Master thesis
Department of Gynaecology and Obstetrics

“A systematic review on Enhanced Recovery After Surgery (ERAS) pathways designed for women undergoing elective open abdominal surgery due to advanced ovarian cancer”.

A thesis submitted in part fulfillment for the degree of Master of Medicine.

Ban Shakir
Medical Faculty
Supervisor: Doc. Eimantas Švedas

Lithuanian University of Health Sciences
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SUMMARY

Author’s name and surname: Ban Shakir

Research title: A systematic review on Enhanced Recovery After Surgery (ERAS) pathways designed for women undergoing elective open abdominal surgery due to advanced ovarian cancer.

Aim: To evaluate the effect of implementing ERAS pathways in the surgical management of advanced ovarian cancer.

Objectives: To determine if ERAS pathways (in the treatment of ovarian cancer):

1. Shorten the length of hospital stay
2. Decrease postoperative complications
3. Reduce readmissions
4. Reduce time to tolerance of diet
5. Reduce time to flatus/defecation
6. Improve quality of life
7. Reduce costs

Methodology: I performed a systematic literature search on gynaecological oncology in May 2016 using PubMed/MEDLINE, EMBASE, Cambridge journals online and The Cochrane Library. All study types were included. Using the given keywords I found 34 articles in total. Seven investigations that examined the role of enhanced recovery pathways in gynaecologic oncology were identified. Finally, three of these, which specifically highlight ovarian malignancy, were chosen in the final assessment.

Results: Three non-randomized studies, which investigate the effect of enhanced recovery pathways in the management of ovarian cancer, were selected. Hence, it wasn’t possible to create a forest plot with the results of the aforementioned studies. However, a separate analysis of each study and its’ results was done instead.

The median length of hospital stay in Marx 2006 was reduced from 6 days in the conventional group to 5 days in the enhanced recovery group (p < 0.05) and in Gerardi 2008 from 10 vs 7 days (p = 0.014). The number of 30-day postoperative complications in Marx 2006 was 23 (31.9%) in the conventional group as compared to 17 (24.6%) in the enhanced recovery group (p > 0.05), in Gerardi 2008 28 (62.2%) vs 11 (57.9%) (p = 0.746) and in Eberhart 2008 15 (37.5%) vs 14 (30%). The number of readmissions in Marx 2006 was 7 (12.5%) in the conventional group as compared to 2 (2.9%) in the enhanced recovery group (p > 0.05) and in Gerardi 2008 15 (33.3%) vs 4 days (21.1%)
(p = 0.326). Time to tolerance of diet and/or flatus/defecation was only presented in Gerardi 2008 where the conventional group tolerated oral feeding by day 6 as compared to day 3 in the enhanced recovery group (p = 0.013). Time to flatus was 6 days in both groups (p = 0.630). Eberhart 2008 found that the majority of patients in the enhanced recovery group were fully recovered on the 5th postoperative day, as in comparison to the conventional group, where only 30% of patients had reached that stage. Gerardi 2008 assessed postoperative hospital costs and found that compared to the conventional group, patients in the enhanced group had a significantly lower median 30-day postoperative hospital cost ($19,700 vs $25,110, p=0.028) which means that the introduction of enhanced recovery pathways was associated with a median reduction in hospital cost of $5410 per patient.

**Conclusions:** The implementation of ERAS pathways in gynaecologic oncology enables the patient to recover earlier, hence decreasing the length of hospital stay and consequently hospital costs per patient. According to data from the national cancer institute of Lithuania, ovarian cancer is usually diagnosed in late stage (III-IV), with a peak incidence in women between 60-80 years old. These patients, in particular, would benefit from a systemized perioperative program (such as ERAS) that optimizes their hospital stay, hastens their recovery and improves their quality of life postoperatively.

**Recommendations:** To implement enhanced recovery pathways with the help of ERAS guidelines modified for gynaecologic oncology. Regular audit of the program is also necessary in order to ensure compliance and help medical staff to improve the care delivered to patients.

**Keywords:** Enhanced Recovery After Surgery, Fast Track Surgery, gynaecologic oncology, ovarian cancer.
ACKNOWLEDGEMENTS

I would like to thank my supervisor for encouraging me to write about this topic, which I find important and interesting. I also would like to thank Dr. Laura Malakauskienė, who unofficially acted as my co-supervisor. Moreover, I give thanks to Dr. Vita Špečkauskienė at the department of physics, mathematics and biophysics for helping me find a suitable method while analysing the literature. Dr. Emil Sundström, who helped me create figure 1 (ERAS modified for gynaecological oncology), thanks for your technical brilliance. Finally I would like to thank my dear friend Dr. Imante Lasytė for all the time she invested in order to help me create this thesis, it wouldn’t have been possible to finish it without her guidance and support.
CONFLICT OF INTEREST

The author reports no conflicts of interest.
ABBREVIATIONS LIST

AB - antibiotics
BMI – body mass index
C - Conventional
EOF – early oral feeding
ER – enhanced recovery
ERAS – enhanced recovery after surgery
FTS – fast-track surgery
IV – intravenous
IV-PCA – intravenous patient controlled analgesia
LOS – length of hospital stay
MBP – mechanical bowel preparation
MIS – minimally invasive surgery
PONV – postoperative nausea and vomiting
QoL – quality of life
RCT – randomized controlled trial
SAP – standard anaesthetic protocol
TEA – thoracic epidural analgesia
VTE – venous thromboembolism
INTRODUCTION

Gynaecological malignancies contribute to 10-15% of cancers in women worldwide (1). Ovarian cancer, the sixth most common cancer, accounts for the most frequent cause of death from gynecological malignancies in the Western world (2). According to data from the national cancer institute of Lithuania, the prevalence of ovarian cancer in 2012 accounted for approximately 4% of the most common malignancies in Lithuanian women, with a higher incidence rate (23,4) than compared to Europe (16,8) and the world (12,4) (3). Surgery with/without chemotherapy is proven to have a central role in the treatment of ovarian cancer (1).

Enhanced Recovery after Surgery (ERAS) pathways are multimodal evidence-based treatment protocols designed to optimize the patient’s experience, standardize perioperative care and improve surgical outcomes (4-5). These pathways reduce catabolic insults of surgery and anaesthesia, hence shortening the length of hospital stay and lowering health care costs (5-6). Stress reduction during elective surgical procedures not only provides faster recovery but also improves patient outcome by diminishing the risk of organ dysfunction and postoperative complications, which is of great relevance especially to those with malignant diseases (7-8).

Due to its successful implementation in other surgical specialties, e.g. colorectal surgery, there has been a need of investigating the benefits of ERAS in gynaecological surgical management. Recent prospective studies made in gynaecological literature attest for the safety and improved outcomes having implemented enhanced recovery pathways in gynaecological surgery (9). However, compliance to ERAS in surgical practice is problematic since it requires participation and commitment of the entire surgical care team, which does not only include surgeons but also anaesthesiologists, nurses and physiotherapists. Moreover, ERAS programs incorporate a number of elements that need to be fulfilled in order to achieve results (figure 1). Despite the fact that surgeons already practice most elements, few embrace the entirety of the ERAS concept to gain maximum benefits for the patient (10).

The purpose of this study is to assess the effect of ERAS implementation in the surgical management of ovarian cancer by determining whether it has an impact on certain outcomes such as e.g. length of hospital stay. This will be done by gathering and assessing data from different studies, which specifically address the implementation of enhanced recovery pathways in the surgical management of advanced ovarian cancer.
AIM AND OBJECTIVES

The aim of this study is to evaluate the effect of implementing ERAS pathways in the surgical management of women with advanced ovarian cancer with the help of the following objectives.

Objectives:
To determine if ERAS pathways (in the treatment of ovarian cancer):

1. Shorten the length of hospital stay
2. Decrease postoperative complications
3. Reduce readmissions
4. Reduce time to tolerance of diet
5. Reduce time to flatus/defecation
6. Improve quality of life
7. Reduce costs
LITERATURE REVIEW

Background of ERAS

The original idea concerning the concept of multimodal surgical care, also known as Fast-track Surgery (FTS), was first described by Professor Henrik Kehlet at the University of Copenhagen Denmark. This program was developed in an attempt to improve perioperative care of patients undergoing elective colonic surgery (11). Due to its successful outcome, the concept was further developed by the Enhanced Recovery after Surgery (ERAS) society, which was established in 2001 by Professor Ken Fearon, University of Edinburgh, UK and Professor Olle Ljungqvist, Karolinska Institutet, Sweden. The mission of the Society is to develop perioperative care and to improve patient recovery through research, education, audit and implementation of evidence-based practice (12). Today FTS and ERAS are used as synonyms in surgical terminology, describing the concept of facilitating and expediting the patients’ recovery after major surgical intervention (6). Apart from elective bowel surgery, ERAS programs have been successfully applied in other fields of elective surgery, such as aortic aneurysm (13) and pulmonary lobectomy (14).

Description of the current condition

Ovarian cancer has often been called the “silent killer” because symptoms are not thought to develop until advanced stages when the chance of cure is poor (15). Indeed ovarian cancer continues to hold the dubious distinction as the most deadly of all the gynaecological cancers with more women dying from ovarian cancer than from cervical and uterine cancer combined (10). It has the highest incidence in Scandinavian countries (20/100 000) and lowest in Japan (3/100 000) (1). In the UK the incidence of ovarian cancer over a woman’s lifetime is 1 in 50 according to Cancer research UK 2009. The standard management is surgical staging in early-stage disease and adjuvant therapy for high-risk early-stage patients. Explorative laparotomy and surgical cytoreduction or debulking is the mainstay of treatment in advanced stage disease (10).

Prevalence, incidence and mortality of ovarian cancer in Lithuania during 2012

According to data from the national cancer institute of Lithuania, the prevalence of ovarian cancer in 2012 accounted for approximately 4% of the most common malignancies in Lithuanian women, with a higher incidence rate (23.4) than compared to
Europe (16,8) and the world (12,4). Data also show that the timing of diagnosis was higher in patients with advanced disease; stage III – 28,4% and stage IV – 35%, than compared to stage I – 18,8% and stage II – 4,8 %. The peak incidence according to age is highest in women between 60-80 years old. Mortality among all age groups accounts for 7% of all deadly malignant diseases in Lithuania (3).

**ERAS guidelines for perioperative care in gynaecologic/oncology surgery**

The ERAS program is divided into three main sections; preoperative preparation, intraoperative principles of management and postoperative care. Each section incorporates a number of elements that need to be fulfilled in order to attenuate surgical trauma and consequently maximize benefits for the patient (6). In 2015 standardized evidence-based guideline for gynaecologic oncology surgery was presented by Nelson et al (16-17). This was the result of a review about enhanced recovery pathways in gynaecologic oncology, which showed marked dissimilarities in protocols and highlighted the need of establishing evidence-based guidelines specifically for the management of patients undergoing gynaecologic oncology surgery (9). The following text represents a summary of the aforementioned evidence-based guidelines/recommendations for gynaecologic oncology surgery, divided according to pre-, intra- and postoperative management.

**Preoperative elements**

- **Preadmission information, education and counseling**

  Patients who are well informed about the strategy of care during their hospital stay exhibit less fear, anxiety, fatigue and pain. Hence, counseling helps set expectations about the length of hospital stay after surgery making early discharge possible (16).

- **Preadmission optimization**

  Patients who smoke and drink alcohol on a regular basis are advised to stop at least 4 weeks prior to surgery, due to possible peri- and/or postoperative complications. Identification and correction of iron deficiency anaemia should also be done preoperatively, due to the increased risk of postoperative anaemia associated morbidity and mortality (16).
• Mechanical bowel preparation
The rationale of MBP in gynaecologic oncology surgery, particularly if bowel resection is being contemplated, was to reduce the risk of anastomotic leakage and perioperative infectious morbidity by reducing fecal flora (16). In a recent Cochrane review of 18 RCTs the authors concluded that in colonic surgery, bowel cleansing may be safely omitted (18). Since MBP often results in patient distress and also may cause dehydration, routine oral MBP should not be used in gynaecologic oncology surgery, including patients with a planned enteric resection (16).

• Fasting and carbohydrate treatment
Patients should fast 6 hours from solid food intake and 2 hours from clear liquid intake prior to induction of anaesthesia, in order to reduce the risk of aspiration. Oral carbohydrate loading preoperatively reduces postoperative insulin resistance and associated surgery related complications. This approach also improves patient wellbeing and reduces post-operative nausea and vomiting (16).

• Preanesthetic medication
Administration of long-acting sedatives within 12 hours of surgery should be avoided due to its negative effects on immediate postoperative recovery, impairing the patient's ability to ambulate, eat and drink (16).

• Thromboembolism prophylaxis
Venous thromboembolism is a major risk in gynaecologic oncology patients with rates as high as 38 % in ovarian cancer. All gynaecologic oncology patients with major surgery > 30 min should receive VTE prophylaxis with either low molecular weight heparin or heparin. Prophylaxis should be started preoperatively, combined with mechanical methods (pneumatic compression stockings) and continued postoperatively (16).

Intraoperative elements

• Antibiotics prophylaxis
IV antibiotics should be administered within 60 min before skin incision. Cephalosporins are the most commonly recommended antibiotic class given their broad spectrum, low cost and low allergic potential. The dose should be repeated in case of prolonged operations or severe blood loss of > 1500 ml and increased in obese patients with a body mass index of 35 (16).
The addition of regional anaesthesia to general anaesthesia helps reduce PONV and is opioid sparing, hence allowing more rapid awakening. For general anaesthesia it is recommended to use short acting volatile agents such as sevoflurane/desflurane or continuous target controlled IV infusions of propofol, both of which allow rapid awakening. For regional anaesthesia, local anaesthetics such as bupivacaine are administered through thoracic epidural anaesthesia. This approach is converted into thoracic epidural analgesia postoperatively. The aim of a thoracic epidural is to selectively block pain fibers from the surgical site and the thoracic sympathetic chain bilaterally (16).

PONV prophylaxis
PONV is very common and troubling among patients undergoing major gynaecologic surgery (16). Nausea occur in 22-80% and vomiting in 12-30%, potentially causing the patient unnecessary distress and longer LOS (19). It is recommended to consider a multimodal approach in the prevention of PONV. Firstly, a combination of more than two antiemetic agents (eg. ondansetron and dexamethasone) is recommended. Secondly, utilizing regional anaesthesia and propofol use while avoiding opioids, neostigmine and volatile anaesthetics minimizes the risk of developing PONV (16).

Nasogastric intubation
In a prospective RCT comparing postoperative early oral feeding with nasogastric decompression, the LOS was significantly shorter in patients that do not undergo nasogastric intubation prior to surgery (20). Routine nasogastric intubation should therefore be avoided and if utilized removed before reversal of anaesthesia (16).

Preventing intraoperative hypothermia
Intraoperative hypothermia impair drug metabolism, adversely affect coagulation, and increase bleeding, cardiac morbidity and wound infection. Normothermia during surgery is achieved by using special devices such as warm air blankets and underbody warming mattresses. Intravenous fluids should be warmed prior to administration and temperature monitoring used to guide therapy. Warming should be continued into the postoperative period to ensure that the patient leaves OR with a temperature > 36°C (16).

Intraoperative fluid therapy and advanced hemodynamic monitoring
Since both generous and very restricted fluid regimens cause increased postoperative morbidity, it is necessary to maintain euvolemia during the perioperative period.
Anaesthetic drugs may cause hypotension during surgery in which case vasopressors should be used to maintain mean arterial pressure. Hemodynamic monitoring utilizes arterial lines that give information about oxygenation, effective ventilation, blood pH and lactate as a marker for cellular perfusion. An oesophageal Doppler monitor may be necessary to detect dynamic changes as systolic pressure, pulse pressure and stroke volume which are useful predictors of fluid responsiveness (16).

**Postoperative elements**

- **Prophylaxis against thromboembolism**
  Pneumatic compression stockings in combination with heparin reduce the rate of VTE in gynaecologic oncology patients. Extended prophylaxis for 28 days should be given to patients after laparotomy for abdominal or pelvic malignancies (17).

- **Postoperative fluid therapy and EOF**
  With the early commencement of oral diet and oral analgesia, the need for postoperative IV fluids beyond 12–24 h is rarely needed. Moreover, patients are encouraged to start drinking high energy protein drinks immediately after surgery in order to ensure early protein and calorie intake. Effects of oral feeding within 24 h after surgery include an accelerated return of bowel activity, reduced LOS, with no increase in complication rates related to wound healing, anastomotic leaks or pulmonary complications (17).

- **Prevention of postoperative ileus**
  Laxatives are commonly used within enhanced recovery protocols to hasten the return of bowel function, but no high quality data is available in gynaecologic oncology. Despite this fact, continued use of laxatives and chewing gum should be considered given the low cost and side effect profile (17).

- **Postoperative glucose control**
  Avoidance of MBP, preoperative oral carbohydrate loading and EOF should be employed to reduce insulin resistance and hyperglycaemia, both of which correlate with perioperative complications and increased LOS. Perioperative maintenance of blood glucose levels <10.0–11.1 mmol/L results in improved outcomes. Levels above this range should be treated with insulin followed by regular blood glucose monitoring to avoid iatrogenic hypoglycaemia (17).
• Postoperative analgesia

Multimodal analgesia: There is a strong association between uncontrolled postoperative pain and patient dissatisfaction, postoperative complications and the development of chronic pain. Usually, morphine is used to relieve this type of pain at the expense of slower recovery associated with somnolence, hypotension, depressed respiratory drive, urinary retention, nausea/vomiting, ileus and prolonged time to mobilization. Therefore, the strategy of recovery must aim at effectively controlling post-operative pain whilst reducing the need for opiates. To do so a multimodal analgesia strategy should be employed depending on the patient's needs: acetaminophen and NSAIDs in combination should be administered regularly to all patients unless contraindicated; Dexamethasone may be administered to prevent PONV and reduce pain, but should be used with caution in diabetic patients; Gabapentin may reduce pain and opioid side effects. The aforementioned options reduce the postoperative opioid requirement and help the patient recover faster (17).

Analgesia for major gynaecologic oncology surgery: Postoperative pain in patients undergoing cytoreductive surgery is usually severe due to the large surgical area involved and complex patient pain history. In one observational study TEA was associated with superior pain control for the first 3 postoperative days (21). However, intravenous patient controlled analgesia is often required in addition to TEA in order to achieve adequate analgesia. Moreover, TEA is associated with the development of acute hypotension which may be dangerous, in particular for patients with ovarian cancer in whom large volumes of ascites are removed early in the operation (17). Prioritizing euvolemia, a recent study showed that IV-PCA alone is a suitable alternative to TEA with a 4-day LOS reduction, improved pain scores, and an 80% reduction in the use of opioids than compared to historic controls (22).

• Peritoneal drainage

The rationale of peritoneal drainage was to reduce early perioperative fluid collections that may serve as a nidus of infection. However, drains may have detrimental effects including increased risk of infection, impairment of anastomotic healing, bleeding, pain or intra-abdominal retention. When utilized, drains should therefore be removed within the first few postoperative days (17).
• Urinary drainage
The primary indications for postoperative bladder drainage are to monitor urine output and prevent urinary retention (17). However, since the rate of re-catheterization and urinary tract infection is prominent, the optimal timing of catheter removal following uncomplicated total abdominal hysterectomies was investigated in one study. It compared patients who underwent urinary catheter removal immediately after surgery, 6 h and 24 h after surgery. The intermediate group had fewer re-catheterizations compared to the immediate removal group and lower rates of urinary tract infection than the prolonged users (23). Urinary catheters should therefore be used for a short period of time, preferably <24 h postoperatively (17).
• Early mobilization
There are many hypothesized benefits to early mobilization, including a reduction in pulmonary complications, decreased insulin resistance, less muscle atrophy, reduced LOS and risk of developing VTE complications. Foley catheters, poor pain control, and IV lines have been identified by gynaecologic surgical patients as barriers to ambulation. Hence, compliance with all elements of ERAS improves early mobilization by limiting these barriers. A care plan listing daily mobilization goals and patient engagement with an activity diary are helpful (17).

Why is the ERAS pathway difficult to implement?
Compliance to ERAS pathways in surgical practice is problematic since it requires participation and commitment of the entire surgical care team, which does not only include surgeons but also anaesthesiologists, nurses and physiotherapists (4). Moreover, ERAS pathways incorporate a number of elements that need to be fulfilled to achieve results (figure 1). Despite the fact that surgeons already practice most elements, few embrace the entirety of the ERAS concept to gain maximum benefits for the patient (10). Standardizing perioperative care ensure that all patients receive optimal treatment and is also required to measure compliance, which has proven to be a key factor to successfully implement and sustain ERAS pathways (16).
Figure 1. Pre- intra and postoperative care in gynaecologic oncology surgery according to ERAS society recommendations 2015.
RESEARCH METHODOLOGY AND METHODS

I performed a systematic literature search on gynaecological oncology in May 2016 using PubMed/MEDLINE, EMBASE, Cambridge journals online and The Cochrane Library. All study types were included. Using the given keywords I found 34 articles in total. Having read the abstracts of these articles, seven investigations that examined the role of enhanced recovery pathways in gynaecologic oncology were identified. Having read all seven studies, three of them, which specifically highlight the management of ovarian malignancy, were chosen according to the inclusion criteria below.

Criteria for considering studies in this review

Types of studies
All types of studies were included, irrespective of being randomized or non-randomized clinical trials. However, I only chose studies based on a pre- and post enhanced recovery implementation approach, in order to highlight the effect of ERAS system. There were no restrictions in time or country from where the study was issued.

Constructing the research question
I chose to use the PICO mnemonic (population, intervention, comparator and outcomes), which is a structured format applied to improve the scientific validity of a systematic review and help formulate an evidence question, in the formulation of my research question. As for the outcomes, a systematic review should “seek to address all outcomes that are important to patients and clinicians including benefits, possible adverse effects, quality of life, symptom severity and economic outcomes” (24), which is why I investigated the following aspects in order to accurately assess the effect of ERAS.

P-population: Ovarian cancer patients with indications for elective surgical treatment requiring open surgical techniques.
I-intervention: Open abdominal surgery within the framework of ERAS.
C-comparator: Open abdominal surgery with a conventional treatment approach.
Outcomes:

1. Postoperative length of hospital stay (LOS), where the day of operation is day 0.
2. Postoperative complications within 30 days of discharge: cardiopulmonary, acute confusion, nausea and vomiting, postoperative fever, wound infection, pneumonia, wound or anastomosis dehiscence, embolism and DVT, acute urinary retention, bowel obstruction owing to fibrinous adhesions, paralytic ileus, incisional hernia and persistent fistula.
3. Readmission rate within 30 days of discharge.
4. Time to tolerance of diet (in days).
5. Time to flatus/defecation (in days).
6. Quality of life: full autonomy, no physical complaints or postoperative pain.
7. Hospital costs.

Having applied the PICO mnemonic I constructed the final research question:

“What is the effect of implementing ERAS pathways in the surgical management of women with advanced ovarian cancer?”
RESULTS

Three non-randomized studies, which investigate the effect of enhanced recovery pathways in the management of ovarian cancer, were selected. Hence, I wasn't able to create a forest plot with the results of the Eberhart. However, a separate analysis of each study was done, with the main results summarized in tables 1-3.

Marx et al. (25) compared 72 patients undergoing ovarian cancer surgery via laparotomy with conventional care (group 1) versus 69 patients undergoing similar surgery but receiving “multimodal rehabilitation” (group 2). There was an equivalent number of patients requiring colonic resection in each group (n= 5). The median postoperative stay was reduced from 6 days in group 1 (mean 7.3) to 5 days in group 2 (mean 5.4) (p < 0.05). There was no difference in the overall complication rate (31.9% versus 24.6%; p = 0.01). The readmission rate was higher in group 1 than in group 2 (12.5% versus 2.9% respectively; p > 0.05).

Eberhart et al. (26) evaluated 86 patients undergoing major abdominal surgery among which 40 patients were treated by a traditional algorithm (8 required bowel resection) compared to 46 patients treated by a “fast-track” algorithm (10 required bowel resection). Indicators of postoperative recovery were documented using a validated quality-of-life tool (PPP33 questionnaire). The main study findings were that patients in the fast-track program reported faster improvement in “physical and mental autonomy,” “physical complaints,” and “postoperative pain” than compared to the conventional group. There was no difference in postoperative complications between the groups.

Gerardi et al. (27) studied only those patients who required recto-sigmoid colectomy as part of cytoreductive surgery for advanced ovarian and primary peritoneal cancers. 19 patients had their postoperative management prescribed by a standardized clinical pathway (Group A) whereas the comparison group of 45 patients (Group B) had care directed by individual surgeon preference. Group A had a shorter median length of hospital stay (7 days versus 10 days; p= 0.014) and there was no difference in the 30-day readmission rate (Group A 21% versus Group B 33%; p = 0.379).
Table 1. Characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Enhanced recovery group (N)</th>
<th>Conventional group (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marx et al. (2006)</td>
<td>“Multimodal rehabilitation” (N = 69)</td>
<td>“Conventional care” (N = 72)</td>
</tr>
<tr>
<td>Eberhart et al. (2008)</td>
<td>“Fast Track rehabilitation” (N = 46)</td>
<td>“Traditional care” (N = 40)</td>
</tr>
<tr>
<td>Gerardi et al. (2008)</td>
<td>“Postoperative management dictated by a prescribed clinical pathway” (N = 19)</td>
<td>“Postoperative management directed by preferences of the individual surgeon” (N = 45)</td>
</tr>
</tbody>
</table>

N: number of participants in each group.

Table 2. Description of enhanced recovery pathways of included studies using ERAS guidelines from 2015 as a template.

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Preoperative</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Provide patient</td>
<td>n/a</td>
<td>+</td>
<td>n/a</td>
</tr>
<tr>
<td>counseling/optimization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avoid MBP</td>
<td>+</td>
<td>-</td>
<td>n/a</td>
</tr>
<tr>
<td>Minimize fasting</td>
<td>n/a</td>
<td>+</td>
<td>n/a</td>
</tr>
<tr>
<td>Avoid sedatives</td>
<td>+</td>
<td>-</td>
<td>n/a</td>
</tr>
<tr>
<td>Provide VTE prophylaxis</td>
<td>+</td>
<td>+</td>
<td>n/a</td>
</tr>
<tr>
<td>Intraoperative</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Provide AB prophylaxis and</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>skin preparation</td>
<td>+</td>
<td>+</td>
<td>n/a</td>
</tr>
<tr>
<td>Apply SAP</td>
<td>+</td>
<td>+</td>
<td>n/a</td>
</tr>
<tr>
<td>Provide PONV prophylaxis</td>
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<td>+</td>
<td>n/a</td>
</tr>
<tr>
<td>Avoid NG intubation</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Prevent hypothermia</td>
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<tr>
<td>Manage/monitor fluid balance</td>
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<td>+</td>
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<tr>
<td>Postoperative</td>
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<tr>
<td>Provide VTE prophylaxis</td>
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<td>n/a</td>
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<tr>
<td>Manage/monitor fluid balance</td>
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<td>+</td>
<td>n/a</td>
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<tr>
<td>Encourage EOF</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Prevent ileus (use of laxatives)</td>
<td>+</td>
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<tr>
<td>Provide glucose control</td>
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<td>n/a</td>
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<tr>
<td>Provide multimodal analgesia</td>
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<tr>
<td>Avoid peritoneal drains</td>
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<tr>
<td>Early removal of drains and urinary catheters</td>
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<tr>
<td>Encourage early mobilization</td>
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<tr>
<td>Follow up/questionnaire</td>
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<td>n/a</td>
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n/a: information not available.
## Table 3. Outcomes of included studies

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<td></td>
<td></td>
</tr>
<tr>
<td>LOS (days)</td>
<td>ER group: 5 (95% CI 2 to 31)</td>
<td>-</td>
<td>ER group: 7 (95% CI 3 to 27)</td>
</tr>
<tr>
<td></td>
<td>C group: 6 (95% CI 2 to 64)</td>
<td></td>
<td>C group: 10 (95% CI 5 to 30)</td>
</tr>
<tr>
<td></td>
<td>P &lt; 0.05</td>
<td></td>
<td>P = 0.010</td>
</tr>
<tr>
<td><strong>Secondary outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative complications¹ within 30 days of</td>
<td>ER group: 17 (24.6%)</td>
<td>ER group: 14 (30%)</td>
<td>ER group: 11 (57.9%)</td>
</tr>
<tr>
<td>discharge</td>
<td>C group: 23 (31.9%)</td>
<td>C group: 15 (37.5%)</td>
<td>C group: 28 (62.2%)</td>
</tr>
<tr>
<td></td>
<td>P &gt; 0.05</td>
<td></td>
<td>P = 0.746</td>
</tr>
<tr>
<td>Readmissions within 30 days of discharge</td>
<td>ER group: 2 (2.9%)</td>
<td>-</td>
<td>ER group: 4 (21.1%)</td>
</tr>
<tr>
<td></td>
<td>C group: 7 (12.5%)</td>
<td></td>
<td>C group: 15 (33.3%)</td>
</tr>
<tr>
<td></td>
<td>P &gt; 0.05</td>
<td></td>
<td>P = 0.326</td>
</tr>
<tr>
<td>Time to tolerance of diet (days)</td>
<td>-</td>
<td>-</td>
<td>ER group: 3 (95% CI 1 to 20)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C group: 6 (95% CI 1 to 14)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P = 0.013</td>
</tr>
<tr>
<td>Time to flatus/defecation (days)</td>
<td>Defecation occurred on day 2 (median) in 50% of patients in the ER group (range 0-5 days).</td>
<td>-</td>
<td>ER group: 6 (95% CI 4 to 20)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C group: 6 (95% CI 2 to 15)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P = 0.630</td>
</tr>
<tr>
<td>QoL – Full autonomy, no physical complaints/postoperative pain on the 5th postoperative day.</td>
<td>-</td>
<td>ER group: 35 (75%)</td>
<td>ER group: 19,700 (95% CI 11,010 to 84,170)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C group: 12 (30%)</td>
<td>C group: 25,110 (95% CI 11,980 to 78,150)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P = 0.043²</td>
</tr>
<tr>
<td>Hospital costs</td>
<td>-</td>
<td>-</td>
<td>ER group: 19,700 (95% CI 11,010 to 84,170)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C group: 25,110 (95% CI 11,980 to 78,150)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P = 0.043²</td>
</tr>
</tbody>
</table>

¹ total number of patients with complications.
²2006 US dollars.
ER: enhanced recovery; C: conventional; CI: confidence interval; QoL: quality of life.
DISCUSSION OF THE RESULTS

Length of hospital stay

The criteria of discharge after abdominal surgery differ between countries and hospitals, but in general the patient must fulfill the following before returning home; eat and drink normally, manage pain with oral analgesics, mobilize independently, void and defecate normally. LOS directly reflects the patient’s status after surgery and by actively attenuating perioperative stress it may be reduced significantly (6, 10, 28).

Marx et al. demonstrated that fast-track rehabilitation with intensified preoperative information, continuous epidural analgesia, enforced early oral nutrition and mobilization leads to a reduction in morbidity and LOS. They mean that preoperative information about possible diagnosis and expected day of discharge may have affected the outcome since all the patients in the ER group reported being ready for discharge in retrospect. The planned LOS for the patients in ER group was on the 4th postoperative day but the actual LOS was on the 5th day. Marx et al. believe that discharge on the 4th day may be obtainable when the nursing staff is “more familiar with the protocol”. Gerardi et al. concluded that patients in the ER group tolerated a regular diet a median of 3 days earlier than patients in the C group. This finding, coupled with a statistically significant reduction in the proportion of patients receiving chemotherapy during the primary hospital stay, yielded a median reduction in the hospital LOS of 3 days compared to patients in the C group.

In a review of a rolling clinical audit from 2008 until 2012, studying the outcome of FTS implementation in gynaecology and gynaecologic oncology, there has been a steady increase in the number of patients discharged on day 2; 10% in the first year of the program to 25% in the second year, 33% in the third and 39% in the fourth year. Moreover, these improvements do not appear to be restricted to simple surgical cases in thin, healthy women undergoing transverse laparotomies but also included overweight or obese women who had complex procedures performed (10).

Longer LOS has not only been correlated with lower quality of life, but also with increased hospital costs (29). Several recent studies about the implementation of ERAS has demonstrated significant improvement in LOS, patient satisfaction and decreased costs for women undergoing major gynaecological surgery (5, 22, 30-32).
Postoperative complications and readmissions

ERAS concept leads to preserved body organ functions rather than the usual postoperative deterioration in pulmonary function, body composition and cardiovascular response to exercise (33).

Marx et al. found that the rate of cardiopulmonary complications and sepsis was 75% higher in the C group than in the ER group. This is the result of the fast-track pathway, which involves reduced intraoperative fluid administration, early completion of postoperative IV fluid administration and routine antibiotic prophylaxis (34). Gerardi et al. discovered that although patients in the ER group were older and their surgeries were associated with a higher estimated blood loss, there were no statistically significant differences in the rate of complications or incidence of hospital readmission within 30 days of discharge compared to the C group. Eberhart et al. also reached the same conclusion, stating that the incidence of postoperative complications did not differ between the ER group and the C group.

According to the study of Marx et al. fast-track ovarian surgery did not increase the readmission rate and no readmissions were connected with acute life-threatening conditions in the ER group, whereas in the C group the reasons for readmission were potentially life threatening in 6 out of the total 7 cases. Gerardi et al. stated that there was no difference in readmissions within 30 days of discharge between the ER group and the C group.

Several studies about pre- and post ERAS implementation in major gynaecologic surgery confirm that the incidence of postoperative complications and readmissions is more or less stable between the ER group and the C group (5, 22, 28). Despite surgery being more challenging in elderly and/or obese women, Carter et al demonstrated that equally good outcomes with the same rate of postoperative complications and readmissions as their younger and/or thinner counterparts can be achieved with ERAS pathway (10).
Time to tolerance of diet

Despite the fact that all entities of the ERAS pathway are critical to success (22), randomized controlled trials in gynaecologic and gynaecologic oncology patients undergoing major surgery have demonstrated that early feeding alone is feasible, well tolerated, and promotes a more rapid recovery compared to those treated conservatively (35-36). A randomized study in patients with ovarian cancer showed a significantly lower rate of complications for patients receiving early feeding. However, complication rates were not different between groups when the analysis was limited to a smaller group of patients undergoing intestinal resections (37-38). Moreover, a non-randomized study showed that despite early feeding was associated with a higher rate of nausea and vomiting in the ER group, 87% rated their satisfaction with nausea and vomiting control as excellent or very good, suggesting that early feeding is overall well tolerated (22).

Post-operatively, gastric emptying function usually returns within 24 h, and colonic activity recovers within 48–72 h of abdominal surgery. Therefore, initiating a diet on post-operative day one or two should be safe and efficacious with regard to overall recovery. Initiating patients who have undergone abdominal or gynaecologic procedures on a regular diet as opposed to a clear liquid diet has not been associated with an increase in gastrointestinal complaints (39-40).

EOF was encouraged in all three studies, but only Gerardi et al. demonstrated that time to tolerance of diet decreased by 3 days in the ER group as compared to the C group.

Time to flatus/defecation

Marx et al. demonstrated that 50% of the patients in the ER group had their first defecation within 48 h after surgery. This, they mean, does not correlate well with studies on accelerated rehabilitation following colonic surgery where about 95% of the patients had their first defecation within 48 h after surgery (41). Other studies in gynaecological oncology however, show that early oral feeding does not only reduce abdominal distension, nausea and vomiting, but also hastens bowel recovery (37, 42). This is another factor, which is closely related to reduced LOS. Gerardi et al. demonstrated no difference in time to flatus/defecation between the ER group and the C group.
Quality of Life

A recent study in pre- and post ERAS implementation show that patient satisfaction is mainly associated with pain control (22). There is no doubt that persistent postoperative pain not only impairs healing but also increase the rate of postoperative complications, cause anxiety, sleep disorders and poor quality of life (43-45).

According to Eberhart et al. recovered patients were considered as fully independent, with no physical complaints or postoperative pain. Results show that the majority of patients in the ER were fully recovered on the fifth postoperative day, as in comparison to the C group, where only 30% of patients had reached that stage.

Hospital costs

Clinical outcomes and economic evaluations of health care are needed to assess the health economy when resources are finite (46). Despite this fact, there are very few economic analyses linked to the introduction of FTS (47-48). Gerardi et al. were the only ones that included a financial aspect in their study, demonstrating that fast-track pathway directed management was associated with a median reduction in hospital cost of $5410 per patient in comparison to the conventional approach. According to Nelson et al. 2014 the most important elements of enhanced recovery such as early diet and mobilization, may be implemented at low or no cost, and universally improve patient comfort and satisfaction (9).

Quality of the study

None of the chosen studies fulfill all requirements of ERAS guidelines (table 2), which may potentially affect the final results by limiting the possibility to compare the studies in between each other and assess the true effect of ERAS. Moreover, no evidence is available from RCTs about the implementation of ERAS in ovarian cancer at present, which affects the reliability of this study.
CONCLUSION

All three non-randomized studies show potential benefits of ERAS pathways in patients with ovarian cancer. Both Gerardi 2008 and Marx 2006 state that ERAS pathways shorten the LOS, without altering the rate of postoperative complications and readmissions. Moreover, time to tolerance of diet and time to bowel function is enhanced in Gerardi 2008, thus directly associated with improved LOS and consequently reduced hospital costs. Finally, Eberhart 2008 concludes that ERAS pathways improve postoperative quality of life without increasing the incidence of postoperative complications.

The implementation of ERAS pathways in gynaecologic oncology enables the patient to recover earlier, hence decreasing the length of hospital stay and consequently hospital costs per patient. It's evident that ERAS pathways have a positive impact on the patient's quality of life during and after the hospital stay, which is of even greater importance considering elderly women with late stage ovarian cancer, as seen in the majority of cases in Lithuania. These patients, in particular, would benefit from a systemized perioperative program (such as ERAS) because it optimizes their hospital stay, hastens their recovery and improves their quality of life postoperatively.
PRACTICAL RECOMMENDATIONS

To implement enhanced recovery pathways with the help of ERAS guidelines modified for gynaecologic oncology. Regular audit of the program is also necessary in order to ensure compliance and help medical staff to improve the care delivered to patients.
LITERATURE LIST

15. Goff BA, Mandel LS, Melancon CH, Muntz HG. Frequency of symptoms of ovarian


