic view that ignores other elements critical for surgical success, such as for instance postoperative care. However, precise knowledge of laparoscopic surgical anatomy, mastery of the various steps of a procedure, well-developed skills, and the skillful use of auxiliary devices are indeed of paramount importance to a good outcome. Effective teaching of these components of laparoscopic colectomy will enable more patients to benefit from its advantages.

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CHAPTER 5

Predictive factors of conversion in laparoscopic colectomy for cancer

COLOR study group

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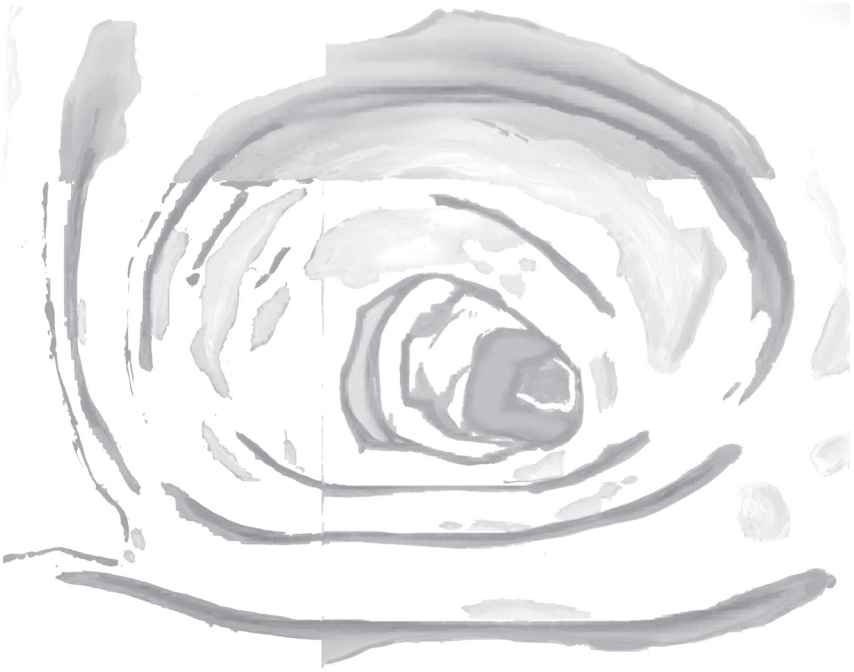

ABSTRACT

Introduction In laparoscopic colectomy for cancer, conversion is associated with an increase in postoperative morbidity and mortality. In spite of this, strict criteria to select patients for minimally invasive colonic surgery are not yet available.

Patients & Methods Short-term outcomes after converted procedures and predictive factors of conversion were analyzed in patients undergoing laparoscopic colectomy for cancer within the framework of the COLOR trial.

Results Conversion to a laparotomy was associated with an increase in both morbidity (18% vs 30%, p<0.001) and mortality (0 vs 6%; P<0.001). Furthermore, converted procedures took significantly longer to perform (154 vs 181 minutes; p<0.001) and re-interventions occurred more often after conversion to open surgery (5% vs 16%; p=0.001). Average time until discharge from hospital increased by 3 days for patients undergoing a converted procedure (8 vs 11 days; p<0.001). Size of the tumor and tumor stage were both associated with increased conversion rates (p<0.001).

Conclusions Conversion in laparoscopic colectomy for cancer is associated with a significant increase in morbidity, mortality, re-interventions, operating time and hospital stay. Prior to surgery, imaging studies in order to assess size and possible fixation or invasion of the tumor should be performed in order to improve patient selection.

INTRODUCTION

Short-term benefits of laparoscopic colectomy for cancer include a lower morbidity rate, shorter recovery periods and fewer analgesic requirements [1,2]. Postoperative mortality rates are comparable to rates after open surgery [3]. However, in case of conversion to a laparotomy, morbidity and mortality after surgery are higher compared to planned open procedures [4,5]. In order to maximize short-term benefits and reduce hospitalization costs, a careful preoperative patient selection is important. However, due to the limited experience with laparoscopic colectomy, patient selection criteria are not clearly defined at present. The recently reported trials did not aim to define patient selection criteria.

Currently, intra-operative problems necessitating conversion to open surgery occur in approximately 20-25% of laparoscopic colectomies [2,3]. The need for conversion is a problem inherent to laparoscopic surgery. The decision to convert depends on the surgeon's assessment of the risk associated with proceeding the procedure laparoscopically. This assessment may be affected by patient characteristics, such as Body Mass Index, age and co-morbidity. It may also be influenced by complications that occur during surgery or by doubts about the possibility to perform an oncologically safe procedure. In some cases a decision to convert mainly depends on time factors. Conversions should therefore be regarded as a limit to the feasibility of laparoscopy, not as a complication of the technique.

For certain groups of patients, laparoscopic colectomy may offer substantial benefits compared with open surgery. In determining which approach is best suitable for a patient, knowledge of factors that predict conversion is necessary. Better knowledge regarding predictive factors should result in better criteria for selecting patients. This might reduce conversion rates and consequently improve short-term outcome and reduce costs. In order to study possible outcomes after conversion and to isolate any predictive factors, an analysis was carried out of patients who underwent laparoscopic colectomy within the framework of the COLOR trial (Colon cancer Laparoscopic or Open Resection).

PATIENTS & METHODS

The COLOR trial is a European randomized clinical trial, comparing laparoscopic and open surgery for colonic cancer. Patients with a single tumor of the caecum, ascending colon, descending colon aboral to the splenic flexure or sigmoid colon orally to the peritoneal deflection, were eligible for inclusion. Patients with metastasized disease were excluded from the trial, as were patients with malignancies or ipsilateral colon surgery in their medical history and patients who required emergency surgery due to intestinal obstruction. Patients with a Body Mass Index exceeding 30 kg/m2, a tumor of the splenic flexure, pre-operative indications of invasion of adjacent organs or severe cardiovascular or respiratory disease were also excluded. In total, 1248 patients were allocated to undergo either a laparoscopic or an open procedure. In the laparoscopic arm of the trial, 627 patients were included. Eighty-three patients were excluded after randomization for various reasons (see Figure I).

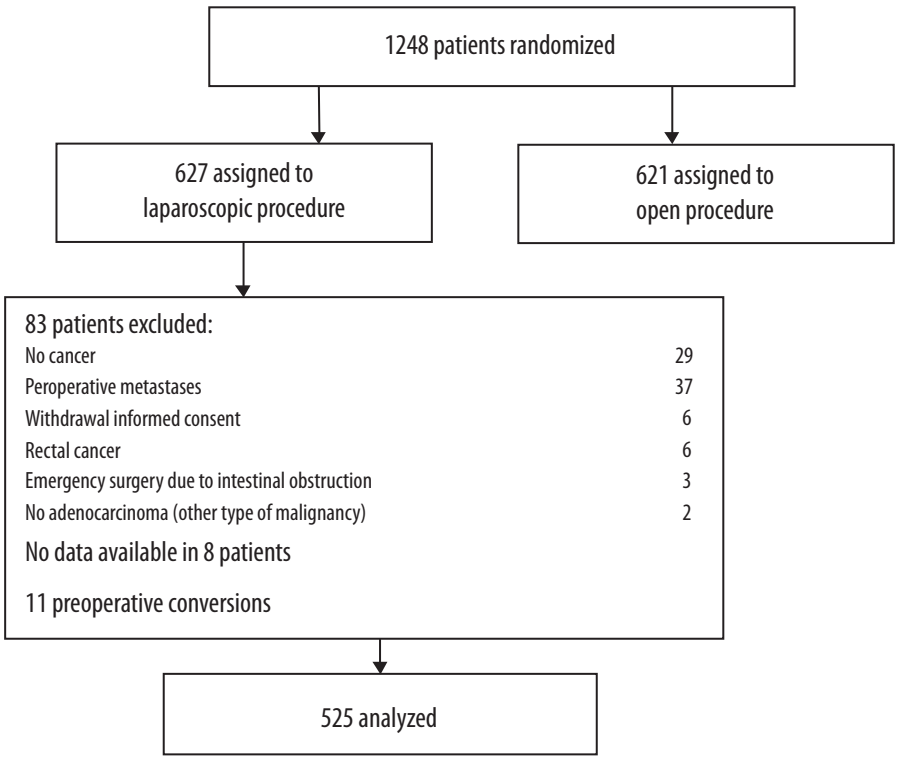

Figure I. Randomization process

Eight patients could not be analyzed due to missing data. In eleven patients, laparoscopy was converted to open surgery prior to the start of the operation due to, for instance, unavailability of the surgical team or failure of technical equipment. These patients were excluded from the current analysis, which focuses on conversions during the surgical procedure. In the remaining 525 patients, the consequences of conversion and the associated predictive factors were studied.

Data were collected centrally at the co-ordinating center in Rotterdam, The Netherlands. Randomization was performed by a computer-generated randomization list and stratified for type of resection and participating center. Approval of the Medical Ethics Committee of each participating hospital was acquired and informed consent was obtained from all patients prior to randomization.

Laparoscopic inspection, mobilization of the bowel and ligation of the main vessels were mandatory for the procedure to qualify as a "laparoscopic procedure". It was however, allowed to perform resection and anastomosis through a small incision. In cases where the procedure was commenced but could not be completed by a laparoscopic approach, as defined above, the procedure was considered "converted".

In order to identify factors that might be predictive of conversion, the following data were analyzed: age, gender, ASA classification, Body Mass Index (BMI), number of previous abdominal operations, tumor size, localization of the tumor and T-classification. Tumor staging was based on the TNM-staging criteria of the American Joint Committee on Cancer/International Union against Cancer (AJCC/UICC) [6].

To assess possible consequences of conversion during laparoscopic colectomy for cancer, data on duration of operation, postoperative complications, hospital stay and postoperative mortality were compared between converted and non-converted cases. Time in theater was defined as the total time spent in the operating theater. Skin-to-skin time was defined as time between first incision and closure of the skin. A postoperative complication was defined as a complication that occurred within 28 days after surgery or until discharge from hospital. Postoperative mortality was defined as mortality within 28 days after surgery or until the patient was dismissed from hospital. Univariate analyses to compare consequences and possible predictive factors for conversion were all performed by means of the chi-square test. P values less than 5% were considered statistically significant.

The sponsor of the trial had no influence on data collection, data analysis, data interpretation or content of the paper.

RESULTS

In total, 525 patients were included in the analysis. In 91 cases, intraoperative problems necessitated conversion to open surgery (17%). Most important reasons for converting a procedure to a laparotomy were fixation or invasion of the tumor, a bulky tumor, adhesions and problems localizing the tumor, respectively. For details regarding the reasons for conversion we refer to Table I.

Converted procedures took significantly longer to perform than non-converted procedures. The mean skin-to-skin time was 181 minutes in converted, compared to 154 minutes in non-converted laparoscopic colectomies ($p<0.001$). The total time spent in the operating theater also significantly increased in converted cases (250 vs 214 minutes for converted and non-converted procedures respectively; $p<0.001$).

Postoperative complications occurred in 30% of converted cases, compared to 18% in non-converted procedures ($p=0.013$). No difference in the occurrence of anastomosis-related complications, including anastomotic leakage, was observed between both groups ($p=0.62$). For details regarding postoperative complications see Table II.

Table I. Reasons for conversion

	N
Fixation/invasion tumour	31
Bulky tumour	8
Adhesions	8
Problems localising tumour	7
Bleeding	6
Tumour in transverse colon	4
Bad vision	4
Takes too long	3
Anatomy	3
Lymph	3
Other	14
Total	91

Table II. Converted versus non-converted procedures

	Non-converted cases (n=445)	Converted cases (n=91)	P
Skin-to-skin time (min)	154.0 ± 52.1	181.4 ± 64.0	< 0.001
Time in theatre (min)	214.4 ± 69.0	249.5 ± 83.6	< 0.001
Postoperative complications (%)	18.4	30.0	0.013
Pulmonary	1.4	1.1	0.84
Cardiac	0.5	1.1	0.46
Anastomosis related	2.1	5.6	0.62
Wound infection	3.2	6.7	0.12
Urinary tract infections	2.3	2.2	0.96
Bleeding	2.5	1.1	0.41
Ileus	2.1	1.1	0.54
Wound dehiscence	0	2.2	0.02
Other	7.2	14.4	0.02
Day of first defecation	3.5	4.5	<0.001
Postoperative re-interventions (%)	5.1	15.6	0.001
Hospital stay (days)	7.6	10.5	<0.001
Mortality (%)	0	5.6	<0.001

First defecation occurred a day earlier in non-converted cases (3.5 vs 4.5 days, p<0.001). Postoperative re-interventions occurred significantly more after converted procedures (p=0.001).

Postoperative mortality was 5.6% in converted cases as against none in the procedures that were performed laparoscopically (p<0.001). Causes of mortality were Multiple Organ Failure (n=2), sepsis (n=1), CVA (n=1), ruptured inflammatory aneurysm (n=1) and a major haemorrhage of unknown origin (n=1). In one patient, who died due to Multiple Organ Failure, an anastomotic leakage was found during re-operation.

After analyzing outcomes after converted procedures, we tried to identify factors that might predict conversions, in order to effect improved patient selection. Mean

Table III. Factors predicting conversion

	Conversion	P
Gender (%)		0.79
Male	17 (46/272)*	
Female	18 (45/253)	
ASA (%)		0.80
1	17 (23/138)	
2	17 (49/295)	
3	20 (16/82)	
4	0 (0/3)	
Body Mass Index (kg/m^2)		0.38
<25	16 (46/293)	
25	19 (40/209)	
Previous abdominal operations (%)		0.41
0	16 (51/327)	
1	18 (25/138)	
2	22 (8/37)	
3	31 (4/13)	
Performed operative procedure (%)		0.29
Right hemicolectomy	20 (49/251)	
Left hemicolectomy	9 (5/56)	
Sigmoidectomy	17 (33/197)	
Other	20 (4/20)	
Tumour size (cm)		0.001
6	14 (54/386)	
>6	27 (37/138)	
T-classification (%)		0.003
T1	15 (6/40)	
T2	11 (11/104)	
T3	18 (60/343)	
T4	40 (12/30)	

*Data given are percentage of conversions within subgroup (number of conversions/number of patients within subgroup)

age was 70.1 years for converted compared to 69.7 years for non-converted cases (p=0.73). There was no difference in the distribution of gender between both groups (p=0.79). Co-morbidity, as assessed by ASA classification, did not differ between groups (p=0.80). No significant increase in conversion rate was observed in patients with a Body Mass Index exceeding 25. However, patients with a Body Mass Index over 30 were excluded from the COLOR trial due to the protocol and thus obesity could not be analysed in this setting.

Number of previous abdominal operations was not associated with conversion risk (p=0.41). Type of performed operative procedure (right hemicolectomy, left hemicolectomy, sigmoidectomy or other) had no influence on conversion rates (p=0.29).

When the size of the tumor, as described in the pathology report, was less than 6 cm in diameter, conversion took place in 14%. In case the tumor was bigger than 6 cm, the procedure was converted in 27% (p=0.001). When invasion in adjacent structures was present (T4), the conversion risk was as high as 40% (p=0.003).

DISCUSSION

Laparoscopic colectomy for cancer has been a matter for debate for over a decade. Since its introduction in 1991 [7], surgeons have been concerned about possible non-compliance with radicality criteria for malignancy. The possibility of non-compliance was strongly suggested by reports of case series with high incidences of port-site metastases after laparoscopic colorectal surgery [8,9]. However, since the publication of long-term outcome data of two randomized clinical trials anxiety has abated. These data showed that cancer-free survival after laparoscopic colectomy for cancer is equal to or better than cancer-free survival after open surgery [2,10]. Now that long-term outcome of laparoscopic colectomy appears acceptable, short-term outcome and cost-effectiveness of the approach are of great interest.

Known benefits of laparoscopic colectomy for cancer include a lower morbidity rate, shorter recovery period and less postoperative pain [1,2]. However, there are some drawbacks to the technique as well. Although laparoscopic colectomy for cancer is as costly to society as is open surgery, it is more expensive for hospitals, due to expensive equipment and increased operating times [11]. Furthermore, there is a risk of conversion to open surgery. The current analysis shows that conversion to

laparotomy is associated with a considerable increase in both morbidity and mortality. In addition, converted procedures take longer to perform and are associated with an increase in hospital stay. Results regarding morbidity, operating time and hospital stay are comparable to those obtained by Slim et al. [4], who observed a significant increase in morbidity rate in patients requiring a converted operation (21 vs 50% in non-converted vs converted procedures respectively; $p<0.001$). In addition, operative times, duration of postoperative ileus and time until discharge from hospital were increased in patients undergoing converted laparoscopic colectomies for cancer. In a prospective review of 377 laparoscopic colorectal procedures performed by Moloo et al [5], survival rates at 2 years were lower for patients in whom the laparoscopic procedure was converted to open surgery (75.7% vs 87.2%; $p=0.02$).

These outcomes show the importance of identifying patients with a high conversion risk. Although it may be assumed that conversion will never be totally preventable, rates of conversion can be reduced by better patient selection.

Factors that might influence conversion rates are patient-, surgeon- or tumor-related. In the beginning of the laparoscopic era, strict criteria in selecting patients for laparoscopy were used. As technical equipment and surgical expertise improved, contraindications to laparoscopic colectomy evolved. Currently, most of the contraindications, such as obesity, impaired cardiopulmonary status and previous abdominal surgery, are no longer absolute [12]. In this analysis, no correlation between gender, age, co-morbidity or number of previous abdominal operations and conversion to open surgery was observed. This is comparable to other studies, which also show no correlation between conversion to open colectomy and gender [13], age [14,15] and comorbidity [5]. In addition, no correlation between BMI and conversion to open surgery was observed. However, patients with a BMI exceeding 30 were not eligible for inclusion in the COLOR trial. Therefore, we cannot analyze obesity as a possible risk for conversion. It may be assumed that obesity reduces technical feasibility of laparoscopic colectomy, since it makes clear distinction of anatomical planes more difficult. Schlachta et al. developed a clinical scoring system to predict the individual conversion risk in patients undergoing laparoscopic colorectal surgery [13]. With this scoring system they were able to accurately predict conversions using three factors: diagnosis of malignancy, experience of the surgeon and weight. A weight level of 90 kg or more was associated with an increased conversion risk. Pikarsky et al [16]

found a significantly increased conversion rate in patients with a BMI of over 30 (39 vs 14% in obese vs non-obese patients respectively, p=0.01). In a study by Pandya et al [17], conversion to open colectomy for both benign diseases and cancer occurred in 15% of 200 patients with a BMI of less than 28. Patients with a BMI exceeding 29 had their operation converted to a laparotomy in 28% of the cases ($p<0.05$). It is clear that conversion rates rise with increasing BMI. However, open surgery in obese patients is also associated with high morbidity. It is therefore difficult to say which approach should be preferred and additional evidence is needed.

In the current analysis, increased size and stage of the tumor were associated with a higher risk of conversion. The risk of conversion in T4 tumors was as high as 40%. Although most experts currently consider T4 colonic cancer an absolute contraindication, hard evidence to support this theory is still unavailable while abdominal CT scans for identification of T4 tumors are not yet routinely performed in patients undergoing laparoscopic colectomy for cancer. CT scans prior to surgery were performed in only 5% of the patients undergoing laparoscopic colectomy for cancer within the framework of the COLOR trial. Since the COLOR trial is a multi-center study in which both large university hospitals and smaller regional hospitals distributed across Europe participated, these percentages are presumably representative of European hospitals.

Laparoscopic colectomy for cancer is a technically demanding procedure, requiring advanced laparoscopic skills. Surgical dexterity is therefore presumed to be an important factor, in that it affects rate of conversion. Several studies have observed higher conversion rates in hospitals with lower case volumes [18,19]. Patient selection in laparoscopic colectomy for cancer should therefore be adapted to individual surgeon experience. Surgeons with little or no experience should comply with stricter criteria for selecting patients than highly experienced surgeons.

Conversion in laparoscopic colectomy for cancer is associated with a significant increase in morbidity, mortality, operating time and hospital stay. Prior to surgery, imaging studies to assess size and possible invasion or fixation of the tumor should be performed, permitting better patient selection.

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CHAPTER 6

Laparoscopically assisted versus open colectomy for colon cancer – a meta-analysis

The Trans Atlantic Laparoscopically assisted
versus Open Colectomy Trials Study Group

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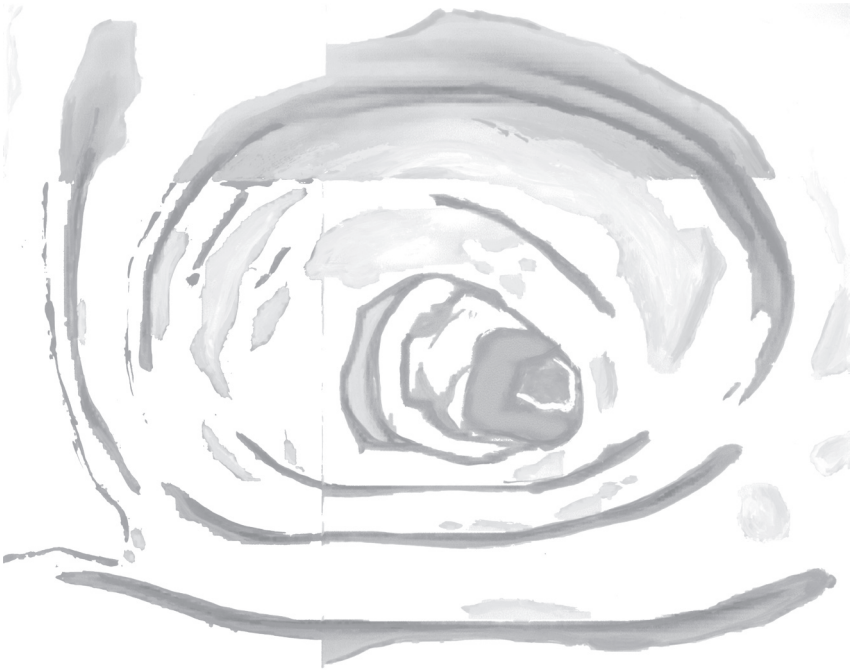

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ABSTRACT

Introduction: Laparoscopic colectomy for cancer has not yet been widely accepted due to concerns about tumor recurrence. To enhance the power in determining whether laparoscopic colectomy for cancer is oncologically safe, a meta-analysis of four trials randomizing patients with colonic cancer to either laparoscopically assisted or open colectomy (COST trial, Barcelona trial, CLASICC trial and COLOR trial) was performed.
Methods: Patients with colonic cancer randomized to these four trials who had undergone curative surgery before March 1, 2000 were studied. Three-year disease free survival and overall survival were the primary outcomes that were assessed.
Results: Of 1765 patients, 229 were excluded leaving 796 patients in the laparoscopic arm and 740 patients in the open arm for analysis. During laparoscopically assisted colectomy 11.8 lymph nodes were removed while 12.2 lymph nodes were resected during open surgery. Positive resection margins were found in 1.3 % of the specimens after laparoscopic surgery and in 2.1 % of the specimens after open surgery. Three-year disease free survival rates in the laparoscopic and open arms were 75.8 % and 75.3 % respectively (95 % confidence interval of the difference -5 % to +4 %). The associated common hazard ratio (laparoscopically assisted/ open, with adjustment for gender, age and stage) was 0.99 (P=0.92; 95% CI: 0.80-1.22). Three year overall survival rate after laparoscopic surgery was 82.2 % and after open surgery 83.5 % (95 % confidence interval of the difference -3 % to +5 %). The associated hazard ratio was 1.07 (P=0.61; 95% CI: 0.83-1.37). Disease free and overall survival rates for stages I, II and III separately did not differ between the two treatments.
Conclusion: Laparoscopically assisted colectomy for cancer is oncologically safe.

INTRODUCTION

Minimally invasive surgery for symptomatic gallbladder stones was first performed by Muhe in 1985 [1]. Since that time, laparoscopic cholecystectomy has become the treatment of choice for cholecystolithiasis because the use of small incisions is followed by less pain and earlier recovery [2]. Minimally invasive approaches to other diseases, such as small adrenal tumours and gastro-esophageal reflux, have now been adopted by the majority of surgeons as well.

A successful laparoscopic sigmoidectomy for cancer was already reported in 1991 by Jacobs and Verdeja [3]. However, reports of port site metastases after laparoscopic removal of colonic cancer caused serious concern among surgeons and halted the rapid adoption of minimally invasive surgery for colonic cancer [4,5]. Trials randomising patients with colonic cancer to either laparoscopically assisted surgery or open resection were initiated simultaneously in Europe and North America to evaluate the oncological safety of laparoscopic colectomy. The trial conducted by the Clinical Outcomes of Surgical Therapy Study Group (COST trial) in North America started in August 1994 and closed in August 2001 [6]. The Barcelona trial started in November 1993 and closed in July 1998 [7]. The Conventional versus Laparoscopic-assisted Surgery in Colorectal Cancer (CLASICC) trial in the United Kingdom accrued patients from July 1996 until July 2002 [8]. The COlon cancer Laparoscopic or Open Resection (COLOR) trial randomised patients from March 1997 to March 2003 [9]. The main outcomes of all these trials were disease free and overall survival. Three year survival data of the Barcelona trial were published in 2002 and involved 206 patients whilst the three year disease free and overall survival rates of 863 patients who had been enrolled in the COST trial were reported in May 2004 [6,7]. Both these trials showed that laparoscopically assisted colectomy resulted in similar survival rates and concluded that laparocopically-assisted colectomy was a safe procedure for cancer. However, the total number of patients in the Barcelona trial was relatively low and the conclusions of the COST trial have been debated as the confidence intervals of the differences between the two procedures in this trial were considered by some to be insufficiently wide to allow overshadowing of clinically important differences of recurrence rates between open and laparoscopic colectomy or cancer [10].

To enhance the power in determining whether laparoscopic colectomy for cancer is oncologically safe, a meta-analysis of the two published trials (COST and Barcelona trials) and two unpublished trials (CLASICC and COLOR trials) has been conducted.

METHODS

Identification of trials

Randomised clinical trials comparing laparoscopic and open surgery for colonic cancer were identified. Only trials with a primary endpoint of survival which accrued more than 150 patients with colonic cancer were included. The Barcelona (A.M.L., A.C. and S.D), CLASICC (P.J.G., H.T. and J.B.), COST (H.N. and D.J.S.) and COLOR (H.J.B., W.C.J.H., E.K., E.H., L.P.) trials fit these criteria.

Trial designs

In the COST trial, patients with adenocarcinoma of the colon were included when they were older than 18 and prohibitive abdominal adhesions were absent. Exclusion criteria included advanced local or metastatic disease, rectal or transverse colon cancer, acute bowel obstruction or perforation from cancer, inflammatory bowel disease, familial polyposis, pregnancy and concurrent or previous malignant tumours. Forty-eight centres participated in the COST trial. Laparoscopically assisted and open colectomies were performed according to similar protocols, the only difference being the manner of exposure. For laparoscopically assisted left-sided and sigmoid colectomies, mobilization of the colon as well as ligation of the vascular pedicle was performed using an intracorporeal approach. Bowel resection and anastomosis were done extracorporeally. Patients were randomly assigned to undergo either laparoscopically assisted or open colectomy. Randomisation was performed centrally and was stratified according to site of the primary tumour, ASA classification and surgeon. In total, 872 patients were randomised while 863 patients were analysed in the COST trial.

The Barcelona trial enrolled patients with colonic cancer at least 15 cm above the anal verge. Exclusion criteria were cancers located at the transverse colon, distant metastasis, adjacent organ invasion, intestinal obstruction and past colonic surgery. Both laparoscopy-assisted and open procedures were performed by a single surgical team. Initial vascular ligation was employed in both arms of the trial. In laparoscopic

procedures, wound protectors were used routinely. Randomisation was stratified for tumour location. In the Barcelona trial, a total number of 219 patients were randomized while 208 patients were included in survival analyses.

In the COLOR trial, patients with colonic cancer above the conjugate line between the promontory and the pubic bone were equally allocated to laparoscopic and open resection. Exclusion criteria were carcinomas located in the transverse colon or splenic flexure, acute intestinal obstruction, synchronous colon cancer, invasion of adjacent organs, distant metastases, previous ipsilateral colon surgery, other malignancies, body mass index greater than 30 and pregnancy. Twenty-nine centres from Western Europe participated in the trial. Similar protocols for conventional open and laparoscopic surgery were used. Randomisation was performed centrally using computerised randomisation schemes and was stratified according to participating centre and planned type of resection. At time of closure of entry of patients in the study, 1248 patients had been randomised to undergo either laparoscopic or open colectomy for cancer.

The CLASICC trial enrolled patients with a clinical diagnosis of solitary colorectal malignancy, who were at least 18 years old at the time of randomisation and suitable for elective surgical resection by left or right hemicolectomy, sigmoidectomy anterior resection or abdominoperineal resection. Patients with cancer of the transverse colon, absolute contraindications to a pneumoperitoneum, acute intestinal obstruction, malignancy within the previous 5 years or synchronous adenocarcinomas were excluded from participation. For laparoscopic left colectomies and sigmoidectomies, a suprapubic incision was made for completion of the resection and for performing an anastomosis under direct vision. It was left to the surgeon's discretion whether or not an intracorporeal anastomosis using a transanal stapling technique was employed. Randomisations were performed centrally using a computer-generated list and was stratified by surgeon, proposed site of operation, presence of liver metastases and pre-operative radiotherapy administration. Patients were allocated at a 2:1 ratio to the laparoscopic arm. 794 patients in total were recruited of which 413 had colonic cancer.

Meta-analysis

The meta-analysis was based on individual patient data focusing on both overall and disease free survival three years after randomisation. The trial statisticians of the COST, CLASICC, COLOR and Barcelona studies (D.S., J.B., H.T., W.C.J.H. and A.C.) performed the meta-analysis in collaboration. They operated under strict confidentiality conditions ruling that data of individual trials were only to be shared between the statisticians of the involved trials. The principal investigators of the four trials only had access to the pooled summary data.

Patients with colonic cancer who were randomised before March 1, 2000 within the context of the four trials and who had undergone curative surgery were included. All efforts were made to obtain complete data to at least three years after randomisation. Disease free survival and overall survival during the first three years following randomisation were evaluated and compared between the two types of surgery. Follow-up after three years of randomisation was censored. The following data were collected: unique patient identification number, date of randomisation, treatment allocation (laparoscopically assisted or open), date of surgery, age, gender, tumour stage, number of resected lymph nodes and lymph node stage, M stage, involvement of margins of the resected specimens, type of performed surgical procedure (laparoscopically assisted, conversion from laparoscopy to open or open surgery), 30 days postoperative or in hospital mortality, date and type (local, distant or combined) of first tumour recurrence, death and date of last follow-up. Tumour staging was based on the TNM-staging criteria of the American Joint Committee on Cancer/International Union against Cancer (AJCC/UICC) [11].

Since some patients had open surgery when they had been randomised to laparoscopic surgery and vice versa, both an analysis based on randomisation and another based on received treatment were performed. Patients who were converted to an open procedure remained in their allocated group for analyses.

The numbers of patients excluded from the meta-analysis with the corresponding reasons of exclusion were provided for each trial to confirm that the study populations were similar between the four trials.

Disease free survival was defined as time from randomisation to death or recurrent disease. Disease free survival and overall survival after randomisation were assessed using the Kaplan-Meier method. Univariate comparisons between the two

randomised procedures were performed using the logrank test. Multivariate analysis of these outcomes, including an assessment of heterogeneity of treatment effects between the four studies, was performed using a stratified Cox regression analysis, which was stratified by study and adjusted for stage, gender and age. A comparison of the number of lymph nodes harvested during surgery was done using analysis of variance (ANOVA). In this analysis, the number of lymph nodes was transformed logarithmically to obtain approximate normal distributions. The proportion of positive resection margins and postoperative mortality was compared between procedures using exact conditional logistic regression, with stratification by trial, and included an assessment of heterogeneity of treatment effects. All p-values given are two-sided and $p<0.05$ was considered the limit to denote statistical significance.

RESULTS

The total number of patients randomised before March 1, 2000 was 1765. Of these, 229 (13%) were excluded from this analysis, the majority for presence of distant metastases (47%) or benign colonic disease (41%) with similar patterns in the laparoscopic and open arms (Figure I). The data of the remaining 1536 patients (COST 640, COLOR 520, Barcelona 208 and CLASICC 168) were analysed. The laparoscopic arm included 796 patients and the open arm 740 patients.

Characteristics

Baseline characteristics were similar in the two treatment groups (Figure I). The mean age was 69 years in both arms and males were as frequently present as females in each treatment group. The stage distribution was similar in both arms. Stage I disease was present in 28 %, stage II in 40% and stage III in 31% of patients, while data were missing to determine the stage in 1% of patients.

The average number of lymph nodes found in laparocopically resected specimens 11.8 (SD 7.4), while 12.2. lymph nodes (SD 7.8) were found in the specimens after open colectomy. ANOVA showed that this was not significantly different ($p=0.40$), and that the difference did not significantly vary between the four studies.

Data on resection margins were missing in 43 patients (20 open and 23 laparoscopic colectomies). Positive resection margins were found in 2.1% of the specimens in the

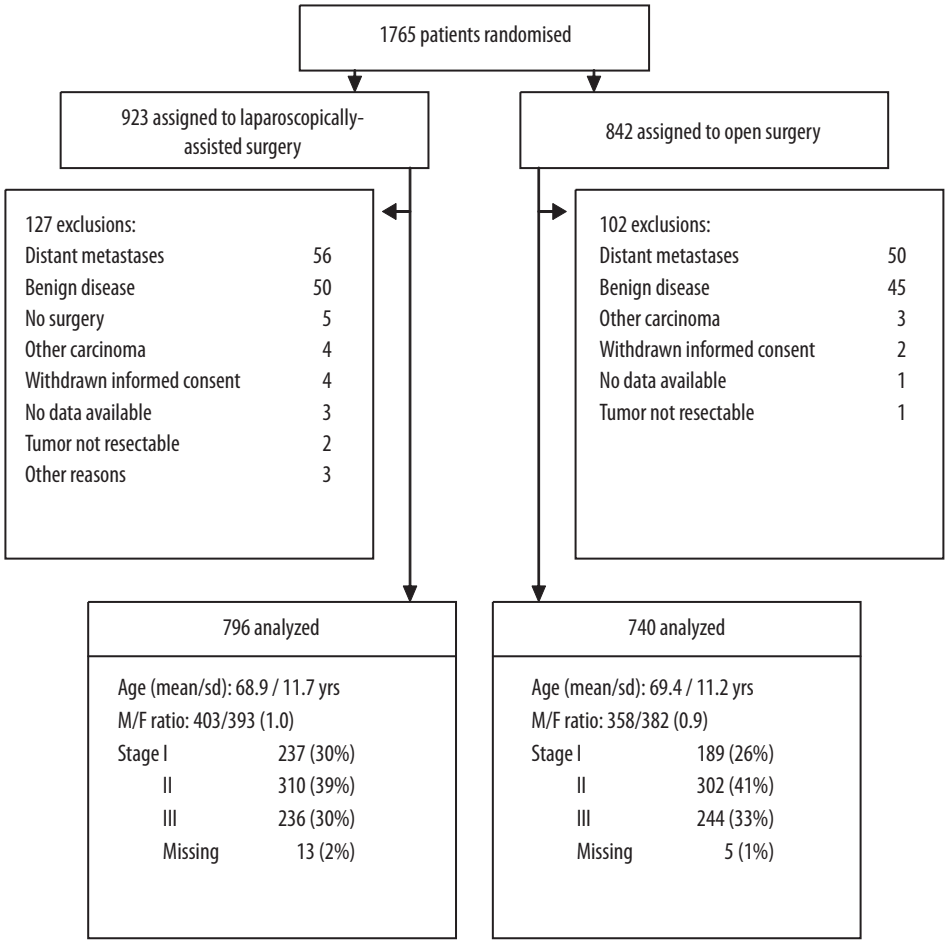

Figure I: Patient characteristics

open arm and 1.3% of the specimens in the laparosopic arm. This was not significantly different between the two groups (common odds-ratio (open/laparocopic) for positivity: 1.8 ; 95% CI: 0.7-4.5; p=0.23).

Conversion of laparoscopic to open surgery occurred in 19 % of patients. Postoperative mortality rates were 1.6 % in the open group and 1.4 % in the laparoscopic group (common odds-ratio (open/laparocopic): 1.3; 95 % CI; 0.5–3.4; p=0.63).

Survival

Analysis according to randomised treatment showed that disease free survival (p=0.83) and overall survival (p=0.56) for all stages combined after either laparoscopically assisted or open resection did not differ (Figure 2).

Three-years disease free survival in the open and laparoscopic group was 75.3% and 75.8% respectively. The 95% confidence interval (CI) for this difference (open minus laparoscopic) ranged from –5% to +4%.

The corresponding figures for overall survival were 83.5% and 82.2% respectively, with the 95% CI for the difference ranging from –3% to +5%.

For various reasons six patients had laparoscopic surgery in spite of randomisation to the open arm and 5 patients had open instead of laparoscopic surgery. The analysis of disease free survival and overall survival based on received treatment did not differ from the analyses based on randomised procedure.

Cox regression analyses for disease free survival and overall survival, stratified by trial, adjusting for tumour stage, age and gender, also did not reveal any differences

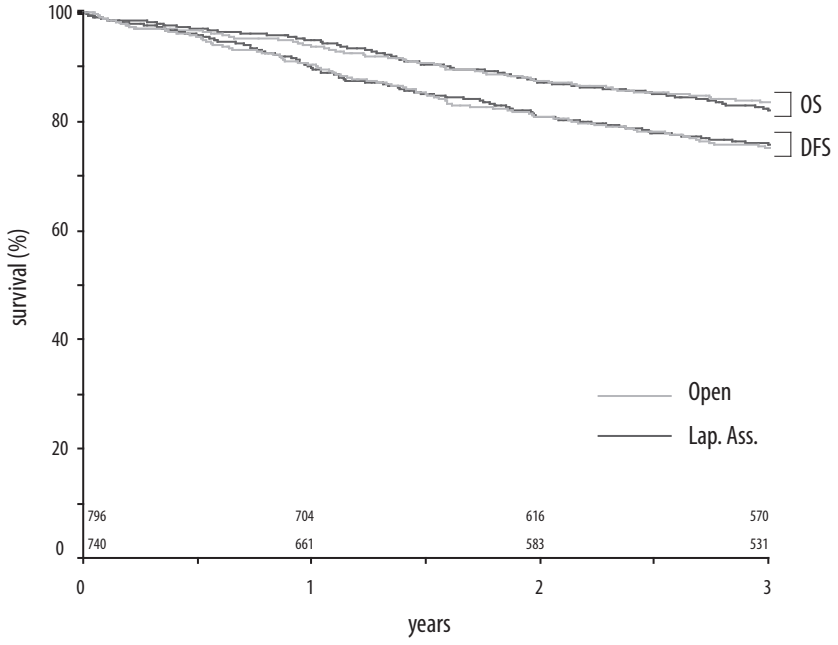

Figure 2: Disease free survival (DFS) and overall survival (OS) according to randomized open or laparoscopy assisted surgery. The numbers of patients at risk with respect to DFS for the two groups are shown at the bottom (top row: laparoscopy assisted).

Table I. Multivariate survival analysis according to various factors. Data given are hazard ratios with 95% confidence interval for disease free survival (Cox-regression with stratification by trial). ¶ Laparoscopically assisted versus open surgery.

Factor	hazard ratio	95%CI hazard ratio	P-value
Procedure¶	0.99	0.80-1.22	0.92
Stage II vs I	10.10	1.50-2.94	<0.001
III vs I	3.81	2.75-5.28	<0.001
Females vs males	0.81	0.66-0.99	0.04
Age >70 years vs ≤ 70 years	1.27	1.03-1.57	0.03

Table II. Multivariate analysis of overall survival according to various factors. Data given are hazard ratios with 95% confidence interval for overall free survival (Cox-regression with stratification by trial). ¶ Laparoscopically assisted versus open surgery.

Factor	hazard ratio	95%CI hazard ratio	P-value
Procedure¶	1.07	0.83- 1.37	0.61
Stage II vs I	1.89	1.29-2.77	<0.001
III vs I	2.88	1.98-4.20	<0.001
Females vs males	0.72	0.56-0.92	0.009
Age >70 years vs ≤ 70 years	1.81	1.40-2.34	<0.001

between both treatments (Table I and II) The treatment effects did not significantly differ between the trials, either for disease free survival (p=0.38) or for overall survival (p=0.35).

The separate hazard ratios for disease free survival of the four trials and the pooled common hazard ratio are shown in Figure 3.

Tumour recurrence was recorded in 234 patients (open 121 and laparoscopic 113). Of the 121 recurrences in the open surgery group, 40 (33%)were local, 73 (60%) were distant metastases and 8 (7%) were combined local and distant metastases. The corresponding figures in the laparoscopic group were 29 (26%), 74 (65%) and 10 (9%). These patterns did not significantly differ between the two treatment groups (Chi-square: p=0.43).

Disease free survival and overall survival according to treatment, grouped by stage, are shown in figure 4.

Significant differences were not found in any stages for disease free survival (p=0.92, 0.44 and 0.53 for stages I, II and III respectively). The associated hazard ratios (laparoscopic/open) with 95% confidence intervals were 1.02 (0.58-1.85), 1.14 (0.82-1.60) and 0.91 (0.68-1.22) respectively. Overall survival was similar between the

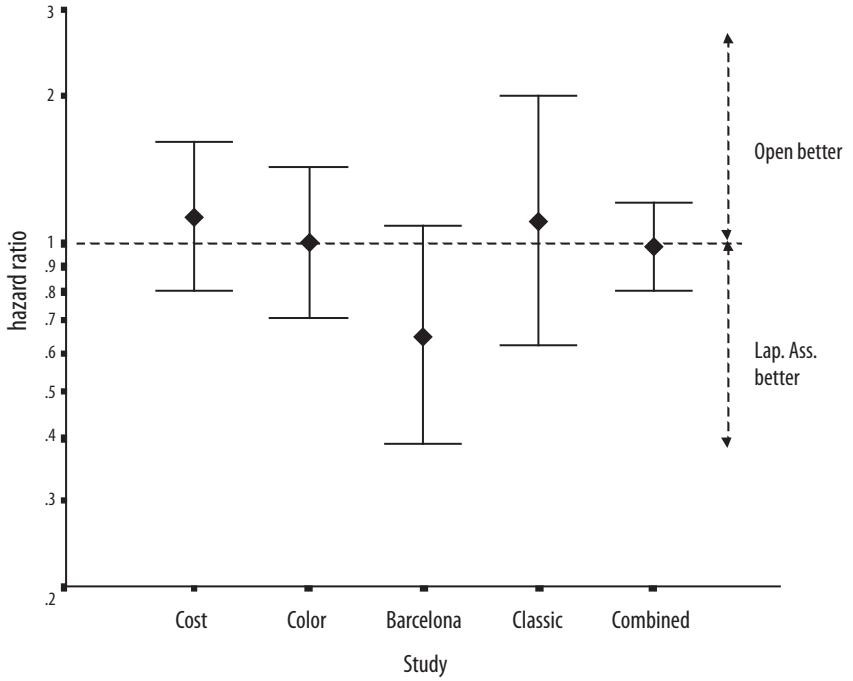

Figure 3: Hazard ratios (laparoscopy assisted / open) regarding disease free survival during the first three years after surgery, according to study and for the four studies combined (adjusted for stage, age and gender).

randomised procedures for all stages as well (p=0.78, 0.09 and 0.52 for stages I, II and III respectively).

DISCUSSION

Colorectal cancer annually affects more than 150,000 Europeans while 100,000 colonic resections are performed each year in the United States. Ageing of the Western population will increase the number of patients with colonic cancer. Although adjuvant chemotherapy can improve survival of these patients, resection of the malignant colonic tumors remains the only curative therapy. The surgical technique to resect cancer of the colon has undergone significant changes in the past decades. Turnbull et al. advocated in the late 60's no touch techniques employing early ligation of mesocolic vessel and bowel and atraumatic manipulation of the tumor to avoid spreading of tumor cells [12]. The value of reducing surgical trauma in cancer was shown by

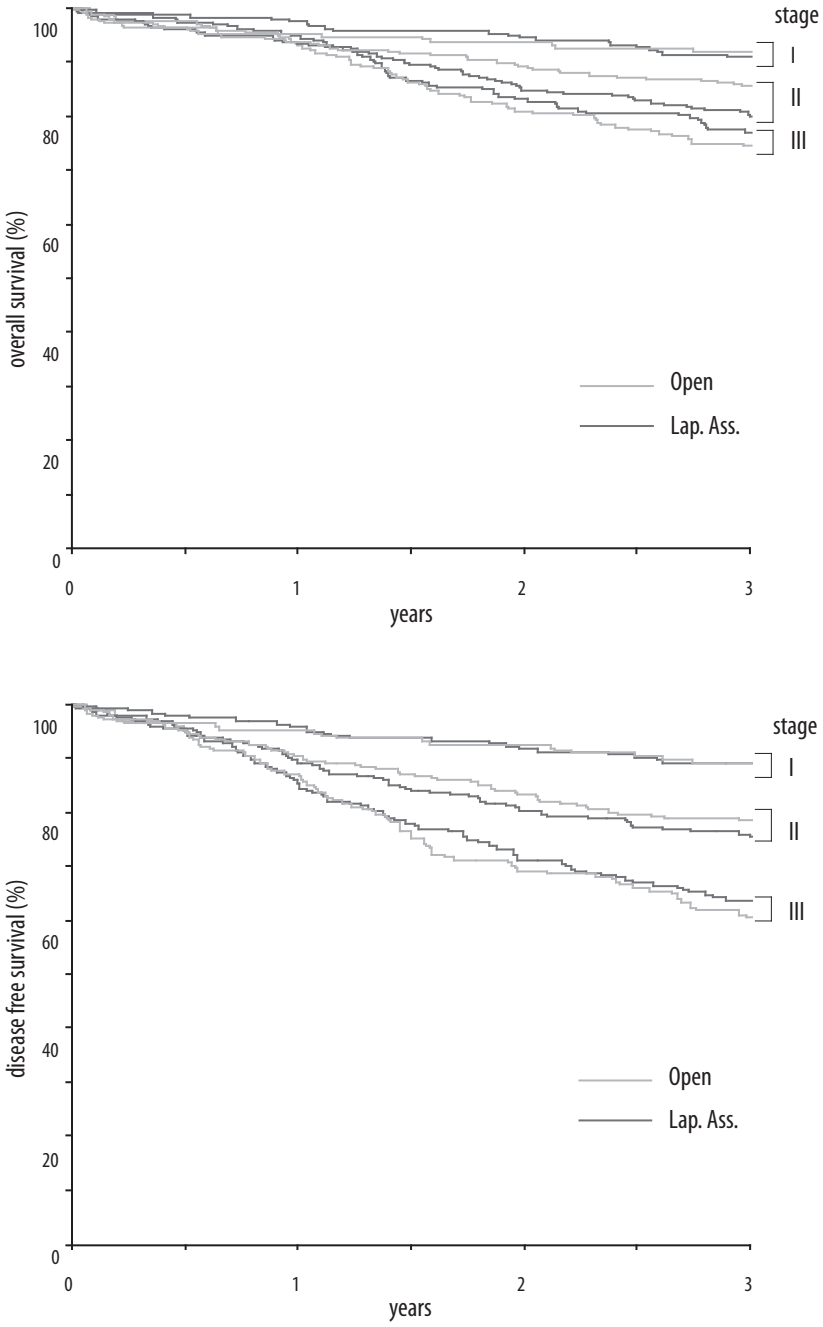

Figure 4: Disease free survival (top panel) and overall survival (bottom panel) according to randomized procedure and stage.

Eggermont et al. in an experimental study [13]. Tumor recurrence rate were found to be proportional to the extent of laparotomy wounds. The greatest advantage of laparoscopic surgery in comparison to open, conventional surgery is reduction of tissue trauma. Access to the peritoneal cavity is established through very small incisions, manual retraction of the viscera is avoided and blood loss is minimal due to meticulous dissection facilitated by videoscopic magnification. Bouvy et al. showed in an experimental study that laparocopic surgery was associated with less tumor recurrence than open surgery [14]. After initial enthusiasm about laparocopic colectomy for cancer in the early 90's, reports on port site metastases after laparocopic resection of colonic cancer withheld many surgeons from adopting this novel technique [4]. As a consequence clinical trials randomizing patients with colonic cancer to either open or laparocopic resection were initiated in the mid 90's simultaneously in North America and Europe to evaluate the oncological safety of laparoscopic colectomy. In 2001, the principal investigators of the COST, Barcelona, CLASICC and COLOR trial convened to explore pooling of data. The incentive was to provide an early robust answer based on all available evidence to the question of whether laparoscopic resection of colonic cancer is oncologically safe since long term result from individual trials were not yet available.

In 2002, Lacy et al. reported improved survival after laparoscopic colectomy in patients with stage III colonic cancer [7]. However, the outcome of this study was criticized since the total number of patients was relatively low and the study involved a single high quality laparoscopic center. The COST study group reported in 2004 similar disease free survival after either laparoscopically assisted or open colectomy for cancer [6]. The COST trial was a multicenter trial and therefore the outcome was a better reflection of general surgical practice in North America. Tinmouth and Tomlinson expressed concern that the confidence intervals of the difference were too wide in the COST trial and stated: "We can conclude with 95 percent certainty that patients who are treated laparoscopically have at most a 16 percent increase in the risk of death and 11 percent increase in the risk of recurrence [10].

This meta-analysis provides data on the largest population available to date across North America and Europe, comparing long-term outcomes after laparoscopically assisted and open surgery for colonic cancer. The current data originate from a total of 48 institutions in North America and 44 institutions in Europe and therefore the

result of this study can be generalized across North America and Europe. This study demonstrates that laparoscopic colectomy for cancer as it was performed until 2000 was oncologically as safe as open colectomy. Since 2000, experience in laparoscopic surgery has further increased and technology has advanced which should only improve the outcome of laparoscopic colectomy. The confidence intervals of the difference between open and laparoscopic colectomy both for disease free survival and overall survival were very narrow in this meta-analysis, which allows a statement that laparoscopic colectomy for cancer is safe.

Time has come to structurally integrate laparoscopic colectomy into surgical training and practice to provide this modality of care safely to all patients who are suitable to a laparoscopic procedure.

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CHAPTER 7

General discussion

Current status of laparoscopic colectomy for cancer

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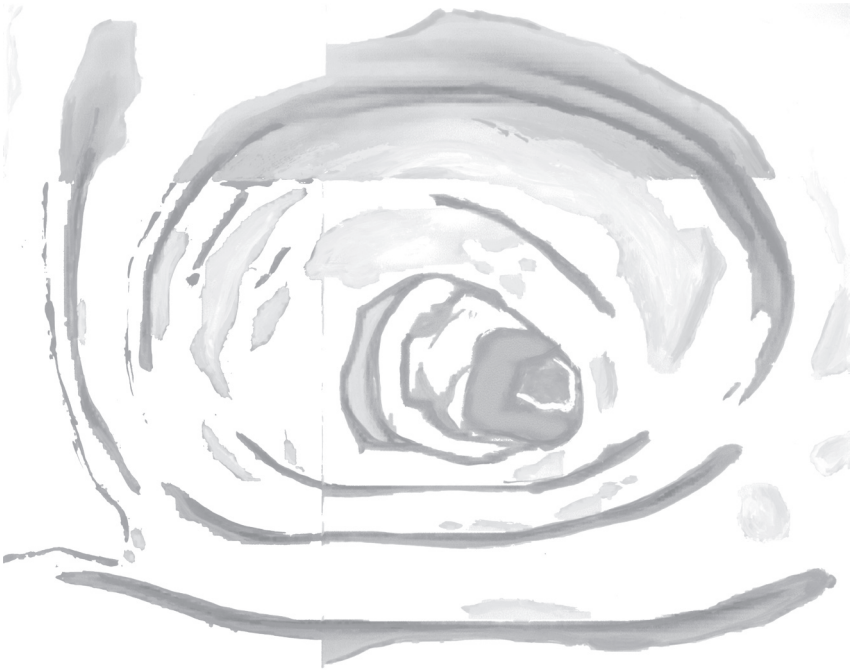

ADVANCES IN COLON CANCER TREATMENT

Colorectal cancer is the second most common cause of cancer-related death in both Europe and the United States. Survival in colon cancer patients depends on stage of disease, radicality of resection and adjuvant therapy. When distant metastases are present, the overall survival rate at 3 years after diagnosis is less than 5%. Non-metastatic colon cancer is associated with overall survival rates of approximately 75% after 3 years. Adjuvant therapy can increase survival, especially in node-positive patients. However, the only treatment with curative intent is surgical resection of the tumour.

Although survival in colon cancer patients has slightly improved over the past years, no major advances have been achieved. The modest improvements in overall survival rates are mainly due to earlier diagnosis of malignancy, alterations in adjuvant therapy and better peri-operative care. This is unlike the situation in the treatment of rectal cancer, which showed major progress during the past two decades. The introduction of the total mesorectal excision (TME) in 1982 [1] lead to a significant reduction in local recurrence rates and a rise in disease-free and overall survival. After conventional surgery for rectal cancer, local recurrences averaged 30% [2]. Due to the introduction of the Total Mesorectal Excision, in which the rectum and the mesorectum are removed en-bloc, local recurrence rates are currently below 7% at 5 years after surgery [3-5]. The sharp dissection along anatomical planes also allows for better identification and preservation of nerves, thus reducing risks of bladder and sexual dysfunction and consequently, improving quality of life.

While principles of rectal cancer surgery have been greatly altered, no major changes in colon cancer surgery have been implemented. The most important principles of radical resection in colon cancer surgery still include a high ligation of the vascular pedicle, a complete resection of the tumour and adjacent colon with free resection margins and en-bloc resection of any involved structure. Although laparoscopic colectomy for cancer is associated with improved short-term outcome compared to open surgery, most procedures are performed using an open approach.

LAPAROSCOPIC APPROACH AND SURVIVAL

While laparoscopic colectomy for cancer was already introduced in the early nineties [6] it has not been generally adopted by the surgical community. One of the main reasons for surgeons to be reluctant to embrace laparoscopic surgery for colonic cancer has been that, for a long period of time, no long-term survival data were available. The idea that laparoscopy might influence survival in colon cancer patients caused anxiety among surgeons, especially after articles on high occurrences of port-site metastases following laparoscopic surgery for colorectal malignancies were published [7,8]. These case-series reported port-site metastases after laparoscopic colorectal procedures for cancer in up to 20% of the patients.

Although experimental research showed reduced tumour growth after laparoscopy compared to open surgery, using a laparoscopic approach appeared to somehow promote tumour growth at port-sites. Extensive research was conducted in order to explain the enhanced tumour take at trocar sites. In experimental settings, possible relations between the growth of tumour cells and use of a pneumoperitoneum were examined. Leakage of gas along the trocars, the so-called "chimney effect" appeared to be associated with an increased concentration of free-floating tumour cells at trocar sites, thereby promoting tumour growth at these sites [9,10]. A correlation between the type of gas used in establishing a pneumoperitoneum and tumour cell implantation at port-sites was found [11-14]. However, results obtained are contradictory. While some authors observed increased incidences of port-site recurrences after a CO2 pneumoperitoneum compared to gasless laparoscopy [11-13], others found the exact opposite to be true [14]. Intra-abdominal pressure and temperature of the insufflation gas have also been related to the occurrence of port-site metastases in animal studies [15-17].

Yet, the most likely pathogenesis of metastases at port-sites is the direct implantation of tumour cells into wounds. It is assumed that spillage of tumour cells potentially occurs during manipulation, resection and extraction of the tumour. However, port-site metastases were also found in early-stage tumours [7,18,19] and at port-sites remote from the incision used for extraction [7,18,20]. A possible explanation for these observations is that direct contact of laparoscopic instruments with the tumour

during surgery causes spreading of tumour cells into the peritoneal cavity and onto the instruments.

At present, port-site metastases are no longer an important issue. Data on large, randomized clinical trials have now demonstrated that the incidences of wound-and port-site recurrences after laparoscopic surgery for colon cancer are comparable to rates of wound metastases after open surgery [21]. Therefore, the initial high incidence of port-site metastases might have been more of a technical issue. Currently, most surgeons use techniques, which can, at least theoretically, prevent port-site metastases. Spillage of tumour cells is reduced by avoiding both manipulation of the tumour and direct contact between the resected specimen and laparoscopic instruments. In order to prevent leakage of gas, trocars are fixated and removed when the gas, used to establish a pneumoperitoneum, has been fully evacuated through the ports. Wound protectors are also commonly used. Although it has not yet been demonstrated that these protectors are actually capable of preventing port-site metastases, it may be assumed that they avoid direct contact between tumour cells and wound edges, thus reducing the chance for malignant cells to implant. Wound excision has significantly reduced tumour implantation at port-sites in a rat model [22]. In clinical practise however, it is rarely used. Irrigation of instruments, trocars, extraction sites and trocar wounds with saline or betadine is applied by some in an attempt to reduce adherence of tumour cells. However, the value of irrigation has not been established so far. In animal studies, irrigation of port-sites with cytotoxic agents had no effect on tumour cell implantation [23]. The value of most of the measures, which have been taken in order to reduce tumour take at trocar sites, has not been proven. However, it is presumable that they cause a significant reduction in the occurrence of port-site metastases.

Soon after the problem of port-site metastases appeared to be dissolved, long-term survival data of the Barcelona trial were published [24]. In total, 219 patients with non-metastatic adenocarcinoma of the colon were included in this trial and randomized to undergo either laparoscopically-assisted or open surgery. After a median follow-up of 43 months, disease-free and overall survival were assessed. Laparoscopically-assisted colectomy appeared to be associated with an increased probability of cancer-related survival compared to open surgery ($p=0.02$). The superiority of laparoscopically-assisted colectomy was mainly due to differences in patients with stage III tumours. The authors propose that improved cancer-related survival in patients undergoing

laparoscopic surgery for cancer might have something to do with preservation of immune function. In the past, reducing surgical trauma has been related to improved preservation of immune function during and after minor surgery. However, immunological benefits of trauma reduction in major surgical procedures, such as laparoscopic colectomy for cancer, are not immediately obvious in studies published so far [25].

Although the Barcelona trial demonstrated that laparoscopic colectomy for cancer does not jeopardise survival and that the procedure might even offer long-term benefits to patients, it did not cause a rapid implementation of laparoscopic for cancer into clinical practise. Part of this was caused by the fact that the trial was criticised by some for being a single centre, single surgeon experience with a relatively low number of patients.

When survival data on the Northern American COST trial were published in 2004, surgeons developed a more positive attitude towards laparoscopic colectomy for malignancy [26]. After a mean follow-up of 4.4 years, similar rates of recurrent cancer were observed after laparoscopically-assisted and open colectomy in 863 patients with non-metastatic colon cancer. The authors concluded that the laparoscopic approach is an acceptable alternative in the surgical treatment of colon cancer.

To enhance the conclusions, drawn from the trials mentioned above, a meta-analysis was performed [27]. Data on patients with a three year follow-up, who were included in one of the four large randomized clinical trials comparing laparoscopic and open surgery for colon cancer, were pooled. The analysis allowed for proper subgroup analyses on tumour stage. In 1536 patients, no differences in disease-free and overall survival at three years after surgery were observed between patients undergoing either laparoscopically-assisted or open colectomy for cancer. Subgroup analyses on tumour stage showed no difference in survival either. And although we have to keep in mind that these data are only applicable to a selected patient population, this analysis has a power big enough to enable us to, finally, conclude that it is safe to perform laparoscopic colectomy in case of malignant disease.

SHORT-TERM BENEFITS

Data on short-term outcome of several prospective randomized trials comparing laparoscopic-assisted and open colectomy for cancer have been published [21,24,

28-30]. Lacy et al. [24] observed a significantly increased operating time in laparoscopically-assisted compared to open surgery. However, blood loss during surgery and morbidity after surgery were lower and recovery of bowel function and initiation of oral intake were faster in patients undergoing laparoscopically-assisted colectomy. These observations are similar to results obtained within the COLOR trial, in which laparoscopic colectomy for cancer was associated with less blood loss, an earlier restoration of bowel function and a shorter hospital stay. In addition, laparoscopic colectomy was related to reduced analgesic requirements and less post-operative pain [28]. In an article by Weeks et al. [21], short-term quality-of-life outcomes following laparoscopic-assisted colectomy and open colectomy for cancer were addressed. A slightly improved quality-of-life at 2 weeks after surgery was found in the laparoscopic arm of the trial. In a study by Stage et al. [29], patients undergoing laparoscopic colectomy for cancer were discharged earlier and suffered less pain compared to patients receiving open surgery. These results were comparable to the results obtained by Schwenk et al. [30], who observed reduced analgesic requirements and pain after laparoscopic colorectal surgery for cancer. In addition, patients undergoing laparoscopic surgery experienced less fatigue. As a consequence, duration of recovery was shortened.

Although most randomized clinical trials, published so far, show an improved short-term outcome after laparoscopic treatment of colonic cancer, differences are not marked. However, one has to keep in mind that it is presumable that a significant learning curve was still present in some of these trials.

The link between hospital case volume and survival has been thoroughly investigated in non-randomized studies, focussing on open colorectal surgery [31-33]. Only a few studies addressed the impact of hospital case volume on short-term outcome after open colorectal cancer surgery [34-37]. Higher hospital case volume has been related to lower complication rates and reduced postoperative mortality in most of these studies [34,36,37]. The association between hospital case volume and short-term outcome after laparoscopic colectomy for cancer has been analysed in a randomized setting within the framework of the COLOR trial [38]. Higher hospital case volume was associated with reduced operating times, lower conversion rates, quicker recovery of bowel function, less post-operative complications and a reduced hospital stay. An analysis on short-term outcome in a high case volume hospital might therefore show differences between laparoscopic and open surgery for colon cancer that are

much more pronounced than results obtained so far. Furthermore, no well-defined criteria to select patients for laparoscopic colectomy are currently available. Conversion of laparoscopic colorectal procedures is associated with a significant increase in both morbidity and mortality [39-41]. Defining criteria to select patients might therefore improve future outcome. So far, several studies tried to identify risk factors for conversion in laparoscopic colorectal surgery. In a prospective study of 1658 patients performed by Marusch [39], patients requiring a conversion were significantly heavier. Rectum resections were also associated with an increased risk of conversion. Schlacta tried to develop a scoring system to predict the individual risk of conversion to open surgery in laparoscopic colorectal procedures [42]. The three factors found to be predictive of conversion were diagnosis of malignancy, surgeon experience and weight level.

In studies focussing on laparoscopic colectomy for malignancy, conversion appears to be associated with invasion of the tumour into surrounding structures, size of the tumour and hospital case volume [38,41]. Imaging studies to assess size and possible fixation of the tumour should therefore be performed prior to surgery and selection criteria should be adjusted to individual surgeon experience. In addition, when a conversion is necessary, the decision to do so should be made early on in order to avoid lengthy dissections.

COSTS ASSOCIATED WITH LAPAROSCOPIC COLECTOMY FOR CANCER

Now that long-term data are available, other issues have become more important. Do short-term benefits associated with laparoscopic surgery justify financial investments and efforts that have to be undertaken in order to obtain skills? How about hospital costs and costs for society?

Data regarding costs associated with laparoscopic colectomy for cancer are not readily available. Only one randomized clinical trial has, up until now, addressed this issue [43]. In this short-term cost analysis, which was performed on a Swedish subset of patients included in the COLOR trial, costs to the health care system were significantly higher for laparoscopic compared to open surgery (E9479 versus 7235; p=0.018). However, in contrast to data on the entire patient population of the COLOR trial, the Swedish subset showed no difference in length of stay between the laparo-

scopic and open arms of the trial. According to the authors, this could be explained by tradition and standardised routines of discharge. At 12 weeks after surgery, total costs for society as a whole were similar in both arms (E11660 versus E9814 for laparoscopic and open surgery respectively; p = 0.104).

Several other studies analysed costs of laparoscopic colectomy for cancer in a non-randomized setting. In a retrospective cost analysis performed by Philipson et al. [44], both hospital costs and costs for society were higher for laparoscopically assisted right hemicolectomy compared to open right hemicolectomy for cancer. Increased costs of laparoscopic colectomy were a direct result of significantly increased operating room utilization time and a greater cost of disposable instruments. Muser and co-workers performed a costs analysis on 24 patients undergoing laparoscopic colectomy for either a benign disease or cancer [45]. They compared their outcomes to a historical group of open colon surgery patients. Average total hospital costs were lower for laparoscopic colectomy.

Most studies published so far showed increased costs associated with a laparoscopic approach. Development and refinement of endoscopic instruments, together with improvement of surgical techniques, might lead to a reduction in operating time in the future. Increased use of nondisposables or reduced costs of disposables might also reduce future costs. However, it may very well be, that laparoscopic colectomy for cancer turns out to be more expensive for hospitals. In addition, costs associated with teaching and training laparoscopic skills are difficult to determine. No clear figures on the costs of implementation of laparoscopic colectomy for cancer are yet available. So the question remains are we willing to pay more in order to enable patients to benefit from improved short-term outcomes?

OVERCOMING THE LEARNING CURVE

The concept of "see one, do one, teach one" has become obsolete. Particularly in case advanced skills are required, such as in minimally invasive surgery, it is generally felt that it is no longer acceptable to acquire those skills by practising on patients [46]. Furthermore, working hours of residents have been cut down, which means that training will have to become more efficient in order to gain the same level of dexterity in a reduced amount of time. Costs of operating room time have increased, while overall

resources available for healthcare have been reduced. These new developments offer a big challenge to those, in charge of developing surgical training programs.

Limitations inherent to laparoscopic surgery, such as loss of depth perception, reduced tactile feedback and a declined range of motion have created a necessity for new training modalities. Minimally invasive surgery requires skills that are not routinely used during open surgery. Therefore, training of these skills has to become a part of every surgical resident's training program. In addition, surgeons require training in order to incorporate laparoscopy into their clinical practices. Teaching of laparoscopic skills can be done in laboratory settings, using box-trainers, virtual reality trainers, animals or cadavers. However, questions have been raised whether the obtained skills can be transferred to the operating theatre. Until now, the value of training *in vitro* has not been well established. Virtual reality training, for instance, was introduced in 1991 [47]. Large, randomized trails evaluating the efficacy of training in a virtual reality environment are not yet available. However, the value has been demonstrated in smaller randomized studies. In a study that was recently published by Grantcharov et al. [48], training by means of virtual reality significantly reduced intraoperative errors in laparoscopic cholecystectomy.

In vitro training is not yet available in every single teaching hospital. Results of a enquiry, held among members of the European Surgical Association, showed that over half of the members believed that laparoscopic skills training should start at the beginning of the residency program [49]. However, only 14% currently used objective measures to assess manual dexterity of trainees in their institutions.

We still have a long way to go in order to develop an effective laparoscopic training program. Furthermore, we have to keep in mind that, although in vitro training may be a way to overcome early learning curves, it will never replace the experience of performing procedures in *real* patients.

Laparoscopic colectomy can be performed safely in case of malignancy and offers several short-term benefits to patients. The laparoscopic approach is associated with increased costs for hospitals. Better selection of patients and effective training of laparoscopic skills might improve future outcomes of laparoscopic colectomy for cancer.

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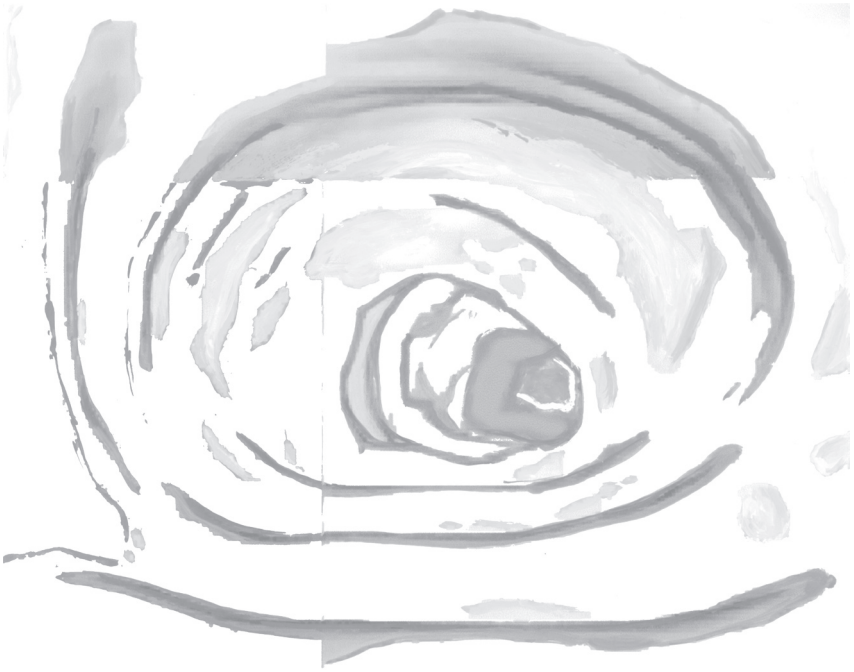
CHAPTER 8

Summary



Chapter 1 provides the general introduction to this thesis. It gives a short overview on the status of laparoscopic colectomy for cancer prior to the initiation of the COLOR trial, on which a large portion of this thesis was based. The aims of the thesis are represented.

In **Chapter 2**, a review on the immunological consequences of laparoscopic colectomy for cancer is performed in order to answer the first question *"Is there evidence based support on the impact of laparoscopy on local and systemic immune responses?"*. Most studies published so far show an increased local immune response after laparotomy compared to laparoscopy. A carbon dioxide pneumoperitoneum appears to be related to decreased peritoneal macrophage function in animal studies. Systemic immune responses are diminished in minor laparoscopic surgery, probably due to the fact that a laparoscopic approach is associated with less tissue trauma in these cases. For major surgical procedures, such as colorectal surgery for cancer, immunological benefits of laparoscopy are less obvious. A definite answer to the question of how immune function is altered after laparoscopic and open colectomy requires additional evidence, preferably from large randomized clinical trials.

In **Chapter 3**, the short-term results of the COLOR trial are presented. Within this chapter, we tried to answer the question: "*Is laparoscopic surgery for colonic cancer safe from an oncological point of view?*". In total, 1248 patients were randomized to undergo either laparoscopic or open surgery for non-metastasised colonic cancer. Postoperative histopathological examination did not show any differences between laparoscopically and conventionally resected specimens. No differences in the number of harvested lymph nodes or the number of positive resection margins was observed between both arms of the trial. In conclusion, laparoscopic surgery allows safe and radical resection of colonic cancer.

The next question we aimed for was: *"Does the manner of approach alter short-term outcome after colonic cancer surgery"*. No differences in morbidity or mortality were observed between patients undergoing laparoscopic or open surgery. Laparoscopic colectomy for cancer was associated with less blood loss, a quicker recovery of bowel function, reduced analgesic requirements and a shorter hospital stay compared to

open surgery. Operating times were significantly increased in laparoscopic procedures.

After open colorectal cancer surgery, high hospital case volume has been related to improved outcome. **Chapter 4** addresses the influence of hospital case volume on short-term outcome after laparoscopic colectomy for cancer. With this study, we tried to answer the question: *"Is hospital case volume associated with short-term outcome after laparoscopic colectomy for cancer?". S*hort-term results of laparoscopic colectomies, performed within the framework of the COLOR trial, were compared between hospitals with a low, medium or high caseload. Operating times were significantly reduced in hospitals with high caseloads. Furthermore, conversion rates were lower and the number of harvested lymph nodes was higher in high case volume hospitals. Post-operative complications and hospital stay were both reduced in hospitals with high caseloads. This study clearly shows a significant relation between the caseload of a hospital and outcome after laparoscopic colectomy for cancer.

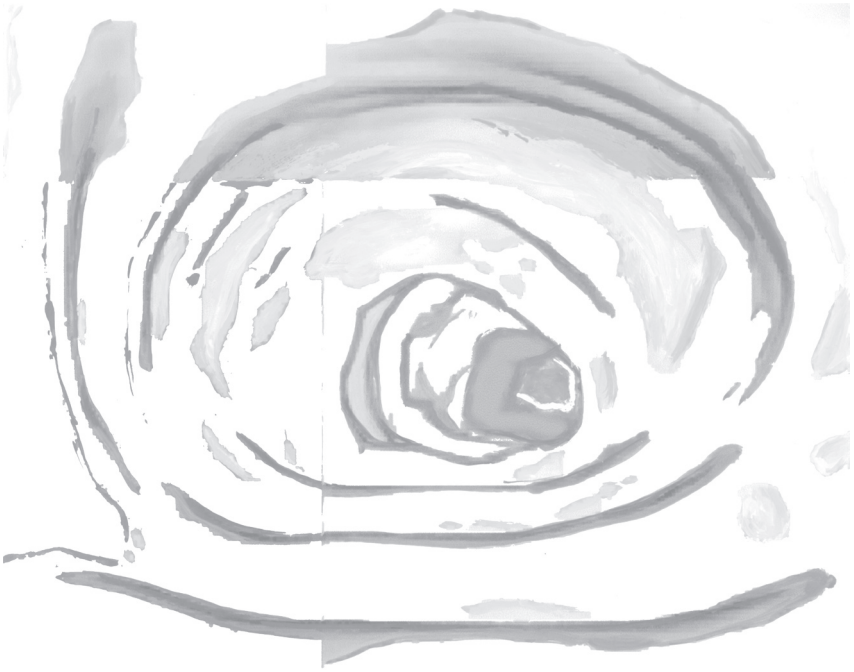
Converting a laparoscopic colectomy for cancer has been associated with an increase in both morbidity and mortality. However, strict criteria to select patients for laparoscopic colonic cancer surgery are not yet available. In **Chapter 5**, converted procedures were studied. Patients undergoing laparoscopic colectomy within the framework of the COLOR trial were included in the analysis. Converted procedures took significantly longer to perform compared to non-converted cases. Furthermore, they were associated with increased post-operative morbidity, mortality, occurrence of re-interventions and hospital stay. Overall, patients in whom the laparoscopic procedure had been converted did significantly worst during the immediate post-operative period. We performed this study in order to answer the question: *"Can we identify predictive factors of conversion, enabling a better patient selection?".* Two predicting factors were identified, namely: T-stage and size of the tumour. Fixation or invasion of the tumour to surrounding structures (T4) and tumour size > 6 cm was associated with a significant increase in conversion rate. In order to improve patient selection, imaging studies should be performed, enabling identification of patients with fixated or bulky tumours.

When evaluating a treatment for cancer, survival should always be the primary outcome measure. In **Chapter 6,** a meta-analysis on large randomized clinical trials comparing laparoscopic and open surgery for colonic cancer is presented. We aimed to answer the following question: *"Is cancer-free survival and overall survival comparable between patients undergoing laparoscopic surgery and open surgery for colonic cancer?".* After analyzing 1536 patients who underwent either laparoscopically assisted or open surgery for non-metastasised colonic cancer, no difference in 3-year disease-free or overall survival was observed. Subgroup analysis on tumour stage also showed no significant differences. This study has a power that is big enough to enable us to conclude that there is no difference in survival between patients undergoing laparoscopically assisted or open surgery for colonic cancer.

Chapter 7 provides a general discussion on laparoscopic colectomy for cancer and an overview of the current literature. Survival, short-term outcome and costs of laparoscopic colectomy for cancer are discussed as well as ways to implement laparoscopic colectomy for cancer into clinical practise and into the training program of surgical residents. Disease-free and overall survival rates after laparoscopic surgery for colonic cancer are comparable to rates after open surgery. The laparoscopic approach is associated with improved short-term outcome, such as a shorter recovery period, a quicker recovery of bowel function, a shorter hospital stay, less pain, a reduced use of analgesics and better cosmesis. The laparoscopic procedure is associated with higher costs for healthcare. Costs for society appear not to be increased compared with open surgery.

CHAPTER 9

Nederlandse samenvatting



In **Hoofdstuk 1** vindt u de algemene introductie. Er wordt een kort overzicht gegeven omtrent de stand van zaken met betrekking tot de laparoscopische chirurgie voor colon carcinoom voorafgaande aan de initiatie van de COLOR trial, waarop een groot deel van deze promotie is gebaseerd. De doelstellingen van de promotie worden weergegeven.

Hoofdstuk 2 bestaat uit een review van de literatuur met betrekking tot de immunologische gevolgen van laparoscopische chirurgie. De meeste studies die tot dus ver zijn gepubliceerd laten een toegenomen lokale immuun respons zien na laparotomie in vergelijking met laparoscopie. Een carbondioxide pneumoperitoneum lijkt gerelateerd te zijn aan een afgenomen functie van peritoneale macrofagen in dierexperimentele studies. De systemische immuun respons is afgenomen bij kleine laparoscopische ingrepen, waarschijnlijk doordat de laparoscopische benadering in dit geval geassocieerd is met minder weefselschade. In het geval van grote chirurgische ingrepen, zoals colorectale chirurgie voor maligniteiten, zijn de immunologische voordelen van laparoscopie minder duidelijk. Om een definitief antwoord te kunnen geven op de vraag hoe immuun functie wordt beïnvloed door chirurgische benadering is additioneel bewijs nodig, het liefst in de vorm van grote, gerandomiseerde studies.

In **Hoofdstuk 3** worden de korte termijn resultaten van de COLOR trial gepresenteerd. In totaal werden 1248 patiënten met ongemetastaseerd colon carcinoom gerandomiseerd om een laparoscopische dan wel een open procedure te ondergaan. Postoperatief histopathologisch onderzoek liet geen verschillen zien tussen laparoscopisch of open gereseceerde preparaten. Er werd geen verschil gevonden in het aantal verwijderde lymfklieren of in het aantal positieve resectievlakken tussen beide groepen. We kunnen dan ook concluderen dat laparoscopische chirurgie veilig is vanuit oncologisch oogpunt gezien en dat het mogelijk is om met behulp van deze benadering een radicale resectie uit te voeren van een maligniteit van het colon.

De korte termijn uitkomsten na laparoscopische en open resectie van colon carcinoom werden geanalyseerd. Er werd geen verschil in morbiditeit of mortaliteit gevonden tussen patiënten die laparoscopische of open chirurgie hadden ondergaan. De laparoscopische benadering was geassocieerd met minder bloed verlies, een sneller

herstel van de darmfunctie, een verminderd gebruik van analgetica en een kortere opnameduur in vergelijking met open chirurgie. De operatieduur was significant toegenomen in laparoscopische procedures.

Na open colorectale chirurgie schijnt een hoog "case volume"* geassocieerd te zijn met verbeterde uitkomsten. **Hoofdstuk 4** is gewijd aan de invloed van case volume op korte termijn uitkomsten na laparoscopische chirurgie voor colon carcinoom. De korte termijn uitkomsten van patiënten die een laparoscopische colectomie ondergingen in het kader van de COLOR trial werden vergeleken tussen ziekenhuizen met een hoog, medium of laag case volume. De operatieduur was significant verminderd in ziekenhuizen met een hoog case volume. Het aantal conversies was lager en het aantal verwijderde lymfklieren was hoger in deze ziekenhuizen. Het aantal postoperatieve complicaties en de opname duur waren beiden verminderd in ziekenhuizen met een hoog case volume. Deze studie laat een duidelijke relatie zien tussen het case volume van een ziekenhuis en uitkomsten op korte termijn na laparoscopische chirurgie voor colon carcinoom.

Conversie van een laparoscopische colectomy is geassocieerd met een toename van zowel morbiditeit als mortaliteit. Duidelijke criteria om patiënten met colon carcinoom te selecteren voor laparoscopische chirurgie zijn echter nog niet voor handen. In **Hoofdstuk 5** worden gegevens van patiënten die een geconverteerde laparoscopische procedure ondergaan geanalyseerd. Geconverteerde procedures duurde langer dan niet-geconverteerde laparoscopische colectomieën. Tevens was conversie geassocieerd met een toegenomen postoperatieve morbiditeit, mortaliteit, kans op re-operatie en opname duur. Patiënten bij wie de laparoscopische procedure moest worden geconverteerd deden het significant slechter in de postoperatieve periode. Er werden twee voorpellende factoren voor conversie gevonden: T-stadium en grootte van de tumor.

Om selectie van patiënten te verbeteren moet er beeldvormend onderzoek plaats vinden voor de operatie, zodat patiënten met ingegroeide of grote tumoren kunnen worden geïdentificeerd.

---

*Case volume = aantal van een bepaalde procedure dat binnen een bepaalde tijd wordt uitgevoerd.

In de beoordeling van een nieuwe therapie voor een maligne aandoening is overleving altijd het belangrijkste eindpunt. In **Hoofdstuk** 6 presenteren we een meta-analyse van grote gerandomiseerde klinische trials die laparoscopische chirurgie en open chirurgie voor colon carcinoom met elkaar vergelijken. Na analyse van de gegevens van 1536 patiënten die laparoscopisch-geassisteerde of open chirurgie hadden ondergaan werd er geen verschil gevonden in ziektevrije en totale overleving 3 jaar na de operatie. Subanalyse per tumor stadium laat ook geen significante verschillen zien.

Hoofdstuk 7 bestaat uit een algemene discussie over laparoscopische chirurgie bij colon carcinoom en geeft een overzicht over de literatuur die op dit moment bekend is. Overleving, korte termijn resultaten en kosten worden besproken, alsmede manieren om laparoscopische chirurgie voor colon carcinoom te implementeren in de kliniek en in de opleiding van de assistenten. De ziektevrije en totale overleving na laparoscopische chirurgie voor colon carcinoom is gelijk aan die na open chirurgie. De laparoscopische benadering is geassocieerd met voordelen voor de patiënt, zoals een sneller herstel van de darmfunctie, een kortere opnameduur, minder pijn, een verminderd gebruik van pijnmedicatie en een beter cosmetisch resultaat. De laparoscopische procedure brengt hogere kosten voor de gezondheidszorg met zich mee vergeleken met open chirurgie. Kosten voor de samenleving lijken echter niet toegenomen.

CONTRIBUTORS TO THE COLOR TRIAL

Chaper 3, 4 and 5 of this thesis are based on data derived from the COlon cancer Laparoscopic or Open Resection (COLOR) trial. On the next few pages you will find the names of the people that contributed to this trial.

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LIST OF PUBLICATIONS

E. Kuhry, M.P. Jansen, C. Vermeij-Keers, et al. Additional malformations in patients with metopic synostosis: a retrospective study, Abstracts of the fourth annual meeting of the European Conference of Scientist and Plastic Surgeons. *Eur J Plast Surg 2001; 224: 221*

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