Patient-reported nausea after implementation of an enhanced recovery after surgery protocol for gynae-oncology patients

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/ijgc-2023-004356).

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Received 12 February 2023
Accepted 2 June 2023
Published Online First 14 July 2023

► http://dx.doi.org/10.1136/ijgc-2023-004355

To cite: Lindemann K, Heimisdottir Danbolt S, Ramberg L, *et al. Int J Gynecol Cancer* 2023;**33**:1287–1294.

ABSTRACT

Objectives This study aimed to analyze the adherence to strategies to prevent post-operative nausea and vomiting after implementation of an enhanced recovery after surgery (ERAS) protocol for gynae-oncology patients. Patient-reported nausea before and after ERAS was also studied.

Methods This prospective observational study included all patients undergoing laparotomy for a suspicious pelvic mass or confirmed advanced ovarian cancer before (pre-ERAS) and after the implementation of ERAS (post-ERAS) at Oslo University Hospital, Norway. Patients were a priori stratified according to the planned extent of surgery into two cohorts (Cohort 1: Surgery of advanced disease; Cohort 2: Surgery for a suspicious pelvic tumor). Clinical data including baseline characteristics and outcome data were prospectively collected.

Results A total of 439 patients were included, 243 pre-ERAS and 196 post-ERAS. At baseline, 27% of the patients reported any grade of nausea. In the post-ERAS cohort, statistically significantly more patients received double post-operative nausea and vomiting prophylaxis (64% pre-ERAS vs 84% post-ERAS, p<0.0001). There was no difference in the need for rescue medication (82% pre-ERAS vs 79% post-ERAS; p=0.17) and no statistically significant difference between pre- and post-ERAS or between the surgical cohorts in patient-reported nausea of any grade on day 2. Patients who reported none/mild nausea on day 2 had significantly less peri-operative fluid administered during surgery than those who reported moderate or severe nausea (median 12.5 mL/kg/hour vs 16.5 mL/kg/hour, p=0.045) but, in multivariable analysis, fluid management did not remain significantly associated with nausea.

Conclusion Implementation of an ERAS protocol increased the adherence to post-operative nausea and vomiting prevention guidelines. Nausea, both before and after laparotomy, remains an unmet clinical need of gynae-oncology patients also in an ERAS program. Patient-reported outcome measures warrant further investigation in the evaluation of ERAS.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Implementation of an ERAS protocol in patients undergoing surgery for suspected or advanced ovarian cancer is feasible. There are insufficient data on the benefit for patient-reported outcome measures such as post-operative nausea and vomiting.

WHAT THIS STUDY ADDS

⇒ Implementation of ERAS leads to increased adherence to guidelines for post-operative nausea and vomiting prophylaxis. Despite the increased use of double prophylaxis, standardization of fluid management and fasting times, and a revised algorithm for rescue medicine, post-operative nausea and vomiting remains a significant burden for all patients undergoing laparotomy for (advanced) ovarian cancer.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Optimization of post-operative nausea and vomiting prophylaxis may include better triage of patients and prolonged nausea treatment for those at particularly high risk. The high patient-reported symptom burden supports a multimodal approach to improve post-operative nausea and vomiting.

INTRODUCTION

Enhanced recovery after surgery (ERAS) protocols provide evidence-based care for surgical patients with the aim of facilitating recovery through a reduction in surgical stress and maintenance of normal physiology.[1] Several protocols have been published in gynae-oncology,[2–5] and the ERAS guidelines for gynae-oncology patients have recently been updated.[6] Evaluations of ERAS pathways have primarily focused on traditional measures such as length of stay and complication rates, but patient-reported outcome (PRO) measures have received little attention.[7–9]

Post-operative nausea and vomiting is a common and distressing side effect for gynecological patients undergoing surgery.[10] Despite a good understanding of the pathophysiology of post-operative nausea and vomiting and the availability of a variety of anti-emetics, post-operative nausea and vomiting affects approximately 30–50% of patients who receive general

anesthesia.[11] Several risk factors have been identified for post-operative nausea and vomiting including age >50 years, gynecologic surgery, laparoscopic surgery, female gender, history of post-operative nausea and vomiting or motion sickness, non-smoking, use of volatile anesthetics, and post-operative opioid use.[11] Based on these risk factors, patients undergoing surgery for gynecological cancer are at a high risk of developing post-operative nausea and vomiting. Mitigation strategies, which are embedded in most ERAS protocols, include the administration of multidrug anti-emetic prophylaxis to all patients receiving abdominal surgery, the avoidance of volatile anesthetics, the use of propofol infusions, and reduced opioid use.[6] The guidelines also emphasize the importance of pre-operative counseling to help set expectations about surgical and anesthetic procedures. Appropriate pre-operative counseling may diminish fear, fatigue and pain, and enhance recovery and early discharge.[12]

The aim of the study was to determine the adherence to strategies to prevent post-operative nausea and vomiting in an ERAS protocol and to explore patient-reported nausea as well as the use of post-operative rescue medicine after surgery for suspected or advanced ovarian cancer after the implementation of ERAS.

METHODS

Study Design and Population

This is a prospective observational study that included all patients undergoing (midline) laparotomy for a suspicious ovarian mass or confirmed advanced ovarian cancer between May 2017 and June 2019 at the Department of Gynecological Oncology, Norwegian Radium Hospital, Oslo University Hospital, Norway. Patients were included prior to the implementation of ERAS (pre-ERAS) from May 15, 2017 to May 6, 2018, and after the implementation of ERAS (post-ERAS) from May 7, 2018 to June 3, 2019. The key elements of the ERAS protocol are listed in Table 1. The patients were a priori stratified according to the planned extent of surgery into two cohorts. Cohort 1 'advanced' included patients planned for surgery of advanced disease, and in Cohort 2 'suspected', patients underwent surgery of a pelvic tumor suspicious of ovarian cancer. The key elements of the ERAS protocol are listed in Online Supplemental Table 1. Adherence to the ERAS protocol has been reported elsewhere (Lindemann *et al*[13]).

Baseline Characteristics and Outcome Measures

Clinical data (baseline characteristics, details on anesthesia, perioperative management and outcome data) were prospectively collected and validated against the electronic medical records.

Table 1 Baseline characteristics

Characteristic		Pre-ERAS* (n=243)	Post-ERAS* (n=196)	P value
Age (years), median (IQR) (n=439)		64 (53–71)	65 (54–72)	0.25
Weight (kg), median (IQR) (n=439)		68 (61–78)	74 (64–82)	0.0060
ESAS nausea (n=379)	None	138/199 (69%)	137/180 (76%)	0.53
	Mild	44/199 (22%)	31/180 (17%)	
	Moderate	12/199 (6%)	8/180 (5%)	
	Severe	5/199 (3%)	4/180 (2%)	
Cohort 1 'advanced' (n=235)		118/243 (49%)	117/196 (60%)	0.021
Cohort 2 'suspected' (n=204)		125/243 (51%)	79/196 (40%)	
ASA score (n=435)	I	23/241 (10%)	6/194 (3%)	0.045
	II	166/241 (69%)	146/194 (75%)	
	II	49/241 (20%)	38/194 (20%)	
	IV	3/241 (1%)	4/194 (2%)	
Age-adjusted Charlson Comorbidity Index (n=439)	<6	229/243 (94%)	187/196 (95%)	0.97
	≥6	14/243 (6%)	9/196 (5%)	
Surgical complexity score† (n=439)	Low	138/243 (57%)	113/196 (58%)	
	Intermediate	84/243 (34%)	64/196 (32%)	
	High	21/243 (9%)	19/196 (10%)	
Pre-operative albumin (n=434)	<35	20/239 (8%)	10/195 (5%)	0.25
	≥35	219/239 (92%)	185/195 (95%)	
Multi-drug PONV prophylaxis (n=439)		155/243 (64%)	164/196 (84%)	<0.0001

*Total number of patients with available data on any specific characteristic are included in the table.
†Aletti surgical complexity score.[15]
ASA, American Society of Anesthesiologists physical status classification system; ESAS, Edmonton Symptom Assessment System; PONV, post-operative nausea and vomiting.

The age-adjusted Charlson Comorbidity Index was used to categorize comorbidity.[14] We further used the Alletti surgical complexity score[15] to categorize procedures into low (≤3), intermediate (4–7), and high complexity (≥8). The mean daily doses of opioid analgesics were calculated in oral morphine equivalents.

Patient-Reported Outcome Data

The administration of the Edmonton Symptom Assessment System, revised version 2010 (ESAS-r) questionnaire is part of the standard pre-operative assessments at our department. ESAS-r questionnaires were administered at baseline (day 0) and post-operative days 2 and 4. ESAS-r is a patient-reported outcome tool covering 10 of the most common symptoms in cancer patients which are rated on a Likert scale from 0 to 10. ESAS-r scores of 0, 1–3, 4–6, and 7–10 were categorized as none, mild, moderate, and severe symptoms.[16 17]

Statistical Analysis

Demographic and clinical characteristics were described by the proportion of included patients for categorical variables and the median and IQR for continuous variables. Associations between categorical variables were evaluated using Fisher's exact test whenever practically feasible and otherwise indicated specifically when Pearson's χ^2 test was used. The Kruskal–Wallis H test was used to evaluate associations between a continuous and a categorical variable. Multivariable logistic regression analysis was performed with nausea (moderate/severe vs none/mild) at post-operative day 2 as a dependent variable and the following independent variables: peri-operative fluid administration (continuous variable), surgical complexity score (variable with three categories), cohort (2 'suspected' vs 1 'advanced'), surgery time (continuous variable), double prophylaxis (yes vs no), and oral morphine equivalent dose (continuous variable). The regression analysis and all analyses of associations included only patients with non-missing values for the variables under consideration. A two-sided p value <0.05 was considered statistically significant. All statistical analyses were carried out with Stata/SE 16.1 (Stata Corp LP, Texas, USA).

RESULTS

Patient Characteristics

We consecutively included 439 patients in our study, 243 in the pre-ERAS group and 196 patients had surgery after the implementation of ERAS (post-ERAS) (Lindemann *et al*[13]). Baseline characteristics and details on surgical procedures are shown in Table 1. Age, self-reported nausea, age-adjusted Charlston Comorbidity Index, and surgical complexity score were not statistically significantly different between the pre- and post-ERAS cohorts, but there was a significant difference in the distribution of the American Society of Anesthesiologists score (ASA score) (p=0.041)[18] and weight (p=0.006). Data on ESAS-r were not available for 13% of the patients at baseline, 25% on day 2, and 37% on day 4. Because of the relatively high number of patients who were not evaluable on day 4 (either due to discharge or missing data), this report focuses on patient-reported nausea on day 2.

Prevalence of Key Patient-Reported Outcomes including Nausea

At baseline, patients in both cohorts reported a considerable symptom burden (Table 2), including psychological symptoms such as depression and anxiety. There were no statistically significant differences in quality of life domains pre- and post-ERAS apart from statistically significantly more patients in cohort 2 reporting moderate or serious pain (16% pre-ERAS vs 4% post-ERAS, p=0.016). At baseline, 31% of the patients reported any grade of nausea (mild, moderate or severe) in the pre-ERAS group and 24% in the post-ERAS group (p=0.17), corresponding to 27% in the total study population. The majority of these patients reported mild symptoms (Table 1). There was no statistically significant difference in patient-reported nausea of any grade between the surgical cohorts (31% cohort 1 vs 23% cohort 2; p=0.083).

Adherence to ERAS Elements Preventing Post-operative Nausea and Vomiting

Post-ERAS, a significantly higher proportion of patients received double post-operative nausea and vomiting prophylaxis with dexamethasone and ondansetron in both cohorts combined (84% post-ERAS vs 64% pre-ERAS, p<0.001). Combination anesthesia was used in 98% of patients post-ERAS and 97% pre-ERAS. Propofol and fentanyl were used to induce anesthesia. Muscle relaxation was obtained with rocuronium and anesthesia was maintained with fentanyl supplementation and desflurane inhalation. Total intra-venous anesthesia with propofol and remifentanil was used in the remaining patients. Thoracic epidural anesthesia was used in 98% and 97% of the patients post- and pre-ERAS, respectively, with continuous epidural infusion of a standardized epidural mixture (bupivacain 1 mg/mL, fentanyl 2 µg/mL, adrenalin 2 µg/mL). Peri-operative fluid administration in both surgical cohorts was significantly reduced after the implementation of ERAS to 11.5 mL/kg/hour (IQR 9.0–15.4) compared with 15.8 mL/kg/hour pre-ERAS (IQR 0.8–22.5) (p<0.001). There was also a significant reduction in oral morphine equivalent dose to a median of 116 mg in the post-ERAS cohort compared with 136 mg pre-ERAS (p=0.002).

There was no difference in the need for rescue medication pre- and post-ERAS (79% post-ERAS vs 82% pre-ERAS in need of at least one rescue medication; p=0.40). The most commonly prescribed rescue drug post-ERAS was ondansetron (55%), with a decrease in the use of metoclopramide to 46% post-ERAS compared with 75% pre-ERAS (p<0.0001). There was an increased use of droperidol post-ERAS (46% post-ERAS vs 23% pre-ERAS, p<0.0001) and cyclizine (44% post-ERAS vs 30% pre-ERAS, p=0.0028). The majority of patients (66%) required a maximum of two different drugs as rescue medication, with no significant difference between pre- and post-ERAS (68% and 61%, respectively, p=0.13).

Patient-Reported Nausea

On day 2 almost one-third (30%) of all patients who reported nausea reported mild symptoms, while more than half (53%) reported no nausea of any grade. There was no statistically significant difference between pre- and post-ERAS or between the surgical cohorts in patient-reported nausea of any grade on day 2 (Figure 1). The largest difference was observed for cohort 2 'suspected', where post-ERAS 64% reported no nausea of any grade compared with 50% pre-ERAS, but this difference was not statistically significant

Table 2 Baseline quality of life domains in the whole cohort on day 0

Quality of life domain		Cohort 1 Pre-ERAS* (n=118)	Cohort 1 Post-ERAS* (n=117)	Cohort 1 P value	Cohort 2 Pre-ERAS* (n=125)	Cohort 2 Post-ERAS * (n=79)	Cohort 2 P value
Lack of well-being	None/mild	46/92 (50%)	62/110 (56%)	0.40	49/98 (50%)	37/67 (55%)	0.53
	Moderate/serious	46/92 (50%)	48/110 (44%)		49/98 (50%)	30/67 (45%)	
Fatigue	None/mild	58/94 (62%)	66/111 (59%	0.78	76/105 (72%)	58/69 (84%)	0.97
	Moderate/serious	36/94 (38%)	45/111 (41%)		29/105 (28%)	11/69 (16%)	
Drowsiness	None/mild	72/95 (76%)	77/111 (69%)	0.35	84/104 (81%)	61/69 (88%)	0.21
	Moderate/serious	23/95 (24%)	34/111 (31%)		20/104 (19%)	8/69 (12%)	
Pain	None/mild	77/95 (81%)	96/111 (86%)	0.34	87/104 (84%)	66/69 (96%)	0.016
	Moderate/serious	18/95 (19%)	15/111 (14%)		17/104 (16%)	3/69 (4%)	
Lack of appetite	None/mild	66/95 (69%)	84/111 (76%)	0.35	81/105 (77%)	59/69 (86%)	0.24
	Moderate/serious	29/95 (31%)	27/111 (24%)		24/105 (23%)	10/69 (14%)	
Dyspnea	None/mild	80/95 (84%)	91/111 (82%)	0.71	90/105 (86%)	65/69 (94%)	0.09
	Moderate/serious	15/95 (16%)	20/111 (18%)		157 105 (14%)	4/96 (6%)	
Depression	None/mild	71/95 (75%)	88/110 (80%)	0.40	86/105 (82%)	52/96 (75%)	0.34
	Moderate/serious	24/95 (25%)	22/110 (20%)		19/105 (18%)	17/96 (25%)	
Anxiety	None/mild	62/94 (66%)	87/110 (79%)	0.04	69/103 (67%)	50/67 (75%)	0.31
	Moderate/serious	32/94 (34%)	23/110 (21%)		34/103 (33%)	17/67 (25%)	

*The total number of patients with available data on any specific quality of life domain are included in the table.

(p=0.10). The corresponding percentages in cohort 1 'advanced' were more similar, being 53% post-ERAS and 48% pre-ERAS (p=0.53). The proportion of patient-reported moderate or severe nausea on day 2 in cohort 1 was also similar post- and pre-ERAS with 15% and 20%, respectively (p=0.54). In cohort 2, 14% reported moderate or severe nausea post-ERAS compared with 18% pre-ERAS (p=0.51). There was also no statistically significant difference between cohorts 1 and 2 with regard to reported moderate or severe nausea on day 2 (p=0.88; p=0.85 pre-ERAS and p=1.00 post-ERAS).

Surgical complexity in both cohorts was characterized by the surgical complexity score categorized into low, intermediate, and high complexity. There was no significant association between surgical complexity score groups and reported nausea of any grade on day 2 (p=0.81) (Figure 2).

Self-reported Nausea and Administration of Rescue Medicine

The grade of self-reported nausea on day 2 was associated with number of drugs used as rescue medicine (p<0.0001 using Pearson's $\chi 2$ test). Of the patients who reported mild symptoms of

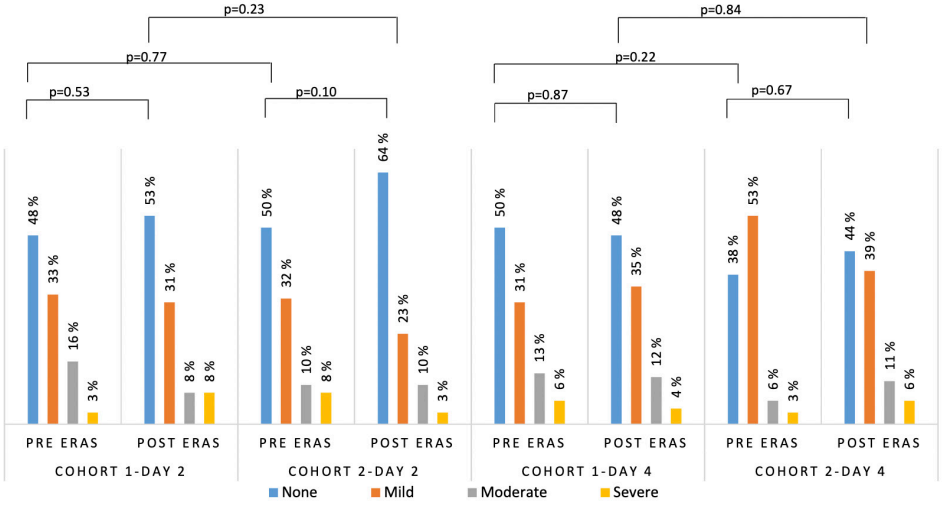

Figure 1 Patient-reported nausea by surgical cohort and enhanced recovery after surgery (ERAS). Each p-value is from testing the association between none and some (mild, moderate, or severe) patient-reported nausea and either ERAS or surgical cohort

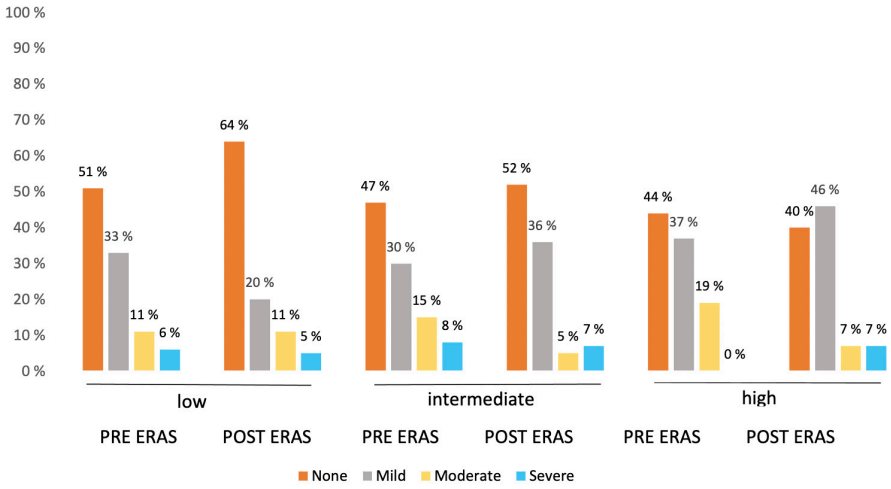

Figure 2 Patient-reported nausea on day 2 by surgical complexity score and enhanced recovery after surgery (ERAS).

nausea on day 2, only 8% needed four different drugs of rescue medicine compared with 47% of those who reported severe nausea (see Online Supplemental Table 2).

Association between Post-operative Nausea and Vomiting and Peri-operative Management

Patients who reported none or mild nausea on day 2 had significantly less peri-operative fluid administered during surgery than those who reported moderate or severe nausea (median 12.5 mL/kg/hour vs 16.5 mL/kg/hour, p=0.045). There was no significant association with any of the other peri-operative variables studied (Table 3). We explored the association between peri-operative fluid administration and self-reported nausea further and observed that the association was not statistically significant in multivariable logistic regression analysis (p=0.285). As almost all patients received combination anesthesia, we could not show any association between type of anesthesia and prevalence of post-operative nausea and vomiting.

DISCUSSION

Summary of the Main Results

This is the first prospective study evaluating patient-reported nausea in patients undergoing laparotomy for suspected or advanced ovarian cancer in an ERAS pathway. Implementation of ERAS led to a significant increase in the use of state-of-the-art double post-operative nausea and vomiting prophylaxis in patients undergoing laparotomy in both surgical cohorts. Despite the increased use of double prophylaxis, standardization of fluid management and fasting times, and a revised algorithm for rescue

Table 3 Selected patient characteristics by patient-reported nausea on day 2

Characteristics	All	None/mild	Moderate/severe	P value
Patients, n (%)	439	266	55	
Cohort 1	235 (54%)	136 (51%)	29 (53%)	0.88
Cohort 2	204 (46%)	130 (49%)	26 (47%)	
Double prophylaxis, n (%)				0.41
No	120 (27%)	76 (29%)	12 (22%)	
Yes	319 (73%)	190 (71%)	43 (78%)	
OMEQ (mg), median (IQR)	128 (89–177)	128 (96–176)	130 (96–176)	0.81
Peri-operative fluid management (ml/kg/hour), median (IQR)	13.3 (9.7–19.7)	12.5 (9.4–19.3)	16.5 (10.5–20.9)	0.045
Surgical complexity score, n (%)				0.84
Low	251 (57%)	154 (58%)	30 (55%)	
Intermediate	148 (34%)	86 (32%)	20 (36%)	
High	40 (9%)	26 (10%)	5 (9%)	
Surgery time (hours), median (IQR)	2.4 (1.7–3.8)	2.3 (1.8–3.7)	2.6 (1.6–3.6)	0.81

OMEQ, oral morphine equivalent dose.

medicine in our ERAS protocol, post-operative nausea and vomiting remains a significant burden for our patients.

Results in the Context of Published Literature

There are only a few studies in patients with gynecologial cancer that have focused on patient-reported outcomes in an ERAS context[8 9] and, to our knowledge, none have focused on nausea. In a recent study on post-operative nausea and vomiting in patients undergoing mastectomy in an ERAS program, any anti-emetic administered to diminish nausea or vomiting in the protocol led to a lower incidence of post-operative nausea and vomiting from 50% to 28%.[19]

Implementation of ERAS led to a change in the use of rescue medicine in line with post-operative nausea and vomiting prophylaxis recommendations, with a significant decrease in the use of metoclopramide as rescue medicine. Ondansetron was still the most common rescue medicine, and institutional guidelines may need to specify that a different drug class should be used in the treatment of post-operative nausea and vomiting in patients who have received ondansetron as part of post-operative nausea and vomiting prophylaxis. Updated guidelines for high-risk patients recommend that double prophylaxis with dexamethasone and a 5-HT3 receptor antagonist should be supplemented by additional anti-emetic prophylaxis with a different mechanism of action or by strategies to reduce risk factors such as the avoidance of volatile anesthesia.[12]

The search for the best cost-effective approach to post-operative nausea and vomiting is far from complete.[20] Newer drugs have therefore been studied in preventing post-operative nausea and vomiting. Aprepitant, a neurokinin-1 antagonist, was observed to be significantly more effective than ondansetron for preventing vomiting at 24 and 48 hours after surgery,[21] but its superiority in preventing post-operative nausea and vomiting in combination with steroids is still unclear. Amisulpride prevents post-operative nausea and vomiting in high-risk patients[22 23] and is the only FDA-approved anti-emetic for rescue treatment after failed prophylaxis.

Other strategies include avoidance of volatile gases such as total intra-venous anesthesia with appropriate monitoring, but may be challenging in patients undergoing long-lasting surgeries.[24 25] Implementing a risk-stratified nausea management and prolonged nausea prophylaxis instead of on demand medication may also be considered. More research is needed to understand the efficacy of opioid-free analgesia for laparotomy in gynecological cancer.[26 27] Furthermore, other aspects such as the role of non-pharmacological interventions need further investigation.[12]

In our study there was no statistically significant increase in patient-reported nausea with increasing surgical complexity. Little is still known about the risk of patient-reported nausea for those undergoing complex surgeries. Our ERAS protocol also included other strategies to prevent post-operative ileus such as chewing gum and shortened fasting times. Consequently, the complexity of the surgery may be a less prominent risk factor for post-operative nausea and vomiting than previously reported.[28] Our findings indicate that factors other than complexity of surgery may play an important role in post-operative nausea and vomiting, and fluid management according to international guidelines remains crucial when aiming at optimal post-operative nausea and vomiting prophylaxis.[29]

Almost one-third of our patients reported some grade of nausea at baseline, independent of disease status. Increased awareness of this symptom and pre-operative management is also important to reduce symptom burden after surgery. Patients with advanced disease often present with a high symptom burden including abdominal distension, dyspnea, nausea, and impaired gastrointestinal function. However, the causes of nausea may be multifactorial and reasons other than disease burden may explain the high prevalence of pre-operative nausea in the 'suspicious' cohort. Self-reported nausea was highly correlated with other patient-reported outcomes such as anxiety, depression, pain, and lack of appetite (data not shown), and there is a need to individualize pre-operative management. Verbalized education, leaflets, and multimedia platforms containing information on expected pre-, peri- and post-operative symptoms and management may improve pain control, nausea, and anxiety before and after surgery. However, evidence on the efficacy of psycho-educative interventions is largely lacking. Studies have shown that multimodal pre-rehabilitation programs in major cancer surgeries may improve patient outcomes, but the studies are heterogeneous and high-level evidence is still lacking.[30]

Strengths and Weaknesses

The strengths of the study include the prospective assessment of clinical variables both in the pre- and post-ERAS period, as well as the analysis of consecutive patients undergoing laparotomy for suspected or advanced ovarian cancer. Clinical data include adherence measures which are crucial when evaluating the effect of implementing an ERAS pathway and the study confirms good compliance with the ERAS protocol. The limitations of the study include the fact that nausea was reported with ESAS-r, which is not a validated post-operative instrument but a validated symptom assessment instrument in both clinical practice and research regarding cancer patients[16] and for symptoms such as nausea. This was a pragmatic study conducted in clinical practice where ESAS-r was already implemented, which ensured the availability of baseline assessments and satisfactorily high completion rates post-operatively. Other scales are available, both general patient-reported outcome tools used in ovarian cancer such as the MD Anderson Symptom Inventory-Ovarian Cancer[8] and specific tools to capture post-operative nausea and vomiting,[31] and there is a need to harmonize the measurement and reporting of patient-reported outcomes in ERAS studies. The effect of the non-responders in the analysis of patient-reported outcomes is particularly important because of the possibility of a non-response bias. We consider this risk as low because the proportion of non-responders was similar at baseline pre-ERAS and post-ERAS. However, reasons for missing data were not assessed and we therefore cannot rule out that non-response bias has influenced our results. There were also differences in the patient-reported symptom burden at baseline, such as pain, with more patients in cohort 2 reporting a higher level of pain pre-ERAS.

Implications for Practice and Future Research

Even though adherence to strategies to prevent post-operative nausea and vomiting was improved after the implementation of an ERAS protocol, prevention of nausea before and management of worsening after open surgery is still an unmet clinical need of gynae-oncology patients in an ERAS program. Advances

in our understanding of peri-operative nausea and its prevention and treatment could contribute to increased patient satisfaction, reduced post-operative morbidity, and ultimately shortening of hospital stays. More research on effective mitigation strategies for post-operative nausea and vomiting in an ERAS protocol is needed, and this study provides important baseline data to determine effect size in an intervention study.

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Acknowledgements We would like to thank Prof Dr Dr h.c. Andreas du Bois, Dr Philipp Harter and Dr Stephanie Schneider at the Department of Gynecology and Gynecological Oncology, Kliniken Essen Mitte, Essen, Germany for their collaboration in setting up the data collection sheet and for the scientific discussions around ERAS when we planned this project. We also thank all staff members at our department for their contribution to data collection and commitment to ERAS. We further acknowledge the support of Farah Naseem and cand med Tuan-Khanh Nguyen in data collection. We would like to thank the MUHC Patient Education Office, McGill University Health Center, Quebec, Canada for their support throughout the development of the patient education material.

Contributors KL: Project initiation, design and methodology, project oversight including funding acquisition, monitoring of data collection, ethical approval, contributed to the initial version of the manuscript, revision of the paper. SHD: Data collection, contribution to drafting the initial version of the manuscript, visualization and interpretation of results. Full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish. LR: Contribution to drafting the initial version of the manuscript, visualization. BE: Project design, data collection, interpretation of results, revising the manus. YYW: Design of data collection tools, data collection. AGH-H/SLW: Project design, design of data collection tools, interpretation of results. OM/GAN/SH: Project design, interpretation of results. KEJ-H: Project design, interpretation of results. LKB/RO: Methodology, supervision, interpretation of results. AK: Statistical analysis plan and statistical analysis, interpretation of results, contributed to initial draft of the manuscript. UK: Design and methodology, interpretation of results, contributed to initial draft of the manuscript. All authors contributed to revision of the final manuscript and read and approved the final version of the paper.

Funding This work was supported by the Radiumhospitalets Legater.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Patient privacy was protected by coding and processing all data anonymously. Approval from the Oslo University Hospital integrated Data protection authority was granted on July 4, 2017 (ID: 2017/7007).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. We will provide our data for the reproducibility of this study in other centers if such is requested. Such sharing would require approval by the data protection office at Oslo University Hospital.

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Supplementary tables:

Supplementary table 1: Key elements of the ERAS protocol implemented at the Department of gynecological oncology, Oslo University Hospital

Phase	Measures pre-ERAS	Measures post-ERAS
Preoperative	• Oral, not-standardized information, education and counselling	• Information, education and counselling, preferably together with relatives based on an ERAS specific leaflet (oral and written) • Stop smoking • Nutritional screening with subsequent nutritional support • Patient diary and information about discharge home criteria
Day before surgery (-1)	• No standardized procedure for bowel preparation for patients in cohort 1, rectal enema for patients in cohort 2. • No fluids or solids after 24:00	• Standardized procedures for bowel preparation (no routine oral bowel preparation, rectal enema for patients in cohort 1) • No long-acting sedatives • Solid foods until 24:00, encourage light meal 21.00-24-00
Perioperatively	• Active body heating • No guidance for nasogastric tubes or drains • Standardized combined anaesthetic (including thoracal epidural) • No guidance for fluid management • No specific guidance for vasopressor use	• Active body heating, specified target temperature >36 degrees • Avoidance of nasogastric tube after surgery • Avoidance of abdominal drains • Standardized combined anaesthetic (including thoracal epidural) • Standardized fluid management: Maintenance peri-operatively: Ringer's acetate 5 ml/kg/h, infusion pump is used; antibiotic liquid is included in the fluid balance; extra fluid guided by BT, pulse, TD, peripheral capillary response, PPV, consider use of Lidco, target MAP >60mmHg; consider albumin if colloids are needed; blood loss is replaced with erythrocyte concentrates; FFP if bleeding > 50% of the blood volume of the blood volume if still ongoing bleeding; fluid balace at the end of the operation; ascites is included in the fluid balance, but not replaced. perspiratio and 3-room losses are not included. • Liberal use of vasopressor medications
Day 0	• No guidance for fluid management • No guidance on oral intake	• 300 ml cordial drink 2 hours before surgery • Standardized fluid treatment: Preferably oral intake, target: 30ml/kg/24h

		• Offer a light meal as soon as possible and start with a nutritional drink (Nutridrink Compact Protein 30 mlx4)

Post-operative	• Encourage early oral intake
	• Encourage mobilization
	• No guidance on tapering of epidural
	• Postoperative management included oral opioids (oxycontin/oxynorm and celekoksib)
		• Standard mobilization including physiotherapy for patients in cohort 1 on day 1 and 2
		• Continuation of nutritional drink 30 ml x 4
		• Standardized anti-emetic treatment
		  ○ 1.choice: Droperidol (Dridol®)
		  ○ 2.choice: Syklizin (Valoid®/Marzine®)
		  ○ 3.choice: Ondansetron (Zofran®)
		  ○ 4.choice: Aprepitant (Emend®)
		• Standard postoperative pain treatment (oxycontin/oxynorm and celekoksib), including tapering of epidural
		• Removal of urinary catheter when epidural <5ml/t
		• Prophylaxis for postoperative ileus
		  ○ Paraffin 30 ml
		  ○ Chewing gum x4 for 30 minutes
		• Discharge criteria

Supplementary Table 2: Use of rescue medicine in groups by patient reported nausea on day 2 (online supplement possible)

Use of Recue Medication	None	Mild	Moderate	Severe	Nausea_d2 Total
0	54	8	1	0	63
1	42	16	5	1	64
2	38	32	14	1	85
3	24	33	8	8	73
4	11	8	8	9	36
Total	169	97	36	19	321

p-value using Pearson's χ^2 test, <0.0001