Enhanced recovery after surgery protocols improve time to return to intended oncology treatment following interval cytoreductive surgery for advanced gynecologic cancers

Joan Isabelle Tankou ,[1] Olivia Foley,[2,3] Michele Falzone,[2] Rajeshwari Kalyanaraman,[4] Kevin M Elias[2,3,5]

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For numbered affiliations see end of article.

Correspondence to
Dr. Kevin M Elias, Department of Obstetrics and Gynecology, Brigham and Women's Hospital, Boston, MA 02115, United States; kelias@bwh.harvard.edu

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HIGHLIGHTS

- An enhanced recovery after surgery (ERAS) protocol was associated with fewer postoperative complications and shorter lengths of hospital stay.
- Intraoperative ERAS compliance was most closely associated with timely return to intended oncology treatment.
- The strongest single predictor for timely return to intended oncology treatment in multivariate analysis was being on the ERAS pathway.

ABSTRACT

Objective The objective of this study was to determine whether the implementation of an enhanced recovery after surgery (ERAS) protocol is associated with earlier return to intended oncology treatment following interval cytoreductive surgery for advanced gynecologic cancers.

Methods Participants comprised consecutive patients (n=278) with a preoperative diagnosis of stage IIIC or IV ovarian cancer, divided into those that received treatment before versus after implementation of an ERAS protocol at our institution. All patients received at least three cycles of neoadjuvant chemotherapy with a platinum based regimen and underwent interval cytoreduction via laparotomy with the intent to deliver additional cycles of chemotherapy postoperatively. The primary outcome was defined as the timely return to intended oncologic treatment, defined as the percentage of patients initiating adjuvant chemotherapy within 28 days postoperatively.

Results The study cohorts included 150 pre-ERAS patients and 128 post-ERAS patients. Median age was 65 years (range 58–71). Most patients (211; 75.9%) had an American Society of Anesthesiologists score of 3, and the median operative time was 174 min (range 137–219). Median length of stay was 4 days (range 3–5 days) in the pre-ERAS cohort versus 3 days (range 3–4) in the post-ERAS cohort (p<0.0001). At 28 days after operation, 80% of patients had resumed chemotherapy in the post-ERAS cohort compared with 64% in the pre-ERAS cohort (odds ratio (OR) 2.29, 95% confidence interval (CI) 1.36 to 3.84; p=0.002). In multivariate logistic regression analysis, the ERAS protocol was the strongest predictor of timely return to intended oncology treatment (OR 10.18, 95% CI 5.35 to 20.32).

Conclusion An ERAS protocol for gynecologic oncology patients undergoing interval cytoreductive surgery is associated with earlier resumption of adjuvant chemotherapy.

INTRODUCTION

Epithelial ovarian cancer is the leading cause of gynecologic cancer death among American women.[1] The preferred treatment is primary cytoreductive surgery followed by platinum and taxane based chemotherapy. In select cases, where a complete primary cytoreduction is not technically feasible due to high disease burden or would be unduly morbid given a patient's poor functional status, similar survival outcomes can be achieved with neoadjuvant chemotherapy followed by interval cytoreductive surgery and adjuvant chemotherapy.[2] For women with epithelial ovarian cancer, the optimal time to initiate adjuvant chemotherapy is 21–37 days after surgery. Delay in initiation of adjuvant chemotherapy beyond 37 days has been associated with decreased survival.[3 4] For this reason, return to intended oncologic treatment postoperatively has been proposed as a standard for oncologic surgical care.[5 6]

Enhanced recovery after surgery (ERAS) programs, initially developed for colorectal surgery patients, aim to facilitate rapid recovery, reduce complications, and prevent readmissions in the postoperative period.[7] In patients with gynecologic malignancies, use of ERAS protocols has been shown to reduce the postoperative length of hospital stay as well as the incidence of postoperative complications.[8] However, whether the benefits of ERAS protocols extend beyond the hospital stay to impact the resumption of postoperative cancer treatment is unknown.

The objective of this study was to determine whether the implementation of an ERAS protocol was associated with improved time to resumption of chemotherapy among women undergoing interval cytoreduction for advanced stage ovarian cancers. As

most patients are counseled to expect to resume chemotherapy within 1 month of surgery, timely return to intended oncology treatment was defined as resumption of chemotherapy by postoperative day 28. We also examined time to resumption of chemotherapy, hospital complications, and length of stay, and prognostic factors for achieving timely return to intended oncology treatment.

METHODS

Study Design, Setting, and Oversight

The study was approved by the Partners Healthcare institutional review board, protocol No 2017P001806. The study was constructed as a retrospective cohort study at a single academic tertiary care institution using a before and after design. The study population included all women undergoing interval cytoreductive surgery at Brigham and Women's Hospital for presumed advanced stage (the International Federation of Gynecology and Obstetrics stages IIIC–IV) ovarian, tubal, or primary peritoneal cancer after completion of neoadjuvant chemotherapy. The decision to perform neoadjuvant chemotherapy followed by interval cytoreductive surgery was based on a low likelihood of achieving complete primary cytoreduction due to advanced stage disease or poor patient functional status, as determined by the primary gynecologic oncologist.

Study Participants

The pre-ERAS cohort included patients who underwent interval cytoreductive surgery from January 2010 to January 2015. ERAS implementation began in 2015 and was completed, following a 2 year implementation period, at the end of 2016. The post-ERAS cohort included patients who underwent surgery after full implementation of the ERAS program, between January 2017 and December 2018. The ERAS protocol was considered fully operational once a compliance audit system was in place. Patients were excluded from the analysis if they had a synchronous malignancy, final pathology revealed a non-gynecologic or non-epithelial malignancy, never underwent definitive surgical intervention, the procedure was for recurrent disease, they did not receive postoperative chemotherapy, or the timing of resumption of chemotherapy and follow-up data were not available.

Variables

Collected demographic variables included patient age at the time of surgery, body mass index, American Society of Anesthesiologists risk score, smoking status, diabetes mellitus, primary tumor site, tumor grade, tumor histology, International Federation of Gynecology and Obstetrics tumor stage, pretreatment and preoperative CA-125 levels, chemotherapy regimen, and total number of chemotherapy cycles (neoadjuvant and adjuvant). Perioperative variables included estimated intraoperative blood loss, operative time, completeness of cytoreduction, surgical complexity, requirement for bowel resection, anesthetic regimen, use of neuraxial analgesia, intraoperative fluid administration, and hospital length of stay. The complexity score was assigned to surgical procedures using a validated scoring system (low <4, medium 4–7, or high >7) from a previously published series.[9] In eight cases involving the post-ERAS cohort, the final pathology suggested an endometrial cancer; these cases were still included in the analysis. All data points were generally available, however, there were 11 specific variables missing among the pre-ERAS cohort and 16 specific variables missing among the post-ERAS cohort. The vast majority of these were missing CA-125 values and not expected to influence the primary outcome. Missing data were excluded from analyses, and not imputed. Complications were determined using the definitions from the Clavien–Dindo grading system.[10]

Treatments

The hospital ERAS protocol follows the guidelines for gynecologic oncology published by the ERAS Society.[11–13] Prior to the initiation of the ERAS protocol, patients were managed with universal mechanical bowel preparation, nothing by mouth after midnight, opioid patient controlled analgesia pumps transitioning to oral oxycodone, delayed feeding and ambulation, and liberal fluid administration. Patients under the ERAS protocol received carbohydrate loading 2 hours prior to induction of anesthesia and liberal clear fluids up to that time. Early feeding and ambulation (defined as postoperative day 0), minimization of narcotics by using a thoracic epidural (prior to September 2018) or wound infiltration with liposomal bupivacaine (after September 2018), and goal directed fluid usage became the standard practice. The complete institutional ERAS protocol is explained in the Reporting on ERAS Compliance, Outcomes, and Elements Research Checklist (online supplemental Table S1).[14] ERAS data are reviewed weekly on a case by case basis at an interdisciplinary conference, including nursing and the surgical team, monthly by department at a hospital wide surgical quality data review, and quarterly at a division level with each individual surgeon in the form of individual 'report cards' of compliance and outcomes.

Outcome Measures

The primary outcome was defined as the timely return to intended oncologic treatment, defined as the time in days from the date of the interval cytoreductive procedure to the date of the first cycle of adjuvant chemotherapy. We chose 28 days as a landmark time point to produce a dichotomous variable as patients are counseled that they can expect to resume chemotherapy about 1 month after surgery. Secondary outcomes were defined as the time to resumption of chemotherapy as a continuous variable, resumption of chemotherapy by 37 days, perioperative complications, hospital length of stay, reoperation, readmission, and death. In the post-ERAS cohort, ERAS protocol compliance was measured as percentage adherence to 20 predefined metrics (see online supplemental Table S2 for complete list). The secondary outcome of resumption of chemotherapy by 37 days was selected based on the publication by Seagle et al, which identified this as an inflection time point for poor oncologic outcomes.[3]

Data

Potential patients for the pre-ERAS cohort were identified from the institutional tumor board registry. Pre-ERAS cohort data were collected through retrospective chart review of electronic medical records. Post-ERAS cohort data were collected from the ERAS Interactive Audit System (Encare AB, Stockholm, Sweden), a web based data auditing system which reflects the ERAS Society guidelines. Compliance with the ERAS protocol was audited prospectively by entry into the ERAS Interactive Audit System. In accordance with the journal's guidelines, we will provide our data in deidentified

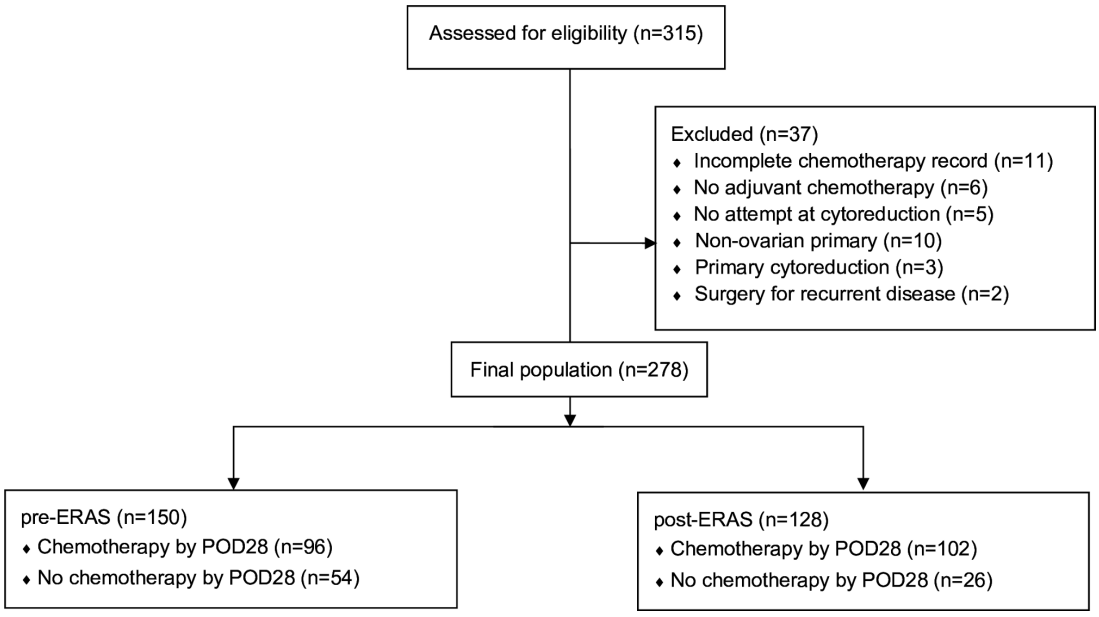

Figure 1 Selection of the study population. ERAS, enhanced recovery after surgery; POD, postoperative day.

form, subject to standard data sharing agreements for the reproducibility of this study in other centers if requested.

Statistical Analysis

Data were analyzed from January 1, 2010 to June 30, 2019. Demographic and clinical characteristics of the two cohorts were compared using χ^2 tests, Fisher's exact test, or the Mann–Whitney U test as appropriate. Odds ratios (ORs) for resumption of chemotherapy by 28 days and 37 days were compared using Fisher's exact test. Return to chemotherapy as a continuous variable was examined using Kaplan–Meier curves with a log rank test. The correlation between timely return to intended oncology treatment and compliance was assessed using a Spearman correlation analysis. Prognostic factors for the primary outcome were evaluated using multivariate logistic regression. Factors included in the multivariate model included cohort, age, body mass index, diabetes, estimated blood loss, hospital length of stay, smoking status, cancer stage, operative time, number of preoperative cycles, and bowel resection. All statistical tests were performed using GraphPad V.8.4.3 (San Diego, California, USA). A two tailed p value ≤0.05 was set as statistically significant.

RESULTS

The final study population included 150 pre-ERAS patients and 128 post-ERAS patients (Figure 1). Table 1 compares the demographic characteristics of the study cohorts. The pre-ERAS group had more participants who actively smoked and stage IVB patients, while the post-ERAS group had significantly higher American Society of Anesthesiologists scores and more stage IVA patients; otherwise there were no clinically significant demographic differences between the two groups. All 150 patients in the pre-ERAS cohort had ovarian/peritoneal/fallopian tube cancer while eight of the post-ERAS cohort had presumed epithelial ovarian cancer but final pathology revealing uterine cancer. Both patient populations were similar in terms of chemotherapy regimen, number of chemotherapy cycles, initial and preoperative CA-125 levels, histologic cancer type, and histologic cancer grade.

The impact of ERAS implementation on perioperative care is shown in Table 2. ERAS was associated with 51% fewer patients receiving more than 2 L of intraoperative intravenous fluids and 33% more patients receiving regional analgesia. Interestingly, there was a trend towards higher rates of medium and high complexity surgeries in the post-ERAS group compared with the pre-ERAS group, with higher rates of bowel resection (9.3% vs 18%; p=0.02). Despite undergoing higher risk surgeries with higher estimated blood loss, post-ERAS patients experienced a 25% shorter median length of stay (4 days vs 3 days; p<0.0001).

ERAS implementation was associated with a reduction in perioperative complications (Table 2). Most notably, the post-ERAS group had a significantly lower rate of gastrointestinal complications, which included ileus, vomiting, and diarrhea (16% vs 6.3%%; p=0.01). In aggregate, ERAS implementation reduced the number of adverse events per patient by 36% (0.56 to 0.36; p=0.0009).

Mean ERAS compliance in the post-ERAS cohort was 71.6% (range 40.9–95.4). We hypothesized that if ERAS implementation was driving the improvement in timely return to intended oncology treatment, then ERAS compliance should be correlated with outcomes (online supplemental Figure S1). There was no statistically significant difference between total compliance and time to chemotherapy (r=−0.05; p=0.54). When we divided compliance by phase of care, intraoperative compliance (r=−0.18; p=0.046) significantly correlated with timely return to intended oncology treatment.

In terms of the primary outcome, by 28 days after operation, 80% of patients had resumed adjuvant chemotherapy in the post-ERAS cohort compared with 64% in the pre-ERAS cohort (OR 2.21; 95% confidence interval (CI) 1.28 to 3.80; p=0.002). This difference persisted to 37 days postoperatively, at which time 97.7% of patients had resumed chemotherapy in the post-ERAS cohort compared with 90.7% in the pre-ERAS cohort (OR 4.29; 95% CI

Table 1 Demographic comparison of the study cohorts

Characteristic (n (%))	Pre-ERAS (n=150)	Post-ERAS (n=128)	P value
Age (years)			0.63*
<50	14 (9.3)	7 (5.5)	
50–59	31 (20.7)	26 (20.3)	
60–69	61 (40.7)	49 (38.3)	
70–79	36 (24.0)	39 (30.5)	
80+	8 (5.3)	7 (5.5)	
Body mass index (kg/m^2)			0.09*
<20	15 (10.0)	8 (6.3)	
20–24	55 (36.7)	37 (28.9)	
25–29	51 (34.0)	39 (30.5)	
30–34	18 (12.0)	25 (19.5)	
35–39	7 (4.7)	9 (7.0)	
40+	4 (2.7)	10 (7.8)	
American Society of Anesthesiologists score			<0.0001*
1	0 (0.0)	0 (0.0)	
2	47 (31.3)	11 (8.6)	
3	100 (66.7)	111 (86.7)	
4	1 (0.7)	6 (4.7)	
5	0 (0.0)	0 (0.0)	
Unspecified	2 (1.3)	0 (0.0)	
Smoker			0.05†
Yes	14 (9.3)	4 (3.1)	
No	136 (90.7)	124 (96.9)	
Diabetes mellitus			0.83†
Yes	12 (8.0)	12 (9.4)	
No	138 (92.0)	116 (90.6)	
Primary disease site			0.002†
Ovary/fallopian/peritoneal	150 (100)	120 (93.8)	
Uterine/unspecified	0 (0.0)	8 (6.3)	
Tumor grade			0.02*
Low/moderate	2 (1.3)	3 (2.3)	
High	140 (93.3)	125 (97.7)	
Unspecified	8 (5.3)	0 (0.0)	
Histology§			0.13†
Serous	137 (91.3)	109 (85.2	
Other	13 (8.7)	19 (14.8)	
Tumor stage (FIGO)			0.01*
IIIC	73 (48.7)	62 (48.4)	
IVA	25 (16.7)	38 (29.7)	
IVB	52 (34.7)	28 (21.9)	
Initial CA-125			0.15*
<50	9 (6.0)	7 (5.7)	
50–200	21 (14.1)	17 (13.8)	
200–500	29 (19.5)	29 (23.6)	
500–1000	17 (11.4)	24 (19.5)	

Continued

Table 1 Continued

Characteristic (n (%))	Pre-ERAS (n=150)	Post-ERAS (n=128)	P value
1000–2500	46 (30.9)	26 (21.1)	
2500+	27 (18.1)	20 (16.3)	
Unspecified	1 (0.7)	5 (3.9)	
Preoperative CA-125			0.03*
<50	82 (57.3)	52 (44.4)	
50–200	42 (29.4)	34 (29.1)	
200–500	14 (9.8)	18 (15.4)	
500–1000	4 (2.8)	5 (9.3)	
1000–2500	0 (0.0)	6 (5.1)	
2500+	1 (0.7)	2 (1.7)	
Unspecified	7 (4.7)	11 (8.6)	
First line chemotherapy			0.23*
Carboplatin/paclitaxel	136 (90.7)	123 (96.1)	
Carboplatin alone	3 (2.0)	1 (3.7)	
Paclitaxel alone	3 (2.0)	0 (0.0)	
Other	8 (5.3)	4 (3.1)	
Total No of chemotherapy cycles‡			0.*19
<6	5 (3.3)	2 (1.6)	
6–7	130 (86.7)	108 (84.4)	
≥8	15 (10.0)	18 (14.1)	

*χ^2 test.
†Fisher's exact test.
‡Including both neoadjuvant and adjuvant chemotherapy.
§Some patients had two histologies.
ERAS, enhanced recovery after surgery; FIGO, International Federation of Gynecology and Obstetrics.

1.20 to 15.28; p=0.02). We also looked at time as a continuous variable. The difference in timely return to intended oncology treatment stemmed from a decline in the outlier population experiencing marked delays in resumption of chemotherapy (Figure 2). Overall, ERAS implementation was associated with shorter time to chemotherapy (hazard ratio 0.70; 95% CI 0.55 to 0.90; p=0.001).

Finally, we performed a multivariate logistic regression analysis examining the effect of ERAS implementation versus other factors that might influence time to resumption of chemotherapy (Table 3). Use of ERAS was the strongest predictor for resumption of chemotherapy by 28 days (OR 10.18; 95% CI 5.349 to 20.32; p<0.0001).

DISCUSSION

Summary of Main Results

Delaying the start of adjuvant therapy after oncologic surgery can negate the survival benefit associated with surgery. Factors associated with delayed timely return to intended oncology treatment include open surgical approach, length of stay >5 days, and any complications.[15] Implementation of ERAS has been associated with an improved timely return to intended oncology treatment in breast, pancreatic, and non-small cell lung cancers.[16 17] Here we report similar effects from ERAS implementation on timely return to intended oncology treatment in gynecologic oncology. We chose to examine patients undergoing neoadjuvant chemotherapy because these patients are typically less fit for surgery and would theoretically benefit most from an ERAS pathway, which strives to reduce the stress response associated with surgery.[2] In addition, focusing on neoadjuvant chemotherapy patients attempts to control for the effect of administrative delays (eg, port placement, infusion scheduling, chemotherapy education) that may affect timely return to intended oncology treatment after surgery.

Results in the Context of Published Literature

Similar to prior reports, we found that the introduction of ERAS changed perioperative management. ERAS was associated with more conservative fluid management and greater reliance on regional analgesia.[18 19] We also found increased use of total intravenous analgesia as opposed to volatile anesthetics, fewer postoperative complications, and shorter lengths of stay. The post-ERAS cohort represented a surgically higher risk group of patients at baseline, as demonstrated by the group's higher American Society of Anesthesiologists score, increased rates of bowel surgery, and trend towards higher body mass index and surgical complexity. We suspect that the observed surgical risk differences between the cohorts may reflect both improved triage of patients to neoadjuvant chemotherapy with low likelihoods of primary cytoreduction as well as implementation of the ERAS pathway leading to increased provider comfort with interval debulking surgery in patients who

Table 2 Perioperative characteristics and complications

Characteristic (n (%))	Pre-ERAS (n=150)	Post-ERAS (n=128)	P value
Estimated blood loss (mL)			0.09*
<100	13 (8.7)	13 (10.2)	
100–499	102 (68.5)	71 (55.5)	
500–999	24 (16.1)	35 (27.3)	
1000–1999	6 (4.0)	8 (6.3)	
2000+	4 (2.7)	1 (0.8)	
Unspecified	1 (0.7)	0 (0.0)	
Operating room time (hours)			0.60*
<2 hours	24 (16.0)	14 (10.9)	
2–4 hours	97 (64.7)	88 (68.8)	
4–6 hours	24 (16.0)	22 (17.2)	
>6 hours	3 (2.0)	4 (3.1)	
Unspecified	2 (1.3)	0 (0.0)	
Residual disease			0.96*
NED	96 (64.0)	81 (63.3)	
<1 cm	45 (30.0)	40 (31.3)	
>1 cm	9 (6.0)	7 (5.5)	
Surgical complexity			0.07*
Low	114 (76.0)	90 (70.3)	
Medium	33 (22.0)	28 (21.9)	
High	3 (2.0)	10 (7.8)	
Bowel surgery			0.05†
Yes	14 (9.3)	23 (18.0)	
General anesthesia			<0.0001*
Volatile	141 (94.0)	111 (86.7)	
TIVA	7 (4.7)	17 (13.3)	
Unspecified	2 (1.3)	0 (0.0)	
Epidural/spinal			0.0001†
Yes	90 (60.0)	104 (81.3)	
Intraoperative fluids (L)			<0.0001*
0–2	12 (8.0)	71 (55.5)	
2–4	95 (63.3)	51 (39.8)	
4–6	32 (21.3)	5 (3.9)	
6+	9 (6.0)	1 (0.8)	
Unspecified	2 (1.3)	0 (0.0)	
Length of stay (days) (median (IQR))	4 (3–5)	3 (3–4)	<0.0001‡
Surgical complication	27 (18.0)	16 (12.5)	0.25¶
Reoperation	2	0	
Wound breakdown	6	3	
Anastomotic leak	0	0	
Estimated blood loss ≥1000 mL	10	9	
Transfusion >4 U pRBCs	5	4	
ICU admission	3	0	
Pancreatic leak	1	0	
Postoperative infection	15 (10.0)	8 (6.3)	0.28¶

Continued

Table 2 Continued

Characteristic (n (%))	Pre-ERAS (n=150)	Post-ERAS (n=128)	P value
UTI	6	3	
Pneumonia	0	0	
Abscess	2	2	
Wound infection	6	3	
Sepsis	1	0	
Gastrointestinal complications	24 (16.0)	8 (6.3)	0.01¶,
Ileus	8	2	
Vomiting	14	4	
Diarrhea	2	2	
Cardiovascular complications	4 (2.7)	0 (0.0)	0.13¶
DVT/PE	4	0	
MI	0	0	
Stroke	0	0	
Readmission	13 (8.7)	14 (10.9)	0.55†
Death within 60 days	1 (0.7)	0 (0.0)	1.0†
Events per patient (95% CI)	0.56 (0.40 to 0.64)	0.36 (0.28 to 0.45)	0.0009**§

*χ^2 test.
†Fisher's exact test.
‡Mann–Whitney Test.
§Including colloid, crystalloid, and blood products.
¶Fisher's exact test for category
**N-1 χ^2 test
DVT, deep vein thrombosis; ICU, intensive care unit; MI, myocardial infarction; NED, no evidence of disease; PE, pulmonary embolism; pRBCs, packed red blood cells; TIVA, total intravenous anesthesia; UTI, urinary tract infection.

previously might never have gone to surgery because of the perceived high risk of perioperative morbidity.

We found that patients who underwent surgery during the post-ERAS period were more likely to have resumption of chemotherapy at both 28 days and 37 days postoperatively, despite being a higher risk surgical population. Importantly, after controlling for factors known to influence timely return to intended oncology treatment, ERAS remained the strongest predictor of timely resumption of adjuvant chemotherapy. There are two potential explanations for this. First, we suspect that ERAS interventions allowed patients to maintain their normal physiology postoperatively and thus recover faster from surgery, consistent with the goal of ERAS protocols. At our institution, the decision to resume chemotherapy is made at the 2-3 week postoperative visit. Although the decision is left to the discretion of the patient's physician, it is based on an objective assessment of the patient's recovery from surgery, including their ability to present

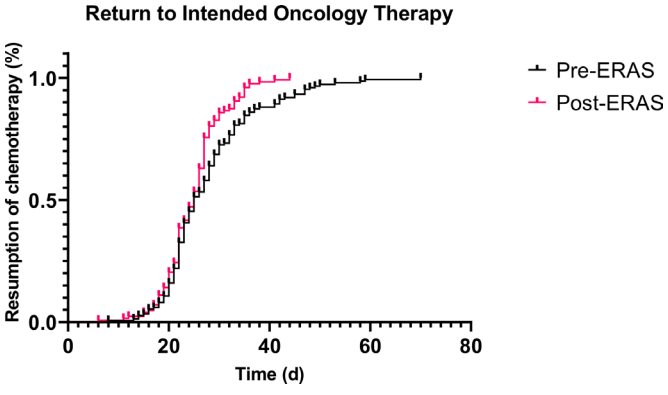

Figure 2 Kaplan–Meir plot of return to intended oncologic therapy at 28 days after surgery. ERAS, enhanced recovery after surgery.

Table 3 Multivariate logistic regression analysis for predictors of timely return to intended oncology treatment

Variable	ORs	95% CI	P value
ERAS (yes, no)	10.18	5.349 to 20.32	<0.0001
Age (years)	1.014	0.9862 to 1.044	0.3270
Body mass index (kg/m^2)	0.9741	0.9319 to 1.018	0.2419
Smoking (yes, no)	2.026	0.6656 to 6.354	0.2137
Diabetes (yes, no)	0.9030	0.3420 to 2.460	0.8383
Stage (III vs IV)	1.278	0.7316 to 2.242	0.3887
Estimated blood loss (ml)	0.9998	0.9990 to 1.001	0.6129
Operating room time (min)	1.005	0.9984 to 1.011	0.1573
Length of stay (days)	1.101	0.9419 to 1.302	0.2326
Preoperative cycles (n)	0.9993	0.7221 to 1.387	0.9967
Bowel surgery (yes, no)	0.3176	0.1217 to 0.8084	0.0171

ERAS, enhanced recovery after surgery.

to clinic, their performance status, lack of laboratory abnormalities that would preclude starting chemotherapy, and adequate wound healing. This assessment is important as the toxicity of chemotherapy might be more severe in patients who have not fully recovered from surgery. It is reasonable to assume that the difference in timely return to intended oncology treatment flowed, at least in part, from the physician's assessment of the patient's readiness to receive chemotherapy. Second, the pre-ERAS cohort had more postoperative complication events per person, and some of these complications led to prolonged hospitalization. Surgical postoperative complications have been shown to delay return to intended oncologic treatment.[20 21] The standardization of perioperative care after the implementation of ERAS reduced the variability in the perioperative course, thus limiting the population of outlier patients who experienced significantly delayed resumption of oncologic treatment.

Previous studies have shown that a minimum of 70% compliance with an ERAS protocol is needed to result in improved outcomes.[7 22–24] Aarts et al conducted a prospective study to determine which component of ERAS had the greatest impact on recovery and determined it was compliance with the postoperative components.[25] Interestingly, our study identified intraoperative compliance as the variable that was most correlated with timely return to intended oncology treatment. While we cannot determine precise causation, the intraoperative ERAS compliance metrics in our protocol specifically include an emphasis on establishing euvolemia and avoidance of long acting opioids. These factors strongly influence early patient mobilization, which has previously been identified as the strongest predictor for postoperative complications.[8 26] Possible reasons for this are that patients receiving too little volume intraoperatively are prone to hypotension, while patients receiving too much volume risk fluid overload, with lower extremity and pulmonary edema and arrhythmias. Either extreme limits patient mobility. Similarly, patients receiving long acting opioids are less likely to ambulate on the day of surgery due to over sedation, and they are prone to the effects of respiratory depression, such as pneumonia and hypoxia.

Strengths and Weaknesses

We acknowledge that our study has several limitations. First, the inherent nature of the retrospective study design may result in potential under-reporting of complications. However, given that the post-ERAS data were entered prospectively, any bias in assessment of complications should serve to overestimate complications in the post-ERAS group and underestimate them in the pre-ERAS group. Even so, complications were lower post-ERAS. In addition, the small sample size and single institution experience limits the study's generalizability and imposes bias. We focused on the patient population receiving neoadjuvant chemotherapy and interval debulking; thus our findings cannot be directly applied to patients undergoing primary cytoreductive surgery or receiving adjuvant radiation therapy. Finally, although we believe that timely return to intended oncology treatment is a meaningful marker for assessing outcomes in gynecologic oncology, no studies have demonstrated that timely return to intended oncology treatment directly affects progression-free and overall survival in this population.

Implications for Practice and Future Research

This study answers the growing call for investigations related to ERAS that focus on functional recovery after surgery and long term outcomes. While we hypothesize that a higher rate of timely return to intended oncologic treatment with an ERAS protocol in place was due to better perioperative recovery, in this study we did not determine the exact factors influencing the decision to restart chemotherapy for each patient. This would be an interesting subject for a future study.

CONCLUSIONS

In conclusion, the impact of ERAS protocols was not limited to the perioperative period but affected the broader oncologic treatment paradigm by supporting timely resumption of adjuvant therapy. Given the previously published association between timely return to intended oncology treatment and improved disease free and overall survival in other populations undergoing oncologic surgery, these results suggest that implementation of ERAS protocols may contribute to improved oncologic outcomes in this population.

Author affiliations
[1]Department of Obstetrics and Gynecology, Gynecologic Oncology, Washington University in St Louis, St Louis, Missouri, USA
[2]Division of Gynecologic Oncology, Department of Obstetrics, Gynecology, and Reproductive Biology, Brigham and Women's Hospital, Boston, Massachusetts, USA
[3]Harvard Medical School, Boston, Massachusetts, USA
[4]Department of Obstetrics and Gynecology, St Francis Hospital, Hartford, Connecticut, USA
[5]Dana-Farber Cancer Institute, Boston, Massachusetts, USA

Twitter Kevin M Elias @kevin_elias

Contributors JIT led the study, primarily led the conceptualization, data curation, and formal analysis of the study, wrote the original draft of the manuscript, and reviewed, edited, and approved the final version of the manuscript. OF collected data for the study and contributed to the drafting, review, and editing of the manuscript. MF and RK assisted in data collection and analysis. KE supervised the conceptualization, design, statistical analysis, and writing of the manuscript.

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ORCID iD
Joan Isabelle Tankou http://orcid.org/0000-0003-0568-6462

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