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Implementation of an Enhanced Recovery Protocol Is Associated with On-time Initiation of Adjuvant Chemotherapy in Colorectal Cancer

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Abstract

Background: Delayed initiation of adjuvant chemotherapy negatively impacts long-term survival in colorectal cancer patients. Colorectal enhanced recovery protocols result in decreased complications and length of stay; however, the impact of enhanced recovery on the timing of adjuvant chemotherapy remains unknown.

Objective: This study aimed to identify factors associated with on-time delivery of adjuvant chemotherapy after colorectal cancer surgery, hypothesizing that implementation of an enhanced recovery protocol would result in more patients receiving on-time chemotherapy.

Design: Retrospective cohort study comparing rate of on-time adjuvant chemotherapy delivery following colorectal cancer resection before and after implementation of an enhanced recovery protocol.

Settings: Large academic medical center.

Patients: All patients who underwent non-emergent colorectal cancer resections for curative intent from January 2010-June 2017, excluding patients who had no indication for adjuvant

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chemotherapy, had received preoperative systemic chemotherapy, or did not have medical oncology records available.

Main Outcome Measures: Patients before and enhanced recovery were compared, with rate of on-time adjuvant chemotherapy delivery as the primary outcome. Adjuvant chemotherapy delivery was considered on-time if initiated ≤ 8 weeks postoperatively, and treatment was considered delayed/omitted if initiated >8 weeks postoperatively (delayed) or never received (omitted). Multivariable logistic regression identified predictors of on-time chemotherapy delivery.

Results: 363 patients met inclusion criteria with 189 (52.1%) patients undergoing surgery following enhanced recovery implementation. Groups differed in laparoscopic approach and median procedure duration, both of which were higher following enhanced recovery. Significantly more patients received on-time chemotherapy following enhanced recovery implementation ($p=0.007$). Enhanced recovery was an independent predictor of on-time adjuvant chemotherapy ($p=0.014$).

Limitations: Retrospective and nonrandomized before-and-after design.

Conclusions: Enhanced recovery was associated with receiving on-time adjuvant chemotherapy. As prompt initiation of adjuvant chemotherapy improves survival in colorectal cancer, future investigation of long-term oncologic outcomes is necessary to evaluate the potential impact of enhanced recovery on survival. See Video Abstract at <http://links.lww.com/DCR/Axxx>.

Abstract

El inicio tardío de la quimioterapia adyuvante afecta negativamente la supervivencia a largo plazo en pacientes con cáncer colorrectal. Los protocolos de recuperación acelerada colorrectales dan lugar a una disminución de las complicaciones y la duración de estancia hospitalaria; sin embargo, el impacto de la recuperación acelerada en el momento de inicio de quimioterapia adyuvante sigue siendo desconocido.

Este estudio tuvo como objetivo identificar los factores asociados con la administración a tiempo de la quimioterapia adyuvante después de la cirugía de cáncer colorrectal, con la hipótesis de que la implementación de un protocolo de recuperación acelerada daría lugar a que más pacientes reciban quimioterapia a tiempo.

Estudio de cohorte retrospectivo que compara la tasa de administración de quimioterapia adyuvante a tiempo después de la resección del cáncer colorrectal antes y después de la implementación de un protocolo de recuperación acelerada.

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Todos los pacientes que se sometieron a resecciones de cáncer colorrectal no emergentes con intención curativa desde enero de 2010 hasta junio de 2017, excluyendo a los pacientes que no tenían indicación de quimioterapia adyuvante, que recibieron quimioterapia sistémica preoperatoria o no tenían registros médicos de oncología disponibles.

Los pacientes se compararon antes y después de la implementación de la recuperación acelerada, con la tasa de administración de quimioterapia adyuvante a tiempo como el resultado primario. La administración de quimioterapia adyuvante se consideró a tiempo si se inició ≤ 8 semanas después de la operación, y el tratamiento se consideró retrasado / omitido si se inició > 8 semanas después

de la operación (retrasado) o nunca fue recibido (omitido). La regresión logística multivariable identificó predictores de administración de quimioterapia a tiempo.

363 pacientes cumplieron con los criterios de inclusión, con 189 (52.1%) pacientes sometidos a cirugía después de la implementación de recuperación acelerada. Los grupos difirieron en el abordaje laparoscópico y la duración media del procedimiento; ambos factores fueron mayores después de la recuperación acelerada. Significativamente más pacientes recibieron quimioterapia a tiempo después de la implementación de recuperación acelerada ($p = 0.007$). La recuperación acelerada fue un factor predictivo independiente de quimioterapia adyuvante a tiempo ($p = 0.014$).

Diseño retrospectivo, tipo “antes y después” no aleatorizado.

La recuperación acelerada se asoció con la recepción de quimioterapia adyuvante a tiempo. Debido a que el inicio rápido de la quimioterapia adyuvante mejora la supervivencia en el cáncer colorrectal, en el futuro será necesario investigar los resultados oncológicos a largo plazo para evaluar el impacto potencial de la recuperación acelerada en la supervivencia. Vea el Resumen en video en <http://links.lww.com/DCR/Axxx>.

Keywords

Adjuvant chemotherapy; Colorectal cancer; Enhanced recovery

INTRODUCTION

Colorectal cancer (CRC) is common in the United States, representing the third highest incidence and mortality.¹ The primary treatment modality for CRC is en bloc resection of the tumor with regional lymphadenectomy.² Adjuvant chemotherapy (AC) has consistently been shown to decrease recurrence and improve survival after curative resection of CRC³⁻⁵ and is recommended for patients with Stage III-IV CRC, Stage II rectal cancer, and Stage II colon cancer with obstruction, perforation, T4 tumors, or other high-risk features.⁶⁻⁸ Despite these benefits, multiple observational studies have demonstrated delays or omission in initiation of AC leading to worse oncologic outcomes.⁹⁻¹¹

Several patient- and disease-related factors—such as age, comorbidities, race, and tumor grade—have been associated with delayed initiation or omission of AC following curative CRC resection.¹² While many of these factors are non-modifiable, the prevention of postoperative complications has been identified as an opportunity for improvement efforts with regard to delayed/omitted treatment.^{13,14}

Enhanced recovery protocols (ERP) have been well described in colorectal surgery and consistently associated with decreased morbidity, length of stay (LOS), and hospital costs.¹⁵⁻¹⁸ Fundamental tenants of ERPs include a focus on judicious intravenous (IV) fluid management, more liberal use of vasopressors to avoid intravascular overload, and multimodal opioid-sparing analgesia with the overall goal of decreasing the physiologic stress during the perioperative period.¹⁹⁻²²

Most studies involving ERPs focus on short-term surgical outcomes. Given the ability of ERP implementation to prevent complications and shorten LOS, we aimed to further investigate the potential impact of a colorectal ERP on the timing and delivery of AC following curative CRC resection.¹⁷ We hypothesized that the adoption of a colorectal ERP would be associated with the on-time initiation of AC.

METHODS

Patients

The University of Virginia Institutional Review Board (#19191) approved this retrospective cohort study with waiver of consent. All patients 18 years of age who underwent non-emergent CRC surgery prior to (January 1, 2010 to August 5, 2013) and following (August 6, 2013 to June 7, 2017) ERP implementation were identified from a prospectively maintained institutional database. Only patients with CRC undergoing surgery for curative intent meriting treatment with AC qualified for study inclusion. Patients who underwent a surgery for palliative intent were excluded.

Indications for AC included Stage III/IV CRC, Stage II rectal cancer, and Stage II colon cancer with obstruction, perforation, or T4 tumors. For patients with an unclear indication—such as patients with Stage IIA colon cancer—medical oncology notes were reviewed, and the patient was deemed to have an indication for AC if the oncologist recommended it. Patients with no indication for AC were excluded from further review. Patients who underwent a total neoadjuvant approach to chemotherapy were also excluded. If records were unavailable, the patient's medical oncologist was contacted for missing data. If the necessary data could not be obtained, the patient was excluded.

Data Collection and Outcomes

Patient factors, procedural characteristics, and postoperative outcome data were obtained from a prospectively maintained database supplemented by data from the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database. ACS NSQIP definitions for all demographic and outcome variables were used and can be found at https://www.facs.org/~media/files/quality%20programs/nsqip/nsqip_puf_userguide_2015.ashx. In addition, the electronic medical record (EMR) was reviewed for all identified surgical CRC patients to confirm the diagnosis of malignancy and indication for AC.

The characteristics of the AC—including timing and delivery—were determined by chart review of medical and surgical oncology notes. The primary outcome of the study was the percentage of patients who experienced on-time AC initiation. AC delivery was considered on-time if initiated 8 weeks postoperatively based on the definition utilized in prior oncologic studies examining timing of AC.^{9,23} Treatment was considered delayed/omitted if initiated >8 weeks postoperatively (delayed) or never received (omitted). The reasons for omission of AC were recorded.

Secondary outcomes included postoperative complications based on NSQIP definitions [surgical site infection (SSI), wound disruption, postoperative pneumonia, unplanned intubation, pulmonary embolism, postoperative ventilator dependency for >48 hours, urinary

tract infection, progressive renal insufficiency, postoperative hemodialysis, cerebrovascular accident, cardiac arrest, myocardial infection, postoperative transfusion within 72 hours, vein thrombosis requiring therapy, postoperative sepsis/septic shock, other postoperative occurrences], LOS, and 30-day readmissions.

Enhanced Recovery Protocol Implementation

Detailed explanations of management strategies for the perioperative care of colorectal surgery patients prior to and following the implementation of the ERP have been previously published.¹⁹⁻²² Prior to the ERP, patients underwent a mechanical bowel preparation the day prior to surgery progressing to nothing by mouth at midnight. Pain management strategies were not protocolized, but typically consisted of a low thoracic epidural with IV opioids as needed for open procedures and patient-controlled analgesia with IV opioids for laparoscopic procedures followed by transition to oral opioids. Intraoperative IV fluid management was left to the discretion of the anesthesia team. Postoperative IV fluids were managed by the surgical team, and decisions involving diet advancement were made by the primary surgeon.¹⁷

In order to standardize perioperative care, a colorectal ERP was initiated on August 6, 2013.¹⁷ Details of the protocol can be found in Table 1. It should be noted that the same mechanical bowel preparation (PEG-based with oral antibiotics) the day prior to surgery was utilized throughout the study period (prior to and following implementation of the ERP). Data on ERP compliance measures including preoperative carbohydrate loading with Gatorade Thirst Quencher (©PepsiCo), ambulation on postoperative day 1, morphine equivalents, and overall fluid balance were prospectively collected.

Statistical Analysis

Categorical variables are reported as frequencies with percentages and continuous variables as median with interquartile range. Univariate analyses were conducted to evaluate for differences between patients treated before and after ERP implementation as well as for patients who did and did not receive on-time AC. Differences were compared using the Chi-square test for categorical variables and Wilcoxon rank-sum test for continuous variables. Given an estimated baseline rate of on-time AC initiation of 30% in the pre-ERP population and a predicted increase in the rate to 45% in the ERP group, 352 patients were required to achieve statistical power (1- β) of 0.80.

A multivariable logistic regression model was fit to identify factors independently associated with on-time initiation of AC. Dependent variables were chosen *a priori* based on clinical factors previously shown to affect the timing and delivery of AC following CRC resection. An alpha value of 0.05 was used as a threshold for statistical significance. All of the statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Four hundred forty-seven patients underwent surgery for CRC between January 2010 and June 2017 with exclusion of 84 patients as described in Figure 1. Ultimately, 363 patients were identified as meeting study inclusion criteria, meaning that AC was indicated. One

hundred seventy-four patients (47.9%) underwent surgery prior to ERP implementation, and 189 patients (52.1%) underwent surgery following implementation. Compliance to the key ERP elements was similar to previously published data from our institution (Supplemental Table).¹⁷

Demographic variables, cancer characteristics, and procedural details for the 2 groups are reported in Table 2. The majority of patients had rectal cancer and received neoadjuvant chemoradiation. Patient characteristics in each group were similar with the exception of a higher rate of dyspnea and malnutrition in the pre-ERP group. More patients in the ERP group received neoadjuvant chemotherapy. Additionally, the ERP group had a higher rate of laparoscopic procedures and a longer median operating room time. Thirty-day postoperative outcomes between patients undergoing surgery prior to and following ERP implementation are also reported in Table 2. SSI occurred less frequently in the ERP group; however, the rate of overall complications did not differ between groups. Median LOS was significantly shorter in the ERP group at 4.0 days compared to 7.0 days prior to implementation of the ERP ($p<0.001$).

Adjuvant Chemotherapy Delivery

A total of 255 patients out of 363 received AC, with an overall AC delivery rate of 70.2% [118 patients in the pre-ERP group (67.8%) and 137 patients in the ERP group (72.5%); $p=0.359$]. One hundred eight total patients never received AC, 56 of the 174 (32.2%) patients prior to and 52 of the 189 patients (27.5%) following ERP implementation ($p=0.022$) (Figure 1; Table 2). Patients who underwent surgery pre- and post-ERP implementation had similar reasons for omitting therapy with patient discretion representing the highest proportion in both groups ($p=0.543$) (Figure 2).

Of the 255 patients that received AC, 141 of those patients received their AC on-time. More patients received delayed AC in the pre-ERP group as compared to the ERP group [63 (36.2%) vs 51 (27.0%)]. The proportion of patients receiving on-time initiation of AC was significantly higher in the ERP group [55 (31.6%) vs 86 (45.5%)] ($p=0.022$) (Table 2).

Demographic variables, cancer characteristics, and procedural details for patients who received on-time versus delayed/omitted AC are reported in Table 3. Patients receiving on-time AC were younger [59.1 (51.2-66.2) vs 63.9 (55.4-73.5) years; $p<0.001$] with higher stage disease as compared to patients with delayed/omitted AC. Groups also differed in American Society of Anesthesiologists physical status classification (ASA). Additionally, more patients receiving on-time AC underwent laparoscopic surgery; however, procedure duration did not differ. Thirty-day postoperative outcomes between patients who did and did not receive on-time AC initiation are reported in Table 3. The rates of both SSIs and overall complications were significantly decreased in the group receiving on-time AC. LOS was shorter in patients who received on-time AC, and these patients also had decreased rates of reoperation and 30-day readmission.

The multivariable logistic regression model identified younger age ($p=0.001$), white race (0.038), higher stage disease ($p=0.002$), ileostomy ($p=0.030$), and shorter LOS ($p=0.025$) as independent predictors of on-time delivery of therapy (Table 4). Importantly, the ERP was

independently associated with on-time delivery of AC ($p=0.014$). Laparoscopy was not independently associated with on-time delivery of therapy (0.697). The C-statistic was 0.794 indicating a good ability to discriminate between patients with and without on-time AC delivery.

DISCUSSION

To our knowledge, this study is the first to date evaluating the effect of enhanced recovery on timing and delivery of AC following CRC resection. Following the implementation of a highly standardized colorectal ERP, a higher percentage of patients received on-time AC compared to patients undergoing resection prior to ERP implementation, supporting our initial hypothesis.

The optimal delivery of AC necessitates prompt commencement of therapy following surgery to achieve maximal effect.^{10,23} Multiple observational studies support the benefits of early AC initiation, revealing improvements in both disease-free and overall survival.^{10,24} AC is thought to favorably impact survival in cancer patients through the eradication of circulating tumor cells and micro-metastases in patients who would otherwise be destined to recur.¹⁰ Animal models have suggested that the improved effectiveness of early AC is additionally related to physiologic changes associated with surgery. The insult of a major operation may result in an increased number of metastatic cells leading to the accelerated growth of distant metastases. Additionally, the increase in pro-inflammatory and oncogenic growth factors—including tumor necrosis factor α —seen following surgery makes avoiding delays in AC paramount.¹⁰

The overall rate and timing of AC initiation reported in our study falls within published rates of AC delivery in large population-based studies, which range widely from 30-75%.^{12,13,25} However, while our overall rate of AC delivery was 70.2%, only 55.0% of those who received AC initiated therapy on time. Several studies have sought to identify risk factors for delayed initiation and omission of AC following CRC resection. Many of the identified risk factors in the current study exhibit overlap with previously published literature including increasing age, race, disease stage, and prolonged LOS.^{9,13,25,26}

Most notable for the current analysis is identification of the ERP as a risk-adjusted predictor of on-time delivery of AC following CRC resection. There is an ever-growing body of literature supporting ERPs; however, a paucity of research remains regarding their potential effect on oncologic outcomes. ERPs have been widely recognized as a major advancement in perioperative care, particularly in the field of colorectal surgery, due to resulting improvements in clinical outcomes including reductions in postoperative complications, hospital LOS, and health system costs.^{17,27,28}

There are several possible relationships driving the association between the colorectal ERP and on-time delivery of AC identified in this study. Several retrospective analyses have associated longer LOS and postoperative complications with increased rates of delayed and omitted AC. As ERPs have been shown to decrease both LOS and the rate of postoperative complications, it is possible that these improvements are driving the effect of our

institutional ERP on improved AC delivery.¹⁷ While we did identify a reduction in overall number of complications, there were significantly fewer SSIs in the ERP group [33 (19.0%) vs 20 (10.6%; $p=0.024$). Surgical site infections have been previously shown to impact rates of both delayed and omitted AC and thus likely contributed to our increased rate of on-time AC delivery in the ERP group.^{14,29} Similar to the current analysis, multiple prior studies have also demonstrated improvements in SSI rates following ERP implementation.^{17,30}

Minimally invasive surgery was also far more common among patients undergoing resection following ERP implementation. This increased utilization is attributable to the expansion of robot-assisted rectal surgery at our institution, particularly during the first two years following ERP implementation.³¹ While other observational studies have linked laparoscopic surgery to shorter LOS and fewer postoperative complications, minimally invasive surgery was not significantly associated with the on-time delivery of AC in this analysis.

Ultimately, the inclusion of the aforementioned factors in the logistic regression indicates that the positive effect of the ERP on AC delivery is independent of these outcome improvements. Tanzer et al. was able to show reductions in hospital LOS within an ERP for total hip arthroplasty simply by reducing the expected LOS communicated to patients.³² Similarly, a systematic review suggested that positive patient expectations can drive better health outcomes.³³ This type of expectation management could also be playing a role in the ERP's positive effect on the timing and delivery of AC, given the increase in structured perioperative patient counseling and improved methods of communication between health care providers and patients that occurs within the protocol. It is possible that patients may be more prepared to undergo AC—even after a complicated postoperative course—if they are better prepared preoperatively from a psychological standpoint.

In both colon and rectal adenocarcinoma, the approach to AC is rapidly evolving. Results from the International Duration Evaluation of Adjuvant Chemotherapy (IDEA) collaboration will likely result in shorter and less toxic courses of AC for moderate-risk patients, potentially making the prospect of AC less daunting.³⁴ With the clear benefit of anti-PD-1 targeting immunotherapy for microsatellite unstable patients with metastatic disease, the ongoing Alliance A021502 study will evaluate the benefit of anti-PD-L1 in the adjuvant setting.³⁵ In rectal cancer, increasing use of total neoadjuvant therapy may also reduce the necessity or duration of AC.³⁶ Given these practice changes, ERPs will be increasingly important to ensure patients who receive less AC benefit from starting on time.

There are several notable limitations to the current study. The retrospective before-and-after study design inherently imposes the potential for selection bias, though all patients undergoing surgery after implementation of the ERP were treated on protocol without exception. In addition, the potential for confounding factors is mitigated by the inclusion of potential confounders in the regression model and the well-matched baseline demographics of the pre- and post-implementation groups. This study included patients with both colon and rectal cancer. While there are fundamental differences in the oncologic treatment of these diseases, the inclusion of patients whose final staging merited adjuvant chemotherapy according to National Comprehensive Cancer Network (NCCN) guidelines minimizes those

differences in the present study. The before-and-after design also precludes a survival analysis, given that a significant proportion of the ERP patients have not yet accrued meaningful postoperative follow up time. Long-term oncologic outcomes will be assessed once long-term follow-up data become available for all patients. While we are able to demonstrate only association and not causation, there were no institutional or accreditation efforts targeting the timing and delivery of AC for CRC during the study period. Finally, given the institutional variability in ERPs, results from this single institution study may not be broadly generalizable.

CONCLUSION

This study identified a higher rate of on-time AC delivery following the implementation of an institutional ERP. Several risk-adjusted predictors of the on-time delivery of AC following CRC resection were also identified. As the prompt initiation of AC has been shown to decrease recurrence and improve survival in CRC patients, further investigation of long-term oncologic outcomes will be necessary to evaluate the potential impact of ERPs on overall and disease-free survival.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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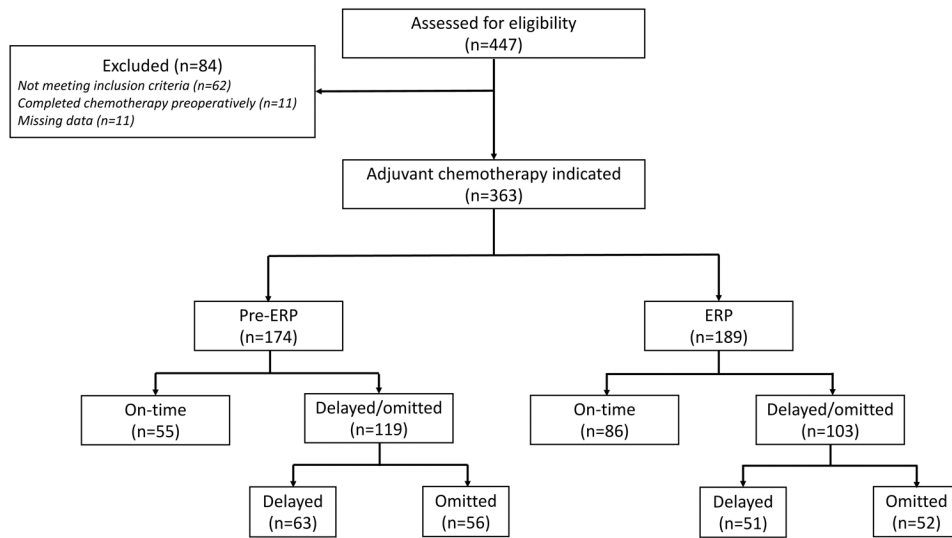


Figure 1.
Flow diagram of included study patients

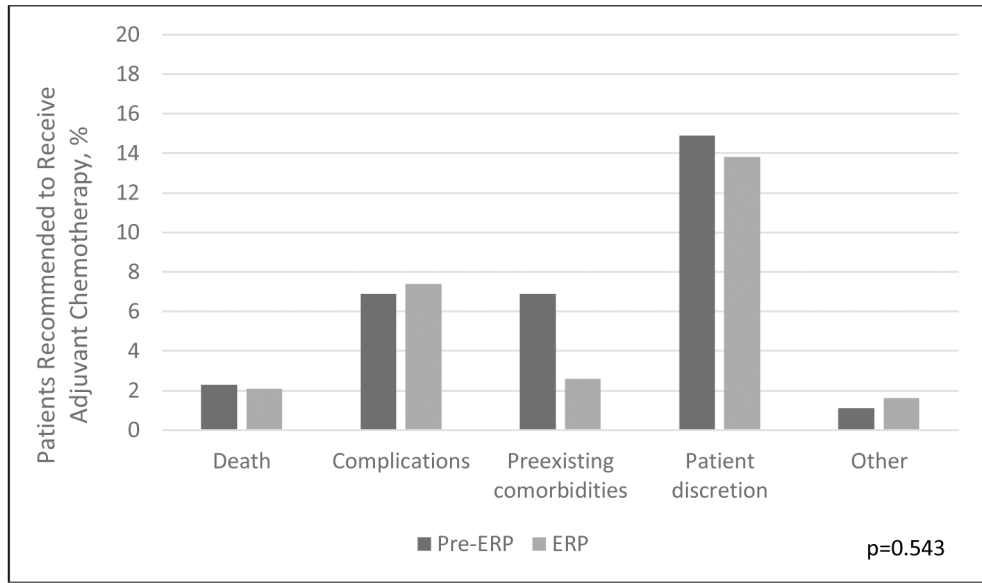


Figure 2. Reasons for omission of adjuvant chemotherapy before and after implementation of enhanced recovery

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Table 1.

Key elements of the enhanced recovery protocol

<i>Day prior to surgery</i>
Regular diet until 1800
Mechanical bowel prep with oral antibiotics
Chlorohexidine shower
<i>Day of surgery</i>
Clears until 2 hours prior to surgery
20 ounces of Gatorade Thirst Quencher (©PepsiCo) 2 hours prior to induction
Alvimopan 12 mg PO
Multimodal analgesia:
Celecoxib 200 mg PO
Gabapentin 600 mg PO
Acetaminophen 975 mg PO
<i>Intraoperative care</i>
Intrathecal morphine (250 µg) prior to induction
No intravenous opioids
IV analgesia:
Lidocaine 40 µg/kg/min
Ketamine 0.6 mg/kg/min
Goal-directed fluid algorithm based on the Pleth Variability Index
<i>Postoperative care</i>
Diet: clear liquids, solid food postoperative day 1
Analgesia:
Acetaminophen 975 mg IV every 6 hours
Lidocaine infusion 0.5-1 mg/min until postoperative day 2
Oxycodone 5 mg PO every 4 hours as needed
Ambulation: begins evening of postoperative day 0
Other medications:
Alvimopan 12 mg BID for 7 days
Magnesium oxide 400 mg PO daily
Fluids: lactated ringers 40 mL/h for 24 hours
PO=By mouth; IV=Intravenous; BID=Twice daily

Table 2.

Patient characteristics, oncologic factors, procedural details, and postoperative outcomes before and after implementation of an enhanced recovery protocol

	Pre-ERP n = 174	ERP n = 189	p value
<i>Patient characteristics</i>			
Age (years)	61.1 (53.1-68.7)	62.4 (53.6-72.2)	0.262
BMI (kg/m ²)	28.3 (24.3-32.0)	28.3 (24.1-32.4)	0.922
Male	93 (53.5%)	110 (58.2%)	0.362
Race			0.659
White	148 (85.1%)	163 (86.2%)	
Black	23 (13.2%)	20 (10.6%)	
Asian	1 (0.6%)	1 (0.5%)	
Not reported	2 (1.2%)	5 (2.7%)	
Hypertension	96 (55.2%)	96 (50.8%)	0.404
Diabetes mellitus	38 (21.8%)	32 (16.9%)	0.236
ESRD	1 (0.6%)	1 (0.5%)	0.953
COPD	8 (4.6%)	10 (5.3%)	0.761
Dyspnea	33 (19.0%)	12 (6.4%)	<0.001
Ascites	3 (1.7%)	2 (1.1%)	0.587
Bleeding disorder	3 (1.7%)	3 (1.6%)	0.919
Current smoker	37 (21.3%)	31 (16.4%)	0.236
10% body weight loss	23 (13.2%)	11 (5.8%)	0.016
Preoperative transfusion	1 (0.6%)	2 (1.1%)	0.611
Chronic steroid use	4 (2.3%)	6 (3.2%)	0.611
Functional health status			0.172
Independent	167 (96.0%)	187 (98.9%)	
Partially dependent	6 (3.5%)	2 (1.1%)	
Totally dependent	1 (0.6%)	0 (0.0%)	
ASA classification			0.755
ASA 1	0 (0.0%)	1 (0.5%)	
ASA 2	75 (43.1%)	76 (40.2%)	
ASA 3	93 (53.5%)	105 (55.6%)	
ASA 4	6 (3.5%)	7 (3.7%)	
<i>Oncologic factors</i>			
Site			0.399
Colon	67 (38.5%)	81 (42.9%)	
Rectum	107 (61.5%)	108 (57.1%)	
Neoadjuvant chemoradiation	97 (55.8%)	102 (54.0%)	0.734
Neoadjuvant chemotherapy	7 (4.0%)	19 (10.1%)	0.026

	Pre-ERP n = 174	ERP n = 189	p value
High grade	58 (33.3%)	58 (30.7%)	0.589
Final stage			0.890
2	55 (31.6%)	58 (30.7%)	
3	91 (52.3%)	97 (51.3%)	
4	28 (16.1%)	34 (18.0%)	
Adjuvant chemotherapy			0.022
On-time	55 (31.6%)	86 (45.5%)	
Delayed	63 (36.2%)	51 (27.0%)	
Omitted	56 (32.2%)	52 (27.5%)	
<i>Procedural details</i>			
Laparoscopic/Robotic	16 (9.2%)	73 (38.6%)	<0.001
Wound classification			0.790
Clean	2 (1.2%)	2 (1.1%)	
Clean/contaminated	160 (92.0%)	170 (90.0%)	
Contaminated	11 (6.3%)	14 (7.4%)	
Dirty/infected	1 (0.6%)	3 (1.6%)	
Ileostomy	77 (53.1%)	68 (46.9%)	0.108
Procedure duration (minutes)	221.5 (164.0-284.0)	260.0 (205.0-336.0)	<0.001
<i>Postoperative Complications</i>			
Unplanned intubation	4 (2.3%)	4 (2.1%)	0.906
Superficial incisional SSI	22 (12.6%)	5 (2.7%)	<0.001
Deep incisional SSI	2 (1.2%)	3 (1.6%)	0.721
Organ space SSI	12 (6.9%)	12 (6.4%)	0.834
Composite SSI	33 (19.0%)	20 (10.6%)	0.024
Wound disruption	4 (2.3%)	0 (0.0%)	0.036
UTI	5 (2.9%)	4 (2.1%)	0.643
Sepsis	4 (2.3%)	5 (2.7%)	0.832
Intraoperative/postoperative transfusion	26 (14.9%)	20 (10.6%)	0.212
Progressive renal insufficiency	2 (1.2%)	8 (4.2%)	0.073
Acute renal failure	3 (1.7%)	1 (0.5%)	0.276
Myocardial infarction	3 (1.7%)	2 (1.1%)	0.587
Cerebrovascular accident	2 (1.2%)	1 (0.5%)	0.514
Vein thrombosis requiring therapy	4 (2.3%)	2 (1.1%)	0.354
Pulmonary embolism	2 (1.2%)	0 (0.0%)	0.139
Total Complication(s)	61 (35.1%)	52 (27.5%)	0.121
Return to OR	9 (5.2%)	10 (5.3%)	0.960
Length of stay (days)	7.0 (5.0-10.0)	4.0 (3.0-7.0)	<0.001
30-day readmissions	30 (17.2%)	29 (15.3%)	0.625

Categorical variables listed as N (%) and continuous variables listed as median (interquartile range)

ERP=Enhanced recovery protocol; BMI=Body mass index; ESRD=End stage renal disease; COPD=Chronic obstructive pulmonary disease; ASA Classification=American Society of Anesthesiologists physical status classification, SSI=Surgical site infection; UTI=Urinary tract infection; OR=Operating room

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Table 3.

Patient characteristics, oncologic factors, procedural details, and postoperative outcomes in patients with on-time compared to delayed/omitted delivery of adjuvant chemotherapy

	On-time Chemotherapy n = 141	Delayed/Omitted Chemotherapy n = 222	p value
<i>Patient characteristics</i>			
Age (years)	59.1 (51.2-66.2)	63.9 (55.4-73.5)	<0.001
BMI (kg/m ²)	28.3 (24.0-32.2)	28.1 (24.1-32.3)	0.761
Male	78 (55.3%)	125 (56.3%)	0.854
Race			0.296
White	126 (89.4%)	185 (83.3%)	
Black	11 (7.8%)	32 (14.4%)	
Asian	1 (0.7%)	1 (0.5%)	
Not reported	3 (2.1%)	4 (1.8%)	
Hypertension	62 (44.0%)	130 (58.6%)	0.007
Diabetes mellitus	23 (16.3%)	47 (21.2%)	0.253
ESRD	0 (0.0%)	2 (0.9%)	0.258
COPD	9 (6.4%)	9 (4.1%)	0.319
Dyspnea	17 (12.1%)	28 (12.6%)	0.876
Ascites	1 (0.7%)	4 (1.8%)	0.384
Bleeding disorder	1 (0.7%)	5 (2.3%)	0.261
Current smoker	25 (17.7%)	43 (19.4%)	0.700
10% body weight loss	14 (9.9%)	20 (9.0%)	0.769
Preoperative transfusion	1 (0.7%)	2 (0.9%)	0.844
Chronic steroid use	5 (3.6%)	5 (2.3%)	0.463
Functional health status			0.218
Independent	140 (99.3%)	214 (96.4%)	
Partially independent	1 (0.7%)	7 (3.2%)	
Totally dependent	0 (0.0%)	1 (0.5%)	
ASA classification			0.007
ASA 1	1 (0.7%)	0 (0.0%)	
ASA 2	73 (51.8%)	78 (35.1%)	
ASA 3	64 (45.4%)	134 (60.4%)	
ASA 4	3 (2.1%)	10 (4.5%)	
<i>Oncologic factors</i>			
Colon cancer	62 (44.0%)	86 (38.7%)	0.323
Neoadjuvant chemoradiation	71 (50.4%)	128 (57.7%)	0.173
Neoadjuvant chemotherapy	14 (9.9%)	12 (5.4%)	0.103
High grade	49 (34.8%)	67 (30.2%)	0.363
Final stage			0.001

	On-time Chemotherapy n = 141	Delayed/Omitted Chemotherapy n = 222	p value
2	32 (22.7%)	81 (36.5%)	
3	74 (52.5%)	114 (51.4%)	
4	35 (24.8%)	27 (12.2%)	
<i>Procedural details</i>			
ERP	86 (61.0%)	103 (46.4%)	0.007
Laparoscopic/Robotic	45 (31.9%)	44 (19.8%)	0.009
Wound classification			0.206
Clean	3 (2.1%)	1 (0.5%)	
Clean/contaminated	123 (33.9%)	207 (93.2%)	
Contaminated	13 (9.2%)	12 (5.4%)	
Dirty/infected	2 (1.4%)	2 (0.9%)	
Ileostomy	63 (44.5%)	82 (36.9%)	0.142
Procedure duration (minutes)	236.0 (179.0-304.0)	241.0 (187.0-326.0)	0.600
<i>Postoperative Outcomes</i>			
Unplanned intubation	0 (0.0%)	8 (3.6%)	0.023
Superficial incision SSI	5 (3.6%)	22 (9.9%)	0.024
Deep incisional SSI	0 (0.0%)	5 (2.3%)	0.073
Organ space SSI	2 (1.4%)	22 (9.9%)	0.002
Composite SSI	7 (5.0%)	46 (20.7%)	<0.001
Wound disruption	0 (0.0%)	4 (1.8%)	0.109
UTI	1 (0.7%)	8 (3.6%)	0.084
Sepsis	1 (0.7%)	8 (3.6%)	0.084
Intraoperative/postoperative transfusion	14 (9.9%)	32 (14.4%)	0.211
Progressive renal insufficiency	1 (0.7%)	9 (4.1%)	0.058
Acute renal failure	1 (0.7%)	3 (1.4%)	0.568
Myocardial infarction	0 (0.0%)	5 (2.3%)	0.073
Cerebrovascular accident	0 (0.0%)	3 (1.4%)	0.166
Vein thrombosis requiring therapy	1 (0.7%)	5 (2.3%)	0.261
Pulmonary embolism	0 (0.0%)	2 (0.9%)	0.258
Complication(s)	23 (16.3%)	90 (40.5%)	<0.001
Return to OR	3 (2.1%)	16 (7.2%)	0.034
Length of stay (days)	5.0 (3.0-6.0)	6.0 (4.0-10.0)	<0.001
30-day readmissions	12 (8.5%)	47 (21.2%)	0.001

Categorical variables listed as N (%) and continuous variables listed as median (interquartile range)

BMI=Body mass index; ESRD=End stage renal disease; COPD=Chronic obstructive pulmonary disease; ASA Classification=American Society of Anesthesiologists physical status classification; ERP=Enhanced recovery protocol, SSI=Surgical site infection; UTI=Urinary tract infection; OR=Operating room

Table 4.

Multivariable logistic regression results and predictors of on-time delivery of adjuvant chemotherapy following colorectal cancer resection

Variable	OR (95% CI)	p value
Age (years)	0.96 (0.94-0.98)	0.001
BMI (kg/m ²)	1.01 (0.97-1.05)	0.703
Male	0.97 (0.56-1.64)	0.894
White	2.23 (1.05-4.75)	0.038
Diabetes mellitus	1.09 (0.54-2.19)	0.810
Current smoker	0.88 (0.44-1.75)	0.709
10% body weight loss	1.79 (0.74-4.33)	0.194
Chronic steroid use	1.77 (0.36-8.64)	0.478
Independent functional status	0.54 (0.05-5.62)	0.608
ASA class 3	0.65 (0.38-1.12)	0.124
Colon cancer	0.82 (0.25-2.77)	0.761
Neoadjuvant treatment	0.62 (0.20-1.88)	0.396
Final stage	1.93 (1.28-2.91)	0.002
ERP	2.05 (1.16-3.63)	0.014
Laparoscopic	1.19 (0.61-2.33)	0.697
Wound classification (ref=Clean/contaminated)		0.071
Clean	6.46 (0.54-77.90)	
Contaminated	2.95 (1.10-7.93)	
Dirty/infected	3.05 (0.22-42.81)	
Ileostomy	2.03 (1.07-3.84)	0.030
Procedure duration (minutes)	1.00 (0.99-1.00)	0.076
Complication(s)	0.64 (0.39-1.03)	0.067
Return to OR	1.29 (0.25-6.78)	0.762
Length of stay (days)	0.92 (0.86-0.99)	0.025
30-day readmission	0.46 (0.20-1.07)	0.071

BMI=Body mass index; ASA Classification=American Society of Anesthesiologists physical status classification; ERP=Enhanced recovery protocol; OR=Operating room