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Research Article

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Implementation of Enhanced Recovery After Surgery (ERAS) Protocols and Return to Intended Oncologic Therapy: Where We Were and Where We are Going?

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ABSTRACT

Objective: Enhanced recovery after surgery (ERAS) utilizes a multimodal, evidence-based approach to improvepatient postoperative recovery and return to functional baseline. Among gynecologic oncology patients, ERAS protocols are associated with a decrease in complication rate and shorter hospital stays. With the improved return to baseline function recovery times, oncology patients are able to begin adjuvant therapy within the recommended timeframe as to not impact overall survival. We performed a cohort study at the initiation of our gynecologic Oncology ERAD program to determine if this decreased time to planned adjuvant therapy among gynecologic oncology patients after laparotomy. Secondary endpoints included protocol adherence, length of stay, complication rates, and readmission.

Methods: We performed a retrospective chart review of 137 pre-ERAS and 73 post-ERAS patients diagnosed at a NCI-designated comprehensive care center in NJ to compare gynecologic oncologic and peri-operative outcomes before and after implementation of ERAS protocols. The protocols were based on recommendations from the ERAS society for management of gynecologic and gynecologic oncologic patients. Twenty-five interventions were analyzed and 12 were included in the final analysis. Pre-ERAS patients were identified by ICD-10 diagnosis code and CPT laparotomy codes. Patient characteristics, length of hospital stay, and complications rates were recorded. Institutional review board approval was obtained from Rutgers University and the Scientific Review Board approval from the Cancer Institute of New Jersey.

Results: Twenty-five protocol elements were investigated, with an overall decrease in readmission rate and complication rate between the pre- and post-ERAS cohorts. There was no difference in length of hospital stay (median, interquartile range of 5 [4-7] and 5 [3-7] in the pre-ERAS and post-ERAS groups, respectively (P=0.91). Similarly, the two groups did not differ based on time to intended oncologic therapy (38 [29-55] versus 37 [29-53]; P=0.94).

Conclusions: This study highlights the need for further research on ERAS protocol on return to intended oncologic therapy which is known to improve overall oncologic outcomes.

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Introduction

Enhanced recovery after surgery (ERAS) is a multimodal approach to expedite patient rehabilitation. These protocols are composed of evidence-based practices to improve patient-centered clinical and surgical outcomes. The main goal is to return patients more quickly to baseline function by taking into account pre-, intra-, and post-operative factors. These protocols avoid unnecessary interventions that have not been shown to improve patient outcome, such as pre-operative bowel preparation and fasting, and replace them with interventions that are supported by growing evidence that aid patient recovery [1]. Proven benefits include earlier return of gastrointestinal function, reduced opioid use, lower cost, and shorter hospital stay without increasing rehospitalizations complications [2-5]. Many institutions have implemented ERAS protocols to improve patient care while helping cut costs and improve patient outcomes and return to baseline function. In the gynecology oncology patient population, ERAS protocols had a 40% decrease in complication rate, 30% decrease in hospitalization stay, with no increase in readmission rates [5].

Many oncology patients require adjuvant therapy, including radiation and chemotherapy, after surgical intervention as part of their cancer treatment. These treatments can lead to toxicities delayed surgical complications. There are no set criteria or current clinical tools used to determine readiness for adjuvant therapy after surgery, and it is often a balance and clinical judgement to ensure surgical recovery and expeditious initiation of adjuvant therapy. Decreased time to adjuvant therapy after ovarian cancer surgery has been shown to improve survival [6-10]. A meta-analysis by Liu et al in 2017 observed a dose-response association for overall survival for each week delay in adjuvant chemotherapy [6]. The Society for Gynecologic Oncology and Commission on Cancer recommend 42 days from surgery to adjuvant treatment as an evidence-based quality metric [11,12]. Post-surgical patients need to have adequate return to baseline functional status without surgical complication, prior to initiation of adjuvant therapy. Interventions aimed at stress reduction and preservation of immune and organ function in the perioperative period can hasten recovery and therefore time to initiation of adjuvant therapy. Judging when a patient is appropriate for adjuvant therapy requires a balance between adequate surgical recovery and expediting therapy that is known to improve cancer outcomes [13].

ERAS protocols attempt to minimize the physiologic stress, complications, and effects on functional status after oncologic surgery. Therefore, we sought to determine a relationship between a newly implemented ERAS protocol and time to any adjuvant therapy for gynecologic cancer patients. The objective of this study was to determine if adherence to newly developed ERAS protocols decreases the time to intended oncologic therapy in gynecologic oncology patients undergoing laparotomy.

Methods

We performed a retrospective cohort study comparing oncologic and peri-operative outcomes before and after implementation of ERAS protocols that were implemented in a large gynecologic oncology service at a single institution in at the initiation of our ERAS programThe primary objective was to determine whether implementation of a formal ERAS protocol would decrease the time to adjuvant therapy for patients undergoing laparotomy for gynecologic malignancies. Secondary endpoints included protocol adherence, length of stay, complication rates, and readmission.

The program and protocols were based on recommendations from the ERAS society for management of gynecologic and gynecologic oncologic patients [1,14]. These included pre-, intra-, and post-operative protocols and management that differed from usual peri-operative care on the gynecologic oncology service. A multidisciplinary team including surgeons, anesthesiologists, and nurses developed the protocols and order sets. Institutional review board approval of this study was obtained from Rutgers University and the Scientific Review Board approval from the Cancer Institute of New Jersey.

The pre-operative visit included surgical counseling, diabetic screening, avoidance of bowel preparation, and an order set for surgical site infection prevention. The main tenets of the intra-operative interventions included use of regional anesthesia, maintenance of euglycemia and normothermia, prophylaxis of DVT and infection, limitation of nasogastric tubes and surgical drains, and use of self-retaining retractors and silver impregnated dressings. The post-operative focuses included non-opioid pain control, early ambulation, early refeeding, Foley and fluid management (Table 1).

Table 1: Enhanced Recovery After Surgery (ERAS) Protocol

Pre-operative	• Provided with information regarding ERAS post-op care
	• Meet with member of general anesthesia team, where standard pre-operative testing is performed
	• Standard lab work includes complete blood count, comprehensive metabolic panel, type and screen
	• Diabetic screening with HbA1C
	• Smoking and alcohol cessation referrals
	• Counseled to avoid bowel preparation
	• Provided with carbohydrate loading instructions
	• Instructed that consumption of clear liquids up to 6 hours prior to surgery is acceptable
	• Instructed to bathe / shower with Hibiclens soap or antiseptic agent the night before surgery

Immediate pre-operative	• Analgesia options include any of the following:
	o Acetaminophen 1000 mg PO/IV once
	o Celecoxib 400 mg PO once
	o Tramadol ER 300 mg PO once
	o Gabapentin 300-600 mg PO once
	o Pregabalin 75 mg PO once
	• Venothromboembolic (VTE) prophylaxis
	o Heparin 5000 U subcutaneous
	o Sequential compression devices
	• Appropriate Antimicrobial Prophylaxis based on weight and allergies.
	o If bowel resection is anticipated, add one of the following:
	■ Metronidazole 500 mg IV
	■ Ertapenem 1 g IV
	• Chlorhexidine-alcohol for skin cleansing is applied
	• Euglycemia protocols
	• Hypothermia protocols
Intra-operative	• Anesthesia recommendations include the following:
	o Epidural, spinal when indications allow
	o Opioid-sparing techniques with multimodal analgesia
	• Surgical drains and nasogastric tubes are avoided when possible
	• Normothermia is maintained with warm air circulating device and keeping the OR room temperature at 70°F
	• Euvolemia is maintained with goal-directed fluid therapy
	• Alexis retractors are used
	• Wound is irrigated
	• Gloves are changed prior to closure
	• Silver-impregnated dressing is applied
Post-operative	• Multi-modal anti-emetics options (at least 1) include the following:
	o Aprepitant 40 mg PO at induction
	o Dexamethasone 4-5 mg IV induction
	o Droperidol 0.625 - 1.25 mg IV at end of surgery
	o Ondansetron 4 mg IV at end of surgery
	o Promethazine 6.25 - 12.5 mg IV at induction / end of surgery
	o Scopolamine transdermal patch
	• Nutrition:
	o Regular diet on post-operative day (POD) 0 allowed
	o Oral nutritional support such as Ensure may be added
	o Gum may be chewed for 30 mins after meals 3x a day to stimulate resumption of bowel function
	• Glycemic control to maintain blood glucose levels <200 mg / dL, followed by finger sticks and insulin sliding scale
	• Pain control regimen:
	o Acetaminophen 1000 mg PO q 6 hr on POD0
	o Ibuprofen 400-800 mg PO q 6 hr on POD1
	o Pregabalin 75 mg PO BID x 48 hr prn on POD1
	If pain not controlled on these regimens, patients may use the following regimen:
	o Oxycodone 5-10 mg PO q 4 hr
	o Tramadol 100 mg PO q 4-6 hr
	o Opioid IV medication if PO opioid medication fails
	o PCA only if patient requires two doses or more of IV opioids in a 24-hour period

Post-operative	• Fluid management:
	o IV fluids to maintain urine output of >40 mL/hour for 8-12 hours post-operatively
	o A fluid bolus of 250-500 mL only when urine output is <20 mL/hr
	o Peripheral lock IV when patient has tolerated 600 mL of oral intake
	o Foley catheter removed in POD1 in the absence of any contra-indications
	• Early mobility:
	o Ambulation encouraged at least 8 times / day
	o Consume all meals in a chair
	o Be out of bed for 8 hours / day
	• Bowel regimen includes any of the following:
	o Senna 1-2 tabs PO qhs
	o Magnesium hydroxide 25 mL PO qhs
	o Lactulose 15-30 mL PO TID
	o Polyethylene glycol 3350 17 g PO daily
	o Psyllium mucilloid powder 1-2 packets PO daily
	• VTE prophylaxis: sequential compression devices while in bed at hospital and low molecular weight heparin starting on POD 1, continued for 28 days in all confirmed cancer patients.

After implementation of the protocol for 6 months to ensure education and adherence amongst the clinical teams, women were identified over a 12-month period who underwent a planned exploratory laparotomy for suspected gynecologic malignancy and met criteria for adjuvant treatment based on final pathology. During admission for surgery, the aim was to have all patients treated according to the standardized ERAS protocol. Twenty-five interventions were analyzed and 12 were included in the final analysis. The adherance to these interventions was primarily a result of decisions made by the surgeon and/or the anesthesiologist and thus represents the "voluntary" physician-driven adherence to the protocol. The final analysis included adherence to twelve ERAS tenants amongst the entire cohort that demonstrated the most change in practice patterns and are known to represent the most critical for return to baseline function based on a meta-analysis of 17 studies [15].

These patients were compared to a "pre-ERAS" cohort that were identified by ICD-10 diagnosis codes and CPT laparotomy codes over a two-year period prior to the initiation of the ERAS program. We recorded and compared patient characteristics, length of surgery, length of stay, and complication rates of all patients initially included in the study. Patients requiring adjuvant oncologic therapy based on final pathology report, and interdepartmental tumor board recommendations and NCCN guidelines were included in the final analysis for the primary outcome of time to adjuvant therapy.

Statistical Analysis

The primary outcome was analyzed among patients who met criteria for needing any adjuvant oncologic therapy and was measured in days to first treatment from the day of surgery. For normally distributed data, we report mean with 95% confidence interval (CI) and for non-normally distributed data, we report median (interquartile range). For continuous data, differences in outcomes between groups were evaluated based on the t-test or the two-sample median test as appropriate. For categorical outcomes, we applied the chi-square or Fisher's exact test, and associations were expressed as relative risk (RR) with 95% confidence interval (CI). Subgroup analysis by disease site in ovarian cancer patients was also examined. The STROBE reporting guidelines were used.

Results

The post-ERAS group included a total of 73 patients who were who were undergoing laparotomy for suspected gynecologic malignancy. Sixty-seven were included in the final analysis due to loss of follow up, not meeting criteria for adjuvant therapy, or non-gynecologic malignancy. We identified 137 women as the comparison group, of whom 124 met inclusion criteria and had received adjuvant therapy for gynecologic malignancy (pre-ERAS group).

Groups were simiilar for relevant clinical and surgical characteristics, including age, BMI, ASA, length of surgery, length of stay, and complication rates. Approximately one half of the patients had ovarian cancer, 54.0% in pre-ERAS and 50.8% in post-ERAS. There were similar rates of chemotherapy as adjuvant treatment, 76.5% in pre-ERAS and 76.9% in post-ERAS (Table 2).

Table 2: Patient and Treatment Characteristics Based on the Implementation of the Enhanced Recovery After Surgery (ERAS) Protocol

	Pre ERAS (n=137)	Post ERAS (n=73)	P-Value
Age (years), mean (SD)	60.5 (13.6)	59.7 (14.4)	0.65
Body-mass index (kg/m^2) mean (SD)	29.5 (7.7)	29.7 (7.3)	0.88
American Society of Anesthesiologists			0.35
1	6 (4.1%)	1 (1.5%)	
2	50 (37.4%)	32 (43.3%)	
3	75 (54.5%)	39 (53.7%)	
4	6 (4.1%)	1 (1.5%)	
Complication rate	57 (41.9%)	22 (30.3%)	0.14
Overall readmission rate	20 (13.7%)	7 (9.1%)	0.42
Readmission rate (site-specific)			
GI	5 (3.6%)	1 (1.4%)	0.63
Surgical Site Infection	10 (7.2%)	2 (2.7%)	0.30
Medical	5 (3.6%)	4 (5.5%)	0.77
Cancer site			0.44
Ovarian	67 (54.0%)	34 (50.8%)	
Uterine	52 (41.9%)	29 (43.3%)	
Cervical	3 (2.4%)	4 (6.0%)	
Other	2 (1.6%)	0 (0%)	
Adjuvant therapy			0.20
Chemotherapy	78 (76.5%)	40 (76.9%)	
Radiation	17 (16.7%)	4 (7.7%)	
Hormonal	4 (3.9%)	5 (9.6%)	
Immunotherapy	2 (2.0%)	3 (5.8%)	
Other	1 (1.0%)	0 (0%)	

Twenty-five ERAS protocol elements were audited (Table 1), and 12 were included for this analysis for both adherence and effect on primary outcome. Protocol compliance in the post-ERAS group was significant for increase in formal preadmission testing which included diabetic screening, smoking and alcohol cessation referrals, and counseling regarding post op expectations. There was a decrease in bowel prep use and increased use of regional anesthesia. Post-operative glycemic control was improved, as well as early refeeding, but there no improvement in early ambulation or early Foley removal (Table 3).

Table 3: Adherence to Enhanced Recovery After Surgery (ERAS) Protocol Compliance

Adherence to ERAS compliance	Pre ERAS (n=137)	Post ERAS (n=73)	P-Value
Pre-admission testing/Counseling	101 (81.5%)	65 (97.0%)	<0.01
Diabetes screen	16 (12.9%)	57 (85.1)	<0.01
Bowel prep	71 (64.0%)	15 (22.4%)	<0.01
Pre-operative Venous thromboembolism prophylaxis	121 (99.2%)	67 (100%)	0.60
Pre-operative antibiotic prophylaxis	121 (99.2%)	67 (100%)	0.60
Regional anesthesia	32 (26.0%)	49 (73.1%)	<0.01
Normothermia	121 (99.2%)	67 (100%)	0.60
Euglycemia	1 (0.8%)	62 (92.5%)	<0.01
Regular diet post-operative day 0	17 (13.8%)	28 (41.8%)	<0.01
Out of bed post-operative day 1	61 (50.0%)	27 (40.3%)	0.29
Foley removal post-operative day 1	52 (42.3%)	17 (25.4%)	0.03
Post-operative glycemic control	70 (56.9%)	63 (94.0%)	<0.01

The length of surgery and length of hospital stay did not differ between the pre-ERAS and post-ERAS groups, but there was a decline in readmission rates from 13.7% to 9.1%, which was not statistically significant (RR 0.95, CI 0.86-1.05). There was also a reduction in complication rates from 41.9% to 30.3% (RR 0.38 95% CI 0.91-2.11) after initiation of ERAS protocols. There was no difference in time to adjuvant therapy in all patients (38 versus 37 days); in the ovarian cancer subgroup, we observed a trend toward improved time to adjuvant chemotherapy (36 versus 31 days) in the post-ERAS cohort that did not reach statistical significance (p=0.23) (Table 4).

Table 4: Length of Hospital Stay and Time to Adjuvant Therapy based on the Implementation of the Enhanced Recovery After Surgery (ERAS) Protocol

	Pre ERAS	Post ERAS	P-Value
Length of surgery (min), median (IQR)	267 (195-328)	279 (220-363)	0.40
Length of hospital stay (days), median (IQR)	5 (4-7) n=100	5 (3-7) n=49	0.91
Time to adjuvant treatment (days), median (IQR)			
All patients	38 (29-55) n=124	37 (29-53) n=67	0.94
Ovarian cancer patients	36 (28-46) n=53	31 (27-47) n=26	0.23

IQR, interquartile range

Discussion

Summary of Main Results

This study was performed at a high volume academic gynecologic oncology practice at a tertiary care center where, prior to ERAS standard perioperative management included bowel prep, liberal fluid resuscitation, intravenous narcotics for pain control, and slow advancement of diet. The new ERAS program consisted of updated evidence-based order sets for perioperative care based on national guidelines as well as patient and provider education across all involved specialties and departments. The adherence to the interventions on the new ERAS program was "voluntary" and primarily a result of decisions made by the surgeon and/or anesthesiologist. This represented a major practice shift for most surgeons and anesthesiologists at our institution. This study analyzed 12 ERAS protocol elements shown to have the most impact on short-term stress and independent from patient factors [15].

Results in the Context of Publiched Literature

The ERAS society released an update for the ERAS protocol recommendations for gynecologic oncology in 2019, supported by growing evidence on the association of ERAS protocols and earlier return of gastrointestinal function, reduced opioid use, shorter hospital stay without increasing rehospitalizations, decrease in complications, and substantial cost reductions [14]. The significance of ERAS protocols was first seen in the field of colorectal surgery over 15 years ago, and has been adopted in some form by most surgical specialties including oncologic surgery. Return to Intended Oncologic Treatment (RIOT) was described as a novel metric in review by Lohsiriwat et al. in 2020 and found a shorter interval between operation and commencement of adjuvant chemotherapy in patients on ERAS pathways [16]. It is likely that the same ERAS interventions that return patients to baseline status, reduce perioperative stress, allow for quicker return to adjuvant oncologic therapy after surgery. There are no set criteria to determine when a patient is deemed fit for chemotherapy; however, if there is a surgical complication, delayed wound healing or prolonged hospitalization this may prevent timely initiation of adjuvant therapy and increase the risks of cancer recurrence, especially in high-grade malignancies. In advanced ovarian cancer, for example, there is strong data to support quick return to chemotherapy and overall improvement in survival.

Strengths and Weaknesses

A strength of this study is that we initiated a new ERAS program for high-complexity gynecologic cancer patients, as demonstrated by ASA and length of surgery, undergoing laparotomy in less than a year with adherence to a majority of important components of the program. At the Mayo Clinic, pioneers of ERAS programs in Gynecologic Oncology, ERAS afforded a 3-day reduction in median length of stay (from 8 days to 5 days) for patients undergoing complex cytoreductive surgeries (20). The mean time to discharge in both groups was 5 days. Interestingly, the majority of patients in the post-ERAS group received epidural anesthesia (73.1% versus 26.0%), which could explain an increased time to Foley removal in this group, in attempt to decrease incidence of epidural-related urinary retention. Education regarding safe timing of foley removal while a "walking epidural" in in place is needed and optimizing time of Foley removal could more accurately reflect the expected improvement in hospital stay using ERAS protocol. Furthermore, a delay in Foley removal secondary to increased epidural use could have masked the expected duration of hospital stay and could account for lack of improvement in the time to discharge in post-ERAS group.

The lack of difference in length of stay in this limited cohort of patients may also reflect that these patients already had an excellent outcome with five-day discharge from surgery and may be why we did not demonstrate a significant difference in time to chemotherapy. Both groups met the goal of 42 days from surgery to adjuvant treatment set out by SGO and the Commission on Cancer as an evidence-based quality metric, and ovarian cancer patients achieved a 5-day improvement in time to adjuvant chemotherapy.

The complication rate was defined as any readmission or post-operative complication within 30 days postoperatively. Our complication rate did not show a decrease after ERAS implementation (41%, n=18 versus 30%, n=4). We further categorized our readmissions into bowel related (ileus or SBO), surgical site infection (superficial or deep) and medical (pneumonia, atrial fibrillation). Of the 20 readmissions in pre-ERAS group, 10 were related to surgical site infection, 5 to bowel related complication, and 5 medical readmissions. The seven post-ERAS readmissions included 2 surgical site infections, 1 bowel related complication, and 4 medical readmissions. This trend represents a clinically important decrease in surgical site infections and readmissions due to delayed return of gastrointestinal function. This is likely due

to the implementation of specific surgical site infection bundled order set that was implemented with ERAS protocol which included euglycemia and hypothermia protocols, chorohexadine shower, as well as appropriate antimicrobial prophylaxis.

Our study was underpowered as it only was assessing patient outcomes for the first year after ERAS implementation, and due to the high volume of minimally invasive surgery performed at our institution many patients were not included in this study. Majority of laparotomies performed at our institution are for advanced ovarian and endometrial cancers, patients most likely to required adjuvant oncologic therapy after surgery.

The patient population was relatively young and with relatively low BMI in comparison to a typical gynecologic oncology population. We hypothesize that a trend in improvement of length of stay and complications could be more meaningful in a sicker or older patient population.

It also takes many years for peri-operative teams to fully adapt to new protocols. There is no specified "wash out" period between old practice patterns and new, and further long term follow up on program compliance is needed as practice changes and providers continue to shift since initiation of the program. Other limitations of this study include lack of potential confounding factors that could influence time to chemotherapy such as coordination between oncology surgeon and medical oncologist. The majority of our patients received chemotherapy, but our study looked at all adjuvant therapy modalities such as radiation, hormonal therapy, chemotherapy and immunotherapy, all of which have subjective criteria for initiation, and have no clearly established benchmarks or quality metrics. Lastly, the timing to start adjuvant therapy is often affected by many non-patient related factors including administrative, logistical, and social factors.

Other potential patient and surgical characteristics need to be investigated in order determine their impact on return to intended oncologic therapy. Our study demonstrated a clinically relevant trend towards lower complication rates, with no surgically related readmissions in our post-ERAS group, which certainly may improve return to intended oncologic therapy. Compliance rates of specific ERAS elements not analyzed in this study, such as prehabilitiation programs, goal-directed fluid therapy, opioid restriction also need to be investigated in regards to role in return to intended oncologic therapy.

Implications for Future Practice and Future research

There is no clear causal relationship between ERAS protocols and time to chemotherapy after gynecologic cancer surgery, but this study suggests a possible association. There remains a paucity of data about the impact of ERAS protocols on oncologic outcomes in the field of gynecologic oncology, and our study highlights the need for further evaluation to establish the impact of ERAS protocols as well as specific elements of ERAS or prehabilitation programs that will most impact return to funtional baseline and therefore oncologic therapy. This is critical for future research, and this metric should be reported as a quality indicator and outcome in future studies. Interventions during the short perioperative period surrounding a cancer operation could significantly improve patients' long-term oncologic outcomes.

Author Contribution Statement

Dr Stephenson contributed conceptualization and writing of the manuscript. Dr Hollingsworth contributed writing and editing of the manuscript. Dr Goldberg contributed conceptualization and writing of the manuscript. Dr Wang contributed data collection. Dr Leiser, Dr Buckley de Meritens, and Dr Aikins contributed editing of the manuscript. Dr Ananth contributed statistical analysis.

Conflict of Interest

Dr. Stephenson has no conflicts of interest to declare.
Dr. Hollingsworth has no conflicts of interest to declare.
Dr. Goldberg has not conflicts of interest to declare.
Dr. Wang has no conflicts of interest to declare.
Dr. Leiser has no conflicts of interest to declare.
Dr. Buckley de Meritens has no conflicts of interest to declare.
Dr. Girda has no conflicts of interest to declare.
Dr. Aikins has no conflicts of interest to declare.
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