Laparoscopy in Combination with Fast Track Multimodal Management is the Best Perioperative Strategy in Patients Undergoing Colonic Surgery

A Randomized Clinical Trial (LAFA-study)

Malaika S. Vlug, MD, PhD, Jan Wind, MD, PhD,* Markus W. Hollmann, MD, PhD, DEAA,† Dirk T. Ubbink, MD, PhD,‡ Huib A. Cense, MD, PhD,§ Alexander F. Engel, MD, PhD,¶ Michael F. Gerhards, MD, PhD,** Bart A. van Wagensveld, MD, PhD,†† Edwin S. van der Zaag, MD,‡‡ Anna A.W. van Geloven, MD, PhD,§§ Mirjam A.G. Sprangers, PhD,¶¶ Miguel A. Cuesta, MD, PhD,*** and Willem A. Bemelman, MD, PhD,* on behalf of the collaborative LAFA study group*

Objective: To investigate which perioperative treatment, ie, laparoscopic or open surgery combined with fast track (FT) or standard care, is the optimal approach for patients undergoing segmental resection for colon cancer.

Summary Background Data: Important developments in elective colorectal surgery are the introduction of laparoscopy and implementation of FT care, both focusing on faster recovery.

Methods: In a 9-center trial, patients eligible for segmental colectomy were randomized to laparoscopic or open colectomy, and to FT or standard care, resulting in 4 treatment groups. Primary outcome was total postoperative hospital stay (THS). Secondary outcomes were postoperative hospital stay (PHS), morbidity, reoperation rate, readmission rate, in-hospital mortality, quality of life at 2 and 4 weeks, patient satisfaction and in-hospital costs. Four hundred patients were required to find a minimum difference of 1 day in hospital stay.

Results: Median THS in the laparoscopic/FT group was 5 (interquartile range: 4–8) days; open/FT 7 (5–11) days; laparoscopic/standard 6 (4.5–9.5) days, and open/standard 7 (6–13) days ($P < 0.001$). Median PHS in the laparoscopic/FT group was 5 (4–7) days; open/FT 6 (4.5–10) days; laparoscopic/standard 6 (4–8.5) days and open/standard 7 (6–10.5) days ($P < 0.001$). Secondary outcomes did not differ significantly among the groups. Regression analysis showed that laparoscopy was the only independent predictive factor to reduce hospital stay and morbidity.

Conclusions: Optimal perioperative treatment for patients requiring segmental colectomy for colon cancer is laparoscopic resection embedded in a FT program. If open surgery is applied, it is preferentially done in FT care. This study was registered under NTR222 (www.trialregister.nl).

(*Ann Surg* 2011;254:868–875)

From the *Department of Surgery; †Department of Anesthesiology; and ‡Department of Quality Assurance and Process Innovation, Academic Medical Center, Amsterdam, the Netherlands; §Department of Surgery, Red Cross Hospital, Beverwijk, the Netherlands; ¶Department of Surgery, Zaans Medical Center, Zaandam, the Netherlands; **Department of Surgery, Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands; ††Department of Surgery, Sint Lucas Andreas Hospital, Amsterdam, the Netherlands; ‡‡Department of Surgery, Gelre Hospital, Apeldoorn, the Netherlands; §§Department of Surgery, Tergooi Hospital, Hilversum, the Netherlands; ¶¶Department of Medical Psychology, Academic Medical Center, Amsterdam, the Netherlands; and ***Department of Surgery, VU Medical Center, Amsterdam, the Netherlands

Reprints: Willem A. Bemelman, Department of Surgery, Academic Medical Center, P.O. Box 22660, 1100 DD Amsterdam, the Netherlands. E-mail address: w.a.bemelman@amc.uva.nl.

The study was supported by Johnson and Johnson International and Nutricia and funded by a governmental subvention (ZonMW).

Financial Disclosure and Commercial Sponsorship: The authors received a governmental subvention (ZonMW) and a financial support of Johnson and Johnson International and Nutricia. None of them had a role in study design, data collection, data analysis, data interpretation, or writing of the report.

All the authors have made substantial contributions to conception and design, and/or acquisition of data, and/or analysis and interpretation of data; all participated in drafting the article or revising it critically for important intellectual content; and all authors gave final approval of the version to be published.

Collaborative LAFA Study Group: Benedikt Preckel, MD, MA, DEAA; Patrick Bossuyt, PhD; Dirk Gouma, MD, PhD; Mark van Berge Henegouwen, MD, PhD; Jan Fuhring, BSc; Ineke Picard van Lenthe, BSc; Chris Bakker, BSc; Bellinda King-Kalimanis, MSc (Academic Medical Center, Amsterdam the Netherlands); Jan Hofland, MD, PhD (Erasmus Medical Center, Rotterdam, the Netherlands); Cornelis Dejong, MD, PhD; Ronald van Dam, MD, PhD (Academic Center Maastricht, Maastricht, the Netherlands); Donald van der Peet, MD, PhD; Edith van Zalingen, MD; Astrid Noordhuis, BSc; Dick de Jong, BSc (VU Medical Center, Amsterdam, The Netherlands); T. Hauwy Goei, MD; Erica de Stoppelaar, MD; Marjon van den Dongen, BSc (Zaans Medical Center, Zaandam, the Netherlands); Willem van Tets, MD, PhD; Maarten van den Elsen, MD; Annemiek Swart, BSc (Sint Lucas Andreas Hospital, Amsterdam, the Netherlands); Laurens de Wit, MD, PhD; Muriel Siepel, MD; Glaresa Molly, BSc (Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands); Jan Juttmann, MD, PhD; Wilfred Clevers, MD; Andrea Bieleman, BSc (Tergooi Hospitals, Hilversum, the Netherlands); Ludo Coenen, MD; Elly Bonekamp, BSc (Gelre Hospitals, Apeldoorn, the Netherlands); Jacobus van Abeelen, MD; Diana van Iterson – de Jong, MD; and Margriet Krombeen, BSc (Red Cross Hospital, Beverwijk, the Netherlands).

ISSN: 0003-4932/11/25406-0868
DOI: 10.1097/SLA.0b013e31821fd1ce

Worldwide, colon cancer is the second most common cancer. Its incidence is expected to rise with the increasing longevity of the Western population. Surgical resection is the first line strategy to treat colonic cancer and the implementation of screening programs is likely to further increase the number of patients requiring colonic surgery.

Over the past 20 years there have been 2 important developments in elective major abdominal surgery; the introduction of laparoscopic surgery and the implementation of an enhanced recovery after surgery (ERAS) program, also referred to as "fast track" (FT) perioperative care, both focusing on accelerated recovery resulting in shorter hospital stay.[1,2]

Laparoscopic resection of bowel cancer was first described in 1991.[1] Randomized clinical trials have shown that this technique is safe and effective for malignant disease, and results in a shorter hospital stay of about 1 to 4 days, and less morbidity and postoperative pain than open colorectal surgery.[3–5]

During the mid-1990s FT perioperative care was pioneered by Henrik Kehlet.[2,6–8] FT programs consist of a multidisciplinary approach, involving dieticians, nurses, surgeons, and anesthesiologists and aim at reducing surgical stress response, organ dysfunction, and morbidity, thereby promoting a faster recovery after surgery.[7,9] FT

perioperative care comprises extensive preoperative counseling, no bowel preparation, no sedative premedication, carbohydrate-loaded liquids up to 2 hours before surgery, effective multimodal pain management, short acting anaesthetics, adequate perioperative fluid management, small incisions, and no routine use of drains and nasogastric tubes. Postoperative care includes early oral feeding, enforced mobilization, early removal of urinary catheter, and standard laxatives.

Similar or even faster rates of recovery have been reported for FT open colectomy on comparison with laparoscopic colectomy in a standard perioperative care setting.[10,11] Because the leading trials[3–5] comparing laparoscopic with open surgery have been done in a traditional perioperative care setting, this comparison needs to be re-evaluated within an enhanced recovery program.

There are no trials to be found in literature addressing the 4 combinations of standard or FT care with laparoscopic or open surgery. The longstanding question of which of the 4 perioperative treatment options is the optimal one for the patient with respect to postoperative recovery remains unanswered.[12,13] Two systematic reviews looked at all available studies comparing open surgery with laparoscopic surgery within a FT program, but no firm conclusion could be made due to lack of data.[14,15]

Hypothetically, combining the 2 new developments, ie, FT care and laparoscopy, will result in the fastest postoperative recovery. At the same time, it is questionable if both of them are as important with respect to postoperative recovery.

Hence, our aims were to determine which form of perioperative treatment, laparoscopic or open surgery combined with FT or standard care, is the optimal approach for patients undergoing segmental resection for colon cancer, and to investigate if either laparoscopy, FT care, or the combination of both is the main predictive factor for a faster postoperative recovery.

METHODS

Patients treated in 9 Dutch hospitals (3 University hospitals and 6 teaching hospitals) were eligible if they were between 40 and 80 years of age, had an American Society of Anesthesiologists (ASA) grade of I, II, or III, were to undergo elective segmental colectomy for histologically confirmed adenocarcinoma or adenoma, and without evidence of metastatic disease. Exclusion criteria were prior midline laparotomy, unavailability of a laparoscopic surgeon, emergency surgery, or a planned stoma. The study was conducted in accordance with the principles of the Declaration of Helsinki and according to the CONSORT statement.[16] The independent medical ethics review boards of the participating hospitals approved the study protocol. The study was registered under NTR222.[17]

Design

A randomized trial of a 2 × 2 balanced factorial design was performed. After written informed consent had been obtained, patients were randomized by means of an Internet randomization module. Block-randomization was used and randomization was stratified for the randomizing centers. Patients were randomized to laparoscopic or open colectomy, and to the FT program or standard care. This resulted in 4 treatment groups: (a) laparoscopic colectomy with FT care (Lap/FT); (b) open colectomy with FT care (Open/FT); (c) laparoscopic colectomy with standard care (Lap/Standard); and (d) open colectomy with standard care (Open/Standard). Patients and nursing staff were routinely informed about the perioperative care program, ie, FT care or standard care, but were blinded to the type of intervention, ie, laparoscopic or open surgery.

Outcomes

Primary outcome was total postoperative hospital stay (THS), measured in days. THS was defined as postoperative hospital stay (PHS) plus the additional hospitalization period in case patients were readmitted within 30 days of surgery. All patients were discharged if they complied with the following predefined discharge criteria: (1) adequate pain control with paracetamol and/or nonsteroidal anti-inflammatory drugs (2) ability to tolerate solid food (3) absence of nausea (4) passage of first flatus and/or first stool (5) mobilization as preoperative, and (6) acceptance of discharge by the patient.

Secondary outcomes were PHS, overall morbidity, reoperation rate, readmission rate, in-hospital mortality, quality of life at 2 and 4 weeks, patient satisfaction 4 weeks postoperatively and in-hospital costs.

General quality of life was assessed with the validated and widely used Short Form-36 (SF-36).[18] Bowel-related quality of life was assessed with the validated Gastro-Intestinal Quality of Life Index (GIQLI).[19] Physical functioning, bodily pain and social functioning scales (SF-36) and social functioning scale (GIQLI) were secondary outcomes.

Additionally, a self-reported patient satisfaction questionnaire, routinely used at our center, was sent to all patients. It comprises 16 items, addressing issues including satisfaction with personal attention from the surgeon and nurses and medical information. Total patient satisfaction scores ranged from 16 (lowest patient satisfaction) to 80 (highest patient satisfaction).

The marginal direct medical in-hospital costs were calculated for the 4 treatment strategies per patient. These costs included outpatient care, operating time, patient-days, the additional costs of laparoscopy and of FT care, as well as the costs of complications, reoperations and readmissions within 30 days after the index operation.

FT Care versus Standard Care

To avoid cross-over treatment by the nursing staff, patients were admitted either to a ward providing FT care or a ward providing standard care, depending on randomization. These treatment protocols are described in detail elsewhere.[17] Nursing and medical staff working on the FT care ward were already familiar with FT care before this study.

Surgical Technique

The technique of the open or laparoscopic procedure was at the discretion of the local surgeon. Participating laparoscopic surgeons were required to have performed a minimum of 20 laparoscopic colectomies for benign disease as stated in the proclamation of the American Society of the Colon and Rectum Surgeons in 2004, before they were allowed to perform laparoscopic colectomy for cancer. A laparoscopic procedure was considered converted if there was an unplanned enlargement of the incision. No quality requirements were set for open surgery as this was standard care in all centers. A right colectomy was typically done via midline laparotomy. At the end of surgery the abdomen was covered with a large dressing to hide the type of approach to blind the patient, doctors and nurses on the ward, ie, the operating surgeon was not the physician who took care of the patients at the ward.

Data Collection

Data were collected via a secured dedicated website. Up to discharge, nursing staff reported daily on the patient's progress, ie, intake, passage of flatus, and predefined discharge criteria were checked. After 30 days of follow-up, the anesthetic and clinical dossiers (nursing and medical) were checked for missing data. Outpatient medical dossiers were checked for any complication that had occurred after discharge within 30 days of the operation. The SF-36 and GIQLI were mailed to the patients prior to and at 2 and 4 weeks after the operation. The patient satisfaction questionnaire was mailed 4 weeks

postoperatively. All quality of life data from patients who had returned baseline questionnaires were incorporated into the analysis, even if 1 or 2 follow-up measurements were missing.

Sample Size Calculation

Because both FT care and laparoscopy aim at faster recovery resulting in a reduction of hospital stay, hospital stay was used as the primary efficacy parameter. Using a 5% significance level, a total sample size of 400 had a power of >95% to detect a minimum reduction in THS of 1 day between laparoscopic and open surgery, 1 day reduction in THS between FT and standard care, and a power of 80% to detect the same difference between the combination of FT with laparoscopic surgery and open surgery with standard care.[17]

Statistical Analysis

Statistical analyses of any differences between the 4 groups were performed using SPSS for Windows version 16 (SPSS Inc. Chicago, IL). Data were analyzed in according to the intention to treat principle. Data were presented as means ± standard deviations or as medians and interquartile ranges where appropriate. For dichotomous outcomes, treatment groups were compared by means of the χ^2 test. The Mann–Whitney *U* test and Kruskal–Wallis tests were used for continuous, not normally distributed outcomes. For continuous normally distributed data, the ANOVA test was used. Univariate and multiple linear or logistic regression analyses were performed to analyze the effect of laparoscopy, FT care and the combination of both on the primary and secondary endpoints. As the length of hospital stay was not normally distributed, these data were log-transformed. Quality of life was investigated through multilevel modeling, with fixed measurement occasions (level 1) nested within patients (level 2). The appropriate covariance structure for the data was unstructured and all models included time and treatment interactions. In-hospital costs were separately analyzed for the university and teaching hospitals. A 2-sided P value < 0.05 was considered to be statistically significant.

RESULTS

Between July 2005 and August 2009, 427 patients were randomly assigned to 1 of the 4 treatment groups (Fig. 1). Baseline characteristics between the 4 treatment groups did not differ significantly (Table 1).

Protocol Compliance

Fifteen FT elements were evaluated per patient. The following elements were scored if successfully applied; preoperative counseling, omission of bowel preparation, intake of carbohydrate-loaded drinks at the day before surgery, intake of carbohydrate-loaded drinks at the morning before surgery, no preoperative fasting since midnight, omission of premedication, thoracic epidural analgesia, prevention of hypothermia, adequate perioperative fluid loading, removal of nasogastric tube before extubation, omission of abdominal drains, suprapubic catheter or no catheter, more than 500 mL of intake at postoperative day (POD) 0 including 200 mL carbohydrate-loaded drink, more than 15 minutes mobilization at POD 0, and starting with laxative at POD 1. In the Lap/FT group 11.2 ± 2.2 out of the 15 elements and

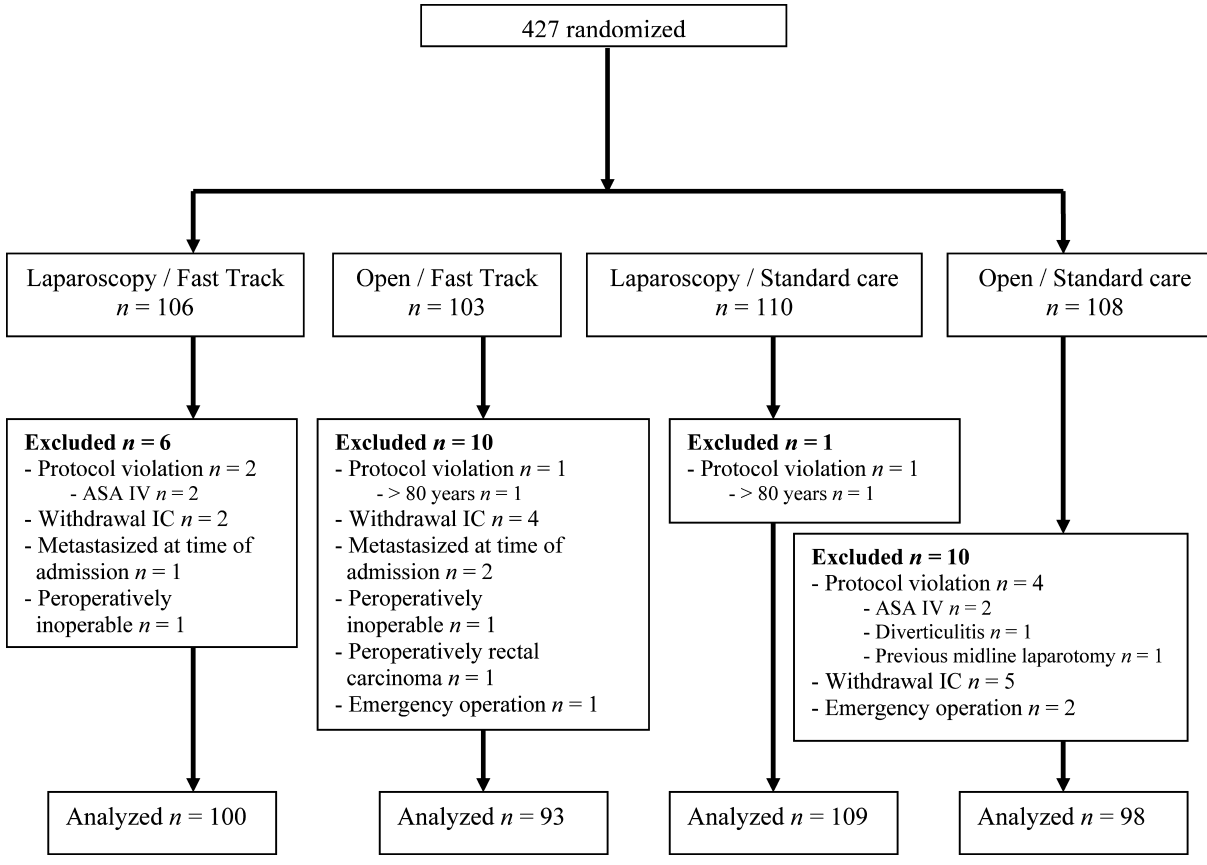

FIGURE 1. Study flow.

TABLE 1. Baseline Characteristics and Surgical Aspects of the Included Patients per Group

	Laparoscopy and Fast Track (n = 100)	Open and Fast Track (n = 93)	Laparoscopy and Standard care (n = 109)	Open and Standard care (n = 98)	*P*
Age, mean (SD), year	66 ± 8.6	66 ± 10.3	68 ± 8.8	66 ± 7.1	
Male sex (%)	53	58	62	60	
Body mass index, mean (SD, kg/m^2)	26.8 ± 4.0	26.3 ± 4.2	25.5 ± 3.9	26.5 ± 5.0	
ASA (%)					
Grade I or II	82	81	80	77	
Comorbidity (%)	71	59	68	68	
Type of colectomy (%)					
Right-sided	45	35	44	55	
Left-sided	55	65	56	45	
T stage (%)					
T0	13	16	15	16	
T1	10	7	5	5	
T2	24	19	27	21	
T3	48	55	50	53	
T4	5	3	3	5	
N stage (%)					
N0	64	61	68	70	
N1	29	31	25	24	
N2	7	8	7	6	
M stage (%)					
M0	98	96	94	94	
M1	2	4	6	6	
Conversion (%)	12		11		
Duration of surgery, median (IQR) (minutes)	171 (139–198)	129 (101– 175)	165 (135–204)	129 (110–151)	<0.001*
Blood loss, median (IQR, mL)	50 (0–150)	200 (100–306)	100 (0–200)	200 (100–350)	<0.001*

*ANOVA test.
ASA indicates American Society of Anesthesiologists; IQR, interquartile range.

in the Open/FT group 11.1 ± 2.2 elements were successfully applied per patient (Table 2).

As illustrated in Table 2 some FT elements have also been implemented in the standard care group; in the Lap/Standard 6.0 ± 1.5 elements and in the Open/Standard 5.8 ± 1.4 elements per patient. Other applied elements were; prevention of hypothermia in 97% of the patients, removal of the nasogastric tube before extubation in 82%, and omission of abdominal drains in 93%. Although thoracic epidural analgesia was applied at an equal rate in all groups, the epidural catheter remained significantly longer in situ in the standard care groups (a median [IQR], ie, 3 [2–4] days compared with 2 [2–3] days in the FT groups [$P < 0.001$]).

Primary Outcome

THS and PHS in patients randomized to the Lap/FT group was significantly (median 1 day) shorter than in the other 3 treatment groups ($P < 0.001$). There was no significant difference in THS or PHS between patients treated with Open/FT and patients treated with Lap/Standard. Patients who underwent Open/Standard treatment had a significantly longer PHS than Lap/FT, Open/FT, and Lap/Standard. THS after Open/Standard treatment was significantly longer than Lap/FT and Lap/Standard (Table 3).

Linear regression analysis identified laparoscopy as the only independent factor to influence THS (B = 0.79, confidence interval [CI] 0.69–0.91, $P = 0.001$), ie, laparoscopic surgery would lead to a reduction in THS of 21% (CI: 9–31%). FT care showed a trend toward a shorter THS (B = 0.88, CI: 0.77–1.01, $P = 0.070$), but the combination of both showed no additional benefit. PHS was significantly influenced by both laparoscopy (B = 0.80, CI: 0.70–0.91, $P = 0.001$), ie, leading to a reduction in PHS of 20% (CI: 9–30%), and FT care (B = 0.86, CI: 0.76–0.98, $P = 0.025$), ie, a reduction of 14% (CI: 10–20%). The combination of both did not add any benefit.

Secondary Outcomes

There were no significant differences between the 4 treatment groups regarding overall-, major-, or minor morbidity, reoperation rate, readmission rate and in-hospital mortality (Table 4). Logistic regression analysis showed that laparoscopic resection resulted in a significantly lower overall- and major morbidity (OR 1.53, CI: 1.02–2.29, $P = 0.041$, and OR 1.73, CI: 1.01–2.95, $P = 0.045$, respectively). Neither FT care nor the combination of both reduced overall- and major morbidity. Minor morbidity, reoperation and readmission rate were not significantly influenced by the different surgical regimens.

There were no statistically significant differences, adjusted for the type of hospital, in in-hospital costs among the treatment groups as tested with the Kruskall–Wallis test and linear regression analysis (Table 3).

The discharge criterion "absence of nausea" was achieved at the same postoperative day in all groups. Lap/FT patients had a significantly faster recovery, ie, achieved 5 discharge criteria earlier, than patients in the Lap/Standard or Open/Standard groups. Lap/FT patients showed a significantly quicker "passage of first stool" and "acceptance of discharge" than those in the Open/FT group (Table 3).

Five discharge criteria were achieved significantly earlier in Open/FT than in Open/Standard treatment; the criteria "tolerate solid food" and "mobilization as preoperative" were achieved significantly earlier in Open/FT than in Lap/Standard.

Apart from the criteria "absence of nausea," "tolerate solid food" and "passage of first flatus," Lap/Standard patients achieved all other discharge criteria significantly earlier than Open/Standard patients.

TABLE 2. Protocol Compliance

	Laparoscopy and Fast Track (n = 100)	Open and Fast Track (n = 93)	Laparoscopy and Standard care (n = 109)	Open and Standard care (n = 98)
Cross-over* – no. (%)	3[a] (3)	3[b] (3)	3[c] (2)	2[d] (2)
Preoperative phase – Yes, no. (%)				
Preoperative counseling†	96 (96)	92 (99)	6 (6)	1 (1)
Omission of bowel preparation	96 (96)	90 (97)	85 (78)	83 (85)
Intake of CHL – day before surgery median (IQR), liter	0.8 (0.3–0.8)	0.8 (0–0.8)	0.0 (0–0)	0.0 (0–0)
Day of surgery – Yes, no. (%)				
Intake of CHL – 2 hours before surgery median (IQR), liter	0.4 (0.2–0.4)	0.4 (0–0.4)	0.0 (0–0)	0.0 (0–0)
No preoperative fasting since midnight	87 (87)	77 (83)	29 (27)	28 (29)
Omission of premedication	69 (69)	61 (66)	23 (21)	20 (20)
Thoracic epidural analgesia	87 (87)	84 (90)	72 (66)	74 (76)
Intraoperative fluid loading, median (IQR), liter	2.2 (1.6–3)	2.5 (2–3)	2.5 (2–3.1)	2.6 (2–3.5)
Suprapubic catheter or no catheter‡	47 (47)	54 (58)	42 (39)	30 (31)
Intake of CHL – after surgery, median (IQR), liter	0.0 (0–0.2)	0.0 (0–0.2)	0.0 (0–0)	0.0 (0–0)
Total oral intake – after surgery, median (IQR), liter	0.5 (0.1–0.8)	0.3 (0–0.8)	0.05 (0–0.2)	0.0 (0–0.2)
Mobilization – after surgery, median (IQR), liter	0.0 (0–19)	0.0 (0–20)	0.0 (0–0)	0.0 (0–0)
Start laxative POD 1 – Yes, no. (%)	85 (85)	77 (83)	9 (8)	7 (7)
Intake of CHL, median (IQR, L)				
POD 1	0.2 (0–0.4)	0.2 (0–0.4)	0.0 (0–0)	0.0 (0–0)
POD 2	0.2 (0–0.4)	0.2 (0–0.4)	0.0 (0–0)	0.0 (0–0)
POD 3	0.2 (0–0.4)	0.0 (0–0.4)	0.0 (0–0)	0.0 (0–0)
Total oral intake, median (IQR, L)				
POD 1	1.5 (0.9–1.9)	1.1 (0.7–1.6)	0.9 (0.5–1.5)	0.7 (0.3–1.0)
POD 2	1.7 (1.0–2.0)	1.4 (0.8–2.0)	1.2 (0.8–1.7)	1.0 (0.4–1.5)
POD 3	1.8 (1.2–2.0)	1.8 (1.0–2.0)	1.5 (1.0–2.0)	1.0 (0.7–1.8)
Mobilization, median (IQR, minutes)				
POD 1	120 (50–240)	120 (60–215)	30 (15–60)	20 (0–60)
POD 2	200 (90–360)	120 (60–240)	90 (45–180)	60 (20–115)
POD 3	300 (120–400)	220 (100–360)	135 (60–240)	100 (53–195)

*Analysis according to intention to treat: [a]2 pt. received Open FT/1 pt. received Lap Standard; [b]2 pt. received Lap FT/1 pt. received Open Standard; [c]1 pt. received Open Standard/1 pt. received Lap FT; and [d]2 pt. received Open FT.

†Preoperative counseling = separate consultation before admission with a "fast track" trial nurse to discuss the essence of the fast track program.

‡In patients in whom this element was not achieved, a Foley catheter was placed.

CHL indicates carbohydrate-loaded drink; IQR, interquartile range; POD, postoperative day.

TABLE 3. Postoperative Data

	Laparoscopy and Fast Track (n = 100)	Open and Fast Track (n = 93)	Laparoscopy and Standard care (n = 109)	Open and Standard care (n = 98)	*P*
Total hospital stay, median (IQR), days	5 (4–8)	7 (5–11)	6 (4.5–9.5)	7 (6–13)	<0.001*†
Postoperative hospital stay, median (IQR), days	5 (4–7)	6 (4.5–10)	6 (4–8.5)	7 (6–10.5)	<0.001*‡
Days to fulfill discharge criteria, median (IQR)					
(1) Pain control with oral medication	2 (2–3)	2 (2–4)	3 (2–4)	3 (2–5)	
(2) Tolerate solid food	1 (1–2)	1 (1–3)	2 (1–3)	3 (2–5)	
(3) Absence of nausea	1 (1–3)	2 (1–5)	1 (1–3)	1 (1–4)	
(4a) Passage of first flatus	1 (1–2)	1 (1–3)	2 (1–3)	2 (1–3)	
(4b) Passage of first stool	2 (1–4)	3 (2–4)	3 (2–4)	4 (3–6)	
(5) Mobilization as preoperative	3 (2–5)	4 (3–7)	5 (4–7)	6 (5–8)	
(6) Acceptance of discharge	4 (3–6)	5.5 (4–9)	5.5 (4–8)	7 (5–12)	
In-hospital costs					
University hospitals, median (IQR, €)	10,594 (5461–16,763)	12,805 (6847–20,658)	11,967 (6222–17,039)	10,479 (6608–16,875)	0.56*
Teaching hospitals, median (IQR, €)	5768 (4873–8917)	5497 (4506–6513)	6228 (5280–6604)	5650 (4836–8003)	0.41*

*Kruskal–Wallis test/Groups individually tested by mann–whitney *u* test.

†Significant difference between Lap/FT and Open/FT (0.008)/Lap/FT and Lap/Standard (0.026)/Lap/FT and Open/Standard (0.000)/Lap/Standard and Open/Standard (0.010).

‡Significant difference between Lap/FT and Open/FT (0.005)/Lap/FT and Lap/Standard (0.020)/Lap/FT and Open/Standard (0.000)/Open/FT and Open/Standard (0.032)/Lap/Standard and Open/Standard (0.004).

TABLE 4. Postoperative Data

	Laparoscopy and Fast Track (n = 100)	Open and Fast Track (n = 93)	Laparoscopy and Standard care (n = 109)	Open and Standard care (n = 98)	*P*
Overall morbidity < 30 days, No. (%)	34 (34.0)	43 (46.2)	37 (33.9)	41 (40.8)	0.20*
Patients with one or more major complications, No. (%)	15 (15.0)	18 (20.4)	12 (11.0)	21 (21.4)	0.19
Total no. of major complications	18	25	17	29	
Intraoperative complication	2	0	1	1 of which 1†	
Anastomotic leakage	7	8 of which 2†	6 of which 1†	7	
Mechanical ileus requiring reoperation	3	2	0	5	
Iatrogenic bowel perforation	0	2	2 of which 1†	1	
Abdominal wall dehiscence	0	6	1	3	
Other surgical complication‡	2	2	2	2	
Myocardial infarction	0	1	0	0	
Respiratory	2 of which 1†	2 of which 1†	2	4	
Infectious	0	2 of which 1†	3	3	
Cerebral vascular accident	1 of which 1†	0	0	2 of which 1†	
Acute tubular necrosis	1	0	0	1	
Patients with one or more minor complications, no. (%)	19 (19.0)	25 (26.8)	25 (23.8)	20 (19.4)	0.58*
Total no. of minor complications	36	46	43	43	
Prolonged postoperative ileus§	7	5	8	5	
Other surgical complication¶	2	2	2	2	
Wound infection	6	16	8	10	
Other infectious complication	8	11	9	14	
Urine retention	4	6	6	1	
Cardiac	3	4	3	3	
Central nervous system	4	2	4	4	
Renal failure	2	0	0	1	
Other	0	0	3	3	
Reoperations, no. (%)	10 (10.0)	13 (14.0)	11 (10.1)	18 (18.4)	0.24*
Readmission < 30 days, no. (%)	6 (6.0)	7 (7.5)	7 (6.4)	7 (7.1)	0.97*
In-hospital mortality, no. (%)	2 (2.0)	4 (4.3)	2 (1.8)	2 (2.0)	0.65*

*Chi-square test.
†Died.
‡Other surgical complication, eg, postoperative bleeding and abdominal abscess requiring intervention, bowel necrosis.
§Prolonged postoperative ileus = unable to tolerate food with abdominal distension and had no bowel sounds, flatus and defecation after 5 days.
¶Other surgical complication, eg, intraperitoneal haematoma, suprapubic catheter sutured into laparotomy wound, postoperative bleeding with expectative policy.

Because of the missing data at baseline, the overall analysis of data generated by the SF-36 and GIQLI was conducted in 352 patients (88%). At follow-up there was an overall response rate of 80% and 84% at 2 and 4 weeks postoperatively.

Quality of life at baseline was not significantly different among the groups for the scales assessed. Overall, physical functioning, bodily pain and social functioning measured with the SF-36, and social functioning measured with the GIQLI, significantly declined at 2 weeks postoperatively. Four weeks after surgery bodily pain and social functioning measured with the SF-36 returned to baseline values. The other functioning scales remained significantly lower. There were no statistically significant differences on any of the scales among the 4 treatment groups at any time point. Patient satisfaction was similar across all groups.

DISCUSSION

This trial showed that the combination of laparoscopic surgery with FT care resulted in a significantly faster recovery after colonic surgery than all other combinations, ie, Open/FT, Lap/Standard, or Open/Standard. Patients treated with Open/FT or Lap/Standard had a similar postoperative recovery; Open/Standard treatment resulted in the worst outcome. Treatment groups had similar morbidity, reoperation and readmission rates, equal in-hospital mortality, comparable levels of quality of life and patient satisfaction, and similar in-hospital costs. Laparoscopy was found to be the only significant independent factor to reduce THS and morbidity.

The main goal of the FT concept is not to discharge patients earlier, but to accelerate the patient's postoperative recovery resulting in a shorter hospital stay. The primary outcome, THS, was standardized by predefined objectively quantified discharge criteria, which is in contrast to other studies where discharge criteria have not been defined properly.[9,12,20–22] In our study, discharge criteria were scored daily.

Length of hospital stay after a Lap/FT or Open/FT treatment in our study was in accordance with the literature,[12,21,23,24] but longer than that reported by Kehlet et al.[9,20,25] It should be pointed out that Kehlet's results were achieved at the center where FT was developed, and at the expense of a higher readmission rate. Our study might therefore reflect daily practice more accurately.

On comparison with the literature overall morbidity in the 4 treatment groups was relatively high. This can be explained by the fact that all complications both intra- and extramural, were scored prospectively and by the inclusion of patients aged up to 80. Two systematic reviews comparing FT with standard care suggest reduced morbidity and mortality in FT.[10,11] We found no significant difference in overall morbidity and mortality between the 4 groups. However, less morbidity was associated with laparoscopic surgery, whereas this was not the case for FT care. It is remarkable and yet unexplained, that in this trial patients treated in the Open/Standard group

underwent reoperation more frequently (18%) than literature reports. In the Netherlands the mean figure is 11%.

Quality of life 2 and 4 weeks postoperatively were similar across the groups, which is in accordance with a recently published systematic review.[26] This is probably explained by the fact that all patients were operated for cancer and therefore the most important aim for them was to get cured. Another explanation is that differences in quality of life are expected to be the most prominent in the first week after surgery.

Most studies investigating the effectiveness of FT protocols did not assess how many of the FT elements were actually implemented in practice. It is important to evaluate this, particularly as implementation of this multidisciplinary protocol in clinical practice has proven difficult.[7,27–29] In this study, 11 of the 15 predefined FT elements were successfully applied in the FT groups. Obviously, it was intended to apply all FT elements in the patients randomized to the FT group. In daily practice though, when implementing a new protocol, it is hard to achieve all elements. Reason is breaking with longstanding traditions, for example. Scoring which FT elements are actually successfully achieved is therefore the strength of this study. Three systematic reviews[10,11,15] reported means of between 8.5 and 13 FT elements applied, whereby applied does not necessarily mean achieved. The reduction in hospital stay of only 1 day, as found in the Lap/FT group, is probably due to the fact that standard care actually meant modern care. In the participating centers, standard care included 6 of the 15 predefined FT items. On the basis of the existing evidence we felt that it would have been unethical and unreal to withhold these in trial setting.[30,31]

Laparoscopy as well as FT care is more expensive than open surgery and standard care. Nevertheless, in-hospital costs were similar between the groups. A cost-effectiveness analysis was therefore not performed. The higher costs of laparoscopy and FT care were most likely counterbalanced by a shorter hospital stay and, although not significant, less overall morbidity. Moreover, saving 1 to 2 days per treated patient, hospital bed utilization will be reduced by 20%.

Apart from the set of items applied, the discriminating feature of the FT program is the rehabilitation process, which is always implemented in the same way. For example, the protocol precluded the discussion of, if, and when the patient could eat and mobilize after surgery, or the time of removal of the epidural. It is likely to be the fact that perioperative care is protocolized, rather than the combination and number of applied FT elements, that is the true source of the success of the FT program. In a side study of this study it will be determined which baseline characteristics and/or which successfully achieved FT elements are independent predictors of faster postoperative recovery in patients undergoing colonic resection for colon cancer.

The limitations of our study were the blinding of the treatment, which was difficult to achieve as the majority of the patients could not resist looking under the abdominal dressing. Wound inspection was not a limiting factor as this was not carried out until the day of discharge, but obviously only in those patients without wound complaints or complications. Nonetheless, this possible failure has not influenced our primary outcome as discharge was clearly defined by applying strict discharge criteria. Secondly, after randomization more patients in the open groups ($n = 20$) than in the laparoscopic groups ($n = 7$) were excluded, nevertheless we can assume that this is coincidental. Thirdly, as patients have been enrolled for over 4 years, there might have been in drift in care, ie, patients included in a later phase of the study, allocated to standard care, might have received more FT elements than patients included at the start of the study. We tried to avoid this though by admitting patients to a ward providing FT care or a ward providing standard care.

In conclusion, the optimal treatment combination for patients requiring segmental colectomy for malignancy is a laparoscopic approach within a FT perioperative care program. If open surgery has to be performed, for example because of the lack of laparoscopic expertise or patient-related factors, then this should preferentially be embedded in a FT protocol.

ACKNOWLEDGMENTS

The authors would like to thank all investigators of the LAFA study group and all patients that participated in the LAFA-trial, without them the study would not have been possible. Further we are grateful for the governmental subvention (ZonMW) and the financial support of Johnson and Johnson International and Nutricia.

REFERENCES

1. Jacobs M, Verdeja JC, Goldstein HS. Minimally invasive colon resection (laparoscopic colectomy). *Surg Laparosc Endosc*. 1991;1:144–150.
2. Wilmore DW, Kehlet H. Management of patients in fast track surgery. *BMJ*. 2001;322:473–476.
3. A comparison of laparoscopically assisted and open colectomy for colon cancer. *N Engl J Med*. 2004;350:2050–2059.
4. Guillou PJ, Quirke P, Thorpe H, et al. Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. *Lancet*. 2005;365:1718–1726.
5. Veldkamp R, Kuhry E, Hop WC, et al. Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. *Lancet Oncol*. 2005;6:477–484.
6. Fearon KC, Ljungqvist O, Von MM, et al. Enhanced recovery after surgery: a consensus review of clinical care for patients undergoing colonic resection. *Clin Nutr*. 2005;24:466–477.
7. Kehlet H. Fast-track colorectal surgery. *Lancet*. 2008;371:791–793.
8. Kehlet H, Wilmore DW. Evidence-based surgical care and the evolution of fast-track surgery. *Ann Surg*. 2008;248:189–198.
9. Basse L, Thorbol JE, Lossl K, et al. Colonic surgery with accelerated rehabilitation or conventional care. *Dis Colon Rectum*. 2004;47:271–277.
10. Gouvas N, Tan E, Windsor A, et al. Fast-track vs standard care in colorectal surgery: a meta-analysis update. *Int J Colorectal Dis*. 2009;24:1119–1131.
11. Wind J, Polle SW, Fung Kon Jin PH, et al. Systematic review of enhanced recovery programmes in colonic surgery. *Br J Surg*. 2006;93:800–809.
12. Muller S, Zalunardo MP, Hubner M, et al. A fast-track program reduces complications and length of hospital stay after open colonic surgery. *Gastroenterology*. 2009;136:842–847.
13. Slim K, Fingerhut A. Laparoscopy or fast-track surgery, or both? *Surg Endosc*. 2009;23:465–466.
14. Khan S, Gatt M, MacFie J. Enhanced recovery programmes and colorectal surgery: does the laparoscope confer additional advantages? *Colorectal Dis*. 2009;11:902–908.
15. Vlug MS, Wind J, Van Der ZE, et al. Systematic review of laparoscopic vs open colonic surgery within an enhanced recovery programme. *Colorectal Dis*. 2009;11:335–343.
16. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010;340:c332.
17. Wind J, Hofland J, Preckel B, et al. Perioperative strategy in colonic surgery; LAparoscopy and/or FAst track multimodal management versus standard care (LAFA trial). *BMC Surg*. 2006;6:16.
18. Aaronson NK, Muller M, Cohen PD, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol*. 1998;51:1055–1068.
19. Eypasch E, Williams JI, Wood-Dauphinee S, et al. Gastrointestinal Quality of Life Index: development, validation and application of a new instrument. *Br J Surg*. 1995;82:216–222.
20. Andersen J, Hjort-Jakobsen D, Christiansen PS, et al. Readmission rates after a planned hospital stay of 2 versus 3 days in fast-track colonic surgery. *Br J Surg*. 2007;94:890–893.
21. Khoo CK, Vickery CJ, Forsyth N, et al. A prospective randomized controlled trial of multimodal perioperative management protocol in patients undergoing elective colorectal resection for cancer. *Ann Surg*. 2007;245:867–872.
22. King PM, Blazeby JM, Ewings P, et al. Randomized clinical trial comparing laparoscopic and open surgery for colorectal cancer within an enhanced recovery programme. *Br J Surg*. 2006;93:300–308.

23. Polle SW, Wind J, Fuhring JW, et al. Implementation of a fast-track perioperative care program: what are the difficulties? *Dig Surg*. 2007;24: 441–449.
24. Zutshi M, Delaney CP, Senagore AJ, et al. Randomized controlled trial comparing the controlled rehabilitation with early ambulation and diet pathway versus the controlled rehabilitation with early ambulation and diet with preemptive epidural anesthesia/analgesia after laparotomy and intestinal resection. *Am J Surg*. 2005;189:268–272.
25. Basse L, Jakobsen DH, Bardram L, et al. Functional recovery after open versus laparoscopic colonic resection: a randomized, blinded study. *Ann Surg*. 2005;241:416–423.
26. Khan S, Wilson T, Ahmed J, et al. Quality of life and patient satisfaction with enhanced recovery protocols.*Colorectal Dis*. 2009.
27. Kehlet H, Buchler MW, Beart RW, Jr., et al. Care after colonic operation–is it evidence-based? Results from a multinational survey in Europe and the United States. *J Am Coll Surg*. 2006;202:45–54.
28. Lassen K, Hannemann P, Ljungqvist O, et al. Patterns in current perioperative practice: survey of colorectal surgeons in five northern European countries. *BMJ*. 2005;330:1420–1421.
29. Maessen J, Dejong CH, Hausel J, et al. A protocol is not enough to implement an enhanced recovery programme for colorectal resection. *Br J Surg*. 2007;94:224–231.
30. Guenaga KF, Matos D, Castro AA, et al. Mechanical bowel preparation for elective colorectal surgery. *Cochrane Database Syst Rev*. 2003:CD001544.
31. Nelson R, Edwards S, Tse B. Prophylactic nasogastric decompression after abdominal surgery. *Cochrane Database Syst Rev*. 2005:CD004929.

