ORIGINAL ARTICLE

The effect of the introduction of the ERAS protocol in laparoscopic total mesorectal excision for rectal cancer

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Abstract

Objective The aim of the study was to determine whether the introduction of the Enhanced Recovery after Surgery (ERAS) protocol in laparoscopic total mesorectal excision (TME) for rectal cancer offers additional advantages concerning postoperative hospital stay compared to laparoscopy and conventional care.

Methods A consecutive series of patients that underwent a laparoscopic TME for rectal cancer in a single institution between January 2004 and July 2009 were retrospectively included in this study. The ERAS protocol was introduced in this cohort in January 2007. The study cohort was divided in a conventional care group and an ERAS group. Both groups were compared for primary and secondary outcome measures. The primary outcome measure was postoperative length of hospital stay.

Results Seventy-six patients were included: 43 in the ERAS group and 33 in the conventional care (control) group. Median hospital stay was 7 days (range 2-83 days) in the ERAS group and 10 days (range 4–74 days) in the control group (p=0.04). Return of bowel function occurred on days 2 and 3 respectively (p<0.001). There were no significant differences between both groups concerning postoperative complications, readmission rate and reoperations. Thirty-day mortality was absent in both

Conclusion These results suggest that the introduction of the ERAS protocol in laparoscopic TME leads to a further reduction in length of hospital stay.

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Introduction

Laparoscopic surgery has several advantages over open surgery. These advantages are less postoperative pain, quicker return of bowel function, less postoperative morbidity and shorter duration of hospital stay [1, 2].

Laparoscopic TME is relatively new, but has proven to be a reliable and safe alternative for the conventional open TME. It seems that laparoscopic TME is the treatment of choice when there are no (relative) contraindications for laparoscopic surgery [3, 4].

The Enhanced Recovery after Surgery (ERAS) protocol, also known as 'fast-track' surgery, was originally developed to enhance postoperative recovery and thereby shorten hospital stay for patients undergoing elective colonic resection [2]. The first results of randomised trials are very promising, reporting postoperative hospital stay of 2-4 days in favour of laparoscopic resections [5–7].

The key pathogenic factor in postoperative morbidity, when failures of surgical and anaesthetic techniques have been excluded, is the surgical stress response with subsequent increased demands on organ functions [8].

The body responds to surgical stress with profound changes in neural, endocrine and metabolic systems in addition to alterations in organ functions. Postoperatively, this may lead to complications such as myocardial infarction, delirium, pulmonary dysfunction, thromboembolism and infectious complications. Much effort was made to improve each of these specific outcome variables by unimodal therapeutic strategies [8]. The ERAS protocol, however, is a multimodal approach to all of these 'medical' complications. By reducing

stress and pain in patients undergoing colorectal resections together with aggressive postoperative mobilisation and early oral feeding, the body's stress response and organ dysfunction are reduced to a minimum, thus facilitating early recovery and reducing postoperative morbidity and mortality [9].

With respect to postoperative recovery and the duration of postoperative hospital stay, both laparoscopic surgery and the ERAS protocol share the same objective. If both laparoscopic TME and ERAS are combined, can additional advantages be expected concerning postoperative recovery and the duration of hospital stay?

In order to investigate this question, a consecutive series of patients treated for rectal cancer were retrospectively divided in two groups. One group consisted of patients treated in the pre-ERAS era (the conventional care group), and the other group formed the ERAS group. Both groups were compared for length of postoperative hospital stay.

Patients and methods

All 124 patients diagnosed with rectal cancer in a single centre between January 2004 and July 2009 were analysed. Eighty-four patients underwent an elective laparoscopic TME. Eight patients were excluded due to conversion to open surgery. The remaining 76 patients were all included in this study.

The ERAS protocol for laparoscopic rectal surgery was introduced in this hospital in January 2007. Therefore, all patients operated between January 2007 and July 2009 formed the ERAS group (N=43). The patients that underwent a rectal resection between January 2004 and January 2007 were assigned as a control group (N=33).

All data were retrospectively collected from patient charts. Collected data included age, body mass index (BMI), smoking, hypertension, diabetes mellitus, the American Society of Anaesthesiologists' (ASA) classification, the type of procedure, operation time, estimated blood loss, tumour distance from the anal verge, preoperative treatment, type of anastomosis, creation of a temporarily diverting or permanent stoma, return of bowel function after surgery, postoperative complications, readmission and reoperation rate, 30-day mortality and the primary outcome: length of postoperative hospital stay (LOS). In addition, pathologic tumour characteristics were obtained.

Tumour distance in centimetres from the anal verge was measured using a rigid sigmoid scope. Preoperative treatment consisted either of a limited (5×5.0 Gy) or extended (25×2.0 Gy) radiotherapy (RT) regimen or chemo radiation (25×2.0 Gy + capecitabine). All patients underwent either a laparoscopic low anterior resection (LAR) or a laparoscopic abdominal perineal resection (APR) according to the TME principle. In both groups the operations were performed by the same three surgeons, who were all well-trained in

laparoscopic rectal surgery. The type of anastomosis was defined as end-to-end, end-to-side or side-to-side anastomosis. Patients either received a diverting loop ileostomy or, in the case of APR, a permanent colostomy. Return of bowel function was defined as the first reported stoma production. The postoperative complications considered were bleeding, wound infection, anastomotic leakage and intra-abdominal abscess. Anastomotic leakage was defined as clinical signs of peritonitis together with a visualized anastomotic defect on colonoscopy or colonic enema radiography, with or without an intraabdominal abscess. Intra-abdominal abscesses were radiographically detected pockets of fluid in a presacral cavity. The length of hospital stay was defined as the number of postoperative days in the hospital (day of surgery = day 0). Readmission days were not added to this calculation. Readmissions and reoperations within 30 days after surgery were scored as either "yes" or "no". Readmissions and reoperations more than 30 days after discharge were not evaluated. Tumour characteristics comprising maximal tumour diameter on pathological examination, tumour differentiation grade, TNMclassification and radicality of the resection were obtained.

The pre-ERAS protocol

Patients were admitted the day before their operation. They received 4 L of oral bowel preparation (Klean-prep® Norgine B.V., Amsterdam, The Netherlands). A daily dose of 0.3 ml Fraxiparine® was administered. Patients were allowed a normal diet until midnight.

In the operating room all patients received a urinary catheter. Thirty minutes before the first incision, cefazoline (1,000 mg) and metronidazole (500 mg) were given intravenously. Patients were operated under general anaesthesia. Nasogastric tubes were routinely used. In general, one drain was placed in the pelvis.

Postoperatively, oral intake was prohibited, and standard intravenous fluid was set at 2–2.5 L/24 h. Patients received 4,000 mg of paracetamol (in four separate doses of 1,000 mg). If necessary, diclofenac 150 mg in three doses of 50 mg and morphine substitutes were also given. Nasogastric tubes, drains and catheters were removed at the surgeon's decision. After removal of the nasogastric tube, patients were allowed clear fluids. Discharge was arranged when the following criteria were met: There are no remaining lines or catheters, solid food is tolerated, there has been passage of stool, pain is controlled using oral analgesics only and the patient is able to restart basic daily activities and self-care, or function at the preoperative level.

The ERAS protocol

Within the ERAS protocol perioperative care is standardised to promote early mobilisation and resumption of a normal



diet as first described by H. Kehlet [5, 8, 10]. All patients that received the 'multimodal approach' (ERAS) agreed to an informed consent preoperatively in an outpatient setting. Patients were admitted the day before their operation to receive an epidural catheter, placed at a low level (Th 9–11, Table 1). Oral bowel preparation was omitted, but patients received two enemas on the evening before surgery.

Table 1 The ERAS protocol

The ERAS protocol

Day before surgery

- Normal diet until midnight
- Omission of oral bowel preparation
- 2 enemas in the evening
- An epidural catheter is placed at Th 9-11
- 0.3 ml Fraxiparine, 4000 mg paracetamol, 20 mg pantoprazole (every day until discharge)

Day of surgery

- 1 enema in the morning
- 2 packages of carbohydrate drinks
- Oral intake until 2 h before surgery
- Target body temperature ≥36°C
- Urinary catheter is placed
- Dexamethasone (5 mg) and ondansetrone (4 mg) preoperatively
- Cefalozine (1000 mg) and metronidazole (500 mg) i.v. 30 min before first incision
- Haloperidol (1.5 mg) intraoperatively
- Ventilation with 60-80% oxygen
- No nasogastric tubes
- All analgesics through the epidural catheter
- 1 intra-abdominal drain
- Oral fluid intake allowed and stimulated directly after surgery
- i.v. fluid restriction of 1 L per 24 h
- Liquid diet in the evening

Postoperative day 1

- Disconnection of the intravenous catheter
- Start magnesium oxide
- Restart normal diet at noon
- 2-3 h of mobilisation

Postoperative day 2

- Diclofenac 50 mg, 3 times daily
- Removal of epidural catheter (when pain is controlled properly)
- Removal of urinary catheter and intra-abdominal drain
- Full mobilisation

Discharge criteria

- No remaining lines or catheters
- Toleration of solid food
- There has been passage of stool
- Pain can be controlled using only oral analgesics
- Ability to conduct self-care or function at preoperative level

Daily doses of 0.3 ml Fraxiparine®, 4,000 mg of paracetamol (in four separate doses of 1,000 mg) and 20 mg of pantoprazole were administered, starting on the day before surgery and continued until discharge. Patients were allowed to maintain their normal diet until midnight. On the day of surgery patients received another enema and two packages of carbohydrate drinks. Patients were allowed oral intake until 2 h before surgery.

In the operating room body temperature was maintained using warm blankets. Target body temperature was ≥36°C. All patients received a urinary catheter. Thirty minutes before the first incision, cefazoline (1,000 mg) and metronidazole (500 mg) were given intravenously. This was repeated every 3.5 h. Five milligrams of dexamethasone and 4 mg of ondansetrone were given preoperatively, and 1.5 mg haloperidol was given intraoperatively. Patients were ventilated with 60 to 80% oxygen. Nasogastric tubes were not routinely used. All analgesics were given through the epidural catheter (levobupivacaine and sufentanil); the use of morphine and diclofenac was avoided. In general, one intraabdominal drain was left behind.

Postoperatively, oral fluid intake was directly encouraged, and intravenous fluid was restricted to 1 L per 24 h. In the evening after surgery, a liquid diet was introduced. On the first day after surgery, if oral fluid intake was sufficient, the intravenous catheter was disconnected. Magnesium oxide was started, and the patient was allowed to restart a normal diet at noon. Patients were stimulated to mobilise 2–3 h on the first day.

On the second day after surgery, diclofenac was started in a dose of 50 mg, three times daily, and the epidural catheter was removed when pain was controlled properly (VAS<4/10). The urinary catheter and unproductive abdominal drains were removed, and patients were stimulated to fully mobilise.

Discharge was arranged when the following criteria were met: There are no remaining lines or catheters, solid food is tolerated, there has been passage of stool, pain is controlled using oral analgesics only and the patient is able to restart basic daily activities and self-care, or function at the preoperative level.

Statistical analysis

All collected data were entered in a database and analysed using SPSS Statistics 17.0 for Windows. To determine significant differences between the ERAS and control groups, statistical analysis was performed using a χ^2 test. A p-value <0.05 was considered statistically significant.

Continuous data are expressed as median (range) or as mean (\pm SD) and were analysed using Mann–Whitney U test. BMI was converted to a categorical variable, representing



certain risk groups. All categorical and dichotomous variables were analyzed using χ^2 test.

Primary outcome was length of hospital stay. To determine independent outcome predictors, all possible predictors of the primary outcome were analysed in univariate and multivariate regression models. In the multivariate analysis, the backward regression method was used.

Results

In all patients in the ERAS group (43), an epidural catheter was successfully placed. In two (4.7%) patients, the epidural catheter had to be removed before day 2 because of dislocation of the catheter. Twenty-one patients (49%) could be disconnected from the intravenous catheter on day 1. In 37 (86.0%) patients the epidural catheter could be removed on day 2. Twenty-one patients (49%) had their urinary catheter removed on day 2. In total, 16 (37%) patients were managed exactly according to the ERAS protocol.

Both groups were compared for demographics and patient-related and tumour-related factors (Table 2). No significant differences were found between both groups, except for a history of diabetes. Nine patients in the ERAS group and one in the conventional care group had diabetes. Nearly all patients received preoperative treatment, consisting of a short scheme (5×5.0 Gy) radiotherapy (RT), long scheme (25×2.0 Gy) RT or chemo radiation (25×2.0 Gy + capecitabine). Chemo radiation is a relatively new treatment regimen for patients with locally advanced rectal cancer. Therefore, this therapy was only observed in the ERAS group. All patients underwent either laparoscopic low anterior resection (LAR) or laparoscopic abdominal perineal resection (APR). There was no difference between both groups regarding the type of procedure.

Mean (total) operating time was 319 ± 75 min in the ERAS group and 356 ± 91 min in the conventional care group (p=0.068). Median blood loss was 300 ml (0–2400) and 400 ml (0–2400) respectively (p=0.346). Operating time tended to be longer for LAR, and mean blood loss tended to be more for APR, but the differences did not reach statistical significance (Table 3).

There is a significant difference in length of postoperative hospital stay between both groups. The median postoperative hospital stay was 10 (4–74) days for patients receiving conventional care and 7 (2–83) days for patients that had followed the ERAS protocol (p=0.042). Furthermore, return of bowel function occurred significantly earlier in the ERAS group compared to the control group, with a median of 2 (1–7) and 3 (1–14) days respectively (p<0.001).

No significant differences were found when both groups were compared for postoperative complications, factors delaying early discharge, and readmission and reoperation

 Table 2
 Baseline characteristics

	No ERAS (N=33)	ERAS (<i>N</i> =43)	p-Value*
Age (years)			
Median (range)	64 (27–88)	66 (36–79)	0.156
Gender			0.726
Male	22 (66.7)	27 (62.8)	
Female	11 (33.3)	16 (37.2)	
BMI			0.456
<25	17 (58.6)	16 (41)	
25–30	7 (24.1)	13 (33.3)	
30–35	2 (6.9)	6 (15.4)	
>35	3 (10.3)	4 (10.3)	
Smoking (N=63)	8 (24.2)	10 (23.3)	0.872
Hypertension	10 (30.3)	16 (38.1)	0.482
Diabetes	1 (3)	9 (21.4)	0.020
ASA classification			0.484
I	9 (27.3)	18 (41.9)	
II	17 (51.5)	15 (34.9)	
III	6 (18.2)	9 (20.9)	
IV	1 (3)	1 (2.3)	
UICC stage			0.155
0	1 (3.0)	1 (2.3)	
I	12 (36.4)	11 (25.6)	
II	13 (39.4)	11 (25.6)	
III	7 (21.2)	20 (46.5)	
Preoperative treatment			< 0.001
No preoperative treatment	4 (12.1)	1 (2.3)	
RT short (5×5.0 Gy)	19 (57.6)	23 (53.5)	
RT long (25×2.0 Gy)	10 (30.3)	3 (7)	
Chemo radiation $(25 \times 2.0 \text{ Gy} + \text{capecitabine})$	0	16 (37.2)	
Tumour distance from anal verge (cm)			0.635
0–4	12 (36.4)	18 (41.9)	
5–8	14 (42.4)	17 (39.5)	
>8	7 (21.2)	8 (18.6)	
Procedure			0.228
Lap. low anterior resection (LAR)	25 (75.8)	27 (62.8)	
Lap. abdominal perineal resection (APR)	8 (24.2)	16 (37.2)	

Values in parentheses are percentages unless indicated otherwise BMI body mass index, ASA American Society of Anaesthesiology, UICC Union for International Cancer Control, RT radiotherapy *p-Value calculated by χ^2 test

rates within 30 days after surgery. In both groups 30-day mortality was absent.

Haemorrhage occurred in one patient in the ERAS group (p=0.38); this patient needed reoperation. Four (9.3%) ERAS patients developed a wound infection and two (6.1%) patients



Table 3 Results

Values in parentheses are percentages unless indicated

^aCardiovascular events, pneumonia and urinary tract infections

LAR low anterior resection, APR abdominal perineal resection
*p-Value calculated using Mann–Whitney U test;
**p-value calculated using

otherwise

 χ^2 test

0.068*
0 346*
0 346*
0.346*
0.5 10
0.042*
<0.001*
0.378**
0.603**
0.947**
0.358**
0.216**
0.421**
0.894**

in the conventional care group (p=0.60). Anastomotic leakage occurred in five (11.6%) and four (12.1%) patients respectively (p=0.95). Intra-abdominal abscesses were reported in seven (16.3%) and three (9.1%) cases respectively (p=0.36). Furthermore, factors delaying early discharge were reported and divided into gastro-intestinal factors (ileus, gastric paresis), urological factors (bladder retention, prolonged requirement of urinary catheter) and other factors (cardiovascular events, pneumonia and urinary tract infections). No significant differences were found between both groups regarding these factors.

LOS was converted to a dichotomous variable, in order to be able to perform logistic regression. The median hospital stay of all patients was 8 days. Therefore, LOS of 1-7 days and ≥ 8 days were used as cutoff points. All variables with pvalues less than 0.2 in the univariate analysis were entered in the multivariate regression model. After univariate analysis, four possible predictors for length of hospital stay were identified, including: age at time of operation, ASA classification, diabetes and the ERAS protocol (Table 4). Preoperative treatment was added to the multiple regression analysis due to the significant differences between the ERAS and control groups at baseline. After multivariate analysis, both diabetes (OR 0.12, 95% CI 0.02–0.66, p=0.015) and the ERAS protocol (OR 5.14, 95% CI 1.80-14.65, p=0.002) were independent predictors of the outcome, a hospital stay of 1-7 days.

Discussion

In this study the authors found that since the introduction of the ERAS protocol in laparoscopic TME for rectal cancer, postoperative hospital stay was significantly reduced and bowel function was restored earlier compared to laparoscopic TME and conventional care. Although the results seem very promising, the authors realize that this is a retrospective study from which no definitive conclusions can be drawn.

Table 4 Univariate analysis investigating the effect on LOS (Univariate results of variables added to the multivariate analysis)

Variable	OR	95% CI	<i>p</i> -Value
Age	1.04	0.99-1.08	0.055
ASA I	1	Reference	0.096
ASA II	0.39	0.13-1.13	0.081
ASA III	0.18	0.05-0.74	0.017
ERAS	3.52	1.35-9.20	0.010
Diabetes	0.24	0.48 - 1.23	0.087
Chemo radiation	1	Reference	0.235
Short $(5 \times 5.0 \text{ Gy})$	0.31	0.09 - 1.05	0.060
Long (25×2.0 Gy)	0.28	0.06-1.32	0.109

OR odds ratio, CI confidence interval, ASA American Society of Anaesthesiology



To our knowledge no comparative studies on ERAS and conventional care in laparoscopic rectal surgery have been published so far. One recent study reported the results of laparoscopic rectal resections combined with fast-track surgery [11]. In that study (N=37) the authors found a mean hospital stay of 3 days (range 1–8). This is an excellent result which has not been published before. However, there were only 46% of the patients in the study that had a rectal carcinoma, and all patients underwent a laparoscopic LAR. In 19% a diverting loop ileostomy was performed. Mean hospital stay in that group was 4 days (range 2–7). The 30-day readmission rate was 8% and was not elevated by early discharge. No anastomotic leakage occurred.

Similar results regarding LOS have been described for laparoscopic colonic resections, but rectal resections have been associated with median hospital stays of 12 or 13 days. The introduction of the laparoscopic technique for TME has led to a reduction in LOS, with a median hospital stay of approximately 10 days [12–14]. This corresponds with the results in the control group in our study (median hospital stay of 10 days).

In our study, nearly all patients (98%) that underwent a LAR with an anastomosis received a temporary diverting stoma. Recently, a randomised multicenter trial, a multicenter analysis and meta-analysis have been published on this subject, reporting a significant decline in symptomatic anastomotic leakage after low anterior resections when a diverting stoma was performed [15–18]. However, many recent studies on laparoscopic low anterior resections showed a temporary diversion rate as low as 19-26%, suggesting this assumption is not widely accepted [11, 19, 20]. The symptomatic anastomotic leakage rate among all low anterior resections performed in our study was 17.3%, which is relatively high compared to other studies including patients with a diverting stoma (7.8% in a multicenter analysis) [16]. This could partly be due to the preoperative treatment. Seven of these nine patients received short scheme RT followed by a LAR. The other two patients received a long scheme RT. Preoperative RT has been associated with higher anastomotic leakage rates, compared with no preoperative treatment [21-23]. Furthermore, in our study LAR was also performed in cases with very low tumours located at 2-4 cm from the anal verge. Low anastomoses have also been associated with higher rates of anastomotic leakages [22, 23].

In addition, a stoma requires extra postoperative care and can be a source of postoperative complications. Furthermore, patients could only be discharged when stoma care was sufficient. Therefore, the presence of a stoma could be a factor delaying early discharge. There was no difference in diversion rate between ERAS and control groups. Nevertheless, the overall hospital stay might have been shorter and better comparable with other study results if a diverting stoma was not routinely performed.

Both groups were comparable for demographics and patient-related factors, except for the presence of diabetes, which was more likely to occur in the ERAS group (N=9)compared to the control group (N=1). This will not bias our results in favour of our hypothesis because diabetes has been associated with delayed wound healing and impaired anastomotic strength. These factors are more likely to complicate and delay recovery than accelerate it [24, 25]. Additionally, the multivariate regression analysis supported this assumption. As mentioned earlier, the preoperative therapy with chemo radiation was only used in the ERAS group. Long scheme RT was more frequent within the control group. Patients treated with chemo radiation preoperatively are more prone to develop postoperative complications such as wound healing problems and anastomotic dehiscence, due to elevated metalloproteinase activity [26, 27]. The higher incidence of chemo radiation in the ERAS group would therefore be more of a disadvantage than an advantage with respect to postoperative recovery and length of hospital stay, possibly even underestimating the results presented in this study. On the other hand, no higher anastomotic leakage rate was found in the chemo radiation group.

Another possible confounder of the study could be the learning curve for a surgeon to become an expert in laparoscopic colorectal surgery. The laparoscopic technique for TME was introduced in our institution in 2003. In order to rule out factors that could be associated with the learning curve of the surgeons, we excluded all patients who received a laparoscopic rectal resection in the first year after the introduction of this technique. However, the learning curve for laparoscopic left sided colorectal resections is long (up to 62 cases) [28]. The surgeons in our institution had done approximately 25-30 cases per surgeon in the first year. The mean operating time, a factor that is negatively correlated with the learning curve, tended to be longer in the control group, but this difference did not reach statistical significance (p=0.068). The conversion rate, also associated with a learning curve, was 6.5% in the ERAS group and 13.2% in the control group (p=0.30). Although both variables that indicated the presence of a learning curve did not differ significantly between the ERAS and control groups, we cannot safely exclude these factors as possible confounders in our results, based on our relatively small study sample.

After reviewing factors that could possibly delay discharge, we found a trend towards more urological complications in the ERAS group. Many patients required a urinary catheter longer than 2 days postoperatively (according to the protocol), mostly because of persistent urinary bladder retention. Twelve patients within this group even left the hospital with their urinary catheter still in place. We could not find a reasonable explanation for the difference between both groups regarding the urological complications. There could be a correlation with the preoperative treatment (chemo radiation), possibly leading to more nerve damage, but there are no studies confirming this hypothesis. Another explanation could be a better



registration of urological complications in the ERAS group by the nursing and medical staff, leading to possible bias.

Recommendations

Although this study shows a significant reduction in hospital stay after the introduction of the ERAS protocol in laparoscopic TME for rectal cancer, no definitive conclusions can be drawn. The results suggest this decline in postoperative hospital stay is directly related to the ERAS protocol. However, based on our study design, we cannot confirm ERAS to be the causal factor.

In the future, a randomised controlled clinical trial is required to validate the results we presented here.

Disclosures CJA Huibers, MAJ de Roos and KH Ong have no conflicts of interest or financial ties to disclose.

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