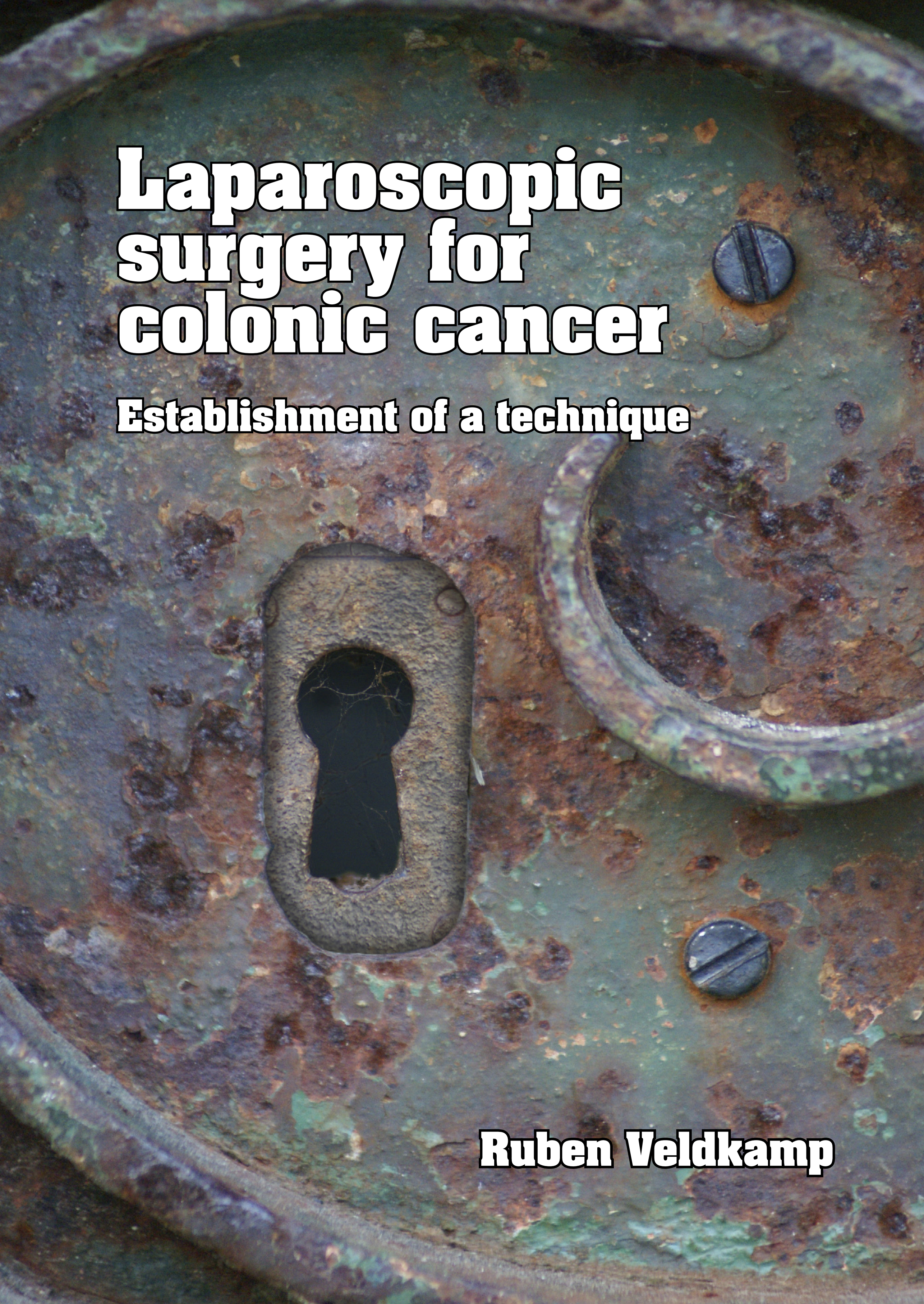
Laparoscopic surgery for colonic cancer

Establishment of a technique



Ruben Veldkamp

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Front cover: Keyhole in garden gate in Tourteron, France; photographed by R. Veldkamp, September 3rd, 2011

ISBN 978-94-6169-147-7

Published online: www.laparoscopicsurgeryforcoloniccancer.eu

Design: Optima Grafische Communicatie, Rotterdam, The Netherlands (www.ogc.nl)

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Establishment of a technique

Laparoscopische chirurgie voor het coloncarcinoom
Een techniek bevestigd

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de Rector Magnificus

Prof. Dr. H.G. Schmidt

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
Woensdag 26 oktober 2011 om 13.30 uur

door

Ruben Veldkamp
Geboren te Hilversum

ERASMUS UNIVERSITEIT ROTTERDAM

PROMOTIECOMMISSIE

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Introduction and outline of the thesis

INTRODUCTION

Colorectal carcinoma is one of the most frequent forms of cancer in the Western society. It is the second largest cause of cancer related death for men and women. In the European Union an estimated three-hundred and eighty thousand men and women are diagnosed and over two hundred thousand men and women die of cancer of the colon and rectum annually[1].

Segmental resection of the colon is the only curative treatment option for colon cancer and can only be curative if the cancer is in its early stages and no distant spread has occurred. Prognosis for survival is strongly dependent on the stage of the disease. The earlier the colorectal malignancy is diagnosed, the better the prognosis for survival. In early stages of colon cancer, when the tumor is entirely confined to the intestinal wall and lymph node or distant metastases are absent, prognosis for survival is quite good, in the 90% range for a permanent cure. The chance for a cure declines substantially in people whose cancer has escaped outside the bowel wall through penetration or distant spread. If a tumor has penetrated through the bowel wall into the tissues closely surrounding the bowel wall, the prognosis declines to somewhere around 50% for cure, and if the regional lymph nodes are involved the prognosis for a cure declines to the 25-35% range. If distant organ spread has occurred, for example to the liver, the chances for cure become rare indeed[2].

To approach the colon a laparotomy is performed, the site of which depends on the localization of the tumor and the preferences of the surgeon. Most colorectal surgeons recommend sufficient resection of the affected part of the colon, with preferred distal and proximal tumor-free margins of at least 5 cm and resection of the mesocolon with its lymphatic tissue.

The introduction of laparoscopy into the field of general surgery, although a relatively recent development, has emerged from techniques developed in over a century. In the early 1930's, the first reports of laparoscopic interventions for non-diagnostic purposes were published. Initial procedures included lysis of abdominal adhesions and diagnostic biopsies of abdominal organs under direct visualization. Throughout the 1960's and 1970's, laparoscopy became a vital part of gynecological practice. Despite these technological advances, it was not until after 1986, following the development of a video computer chip that allowed the magnification and projection of images onto television screens, that the techniques of laparoscopic surgery truly became integrated into the discipline of general surgery. In 1987, the first cholecystectomy was performed through laparoscopy[3]. Minimally invasive techniques diminished the additional tissue damage during surgery, necessary to approach the target organ. Patients experienced less postoperative pain, less use of analgesics and could be discharged of the hospital sooner. Encouraged by these results, this new technique was soon adapted throughout the surgical community. The technique has become the standard for gallbladder surgery[4]. The rapid acceptance of the technique of laparoscopic surgery by the general population is unparalleled in surgical history. It has changed the field of general surgery more drastically and more rapidly than any other surgical milestone[5].

Since then, laparoscopy has developed itself in an overwhelming pace. With the widespread use of laparoscopy, the quality of camera and instruments and the experience of the surgeon improved. Minimal invasive techniques are now used for a wide array of surgical procedures, i.e. appendectomy, donor nephrectomy, groin hernia surgery, bariatric surgery and endocrine surgery.

Early experience with laparoscopic colectomy involved predominantly right hemicolectomy and sigmoidectomy for benign colon disease such as polyps and diverticulitis. With growing experience, the technique was also used for cancer surgery. For laparoscopic surgery to be introduced as a new technique in colon cancer surgery, oncological radicality of laparoscopic colectomy should mirror that of open colectomy, which is considered the gold standard.

Jacobs and Verdeja first reported laparoscopic resection of colon cancer in 1991, only 5 years after the first laparoscopic cholecystectomy[6]. This early report incinerated enthusiasm among surgeons to employ laparoscopic techniques in patients with colonic cancer. Short-term advantages, demonstrated for laparoscopic cholecystectomy, were also expected for laparoscopic colectomy.

However, as in all cancer treatment, the most important outcome is disease free survival. Despite the anticipated advantages of laparoscopic colonic resection in the short term, minimal invasive cancer surgery can only be regarded to be an alternative to open surgery if survival of laparoscopic surgery is not worse than that of open surgery.

In 1994, Berends et al. reported port-site metastases in 3 (21%) out of 14 laparoscopically operated patients[7]. Thereafter, apparent high rates of port-site metastases have been the focus of many reports on laparoscopic resection of colon cancer and various case reports and case series reported in total over 80 port-site metastases after laparoscopic resection of colon cancer. Although the exact incidence of abdominal wall metastasis following open colon cancer resection is not known, it is rare and estimated to be less than 1%.

These case reports turned initial optimism to treat colon cancer laparoscopically into skepticism. Port-site metastases were considered a complication specifically related to laparoscopic surgery. Many surgeons who had commenced to perform laparoscopic colectomy for cancer abandoned this novel technique. Those surgeons who continued to perform laparoscopic removal of colonic cancer entered their patients into either registries or randomized trials.

Therefore, to evaluate the clinical consequences of laparoscopic cancer surgery, a large randomized controlled trial was initiated in the mid-nineties to allow for a thoroughly based assessment of the clinical value of laparoscopic resection of colonic cancer. The COlon cancer Lapaproscopic or Open Resection (COLOR) trial has been conducted in more than thirty hospitals throughout Western Europe. Over 1200 patients were randomized to either a laparoscopic or open colon resections to treat colon cancer with curative intent.

OUTLINE OF THE THESIS:

The role of laparoscopy in the curative treatment of colonic cancer is still under debate. In this thesis, the short and long term results of the COLOR trial are presented to identify clinically significant differences in short and long term outcome between laparoscopic and open resection of colon cancer. For the COLOR trial only colon cancer patients without evidence for distant metastatic disease were selected. In patients with stage III disease, the treatment was followed by adjuvant chemotherapy, according to local protocols. Therefore, in this thesis, patients with distant spread of colon cancer are not regarded[8].

Chapter 2:

The guideline of the European Association for Endoscopic Surgery (EAES) presents a culmination of a systematic review of the literature on laparoscopic resection of colon cancer and a consensus development conference of experts in the field and members of the EAES. Statements and recommendations are given for the pre-, intra- and postoperative period of laparoscopic colon cancer surgery. An update of recent literature is presented in an epilogue.

Chapter 3:

The short term results of the COLOR trial are presented. Differences in intraoperative and immediate postoperative results are discussed, answering the following questions:

- Is laparoscopic resection of colon cancer safe and efficacious, resulting in at least similar extent of resection?

- Are there clinically significant differences in the intraoperative and immediate postoperative outcome following laparoscopic compared to open surgery?

Chapter 4:

A prospective analysis regarding health related quality of life outcomes in a randomized clinical trial comparing laparoscopic to open surgery is given. Laparoscopic surgery is associated with improved short-term results, less postoperative pain and a shorter hospital stay.

- Is health related quality of life improved following laparoscopic compared to open surgery for colon cancer?

Chapter 5:

Since laparoscopic resection for colon cancer is a relatively new surgical technique when compared to the open technique, a learning curve effect is expected to take place within the results of the COLOR trial, despite the already extensive laparoscopic experience within the group of participating surgeons in the trial. To evaluate these learning curve effects, a subanalysis was performed to compare peroperative and immediate postoperative results between low, medium and high case volume hospitals.

- What is the role of experience on per- and postoperative results following laparoscopic colon cancer surgery?

Chapter 6:

The primary endpoint of the COLOR trial was disease free 3 year survival. The long term results of the COLOR trial are presented.

- Is there a difference in survival between patients operated laparoscopically or open for colon cancer?

Chapter 7:

Trauma to the tissues is followed by an attenuation of the immune response. Alterations of the inflammatory response to surgery have been associated with alterations in susceptibility to tumor take and metastatic spread. Laparoscopic surgery is associated with less operative trauma and blood loss. To evaluate current knowledge on the possible role of the immune system on differences between laparoscopic and open surgery, a review of the literature is presented.

- Can differences in clinical outcome between open and laparoscopic colon cancer surgery be explained by differences in acute local and systemic immunological response?

Chapter 8:

General discussion of data presented in this thesis. Future role of laparoscopy in colon cancer surgery and pitfalls for implementation are discussed.

Chapter 9:

Summary. This chapter summarizes the findings, answers and recommendations presented in this thesis.

Chapter 10:

Summary in Dutch

Epilog

Contributors to the COLOR trial
Acknowledgements
List of publications
Curriculum vitae

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Laparoscopic Resection of Colon Cancer: Consensus of the European Association of Endoscopic Surgery (E.A.E.S.)

Veldkamp R, Gholghesaei M, Bonjer HJ, Meijer DW, Buunen M, Jeekel J, Anderberg B, Cuesta MA, Cuschieri Sir A, Fingerhut A, Fleshman JW, Guillou PJ, Haglind E, Himpens J, Jacobi CA, Jakimowicz JJ, Koeckerling F, Lacy AM, Lezoche E, Monson JR, Morino M, Neugebauer E, Wexner SD, Whelan RL

Surg Endosc. 2004 Aug; 18(8):1163-85

ABSTRACT

Background: The European Association of Endoscopic Surgery (EAES) initiated a consensus conference on laparoscopic resection of colon cancer during the annual congress in Lisbon, Portugal, in June 2002.
Methods: A systematic review of the current literature was combined with the opinions of experts in the field of colon cancer surgery to formulate evidence-based statements and recommendations on laparoscopic resection of colon cancer.
Results: Advanced age, obesity and previous abdominal surgery are not considered absolute contra-indications to laparoscopic colon cancer surgery. The most common cause for conversion is the presence of bulky or invasive tumors. Laparoscopic operation takes longer to perform than the open counterpart, but the outcome is similar in terms of specimen size and pathological examination. Immediate postoperative morbidity and mortality are comparable for laparoscopic and open colon cancer surgery. The laparoscopically operated patients had less postoperative pain, better-preserved pulmonary function, earlier restoration of gastrointestinal function and an earlier discharge from the hospital. The postoperative stress response is lower after laparoscopic colectomy. The incidence of port-site metastases is <1%. Survival after laparoscopic resection of colon cancer appears to be at least equal to survival after open resection. The costs of laparoscopic surgery for colon cancer are higher than those for open surgery.
Conclusion: Laparoscopic resection of colon cancer is a safe and feasible procedure that improves short-term outcome. Results regarding the long-term survival of patients enrolled in large multicenter trials will determine its role in general surgery.

INTRODUCTION

Laparoscopic surgery for colon cancer remains controversial. Because of early reports of port site metastases, many surgeons refrained from following the laparoscopic approach to colon cancer, despite evidence from experimental tumor biology studies that have indicated clear oncological benefit of laparoscopic surgery.

Multi-center clinical trials randomizing patients with colon cancer to either laparoscopic or open resection were initiated in the mid 1990s to assess the oncological safety of laparoscopic surgery. Because a minimum follow-up period of 3 years is required to establish cancer-free survival rates, none of these ongoing randomized trials has yet accumulated sufficient data that enable reliable and definite assessment of laparoscopic colectomy for cancer.

This consensus conference (CC) addresses only colon cancer. Rectal cancer has been excluded because the available experience with laparoscopic surgery for rectal cancer is limited and because the treatment of rectal cancer differs from that of colon cancer in many respects.

The objectives of the consensus conference were:

- To establish the preferred diagnostic procedures, selection of patients and surgical technique of laparoscopic resection of colon cancer.
- To assess radicality, morbidity, hospital stay, costs and recovery from laparoscopic resection of colon cancer.
- To define standards and optimal practice in laparoscopic colon cancer surgery and provide recommendations/ statements that reflect what is known and what constitutes good practice.

METHODS

The consensus recommendations and statements are based on a systematic review of the literature and a consensus development conference (CDC) held in Lisbon, Portugal, during the 2002 congress of the EAES. They are summarized in the Appendix.

A panel of experts in both open and laparoscopic surgery were recruited for the CDC and to assist in the formulation of the consensus. Each expert had to complete independently a detailed questionnaire on laparoscopic resection of colon cancer, participate in the CDC, and review the consensus document. A reference list with accompanying abstracts was provided to the experts, who were asked to provide details of published articles not included in the bibliography that had been sent to them. The questionnaire covered key aspects of laparoscopic resections of colon cancer. The personal experience of the experts, their opinions, or references drawn from the literature search formed the basis for completion of the questionnaire. In parallel, the questions were also addressed by performing a systematic review of the relevant literature.

The systematic review was based on a comprehensive literature search of Medline, Embase, and the Cochrane Library. The following query was used to identify relevant articles: (colectom* OR hemicolectom* OR colon resection) AND (laparoscop* OR endoscop* OR minimal* invasive) AND (colorect* OR colon OR intestine, large) AND (malignanc* OR cancer OR adenocarcinoma* OR carcinoma* OR tumor* OR tumour* OR metastas* OR neoplas*) NOT (FAP OR familial adenomatous polyposis OR HNPCC OR hereditary nonpolyposis OR inflammatory bowel disease OR ulcerative colitis OR Crohn* OR diverticulitis). Only the terms "colon cancer" and "laparoscopy" were used in the Cochrane search because the previous query was too restricted and hence inappropriate for the Cochrane database. Relevant articles were first selected by title; their relevance to the objectives of the consensus conference was then confirmed by reading the corresponding abstracts. Missing articles were identified by hand searches of the reference lists of the leading articles and from articles brought to the attention of the organizing group by the experts. The primary objective of the search was to identify all clinically relevant randomized controlled trials (RCT). However, other reports (e.g., using concurrent cohort, external, or historical control), population-based outcomes studies, case series, and case reports were also included. All articles were categorized by two reviewers (R. Veldkamp and H. J. Bonjer) according to the quality of data and evidence they provided (Table 1).

The systematic review of the literature provided evidence on extent of the resection, morbidity, mortality, hospital stay, recovery, and costs of laparoscopic colon cancer surgery. Regrettably, the level of evidence of articles on surgical technique is low according to the Cochrane classification, indicating that surgical techniques are difficult to evaluate scientifically because many important aspects—e.g., multilimb coordination, dexterity, tactile and visual appreciation of anatomical structures, and surgical experience—cannot be measured objectively.

Analysis of the completed questionnaires and the information culled from the systematic review as outlined above formed the basis for the formulation of the draft consensus document, which was reviewed by the experts 3 weeks before the CDC in Lisbon, when all the panelists met for the first time on 2 June 2002. All statements, recommendations, and clinical implications with grades of recommendation were discussed during a 6-h session in terms of the prevailing internal (expert opinion) and external evidence. The following day, the consensus document with its clinical implications was presented to the conference audience

Table 1: A method for grading recommendations according to scientific evidence*

Grade of recommendation	Level of evidence	Possible study designs for the evaluation of therapeutic interventions
A	1a	Systematic review (with homogeneity) of RCTs
	1b	Individual RCT (with narrow confidence interval)
	1c	All or none case series
B	2a	Systematic review (with homogeneity) of cohort studies
	2b	Individual cohort study (including low quality RCT)
	2c	"Outcomes" research
	3a	Systematic review (with homogeneity) of case-control studies
	3b	Individual case-control study
C	4	Case-series (and poor quality cohort and case-control studies)
D	5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles", animal studies

RCT: randomized controlled trials
* Sackett DL, Straus SE, Richardson WS, Rosenberg W, Haynes RB. Evidence-based medicine: How to practice and teach EBM. (2nd Ed.) London/UK: Churchill Livingstone, 2000.

by all panelists for public discussion. All suggestions from the audience were discussed, and the consensus document was modified where appropriate. In the following months, the consensus proceedings were published online on the Internet page of the EAES. All members of the EAES were invited to comment on the consensus proceedings on a forum Web page. Sixteen surgeons commented on the consensus proceedings through the Internet forum. The modified final consensus document was approved by all the panelists before publication.

PREOPERATIVE EVALUATION AND SELECTION OF PATIENTS

Preoperative imaging

In current practice, the same preoperative workup is done prior to both laparoscopic and conventional colectomies. Metastatic spread of colonic cancer is commonly investigated by ultrasonography of the liver and plain radiography of the chest. Colonoscopic biopsy specimens from the tumor are taken in most patients to confirm the presence of cancer. However, colonoscopy does not accurately localize the lesion[1]. Abdominal CT imaging to assess the size of the tumor and possible invasion of adjacent tissues is performed selectively at some European centers and more extensively in the United States.

The size of the colonic tumor is one of the important criteria for establishing the suitability of laparoscopic resection. The atraumatic and protected removal of a tumor that has been mobilized laparoscopically requires an incision of the abdominal wall. The laparoscopic approach is not indicated when the size of this incision for extraction approximates the size of a conventional laparotomy. Hence, preoperative knowledge about the size of the tumor improves selection and reduces the need for conversion.

Barium enema studies provide reliable data on the localization of colon cancer but do not show invasion of the tumor in the colonic wall or surrounding structures[2]. Conventional CT of the colon can also provide information about the localization of the tumor. In the near future, more advanced radiologic techniques, such as virtual colonoscopy, may be able to assess the site of the tumor more precisely[3,4].

Cancerous invasion of organs adjacent to the colon can be detected by CT. However, the accuracy of preoperative staging of colon cancer by CT varies from 40% to 77%[3] because of the limited soft tissue contrast of CT, which impairs assessment of mural invasion by the tumor. The importance of tumor size and infiltration of surrounding structures is documented by a review of the causes of conversion during laparoscopic colonic surgery which indicated that almost 40% of conversions were due to a bulky or adherent tumor (See section: Conversion rate).

Laparoscopy has the potential to assess tumor invasion of adjacent organs, but there are no published reports on the value of laparoscopic staging in the workup and selection of patients for open or laparoscopic resection of colon cancer as distinct from its established use in gastric, pancreatic, and esophageal tumors.

Recommendation 1: Preoperative imaging
Preoperative imaging studies of colon cancer to assess the size of the tumor, possible invasion of adjacent structures and localization of the tumor are recommended in laparoscopic surgery for colon cancer (Level of evidence: 5, Recommendation: Grade D).

Contra-indications

Age
The experts agreed that age is not a contraindication. This view is supported by a subanalysis of a case series by Delgado et al.[5], who reported significantly lower morbidity after laparoscopic resection compared to open colectomy in patients >70 years old. Schwandner et al.[6] performed a subanalysis of 298 patients undergoing

laparoscopic or laparoscopic-assisted colorectal procedures. There were no statistically significant differences among the younger, middle aged, and older patients in terms of conversion rate (3.1% vs 9.4% vs 7.4%, respectively), major complications (4.6% vs 10.1% vs 9.5%, respectively), and minor complications (12.3% vs 15.2% vs 12.6%, respectively). However, duration of surgery, stay in the intensive care unit, and postoperative hospitalization were significantly longer in patients older than 70 years ($p < 0.05$).

Complications reported in case series involving elderly patients after laparoscopic cholecystectomy seem to compare favorably with open cholecystectomy studies[7,8].

Statement 2: Contra-indications: age

Age only is not a contra-indication for laparoscopic resection of colon cancer (Level of evidence: 2b)

Cardiopulmonary condition

Cardiopulmonary consequences of the pneumoperitoneum were thoroughly reviewed in the EAES consensus statement of 2002[9]. Relevant parts of this consensus have been enclosed in the current consensus. Decreased Cardiopulmonary function is not regarded a contraindication to laparoscopic resection of colon cancer.

Cardiovascular effects of pneumoperitoneum occur most often during its induction, and this should be considered when the initial pressure is raised for the introduction of access devices. In ASA I–II patients, the hemodynamic and circulatory effects of a 12–14 mmHg capnoperitoneum are generally not clinically relevant (grade A). Due to the hemodynamic changes in ASA III–IV patients, however, invasive measurement of blood pressure or circulating volume should be considered (grade A). These patients also should receive adequate preoperative volume loading (grade A), beta-blockers (grade A), and intermittent sequential pneumatic compression of the lower limbs, especially in prolonged laparoscopic procedures (grade C). If technically feasible, gasless or low-pressure laparoscopy might be an alternative for patients with limited cardiac function (grade B). The use of other gases (e.g., helium) showed no clinically relevant hemodynamic advantages (grade A).

Carbon dioxide (CO_2) pneumoperitoneum causes hypercapnia and respiratory acidosis. During laparoscopy, monitoring of end-tidal CO_2 concentration is mandatory (grade A), and minute volume of ventilation should be increased in order to maintain normocapnia. Increased intraabdominal pressure and head-down position reduce pulmonary compliance and lead to ventilation-perfusion mismatch (grade A). In patients with normal lung function, these intraoperative respiratory changes are usually not clinically relevant (grade A). In patients with limited pulmonary reserves, capnoperitoneum carries an increased risk of CO_2 retention, especially in the postoperative period (grade A). In patients with cardiopulmonary diseases, intra- and postoperative arterial blood gas monitoring is recommended (grade A). Lowering intraabdominal pressure and controlling hyperventilation reduce respiratory acidosis during pneumoperitoneum (grade A). Gasless laparoscopy, low-pressure capnoperitoneum, or the use of helium might be an alternative for patients with limited pulmonary function (grade B). Laparoscopic surgery preserves postoperative pulmonary function better than open surgery (grade A).

Recommendation 3: Contra-indications: cardiopulmonary status

Invasive monitoring of blood pressure and blood gases is mandatory in ASA III-IV patients (Recommendation: Grade A, no consensus: 91% agreement among experts) Low pressure (lower than 12 mm Hg) pneumoperitoneum is advocated in ASA III –IV patients (Recommendation: Grade B)

Obesity

Intraoperative ventilation of obese patients is more often problematic than in normal-weight patients, largely because the static pulmonary compliance of obese patients is 30% lower and their inspiratory resistance is 68% higher than normal[10]. The respiratory reserve of obese patients is thus reduced, with a tendency to hypercarbia and respiratory acidosis.

Obesity also reduces the technical feasibility of the laparoscopic approach. In obese patients, anatomical planes are less clear. This increases the level of difficulty of the dissection and prolongs operation time. Retraction of the small intestine and fatty omentum are more difficult and prevent easy exposure of the vascular pedicle at the base of the colonic mesentery in all parts of the colon. The routine use of hand-assisted laparoscopy may facilitate this.

Pandya et al.[11] have shown that the conversion rate is higher in patients with a body mass index (BMI) >29 due to increased technical difficulties. A similar conclusion was reached by Pikarsky et al. who reported a higher conversion rate in patients with a BMI >30[12].

There is insufficient evidence in the literature to indicate which method should be preferred. Also, in conventionally operated patients, complication rates rise with increasing BMI. In particular, ventilatory complications and wound infections are encountered in these patients. We found no study comparing laparoscopic to open colon-cancer surgery in the obese. For laparoscopic cholecystectomy, many studies have demonstrated similar complication rates after open and laparoscopic surgery[13-18].

Statement 4: Contra-indications: obesity

Obesity is not an absolute contra-indication but the rates of complications and conversions are higher at BMI greater than 30 (Level of evidence: 2c, No consensus: 93% agreement among experts).

Characteristics of the tumor

Radical resection of colonic cancer is essential for cure. Atraumatic manipulation of the tumor and wide resection margins (longitudinal and circumferential) are the basic elements of curative surgery[19]. Laparoscopic radical resection of locally advanced colorectal tumors is problematic because adequate laparoscopic atraumatic dissection of bulky tumors is difficult. Furthermore, laparoscopic resection of adjacent involved organs or the abdominal wall compounds the technical problem. Hence, the role of laparoscopic surgery in patients with T4 cancers remains controversial. The majority of the experts consider T4 colonic cancer an absolute contraindication to laparoscopic resection; en bloc laparoscopic resection is possible only in a limited number of patients. The routine use of hand-assisted laparoscopy may change this in the future.

The laparoscopic approach is useful for palliative resections of colonic cancer. Most experts do not consider peritoneal carcinomatosis to be a contraindication for laparoscopic surgery.

Recommendation 5: Contra-indications: tumor characteristics

Potentially curative resections of colon cancer suspected of invading the abdominal wall or adjacent structures should be undertaken by open surgery (Level of evidence: 5, Recommendation: Grade D, No consensus: 83% agreement among experts)

Adhesions

Adhesions account for 17% of all conversions. However, prior abdominal operation appears to play a less important role in the completion rate of laparoscopic colon resection, as reported by Pandya et al.[11]. In this study, conversion rates did not differ between patients who had previous abdominal operation and those who did not. In this series of 200 patients, 52% of whom had had a previous laparotomy, only five required conversion to laparotomy because of extensive intraabdominal adhesions. Hamel et al.[20] compared the morbidity rate following right hemicolectomy between patients with and without prior abdominal operation. The complication rates for the two groups were similar despite the presence of more adhesions in the previously operated group.

To our knowledge, no studies have been published comparing laparoscopic to open surgery for patients with previous abdominal operation.

Statement 6: Contra-indications: adhesions
Adhesions appear not a contra-indication to laparoscopic hemicolectomy (Level of evidence: 4)

Localization
Half the experts do not recommend laparoscopic resections of the transverse colon and the splenic flexure. The omentum, which is adherent to the transverse colon, renders dissection of the transverse colon difficult. Mobilization of a tumor at the splenic flexure can be very demanding.

OPERATIVE TECHNIQUE

Anesthesia

Nitrous oxide, when employed as inhalational anesthetic, does not cause intestinal distention assessed by girth of transverse colon and terminal ileum at the beginning and end of the procedure[21]. The first study investigating the usefulness of nitrous oxide during laparoscopic surgery was completed by Taylor et al.[22]. In one group, isoflurane with 70% N_2O in oxygen (O_2) was used, in the other; isoflurane in an air/O_2 mixture was used during laparoscopic cholecystectomy. No significant intraoperative differences were found between the two groups with respect to operating conditions or bowel distension. However, the consequences of the use of nitrous oxide during longer laparoscopic procedures have not been investigated.

Most experts employ general anesthesia without epidural analgesia.

Pneumoperitoneum

Recommendations regarding the creation of a pneumoperitoneum are given in the EAES consensus statement of 2001[9].

Trocars position

Positioning of the trocars is based on the experience and preference of the individual surgeon. For right hemicolectomies, 50% of experts use four trocars, 30% use 3 trocars and 20% 5 trocars. The majority extracts the specimen through an incision made at the site of the umbilical trocar. A Positioning of the trocars is based on the experience and preference of the individual surgeon. For right hemicolectomies, 50% of experts use four trocars, 30% use three trocars, and 20% use five trocars. Most of them extract the specimen through an incision made at the site of the umbilical trocar. At the umbilicus, a 10–12-mm trocar is placed. A 10-mm trocar is placed suprapubically and another trocar in the epigastric region by 70% of authors. Some experts place a 5-mm trocar at the left iliac fossa or at the right subcostal space.

For left hemicolectomy and for sigmoid resection, trocars are positioned at almost the same sites. Thirty percent of experts perform these procedures using a hand-assisted technique. Five trocars are used by >70% of experts. A 10–12-mm trocar is placed at the umbilicus; two 10-mm trocars are placed by 80% of experts in the right iliac fossa and in the right suprapubic region. The incision for specimen extraction is made at the left iliac fossa, or, if the hand-assisted technique is used, the specimen is extracted through the hand port incision, usually in the upper lateral abdomen. For left hemicolectomy, the specimen is extracted through a suprapubic incision or through an incision at the left iliac fossa.

Statement 7: Placement of trocars
Placement of trocars is based on the experience and the preference of the individual surgeon (Level of evidence: 5)

Camera

There is unanimous agreement about the use of a three-chip camera, because of its better resolution. The laparoscope can be 30° or 0°, depending on the surgeon's preference. Two experts use a flexible videolaparoscope. The camera is hand-held by most experts. Mechanical and robotic devices are available, but they are used by <10% of experts.

Recommendation 8: Videoscopic image
High quality videoscopic imaging is strongly recommended (Level of evidence: 5, Recommendation: Grade D).

Prevention of port site metastasis

Port site metastases after laparoscopic resection of colon cancer have caused great concern in the surgical community. Therefore, the causative mechanisms in the occurrence of port site metastases has become an important subject for experimental research. Many mechanisms have been proposed and have been subject of extensive research[23]. However, so far no conclusive pathogenesis of port site metastases has been established. We will discuss the most common preventive measures for port site metastases and their pathogenesis. No levels of evidence and grades of recommendation are given for each individual measure because most evidence is derived from experimental research and there is no consensus among the experts on which measures to use.

Surgical experience
The incidence of port site metastases has decreased dramatically with growing experience. The initial incidence of port site metastases of 21% has dropped to <1% (see Port-site metastases). Surgical experience thus appears the main determinant for the occurrence of port site metastases.

Wound protectors
Experimental studies have shown that tumor growth is increased at the site of extraction of a malignant tumor[24]. All experts protect the abdominal wall or place the specimen in a plastic bag prior to extraction to prevent tumor cell implantation and growth. However, port site recurrences have been reported after extraction of a right colonic cancer that was placed in a plastic bag[25]. Therefore, wound protection is considered safer.

Gasless laparoscopy
In view of the possibility that a positive pressure pneumoperitoneum may be responsible for wound tumor deposits, some surgeons have suggested the use of gasless laparoscopy. In this respect, experimental findings on gasless laparoscopy are controversial. Bouvy et al.[24] and Watson et al.[26] reported a significant decrease in the occurrence of port site metastasis when gasless laparoscopy was used in an animal model. Gutt et al.[27] and Iwanaka et al.[28] could not confirm these observations. Wittich et al. reported in an experimental study that tumor growth was proportional to the insufflation pressure[29]. Hence, low insufflation pressures may reduce the risk of dissemination.

Different types of gas

Carbon dioxide attenuates the local peritoneal immune response, which might enhance the risk of tumour cell implantation and tumor growth in the traumatized tissues[28,30-34]. Neuhaus et al.[35], Jacobi et al.[36], and Bouvy et al.[37] assessed tumor growth in animals after abdominal insufflation with different gases. Only helium significantly reduced the rate of wound metastasis. However, the clinical implications of the use of helium in humans have not been explored fully.

Wound excision

Because cancer cells can implant in wounds during surgery, it might be expected that excision of the wound edges would reduce the rate of neoplastic wound recurrences. This has not been confirmed in animal studies. Wu et al.[38] reported a reduction in port site metastases rates from 89% to 78% after wound excision, whereas Watson et al. reported that wound excision was followed by a significant increase of wound recurrence[39].

Irrigation of peritoneal space and port site

Irrigation of the peritoneal cavity with various solutions to reduce the incidence of peritoneal and port site metastases has been studied mostly in animal models. These studies have shown that peritoneal irrigation with povidone-iodine[40,41], heparin[42], methotrexate[40], and cyclophosphamide[28] all reduced the rate of port site metastasis. Intraperitoneal tumor growth and trocar metastases were suppressed by the use of taurolidine in a rat model[36,43,44]. Eshraghi et al.[45] irrigated the port sites with distilled water, saline, heparin, and 5-FU. They found that 5-FU reduced the recurrence rate. Half of the experts irrigate the port sites with either betadine, distilled water, or tauroline.

Trocar fixation

Tseng et al.[46] showed in an experimental study that gas leakage along a trocar ("chimney effect") and tissue trauma at the trocar site predisposed to tumor growth. However, the chimney effect has never been validated clinically.

Aerosolization

In experimental studies[47,48], aerosolization occurs only when very large numbers of tumor cells are present in the abdominal cavity. The clinical significance of the aerosolization of tumor cells has not been proven. Some experts advocate desufflation of the pneumoperitoneum at the end of the operation before removal of the ports.

No-touch technique
The no-touch technique is based on the risk of dislodging tumor emboli during manipulation of the colorectal carcinoma. The value of the no-touch technique in colon surgery remains controversial. An improvement in the 5-year survival was reported by Turnbull et al. in a retrospective analysis[49]. In the only prospective randomized trial, which evaluated 236 patients, Wiggers et al.[50] showed that the no-touch technique did not impart a significant 5-year survival advantage. The absolute 5-year survival rates were 56.3% and 59.8% in the conventional arm and no-touch surgical groups, respectively. In the conventional group, more patients had liver metastases and the time to metastasis was shorter, but differences in survival were not statistically significant.

Bowel washout
Studies have shown that viable tumor cells exist in the lumen of the colon and rectum. Rectal washout may thus reduce risk of recurrence, but the potential benefit remains unproven[19]. Exfoliated tumor cells have been detected in resection margins, rectal stumps, and circular stapling devices[51-53]. Furthermore, the viability and proliferative and metastatic potential of exfoliated malignant colorectal cells have been confirmed[52,53], Several washout solutions, including normal saline, have been shown to eliminate exfoliated malignant cells in the doughnut of rectal tissue from circular staplers[54]. Despite these observations, there is no conclusive evidence that bowel washouts reduce local recurrence and hence no data to support their use in surgery for colon cancer.

Statement 9: Preventive measures for port site metastasis
Proper surgical technique and practice reduces the likelihood of port site metastasis (Level of evidence: 5)

Tumor localization

Preoperative tumor localization is important in the laparoscopic resection of colonic cancer because intraoperative localization by palpation of the colon for tumors that are not visible on the serosal side is not possible unless the hand-assisted laparoscopic surgery (HALS) technique is used. The risk of incorrect tumor localization includes resection of the wrong bowel segment or less than radical resection because of insufficient proximal or distal margins[55-57].

Many colonoscopic techniques are used for marking the site of a tumor. Two of these, metal clip placement[58,59] and tattooing[60,61], are most commonly used. Tumor localization is advisable except for tumors located near the ileo-cecal valve, which forms a clear landmark during colonoscopy[62]. Special equipment is needed for clip placement. Before surgery, plain abdominal radiography is performed to exclude the migration of clips. During surgery, the clips are identified by intraoperative ultrasound or fluoroscopy. Hence, this is an expensive and time-consuming technique[63], although it is very reliable[59,64].

Intra-operative colonoscopy is an alternative modality to localize the colonic lesion. However, this technique can induce distention of the colon and small bowel, particularly in right-sided lesions[65]. The colonoscopic tattooing technique with india ink or methylene blue is efficient. Tattoo injection with ink can be carried out at the time of the first colonoscopy because ink remains in place for several weeks. It is important to inject the dye in all quadrants, at an angle of 45°, and to mark the oral and aboral margins of the lesion. A thick omentum or tattooing along the mesocolic margin can mask a tattoo such that localization fails. Reported success rates for detection of the tumor after tattooing vary between 78.6% and 98%[61,66]. The reported morbidity rate for tattooing is 0.22%[67]. In this review, only one patient was found in whom overt clinical complications developed. Injection into the peritoneal space has been reported in 0.5–8%[63,68].

Recommendation 10: Intraoperative localization of tumor
Preoperative tattooing of small colon tumors is advised. The alternatives are intraoperative colonoscopy, or pre-operative colonoscopic clipping followed by peroperative fluoroscopy or ultrasonography (Level of evidence: 5, Recommendation: Grade D).

Hand assisted or laparoscopic assisted approach

Basically, three different techniques are described for laparoscopic colon resection: totally laparoscopic, laparoscopic-assisted, and hand-assisted colectomy.

During totally laparoscopic procedures, the resected specimen is removed through the anus. It can be performed during low anterior resection or sigmoidectomy. The anastomosis is done laparoscopically using a circular stapler introduced through the anus. Totally laparoscopic procedures have been abandoned, largely because early experience indicated a high recurrence rate at the extraction site and no apparent advantage[69].

In laparoscopic-assisted colon resection, part of the procedure is performed in an open fashion through an incision of the abdominal wall made for the extraction of the resected specimen. This is the most common procedure for all colectomies.

Hand-assisted laparoscopic surgery (HALS) is an alternative to laparoscopically assisted colectomy. This procedure enables the surgeon to use his or her hand, with the dual benefit of magnified view and restoration of the tactile sense by the internal hand, which also provides atraumatic retraction and effective control of sudden bleeding. In addition, the internal hand is able to locate small tumors that are not visible from the serosal aspect.

With the early hand access devices, maintenance of the pneumoperitoneum was difficult, but this problem has been resolved with the second generation of hand access devices[70]. HALS appears to be at least as effective as the laparoscopically assisted technique in terms of operative time, conversion rate, and postoperative outcome[71]. Only two experts use HALS for laparoscopic colectomy.

Dissection of mesocolon

Most experts dissect the mesocolon before taking down the lateral attachments of the colon. Fifty-four percent of experts use a vascular stapling device, 27% employ an external knotting technique, and 18% use clips to ligate the large-caliber mesocolic vessels. Most experts dissect the mesocolon from medially to laterally over Toldt's fascia. All agree that the surgeon must know both approaches to be able to deal with a difficult problem during the procedure.

For right hemicolectomy, the mobilization of the bowel is always performed laparoscopically. Dissection of the mesocolon and bowel transection can both be performed laparoscopically or after the colon has been exteriorized. Transection of the ileum is performed laparoscopically by 71% of experts. Aboral transection of the colon, as well as the anastomosis, is performed after exteriorization. In left hemicolectomy, dissection of the mesocolon, mobilization of the colon, and transection of the aboral colon are done laparoscopically. The anastomosis is performed using a circular stapler introduced through the anus by 66% of experts. Others perform a stapled or hand-sewn anastomosis after exteriorization of the colon. No preference exists for either end-to-end, end-to-side, or side-to-side anastomosis.

Sigmoidectomy involves the same steps as left hemicolectomy, but all experts use a circular stapler for the anastomosis.

Recommendation 11: Dissection of mesocolon
Dissection of the mesocolon from medial to lateral is the preferred approach in laparoscopic colon surgery (Level of evidence: 5, Recommendation: Grade D).

Learning curve

"Learning curve" can be defined in various ways. Simons et al. considered the learning curve completed when the operative time stabilizes and does not vary by more than 20 min[72]. Schlachta et al.[73] demonstrated that operating time, intraoperative complications, and conversion rates decline after the performance of 30 colorectal resections. Bennett et al.[74] reported that experience plays an important role in reducing complication rates and has less impact on reducing the operating time. Lezoche et al. reported that the conversion rate dropped from 17% to 2% after 30 laparoscopic colectomies[75]. Many surgeons consider the learning curve for laparoscopic colonic resection to be longer than that for laparoscopic cholecystectomy.

INTRAOPERATIVE RESULTS OF LAPAROSCOPIC RESECTION OF COLON CANCER

Conversion rate

Reported conversion rates in laparoscopic surgery depend on the definition of conversion, the selection of patients, and the experience of the surgeon. Conversion rates between 4% and 28% have been reported in comparative studies (Table 2)

There is currently no standardized definition of conversion. In most studies, an operation is considered to be converted when a laparoscopic procedure was commenced but could not be completed by this approach. In two studies, a diagnostic laparoscopy was performed before every operation to establish the feasibility of a laparoscopic resection[76,77]. If laparoscopy indicated that resection would not be possible, open surgical resection was performed. These operations were not considered as converted. In two case series, high conversion rates of 41% and 48% were reported[78,79]. Both studies reflected a very early experience with laparoscopic surgery, and no attempt was made to select patients according to weight, tumor stage, or number of previous abdominal operations. None of the other case series that have been reviewed reported higher conversion rates[56,76,80-83].

In a study by Lezoche et al., conversion rates were calculated for the first 30 patients operated laparoscopically and for the consecutive 26 patients[84]. The conversion rate in the early experience group was 16.8%, whereas in the subsequent group it was 1.8%; this finding underscores the importance of experience in reducing the conversion rate. This finding was confirmed by several other reports analyzing early and later experiences with laparoscopic colon surgery[11,56,81,85]. All

Table 2: Reported conversion rates in studies on laparoscopic resection of colorectal cancer

Study	N	Conversion rate	Cause
1			
Weeks[86]	58/228	25%	11 advanced disease, 3 positive margins, 10 inability to visualize structures, 4 inability to mobilize colon, 12 adhesions, 4 intraoperative complications, 2 associated complicating disease, 12 other
2			
Schwenk[87]	0/30	0%	After diagnostic laparoscopy
Milsom[77]	4/59	7%	2 bowel distension, 1 tumor too low, 1 adhesions
Delgado[5]	18/129	14%	15 invasion adjacent organs, 1 adherence, 2 NS
Curet[88]	7/25	28%	3 tumor fixation to adjacent organs, 3 extensive adhesions, 1 abscess around ureter
Stage[89]	3/18	17%	3 extensive tumor growth
Lacy[90]	4/25	16%	4 invasion small bowel
3			
Lezoche[84]	6/140	RHC 0% LHC 7% Total 4%	2 hemorrhage, 2 anastomotic defects, 1 obesity, 1 inadequate splenic flexure mobilization
Feliciotti[91]	5/104	4.8%	2 anastomotic defects, 1 obesity, 1 inadequate splenic flexure mobilization, 1 hemorrhage
Bouvet[92]	38/91	42%	12 adhesions, 8 poor exposure, 5 extensive tumor growth, 3 excessive procedure time, 2 bleeding, 2 inability to identify the ureter, 1 inadequate distal margin, 1 equipment failure, 4 combination of factors
Hong[93]	12/98	12%	5 adherence, 5 size of tumor, 2 adhesions
Psaila[94]	3/25	12%	NS
Khalili[95]	6/80	8%	3 extensive tumor, 2 adhesions, 1 intraoperative bleed
Pandya[11]	47/200	23.5%	6 hypercarbia, 2 unclear anatomy, 2 stapler misfiring, 5 too ambitious, 6 bleeding, 1 cystotomy, 2 enterotomy, 5 adhesions, 3 obesity, 10 size/invasion tumor, 5 phlegmon
Bokey[96]	6/34	18%	1 injury caecum, 1 adherence, 1 adhesions, 1 hypercapnia, 2 lack of progress
Franklin[97]	8/192	4.2%	7 large invasive tumor, 1 bleed
Santoro[98]	0/50	0%	-
Leung[99]	8/50	4%	2 adhesions, 2 bleeding, 3 large/ invasive tumors, 1 low tumor
Van Ye[100]	1/15	6.7%	1 adhesions
Leung[101]			
4			
Schiedeck[102]	25/399	6.3%	NS
Bokey[103]	9/66	14%	2 lack of progress, 2 adherence, 1 adhesions, 1 caecal injury, 1 hypercapnia, 1 ureter not identified, 1 bleed

Table 2 (*continued*)

Study	N	Conversion rate	Cause
Fleshman[104]	58/372	15.6%	NS
Franklin[105]	3/50	6%	3 bulky/invasive tumor
Poulin[106]	12/131	9%	6 fixed tumor, 3 adhesions, 1 oncologic resection impossible, 1 hemorrhage, 1 perforation small bowel
Leung[107]	54/201	26.9%	22 conversions after diagnostic laparoscopy (not further specified)
Total	395/2812	14%	Invasive or bulky tumor: 36% ; Adhesions: 18%; Technical problem: 22% (12 lack of progress, 18 poor exposure, 8 hypercarbia, 6 anastomotic problem, 2 bowel distension, 6 inadequate mobilization, 1 equipment failure); Bleed: 7%; Safe oncol resection impossible: 2%; Visceral injury: 3%; Obesity: 2%; Others: 10%

NS, not specified

found a clear decrease in the number of conversions as more operations were performed.

Laparoscopic colectomies are converted for a variety of reasons. Locally advanced bulky or invasive tumors, adhesions, and technical problems account for most conversions (Table 2). Because many conversions are for invasive or bulky tumors, improved preoperative selection of patients based on more accurate clinical staging may decrease conversion rates. Preoperative CT or MRI scanning can provide more information on the localization of the tumor and the invasion of surrounding structures.

Statement 12: Conversions

Laparoscopic colectomy is converted to open surgery in 14% (0 – 42%) of cases. The most common causes of conversion are tumor invasion of adjacent structures or bulky tumor, adhesions and technical failure (Level of evidence: 3a).

Duration of surgery

In general, laparoscopic resection of colonic cancer takes longer to perform than open resection. Although operating time decreases with increasing experience[75,78,81,84,108], it is difficult to compare operating times between open and laparoscopic resections for colon cancer because most studies include a wide variety of procedures and do not specify per type of resection performed. Studies that included rectal procedures reported longer operating times[77,88,92].

Reported operating times vary between 140 and 251 min for laparoscopic colorectal resections and 120 and 175 min for open surgery (Table 3). In some studies, benign lesions were also included[77], and rectal procedures were excluded

Table 3: duration of surgery

Study	Laparoscopic	Open	*p* value
2			
Lacy[109]	142±52	118±45	0.001
Hewitt[111]	165	107.5	0.02
Milsom[77]	200±40	125±51	<0.0001
Delgado[5]	<70 yr: 144±40 >70 yr: 150±60	122±45 119±51	0.005 0.001
Curet[88]	210(128-275)	138(95-240)	<0.05
Stage[89]	150 (60-275)	95 (40-195)	0.05
Lacy[90]	148.8±45.5	110.6±49.3	0.006
Schwenk[112]	219±64	146±41	<0.01
3			
Lezoche[84]	RHC 190 First 30: 226 Last 20: 153 LHC 240 First 30: 260 Last 20: 210	140 190	0.03 0.04
Bouvet[92]	240 (150-516)	150 (60-376)	<0.01
Fukushima[113]	231	169	NS
Hong[93]	140±49.5	129±53.5	NS
Psaila[94]	179±41	123±41	<0.05
Khalili[95]	161±7	163±8	NS
Lezoche[75]	Mean 251 (90-480) RHC 203 (90-330) LHC 282 (150-480)	175 (90-340) 140 (90-280) 190 (130-340)	<0.001 <0.001 <0.001
Marubashi[110]	RHC 211.9 (134-330)	148.7 (104-173)	<0.05
Leung[99]	196±44.4	150±61.1	<0.001

Results given as mean ± SD or median (range), NS, not significant; RHC, right hemicolectomy; LHC, left hemicolectomy

in only one RCT[109]. In two RCT[77,88] and in five nonrandomized comparative studies, the intention-to-treat principle was violated[75,92,95,99,110], resulting in selection bias, possibly favoring the laparoscopic group.

Statement 13: Duration of surgery

Laparoscopic colectomy requires more operating time than open colectomy (Level of evidence: 2a).

Extent of resection

For a laparoscopic oncological resection to be as safe as an open resection, the extent of resection of colonic and lymphatic tissue should not differ from that of open colectomy. All RCT report similar numbers of lymph nodes harvested in laparoscopic and open surgical specimens. Also, the length of the retrieved bowel segments and tumor-free margins were comparable[5,77,88-90] (Table 4).

In nonrandomized comparative studies, no differences between open and laparoscopic groups were found for number of lymph nodes, length of the retrieved

Table 4: Number of lymph nodes harvested and extent of resection

Study	No of lymph nodes			Resection margins (cm)		
2	Lap	Open	*p* value	Lap	Open	*p* value
Milsom[77]	19 [a]	25 [a]	--	Clear in all	Clear in all	
Delgado[5]	<70 yr 9.6 >70 yr 12.2	10.5 10.5	NS NS			
Curet[88]	11	10	NS	Length 26	25	--
Stage[89]	7	8	--	Margins 4	4	
Lacy[90]	13	12.5	NS			
3						
Lezoche[84]	RHC 14.2 LHC 9.1	13.8 8.6	NS NS	Length 28.3 Length 22.9 LHC TFM 5.2	29.1 24.1 5.3	NS NS NS
Bouvet[92]	8	10	NS	Prox 10 Dist 6	10 9	NS 0.03
Hong[93]	7	7	NS	Dist 7,9	7,2	NS
Koehler[114]	14	11	--	Length 24.1 Prox 13.2 Dist 7.9	22.6 10.1 8.6	-- -- --
Psaila[94]	7,0	7,7	NS			
Khalili[95]	12	16	--			
Lezoche[75]	10,7	11	NS	Length 26.8 LHC TFM 5.2	29.4 5.3	NS NS
Marubashi[110]				LoD 1,7	2,25	P<0.01
Bokey[96]	17	16	NS	Prox 10,1 Dist 10,0	11,9 13,4	NS 0.03
Franklin[97]	NA	NA	NS	NA	NA	NS
Santoro[98]						
Leung[99]	9 [a]	8 [a]		Dist 3 [a]	3,5 [a]	

Results given as mean or [a]median; NS, not significant; Length, length of resected specimen; Prox, proximal resection margin; Dist, distal resection margin; LHC, Left hemicolectomy; RHC, right hemicolectomy; TFM, Tumor Free Margin; LoD, Level of Dissection specimen, tumor-free proximal and distal margins, and total length of specimen. In two studies, a smaller distal resection margin was recorded[92,96]. However, in these studies, the mean distal tumor-free resection margins were still 6 and 10 cm, respectively, which is oncologically acceptable.

There are reports of laparoscopic colon resections not containing the primary tumor or missing a synchronous second colonic carcinoma[55-57]. This type of result underscores the importance of tumor localization by either tattooing the tumor with ink or intraoperative colonoscopy.

Statement 14: Extent of resection

The extent of laparoscopic lymphadenectomy and bowel resection is similar to those obtained by open colectomy (Level of evidence: 2b).

CLINICAL OUTCOME

Short-term

Morbidity

The reported morbidity and mortality rates for open conventional colorectal surgery range from 8% to 15% and 1% to 2%, respectively[115]. Serious complications include anastomotic leakage, bowel obstruction, and abdominal and pulmonary infection.

Table 5 summarizes the studies describing morbidity following laparoscopic colectomy. Data from the RCT indicated a significantly lower overall complication rate after laparoscopic surgery[5,90,109]. In a subset analysis comparing laparoscopic to open resection, reduction of postoperative morbidity after laparoscopic resection was more pronounced than in patients under 70 years of age[5].

Morbidity of laparoscopic resection of colonic cancer has not been reported in sufficient detail by most authors[116]. Specific complications of laparoscopic surgery involve vascular and visceral injuries, trocar site hernias[100,117], and transection of the ureter[79]. Vascular injuries may be caused by blind introduction of the Veress needle or first trocar[78,79,116,118]. Winslow et al. reported incisional hernias at the extraction site in 19% after laparoscopic colectomy, whereas incisional hernias occurred in almost 18% after open colectomy[119].

Experience is an important factor in preventing complications, as shown in three studies that reported lower morbidity with increasing experience[56,74,85]. A recent systematic review[115] analyzed morbidity as reported in 11 studies[89,90,99,101,103,107,111,120-123] (Table 6).

The infectious complications of laparoscopic colectomy have not been assessed by large-scale prospective randomized studies. Wound infection at the extraction

Table 5: Morbidity

Study	Laparoscopic (%)	Open (%)	*P* value
2			
Lacy[109]	11	29	0.001
Milsom[77]	15	15	NS
Delgado[5]	Mean 10.9 <70 yr 11.4 >70 yr 10.2	25.6 20.3 31.3	0.001 NS 0.0038
Curet[88]	1.5	5.28	NS
Stage[89]	11	0	--
Lacy[90]	8	30.8	0.04
Schwenk[87]	7	27	0.08
3			
Lezoche[84]	RHC 1.9 LHC 7.5	2.3 6.3	NS NS
Bouvet[92]	24	25	NS
Hong[93]	Major 15.3 Minor 11.2	14.6 21.5	NS 0.029
Khalili[95]	19	22	NS
Lezoche[75]	Total 13 Minor 3.6 Major 9.4	14.3 7.5 6.8	NS NS NS
Marubashi[110]	27.5	25	--
Bokey[96]	NA	NA	NS
Franklin[97]	Early 17 Late 5.2	23.8 8.9	NA
Santoro[98]	Early 28 Late 12	28 0	--
Leung[99]	26	30	NS

NS, not significant; NA, not available; LHC, Left hemicolectomy; RHC, right hemicolectomy

site was encountered in 14 % of patients after laparoscopic colectomy vs. 11 % of patients after open colectomy[119].

Statement 15: Morbidity

Morbidity after laparoscopic colectomy does not differ from that after open colectomy (Level of evidence: 2b).

Mortality

Mortality rates, defined as death within 30 days after surgery, are similar for both open and laparoscopic colectomy. However, no randomized controlled trials on laparoscopic vs. open colectomy have yet been conducted with sufficient numbers

Table 6: Complication rates in an analysis of 11 studies

Complication	N	%
Wound infections	30	5.7
Respiratory	16	3.1
Cardiac	15	2.9
Hemorrhage	10	1.9
Anastomotic leaks	8	1.5
Urinary tract infections	3	0.6
Small bowel perforations	3	0.6
Port site herniation	2	0.4
Hematoma	2	0.4
Septicemia	1	0.2
Peritonitis	1	0.2
Anastomotic stricture	1	0.2
Anastomotic edema	1	0.2
Hypoxia	1	0.2
Acute renal failure	1	0.2
Discompensated renal insufficiency	1	0.2
Urinary retention	1	0.2
Deep vein thrombosis	1	0.2
Small bowel obstructions	1	0.2
Phlebitis	1	0.2
Intraabdominal abscesses	1	0.2

to distinguish small differences. In two RCT, a 0% mortality rate was reported for both open and laparoscopic procedures[111,124]. In the RCT by Schwenk et al.[87], one death occurred in the conventional group and none in the laparoscopic group. In another RCT, three deaths occurred, but this study failed to report to which group these patients were assigned to and the causes of death[89].

In nonrandomized reports, mortality was reported in only five studies[93,96,98,101,114]. None of these studies showed any significant differences between the open and laparoscopic groups, although the cohorts were too small to detect small differences.

Statement 16: Mortality

Mortality of laparoscopic colectomy appears similar to that of open colectomy (Level of evidence: 2b).

Recovery

Length of hospital stay

Many factors determine length of hospital stay after surgery, and length of stay differs by country and hospital. Clinical condition of the patient is only one such factor. Type of insurance, social and economic status, and perception of postoperative recovery by both surgeon and patient are also important factors. Table 7 summarizes all studies comparing length of hospital stay after laparoscopic and open colectomy for cancer. The COST trial reported by Weeks et al.[86] is currently the multicenter RCT with the highest power and most published data. In this trial, a highly significant shorter hospital stay was found after laparoscopic colectomy (5.6 ± 0.26 vs 6.4 ± 0.23 days, $p < 0.001$),

Table 7: Length of hospital stay

Study	Laparoscopic	Open	*p* value
1			
Weeks[86]	5.6 ±0.26	6.4±0.23	<0.001
2			
Hewitt[111]	6 (5-7)	7 (4-9)	--
Milsom[77]	6.0 (3-37)	7.0 (5-24)	NS
Delgado[5]	<70 yr 5 >70 yr 6	7 7	0.0001 0.0009
Curet[88]	5.2	7.3	<0.05
Stage[89]	5 (3-12)	8 (5-30)	0.01
Lacy[90]	5.2 ± 1.2	8.1 ± 3.8	0.0012
3			
Lezoche[84]	RHC 9.2 LHC 10.0	13.2 13.2	0.001 0.001
Bouvet[92]	6 (2-35)	7 (4-52)	0.01
Hong[93]	6.9 ± 5.4	10.9 ± 9.3	0.003
Koehler[114]	8.1 (6-14)	15.3 (9-23)	--
Psaila[94]	10.7 ± 4.7	17.8 ± 9.5	0.001
Khalili[95]	7.7 ± 0.5	8.2 ± 0.2	NS
Lezoche[75]	10.5	13.3	0.027
Marubashi[110]	18.7	35.8	<0.0001
Franklin[97]	<50 yr 5.2 (2.0-9.2) >50 yr 7.84 (4-48)	9.35 (5-17) 12.85 (9-41)	--
Leung[99]	6 (3-22)	8 (3-28)	<0.001

Results given as mean ± SD or median (range); NS, not significant; RHC, right hemicolectomy; LHC, left hemicolectomy even though the analysis was performed on an intention-to-treat basis and patients converted to open operation were included in the laparoscopic group.

Six other RCT reported on length of hospital stay[5,77,88-90,111]. In four RCT, a significant earlier hospital discharge was reported for the laparoscopic group[5,88-90]. In one RCT with a sample size of 16, no statistical analysis was performed[111]. Median and range of length of hospital stay did not differ in this study (6 [5-7] vs 7 [4-9] days). In one RCT, the difference was not significant[77].

In the nonrandomized comparative studies, hospital stay after laparoscopic surgery varies from 5.7 to 18.7 days and between 8 and 35.8 days after open surgery[75,84,92-95,97,99,110,114]. In all these studies, hospital stay was shorter in the laparoscopic group, although in three studies the differences were not significant[95,114,125]. Differences in hospital stay between laparoscopic and open colectomy groups vary from 1 to 7 days.

A recent article by Wilmore et al.[126] reviewed "fast-track" surgery for open procedure. Fast-track surgery is a multimodal approach that combines various techniques used in the perioperative care of patients to achieve a faster recovery and discharge after surgery. Methods include epidural or regional anesthesia, optimal pain control, early enteral feeding, and early mobilization. This Danish research group managed to shorten the postoperative hospital stay to 2 days after conventional open colectomy. So far, this approach has not been studied for patients undergoing the laparoscopic resection of colon cancer.

Statement 17: Length of hospital stay

Hospital stay after laparoscopic resection of colon cancer is shorter than after open colectomy (Level of evidence: 1a).

Postoperative pain

Postoperative pain is an endpoint that impacts on the perceived health status, quality of life, hospital stay, and resumption of normal activities. In general, less postoperative pain is perceived after endoscopic surgery than after open surgery. In one RCT, statistically significantly less pain at rest after laparoscopic resection of colonic cancer was observed for ≤ 30 days postoperatively, when compared to open colectomy[89]. Also pain during mobilization was reported to be less severe. The number of patients included in this trial, however, was limited and the methodology used was flawed because the intention-to-treat principle was violated. Similar results were obtained by another RCT[114]. This study showed differences in pain at rest and during mobilization for ≤ 12 days, but these differences were not significant. In a recent RCT, postoperative pain was analyzed using the Symptoms Distress Scale, which includes self-reported symptoms such as pain, along with the duration of use of analgesics[86]. In this study, only a shorter duration of use of analgesics was observed in the laparoscopic arm.

Statement 18: Pain

Pain is less severe after laparoscopic colectomy (Level of evidence: 2a).

Postoperative analgesia

The need for analgesics after surgery can be measured in several ways. Table 8 summarizes all studies comparing postoperative analgesia after laparoscopic or open resection of coloncancer. Some authors assessed the number of pills or injections per day[75,77,99], whereas others recorded the number of days the patient needed analgesics[93,96,110]. In the COST trial, patients in the laparoscopic arm required parenteral and oral analgesics for a shorter period of time[86]. In another RCT, significantly less morphine was used in the laparoscopic groups only on the 1st postoperative day[77].

Table 8: Postoperative analgesia

Study			Laparoscopic	Open	*p* value
1					
Weeks[86]	Oral (days)		2.2 ± 0.15	1.9 ± 0.15	0.03
	Parenteral (days)		4.0 ± 0.16	3.2 ± 0.17	<0.001
2					
Milsom[77]	Morphine	Day 1	0.78 ± 0.32	0.92 ± 0.34	0.02
		Day 2	0.45 ± 0.29	0.50 ± 0.31	NS
		Day 3	0.39 ± 0.32	0.36 ± 0.24	NS
Schwenk[127]	PCA (morphine)	Cumulative dose until day 4	0.78 (0.24-2.38)	1.37 (0.71-2.46)	<0.01
Hewitt[111]	Morphine	Cumulative dose until day 2	27 (0-60)	62 (28-88)	0.04
3					
Hong[93]	Days till stop iv or im analgesia		2.7 ± 1.5	3.2 ± 2.0	0.021
Lezoche[75]	Analgesics in percentage of patients	Day 1	75%	98%	<0.001
		Day 2	49%	91%	<0.001
		Day 3	10%	71%	<0.001
		Day 4	0.7%	49%	<0.001
		Day 5		21%	
Marubashi[110]	Days till stop epidural		2.98	4.04	<0.05
	No. of pills		1.49	2.68	NS
Bokey[96]	Days till stop (parental analgesia)		4.4	4.9	NS
Leung[99]	No. of injections		3 (0-16)	6 (0-32)	<0.001

Results given as mean ± SD or median (range); NS, not significant

In all other studies, the laparoscopic group used fewer analgesics, although the difference was not always significant[75,93,96,99,110,111,127].

Statement 19: postoperative use of analgesics
Less analgesia is needed after laparoscopic colectomy compared to open colectomy (Level of evidence: 1b).

Gastro-intestinal function
Resumption of intestinal function can be measured by several parameters: time to first bowel movement, first passage of flatus or defecation (Table 9), and time to resume intake of liquid or solid foods (Table 10). In the RCT, data on passage of first flatus and defecation are consistent with a faster recovery in the laparoscopic group. In two studies, the differences were not significant[75,103]. In all RCT, first bowel movement and resumption of diet were earlier after laparoscopic colorectal surgery.

Table 9: Gastro-intestinal function

Study	Flatus/defecation (days)			Bowel movement		
	Laparoscopic	Open	*p* value	Laparoscopic	Open	*p* value
2						
Lacy[109]				36 ± 31	55 ± 40 (hrs)	0.001
Milsom[77]	3 (0.8-8)	4 (0.8-14)	0.006	4.8 (1.5-8)	4.8 (1.5-14.5)	NS
Delgado[5]				< 70 yr 35 ± 36 > 70 yr 37 ± 19	53 ± 26 57 ± 33	0.0007 0.0005
Lacy[90]	35.5±15.7 hrs	71.1 ± 33.6 hrs	0.0001			
Schwenk[112]	50±19	79 ± 21	<0.01	70 ± 32	91 ± 22	<0.01
3						
Lezoche[84]	Flatus RHC 2.9 LHC 2.7 Defecation 3.5 3.8	 3.0 3.5 4.0 5.2	 NS <0.0001 <0.0001 <0.0001			
Hong[93]	3±1.7	4,1 ± 1.8	<0.0001	3.5 ± 2	4,9 ± 2.1	<0.0001
Koehler[114]	3.4 (2-5)	5.8 (3-7)	--			
Khalili[95]						
Lezoche[75]	3.0	3.7	NS	3.4	4.5	0.036
Marubashi[110]	2.1	3.75	<0.0001			
Bokey[96]	4.5	4.4	NS	4.9	5.5	NS

Results given as mean ± SD or median (range); NS, not significant; RHC, right hemicolectomy; LHC, left hemicolectomy

Table 10: start of postoperative oral intake

Study	Parameter	Laparoscopic	Open	*p* value
2				
Lacy[109]	Oral intake	54 ± 42	85±67	0.001
Delgado[5]	Oral intake	<70 yr 50 ± 45 >70 yr 59 ± 33	59±33 81±48	0.0001 0.002
Curet[88]	Clear liquids Regular diet	2.7 4,1	4,4 5,8	<0.05 <0.05
Lacy[90]	Oral intake	50,9 ± 20	98,8 ± 48.6 s	0.0001
Schwenk[112]	Regular diet	3.3 ± 0.7	5.0 ± 1.5	<0.01
3				
Hong[93]	Fluids Solid food	2,1 ± 1.8 5,2 ± 3.1	4,0 ± 2.0 7,1 ± 2.8	<0.0001 <0.0001
Koehler[114]	Regular diet	3,2 (2-6)	6,2 (4-10)	--
Khalili[95]	Oral intake	3,9 ± 0.1	4,9 ± 0.1	0.001
Lezoche[75]				
Marubashi[110]	Oral intake	5,13	10,04	<0.0001
Bokey[96]	Fluids Full diet	4,3 6,9	4,2 7,6	NS NS
Leung[99]	Normal diet	4 (2-20)	4 (3-17)	NS
Van Ye[100]	Normal diet	4.8	7.2	0.001

Results given as mean ± SD or median (range); NS, not significant

Statement 20: Gastro-intestinal function and start of postoperative oral intake

Gastro-intestinal function recovers earlier after laparoscopic colectomy (Level of evidence: 2b).

Pulmonary function

Laparoscopic surgery causes less impairment of pulmonary function, enabling faster recovery. Postoperative pulmonary function after laparoscopic cholecystectomy, as compared to the open counterpart, is improved[128]. Postoperative pulmonary function after colorectal resection has been investigated in an RCT by Schwenk et al.[87]. Parameters shown in Table 11 were measured preoperatively and at different time points postoperatively. Forced vital capacity and forced expiratory volume were more profoundly impaired in patients who underwent conventional resections than in the laparoscopic group. Similar results were found for the peak expiratory flow and the midexpiratory phase of the forced expiratory flow. Also, the postoperative oxygen saturation was lower in the conventional group than in the laparoscopic group. Two pneumonias occurred in the conventional group vs none

Table 11: Postoperative pulmonary function

Study	Parameters	Laparoscopic	Open	*p* value
1				
Schwenk[87]	FVC (p.o. day 1)	2.59 ± 1.11	1.73 ± 0.60	<0.01
	FEV1 (p.o. day 1)	1.80 ± 0.80	1.19 ± 0.51	<0.01
	PEF (p.o. day 1)	3.60 ± 2.22	2.51 ± 1.37	<0.05
	FEF 25-75% (p.o. day 1)	2.67 ± 1.76	1.87 ± 1.12	<0.05
	SaO2 % (p.o. day 1)	93.8 ± 1.9	92.1 ± 3.3	<0.05
2				
Milsom[77]	FEV1 and FVC (days till 80% recovery of preoperative values)	3.0	6.0	0.01
Stage[89]	FEV1	NA		NS
	FVC	NA		
	PEF	NA		

Results given as mean ± SD or median (range); NS, not significant; NA, not available; p.o., postoperative; FVC, foced vital capacity; FEV_1, forced expiratory volume in 1 second; PEF, peak exporatory flow; FEF 25-75%, Forced expiratory flow at 25-75% of forced vital capacity; SaO_2, arterial oxygen saturation

in the laparoscopic group. The difference was not significant, but the sample size of the study was only 30 patients.

Postoperative pulmonary function was investigated in two other RCT. Milsom et al.[129] found a significantly earlier postoperative recovery of pulmonary function after laparoscopic surgery. The RCT conducted by Stage et al.[89] showed no significant differences between the two groups in pulmonary function.

Statement 21: Postoperative pulmonary function

Postoperative pulmonary function is less impaired after laparoscopic compared to open resection of colon cancer (Level of evidence: 1b).

Return to work / daily activity

The parameters of early recovery are strongly influenced by societal and economic organization of health care within a community. This may explain the wide variability between studies. Only in randomized trials can one assume that these factors are evenly distributed in both groups. None of the available randomized trials addressed this topic.

Long-term outcome of laparoscopic colectomy

Overall and disease free survival

Recently, Lacy et al. published the results of their single-center randomized controlled trial on laparoscopic curative resection of coloncancer[109]. In this study of 219 patients, 111 underwent laparoscopic colectomy. A significantly better 3-year cancer-related survival was found in the laparoscopically operated patients than in the open group (91% vs 79%, respectively). This difference in survival could be attributed mainly to the markedly better survival in stage III coloncancer patients. Follow-up data of large multicenter randomized controlled trials the (CLASICC[130], COST[131], and COLOR[132] trials) will provide a more definitive assessment of survival after laparoscopic vs open colon resections.

In smaller nonrandomized comparative studies, no significant differences in disease-free and overall survival have been observed between open and laparoscopic patient groups (Table 12 and Table 13). No significant differences were found between open and laparoscopically operated patients in a nonrandomized

Table 12: Overall survival rates

Study	Follow-up	Laparoscopic	Open	*p* value
2				
Lacy[109]	43 mo	82	74	NS
3				
Leung[101]	21.4 mo (median)	90.9 (n=28)	55.6 (n=56)	NS
Leung[99]	32.8 mo (median)	67.2 (n=50)	64.1 (n=50)	NS
Khalili[95]	19.6 mo	87.5 (n=80)	85 (n=90)	NS
Santoro[98]	5 yr	72.3 (n=50)	68.8 (n=50)	NS
Hong[93]	Lap 30.6 mo Open 21.6 mo	NA (n=98)	NA (n=219)	NS
4				
Delgado[133]	42 mo	AR 83, SR 87 (n=31)		NS
Cook[134]	Until patient's death	20 (n=5)		NS
Hoffman[135]	2 yr	Node -: 92 (n=89) Node +: 80		NS
Molenaar[136]	3 yr	All: 59%, By Dukes stage (n=35): A=86, B=66, C=68, D=0		NS
Quattlebaum[137]	8 mo	90 (n=10)		NS
Poulin[106]	Stg I-III: 24 mo Stg IV: 9 mo	81		NS

NS, not significant; NA, not available; AR, anterior resection; SR, sigmoid resection

Table 13: Disease-free survival rates

Study	Follow-up	Laparoscopic	Open	*p* value
2				
Lacy[109]	43 mo	91	79	0.03
3				
Leung[101]	5 yr	95.2	74.7	NS
Leung[99]	4 yr	80.5	72.9	NS
Feliciotti[91]	48.9 mo	86.5	86.7	NS
Lezoche[84]	42.2 mo 42.3 mo	RHC 78.3 LHC 94.1	75.8 86.8	NS
Bouvet[92]	26 mo	93	88	NS
Santoro[98]	NA	73.2	70.1	NS
Hong[93]	Lap 30.6 mo Open 21.6 mo	NA	NA	NS
Franklin[97]	5 yr	87	80.9	NS
4				
Delgado[133]	42 mo	AR: 78 SR: 70		NS
Hoffman[135]	2 yr	Node - : 96 Node + : 79		

NS, not significant; NA, not available; RHC, right hemicolectomy; LHC, left hemicolectomy

matched control study with 5-year follow-up[101]. Another study using historical controls also showed no difference in long-term survival, with survival rates of 64.1% and 67.2% in the open and laparoscopic arms, respectively[99]. In a further six comparative studies, no differences of overall survival were found between laparoscopic and open resections of coloncancer[84,91-93,97,98].

Statement 22: Overall and cancer related disease free survival

Cancer related survival following laparoscopic resection appears at least equal to open resection (Level of evidence: 2a).

Port-site metastases after laparoscopic colectomy

Early reports of port site metastases after laparoscopic resection of colonic cancer generated considerable concern in the surgical community in the early 1990s. Initial enthusiasm for the laparoscopic approach to coloncancer was replaced by skepticism. Abdominal wall recurrence after open colectomy was considered to be rare—~0.7% according to a retrospective study by Hughes et al.[138]. However, Cass et al. reported abdominal wall recurrence in 2.5% of patients after open resection of coloncancer[139], and Gunderson et al. showed that two-thirds of abdominal wall recurrences are missed by physical examination of the abdominal wall[140]. At second-look laparotomy 3 months after the open curative resection of coloncancer, 3.3% of patients suffered a recurrence in the abdominal wall.

In the literature on laparoscopic resection of coloncancer published before 1995, high incidences of port site metastasis were reported, ranging from 0.6% to 21%[141-144]. In a review of data from reports on laparoscopic resection of colon-cancer published later, a much lower rate of 0.85% was recorded in an analysis of 1,769 operation[23]. Wittich et al. analyzed data from 16 studies, including a total of 3,547 patients, 30 of whom (0.85%) developed port site metastases[145]. In a recent systematic review, 11 port site metastases were found in 1,114 operations, translating to an incidence of 1%[115]. The high incidences of port site metastasis in early reports on laparoscopic surgery appear to reflect inexperience with the technique, such that an oncologically appropriate operation was not performed. The details of the published port site metastases are shown in Table 14 and Table 15.

Table 14: Port site metastasis after resection of colorectal carcinoma

Study	Design	*n*	Follow-up	PSM
Lacy[109]	RCT	111	Median 43	1
Milsom[77]	RCT	42	Median 18	0
Lacy[124]	RCT	31	21.4	0
Ballantyne[146]	Registry	498	NA	3
Fleshman[147]	Registry	372	NA	4 (1.3%)
Rosato[148]	Registry	1071	NA	10 (0.93%)
Vukasin[149]	Registry	480	>12	5 (1.1%)
Schiedeck[102]	Registry	399	Mean 30	1 (0.25%)
Leung[107]	Prospective	217	Mean 19.8	1 (0.65%)
Poulin[106]	Prospective	172	Mean 24	0
Franklin[97]	Prospective	191	>30	0
Bouvet[92]	Prospective	91	26	0
Lezoche[150]	Prospective	158	Mean 48.9	2
Bokey[103]	Retrospective	66	Median 26	1 (0.6%)
Fielding[108]	Retrospective	149	NA	2 (1.5%)
Gellman[151]	Retrospective	58	NA	1 (1.7%)
Hoffman[135]	Retrospective	39	≥24	0
Huscher[80]	Retrospective	146	Mean 15	0
Leung[99]	Retrospective	50	>32	1 (
Khalili[95]	Retrospective	80	Mean 21	0
Kwok[152]	Retrospective	83	NA	2 (2.5%)
Leung[107]	Retrospective	179	Mean 19.8	1 (0.65%)

Table 14 (*continued*)

Study	Design	*n*	Follow-up	PSM
Lord[117]	Retrospective	71	Mean 16.7	0
Lumley[82]	Retrospective	103	NA	1 (1.0%)
Khalili[95]	Retrospective	80	Mean 19.6	0
Guillou[153]	Retrospective	59	NA	1 (1.7%)
Larach[56]	Retrospective	108	Mean 12.6	0
Croce[154]	Retrospective	134	NA	1 (0.9%)
Kawamura[155]	Retrospective	67 (gasless)	NA	0
		5305		38 (0.72%)

RCT, randomized controlled trial; NA: not available, PSM: port site metastases

Table 15: Case reports on port site metastasis

Study	Year	Duke's stage	Months to recurrence
Alexander[156]	1993	C	3
O'Rourke[157]	1993	B	10
Walsh[158]	1993	C	6
Fusco[159]	1993	C	10
Cirocco[160]	1994	C	9
Nduka[161]	1994	C	3
Prasad[161]	1994	B	6
		A	26
Berends[141]	1994	B	NA
		C	NA
		D	NA
Lauroy[162]	1994	A	9
Ramos[163]	1994	C	NA
		C	NA
		C	NA
Cohen[164]	1994	B	3
		B	6
		C	6
		C	9
		C	12
Jacquet[165]	1995	B	10
		B	9
Montorsi[25]	1995	B	2

NA: not available

Statement 23: Port site metastasis
The incidence of port site metastases after laparoscopic colectomy is less than 1 % (Level of evidence: 2c).

QUALITY OF LIFE

Health-related quality of life associated with laparoscopic colon resection for malignancy has been addressed only by Weeks et al.[86]. The investigators used the Symptoms Distress Scale, Quality of Life Index (QLI), and a global rating scale. The only statistically significant difference reported was the global rating scale score 2 weeks postoperatively ($p = 0.009$). In this study, both the global rating scale and the QLI were not employed during the first 2 postoperative weeks, despite the probability that differences in quality of life are likely to be most evident and most pronounced in the early days after surgery.

COSTS

The issue of costs associated with the implementation of health care technologies is of increasing importance. Not only are financial demands on health care increasing, but at the same time health budgets are limited. Currently, there are no prospective cost-effectiveness evaluations available for laparoscopic colon resection. Some evaluations are currently being conducted alongside large multicenter RCT. In the CLASICC[130], COST[131], and COLOR[132] trials, cost-effectiveness of the two approaches is being evaluated. Such analyses include both direct costs (costs primarily associated with treatment) and indirect costs (costs secondarily related to disease or treatment).

Direct costs

In-hospital costs need to be carefully evaluated. In a retrospective review, the in-hospital costs of laparoscopically assisted right hemicolectomy were compared to the costs of open colectomy[166]. Costs were collected only from the time of operation until the time of discharge and thus reflected only hospital costs. This study reported higher direct costs for laparoscopic hemicolectomy than for open hemicolectomy due to increased operating time and the use of disposables (ADD 9,064 vs AUD 7,881, respectively). A review of the hospital costs of laparoscopic colectomy concluded that the shorter hospital stay in the laparoscopy arm more than compensated for the increased operating room costs, resulting in lower total hospital costs for laparoscopic colectomy (USD 9,811 vs USD 11,207)[167]. This evaluation included operations for both benign and malignant disease of the colon. In a prospective study, direct in-hospital costs for laparoscopic colectomy were also lower than those for open surgery (DM 5,400 vs DM 7,500)[114]. However, this large study included operations for both benign and malignant colorectal disease and violated the intention-to-treat principle.

Out-of-hospital costs

Out-of-hospital costs, such as visits to outpatient clinics, home care, and visits to family doctors, have not yet been estimated for laparoscopic colectomy.

Indirect costs

The preferred method of cost analysis is to evaluate cost-effectiveness from a societal perspective. This implies the measurement of indirect costs. The most important indirect costs are incurred from patients who are employed but are unable to work, causing loss of productivity. One might argue that a faster recovery would lead to patients returning to work earlier. Koehler et al.[114] reported that such costs were lower for laparoscopic colectomy (DM 1,600) than for open colectomy (DM 2,200).

Cost-effectiveness

For policy making and the implementation of new techniques, one must assess both the costs associated with this technique as well as the effects of this technique and its widespread safe applicability. Survival is the most important endpoint after the resection of coloncancer. The differences in costs between laparoscopic and open colorectal surgery have to be assessed in the context of survival rates obtained by the two approaches. The next endpoint in order of importance is quality of life. The calculation of quality-adjusted life years combines both. No cost-effectiveness studies have been reported.

Statement 24: Costs
Operation costs of laparoscopic resection of colon cancer are higher because of a longer operating time and the use of more expensive (disposable) devices. (Level of evidence: 3b)

POSTOPERATIVE STRESS RESPONSE

Stress response after laparoscopy

Laparoscopic surgery induces less trauma than conventional surgery and is thus likely to depress the immune response to a lesser extent. The preservation of the peritoneal and systemic immune system is important to prevent infections, sepsis, and the implantation of tumor cells to the traumatized tissues. In general, open surgery appears to inflict a greater nonspecific depression of the immune response than the laparoscopic approach.

Carbon dioxide pneumoperitoneum may impair the local immunity of the peritoneal lining. Peritoneal macrophages produce less cytokines[31,32], and their intrinsic function (phagocytosis)[30,168] diminishes on exposure to carbon dioxide insufflation.

Systemic immunity is depressed to a lesser extent by laparoscopic surgery than conventional open surgery. Both experimental and clinical studies on delayed-type hypersensitivity (DTH) response[169,170], production of cytokines[171], and expression of HLA-DR receptors[169,172] have confirmed this.

Stress response during colectomy

It has been suggested that survival may be improved if immunosupression induced by surgery could be reduced or eliminated[173]. The acute-phase response is a good index of the immune status of patients. Production of acute-phase proteins by hepatocytes often increases a thousandfold, as does C-reactive protein (CRP) after tissue injury. This reaction of liver cells is induced by corticoids and cytokines, of which interleukin-6 (IL-6) is the main activator. During recovery, the levels of acute-phase proteins normalize. This acute-phase reaction has been measured in most studies by monitoring the levels of IL-6 and CRP (Table 16 and Table 17).

Most studies demonstrated lower IL-6 levels after laparoscopic colorectal resection compared with open conventional surgery[38,111,172,174,176-179]. Only one study reported a significant raise in IL-6 serum level after laparoscopic sigmoidectomy[113]. Although IL-6 was lower after laparoscopic colectomy, studies have shown conflicting CRP data (see Table 17).

In addition to cytokines, other cell-related parameters, such as DTH and CD4/CD8 markers, have been assessed after laparoscopic colectomy, with no significant changes reported between laparoscopic and open colorectal surgery[111,180].

Table 16: Measurements of plasma interleukin-6 (IL-6) levels (in pg/ml)

Study	Preoperative	Laparoscopic	Open	*p* value
1-2				
Ordemann[172]	NA	Significantly lower after laparoscopy		< 0.01
Schwenk[174]	4.25 (3.4-7.7)	34.0 (25.6-48.7)	50.5 (39.8-75.7)	0.03
Hewitt[111]	NA	173 ±156	313 ± 294	0.25
Wu[175]	NA	83 ± 7	105 ± 33	< 0.05
3				
Sietses[176]	1.75 ± 1.64	85.6 ± 82.3	132.1 ± 143.8	NS
Fukushima[113]	NA	Significantly higher after laparoscopy		< 0.05
Delgado[177]	NA	239.5 (49.1-645.7)	372.7 (31.4-3,226)	< 0.05
Nishiguchi[178]	NA	Significantly lower after laparoscopy		< 0.05

Results given as mean ± SD or median (range); NS, not significant; NA, not available

Table 17: Measurements of plasma C-reactive protein (CRP) in mg/dl.

Study	Preoperative	Laparoscopic	Open	*p* value
1-2				
Schwenk[174]	NA	40 (33.0-49.4)	61.2 (52.0-77.9)	0.002
Wu[175]	NA	NA	NA	NS
3				
Fukushima[113]	NA	NA	NA	NS
Delgado[177]	NA	6.9 +- 4.5	9.1 +- 4.8	0.01
Nishiguchi[178]	NA	Significantly lower after laparoscopy		< 0.05

Results given as mean ± SD or median (range); NS, not significant; NA, not available

Statement 25: Stress response

Stress response after laparoscopic colectomy is lower (Level of evidence: 1b)

APPENDIX

Summary of all statements and recommendations

	Nr	Statements and recommendations	Level of evidence	Grade of recommen-dation
		Preoperative evaluation and selection of patients		
Recommendation	*1*	Preoperative imaging studies of colon cancer to asses the size of the tumor, possible invasion of adjacent structures. And localization of the tumor are recommended in laparoscopic surgery for colon cancer.	5	Grade D
Statement	*2*	Age only is not a contra-indication for laparoscopic resection of colon cancer.	2b	-
Recommendation	*3*	Invasive monitoring of blood pressure and blood gases is mandatory in ASA III-IV patients (No consensus: 91% agreement among experts)		Grade A
Recommendation		Low pressure (lower than 12 mm Hg) pneumoperitoneum is advocated in ASA III –IV patients		Gr ade B
Statement	*4*	Obesity is not an absolute contra-indication but the rates of complications and conversions are higher at BMI greater than 30 (No consensus: 93% agreement among experts).	2c	-
Recommendation	*5*	Potentially curative resections of colon cancer suspected of invading the abdominal wall or adjacent structures should be undertaken by open surgery (No consensus: 83% agreement among experts)	5	Grade D
Statement	*6*	Adhesions are not a contra-indication to laparoscopic colectomy.	4	-
		Operative technique		
Statement	*7*	Placement of trocars is based on the experience and the preference of the individual surgeon.	5	-
Recommendation	*8*	High quality videoscopic imaging and instrumentation is strongly recommended.	5	Grade D
Statement	9	Proper surgical technique and practice reduces the likelihood of port site metastasis.	3a	-
Recommendation	*10*	Preoperative tattooing of small colon tumors is advised. The alternatives are intraoperative colonoscopy, or pre-operative colonoscopic clipping followed by peroperative fluoroscopy or ultrasonography. Peroperative ultrasonografy can be employed as well at the hands of experts.	5	Grade D

	Nr	Statements and recommendations	Level of evidence	Grade of recommen-dation
Recommendation	*11*	Dissection of the mesocolon from medial to lateral is the preferred approach in laparoscopic colon surgery. During hand-assisted laparoscopic surgery for colon cancer, the mesocolon can also be resected from lateral to medial.	5	Grade D
		Intraoperative results of laparoscopic resection of colon cancer		
Statement	*12*	Laparoscopic colectomy is converted to open surgery in 14% of cases(0 – 42%). The most common causes of conversion are tumour invasion of adjacent structures or bulky tumor, adhesions and technical failure.	3a	-
Statement	*13*	Laparoscopic colectomy requires more operating time than open colectomy.	2a	-
Statement	*14*	The extent of laparoscopic lymphadenectomy and bowel resection is similar to those obtained by open colectomy.	2b	-
		Clinical outcome		
Statement	*15*	Morbidity after laparoscopic colectomy does not differ from that after open colectomy.	2b	-
Statement	*16*	Mortality of laparoscopic colectomy appears similar to that of open colectomy.	2b	-
Statement	*17*	Hospital stay after laparoscopic resection of colon cancer is shorter than after open colectomy.	1b	
Statement	*18*	Pain is less severe after laparoscopic colectomy.	2a	-
Statement	*19*	Less analgesia is needed after laparoscopic colectomy compared to open colectomy.	1b	-
Statement	*20*	Gastro-intestinal function recovers earlier after laparoscopic	2b	-
Statement	*21*	Postoperative pulmonary function is less impaired after laparoscopic compared to open resection of colon cancer.	1 or 2b	-
Statement	*22*	Cancer related survival following laparoscopic resection appears at least equal to open resection.	2a	-
Statement	*23*	The incidence of port site metastases after laparoscopic colectomy is less than 1%.	2c	-
		Costs		-
Statement	*24*	Operation costs of laparoscopic resection of colon cancer are higher because of a longer operating time and the use of more expensive (disposable) devices.	3b	-
		Postoperative stress response		
Statement	*25*	Stress response after laparoscopical colectomy is lower.	1b	-

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Chapter 2 epilogue

Laparoscopic Resection of Colon Cancer: Consensus of the European Association of Endoscopic Surgery

Update 2006

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EAES Guidelines for Endoscopic Surgery Twelve Years Evidence-Based Surgery in Europe
Neugebauer, E.A.M.; Sauerland, S.; Fingerhut, A.; Millat, B.; Buess, G. (Eds.) 2006, XXIV, 414 p.
2 illus., Softcover,

ISBN: 978-3-540-32783-7

CHOICE OF SURGICAL APPROACH AND PROCEDURE

The choice of surgical approach, laparoscopic or open, in colon cancer is dependent on both short- and long-term results. Since publication of the consensus on laparoscopic resection of colon cancer, one single center and three multicenter randomized controlled trials published their results following laparoscopic versus open surgery for colon cancer. The Clinical Outcomes of Surgical Therapy study group (COST) trial[1] and the trial by Leung et al. (Hong Kong)[2] reported the long-term outcome. The Conventional versus Laparoscopic Assisted Surgery In patients with Colorectal Cancer (CLASICC) trial[3] and the COlon cancer Laparoscopic or Open Resection (COLOR) trial[4] published the short-term results. In this update, we will discuss these studies.

INTRAOPERATIVE AND IMMEDIATE POSTOPERATIVE RESULTS

In the COLOR trial[4], a European multicenter randomized study, 1248 patients with colon cancer were included. The duration of surgery was 32 minutes longer in the laparoscopic group (202 vs. 170 minutes, $p<0.0001$), while blood loss was 75 ml less (175 vs. 100ml, $p<0.0001$). Similar differences in intraoperative results between laparoscopic and open colon resection were reported in the Hong Kong trial. The laparoscopic procedure took 45 minutes longer (189 vs. 144 minutes, $p<0.001$), but was associated with less blood loss (169 vs. 238 ml, $p=0.06$).

After surgery, the recovery of patients was faster following laparoscopic surgery in the COLOR trial: one day earlier recovery of bowel movements (3.6 vs. 4.6 days, $p<0.0001$) and fluid intake (2.9 vs. 3.8, $p<0.0001$) and fewer analgesics requirements. This resulted in a shorter hospital stay (8.2 vs. 9.3, $p<0.0001$). The Hong Kong and CLASICC trials also documented faster postoperative recovery of bowel function, less need for analgesics and shorter hospital stay. The COST[1], COLOR[4], CLASICC[3] and Hong Kong[2] trials did not report a difference in postoperative in-hospital morbidity, mortality, resection margins or number of harvested lymph nodes.

The costs of laparoscopic and open surgery for colon cancer were investigated by Janson et al. in a subset of Swedish patients randomized in the COLOR trial[5]. Costs were calculated up to 12 weeks after surgery. All relevant costs to society were included. Two hundred and ten patients were included in the primary analysis, 98 of whom were operated on laparoscopically and 112 with open surgery. The cost of surgery was significantly higher for the laparoscopic group than for the open group (difference in means Euro1171; $P < 0.001$), as was the cost of the first admission (difference in means Euro 1556; P = 0.015) and the total costs to the healthcare system (difference in means Euro 2244; P = 0.018). Total costs to society did not differ significantly between groups (difference in means for laparoscopic versus open surgery Euro 1846; P = 0.104). Janson et al. concluded that within 12 weeks of surgery for colon cancer, there was no difference in total costs to society. However, the laparoscopic procedure was more costly to the healthcare system.

The results of the aforementioned large randomized trials confirm the conclusions from the original consensus statement regarding intraoperative and immediate postoperative results of laparoscopic resection of colon cancer compared to those for the open procedure. Laparoscopic surgery for colon cancer is a safe and feasible procedure, improving short-term outcome.

LONG-TERM RESULTS

Since publication of the consensus on laparoscopic versus open surgery for colon cancer, all major randomized controlled trials no longer include patients and two trials published their results. Results of the trial by Lacy et al.[6] have already been discussed in the consensus.

The Cost trial is so far the only large multicenter trial to have published long-term outcome comparing laparoscopic to open surgery for colon cancer. In this study, three year overall and cancer-free survival were not different. However, this trial did not achieve its accrual goal and stopped randomization after 872 patients. Tinmouth and Tomlinson[7] stated that "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". The number of patients treated per center was low, which may have led to learning curve effects in this trial. Therefore this trial did not close the debate on long-term safety of laparoscopic colon cancer surgery.

Leung et all.[2] included 403 patients with rectosigmoid cancer in a single-center randomized trial. Survival after laparoscopic and open colectomy was similar. The long-term outcomes of the CLASICC and COLOR trials have not yet been published.

It can be concluded that patients with colon cancer who are operated on laparoscopically have similar long-term survival to open operated patients. However, a meta-analysis of all major randomized trials is to be performed to achieve the highest level of evidence for this subject. Given the advantages of laparoscopic surgery in the immediate postoperative period, laparoscopy should be implemented in the treatment of colon cancer with curative intent.

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3

Laparoscopic versus open surgery for colonic cancer: short-term outcomes of a randomized trial

COLOR Study Group

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Lancet Oncol. 2005 Jul;6(7):477-84.

SUMMARY

Background: The safety and short-term benefits of laparoscopic colectomy for cancer remain debatable. The multicentre 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 patients to open surgery. The primary endpoint was cancer-free survival 3 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], $p<0{\cdot}0001$), although laparoscopic surgery lasted 30 min longer than did open surgery ($p<0{\cdot}0001$). Conversion to open surgery was needed for 91 (17%) 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 not differ between groups. Laparoscopic colectomy was associated with earlier recovery of bowel function ($p<0{\cdot}0001$), need for fewer analgesics, and with a shorter hospital stay ($p<0{\cdot}0001$) 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]. 15 years after Muehe first did laparoscopic cholecystectomy, minimally invasive surgery has become the preferred approach for treatment of symptomatic cholecystolithiasis, gastro-oesophageal 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 sceptical about similar advantages of laparoscopic colectomy for cancer.

The European, multicentre 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 postoperative 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 kg/m^2; 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; preoperative 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 anaesthesia; 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 Erasmus University Medical Center, Rotterdam, 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 randomisation 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 committees 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 radiography 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 a 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]; pathologists 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 surgical 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, 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 ($p<0{\cdot}001$) in recurrence between groups.

Postoperative care, including use of narcotics for the first 3 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 and secondary outcomes

The primary outcome of the trial was cancer-free survival 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 80% power.

Percentage differences between groups were compared with the χ^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 number of patients 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. $p=0{\cdot}05$ (two-sided) was the limit of significance in all analyses.

Role of the funding source

The sponsor of the trial had no 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.

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

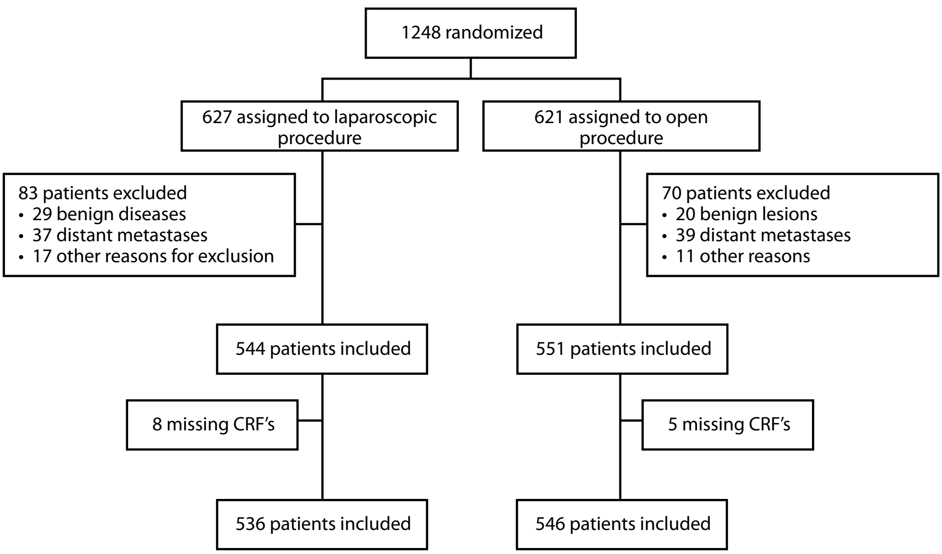

Figure 1: trial profile

Table 1. Baseline characteristics

Characteristics	Laparoscopic colectomy (n=627)	Open colectomy (n=621)
Age (years)		
Median (range)	71 (27–92)	71 (31–95)
Sex		
Men	326 (52%)	336 (54%)
American Society of Anesthesiologists 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)		
Median (range)	24·5 (12·1–37·1)	24·9 (14·5–40·5)
Previous abdominal surgery *		
No	386 (62%)	384 (62%)
Once	167 (27%)	163 (26%)
Twice	41 (7%)	49 (8%)
Three or more times	13 (2%)	9 (1%)
Missing data	20 (3%)	16 (3%)

* Does not total 100% because of rounding.

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 groups. The median time between randomisation and surgery was longer in the laparoscopic group than in the open-surgery group (6 days [range 1–85] *vs* 5 days [1–63]; p=0·02).

Table 2 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.

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

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 (45–420)	115 (40–355)	<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.

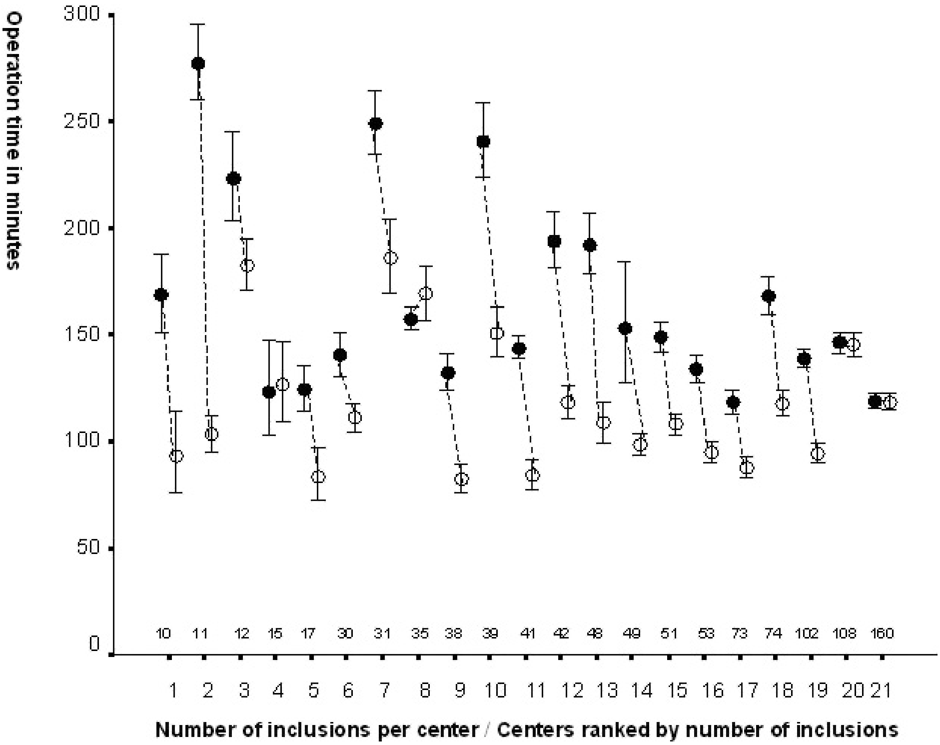

Figure 2: mean operating time by center
The 21 centers are ranked according to number per center. Closed dots: laparoscopic procedure, open dots: open procedure. Vertical bars are SE.

adhesions (n=10); 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 bowls 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 (0·36–2·68, 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 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).

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,

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 ‡			
T1	41 of 528 (8%)	39 of 537 (7%)	0·95
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 § ¶			
N0	347 of 528 (66%)	364 of 539 (68%)	0·44
N1	125 of 528 (24%)	122 of 539 (23%)	
N2	45 of 528 (9%)	48 of 539 (9%)	
N3	11 of 528 (2%)	5 of 539 (1%)	
Tumour stage § ¶			
I	129 of 528 (24%)	125 of 539 (23%)	0·60
II	218 of 528 (41%)	239 of 539 (44%)	
III	181 of 528 (34%)	175 of 539 (32%)	
Histology § ¶			
Well differentiated	90 of 529 (17%)	86 of 538 (16%)	0·89
Well to moderately differentiated	28 of 529 (5%)	32 of 538 (6%)	
Moderately differentiated	321 of 529 (61%)	315 of 538 (59%)	
Moderately to poorly differentiated	13 of 529 (2%)	15 of 538 (3%)	
Poorly differentiated or undifferentiated	46 of 529 (9%)	55 of 538 (10%)	
Not specified	31 of 529 (6%)	35 of 538 (7%)	
Number of positive lymph nodes in resected sample ‖			
Median (range)	10 (0–41)	10 (0–42)	0·35

* 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.

Table 4. Postoperative recovery, morbidity, and mortality

	Laparoscopic colectomy (n=536)	Open colectomy (n=546)	Mean difference between groups (95% CI)	P
Fluid intake >1 L (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 16)	0·0003
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)	0·0002
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)	0·28
Bleeding	13 of 534 (2%)	8 of 544 (2%)	-0·9 (-3 to 1)	0·36
Urinary-tract infection	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.

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 started in 1997 when the laparoscopic 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'[11] trial, which recorded shorter postoperative use of parenteral analgesics after laparoscopic colectomy than after open colectomy ($p<0{\cdot}001$).

Bowel obstruction after colectomy, as defined by postoperative day of 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 with laparoscopic colectomy 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[18] 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 needed in 19% of patients, mainly because of 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 time 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 unsubstantiated.

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 the 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 ten lymph nodes were removed during surgery in both groups. It has been suggested[23] that at least 12 lymph nodes should be removed to ensure radical resection. However, the number of removed 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 kg/m^2 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-workers[25] studied patients with a BMI of more than 30 kg/m^2 who had either laparoscopic colectomy 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 more than 30 kg/m^2 needed 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 as 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 with open surgery may be a 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, and 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 ($p<0{\cdot}007$).

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 optimum procedure for the individual patient with colon cancer.

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4

Quality of life after laparoscopic versus open colectomy; a randomized clinical trial

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Submitted for publication

ABSTRACT

Background: Laparoscopic colectomy for cancer has similar morbidity and oncologic long-term outcomes as open surgery. We compared health related quality of life after laparoscopic and open colectomy for patients with colon cancer.
Trial design, setting: Randomized clinical trial. All 6 participating Dutch medical centers provided quality of life data, as a substudy of the COLOR (COlon cancer Laparoscopic or Open Resection) trial.
Methods: We prospectively measured health related quality of life outcomes in a randomized clinical trial comparing laparoscopic and open surgery. All patients who met inclusion criteria and were randomized in one of the six Dutch participating hospitals were invited to complete the EuroQoL-5D, Short Form-36 and EORTC-CR38 questionnaires. The primary outcome of the trial was disease free survival 3 years after index surgery. Analyses were according to the intention to treat principle.
Results: Recruitment was stopped in March 2003. By that time 329 Dutch patients were randomized of whom 164 were assigned to laparoscopic surgery and 165 were assigned to open surgery. A total of 57 patients were excluded. In the open surgery group, the use of epidural anesthesia on the first two post-operative days was significantly higher compared to the laparoscopic surgery group ($p<0.01$). No differences in response rates of questionnaires were noted. The EuroQol-5D index score ($p=0.61$), SF36 mental component scale ($p=0.43$) and physical component scale ($p=0.62$) did not differ between the two operating groups. Significantly more patients reported micturition problems 4 weeks after surgery in the open group compared to the laparoscopic group ($P = 0.03$).
Conclusions: Although the use of analgesics is lower and fewer micturition problems were reported after laparoscopic surgery, laparoscopic and open surgery for colon cancer result in equal health related quality of life.

INTRODUCTION

The subject of health related quality of life has gained importance in daily practice. Since the introduction of laparoscopic surgery, quality of life related benefits of laparoscopic surgery have been reported following a broad range of procedures. Several groups already compared conventional and laparoscopic colectomy on quality of life related issues[1-6]. Few of these studies were multi-center and randomized[3,4,6]. The COLOR (COlon cancer Laparoscopic or Open Resection) trial was initiated by a group of European surgeons to assess and compare oncologic outcome after colon cancer surgery. The short and long-term results have been published earlier[7,8]. During the study period, Dutch patients were invited to participate in a quality of life substudy. The results of this substudy are reported.

METHODS

The COLOR trial is an international randomized clinical trial comparing outcomes of laparoscopic and open surgery in the curative treatment of colon cancer[9]. Between March 1997 and March 2003, 29 European hospitals randomized 1248 patients to either laparoscopic or open colectomy. During this study period all Dutch patients were invited to complete three health related quality of life questionnaires; EuroQoL-5D, Short Form 36 and EORTC-C30, prior to and at different time intervals after surgery. The ethics committee of each participating centre gave their approval for the trial.

Patients

Patients with a solitary tumor of the right or left colon, at least 18 years of age, providing written informed consent were eligible for this study. Exclusion criteria were: body-mass index (BMI) of more than 30 kg/m^2; adenocarcinoma of the transverse colon or splenic flexure; metastases in liver or lungs; acute intestinal obstruction, multiple primary tumors of the colon; scheduled need for synchronous intraabdominal surgery; preoperative 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 anaesthesia and/or a long-term pneumoperitoneum. In addition, patients who were cognitively impaired or who had language difficulties were excluded from the trial as well.

Patients were randomly assigned to either laparoscopic or open resection. Randomization was done centrally at the coordinating centre by phone or fax using a computer-generated list, stratified by centre and type of resection (left colectomy, right colectomy or sigmoidectomy). Surgical procedures have been described in detail before[8]. Medical staff and patients were not blinded for the allocated procedure.

Quality of life assessment

Health related quality of life (HRQL) was assessed by using three validated self-administered questionnaires in the Dutch translations; EuroQol-5D (EQ5D), Short Form 36 (SF36) and European Organisation for Research and Treatment of Cancer QLQ-C38 (EORTC-C38). EQ5D is a non-disease specific generic instrument to measure self-reported health status (EuroQol.org). Five dimensions of health were assessed: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has three levels: no problems, some problems and severe problems. The respondent is asked to indicate his or her health state by giving the most appropriate statement in each of the five dimensions. All dimensions can be summarized in the EQ5D weighted index score ($EQ5D_{index}$). The EQ5D visual analogue scale ($EQ5D_{VAS}$) was used as a quantitative measure of health outcome as judged by the individual respondents, by asking patients "on a scale of 0 to 100, with 0 as 'the worst imaginable health state' and 100 as 'the best imaginable health state', in your opinion which number would indicate how good or bad your own health is today". We have analyzed the EQ5D weighted index score using the Dutch Time Trade-Off (TTO) value set. The time frame consisted of the 24 hours prior to completing the questionnaire.

The second questionnaire used, was the SF36 (version 2.0, SF-36.org). It is a generic measure of quality of life, comparing general and specific populations. It compares the relative burden of disease and differentiates the health benefits produced by different treatments. The questionnaire consists of 36 questions and generates an eight-scale profile of scores (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health) as well as two summary scales, i.e. physical and mental health summary measures (resp. $SF36_{pcs}$ and $SF36_{mcs}$). The last four weeks was the time frame for this.

EORTC-CR38 (version 1.0, European Organization for Research and Treatment of Cancer) is a cancer specific questionnaire used to assess HRQL of colorectal cancer patients. It is a 38-item instrument designed for self-administration. This questionnaire assesses four functioning scales (body image, sexual functioning, sexual enjoyment and future perspective) and eight symptom scales (micturition problems, chemotherapy side-effects, symptoms in the area of the gastro-intestinal tract, male and female sexual problems, defecation problems, stoma-related problems and weight loss). Each scale has four response levels (not at all, a little, quite a bit and very much) with the last week as the time frame.

Patients were surveyed less than five days before the surgery and four weeks, six months and 12 months after surgery. The EQ-5D questionnaire was also administered on day 3, day 7 and day 14 after the initial operation. This was done either at the hospital, at a clinic or at home. Questionnaires needed to be completed six and 12 months after operation were sent to the patients by regular mail with a prepaid return envelope. Telephone interviews were not allowed to ensure self-administration of the questionnaires, thus to avoid investigator bias. Data was collected centrally at the coordinating center at the Erasmus University Medical Center in Rotterdam, the Netherlands. The trial-coordinator supervised data gathering and provided progress data to the protocol committee and monitoring committee.

Statistical analysis

The primary endpoint of the COLOR trial is disease free survival at three years after index surgery, requiring an accrual of 1200 patients. However for the quality of life substudy it was recognized that it would not be necessary to evaluate the entire study population. A sample size calculation for the quality of life outcomes was not performed.

All comparisons between groups were based on the intention-to-treat principle. All included patients were analyzed according to their initial treatment assignment. Reasons for (pre-) operative conversions were recorded. No additional analysis was performed comparing outcomes between groups defined by actual operative procedure.

A questionnaire was deemed analyzable if any domain or single item is completed. Return of a cover sheet was not considered to be a return of the questionnaire. Missing questionnaires were categorized as intermittent missing forms. Completion rates were calculated for specific study periods, such as baseline, on treatment (in hospital stay) and off treatment follow-up. Missing data were handled according to the individual manual of each questionnaire, no imputation was performed.

Descriptive data are reported as mean (standard deviation), 95 confidence interval (CI), or number of patients and percentages. Comparison between groups for binomial data was made by Chi-square test or the Fisher's exact test. The Student's *t*-test was used in case of measurements with a Gaussian distribution. The change scores were compared using the Mann-Whitney test separately for each time point and linear mixed model analysis was performed to compare groups over time. All p-values reported are 2-sided and considered statistical significant when $P < 0.05$.

RESULTS

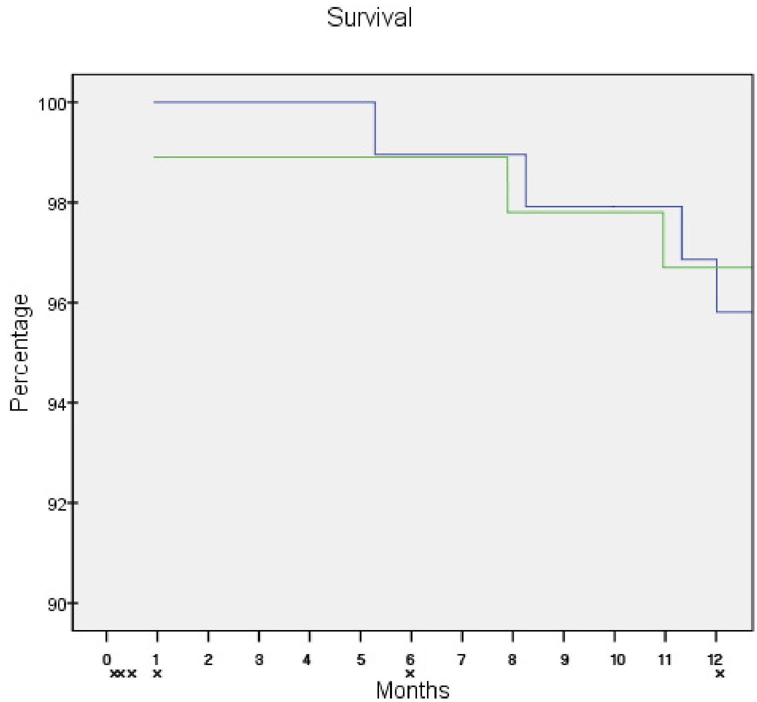
Patient characteristics

Between March 1997 and March 2003 a total of 329 patients were randomized in six hospitals in the Netherlands; 164 patients were randomized in the laparoscopic group and 165 patients were randomized in the conventional group. A total of 57 patients were excluded (14 were found to have nonmalignant disease, 28 appeared to have metastasized disease at operation and 15 were ineligible for other reasons). 187 (69%) patients returned their questionnaires and were deemed analyzable (figure 1). No significant differences in response rates between the two groups were found. No relevant differences between groups were found in terms of age, gender, Body Mass Index (BMI), American Society of Anesthesiologists (ASA) classification, stage of the disease, operative procedure or hospital case volume (table 1).

Clinical outcomes

Mean hospital stay in the laparoscopic group was eight days, compared to 9 days in the open group (p=0.56). Twenty-eight patients in the laparoscopic group converted to open surgery, were analyzed according to the "intention to treat" principle and remained in the laparoscopic arm for analysis. Three patients were converted pre-operatively because of malfunctioning laparoscopic equipment or absence of a skilled laparoscopic surgeon. Twenty-five (26%) patients were converted because of fixation to, or invasion, of adjacent structures by the tumor (n=6), inability to localize the tumor (n=4), tumor was localized in the transverse colon or below promontory (n=4), size of the tumor (n=2), macroscopic suspicious lymph nodes needing extensive resection (n=2), bad vision (n=2) and anatomical problems (n=5).

The use of opiates and non-opiates after surgery did not differ significantly between groups. However, epidural analgesics were significantly less frequently used in the laparoscopic group during the first two days after surgery. No significant differences between laparoscopically and open treated patients were



	Baseline	3 days	7 days	2 weeks	4 weeks	6 months	12 months
EuroQol 5D							
Expected	187	187	187	186	184	179	173
Received	160	147	139	137	176	172	167
Short Form 36							
Expected	187	NA	NA	NA	184	180	174
Received	159	NA	NA	NA	175	172	165
EORTC-CR38							
Expected	187	NA	NA	NA	184	180	173
Received	158	NA	NA	NA	175	173	166

Figure 1. Kaplan-Meier estimates of the survival curves (lap = blue; open =green). The times at which quality of life assessments were scheduled are indicated beneath the time axis(x). The panel indicates the quality of life assessments made for the three questionnaires during the first year as a percentage of those anticipated from the currently living patients.

found regarding post-operative adjuvant chemotherapy use, complication rates, mortality rates in the 28 day post-operative period and mortality rates one year after index surgery (table 2). A total of ten re-interventions were performed in the study group. Seven re-interventions were performed in the laparoscopic group within the first year after initial surgery; three abscess drainages, one open cholecystectomy, one incisional hernia correction, one excision of a lymph node

Table 1. Patient baseline clinical characteristics.

	Laparoscopic (n=96)	Open (n=91)	Total (n=187)
Age (years), median (range)	70 (54-83)	70 (54-84)	70 (54-83)
Sex, n (%)			
Women	50 (52)	35 (38)	85 (45)
Men	46 (48)	56 (62)	102 (55)
Body Mass Index (kg/m²), median (range)	25.1 (20.4-29.6)	25.3 (20.7-30.3)	25.1 (20.6-29.7)
ASA, n (%)			
I	34 (35)	36 (40)	70 (37)
II	45 (47)	43 (47)	88 (47)
III	16 (17)	9 (10)	25 (13)
missing	1 (1)	2 (2)	3 (2)
Stage, n (%)			
I	27 (28)	22 (24)	49 (26)
II	39 (41)	36 (38)	75 (40)
III	30 (31)	33 (34)	63 (34)
Intervention, n(%)			
Left hemicolectomy	9 (9)	8 (9)	17 (9)
Right hemicolectomy	52 (54)	47 (49)	99 (53)
Sigmoidectomy	30 (31)	35 (36)	65 (35)
Other	5 (5)	1 (1)	6 (3)
Conversion, n (%)	28 (29)	NA	28 (15)
Hospital case volume, n (%)			
High	75 (78)	77 (85)	152 (81)
Low	21 (22)	14 (15)	35 (19)

Range 10^{th} to 90^{th} percentile. ASA = American Society of Anesthesiologists.

metastasis, one splenectomy for B-cell lymphoma. Three re-interventions were necessary in the open group; one abdominal hysterectomy for endometrial carcinoma, one open cholecystectomy and one abscess drainage.

As approximately one third of patients did not return their questionnaires an additional comparison was made on baseline data and clinical outcome between the patients who did return their questionnaires and the patients who did not return their questionnaires. The following outcomes showed no significant differences between participants vs non-participants, stage of the disease, hospital stay, analgesic use and mortality rates. However a difference between groups was found for the number of complications (41.7% vs 20.3%) and post-operative re-interventions (13.4% vs 5.4%), for respectively non-participants and participants.

Table 2. Clinical outcome.

	Laparoscopic (n=96)	Open (n=91)	Mean difference between groups (95% CI)	P
Hospital stay (in days), median (range)	8 (5-17)†	9 (6-16)‡	0.84 (-3.6 to 2.0)	0.56
Analgesic use				
Day 1				
Opiates	35 of 89 (60%)	29 of 83 (35%)	n.a.	0.55
Non-opiates	52 of 90 (58%)	43 of 83 (52%)	n.a.	0.43
Epidural	41 of 90 (46%)	58 of 83 (70%)	n.a.	0.001
Day 2				
Opiates	25 of 88 (28%)	22 of 83 (27%)	n.a.	0.78
Non-opiates	69 of 88 (78%)	55 of 83 (66%)	n.a.	0.08
Epidural	33 of 88 (38%)	53 of 83 (64%)	n.a.	0.0006
Day 3				
Opiates	14 of 88 (16%)	20 of 83 (24%)	n.a.	0.18
Non-opiates	58 of 88 (66%)	53 of 83 (64%)	n.a.	0.78
Epidural	14 of 88 (16%)	22 of 83 (27%)	n.a.	0.09
Chemotherapy (within 28 days after surgery)	12 of 95 (13%)	14 of 91 (15%)	n.a.	0.54
Complications (within 28 days after surgery)	18 of 96 (19%)	20 of 91 (22%)	n.a.	0.58
Reinterventions, n (%) (within 1st year after surgery)	7 of 96 (7%)	3 of 91 (3%)	n.a.	0.23
Mortality (within 28 days after surgery)	1 of 96 (1%)	1 of 91 (1%)	n.a.	0.97
Mortality (within 1st year after surgery)	5 of 96 (5%)	3 of 91 (3%)	n.a.	0.52

Range 10th to 90th percentile. † data missing in 2 patients. ‡ data missing in 1 patient.

Quality of life assessments

As shown in table 3, the results of the EQ5D and SF36 questionnaires did not reveal any differences between laparoscopic and open surgery patients. EQ5D showed that patients in the laparoscopic group recovered (ie. returned to baseline values) within two weeks after initial surgery. Scores in the open group returned to pre-operative values within four weeks. The same difference was observed in the SF36 mental component scale; laparoscopically operated patients had a significant improvement compared to baseline values within six months after surgery. This compared to conventionally operated patients who had a significant improvement within 12 months after surgery. However significant differences between groups on all time

Table 3. Comparison of EQ5D and SF36 outcomes between surgical groups at different time points from index surgery (high scores indicate better quality of life).

	Lap (n=96): mean (SD)	Open (n=91): mean (SD)	Crude difference: mean (SE)	Difference adjusted for baseline score: mean (SE)	P
EQ5D weighted index score					
Baseline	0.78 (0.23)	0.78 (0.22)	0.01 (0.03)	Ref	
3 days	0.46 (0.30)†	0.42 (0.22)†	0.06 (0.04)	0.04 (0.05)	0.26
7 days	0.65 (0.30)†	0.69 (0.27)	-0.03 (0.05)	-0.03 (0.05)	0.46
2 weeks	0.73 (0.25)	0.66 (0.27)†	0.05 (0.04)	0.07 (0.06)	0.15
4 weeks	0.79 (0.19)	0.80 (0.21)	-0.01 (0.03)	-0.004 (0.04)	0.69
6 months	0.83 (0.20)	0.85 (0.17)	-0.03 (0.03)	0.01 (0.04)	0.76
12 months	0.86 (0.22)	0.85 (0.18)	0.01 (0.03)	0.01 (0.04)	0.50
SF36 physical component summary					
Baseline	42.17 (7.84)	42.56 (9.75)	-0.39 (1.74)	Ref	
4 weeks	37.58 (7.92)†	36.99 (7.74) †	0.59 (1.40)	0.21 (2.10)	0.97
6 months	42.75 (7.39)	40.76 (8.57)	1.99 (1.45)	-3.69 (1.93)	0.08
12 months	41.95 (7.77)	42.08 (7.50)	-0.13 (1.34)	-1.51 (1.78)	0.48
SF36 mental component summary					
Baseline	48.05 (11.80)	46.98 (9.75)	1.06 (2.39)	Ref	
4 weeks	51.47 (10.88)	51.08 (10.47)	0.39 (1.90)	0.34 (2.95)	0.69
6 months	53.09 (10.85)†	51.58 (10.09)	1.51 (1.90)	0.33 (3.01)	0.84
12 months	53.00 (11.46)†	53.98 (8.64)†	0.58 (1.78)	2,68 (2.93)	0.45

SD = standard deviation, SE = standard error. † Significant difference compared to baseline within group ($P < 0.05$).

points were not found, nor were there differences between groups when the results were adjusted for baseline scores. No differences were found between both groups over time for the $EQ5D_{index}$ (p=0,61; 95% CI -2,3 – 5,1), the $SF36_{mcs}$ (p=0,43; 95% CI -2,10 – 4,84), the $SF36_{pcs}$ (p=0,62; 95% CI -1,66 – 2,80) and the EORTC gastrointestinal scale (p=0.52; 95% CI -4,92 – 2,51). As the conversion rates were substantial we repeated the same analyses following the as-treated principle, no significant differences were found between groups.

Regarding the $EQ5D_{VAS}$ scores, no significant differences were found between groups (figure 2). The first three days after surgery resulted in a significantly lower health outcome compared to baseline (laparoscopic: P = 0.01; open: P < 0.0001). At six and 12 months after surgery a significant increase in general health compared to baseline was noted for each individual group (laparoscopic: P = 0.01 and P = 0.02; open: P = 0.003 and P = 0.002; respectively).

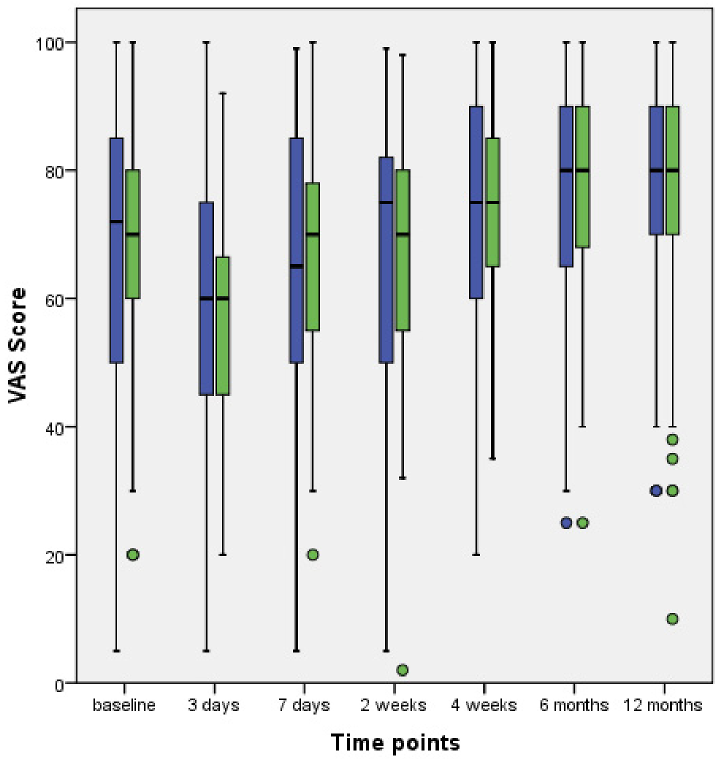


Figure 2. Boxplots of the $EQ5D_{VAS}$ scores at different time points for laparoscopic surgery (blue) and conventional surgery (green) with five statistics (minimum, first quartile, median, third quartile and maximum). Outliers for each group are symbolized by circles in green and blue.

Univariate analyses of the EORTC-CR38 showed no differences in the four functional scales at four weeks, six months and 12 months after surgery compared to baseline data for both groups. The symptom scales remained practically the same throughout the follow-up period. A significant increase of micturition problems was found in the open group after 4 weeks of surgery, compared to patients operated upon laparoscopically (p=0.03, Mann-Whitney *U*) (table 4).

DISCUSSION

Health has traditionally not only been defined as the absence of disease and infirmity but also the presence of physical, mental and social well-being. Health related quality of life studies have gained importance in health care practice and research. The increasing number of health related research acquired a substantial role in the evaluation of effectiveness and efficacy of new therapeutic strategies and their associated

Table 4. EORTC-CR38 scores for 4 functional scales (higher score, a higher level of functioning) and 8 symptom scales (a higher score, a higher level of symptomatology). Mean scores and 95% confidence interval are shown at baseline. Absolute changes are shown after 4 weeks, 6 months and 12 months after index surgery.

	Baseline score†		**4 weeks**			**6 months**			**12 months**		
			Δ baseline		**P**	**Δ baseline**		**P**	**Δ baseline**		**P**
	Lap	**Open**	**Lap**	**Open**		**Lap**	**Open**		**Lap**	**Open**	
Body Image	89 (84-93)	90 (86-93)	-0.4	-2.4	0.29	1.6	-3.0	0.10	1.0	-1.3	0.41
Future perspective	55 (48-63)	64 (60-70)	14.6	8.6	0.22	18.3	12.5	0.21	12.9	9.8	0.31
Sexual functioning	17 (13-22)	20 (14-26)	-1.9	-3.3	0.27	6.1	4.4	0.53	4.4	8.45	0.83
Sexual Enjoyment	44 (32-55)	57 (46-69)	8.2	3.2	0.47	11.3	0.15	0.09	12.6	-.047	0.12
Micturition problems	29 (26-33)	27 (23-30)	0.2	6.0	0.03	-2.0	-0.7	0.12	-4.7	-1.8	0.60
Chemotherapy side effects	15 (11-20)	15 (12-19)	3.4	4.3	0.18	2.7	7.1	0.32	0.4	-1.8	0.82
Gastro-intestinal symptoms	24 (21-28)	23 (20-27)	-2.9	-2.4	0.25	-5.4	-3.9	0.70	-5.4	-5.9	0.61
Male sexual problems	41 (27-55)	27 (15-39)	-1.2	-5.9	0.87	-6.6	3.4	0.14	-2.3	2.4	0.36
Female sexual problems	4 (-2-9)	14 (0-28)	15.1	35.7	0.08	14.2	-2.4	0.43	11.8	10.7	0.53
Defecation problems	17 (13-20)	19 (16-21)	-0.3	-4.2	0.18	-5.2	-6.5	1.00	-4.9	-7.9	0.98
Stoma-related problems§	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Weight loss	26 (19-32)	30 (22-38)	1.6	-0.7	0.86	-17.3	-22.3	0.13	-16.1	-26.8	0.12

† No significant differences between groups (Mann-Whitney *U*). § number of stomas in the laparoscopic group and open group were: 2 and 0 at 4 weeks, 2 and 1 at 6 months, 1 and 0 at 12 months.

costs. After the introduction of laparoscopic surgery for colon cancer, the number of health related quality of life reports on this subject grew rapidly. However most results are based upon the experience of a single surgeon or are collected at a single institution. The results presented here are from a randomized multi-center clinical trial.

The EQ5D and the SF-36 physical component scale showed a non-significant difference in an earlier return to baseline values in favor of laparoscopic surgery. However time frames between the questionnaires do not match. The EQ5D showed an improvement in the first two to four weeks for laparoscopic surgery. Yet in the

SF36 a difference was noticeable in 6-12 months. This mismatch could possibly be explained by the fact that this study was not powered for HRQL outcomes. A study specifically powered for HRQL outcomes may show significant outcomes.

The only significant difference in HRQL found in this study was a difference in 'micturition problems' as a symptom scale of the EORTC-CR38 at four weeks after surgery. This fact remains unexplained as performed operative procedure (right hemicolectomy, left hemicolectomy and sigmoidectomy), tumor characteristics and post-operative complication rates did not differ between groups. Possibly the open group was negatively affected by the more frequent use of epidural catheters which required a prolonged usage of bladder catheters. The failure of the EORTC-CR38 to show any difference between baseline and post-operative outcomes might be attributable to the fact that this study was not powered for HRQL outcomes. In addition, one might question whether the correct questionnaires were used. All of the used questionnaires are general health questionnaire except for the EORTC-C38, which is disease specific. Nevertheless no specific *colon* cancer questionnaire was used, which in turn might accredit to the inability of finding differences between groups.

Other groups did find differences in HRQL all in favor of laparoscopic surgery. Janson et al (2007) reported a better health related quality of life at two and four weeks in social functioning and role functioning scales of the EORTC-C30 questionnaire[3]. Furthermore Weeks et al (2002) only found a significant difference in the Global Rating Scale at two weeks after surgery, resulting in minimal HRQL benefits following laparoscopic surgery.[6]

Previously published short term results show a benefit in hospital stay, blood loss and analgesics requirements for patients who are operated upon laparoscopically[6,8,10]. In the Dutch subset of patients hospital stay did not differ but analgesic requirements on postoperative day one and two after surgery were significantly lower after laparoscopic surgery. However, additional analysis on the individual pain dimension of the EQ5D at day 3 could not objectify this clinical finding (data not shown). With a response rate of 73% and absolute number of 96 and 91 patients in each group are apparently insufficient to detect a statistical significant difference.

Several limitations of this study should be noted. Firstly, the average age of patients is 70 years. This had implications for the design of the trial, as well as on the results. The aim was to assess HRQL as accurately as possible and to minimize burden on participating patients. At each time point we have limited the number of questions from just six of only the EQ5D (on day 3, day 7 and 2 weeks post-operative) to a maximum of 80 of all questionnaires (on five days pre-operative, four weeks, six months and 12 months post-operative). Secondly, although internet based questionnaires supposedly result in higher accuracy of data we chose for a paper-and-pencil version as the accessibility to and familiarity with internet was expected to be low in this group of patients[11].

The response rates were 73% in the laparoscopic group and 65% in the open group. Adequate recording of non-eligibility and drop-outs was not performed which increased the risk of a selection bias. Despite non-recording, dropout numbers (ie. missing all quality of life assessments) in both groups appear to be the same and in equal percentages in all six hospitals. Other quality of life studies on colon cancer surgery report comparable inclusion rates ranging from 73%-78%[1,3,6].

The operative conversion rate in the Dutch subgroup was relatively high (29%). Reported conversion rates in comparable studies range from 4.2% to 77%[12]. As the reasons for conversion in our study were mostly related to tumor characteristics, future conversions are possibly be prevented by improved pre-operative assessment of size of the tumor and the extensiveness of the disease by using computed tomography preoperatively.

The follow-up period of one year is relatively short and measures of quality of life may change further with longer follow-up. The choice of time points in the present trial was based upon the expectation to find a difference in the short term.

The COLOR trial was initiated by a group of European surgeons in the 1990's with the aim to compare long-term outcomes between laparoscopic and open surgery. The health related quality of life sub study was build upon this international randomized clinical trial. The long term results have been published earlier and showed us that although the predetermined non-inferiority boundary of 7% was passed by a mere 0.3%, no clinically significant differences in disease free survival between the two operating groups were found[7]. In combination with the results from the present study we feel that no barriers remain to implement laparoscopic surgery into the daily practice in general surgery. Moreover, our short term results (published before) showed an experience effect on operating time[8]. Future studies on health related outcomes after laparoscopic colon cancer surgery with a larger sample size are warranted.

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5

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

COLOR Study Group

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Surg Endosc. 2005 May;19(5):687-92.

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 min in centers with low, medium, and high case volumes, respectively ($p < 0.001$). A significant difference in conversion rate was observed among low, medium, and high case volume hospitals (24% vs 24% vs 9%; $p < 0.001$). A higher number of lymph nodes were harvested at 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 at 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[1].

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[2]. Laparoscopic colectomy appears to be associated with less morbidity and an earlier recovery than open colectomy[3,4]. However, laparoscopic colorectal surgery is technically demanding and therefore associated with a considerable learning curve[5-7].

To determine the impact of hospital case volume on short-term outcome after laparoscopic colon resection for cancer, all patients who underwent laparoscopic operation 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 anesthesia or a prolonged pneumoperitoneum were excluded as well. Randomizations were performed at the central coordinating 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 to which they had been assigned.

To ensure quality control, one member of the surgical team should have experience with ≥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 coordinating 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 total 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, theater time, and number of lymph nodes harvested were compared among the three 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 theater time, days until first defecation, and blood loss among the three groups. In these analyses, outcomes had to be transformed logarithmically 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 Steindamm 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 laparoscopic 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 the operation (n = 37), benign lesions (n = 29), withdrawal of informed consent (n = 6) or other reasons (n = 11). For details regarding exclusions after randomization, see figure 1.

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 classified as low case volume hospitals. The average number of surgeons who reported cases was five, four, and two 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 observed. Patients with an ASA III classification were more prevalent at high and low case volume hospitals than at medium case volume hospitals. Fewer right hemicolectomies and more left hemicolectomies were performed at high caseload hospitals. Patient, tumor, and treatment characteristics are shown in Table 1.

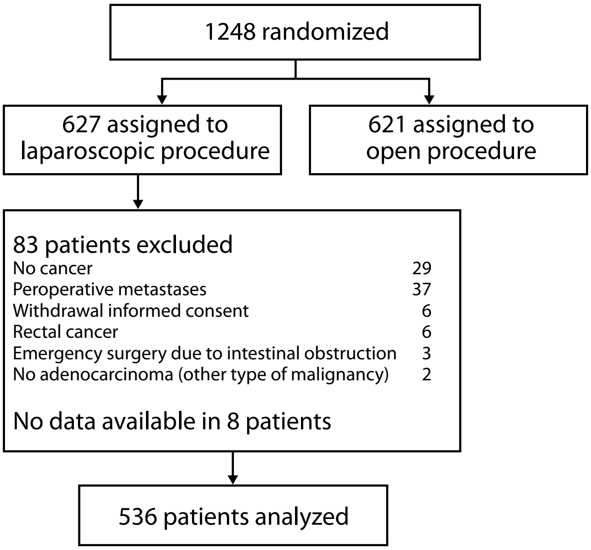

Figure 1. Randomization process

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 the 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 min at low case volume hospitals, 153 min at medium case volume hospitals, and 130 min at high case volume hospitals. For this reason, low and medium caseload hospitals reported significantly longer skin-to-skin times than to high volume hospitals ($p < 0.001$). Median time in the operating theater was 240 min for laparoscopic colon resection at hospitals with a low case volume vs 210 min at medium case volume hospitals and 188 min 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 ($p < 0.001$).

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 ($p < 0.001$).

Table 1: Patient, tumor, and treatment characteristics

	Low (n = 161)	Medium (n = 186)	High (n = 189)	p value
Sex (%)				
Male	47	51	57	NS
Female	53	49	43	NS
Age (yr) (mean)	70.3	70.2	69.3	NS
No. of previous abdominal operations (mean)	0.52	0.42	0.52	NS
Operative procedure (%)				
Left	6	8	18	0.001
Right	53	57	37	0.001
Sigmoidectomy	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 as means or percentages (within volume group)

Table 2: Operative findings

	Low (n = 161)	Medium (n = 186)	High (n =189)	p value
Perioperative inadvertent events (n)				
Hypercapnia	1	0	0	NS
Bleeding	3	8	6	NS
Fixation of tumor	11	4	8	NS
Perforations	3	0	0	NS
Adhesions	13	7	6	NS
Problems with anastomosis	6	0	3	0.03
Other	9	11	10	NS
Total no. of patients with inadvertant 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 theater time (min)	240	210	188	<0.001
Conversion rate (%)	24	24	9	<0.001
Median no. of lymph nodes harvested	9	8	12	<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 the 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 reoperation.

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

Table 3: Postoperative outcomes

	Low (n = 161)	Medium (n = 186)	High (n = 189)	p value
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
Reinterventions (n)	13	14	10	NS
Readmissions (n)	9	11	1	0.011
First defecation[a]	3	4	3	0.004
Day of discharge[a]	8	7	6	<0.001

[a] Median number of days

The number of reinterventions during the first 28 days after surgery showed no significant correlation with hospital caseload ($p = 0.261$). There were significantly fewer 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 three 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[9], 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[10,11]. 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[3,4,11,12]. 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[4,13]. 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[4]. In the multicenter Clinical Outcomes of Surgical Therapy (COST) trial, no differences in survival were observed between laparoscopically assisted and open operation 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[13].

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 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. 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[14]. 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[15]. They found significant differences in the rate of abdomino-perineal 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[16]. 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 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%)[17]. 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%; $p = 0.006$)[18]. 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[19]. 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 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 per 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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6

Survival after laparoscopic surgery versus open surgery for colon cancer: long-term outcome of a randomized clinical trial

COLOR Study Group

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Lancet Oncol. 2009 Jan;10(1):44-52.

SUMMARY

Background: Laparoscopic surgery for colon cancer has been proven safe, but debate continues over whether the available long-term survival data justify implementation of laparoscopic techniques in surgery for colon cancer. The aim of the COlon cancer Laparoscopic or Open Resection (COLOR) trial was to compare 3-year disease-free survival and overall survival after laparoscopic and open resection of solitary colon cancer.

Methods: March 7, 1997, and March 6, 2003, patients recruited from 29 European hospitals with a solitary cancer of the right or left colon and a body-mass index up to 30 kg/m^2 were randomly assigned to either laparoscopic or open surgery as curative treatment in this non-inferiority randomised trial. Disease-free survival at 3 years after surgery was the primary outcome, with a prespecified non-inferiority boundary at 7% difference between groups. Secondary outcomes were short-term morbidity and mortality, number of positive resection margins, local recurrence, port-site or wound-site recurrence, and blood loss during surgery. Neither patients nor health-care providers were blinded to patient groupings. Analysis was by intention-to-treat.

Findings: During the recruitment period, 1248 patients were randomly assigned to either open surgery (n=621) or laparoscopic surgery (n=627). 172 were excluded after randomisation, mainly because of the presence of distant metastases or benign disease, leaving 1076 patients eligible for analysis (542 assigned open surgery and 534 assigned laparoscopic surgery). Median follow-up was 53 months (range 0·03–60). Positive resection margins, number of lymph nodes removed, and morbidity and mortality were similar in both groups. The combined 3-year disease-free survival for all stages was 74·2% (95% CI 70·4–78·0) in the laparoscopic group and 76·2% (72·6–79·8) in the open-surgery group (p=0·70 by log-rank test); the difference in disease-free survival after 3 years was 2·0% (95% CI -3·2 to 7·2). The hazard ratio (HR) for disease-free survival (open vs laparoscopic surgery) was 0·92 (95% CI 0·74–1·15). The combined 3-year overall survival for all stages was 81·8% (78·4–85·1) in the laparoscopic group and 84·2% (81·1–87·3) in the open-surgery group (p=0·45 by log-rank test); the difference in overall survival after 3 years was 2·4% (95% CI -2·1 to 7·0; HR 0·95 [0·74–1·22]).

Interpretation: Our trial could not rule out a difference in disease-free survival at 3 years in favour of open colectomy because the upper limit of the 95% CI for the difference just exceeded the predetermined non-inferiority boundary of 7%. However, the difference in disease-free survival between groups was small and, we believe, clinically acceptable, justifying the implementation of laparoscopic surgery

into daily practice. Further studies should address whether laparoscopic surgery is superior to open surgery in this setting.

INTRODUCTION

Cancer of the colon is the third most common cancer in men and women in the developed world[1], and resection is the only curative treatment. Traditionally, cancers of the colon were removed through large abdominal incisions. More than a decade ago, the first report on laparoscopic resection of colon cancer was published[2]. Laparoscopic colectomy is associated with improved convalescence and decreased morbidity compared with open resection[3-6]. However, reports of tumour recurrence at the port sites after laparoscopic resection of colon cancer have questioned the oncological safety of laparoscopic surgery in patients with bowel cancer[7]. Thus, disease-free survival after laparoscopic colectomy for cancer needs to be proven non-inferior to that after open resection of bowel cancer.

The European multicentre COlon cancer Laparoscopic or Open Resection (COLOR) trial aimed to assess disease-free survival and overall survival 3 years after laparoscopic surgery or open surgery for colon cancer. The short-term outcomes of the COLOR trial have been published previously[6]. Here, we present the data for long-term outcome.

METHODS

Patients and procedures

Patients with colon cancer presenting at 29 participating hospitals in Europe were considered for inclusion in the trial. Patients with a solitary adenocarcinoma, localised in the caecum, ascending colon, descending colon, or sigmoid colon above the peritoneal deflection, who were aged 18 years or more, and who provided written informed consent, were eligible for random assignment to either laparoscopic or open surgery. Exclusion criteria included: a body-mass index (BMI) greater than 30 kg/m^2 distant metastases; acute intestinal obstruction; multiple primary tumours of the colon; a scheduled need for synchronous intra-abdominal surgery; preoperative evidence of invasion of adjacent structures, as assessed by CT, MRI, or ultrasonography; previous ipsilateral colon surgery; previous malignancies (except adequately treated basocellular carcinoma of the skin or in-situ carcinoma of the cervix); absolute contraindications to general anaesthesia; and a long-term pneumoperitoneum. Because adenocarcinomas of the transverse colon or the splenic flexure are rare, and laparoscopic removal is technically demanding, patients with such tumours were excluded from this study. Randomisation was done centrally at the coordinating centre by fax or telephone using a computer-generated list. This list was stratified by participating centre and proposed type of resection (ie, right hemicolectomy, left hemicolectomy, or sigmoidectomy). Stratification was done by centre because all surgeons who participated in the COLOR trial work in colorectal surgery teams, instead of working as individual surgeons. After randomisation, patients could only be excluded if metastasised disease was detected during surgery, microscopic examination of the resected specimen showed no signs of malignancy, other primary malignancies were discovered before or during surgery, emergency surgery was required, or if patients withdrew their consent. The ethics committee of each participating centre approved the trial.

Diagnosis of colon cancer was confirmed either by barium-enema radiography or colonoscopy. Biopsies were required for polyps, but not for macroscopically evident carcinomas. To exclude distant metastases, radiographic imaging of liver and chest was mandatory. In patients with rectosigmoid carcinoma, a lateral barium-enema radiograph was needed to determine the exact location of the tumour. Bowel preparation, antibiotic prophylaxis, and thrombosis prophylaxis were done according to local standards without consideration of group designation.

Conventional and laparoscopic surgery was done according to standardised protocols as described previously[6]. The planned extent of resection was similar for laparoscopic and conventional open surgery. In laparoscopic procedures, either the specimen or the extraction site was protected during removal of the affected bowel. The decision to convert to conventional surgery was made by the surgical team. Conversion was defined as an inability to complete all intended laparoscopic steps laparoscopically. All surgical teams had done at least 20 laparoscopically assisted colectomies before entering the trial. An unedited videotape of a laparoscopic colectomy was submitted to HJB, EH, MM, or AL before a centre participated in the trial to assess safe and oncologically sound techniques.

Interim analyses were done by an external monitoring committee after 50, 100, and 150 recurrences in the entire study population. The trial was to be stopped if open surgery was associated with a lower recurrence ($p<0{\cdot}01$) than laparoscopic surgery, or if laparoscopic surgery was followed by a lower recurrence ($p<0{\cdot}001$).

Postoperative care, including use of narcotics, was according to the surgeon's standard practice. Preoperative and postoperative adjuvant therapy was allowed at the physician's discretion, according to local standards, as long as patients in each treatment group were treated according to the same protocol. Neither patients nor health-care providers were blinded to patient groupings.

Last follow-up was completed in April, 2006. In view of the variations of practice between countries, minimum requirements for follow-up were determined. These stipulated that annual follow-up at the outpatient clinic was needed for a minimum period of 5 years. At 3 years' follow-up, the entire colon was inspected by barium enema or colonoscopy, the chest was imaged by plain radiography, CT, or MRI, and the liver was assessed by ultrasonography, CT, or MRI. Determining carcinoembryonic antigen levels at follow-up was not mandatory.

The primary outcome of this non-inferiority trial was disease-free survival at 3 years after surgery. Secondary outcomes were short-term morbidity and mortality; number of positive resection margins; recurrence at the site of the primary tumour, at port sites, and at wound sites; distant metastases; overall survival; blood-transfusion requirements; quality of life; and cost. Recurrences at the site of the primary tumour, at port sites, and at wound sites were considered as local recurrences. Distant metastases were considered as distant recurrences. Patient record forms were regularly collected by the coordinating centre in Rotterdam, Netherlands. Short-term morbidity and mortality were defined as 28-day postoperative or in-hospital morbidity and mortality. Morbidity and mortality were separately recorded on patient record forms. The coordinating centre was informed of all postoperative complications within 2 weeks after occurrence. Detailed macroscopic and microscopic examination of the resected specimens was done by local pathologists according to standardised techniques[8]. Pathologists were not informed of the type of resection.

Statistical analysis

The power calculation of the COLOR trial was based on disease-free survival 3 years after surgery. Disease-free survival of patients with colon cancer without distant metastases at surgery was estimated as 75% at 3 years for both groups at the time of the start of the trial[9]. To show non-inferiority, the two-sided 95% CI for the difference (open minus laparoscopic surgery) should not exceed the prespecified non-inferiority margin[10]. The determination of the non-inferiority boundary was based on clinical and statistical considerations. We arbitrarily chose 7% as the non-inferiority margin, which required accrual of 1200 patients (600 in each group) at a power of 80%. The level of significance for this non-inferiority test was set at 0·025 (one-sided test for non-inferiority).

Analyses were done according to the intention-to-treat principle, in such a way that patients who did not receive their allocated surgical procedure were analysed in the treatment group to which they had been randomised. An additional as-treated analysis was also done, taking into account preoperative conversions to the open-surgery group. Overall survival was defined as time from surgery to death from any cause as the event of interest. Disease-free survival was defined as time from surgery to a recurrence or death from any cause as the event of interest.

Percentage differences between groups were compared with the χ^2 test or Fisher's exact test. Comparison of continuous data was done by use of the Mann-Whitney test. Disease-free survival and overall survival after surgery were assessed by use of Kaplan Meier curves. The log-rank test was used to do univariate comparisons. Multivariable analysis of survival outcomes was done by use of Cox regression analysis, taking into account randomised procedure, age, sex, and stage of the tumour. The Cox regression models were tested and met the assumption of proportionality. According to protocol, patients had to be followed for a period of 5 years after their primary surgery. All analyses were restricted to these 5-year intervals. All p values were two-sided and $p<0{\cdot}05$ was considered to be of statistical significance. Data were entered into Microsoft Access 2000 and transported into SPSS version 11.0 for statistical analysis. All survival analyses were done with the Stata package (version 8.2).

Role of the funding source

This trial was supported by Ethicon Endo-Surgery (Hamburg, Germany) and the Swedish Cancer Foundation (grant number 4287-B01-03XCC). Both sponsors had no role in the initiation and design of the study, data collection, analysis and interpretation, writing of the report, or the decision to submit for publication, nor did they have access to the raw data. The corresponding author had full access to all data and the final responsibility to submit for publication.

RESULTS

Between March 7, 1997, and March 6, 2003, 1248 patients were randomly assigned to either laparoscopic or open surgery. 153 patients were excluded after randomisation for various reasons (figure 1) and 19 patients were lost to follow-up. Of the 1076 patients who were available for analysis, 542 had an open colectomy and 534 had a laparoscopic colectomy. The average number of patients included per centre was 37, with a median follow-up in the laparoscopic group of 52 months (SD 17·0; range 0·03–60) and in the open-surgery group of 55 months (SD 17·0; 0·03–60), with a p value for the difference of 0·64.

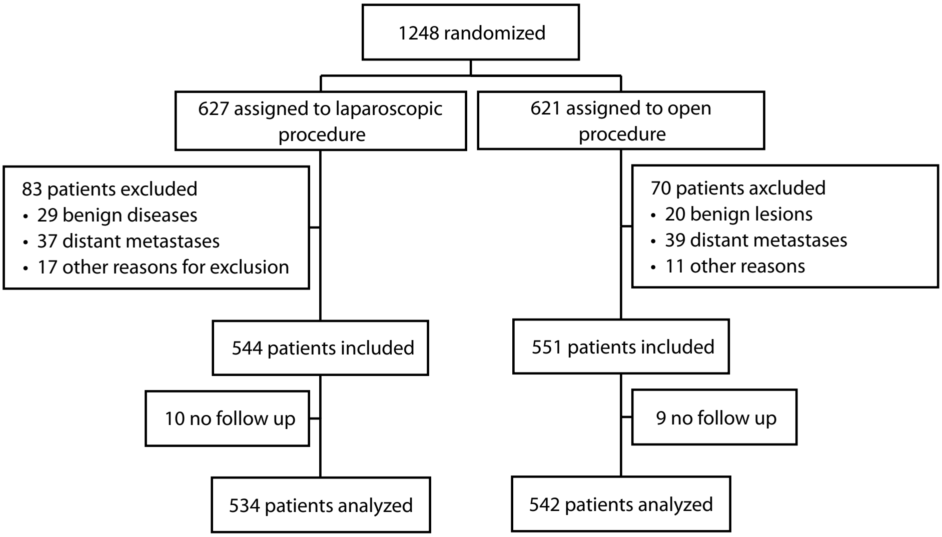

Figure 1: flowchart of patients analyzed in the COLOR trial

No relevant differences were noted between the two groups in terms of age, sex, BMI, American Society of Anesthesiologists classification, number of previous abdominal operations, localisation of the tumour, and operative procedure (table 1).

A comparable number of sigmoid resections and left and right hemicolectomies was done in both groups. Operative time was significantly longer and blood loss was significantly lower in the laparoscopic group compared with the open-surgery group. Macroscopic invasion of the tumour in surrounding tissues was noted in 96 of 1076 patients (9%) during surgery: 49 of 534 (9%) in the laparoscopic group and 47 of 542 (9%) in the open-surgery group, with no significance difference between groups (table 2).

The procedure was converted to open surgery in 102 of 534 patients assigned to undergo laparoscopic surgery (19% [95% CI 16–20]). 11 of 534 patients (2%) randomly assigned laparoscopic surgery underwent open surgery because of malfunctioning laparoscopic equipment or the absence of a skilled surgeon, whereas the remaining 91 patients (17%) had laparoscopic procedures converted to open surgery intraoperatively. 31 of these 91 conversions were because of fixation to, or invasion of, adjacent structures. Reasons for the other conversions have been published elsewhere[6]. 15 of 30 (50%) patients with T4 colon cancers were converted to open surgery, and six of 41 patients (15%) with T1 cancers, 11 of 107 patients (10%) with T2 cancers, and 59 of 348 patients (17%) with T3 cancers had their laparoscopies converted. The frequency of resorting to conversion in patients with T4 cancers was significantly higher than in the other groups (p=0·02). According to the intention-to-treat principle, all converted patients remained in the laparoscopic group for analysis.

Table 1. Patient baseline clinical characteristics

	Laparoscopic colectomy (n=534)	Open colectomy (n=542)	Total (N=1076)
Age (years), median (range)	71 (54–84)	71 (55–83)	71 (54–83)
Sex, n (%)			
Men	277 (52)	289 (53)	566 (53)
Women	257 (48)	253 (47)	510 (47)
ASA group, n (%)			
I	138 (26)	149 (28)	287 (27)
II	301 (56)	276 (51)	577 (54)
III	84 (16)	99 (18)	183 (17)
IV	3 (1)	4 (1)	7 (1)
Data missing	8 (2)	14 (3)	22 (2)
Body-mass index (kg/m^2), median (range)	24·5 (20·0–29·1)	24·9 (20·5–29·7)	24·7 (20·3–29·4)
Previous abdominal surgeries			
0	332 (62)	335 (62)	667 (62)
1	141 (26)	143 (26)	284 (26)
2	36 (7)	42 (8)	78 (7)
3	13 (2)	9 (2)	22 (2)
Missing data	12 (2)	13 (2)	25 (2)

Range=10th to 90th percentile. ASA=American Society of Anesthesiologists.

Operative and postoperative data are shown in table 2. Adjuvant therapy within 28 days after surgery was recorded. Administration of adjuvant chemotherapy was similar after laparoscopic and open surgery (55 of 534 patients [10·3%] and 57 of 542 patients [10·5%], respectively).

Microscopic assessment of the specimens showed no differences in positive resection margins after laparoscopic resection compared with open resection. There were nine circumferential positive margins and one positive aboral longitudinal margin in the laparoscopic group and eight positive circumferential margins, one positive longitudinal oral margin, and one positive longitudinal aboral margin in the open-surgery group. Stage distribution, size of tumour, and histological typing were similar in both groups. The median number of lymph nodes harvested during surgery was ten in both groups (10th to 90th percentile range 3–20 in laparoscopic group and 4–20 in open-surgery group; table 3).

The number of combined events (ie, recurrence or death without recurrence) in the laparoscopic group and open-colectomy group was 166 and 158, respectively. 197 patients had recurrence (92 in the open-colectomy group and 105 in

Table 2: Operative data

	Laparoscopic colectomy (n=534)	Open colectomy (n=542)	p value
Intervention, n (%)			
Right hemicolectomy	258 (48)	252 (47)	0·66
Left hemicolectomy	56 (11)	57 (11)	..
Sigmoid resection	200 (38)	210 (39)	..
Other	20 (4)	23 (4)	..
Duration of intervention (min), median (range)			
In theatre	202 (140–315)	170 (113–255)	<0·001
Skin to skin	145 (102–230)	115 (70–180)	<0·001
Blood loss (mL)	100 (19–410)	175 (40–500)	0·003
Macroscopic metastases, n (%)	15 (3)	28 (5)	0·062
Macroscopic invasion, n (%)	49 (9)	47 (9)	0·095
Conversions, n (%)			
Preoperatively	11 (2)	..	..
Intraoperatively	91 (17)	..	..
Morbidity (<28 days after surgery), n (%)			
Overall	111 (21)	110 (20)	0·90
Wound infection	20 (4)	16 (3)	0·58
Wound dehiscence	2 (0·4)	7 (1)	0·18
Pulmonary	8 (1)	13 (2)	0·40
Cardiac	4 (1)	9 (2)	0·28
Bleeding	13 (2)	8 (1)	0·36
Urinary tract infection	12 (2)	13 (2)	1·00
Anastomotic failure	15 (3)	10 (2)	0·40
Bowel obstruction >3 days	10 (2)	15 (3)	0·44
Other	45 (8)	40 (7)	0·60
Mortality (within 28 days after surgery), n (%)	6 (1)	10 (2)	0·47
Chemotherapy (within 28 days after surgery), n (%)	55 (10)	57 (11)	0·99

Range=10th to 90th percentile.

the laparoscopic-colectomy group; log-rank, p=0·24; hazard ratio (HR; open *vs* laparoscopic surgery) for recurrence of disease was 0·84 (95% CI 0·64–1·12).

In the laparoscopic group, the number of local recurrences, distant recurrences, and combined recurrences (defined as a local and distant recurrence at time of diagnosis) were 26, 56, and 23, respectively. In the open-colectomy group, these numbers were 26, 54, and 12, respectively. These distributions of recurrence did not differ between groups (p=0·24).

Table 3: Pathological characteristics of resected tumours

		Overall	Laparoscopic colectomy	Open colectomy	p value
Size of tumour (cm), median (range; n=1065)[*]		4·5(2·0–8·0)	4·0(2·0–7·5)	4·5(2·1–8·0)	0·07
Resection margins, n (%)[‡]					
Positive		20/1059 (2)	10/524 (2)	10/535 (2)	0·96
Negative		1039/1059 (98)	514/524 (98)	525/535 (98)	..
T[‡]					
	1	80/1059 (8)	41/526 (8)	39/533 (7)	0·94
	2	211/1059 (20)	107/526 (20)	104/533 (20)	..
	3	704/1059 (66)	348/526 (66)	356/533 (67)	..
	4	64/1059 (6)	30/526 (6)	34/533 (6)	..
N[‡]					
	0	707/1061 (67)	345/526 (66)	362/535 (68)	0·44
	1	246/1061 (23)	125/526 (24)	121/535 (23)	..
	2	92/1061 (9)	45/526 (9)	47/535 (9)	..
	3	16/1061 (2)	11/526 (2)	5/535 (1)	..
Tumour stage, n (%)[‡]					
I		254/1061 (24)	129/526 (25)	125/535 (23)	0·57
II		453/1061 (43)	216/526 (41)	237/535 (44)	..
III		354/1061 (33)	181/526 (34)	173/535 (32)	..
Histology differentiation, n (%)[§]					
Well differentiated		175/1060 (17)	90/526 (17)	85/534 (16)	0·87
Well–moderately differentiated		60/1060 (6)	28/526 (5)	32/534 (6)	..
Moderately differentiated		636/1060 (60)	321/526 (61)	315/534 (59)	..
Moderately–poor		28/1060 (3)	13/526 (2)	15/534 (3)	..
Poor/undifferentiated		100/1060 (9)	45/526 (9)	55/534 (10)	..
Not specified		61/1060 (6)	29/526 (6)	32/534 (6)	..
Lymph nodes in resected specimen, median (range; n=1040)[¶]		10 (3–20)	10 (3–20)	10 (3–20)	0·32

Range=10th to 90th percentile. Data missing for: * 11 patients, ‡ 17 patients, ‡ 15 patients, § 16 patients, ¶ 36 patients

Tumour recurrence in the abdominal wall was noted in 1·3% of patients (seven of 534) who had been assigned to laparoscopic colectomy and in 0·4% of patients (two of 542) who had been assigned to open colectomy (p=0·09 by log-rank test). In the laparoscopic group, five of the seven tumours were at trocar sites whereas two tumours were at the extraction site. Isolated abdominal-wall recurrences, in

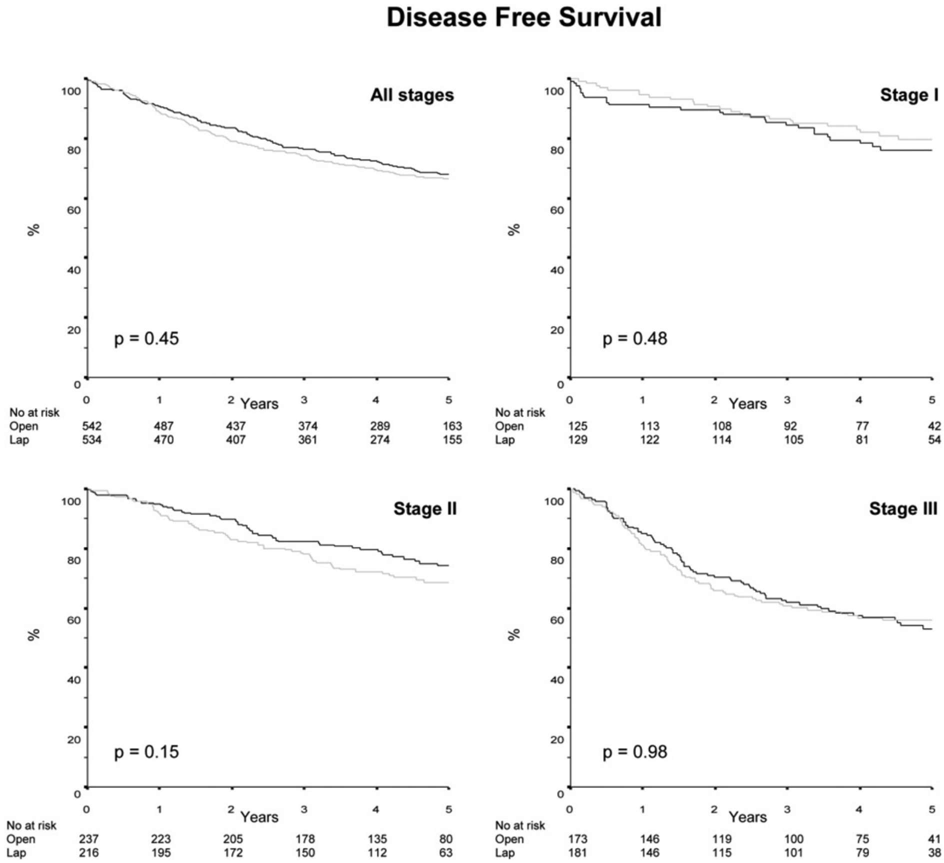

Figure 2: Kaplan-Meier curves for disease-free survival (grey line = LAC, black line = OC)

the absence of recurrent disease elsewhere, were identified in three patients in the laparoscopic group and in one patient in the open-surgery group.

253 patients had died at the time of analysis: 125 in the open-surgery group and 128 in the laparoscopic group. 127 patients (69 and 58 in each group, respectively) died from colon cancer and 11 patients (four and seven in each group, respectively) died as a result of another cancer. Total follow-up, truncated at 5 years, for the laparoscopic and open-surgery groups was 2046 and 2096 person-years, respectively (mean values 3·8 and 3·9 years).

Overall survival and disease-free survival in patients who had laparoscopic surgery did not differ from patients who underwent open colectomy (figure 1, figure 2). The 3-year disease-free survival for all stages combined was 74·2% (95% CI 70·4–78·0) in the laparoscopic group and 76·2% (72·6–79·8) in the open-surgery group (p=0·70 by log-rank test). The overall 3-year survival for all stages was 81·8% (78·4–85·1) in the laparoscopic group and 84·2% (81·1–87·3) in the open-surgery

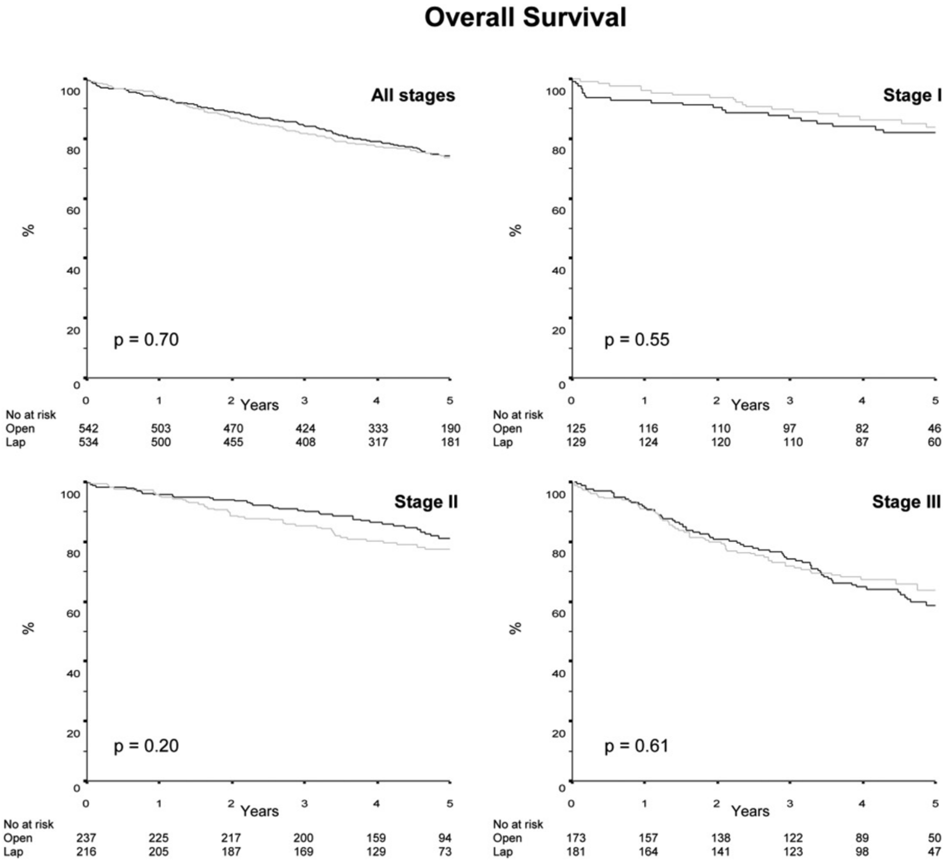

Figure 3: Kaplan-Meier curves for overall survival (grey line = LAC, black line = OC)

group (p=0·45 by log-rank test). When patients were analysed by stage, no differences in disease-free survival (figure 2) or overall survival (figure 3) were present between the treatment groups. It is important to note that the stage-specific comparisons are underpowered.

The difference in disease-free survival at 3 and 5 years (ie, open colectomy minus laparoscopic colectomy) was 2·0% (95% CI -3·2 to 7·2) and 1·4% (-4·6 to 7·5), respectively (HR 0·92 [95% CI 0·74–1·15]). The corresponding differences in overall survival were 2·4% (95% CI -2·1 to 7·0) and 0·4% (-5·3% to 6·1), respectively (HR 0·95 [0·74–1·22]; table 4). The p value for non-inferiority regarding the primary endpoint of 3 years' disease-free survival was 0·030, which does not meet our predetermined significance level of 0·025.

Multivariable analysis of disease-free survival and overall survival did not show differences between laparoscopic and open surgery (table 5). Overall survival was significantly better in women (table 5). Disease-free survival and overall survival

Table 4: Survival at 3 and 5 years according to procedure

	Open colectomy	laparoscopic colectomy	Difference
Disease-free survival			
3 years	76·2 (72·6–79·8)	74·2 (70·4–78·0)	2·0 (-3·2 to 7·2)
5 years	67·9 (63·6–72·2)	66·5 (62·2–70·7)	1·4 (-4·6 to 7·5)
Overall survival			
3 years	84·2 (81·1–87·3)	81·8 (78·4–85·1)	2·4 (-2·1 to 7·0)
5 years	74·2 (70·1–78·2)	73·8 (69·7–77·9)	0·4 (-5·3 to 6·1)

Table 5: Multivariable analysis (Cox-regression) of disease-free survival (DFS) and overall survival (OS) according to various factors

	Cancer recurrence or death from any cause (DFS)		Overall mortality (OS)	
	HR (95% CI)	p value	HR (95% CI)	p value
Procedure				
Open *vs* laparoscopic colectomy	0·93 (0·74–1·15)	0·49	0·95 (0·74–1·22)	0·70
Stage				
II *vs* I	1·29 (0·93–1·79)	0·13	1·13 (0·77–1·65)	0·53
III *vs* I	2·64 (1·92–3·63)	<0·001	2·60 (1·82–3·71)	<0·001
Sex				
Women *vs* men	0·81 (0·65–1·01)	0·06	0·67 (0·52–0·86)	0·002
Age				
Per 10-year increase	1·42 (1·27–1·59)	<0·001	1·80 (1·57–2·06)	<0·001

Reference categories for the categorical variables are laparoscopy procedures, stage I disease, and male sex.

were significantly worse in older patients. Both endpoints were significantly affected by stage (table 5).

Further analysis by investigating appropriate interaction terms in the Cox models showed that the treatment effect did not significantly differ between the three stage groups (effect modification: p=0·36 and p=0·45 for disease-free survival and overall survival, respectively). Additionally, the treatment effect did not differ between centres (p=0·19 for disease-free survival and p=0·21 for overall survival). Repeating these analyses with recurrence of colon cancer as the endpoint showed that only stage of disease was significantly related to recurrence, indicating that the worse outcomes for men and for older patients are not due to a higher incidence of recurrence (data not shown). The adjusted HR (open *vs* laparoscopic surgery) for recurrence in this analysis was 0·86 (95% CI 0·65–1·14; p=0·30).

An as-treated analysis, counting the preoperative conversions as open surgery, did not affect the conclusions: 3-year disease-free survival for the open-surgery group and laparoscopic group was 76·0% (95% CI 72·5–9·5) and 74·3% (70·5–78·0), respectively (difference=1·7% [-3·5 to 6·9; p=0·51]).

DISCUSSION

Data from the COLOR trial could not rule out a difference in disease-free survival at 3 years in favour of open colectomy, because the upper limit of the 95% CI for the difference just passed the predetermined non-inferiority boundary of 7%. However, in a per-protocol analysis, done as per CONSORT guidelines to prevent a false conclusion of non-inferiority[11], in which those patients who were randomly assigned to laparoscopic surgery but were switched pre-operatively to receive open surgery were analysed as treated, laparoscopic surgery was non-inferior to open surgery. Furthermore, the actual difference in disease-free survival between groups was small and, we believe, clinically acceptable; taken together, we feel that these results justify the implementation of laparoscopic surgery into daily practice.

The Clinical Outcomes of Surgical Therapy (COST) and Conventional versus Laparoscopic-Assisted Surgery in Colorectal Cancer (CLASICC) trials have provided disease-free survival data for 770 and 413 patients with colon cancer, respectively, who had either laparoscopic or open resection. Although actual numerical differences in disease-free survival were not reported by these trials, there were no significant differences reported (HR 0·86 in COST; p=0·51 in CLASICC)[3,4,12,13].

Survival data for the first 520 patients recruited in the COLOR trial were included in a meta-analysis of four trials that randomly assigned patients with colon cancer to laparoscopically assisted surgery or open colectomy[14]. This meta-analysis had a censored follow-up at 3 years after primary surgery. Disease-free survival and overall survival for stages I, II, and III, and all three stages combined did not differ between the two treatment groups. The 95% CI of the difference in 3-year disease-free survival was -5% to 4%. One of the four trials of this meta-analysis was done in a single centre with a high volume of laparoscopic surgery. The COST and CLASICC trials had an average case load per centre of 16 and 15 patients, respectively, whereas the COLOR centres accrued 37 patients on average. We reported previously that operating time and the frequency of resorting to conversion is lower in centres with larger patient volumes[15]. The actual frequency with which surgeons resorted to intraoperative conversion in the COLOR trial was 17%, whereas the frequency in the COST and CLASICC trials was 21% and 25%, respectively. The centres that participated in the COLOR trial seem to reflect a realistic cross-section of current practice of open and laparoscopic surgery in Europe. Furthermore, surgeons could only participate in this trial after an expert surgeon had reviewed and approved an unedited recording of a laparoscopic colectomy. We consider that this secured safety and standardisation of the laparoscopic technique.

Bilimoria and colleagues[16] did a retrospective cohort study of 11 038 laparoscopic and 231 381 open colectomies in patients with non-metastatic colon cancer. 5-year overall survival of patients with stage I disease was significantly better after laparoscopic surgery. The design of this study does not justify firm conclusions, but indicates the ongoing close monitoring of outcomes of laparoscopic surgery is crucial.

The findings of Bilimoria and colleagues[16] are also of interest in light of a single-centre trial done by Lacy and colleagues[5], which reported improved survival after laparoscopic colectomy for lymph-node positive disease. Although some have suggested that the improved survival shown by Lacy and colleagues was the consequence of less use of adjuvant chemotherapy and of high locoregional recurrence in the conventional group, further studies remain necessary to establish whether laparoscopic surgery for cancer is associated with improved survival[17-19].

Overall survival differed between men and women and both disease-free survival and overall survival differed between older and younger patients in the current trial (table 5). Such differences are expected in view of general population data. However, no differences were noted regarding colon-cancer recurrence in our study.

In this trial, about half the patients with T4 colon cancers undergoing laparoscopic surgery needed conversion. Preoperative imaging of colon cancer in the COLOR trial was mainly based on barium enema and colonoscopy. CT and MRI can provide more information about size and invasiveness of colon cancers than barium enema and colonoscopy. Less than 5% of all patients in the COLOR trial had preoperative abdominal CT or MRI scans, and this might have resulted in the high need for conversion in our study. Hence, we recommend use of abdominal CT or MRI to identify patients with large or invasive colon cancers who woulds be better served by open surgery. Indeed, the use of barium enema to diagnose cancer of the colon in the COLOR trial decreased steadily during the course of the trial. The rate of barium-enema use in 1998 was 31% and steadily decreased to 7% in 2002 as a result of the advantages of colonoscopy.

On average, we removed ten lymph nodes per patient. A suggestion has been made that at least 12 lymph nodes should be removed to ensure radical resection, However, the number of removed lymph nodes recorded by the pathologist is a function of the scrutiny of the detection method. The common yield of laparoscopic and open colectomy is ten lymph nodes[6].

Although not statistically significant, more recurrences were noted in the abdominal wall after laparoscopic surgery than after open surgery (seven *vs* two; p=0·09). Other studies have not reported different rates of abdominal-wall recurrence between the two treatment groups[3-5].

The role of chemotherapy in the treatment of colon cancer has increased over the past decade. All patients in the COLOR trial received postoperative therapy according to the protocols of the centres, regardless of the type of surgery. In Europe, standard practice is to discuss all patients with cancer in multidisciplinary groups that oversee compliance with standard protocols. There was no difference in administration of adjuvant chemotherapy between the laparoscopic and open-surgery group in this study (table 2).

A limitation of this study is the exclusion of patients with a BMI greater than 30 kg/m^2, due to the fact that obesity is increasing in the developed world. The COLOR trial was started in 1997 at a time when experience with laparoscopic colectomy in obese patients was limited. For the purpose of patient safety, patients with a BMI exceeding 30 kg/m^2 were excluded. Experience with complex laparoscopic procedures in obese patients has increased during the past decade to a point where laparoscopic surgery has become the preferred surgical technique for weight-loss surgery.

Another limitation of this study is an incomplete registry of all eligible patients who could potentially have been enrolled. However, because the characteristics of the patients in our study correspond closely to those of patients in three similar trials that have been published[3-5], we do not think the external validity of our study was compromised by this omission.

Despite current knowledge, further studies are necessary, and should address whether laparoscopic surgery is superior to open surgery. Prospective registries of laparoscopic and open surgeries for cancer are also needed to comprehensively collect accurate data on large numbers of patients. Together, these data should provide direction for the further improvement of treatment for colon cancer.

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7

Stress response to laparoscopic surgery: a review

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Surg Endosc. 2004 Jul;18(7):1022-8.

ABSTRACT

Background: Laparoscopic surgery is associated with reduced surgical trauma, and therefore with a less acute phase response, as compared with open surgery. Impairment of the immune system may enhance surgical infections, port-site metastases, and sepsis. The objectives of this review was to assess immunologic consequences of benign laparoscopic surgery and to highlight controversial aspects.

Methods: A literature search on stress response to nonmalignant laparoscopic and open surgery was conducted using the MEDLINE and Cochrane databases. Cross-references from the reference list of major articles on the subject were used, as well as manuscripts published between 1993 and 2002.

Results: Local (i.e., peritoneal) immune function is affected by carbon dioxide pneumoperitoneum. The production of tumor necrosis factor and the phagocytotic capacity of peritoneal macrophages are less lowered. The systemic stress response, as determined by delayed-type hypersensitivity response and leukocyte antigen expression on lymphocytes, shows a preservation of immune function after laparoscopic surgery, as compared with conventional surgery.

Conclusions: Intraperitoneal carbon dioxide insufflation attenuates peritoneal immunity, but laparoscopic surgery is associated with a lower systemic stress response than open surgery.

BACKGROUND

Laparoscopic surgery has distinct advantages over open surgery such as faster recovery, shorter hospital stay, and quicker return to daily activity. The impact of surgical stress on the immune response (Fig. 1) is a possible predictive factor of patients' clinical outcome[1-4]. Laparoscopic surgery induces less trauma and is therefore less aggravating for the immune system[5,6]. In this review, several different aspects of immunology are considered. To improve insight, a distinction was made between local (i.e., peritoneal) immunity and systemic immunity. Preservation of the peritoneal and systemic immune system is important because it prevents postoperative infections, sepsis, and possible adherence of tumor cells to the port-site wound. There seems to be a general understanding that open surgery has a greater impact on the immune system than the laparoscopic approach[7]. Establishing a carbon dioxide (CO_2) pneumoperitoneum mainly causes peritoneal impairment. Peritoneal macrophages seem to produce fewer cytokines, and their intrinsic function (phagocytosis) diminishes in the presence of CO_2[8,9]. Recent literature showing researchers in search of a new gas for the application of a pneumoperitoneum identifies helium as the most likely substitute. The objectives of this study were to assess the im-

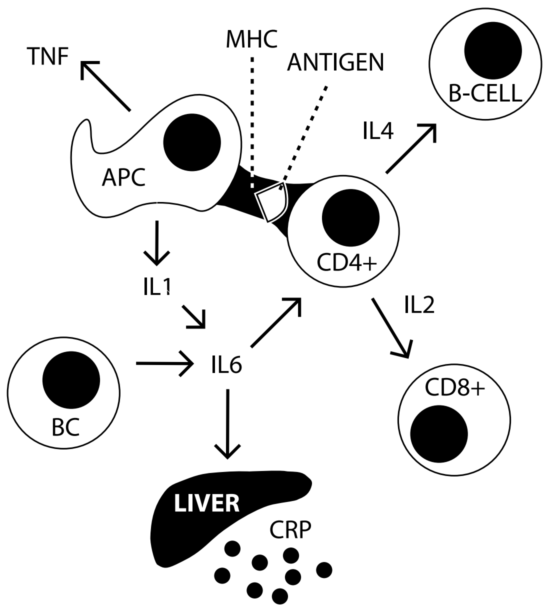

Figure 1 Immune response. TNF, tumor necrosis factor; MHC, major histo compatability molecule; IL1, interleukin 1; IL4, interleukin 4; APC, antigen presenting cell; CD4+, T helper cell; BC, body cell; IL6, interleukin 6; IL2, interleukin 2; CD8+, cytotoxic T Lymphocyte; and CRP, C Reactive Protein.

munologic consequences after nonmalignant laparoscopic surgery and to highlight controversial aspects by reviewing the literature on this subject.

PERITONEAL IMMUNITY

Two immunologic changes within the peritoneal cavity are apparent. Both probably are caused by application of a CO_2 pneumoperitoneum. The first alteration is diminished production of tumor necrosis factor (TNF) by peritoneal macrophages. The second change in the local immune system a reduction in the phagocytosis activity of peritoneal macrophages.

Insufflation gases

Carbon dioxide is the insufflation gas of choice in laparoscopy. It is preferred over air insufflation, which affects the systemic and peritoneal response to a larger degree than CO_2[10]. The usage of CO_2 has some important advantages. It is transparent, noninflammable, and well dissolvable in blood. It has a rapid pulmonary excretion rate[11]. There are, however, some disadvantages associated with its usage. Table 1 shows physical alterations associated with the application of a CO_2 pneumoperitoneum. Any pneumoperitoneum, whether established with CO_2 or any other insufflation gas, reduces car-

Table 1: Alterations associated with the application of pneumoperitoneum using carbon dioxide as the insufflation gas

System	Alteration	Model	Study
Cardiovascular[a]	Reduction in CO	Clinical	Galizia et al. (2001)[12]
	Reduction in SVI	Clinical	Zuckerman et al. (2001)[13]
Respiratory	Acidosis	Swine	Jacobi et al. (2000)[18]
Oncology	Port-site recurrence	Rat	Bouvy et al. (1998)[14]
	Tumor growth	Cell line	Smidt et al. (2001)[21]
Hematology	Activation of tPA, adhesions	Swine	Nagelschmidt et al. (2001)[20]
		Rat	Jacobi et al. (2001)[19]
Immunology	Diminished production of TNF	Cell line	West et al. (1996)[9]
		Mice	Iwanaka et al. (1997)[17]
		Rat	Hajri et al. (2000)[8]
	Reduction in phagocytosis of mononuclear phagocytosis system	Rat	Gutt et al. (1997)[16]
Microbiology	Bacterial translocation	Rat	Erenoglu et al. (2001)[15]

CO, cardiac output; SVI, stroke volume index; tPA, tissue plasminogen activator; TNF, tumor necroses factor, [a] Not solely dependent on pneumoperitoneum, also of Trendelenberg position diac output and stroke volume as a consequence of increased abdominal pressure[12,13]. Literature on specific CO_2-mediated alterations such as respiratory acidosis, port-site recurrence, enhanced formation of tumor growth, immunologic alterations, bacterial translocation, and adhesions are equivocal and conflicting[8,9,14-21].

To avoid problems with local immunity, some researchers have proposed the application of helium as an alternative insufflation gas. Helium is an inert gas, and does not cause an acidosis. Several animal studies on the subject of immunologic alterations during pneumoperitoneum were conducted comparing helium with CO_2 insufflation. Adhesion formation and immunologic changes were found to be fewer after helium than after CO_2 pneumoperitoneum[19,22,23].

For each of these studies, the poor solubility of helium must be taken into consideration. The poor solubility is inherent to the use of helium, increasing the risk of embolisms. This is why helium insufflation should not be used for laparoscopic operations involving an increased risk of embolism (e.g., hepatic resection). The role of helium insufflation in oncologic laparoscopy remains unclear, but experimental studies suggest that helium has advantages in this setting[24].

Macrophage TNF production

In 1996, West et al.[9] used a murine model to investigate production of TNF by peritoneal macrophages stimulated by lipopolysaccharid used as an immune enhancer. Despite sufficient production of messenger ribonucleic acid (mRNA), reversible inhibition of TNF was noticed after 30 min of incubation with CO_2. Interleukin-1 (IL-1) production was reversibly inhibited as well, but also showed a diminished production of mRNA. A comparable significant change in cytokine production by macrophages has not been reported in the helium and air groups. In a study by Watson et al.[10], the production of TNF and superoxide was found to be rather more in the air group. After 2 h of CO_2 peritoneum in rats, Hajri et al.[8] noticed a decline in TNF production and also a reduction in TNF mRNA. One year later West et al.[23] hypothesized that reduction of intracellular pH may cause a decrease in the production of cytokines. They concluded that CO_2 reduces the pH, affecting the inflammatory response in a negative manner.

Kuntz et al.[25] substantiated this finding. The intraabdominal pH diminishes with application of a CO_2 pneumoperitoneum. Using a rat model, they investigated the effect of various gases, pressures, and durations of pneumoperitoneum. Carbon dioxide used as an insufflation gas appears to lower peritoneal, blood, and subcutaneous pH more than helium, which induces smaller changes. After insufflation with CO_2, the intraperitoneal pH is inversely related to the intraabdominal pressure[22].

Peritoneal cell-mediated response

In a rat model, Gutt et al.[16] produced evidence of suppressed phagocytosis activity of the mononuclear phagocytosis system when using CO_2. They found significant changes in carbon clearance by phagocytosis between laparoscopy and laparotomy, with a carbon half-life of 16.1 min for laparotomy and a half-life of 21.91 min for laparoscopy. The fastest elimination of carbon particles was found after gasless laparoscopic surgery (half-life of 12.86 min). The activity of peritoneal macrophages dependents partly on cytokine stimulation, the production of which is also reduced.

In a murine model, Chekan et al.[26], examined the immune competence of mice on the basis of their ability to clear intraperitoneally administered Listeria monocytogenes after CO_2, as compared with helium insufflation or laparotomy. On day 3, they found significant impairment of intraperitoneal immunity after CO_2, insufflation, more so than after helium pneumoperitoneum or after laparotomy. Significantly more bacteria in the spleen and liver were found in the laparoscopic group than in the control subjects. The intraperitoneal immune suppression lasted 5 days.

Clearance of peritoneal bacteria also was investigated by Balague et al.[27]. These authors reported diminished peritoneal macrophage function after intraabdominal contamination with Escherichia coli suspension, as measured by the number of colony-forming units obtained in peritoneal fluid and the positive blood culture rates of 360 mice after laparotomy. In this investigation, pneumoperitoneum seemed to preserve the immune system, despite significantly lower levels of IL-1 and IL-6 levels in the peritoneal fluid.

Other factors

Other factors contributing to the disruption of immunologic balance within the peritoneal cavity seem to be gas pressure and temperature, tissue trauma, and mechanical effects. For example, higher levels of intraperitoneal cytokines (TNF, IL-1, and IL-6) were found when intraperitoneal gasses were used at room temperature after a laparoscopic operation[28].

SYSTEMIC STRESS RESPONSE

The systemic immune response of a CO_2 pneumoperitoneum has been investigated most thoroughly. The results of several studies demonstrate a greater uniformity than peritoneal immunologic changes. Open surgery has more impact on systemic immunity than laparoscopic surgery, as determined primarily by clinical trials after cholecystectomies[7]. Variables used to measure the systemic response to injury are mainly cytokine levels, T-cell function, T-cell subsets, and the expression of major histocompatiblity complex on antigen-presenting cells.

Cytokines

The group of cytokines is diverse. Their effect is restricted mainly to the area surrounding the producing cell, paracrine, or autocrine. Besides activation, cytokines enhance proliferation and differentiation (e.g., IL-6, growth factor for B-cells) as well as chemotaxis. They occasionally exhibit cytotoxic activity (e.g., TNF). The acute-phase response is a good indicator for tissue injury in patients[29]. The production of acute-phase proteins by liver cells often increases a 1,000-fold after conventional surgery, as does C-reactive protein (CRP)[30]. This reaction of liver cells is induced by corticosteroids and cytokines, of which IL-6 is the main activator. A rise in serum IL-1 is one of the early systemic immune events after surgery. It precedes and directs the hepatic release of IL-6, which in turn directs the hepatic release of CRP[8] (Fig. 1). During recovery, levels of acute-phase proteins normalize.

The aforementioned acute-phase reaction is best measured by establishing the levels of CRP and IL-6[31]. These are the most frequently investigated cytokines. Differences between laparoscopic and open surgery are most pronounced 24 h after surgery. At 3 days after surgery, no difference can be found between open and laparoscopic surgery[32]. Postoperative CRP levels are significantly lower after laparoscopy, suggesting a lower burden on immunity[33-37]. No difference was found between minilaparotomy and laparoscopy[38].

The outcomes of both clinical and experimental studies show a less impaired systemic immune reaction after laparoscopic surgery. This is made clear by a diminished production of cytokines IL-1, IL-6, and CRP. Changes in TNF, IL-8, and acute-phase protein fibrinogen, albumin, and transferrin are less clear[7]. These results are derived mainly from clinical trials comparing open cholecystectomy with laparoscopic cholecystectomy.

In recent years, more research has been conducted on other surgical procedures (e.g., gynecologic surgery) and their impact on the immune system[39]. In a randomized clinical trial conducted by Malik et al.[40], no significant changes ($p = 0.066$) were found in CRP concentration between women undergoing laparoscopically assisted vaginal hysterectomy and those undergoing abdominal hysterectomy (AH). There was, however, a significant increase in IL-6 among patients undergoing abdominal hysterectomy, which peaked 2 h postoperatively and remained significantly elevated for 12 h postoperatively, as compared with IL-6 levels in patients undergoing vaginal hysterectomy or laparoscopically assisted vaginal hysterectomy ($p < 0.05$). Besides the elevated IL-6 levels after hysterectomies, a significant difference ($p < 0.05$) in CRP concentration was found in other studies after conventional surgery[41,42].

In a trial by Kishi et al.[34], CRP and leukocyte counts after laparoscopically assisted ileocolectomy were measured and compared with the counts after conventional bowel surgery among patients with Crohns disease. Both CRP and leukocyte counts were significantly (respectively, $p < 0.05$ and $p = 0.05$) lower after laparoscopically assisted ileocolectomy.

A difference in stress response also was found after inguinal hernia repair. Concentrations of CRP and leukocyte count were adversely affected in both the open and laparoscopic groups, but there were significant differences between these two groups. The levels of this protein and the amount of cells were less disturbed after laparoscopic surgery[37].

Cellular immunity

Cellular immunity consists of a nonspecific defense and an antigen-specific host defense. The first system entails natural killer cells, granulocytes, and monocytes/macrophages, all part of the initial reaction to pathogens. The antigen-specific host defense is represented primarily by T-lymphocytes and involved with a durable immune reaction (Fig. 1).

T-Cell function: delayed-type hypersensitivity response

The delayed-type hypersensitivity (DTH) test is of clinical importance for ascertaining cross-reaction on the T-cell level. The tuberculin skin test reaction is well known. In particular, T-cell function is tested on the basis of the DTH response, which consists of three phases: a cognitive phase, an activation phase, and an effector phase (Table 2).

Measurement of the area or magnitude of induration at the site of application determines the immune response. The bigger the area of skin, induration the more active the immune response. Postoperative immune suppression takes place in the effector phase of the DTH response [51]. Absence of the DTH response is associated with a poorer prognosis[43]. Animal studies have shown a better preservation

Table 2: Delayed-type Hypersensitivity (DTH) test: phases of the DTH response

Cognitive phase	Antigen expression to CD4+ T-cells
Activation phase	Cytokine release by CD4+ T-cells
Effector phase	Inflammation, differentiation, and activation of mononuclear phagocytes

of postoperative cell-mediated immune function after laparoscopic surgery, as compared with that after laparotomy[5,44-46].

A more pronounced difference was found in a prospective nonrandomized clinical trial conducted by Schietroma et al.[47]. Two groups of patients underwent cholecystectomy: the one managed by the open technique (n = 31) and the other by the closed technique (n = 32). Until postoperative day 3, a significantly smaller DTH response was found in favor of laparoscopy. In a similar study some years before, Kloosterman et al.[48] drew a comparable conclusion. On the first postoperative day, they demonstrated a significantly diminished reaction on phytohemagglutinin. After 6 days, the immune system seemed to have recovered from the operation.

T-Cell response: CD4/CD8 expression

T-cell metabolism can be expressed in part by measuring the expression of protein molecules on the cell membranes of T-lymphocytes during maturation. They are classified according to their reactivity to the same immunologic markers. These clusters are attached to a code: the CD ("cluster of differentiation") code. The codes for leukocyte antigens of T-helper cells and cytotoxic T-cells are, respectively, CD4 and CD8.

After any kind of operation, the CD4/CD8 ratio changes significantly, as compared with the response to anesthesia alone. This is attributable to an increased in CD4+ cells and a decrease in CD8+ lymphocytes[49]. These findings are validated in animal studies (i.e., rats). From human studies, no clear response can be elucidated. A comparison between laparoscopically performed colorectal resections and open colorectal resections did not demonstrate any significant changes between these operating procedures in terms of T-cell response. However, after laparoscopically assisted colorectal resection, the CD4/CD8 ratio was significantly higher than after conventional colorectal resection[50]. This was confirmed in a randomized clinical trial conducted by Liang et al.[35]. These researchers compared the clinical outcomes and operative stress of laparoscopically assisted colectomy and traditional open management of sigmoid complex polyps. In this trial, 42 patients were equally randomized to either open or laparoscopic resection. The CD4/CD8 ratio was significantly less elevated as were the total lymphocyte counts, in the laparoscopic group. The investigators concluded not only on the basis of CD4/CD8 and lymphocyte counts, but also on the basis of CRP levels and the erythrocyte sedimentation rate 24 h after surgery that laparoscopically assisted sigmoidectomy causes less operative stress. They recommended the use of this technique for the management of sigmoid complex polyps.

In a prospective randomized clinical trial conducted by Perttilä et al.[51] , patients were divided into two groups for Nissen fundoplication, either laparoscopically or by laparotomy. Attention was focused on subsets of lymphocytes. No significant differences were found between the two groups. In both groups the amounts of CD4+ T-cells and CD8+ T-cells increased. After 2 postoperative days, the number of T-cells normalized. Walker et al.[52] also observed fewer CD4+ cells and an increase in CD8+ lymphocytes, contrary to the findings in animals. These researchers investigated the modulation of lymphocytes after laparoscopic cholecystectomy. The CD4/CD8 ratio decreased because of an increase in CD8+ cells up to 7 days after surgery. After cholecystectomy, the CD4 and CD8 levels remained unchanged in patients with postnecrotic liver cirrhosis or hepatitis C until 24 h after surgery[53]. The clinical consequences of changes in the CD4/CD8 ratio remain relatively unknown.

Two kinds of CD4+ T-cells are known: T-helper 1 (Th1) cells producing IL-2, interferon, and TNF, which in turn enhances cellular immunity, and T-helper 2 (Th2) cells enhancing the production of immunoglobulin by producing IL-4–6, IL-10, and IL-13, and thereby maintaining the homeostasis of the host immune system. After laparoscopic surgery, the ratio between these two cells changes. Although clinical relevance is not clear, there is in theory, however, a relative shortage of cellular immunity, and it is assumed that preservation or elevation of the Th1/Th2 ratio is of benefit to the patient[54].

Monocyte function: human leukocyte antigen-DR expression

Expression of class 2 major histocompatibility complex molecules on antigen-presenting cells is a necessity for effective antigen presentation and subsequent elimination of the antigen. In phagocytosis, antigens are incorporated into the cell. The lysosomal system breaks down the antigen into peptides, which bind with human leukocyte antigen (HLA) class 2 within the endosomes. The HLA-2 molecule with this peptide is expressed on the cell membrane. T-helper cells recognize the paired molecules and adhere to it. This leads to an activation of the T-cell. Monocyte HLA-DR expression is a reliable marker for infection. Reduced expression of major histocompatibility complex class 2 molecules, particularly HLA-DR, is associated with an impaired ability to eliminate pathogens effectively. Subsequently, it seems to be associated with an increased risk of infection[55]. Expression of HLA-DR is reduced after open surgery[56], but preserved after laparoscopic surgery[48]. In 1994, Kloosterman et al.[48] demonstrated HLA-DR expression to be significantly less after laparoscopic cholecystectomy than after conventional cholecystectomy. After laparoscopic surgery, an increase was noticed, but it did not differ significantly from baseline levels. Six days postoperatively the expression returned to preoperative values.

More recent studies[47,56] have confirmed these findings. A randomized clinical trial by Hewitt et al.[50] comparing laparoscopically assisted and open surgery for colorectal cancer showed other values of HLA-DR expression on monocytes. A significant reduction was found after both surgical procedures, with no difference between open and laparoscopic surgery. Restoration was not noticed 7 days postoperatively. After 21 days, a complete recovery to baseline was noted.

Systemic phagocytosis function remains unaltered after laparoscopic surgery. Sietses et al.[57] compared phagocytosis by polymorphonuclear lymphocytes after open and laparoscopic Nissen fundoplication. In the laparoscopic group, opsonic capability was not altered, thereby preserving the ability of polymorphonuclear lymphocytes to phagocytose bacteria. In a murine model, Lee et al.[58] evaluated cell-mediated immunity by comparing lymphocyte proliferation rates after laparotomy with those after CO_2 insufflation and anesthesia alone. The lymphocyte proliferation rate was significantly lower in the laparotomy group than in either the control or insufflation group. Between the CO_2 insufflation and control groups, no differences were observed. This suggests greater immunosupression after laparotomy than after CO_2 insufflation.

Particles entering the circulatory system are not removed by circulating macrophages. Macrophages residing in liver (Kupffer cells) and spleen accomplish the clearance of these particles. Opsonization enhances this elimination process. The role of fixed-tissue macrophages is hardly investigated. From what is known, these cells experience an equal suppression if subjected to a CO_2 pneumoperitoneum. Tumor necrosis factor (TNF) and IL-6 production by Kupffer cells, which make up to 90% of the RES, was not altered significantly in a rat model comparing laparoscopy with laparotomy, both using bowel manipulation[59].

CLINICAL ASPECTS

Incision size seems to be correlated in two ways:

1. In many reports, operative technique and clinical outcome are correlated with each other. The exact cause for this better clinical outcome after laparoscopic surgery than with conventional surgery remains to be elucidated.
2. Incision size also seems to be correlated with suppression of immune function. The degree to which this occurs and its duration seem to be determined by the magnitude of the initial surgical insult.

These correlations support the notion that immune function is mutually related to clinical outcome.

Does the difference in immune functioning between open and laparoscopic surgery influence clinical outcome? Despite many publications on the subject of "immune alterations and surgery," little is known about this difference in postoperative clinical outcomes.

Sparse information is available on immune function and clinical outcome. Some data on surgery and immune function, from measurements of DTH response, suggest that patients who are anergic preoperatively have a significantly higher mortality and a higher incidence of sepsis[1,3,60]. An investigation of HLA-DR expression and clinical outcome also shows a direct correlation between an immune parameter and good clinical outcome. For 60 trauma patients, monocyte HLA-DR antigen expression was measured and correlated directly with their clinical course. Its measurement identified a group of patients at high risk for infection and death[2]. Because there still is too little data, no direct correlation could be found between clinical outcome and immunologic changes after laparoscopic surgery, as compared with conventional surgery.

CONCLUSION

Both conventional surgery and laparoscopic surgery affect the immune status of the patient. Trauma induced by open surgery is increased substantially more than with laparoscopic surgery, and seems to be more aggravating to the immune system.

The peritoneal response after laparoscopic surgery seems to be characterized by a brief period of immune suppression attributable to CO_2 insufflation. Peritoneal macrophage functioning is affected, probably because of the CO_2 effect on pH in peritoneal fluid. Not only a diminished production of cytokines has been noticed, but a decline in the intrinsic functioning of monocytes (i.e., phagocytosis) also was apparent. Helium seems to be a favorable substitute except for its property of insolubility. It therefore should not be considered as an alternative to CO_2 for surgery involving patients with increased risk of embolism.

The systemic stress response is less affected after laparoscopic surgery than after conventional surgery. This difference was found for cytokine and cell-mediated immune responses in both animal experiments and clinical trials. Not only does the laparoscopic approach preserve systemic immunity after cholecystectomy. It also seems to maintain this immunity after other surgical procedures. Serum CRP and IL-6 levels are appreciably lower after laparoscopy than after laparotomy. This suggests an immune advantage after laparoscopic surgery. Other cytokine parameters do not show a marked difference between the two operating procedures. There is an inclination toward less immunosuppression, but no real clinical effect is evident. The DTH response, as a quantity for T-cell-mediated immune response, also shows a marked difference between operating procedures. The response is distinct and in favor of laparoscopy. An effective elimination of pathogens in the abdomen requires a reasonable presence of HLA-DR molecules in and on monocytes. After conventional surgery, the expression of these molecules is decreased, but after laparoscopic surgery this expression is maintained.

Because we lack an all-embracing definition of the immune system, we will never be able to provide indisputable evidence of preservation after laparoscopic or conventional surgery. We do have many parameters correlating with host defense. Not all of these parameters seem to be preserved after laparoscopy, but a majority of them indicate preservation of the immune system.

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8

General discussion

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COLON CANCER

As stated in the introduction, colorectal cancer is highly prevalent in Western society. In the Netherlands, colorectal cancer is diagnosed in 10,000 patients a year. It is the third leading cancer in men, with 14% of the total number of newly diagnosed cancer patients, preceded by prostate- (21%) and lung cancer (16%). In women it is the second most frequent cancer with a prevalence of 13%, preceded only by breast cancer (33%) It is expected that the incidence will steadily increase and that 14000 new patients will be diagnosed by the year 2015, also due to population growth and ageing[1,2].

LAPAROSCOPY FOR COLON CANCER

Segmental resection of the affected bowel is still the treatment of choice for colonic cancer. In early stages of colon cancer, when the tumor is entirely confined to the intestinal wall and lymph node or distant metastases are absent, prognosis for survival is quite good, in the 90% range for a permanent cure. The chance for a cure declines substantially in people whose cancer has escaped outside the bowel wall through penetration or distant spread[3].

In the mid-eighties, laparoscopic techniques were first introduced into general surgery. Laparoscopic cholecystectomy became the first procedure to be performed laparoscopically and has become the gold standard for gallbladder surgery. Until the early nineties, surgical technique to treat colonic cancer remained the same. A laparotomy was performed to approach the target organ and resect it. Convinced of the potential benefits of minimally invasive approaches, Verdeja et al published the first report on laparoscopic colon cancer surgery in 1991[4]. Assuming the technique would only benefit patients, as it had done for gallbladder disease, it was soon attempted and adapted by surgeons around the world. However, a few years after its introduction, reports on high rates of port-site metastases were diminishing enthusiasm[5,6]. It seemed from these case-reports that laparoscopic surgery was associated with an altered dissemination pattern, possibly affecting survival. Oncological safety of laparoscopic colectomy for cancer therefore came under debate. The use of the technique was put to a virtual stop throughout the world due to concerns on oncological safety. To properly investigate the outcomes, both experimental and clinical research was initiated.

Clinical studies

In the early nineties, four clinical trials were initiated in the Western world, comparing laparoscopic to open surgery for colonic cancer: in the USA (COST), the UK (MRC CLASICC), Spain (Barcelona trial) and the Netherlands (COLOR).

Short-term outcome

The short term outcome of the COLOR trial has been discussed in this thesis. Rates of morbidity and mortality within 28 days after colectomy did not differ between arms. Laparoscopic surgery allows safe and radical resection of colonic cancer of the right, left and sigmoid colon, when considering the extent of resection and the number of lymph nodes harvested with both surgical techniques. Although laparoscopic colectomy requires more operating time, it is associated with less blood loss, earlier restoration of bowel function, fewer analgesic requirements and shorter hospital stay[7]. These results are confirmed by all other large randomized controlled trials[8-10].

Health related quality of life studies have gained importance in health care practice and research, having acquired a substantial role in the evaluation of effectiveness and efficacy of new therapeutic strategies and their associated costs. A quality of life substudy was performed alongside the COLOR, COST and CLASICC trials. Considering the better short-term results of laparoscopic surgery for colon cancer when compared to conventional surgery, an improvement of health related quality of life was anticipated in the laparoscopically operated patients. However, although the use of analgesics is lower after laparoscopic surgery and patients are discharged earlier, laparoscopic and open surgery for colon cancer result in comparable health related quality of life[11]. Other groups did find small differences in health related quality of life in favour of laparoscopic surgery. Janson et al (2007) found a better health related quality of life at two and four weeks in social functioning and role functioning scales of the EORTC-C30 questionnaire[12]. Weeks et al (2002) only found a significant difference in the Global Rating Scale at two weeks after surgery[8].

Several limitations of the measurement of health related quality of life should be noted. All studies aimed to find differences in quality of life in the short-term period, with a maximum of one year postoperative. Different instruments and time frames to measure health related quality of life were used in each study, rendering comparison impossible. Also, the response rate for the questionnaires was only between 73%-78%[8,12,13] which could have caused selection bias. Although internet based questionnaires may result in higher accuracy of data, a paper-and-pencil version was used in all studies, because the accessibility to and familiarity with Internet was expected to be low in this group of patients during the time frame the study was conducted[14].

These short-term results for laparoscopic colon cancer surgery were achieved by highly experienced laparoscopic colorectal surgeons. All surgeons participating in the large clinical trials were laparoscopic enthousiasts and therefore laparoscopic skills levels of participating surgeons were above average. Data for average health care at large are presented only recently. Data derived from the English National Health Service Trusts between 1996 and 2006, analyzing 192,620 elective colonic and rectal resections, showed better short-term results for laparoscopic colorectal surgery. Athough only 1.9% of all resections was performed laparoscopically, the 30-day and 365-day mortality rates were significantly lower after laparoscopic resection than after open surgery. Similarly, multivariate analysis confirmed that laparoscopic surgery was independently associated with reduced hospital stay[15]. Laparoscopic resection of colorectal cancer can achieve excellent results even in "high risk" patients and is associated with significant reductions in length of stay compared with open resection[16]. These clinical studies show short-term benefits for almost all sorts of patients when operated with minimally invasive techniques. The short-term benefits of laparoscopic colorectal surgery, as observed in controlled trials, therefore appear to be achievable in average health care.

Long-term outcome

All clinical cancer research revolves around recurrence and survival. Clinical studies comparing laparoscopic to open surgery for colonic cancer were initially expected to prove equality of survival with better short-term outcome and quality of life after laparoscopic colectomy. Unexpectedly, the results of the first published randomized controlled trial comparing laparoscopic to open resection of colonic cancer suggested a clear cancer related survival benefit for the laparoscopically operated patients[17]. This observed survival benefit was mainly caused by a marked better survival rate in laparoscopically operated stage III cancer patients.

However, the Barcelona trial represented only a single-center experience including a relatively small number of patients. Outcome of large multi-center clinical trials on laparoscopic resection of colonic cancer was mandatory to confirm these results and make evidence based recommendations on laparoscopic resection of colonic cancer.

In 2002 a virtual stop in the use of laparoscopic techniques in colon cancer surgery was imminent. While most trials on laparoscopic colon surgery were closing patient recruitment, they still had to await follow-up to provide long-term survival data. The existing lack of adequate evidence-base regarding survival following laparoscopic colon cancer surgery, created uncertainty among surgeon to continue the use of the laparoscopic technique. Therefore, the European Association of Endoscopic Surgery (EAES) initiated a consensus conference on laparoscopic resection of colonic cancer during the annual congress in June 2002[18]. Available evidence on safety and feasibility of laparoscopic colon resections for cancer was systematically reviewed and combined with the culled opinion of experts in the field of colonic cancer surgery. The evidence-based statements and recommendations on laparoscopic resection of colonic cancer encouraged the on-going use of laparoscopy in the field of colon cancer surgery.

The Clinical Outcomes of Surgical Therapy (COST) trial was the first multicentre trial to publish their results. A non-inferiority trial was conducted at 48 hospitals in the USA and 872 patients with adenocarcinoma of the colon were recruited in a 5-year period. At three years, the recurrence rate, overall survival rate and disease-free survival rate were very similar in the two groups, with no significant difference between groups in the time to recurrence or overall survival for patients with any stage of cancer[19]. In a follow-up paper, presenting the median 7-year follow-up, disease-free 5-year survival and overall 5-year survival were similar for the two groups. Overall recurrence rates, distribution of recurrences and sites of first recurrence were distributed evenly among groups[20].

The United Kingdom Medical Research Council Conventional versus Laparoscopic-Assisted Surgery in Colorectal Cancer (UK MRC CLASICC trial) also randomised patients with rectal cancer. In this trial, recruiting 794 patients, no differences in the long-term outcomes were found. Survival rates and local recurrence rates were comparable. Long-term outcomes for patients with rectal cancer were similar in those undergoing abdominoperineal resection and anterior resection[11]. In a follow-up paper of this study, the results of the 5-year follow-up analysis are presented. No differences were found between laparoscopically assisted and open surgery in terms of overall survival, disease-free survival, and local and distant recurrence. Wound/port-site recurrence rates in the laparoscopic arm remained stable at 2.4 per cent[21].

In the COLOR trial, as presented in this thesis, there was no significant difference in disease free or overall survival between the two procedures. The combined 3-year disease free survival rate for all stages was 74 % in the laparoscopic group and 76 % in the open group, comparable to results from the other large randomized trials[22].

Finally, a meta-analysis and later a Cochrane review for non-metastasised colorectal cancer has been performed[3,23]. Similar cancer-related mortality was found after laparoscopic surgery compared to open surgery. In the Cochrane review, twelve randomised trials, involving 3346 patients, reported long-term outcome and were included in the analysis. No significant differences in the occurrence of incisional hernia, reoperations for incisional hernia or reoperations for adhesions were found between laparoscopically assisted and open surgery. Recurrence rates in general and rates of recurrence at the site of the primary tumor were similar and no differences in the occurrence of port-site or wound recurrences were observed.

In large multicentre randomized controlled trials, short-term outcome of colonic cancer surgery is better and long-term outcome following laparoscopic resection of colon cancer has been proven at least equal to open resection. Therefore, laparoscopic surgery for colonic cancer has now gained wide-spread acceptance for the treatment of colon cancer.

Long-term results following laparoscopic assisted colectomy outside of experienced centres have only recently been published. To assess outcomes of laparoscopic assisted colectomy and open colectomy in average health care on a large scale, the national cancer data base of the USA was used to assess outcome in patients who underwent laparoscopic assisted colectomy (n = 11 038) and open colectomy (n = 231 381) for non-metastatic colon cancer from 1998 until 2002[24]. Although laparoscopic-assisted colectomy use only increased from 3.8% in 1998 to 5.2% in 2002, significantly higher 5-year survival rates (64.1% vs. 58.5%) were observed following laparoscopic colon cancer surgery. After adjusting for patient, tumour, treatment, and hospital factors, 5-year survival was significantly better after laparoscopic assisted colectomy compared with open colectomy for stage I and II but not for stage III cancer. Highest-volume centers had comparable short- and long-term laparoscopic assisted colectomy outcomes compared with lowest-volume hospitals, except highest-volume centers had significantly higher lymph node counts (12 vs. 8 nodes). This study, representing average health-care in the United States, demonstrates that laparoscopic resection of carcinoma of the colon is associated with a long term outcome that is significantly better than that of open colectomy in selected patients.

Immunology and survival

Although a benefit in survival was anticipated by many surgeons involved in the field of laparoscopic surgery for colon cancer, these results are not easily explained. Less surgical trauma and therefore less attenuation of the acute phase immune response may in part be responsible.

Experimental studies

Experimental studies, mostly involving rat models, have shown that tissue trauma, induced during surgery, facilitates tumor growth and that the extent of surgical trauma determines the degree of tumor growth stimulation[25-28] Which factors play a key role in this process is still under debate. Immunological factors have long been regarded key factors in this process, but angiogenesis may even play a more important role[29-34].

In the immunological defense mechanism of the abdomen, the peritoneum plays a vital role. The peritoneum covers all intra-peritoneal organs and consists of a monolayer of mesothelial cells embedded on a basal lamina. Tissue injury, which is induced during surgery, initiates an acute phase response, aimed at minimizing damage and starting the healing process. Cytokines are the essential mediators of this inflammatory reaction. A damaged peritoneal layer promotes influx of neutrophils and the production of cytokines and growth factors. The cytokine response is related to the degree of surgical trauma. Intraperitoneal release of cytokines causes an upregulation of the adhesionmolecules, like ICAM-1 and VCAM, which enhance the migration and attachment of polymorphonucleocytes (PMN's) to the damaged sites[35]. It has been demonstrated that these PMN's were responsible for enhancing tumorcell adhesion to mesothelial cells due to the production of reactive oxygen species[36]. Adhesion formation is stimulated by this immunological response, as well as tumor cell attachment and subsequent tumor growth[25].

In open conventional surgery, the use of foreign material i.e. surgical gauzes, sutures and lavage fluids may traumatize the peritoneum[25,37]. Use of peritoneal lavage fluids, even non-abrasive fluids such as NaCl 0,9%, has been shown to damage the peritoneal layer and promote adhesion formation in a rat model[38].During laparoscopic surgery, the abdominal cavity is less exposed to physical damage because incisions of the abdominal wall are smaller, the peritoneum is less traumatized by gauzes, hands and peritoneal lavage fluids and dissection tends to be associated with less blood loss. On the other hand the parietal peritoneal layer is substantially stretched by the pneumoperitoneum. Because laparoscopic surgery appears on the whole to be less traumatic, it has been investigated if laparoscopic cancer surgery would cause less stimulation of tumor growth.

Since the mid-nineties, instigated by the less traumatic nature of minimally invasive surgery, experiments were started with a laparoscopic rat model, to determine the differences of tumor growth following laparoscopic and conventional surgery. In this model conventional open surgery stimulated intra-abdominal tumour growth to a greater extent than laparoscopic surgery[26,27].

Although distant metastases are the most important factor determining survival following colorectal cancer surgery, the influence of surgical trauma on their development has been less well studied. The enhancing effect of trauma appears not to be restricted to the inflicted site, but rather has a generalized character. Van den Tol et al. demonstrated that peritoneal trauma also significantly increased tumor take at peritoneal sites not directly traumatized and stimulated growth of ectopic tumors under the renal capsule. The growth-promoting effects could be passively transferred to native recipients[39]. Kirman et al. demonstrated that plasma from patients who underwent open surgery stimulated in vitro tumor growth more than preoperative plasma[40]. The increase of tumor growth correlated with the length of incision. Wildbrett et al. demonstrated in a murine model, that laparotomy stimulated postoperative development and growth of lung metastases to a greater extent than laparoscopic surgery[41]. Upregulation of the immune system with a tumor vaccine in the perioperative period resulted in a decrease in postoperative lung metastases. In other experimental studies, growth of hepatic metastases has been shown to be less following minimal invasive surgery, especially when using gasless techniques[42,43]. The preservation of the systemic immune system therefore seems important in preventing both implantation of tumor cells to the traumatized tissues and formation of distant metastasis. Therefore, survival following oncological surgery may be improved by avoiding unnecessary surgical trauma[28]. Minimally invasive methods may therefore be associated with oncologic advantages that go well beyond less pain, a quicker recovery, and a shorter length of stay.

Clinical studies

Differences in the peritoneal integrity following open and laparoscopic colorectal surgery have been established. To assess the differences in peritoneal microstructure injury between laparoscopic and open radical resection for colorectal cancer, optical microscope and scanning electron microscope have been used to detect postoperative peritoneal injury between patients who received laparoscopic surgery or open surgery. Optical microscope investigation indicated less serosal injury in the laparoscopic group as compared to the open group with regard to serosal integrity, continuity of covering adipocyte and mesothelial cells, and the aggregation level of erythrocytes and inflammatory cells. Scanning electronic microscopy showed more severe injury to colorectal serosa, mesothelium and basement membrane in the open group as compared to the laparoscopic group. It appears that laparoscopic surgery for colorectal cancer causes less peritoneal structural injury as compared with open surgery[44]. This difference may be responsible for less exposure of extracellular matrix on which cancer cells can attach and grow and less attenuation of the acute phase immune response in laparoscopically operated patients.

This systemic acute-phase response following laparoscopic and open colectomy has been clinically assessed in humans by measuring serum levels of acute phase proteins and interleukins after surgery. Interleukin-6 (Il-6), measured in most studies assessing postoperative stress response, is the main activator of this acute phase reaction. In four randomized controlled trials, a lower serum Il-6 concentration was found after laparoscopic colonic cancer surgery[45-48]. Four non-randomized comparative studies found similar results[49-52]. In contrast to cytokines, other cell-related parameters, such as delayed type hypersensitivity (DTH) and CD4/CD8 markers showed no significant changes between laparoscopic and open colorectal surgery[47,53]. A recent study compared the local and systemic inflammatory and angiogenic responses after open and laparoscopic surgery for colonic cancer. Although the serum IL-6 and VEGF levels were lower in the laparoscopic group in the immediate postoperative period, the in vitro angiogenic potency was equal for both.[54].

Differences in acute phase response can only be observed during a short postoperative period. The clinical importance of these differences still remains under debate. Differences in the immunological response to laparoscopic and open surgery cannot be linked directly to differences in recurrence rate and survival found in some studies[17,24]. However, the immediate perioperative period may be of the utmost importance in prevention of recurrent cancer.

GOALS FOR THE FUTURE

Expanding the indications for the laparoscopic approach

The short-term benefits of the laparoscopic approach towards surgery in general has been established for a wide array of indications. Despite these advantages for the laparoscopic approach, its use is still limited. There is debate about performing this type of surgery in the elderly, patients with severe cardiopulmonary disease, previous abdominal surgery or advanced stage cancer.

Age and comorbidity

Advancing age and comorbidities are risk factors for postoperative death in patients undergoing elective colonic resection for cancer. However, there are no studies reporting adverse outcomes in elderly patients or patients with any type of comorbidities. In recent prospective studies, excellent perioperative outcomes are reported for laparoscopic colorectal surgery in high risk patients. Mortality rates, length of hospital stay and rate of complications are all improved when using laparoscopic techniques for colorectal surgery[16,55-58]. In an analysis of data retrieved from the English National Health hospitals, the use of laparoscopy in elderly patients undergoing elective colonic resection, was a significant predictor of reduced perioperative mortality, adjusted for advancing age, gender and comorbidity[59]. Patients selected for a laparoscopic procedure are at lower risk of perioperative death than those undergoing the conventional approach. Laparoscopic colectomy appears a safer option that offers an improved outcome compared with open colectomy in elderly patients. This should encourage a wider adoption of laparoscopic colorectal surgery for elderly patients or patients with comorbidities

Adhesions

In the early days of laparoscopic surgery, the presence of possible adhesions was considered a contraindication to laparoscopic surgery. With evolving experience and improvement of techniques, cameras and instruments, adhesions should not be regarded a contraindication to laparoscopic colon surgery. Laparoscopic Hartmann reversal, a surgical procedure often implicating extensive adhesiolysis, is often performed laparoscopically nowadays. In a systematic review on both laparoscopic and conventional Hartmann reversal, thirty-five studies were included, of which 30 retrospective. A total of 6,249 patients with a mean age of 60 years underwent Hartmann reversal. Laparoscopic Hartmann reversal was associated with lower mean morbidity rates, earlier return of bowel function, earlier restart of alimentation and shorter length of hospital stay[60]. This indicates that adhesions caused by previous abdominal surgery should not be regarded a contraindication for laparoscopic colorectal surgery.

Other types of cancer

The laparoscopic approach towards colon cancer has proven to be at least as safe as the open procedure and may even improve long-term survival. Laparoscopy should therefore be evaluated for other types of oncological surgery also. However, there still is reluctance to pursue laparoscopic surgery for other oncological gastrointestinal procedures. In centres of excellence, oesophageal and stomach surgery is attempted laparoscopically, athough survival data from randomized controlled trials are lacking. The initiation of clinical trials assessing cancer related survival following minimally invasive surgery for other types of cancer, i.e. rectal cancer, gastric cancer and oesofageal cancers is desired.

In the first decade after the introduction of laparoscopic surgery for colon cancer, its use was limited to less demanding procedures. Laparoscopic surgery for locally advanced cancer and cancer of the rectum was considered too difficult to perform and complete laparoscopically and it was thought that the risk of incomplete resection could be higher than in open surgery. Therefore most trials excluded patients with T4 colon cancer and patients with rectal cancer. Only the CLASSICC trial included a limited number of patients with rectal cancer.

Rectal cancer

Rectal cancer is different from colonic cancer in both postoperative course and treatment modalities. Local recurrence is the most important postoperative outcome. Standardization of dissection technique has lowered local recurrence rates dramatically[61]. Preoperative chemoradiotherapy is now standard care for most rectal malignancies and this makes dissection more difficult. As experience is growing, it is now thought that laparoscopy may improve surgical outcome for rectal cancer. The augmented visualisation of structures in the narrow pelvis and the more immaculate sharp dissection of the anatomical planes are expected to improve radicality of the resection and nerve preservation. This may lead to a lower local recurrence rate and better preserved sexual and bladder function.

A first proper evaluation is given in a 2008 Cochrane review[62]. All randomised controlled trials, controlled clinical trials and case series comparing laparoscopic to open total mesorectal resection were included in the evaluation. Furthermore case reports which describe laparoscopic total mesorectal excision were also included. Methodological quality of most of the included studies was poor. Only one randomized controlled trial described primary outcome, 3-year and 5-year disease-free survival rates. Results of all these studies were comparable to results for colon cancer: no significant differences in terms of disease-free survival rate, local recurrence rate, mortality, morbidity, anastomotic leakage, resection margins, or recovered lymph nodes were found. There is evidence that laparoscopic total mesorectal excision results in less blood loss, quicker return to normal diet, less pain, less narcotic use and less attenuation of the immune response.

The safety and short-term efficacy of laparoscopic surgery for rectal cancer after preoperative chemoradiotherapy was investigated by the COREAN trial (randomised Comparison of Open versus laparoscopic surgery for mid and low REctal cancer After Neoadjuvant chemoradiotherapy). Peroperative results were comparable between open and laparoscopic resections. Although surgery time was 45 minutes longer in the laparoscopic group, estimated blood loss was less. Involvement of the circumferential resection margin, macroscopic quality of the total mesorectal excision specimen, number of harvested lymph nodes, and perioperative morbidity did not differ between the two groups. The laparoscopic surgery group showed earlier recovery of bowel function than the open surgery group and the total amount of morphine used was less in the laparoscopic group than in the open group. Three months after proctectomy or ileostomy takedown, the laparoscopic group showed better physical functioning score than the open group, less fatigue and fewer micturition, gastrointestinal and defecation problems in repeated measures analysis of covariance, adjusted for baseline values[63]. It can be concluded that laparoscopic surgery after preoperative chemoradiotherapy for mid or low rectal cancer is safe and has short-term benefits compared with open surgery; the quality of oncological resection was equivalent.

Based on the available evidence, laparoscopic total mesorectal excision has clinically measurable short-term advantages in patients with primary resectable rectal cancer. However, the most important possible short-term advantage, i.e. improved visualisation and preservation of pelvic nerves and therefore an improved outcome on sexual and bladder function, has only been investigated in few studies. Regarding the long-term outcome of laparoscopic total mesorectal excision compared to its conventional counterpart, a large international randomised controlled trial was instigated to investigate this further, the COLOR II trial[64].

T4 cancer

Advanced stage colon cancer is still regarded a contraindication to laparoscopic resection. It is argued that a radical resection with negative resection margins is more difficult to obtain. Only one case series can be found regarding this subject. In this case series by Bretagnol, the overall conversion rate was 18% and postoperative mortality and morbidity were comparable to data published for open resections. The R1 resection rate was 13%. After a median follow-up of 19 months, the overall survival and disease-free survival rates were 97% and 89%, respectively. These data suggest that laparoscopic surgery is feasible for colorectal T4 cancer resection in experienced hands[65]. Comparative (randomized) studies are lacking and are not likely to be performed, because the numbers of patients with resectable stage IV colon cancer are small.

Expanding experience with laparoscopic techniques

Although multiple trials have confirmed that there is no difference in tumor recurrence and long-term survival may even be improved, the use of laparoscopic techniques in colon cancer surgery is still limited. In the Netherlands, the overall use of laparoscopy for colon surgery is limited to only 36 % of cases in 2010. For elective colon resections for cancer, 45 % were performed laparoscopically, where for rectal cancer this was 38%. An annual increase of about 5% is observed since 2004. In 2010, there were 7 hospitals that performed laparoscopic colorectal surgery in over 80% of cases. An increase in the number of laparoscopic resections in the years to come is therefore anticipated. The main reasons for the limited use of laparoscopic techniques in colon surgery are inadequate training and health care reimbursement.

Training

Laparoscopic surgery is a technique that takes time and effort to appraise. Learning curves are usually based on time needed to perform the surgery, percentage of procedures converted to open surgery and results, expressed in morbidity and mortality rates.

Early literature reported the learning curve for laparoscopy to be 20 to 50 cases[66-68] The COST, CLASICC and COLOR trials required a minimum of 20 cases and a reviewed validated video for surgeons to be credentialed to perform laparoscopic colon surgery[10,19,69]. Extrapolating from these trials, some scientific communities recommended 20 as the minimum number of laparoscopic colon resections to be credentialed. Although 20 might serve as a minimum, the issue of credentialing is controversial and it is hard to recommend an absolute number. The general consensus among experts is that twenty procedures are the minimum for already laparoscopically skilled surgeons to responsibly perform this technique.

Since laparoscopic surgery is increasingly proposed as the gold standard technique for colorectal resections and is offered to greater numbers of patients, more trainees and established surgeons need to learn the technique. Already established surgeons have not been trained in complex laparoscopic techniques. Training has to be performed on site by already experienced surgeons (proctorship). In recent years, such a training program has been developed in the Netherlands by surgeons in Leeuwarden (LIMIS). In Leeuwarden the first endosuites, operating rooms specifically equipped for laparoscopy, were installed in 2003. Since then it has become a center of excellence in the Netherlands regarding laparoscopic colorectal surgery. Supervised side-by-side operations are performed both in Leeuwarden and in the surgeon's own hospital.

For surgeons in training, integrated education into surgical training is mandatory to acquire sufficient laparoscopic skills. In several studies the feasibility and safety of supervised on-site training has been established. No adverse clinical outcome was found in studies describing postoperative course of patients following colorectal resection by senior trainees. Postoperative outcome of patients operated on by trainees were comparable to previously published studies. Conversion rates, quality of oncological resections according to Quirke, and postoperative morbidity and mortality were all comparable to percentages published in the literature[70,71]. Thus, clinical outcomes of laparoscopic colon surgery appear not affected by experience when effective training is provided. Adequately trained and supervised trainees can perform major colorectal resections without compromising outcome for the patient. However, the quality of performed studies is poor and no comparative studies have been performed.

The safest way to achieve adequate training would be in a simulator. If laparoscopic skills levels of surgeons could be improved prior to operating on the first real patient, the learning curve could be significantly shortened. In a study to evaluate the responsiveness of surgery residents to simulated laparoscopic sigmoidectomy training, residents underwent simulated laparoscopic sigmoidectomy training for previously tattooed sigmoid cancer with use of disposable abdominal trays in a hybrid simulator. Overall operating time and quality of the anastomosis improved significantly with progressing training. There was a linear relationship between residents' clinical advanced laparoscopic case volume and responsiveness[72].

Laparoscopic colorectal surgery, although technically demanding, is an increasingly desirable skill for colorectal surgeons. Trainees have to acquire these skills with adequate supervision from an experienced trainer. Although short-term outcome appears adversely affected by experience, oncological outcome remains the same. The debate is still ongoing if virtual reality training should be employed to improve skills and shorten the learning curve.

Costs and health care reimbursement

In the Netherlands the reimbursement of laparoscopic surgery is not different from open surgery. Therefore, the incentive to adopt this more expensive, time-consuming technique is lacking for both surgeon and hospital. The costs associated with the laparoscopic colorectal operation are in general higher than in open surgery. Laparoscopic procedures take longer to perform and require more expensive (single-use) materials. However, the in-hospital costs appear to be equal due to a shorter hospital stay and for society in general, cost are estimated lower, owing to quicker recovery and therefore less out-of-hospital care and workdays lost.

In a sub-study of the CLASICC trial, the short-term cost analysis indicates that laparoscopic surgery costs only marginally more than open surgery[73]. The costs associated with the operation were approximately 23 % higher for laparoscopic surgery compared with the open procedure, but they were compensated for by lower non-theatre in-hospital costs for the laparoscopically operated patients. The average cost for reoperations was 200 GBP higher in the laparoscopic group. This resulted in slightly higher overall costs in the laparoscopic group.

In a prospectively study, cost analysis was carried out incorporating cost of surgical bed stay, theater time, and specific equipment costs. Although average cost of surgical equipment used for a laparoscopic resection was greater than for open surgery, cost of hospital stay was significantly less and overall no significant cost difference could be found between open and laparoscopic resection[74].

In an Australian randomized controlled trial, data suggest that laparoscopic colorectal surgery is equivalent in price to open surgery and there may be added benefits in reduced nursing intensity[75].

From these studies, there appears no financial reason to discard laparoscopic surgery as being too expensive. With more companies on the market of laparoscopic instruments and the ever increasing use of disposable instruments, the costs associated with disposable instrument are likely to further decline in the years to come.

Minimizing collateral damage during abdominal access

Single-incision and NOTES

In a further attempt to minimize trauma during surgery, laparoscopic procedures are developing towards even less invasive procedures. Attempts are made to reduce the number of trocarts needed. The single port cholecystectomy is being performed with specialized angulating instruments enabling a dissection through one subumbilical trocart.

Single-incision laparoscopic surgery is developed only recently. Its application in colectomies has been published only in small case series. In a series of 8 patients who underwent colectomy for various colorectal pathologies, early results of single-incision laparoscopic surgery suggest at least equal short-term results compared to laparoscopic surgery. In patients with cancer, all of the resection margins were clear and the median number of lymph nodes examined was sufficient[76]. The largest case series of single-incision colorectal surgery is presented by Gash et.al. In this series, 20 consecutive unselected patients underwent single-incision colorectal surgery for both benign and malignant disease[77]. The short-term data show promising results, although no conclusions can be drawn from this small case series.

When performed by an experienced team, single-incision colorectal resection probably could result in an oncologic resection similar to conventional laparoscopy. The single-incision approach may have advantages in terms of less pain and improved cosmesis. However exposure and manipulation of the target organ may be impaired, which could lead to less meticulous and less extensive resection. A randomized trial is required to confirm whether single-incision resection offers a true patient benefit over standard laparoscopic resection.

Also early experience is gained in the field of natural orifice transluminal endoscopic surgery (NOTES). Recently, NOTES was proposed as a new surgical technique, with the aim of performing abdominal surgical procedures through natural orifices such as the mouth, the vagina or the rectum to avoid visible incisions.

Incisionless surgery has been reported in humans using natural orifice extraction for cholecystectomy and appendicectomy[78]. Natural orifice specimen extraction techniques have been applied to minimally invasive colorectal resection. Very recently, case reports are presented with promising outcome concerning this new technique. Very experienced teams of laparoscopically skilled surgeons, may now be able to perform complex surgery through NOTES procedures[79]. However, its development is still in its experimental stage and potential hazards of this new procedure are to be evaluated. Large randomized controlled trials are in order to evaluate these procedures before wide generalization. Concerns regarding potential morbidity to the extraction site (vagina, stomach or rectum) may outweigh potential complications associated with an abdominal wound, and have limited enthusiasm for the procedure so far.

Robotics

Robotics adoption in general surgery has been a slower process than other specialties due to the nature of abdominal surgery being highly varied all over the abdomen and the already advanced laparoscopic skill set possessed by minimally invasive surgeons. Nonetheless, the next few years are likely to show an increase in minimally invasive robotic surgery as more operations are being described and published, particularly in the pelvic area for rectal cancer. Digital platforms can combine stereoscopic vision, improving depth perception, with other informational systems such as imaging from computed tomography to allow augmented reality of the surgical field. Also ergonomic advantages for the surgeon are evident. The absence of tactile feedback and the extra time needed to install and prepare the robot in the operating room however are current disadvantages of this novel technique.

Robotic surgery may aid the surgeon in performing more complex procedures in small spaces, such as the lower pelvis. Few studies have been carried out to investigate the feasibility of robot-assisted rectal surgery. Recent prospective case series present the perioperative and oncologic outcome of robot-assisted tumor-specific rectal surgery. The short- and long-term results were comparable to those of open series[80-83]_ENREF_340. Robot-assisted rectal surgery appears a safe and feasible procedure that may facilitate mesorectal excision. Randomized clinical trials and longer follow-up are needed to evaluate a possible influence of robot-assisted rectal surgery on patient postoperative outcome and survival.

CONCLUSIONS

The introduction of laparoscopy into the field of general surgery has been a revolution and it is the single most important change in surgical technique of the past decades. It has turned the way of thinking in surgery. The adage "big surgeon, big wounds" no longer applies and is replaced by a collective awareness that the approach in surgery has to be as minimal as possible. For colon surgery the laparoscopic approach should be standard. The postoperative recovery is faster with earlier return to daily activity and there are possible advantages in the long term.

At the same time that laparoscopic surgery was developing, many other aspects of peri-operative care changed that influenced outcomes. Therefore one might argue that not all of these benefits can be solely attributed to laparoscopy. However, especially in large randomized international trials, where postoperative regime is equal in both arms, the benefits of laparoscopic surgery have been established.

It can be expected that the quest towards even more minimally invasive surgery will continue. Efforts are underway to minimize collateral damage further by minimizing the number of ports needed (single port-technology), using thinner ports and instruments or using natural orifices as a way to obtain access to the abdomen (NOTES). The use of technologically advanced aids such as robotic assistance, the use of image overlays and techniques to enhance sensory perception will be developed further and find their way into the operating room of the future.

Despite the proven advantages, the adaptation of laparoscopic techniques in colon cancer surgery has been a relatively slow process. This can mainly be attributed to lack of adequate training facilities in dedicated skills labs with clinical proctorships and a lack of centralization in the treatment of colon cancer. Although the use of laparoscopy in colon cancer surgery is rapidly growing, more structured training is needed. Most surgeons in the Netherlands still perform a relatively wide pallet of surgical procedures. In the past decade, surgeons in the Netherlands are following the international trend towards more and more hyper specialization into ever narrower fields of surgery. The first true colorectal surgeon will soon emerge in the Netherlands.

Hyperspecialization has only recently been introduced into surgical training at an early stage. From their third year of residency, surgeons in training will exclusively be tutored in one of the four main directions in general surgery; i.e. oncologic, gastrointestinal, vascular or trauma surgery. There should be an obligation for the gastrointestinal surgeon performing colorectal surgery to obtain sufficient laparoscopic skills. The advanced laparoscopic skills set needed for minimally invasive colon surgery can only be maintained when the colorectal surgeon performs laparoscopic surgery in sufficient numbers. This warrants further centralization of laparoscopic treatment of colon cancer.

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9

Summary

The role of laparoscopy in the curative treatment of colonic cancer is still under debate. In this thesis, the short and long term results of laparoscopic surgery for colon cancer are compared to open conventional surgery. Clinically significant differences in short and long term outcome between laparoscopic and open resection of colon cancer are identified. Recommendations are given for clinical decision-making and goals for the future are set.

Chapter 2

The guideline of the European Association for Endoscopic Surgery (EAES) presents a cullmination of a systematic review of the literature on laparoscopic resection of colon cancer and a consensus development conference of experts in the field and members of the European Association of Endoscopic Surgery. Statements and recommendations are given for the pre-, intra- and postoperative period of laparoscopic colon cancer surgery. An update of recent literature is presented in an epilog.

Chapter 3

The short term results of the COLOR trial are presented. Differences in intraoperative and immediate postoperative results are discussed, answering the folllowing questions:

- Is laparoscopic resection of colon cancer safe and efficious, resulting in at least similar extent of resection?
- Are there clinically significant differences in the intraoperative and immediate postoperative outcome following laparoscopic compared to open surgery?

Twenty-nine European hospitals participated in the COlon cancer Laparoscopic or Open Resection trial (COLOR trial), a multicenter European study randomizing patients with colonic cancer for either laparoscopic or open resection. Cancer free survival at three years after surgery was the primary outcome. Clinical characteristics, operative findings and postoperative outcome are presented.

Radicality of resection assessed by number of removed lymph nodes and length of resected oral and aboral bowel segments was similar after laparoscopic and open surgery. Rates of morbidity and mortality within 28 days after colectomy did not differ between arms. Intraoperatively, blood loss was significantly less during laparoscopic than during open surgery, while laparoscopic surgery took half an hour longer to perform than open surgery. During the postoperative course, laparoscopic colectomy was associated with earlier recovery of bowel function, fewer analgesics requirements and one day shorter hospital stay.

Laparoscopic surgery therefore allows for a safe and radical resection of colonic cancer of the right, left and sigmoid colon. Although laparoscopic colectomy requires more operating time, it is associated with less blood loss, earlier restoration of bowel function, fewer analgesic requirements and shorter hospital stay.

Chapter 4

Health related quality of life has gained importance in daily practice. Since the introduction of laparoscopic surgery, quality of life related benefits of laparoscopic surgery have been reported following a broad range of procedures. In this chapter health related quality of life is compared after laparoscopic and open colectomy for patients with colon cancer.

All Dutch patients, participating in the COLOR trial, provided quality of life data. Health related quality of life outcomes were prospectively measured in a randomized clinical trial comparing laparoscopic and open surgery. All patients who met inclusion criteria and were randomized in one of the six Dutch participating hospitals were invited to complete the EuroQoL-5D, Short Form-36 and EORTC-CR38 questionnaires. A total of 329 Dutch patients were randomized in the trial, 164 assigned to laparoscopic surgery and 165 assigned to open surgery.

Although the use of analgesics was lower after laparoscopic surgery in the first two postoperative days, laparoscopic and open surgery for colon cancer resulted in equal health related quality of life.

Chapter 5

Since laparoscopic resection for colon cancer is a relatively new surgical technique when compared to the open technique, a learning curve effect is expected to take place within the results of the COLOR trial, despite the already extensive laparoscopic experience within the group of participating surgeons in the trial. To evaluate these learning curve effects, a subanalysis was performed to compare peroperative and immediate postoperative results between low-, medium- and high case volume hospitals.

Median operating time was shorter with increasing experience. The conversion rate was deceased in high case volume hospitals. Also a higher number of lymph nodes were harvested at 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.

We therefore concluded that laparoscopic surgery for colon cancer at hospitals with high caseloads appears to be associated with improved short-term results.

Chapter 6

The primary endpoint of the COLOR trial was disease free 3 year survival. Patients with a solitary cancer of the right or left colon were randomly assigned to either laparoscopic or open surgery as curative treatment. Cancer free survival at three years after surgery was the primary outcome.

1248 patients were randomized, 172 were excluded after randomization leaving 1076 patients for analysis. There was no significant difference in disease free or overall survival between the two procedures ($p=0.45$ and $p=0.70$ respectively). The combined 3-year disease free survival rate for all stages was 74 % in the laparoscopic group and 76 % in the open group.

Long-term outcome following laparoscopic colon cancer surgery is similar to open surgery. Based on these outcomes, it can be recommended outside trials in non-obese patients with right or left sided colon cancers which have not invaded adjacent tissues.

Chapter 7

Trauma to the tissues is followed by an attenuation of the immune response. Alterations of the inflammatory response to surgery have been associated with alterations in susceptibility to tumor take and metastatic spread. Laparoscopic surgery is associated with less operative trauma and blood loss. To evaluate current knowledge on the possible role of the immune system on differences between laparoscopic and open surgery, a review of current literature is presented. Literature search on immunologic changes during laparoscopy and open surgery was conducted using Medline and Cochrane databases.

Peritoneal immune function seems to be altered by the application of a carbon dioxide pneumoperitoneum. A diminished production of Tumor Necrosis Factor (TNF) and phagocytosis capacity of peritoneal macrophages is apparent. The systemic stress response shows a preservation of immune function following laparoscopy in comparison with conventional surgery. A pronounced difference in Delayed Type Hypersensitivity (DTH) response and a diminished reduction of leukocyte antigen expression on lymphocytes sustain the finding of a better preserved immune function.

The peritoneal response to laparoscopic surgery shows suppression of host defence mechanism. However the systemic response and the better maintained immune function postoperatively, compensate this shortcoming of laparoscopic surgery.

Chapter 8

A general discussion of data presented in this thesis is presented. The future role of laparoscopy in colon cancer surgery and pitfalls for implementation are discussed.

Chapter 9
Summarizes the findings, answers and recommendations presented in this thesis.

10

Samenvatting

De rol van laparoscopie in de curatieve behandeling van het coloncarcinoom staat nog steeds ter discussie. In dit proefschrift worden de korte- en lange-termijn resultaten van laparoscopische chirurgie voor dikke darmkanker vergeleken met conventionele open chirurgie. Klinisch significante verschillen in korte- en lange-termijn resultaten tussen laparoscopische en open resectie van dikke darmkanker worden geïdentificeerd. Er worden aanbevelingen voor klinische besluitvorming en doelstellingen voor de toekomst gegeven.

Hoofdstuk 2

In dit hoofdstuk wordt de richtlijn van de European Association of Endoscopic Surgery (EAES) over de laparoscopische resectie van het coloncarcinoom gepresenteerd. De richtlijn is een compilatie van de systematische evaluatie van alle literatuur op het gebied van laparoscopische resectie van dikke darmkanker en een consensus conferentie van deskundigen op het gebied van laparoscopische colonchirurgie en leden van de EAES. Stellingen en aanbevelingen worden gegeven voor de pre-, intra- en postoperatieve periode van laparoscopische chirurgie voor het coloncarcinoom. Een update van recente literatuur wordt gepresenteerd in een epiloog.

Hoofdstuk 3

De korte termijn resultaten van de COlon cancer Laparoscopic or Open Resection trial (COLOR trial) worden gepresenteerd. Verschillen in intraoperatieve en postoperatieve resultaten worden besproken om de volgende vragen te beantwoorden:

- Is laparoscopische resectie van dikke darmkanker veilig en werkzaam en resulteert het in dezelfde uitgebreidheid van resectie?
- Zijn er klinisch significante verschillen in de intra- en postoperatieve resultaten van laparoscopische chirurgie voor het coloncarcinoom in vergelijking met open chirurgie?

Negenentwintig Europese ziekenhuizen hebben deelgenomen aan de COLOR trial, een multicentrische Europese studie waarbij patiënten met dikke darmkanker gerandomiseerd werden voor laparoscopische of open resectie. Ziektevrije overleving drie jaar na de operatie was het primaire eindpunt. Klinische kenmerken, operatieve bevindingen en postoperatieve resultaten worden gepresenteerd. Het aantal verwijderde lymfeklieren en de lengte van het orale en aborale darmsegment was vergelijkbaar na laparoscopische en open chirurgie. Morbiditeit en mortaliteit binnen 28 dagen na dikke darmresectie zijn niet verschillend tussen beide armen van de trial. Intraoperatief bloedverlies was aanzienlijk minder tijdens laparoscopische dan tijdens open chirurgie, terwijl de operatieduur van laparoscopische chirurgie ruim een half uur langer was dan bij open chirurgie. Na laparoscopische colectomie werd in het postoperatieve beloop een snellere terugkeer van darmfunctie, minder analgetica gebruik en één dag korter ziekenhuisverblijf gezien.

Laparoscopische chirurgie resulteert derhalve in een veilige en radicale resectie van dikke darmkanker van het rechter en linker colon en het sigmoid. Hoewel laparoscopische colectomie meer operatietijd vergt, is het postoperatieve herstel sneller en beter.

Hoofdstuk 4

Gezondheid gerelateerde kwaliteit van leven wordt steeds belangrijker bij het maken van beleid in de gezondheidszorg. Voordelen in gezondheid gerelateerde kwaliteit van leven van laparoscopische chirurgie ten opzichte van conventionele open chirurgie worden gemeld voor een breed scala van procedures. In dit hoofdstuk wordt gezondheid gerelateerde kwaliteit van leven vergeleken na laparoscopische en open colectomie voor patiënten met dikke darmkanker. Van alle Nederlandse patiënten die deelnamen aan de COLOR trial werd prospectief kwaliteit van leven gegevens verzameld en vastgelegd. Alle patiënten die voldeden aan de inclusie-criteria en gerandomiseerd werden in één van de zes Nederlandse deelnemende ziekenhuizen werden uitgenodigd voor het voltooien van de EuroQoL-5 D, short-form-36 en EORTC-CR38 vragenlijsten. In totaal 329 Nederlandse patiënten werden gerandomiseerd in de substudie, 164 in de laparoscopische arm en 165 in de open arm.

Alhoewel het gebruik van pijnstillers lager lag in de laparoscopische groep in de eerste twee postoperatieve dagen, werd geen verschil aangetoond in gezondheid gerelateerde kwaliteit van leven na laparoscopische en open chirurgie voor dikke darmkanker.

Hoofdstuk 5

Ondanks de reeds uitgebreide laparoscopische ervaring binnen de groep van deelnemende chirurgen van de COLOR trial werd een leercurve effect verwacht, aangezien laparoscopische chirurgie voor darmkanker een relatief nieuwe techniek is in vergelijking met de open techniek. Om deze leercurve-effecten te evalueren, werden per- en postoperatieve resultaten tussen laag-, middel- en hoogvolume ziekenhuizen vergeleken.

Mediane operatietijd werd korter met toenemende ervaring. Het percentage conversies daalde in hoogvolume ziekenhuizen. In hoogvolume ziekenhuizen werd ook een hoger aantal lymfeklieren geoogst bij laparoscopische colon chirurgie voor maligniteiten. Bij patiënten behandeld in hoogvolume ziekenhuizen werden minder complicaties na operatie en een korter verblijf in het ziekenhuis waargenomen. Hoogvolume ziekenhuizen laten betere korte-termijn resultaten zien voor laparoscopische chirurgie van dikke darmkanker.

Hoofdstuk 6

Het primaire eindpunt van de COLOR trial was ziektevrije overleving na 3 jaar. Patienten met een solitaire tumor van de dikke darm, die in aanmerking kwamen voor in opzet curatieve chirurgie, werden gerandomiseerd voor open of laparoscopische chirurgie. Van de 1248 patiënten die werden gerandomiseerd werden 172 geexcludeerd na randomisatie. Hierdoor bleven 1076 patiënten over voor analyse.

Er werd geen significant verschil in ziektevrije overleving tussen de twee procedures waargenomen. Het gecombineerde percentage 3-jaar ziektevrije overleving voor alle stadia was 74% in de laparoscopische groep en 76% in de open group.

De lange termijn resultaten na laparoscopische chirurgie voor dikke darmkanker zijn vergelijkbaar met open chirurgie. Op basis van deze resultaten, kan laparoscopische chirurgie voor in opzet curatieve resectie van dikke darmkanker worden aanbevolen.

Hoofdstuk 7

Beschadiging van lichaamsweefsels zet een immuunrespons in gang. Veranderingen van de inflammatoire respons na chirurgie zijn mogelijk geassocieerd met veranderingen in de ontvankelijkheid voor de uitgroei van tumor en metastatische verspreiding. Laparoscopische chirurgie wordt geassocieerd met minder operatieve beschadiging en bloedverlies. In dit hoofdstuk wordt een overzicht van de huidige literatuur gepresenteerd om de mogelijke rol van het immuunsysteem bij verschillen tussen laparoscopische en open chirurgie te verklaren. Hiertoe werd een systematische review van de literatuur verricht met behulp van Medline- en Cochrane-databases.

Peritoneale immuniteit lijkt te veranderen door de toepassing van een CO2-pneumoperitoneum. Een verminderde productie van Tumornecrosefactor (TNF) en fagocytose capaciteit van peritoneale macrofagen is aangetoond. De systemische stressrespons toont een behoud van immuunfunctie na laparoscopische in vergelijking met conventionele chirurgie. Een uitgesproken verschil in Delayed Type Hypersensitivity respons (DTH) en minder onderdrukking van leukocyten antigeen expressie op lymfocyten ondersteunen de hypothese van een beter bewaarde immuunfunctie.

De peritoneale respons op laparoscopische chirurgie toont onderdrukking van de locale afweermechanismen. Deze tekortkoming van laparoscopische chirurgie wordt postoperatief gecompenseerd door de systemische respons en de beter behouden immuunfunctie.

Hoofdstuk 8
Een algemene discussie over laparoscopische resectie van het coloncarcinoom. De toekomstige rol van laparoscopie in dikke darmkanker chirurgie en valkuilen voor verdere implementatie worden besproken.

Hoofdstuk 9
Samenvatting.

Epilogue

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Sponsor

Ethicon Endo-Surgery (Hamburg, Germany) and the Swedish Cancer Foundation (grant number 4287-B01-03XCC) financially supported the COLOR trial.

Conflicts of interest

The sponsors had no involvement in the design, analysis or publication of the results of the COLOR trial. All authors declared no conflicts of interest.

Dankwoord

Het schrijven van een proefschrift gaat niet vanzelf. Er gaat de nodige tijd en moeite in zitten. Gelukkig is er altijd een hele schare mensen geweest, die me bij de voltooiing hebben kunnen helpen. Zonder ook maar de schijn van volledigheid, wil ik een aantal mensen in het bijzonder danken:

De promotoren:
Professor Dr. HJ Bonjer: Jaap, je hebt me geïnspireerd om voor het vak van chirurg te kiezen. De ongelofelijke hoeveelheid energie waarmee jij alles aanpakt, kan niets dan bewondering oogsten. Je hebt me geïntroduceerd in de fijne kneepjes van het verrichten van onderzoek. De vrije manier waarop je me begeleid hebt, en het vertrouwen dat ik als jonge onderzoeker direct kreeg, hebben gezorgd voor een zeer steile leercurve. Het meeste heb ik geleerd van de momenten waarin ik onderuit ben gegaan. Je losse manier van sturing geven, gecombineerd met zeer scherpe en snelle analyses, hebben me geïnspireerd en altijd weer verder geholpen. Zonder jou zou ik nooit gepromoveerd zijn. Ik ben blij dat je weer terug bent in Nederland en ik hoop nog vaker met je samen te kunnen werken.

Professor Dr. J Jeekel: U heeft me, als ervaren rot, bij de les gehouden. Gedurende de jaren dat professor Bonjer afwezig was, heeft u regelmatig weer inspiratie gegeven om toch door te gaan. Het kwam bij mij niet vanzelf, toch heb ik nooit een negatief woord gehoord. U bent een inspirator en leermeester die met zacht sturende hand ervoor heeft gezorgd dat ik toch promoveer!

Professor Dr. JF Lange: Johan, als laparoscopisch pionier en participant van het eerste uur in de COLOR trial, kon ik me geen logischer promotor voorstellen. Je hebt me bij de eindsprint perfect begeleid, waardoor ik uiteindelijk deze prestatie neer kon zetten. Heel hartelijk dank.

De commissie:
Professor Dr. MA Cuesta: Miguel, je niet aflatende enthousiasme en passie voor het chirurgisch vak, en in het bijzonder de laparoscopie, zijn een inspiratie en werken aanstekelijk bij het realiseren van mijn eigen dromen en ambities.

Dr. ir. WCJ Hop: Wim, ik kan me zo voorstellen dat je, als echte beta, het zwaar moet hebben in het domein van de gamma's. Gelukkig hadden we goede datamanagers in het Z-gebouw, anders was het denk ik niet goed gekomen. Jouw vak blijft voor de meeste chirurgen een raadsel. Bij de oppositie zal ik in mijn antwoord proberen het goede te gokken.

Professor Dr. HW Tilanus: Hartelijk dank voor het vervullen van de rol van secretaris.

Professor Dr. EJ Kuipers, professor Dr. WA Bemelman en professor Dr. IAMJ Broeders: Hartelijk dank voor het beoordelen van mijn proefschrift en het plaatsnemen in mijn promotiecommissie.

De paranimfen:
Manoucher Gholghesaei: Samen zijn we vrijwel tegelijkertijd begonnen met ons promotietraject en hebben vele late uurtjes in het Z-gebouw doorgebracht, wanneer we weer eens een deadline niet dreigden te halen. Door de intensieve samenwerking is een goede band opgebouwd. We werden door collega's soms spottend Jut en Jul genoemd. Hartelijk dank voor de perfecte sfeer en de vele gesprekken. Voor mijn promotie kon ik me geen andere paranimf voorstellen. Ik hoop nog steeds dat ik nog een keer deze functie voor jou mag vervullen.

Jan Deurhof: Jan, je bent mijn oud-huisgenoot en goede vriend. De perfecte man om naast me te hebben staan in lastige tijden.

De collega's:
Het onderzoeksbureau in het Z-gebouw van het ErasmusMC, het episch centrum van chirurgisch onderzoek in Nederland, is altijd erg gezellig geweest. De voorgangers Eric Hazebroek en Martijne van 't Riet hebben het perfecte klimaat gecreëerd en me ingewerkt. Met de andere onderzoekers van de 8e verdieping van het Z-gebouw, Armagan Albayrak, Yuri Casseres, May Lind en Ruth Ramaker, was het altijd heerlijk koffiedrinken. Esther Kuhrij, mijn opvolgster, is inmiddels waarschijnlijk Noors chirurg: Tusen takk for den flotte tiden! Mark Buunen, wannneer mag jij opponeren? De reizen naar verschillende congressen over de hele wereld waren de slagroom op de taart. Ik heb met zeer veel plezier met jullie gewerkt. Hartelijk dank!

Alle collega arts-assistenten in het ErasmusMC en het Maasstadziekenhuis: hartelijk dank voor de fijne samenwerking en gezellige tijden. Erwin van der Harst en Peter-Paul Coene wil ik bedanken voor het blijven stimuleren van het verrichten van onderzoek tijdens mijn opleiding tot chirurg en de aanmoedigingen om het boekje toch vooral af te maken.

Anneke van Duuren en Conny Vollebrecht: ik heb goede herinneringen aan de vele kopjes koffie en gesprekken die we hadden. Zonder jullie was dit boekje er heel zeker nooit gekomen.

Familie:
Mijn ouders: Dank voor jullie niet aflatende steun. Alleen al door af en toe te laten weten dat jullie best trots zijn op zo'n bijna gepromoveerde zoon, heeft mij elke keer weer energie gegeven om toch door te gaan.

Lieve Christien, ik kan het zelf eigenlijk ook niet geloven, maar mijn boekje is toch echt klaar. Je bent de betere onderzoeker van ons tweeën, maar toch ga ik eerst. Je bent de liefste, slimste en meest eigenwijze vrouw, die ik ken. Door jouw niet aflatende, lieve steun is dit boekje tot stand gekomen. Lieve Madeleine en Annefleur, pappa is klaar met werken achter de computer en komt jullie weer lekker voorlezen en in bed stoppen!

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Curriculum vitae

Ruben Veldkamp was born on June 3rd, 1974 in Hilversum, The Netherlands. After graduating from high school at Gemeentelijk Gymnasium in Hilversum in 1992, he attended medical school at Erasmus University Rotterdam. In 2000, he obtained his medical degree and started working as a physician and research fellow for clinical trials at Erasmus Medical Center Rotterdam under supervision of professor Jaap Bonjer. He began his surgical residency in 2003 at ErasmusMC, University Hospital Rotterdam. In 2005 he continued his residency at Maasstad Ziekenhuis Rotterdam. Since 2009, he is employed as general surgeon at Ziekenhuis Rivierenland Tiel. Ruben is married to Christien and has two beautiful daughters.

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