Original article

Impact of enhanced recovery on oncological outcomes following minimally invasive surgery for rectal cancer

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Background: Oncological outcomes of locally advanced rectal cancer depend on the quality of surgical and oncological management. Enhanced recovery pathways (ERPs) have yet to be assessed for their oncological impact when used in combination with minimally invasive surgery. This study assessed outcomes with or without an ERP in patients with rectal cancer.

Methods: This was a retrospective analysis of all consecutive adult patients who underwent elective minimally invasive surgery for primary rectal adenocarcinoma with curative intent between February 2005 and April 2018. Both laparoscopic and robotic procedures were included. Short-term morbidity and overall survival were compared between patients treated according to the institutional ERP and those who received conventional care.

Results: A total of 600 patients underwent minimally invasive surgery, of whom 320 (53·3 per cent) were treated according to the ERP and 280 (46·7 per cent) received conventional care. ERP was associated with less overall morbidity (34·7 *versus* 54·3 per cent; $P < 0·001$). Patients in the ERP group had improved overall survival on univariable (91·4 *versus* 81·7 per cent at 5 years; hazard ratio (HR) 0·53, 95 per cent c.i. 0·28 to 0·99) but not multivariable (HR 0·78, 0·41 to 1·50) analysis. Multivariable analysis revealed age (HR 1·46, 1·17 to 1·82), male sex (HR 1·98, 1·05 to 3·70) and complications (HR 2·23, 1·30 to 3·83) as independent risk factors for compromised overall survival. Disease-free survival was comparable for patients who had ERP or conventional treatment (80·5 *versus* 84·6 per cent at 5 years respectively; $P = 0·272$).

Conclusion: Treatment within an ERP was associated with a lower morbidity risk that may have had a subtle impact on overall but not disease-specific survival.

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Introduction

It was estimated that 43 030 new cases of rectal cancer would occur in the USA in 2018 (25 920 in men; 17 110 in women)[1]. Although surgical management has evolved with the emergence of minimally invasive techniques, concomitant paradigm changes have developed for perioperative care. The merits of minimally invasive surgery (MIS) have been studied comprehensively in the short-term postoperative period, showing morbidity and mortality benefits[2,3]. Recently, long-term oncological outcomes from the American College of Surgeons Oncology Group (ACOSOG) Z6051 trial[4] confirmed the non-inferiority of laparoscopic rectal cancer surgery. Actively managed programmes for recovery after surgery may improve short-term outcomes including complications, duration of hospital stay and costs[5–7]. However, the long-term oncological impact of an enhanced recovery pathway (ERP) remains controversial[8–10].

It has been hypothesized that uncontrolled surgical stress response and postoperative complications have a negative effect on cancer-related outcomes[11–14]. Studies have confirmed this effect with specific complications such as surgical-site infections[15] and postoperative blood transfusions[16–18]. Given the advantages of ERPs and MIS, a combination of both may potentiate improvements in cancer-related outcomes[19,20]. One recent study[21] within an enhanced recovery framework demonstrated improved

oncological results in MIS surgery, and other authors[22] have described a correlation between ERP compliance and improved 5-year oncological outcomes. Both series used robust follow-up data, but these were aggregated from heterogeneous patient populations, which featured colonic and rectal cancers treated with both open and minimally invasive techniques. The aim of the present study was to assess the oncological impact of an ERP when used in combination with MIS for the treatment of rectal cancer.

Methods

The institutional review board granted approval for retrospective review of a prospectively maintained surgical database of consecutive adults who underwent elective MIS with curative intent for rectal adenocarcinoma between February 2005 and April 2018 at Mayo Clinic, Rochester, Minnesota, and Mayo Clinic, Jacksonville, Florida. Exclusion criteria were: age under 18 years, missing research authorization, open or emergency surgery, stage IV or recurrent cancer, and diagnoses other than adenocarcinoma. All surgeons who performed the procedures are board-certified in colorectal surgery. Data collection was undertaken prospectively and data were stored in an institutional colorectal database by a dedicated team over the entire study period. A specific institutional ERP database has been maintained since the introduction of the programme.

Staging was performed according to the AJCC classification, seventh edition[23]. If neoadjuvant therapy was used, the higher stage on clinical or pathological evaluation was retained. Evaluation of metastatic disease and clinical staging included CT of the chest, abdomen and pelvis, and MRI of the pelvis with or without endorectal ultrasound imaging.

Treatment

Recommendations for rectal cancer treatment followed the guidelines of the National Comprehensive Cancer Network[24]. Patients with stage I disease proceeded directly to surgery. Those with stage II or III tumours generally received long-course neoadjuvant chemoradiotherapy followed by surgery 6–8 weeks later. Of note, in the early years of this series, patients were treated under standards that more frequently advised the use of postoperative radiation, in contrast to today's preferred approach of preoperative radiotherapy. The procedure type (abdominoperineal resection *versus* low anterior resection) was determined by the operating surgeon after preoperative examination and clinical staging, as was the surgical approach (laparoscopic *versus* robotic). The surgical technique has been described previously[25].

The multimodal colorectal ERP featured in this study has been described in detail, analysed for efficacy, and compared with conventional perioperative pathways previously[5,26,27]. The ERP was adopted institutionally in 2009 in Rochester and 2014 in Jacksonville. Barring contraindications to individual components, all patients have been treated in the defined ERP since then. The seven distinct facets of this protocol feature specific institutional hallmarks such as preoperative patient education focusing on recovery expectations, pre-emptive and multimodal analgesia with intrathecal injection, a strong emphasis on minimization of intravenous fluids, return to normal diet within 4 h of surgery, delineated postoperative ambulation beginning the evening of operation, scheduled removal of the urinary catheter and termination of intravenous fluids the following morning. Further details of the institutional ERP protocol and patient compliance have already been reported[5,26].

Outcomes

The primary outcome of the study was 3- and 5-year overall survival (OS) and disease-free survival (DFS) according to care pathway (ERP *versus* conventional). Local recurrence and distant metastasis were also assessed. Duration of follow-up reflected the date of the institution's last contact with the patient as of May 2018. Survival was calculated from the date of surgery, and data censored in the estimation of DFS included both patients who died without recurrence and survivors who were free from recurrence at last follow-up. Secondary outcomes were postoperative duration of hospital stay, 30-day readmission, morbidity and mortality, according to type of treatment. Complications were defined *a priori* according to previous methodology and assessed by trained clinical nurses using standard definitions[5].

Statistical analysis

Continuous variables are summarized as mean(s.d.) or median (i.q.r.) as appropriate. Categorical variables are expressed as number with percentage. Patient and treatment variables, surgical details and postoperative outcomes were compared between the ERP and conventional treatment groups using χ^2 test, two-sample t test or Wilcoxon rank sum test, as appropriate. The Kaplan–Meier survival method was used to estimate OS and DFS at 3 and 5 years, for the entire cohort and for patients with stage III disease

Table 1 Patient and treatment information

	ERP ($n = 320$)	Conventional care ($n = 280$)	Total ($n = 600$)	P‡
Age (years)*	58·2(12·9)	58·9(14·0)	58·5(13·4)	0·481§
Sex ratio (M : F)	203 : 117	200 : 80	403 : 197	0·038
BMI (kg/m^2)†	27·1 (24·6–30·1)	26·7 (24·1–30·4)	26·9 (24·2–30·3)	0·642¶
ASA fitness grade				0·103
I	6 (1·9)	15 (5·4)	21 (3·5)	
II	222 (69·4)	181 (64·6)	403 (67·2)	
III	91 (28·4)	82 (29·3)	173 (28·8)	
IV	1 (0·3)	2 (0·7)	3 (0·5)	
Tumour stage				0·007
I	60 (19·0)	83 (29·6)	143 (24·0)	
II	59 (18·7)	53 (18·9)	112 (18·8)	
III	196 (61·3)	144 (51·4)	340 (57·1)	
Missing	5	0	5	
Neoadjuvant CRT	205 (64·1)	140 (50·0)	345 (57·5)	0·001
Adjuvant chemotherapy	179 of 317 (56·5)	149 of 279 (53·4)	328 of 596 (55·0)	0·453
Adjuvant radiotherapy	16 (5·0)	26 (9·3)	42 (7·0)	0·041

Values in parentheses are percentages unless indicated otherwise; values are *mean(s.d.) and †median (i.q.r.). ERP, enhanced recovery pathway; CRT, chemoradiotherapy. ‡χ^2 test, except §two-sample t test and ¶Wilcoxon signed-rank test.

Table 2 Surgical data

	ERP ($n = 320$)	Conventional care ($n = 280$)	Total ($n = 600$)	P†
Procedure				0·172
Abdominoperineal resection	96 (30·0)	70 (25·0)	166 (27·7)	
Low anterior resection	224 (70·0)	210 (75·0)	434 (72·3)	
Surgical mode				< 0·001
Laparoscopic	52 (16·3)	231 (82·5)	283 (47·2)	
Robotic	268 (83·8)	49 (17·5)	317 (52·8)	
Anastomosis				< 0·001
Stapled	132 (41·3)	170 (60·7)	302 (50·3)	
Handsewn	92 (28·8)	40 (14·3)	132 (22·0)	
None	96 (30·0)	70 (25·0)	166 (27·7)	
Temporary diversion	188 (58·8)	152 (54·3)	340 (56·7)	0·271
Duration of operation (min)*	292 (220–366)	224 (182–282)	254 (195–324)	< 0·001‡
Circumferential radial margin				0·764
Positive	3 (0·9)	2 (0·7)	5 (0·8)	
Negative	317 (99·1)	278 (99·3)	595 (99·2)	
No. of lymph nodes resected*	23 (16–32)	20 (15–29)	22 (15–31)	0·284‡

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.). ERP, enhanced recovery pathway. †χ^2 test, except ‡Wilcoxon signed-rank test.

alone. Univariable analysis for assessment of risk factors for OS and DFS was undertaken using a Cox proportional hazards model for the whole data set and each care pathway individually. Predictors of OS were evaluated by means of a multivariable Cox model using backward selection, including those with univariable $P < 0·200$ as potential co-variables. The collinearity among variables considered in association with OS was examined using Spearman rank correlation. Tests of the proportional hazards assumption for the Cox models were examined using the method suggested by Grambsch and Therneau[28]. There was no evidence of significant departure from the proportional hazards assumption for any of the variables considered. Each Cox model result is reported as a hazard ratio (HR) with 95 per cent confidence interval. The Kaplan–Meier method was also used in the calculation of 3- and 5-year

Table 3 Postoperative outcomes

	ERP ($n = 320$)	Conventional care ($n = 280$)	Total ($n = 600$)	P‡
Any complication	111 (34·7)	152 (54·3)	263 (43·8)	< 0·001
Any cardiopulmonary complication†	13 (4·1)	23 (8·2)	36 (6·0)	0·033
Congestive heart failure	0 (0·0)	10 (3·6)	10 (1·7)	0·001
Atrial fibrillation	6 (1·9)	3 (1·1)	9 (1·5)	0·419
Myocardial infarction	1 (0·3)	1 (0·4)	2 (0·3)	0·925
Respiratory failure	0 (0·0)	3 (1·1)	3 (0·5)	0·063
Pneumonia	0 (0·0)	3 (1·1)	3 (0·5)	0·063
DVT or PE	6 (1·9)	8 (2·9)	14 (2·3)	0·427
Acute renal failure	8 (2·5)	6 (2·1)	14 (2·3)	0·772
Any infection†	35 (10·9)	54 (19·3)	89 (14·8)	0·004
Urinary tract infection	3 (0·9)	16 (5·7)	19 (3·2)	0·001
Cellulitis	4 (1·3)	10 (3·6)	14 (2·3)	0·060
Wound infection	15 (4·7)	10 (3·6)	25 (4·2)	0·495
Abscess/leak	21 (6·6)	16 (5·7)	37 (6·2)	0·666
Ileus	46 (14·4)	55 (19·6)	101 (16·8)	0·085
Duration of hospital stay (days)*	3 (3–5)	5 (4–7)	4 (3–6)	< 0·001§
Readmission	31 (9·7)	42 (15·0)	73 (12·2)	0·047

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.). †Patients may have experienced multiple complications in each category. ERP, enhanced recovery pathway; DVT, deep vein thrombosis; PE, pulmonary embolism. ‡χ^2 test, except §Wilcoxon signed-rank test.

estimates of local recurrence and distant metastasis. All tests were two-sided, and $P < 0·050$ was considered statistically significant. Statistical analysis was performed using SAS® version 9.4 (SAS Institute, Cary, North Carolina, USA).

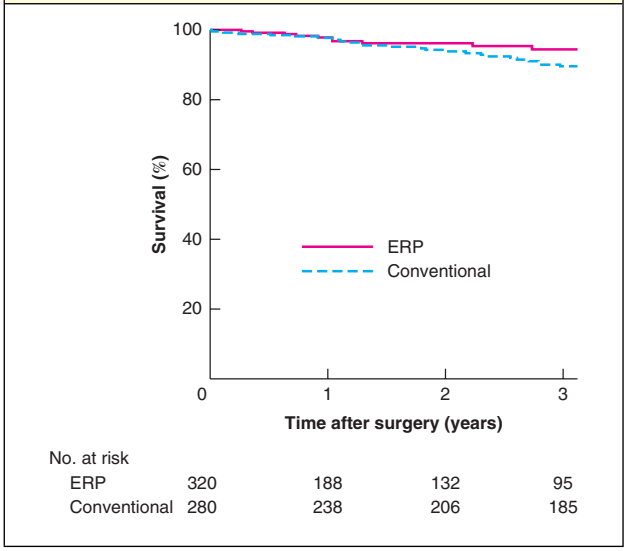
Results

A total of 600 patients met the inclusion criteria, of whom 320 (53·3 per cent) followed the ERP whereas 280 (46·7 per cent) received conventional care. Mean(s.d.) age was 58·5(13·4) years and BMI was 26·9 (i.q.r. 24·2–30·3) kg/m^2. Men comprised 67·2 per cent of the cohort (403). There were no differences in the use of adjuvant chemotherapy between groups. Patient and treatment characteristics are summarized in *Table 1*.

Surgical and postoperative outcomes

Table 2 shows surgical outcomes. A robotic approach was preponderant in the ERP group (83·8 *versus* 17·5 per cent; $P < 0·001$). Among 434 patients undergoing restorative surgery, significantly more anastomoses were handsewn in the ERP group (41·1 *versus* 19·0 per cent; $P < 0·001$). There were no significant differences in the pathological surrogate markers of quality between groups. *Table 3* outlines postoperative outcomes.

Fig. 1 Kaplan–Meier plot showing overall survival after minimally invasive rectal cancer surgery with conventional treatment *versus* enhanced recovery pathway



ERP, enhanced recovery pathway. $P = 0·049$ (log rank test).

Overall and disease-free survival

Median follow-up was 30·7 (9·8–68·0) months. Owing to ERP implementation in a more recent study period, follow-up was significantly longer for the conventional care group than the ERP group: 61·1 (23·8–98·5) *versus*

Table 4 Results of univariable Cox proportional hazards survival analysis

	Overall survival		Disease-free survival	
	Hazard ratio	*P*	Hazard ratio	*P*
ERP (yes *versus* no)	0·53 (0·28, 0·99)	0·049	1·32 (0·81, 2·15)	0·272
Age (per 10 years)	1·73 (1·40, 2·13)	< 0·001	0·92 (0·77, 1·10)	0·344
Sex (M *versus* F)	2·25 (1·21, 4·19)	0·011	1·04 (0·62, 1·72)	0·889
ASA fitness grade (III–IV *versus* I–II)	1·69 (1·04, 2·74)	0·033	1·21 (0·73, 2·02)	0·457
Surgical mode (robotic *versus* laparoscopic)	1·06 (0·61, 1·83)	0·849	1·31 (0·80, 2·14)	0·283
Disease stage				
I	1·00 (reference)		1·00 (reference)	
II	0·91 (0·41, 2·01)	0·814	1·12 (0·49, 2·60)	0·789
III	1·34 (0·75, 2·37)	0·325	1·82 (0·96, 3·44)	0·065
Any complication (yes *versus* no)	2·82 (1·67, 4·74)	< 0·001	0·99 (0·61, 1·59)	0·959
Adjuvant chemotherapy (yes *versus* no)	0·47 (0·29, 0·76)	0·002	1·45 (0·87, 2·41)	0·152
Neoadjuvant CRT (yes *versus* no)	0·75 (0·46, 1·2)	0·225	1·18 (0·73, 1·92)	0·509

Values in parentheses are 95 per cent confidence intervals. ERP, enhanced recovery pathway; CRT, chemoradiotherapy.

Table 5 Results of multivariable Cox proportional hazards analysis of overall survival

	Hazard ratio	*P*
ERP (yes *versus* no)	0·78 (0·41, 1·50)	0·464
Age (per 10 years)	1·46 (1·17, 1·82)	0·008
Sex (M *versus* F)	1·98 (1·05, 3·7)	0·034
ASA fitness grade (III–IV *versus* I–II)	1·13 (0·69, 1·85)	0·639
Any complication (yes *versus* no)	2·23 (1·30, 3·83)	0·004
Adjuvant chemotherapy (yes *versus* no)	0·62 (0·36, 1·03)	0·069

Values in parentheses are 95 per cent confidence intervals. ERP, enhanced recovery pathway.

18·0 (5·4–42·9) months respectively ($P < 0·001$). OS estimates for patients treated within the ERP and those who received conventional treatment were 94·5 and 89·6 per cent at respectively at 3 years, and 91·4 *versus* 81·7 per cent at 5 years (*Fig. 1*). On univariable analysis, age, sex, ASA fitness grade and occurrence of complications predicted worse OS, whereas ERP and adjuvant chemotherapy were protective variables (*Table 4*). Correlations among variables considered in these models were highest for ERP with surgery type ($r = 0·66$) and disease stage with use of adjuvant chemotherapy ($r = 0·60$). Multivariable analysis did not confirm ERP as a significant predictor, whereas age, male sex and complications were identified as independent risk factors for decreased OS (*Table 5*). In a subgroup analysis of patients with stage III disease, estimated 3-year OS for patients in the ERP group was 94·0 per cent, compared with 84·5 per cent in the conventional treatment group ($P = 0·055$). DFS was comparable in the two cohorts, estimated at 84·8 *versus* 87·9 per cent at 3 years ($P = 0·272$), and 80·5 *versus* 84·6 per cent at 5 years ($P = 0·272$), for patients treated in the ERP and those who had conventional treatment respectively.

Oncological recurrence

Overall 3-year probability estimates were 2·4 per cent for local recurrence and 12·0 per cent for distant metastasis. Estimated local recurrence rates at 5 years were 0·5 per cent for patients who completed the ERP and 4·2 per cent for those who received conventional care (HR 0·33, 95 per cent c.i. 0·07 to 1·53; $P = 0·157$). Five-year distant metastasis estimates were 19·5 per cent for the ERP and 13·1 per cent for the conventional treatment group (HR 1·49, 0·89 to 2·50; $P = 0·129$).

Discussion

This series from a single institution identified differences in postoperative outcomes between patients who received conventional perioperative care and those treated within an established ERP. Univariable analysis suggested improved OS for patients treated within the ERP, but this was not confirmed by multivariable analysis. Interestingly, the latter revealed an independent impact of complications on OS, but not disease-specific survival. A recent study[22] reported 5-year OS in a cohort of 911 patients undergoing major surgery for colonic and rectal cancer within an ERP between 2002 and 2007 in Sweden. ERP adherence above 70 per cent, previously suggested as critical compliance threshold[29,30], was associated with improved 5-year survival rates (78·4 *versus* 64·6 per cent; $P < 0·001$).

After adjustment for BMI, tumour location and neoadjuvant treatment, compliance may have been associated with a reduction in 5-year cancer-specific mortality. Others[21] have reported better OS for patients undergoing laparoscopic surgery within an ERP.

The present results showed a significant association between ERP and reduced morbidity, and that complications appeared to influence oncological outcomes. Although it was not an aim of the present investigation, it seems conceivable that use of an ERP may contribute to better oncological outcomes owing to its known association with reduced complication rates[31]. As with all retrospective studies, there are limitations including that a shorter follow-up in the ERP group may have led to overestimation of survival. Modifications to surgical and oncological strategies beyond ERP implementation occurred over the study interval. An institutional shift towards robotic surgery occurred in recent years, but these confounding variables were not significant in the statistical model. The study is prone to bias owing to the long study interval but this was limited by routine data assessment by trained, dedicated staff, and use of *a priori* definitions. Although this institution's current practice is to offer a minimally invasive approach to all patients with primary non-metastatic rectal cancer, individual contraindications to MIS may account for a selection bias in this isolated cohort.

Patients treated according to the ERP had higher rates of handsewn coloanal anastomoses indicating ultralow anterior resection. This finding may be related to paradigm changes regarding the distal resection margin for rectal cancer, which tended to decrease over time[32]. This type of restorative resection would typically be associated with increased morbidity because of its greater complexity. Furthermore, the ERP group had significantly more patients with stage III disease and fewer with stage I tumours than the conventional treatment group. The trend towards less local recurrence among patients treated within the ERP must be interpreted with caution because the duration of follow-up differed between the groups. However, the sizeable data set allowed appropriate OS modelling. Negative influences of both higher tumour stage and more complex operations may have been mitigating factors leading to the outcomes observed. However, cause–effect patterns cannot be assumed because of the observational nature of the study.

The possible mechanisms by which enhanced recovery might affect oncological outcomes have been hypothesized, but yet not confirmed. Reductions in postoperative complications[31,33], along with attenuation of the surgical stress response[11,12,34,35] may have a positive impact on long-term outcome[13–15,36]. Furthermore, recent reports have mentioned that single ERP items such as fluid balance[37], supplementary regional analgesia[38,39], and minimizing opioid use by multimodal pain management[40,41] are associated with better outcomes. Compliance with ERP may magnify this and also contribute to a dose–response effect, as already suggested[42]. However, the pathophysiological mechanism influencing long-term outcomes after treatment according to an ERP deserves future research.

Disclosure

The authors declare no conflict of interest.

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