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Enhanced Recovery after Gynecological Oncologic Surgery

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Abstract

Background: Enhanced Recovery after Surgery (ERAS) is now firmly established as a global surgical quality improvement initiative that results in both clinical improvements and cost benefits to the healthcare system.The aim of this work was to evaluate the impact of the ERAS on outcome of gynecologic oncology surgery. **Conclusions:** Implementation of the policy of enhanced recovery after surgery (ERAS) in gynecologic oncology was associated with an overall improvement in postoperative outcomes.

Key words:ERAS, Gynecologic oncology, Surgery.

INTRODUCTION

Gynecologic oncology is a specialized field of medicine that focuses on cancers ofthe female reproductive system, including ovarian cancer, endometrial cancer, cervical cancer, vaginal cancer and vulvar cancer. As specialists, they have extensive training in the diagnosis and treatment of these cancers.

Cervical cancer:

Globally, cervical cancer continues to be one of the most common cancers among females, being the fourth most common after breast, colorectal, and lung cancer. GLOBOCAN 2020 estimated that, worldwide, there were approximately 604 000 new cases of cervical cancer, with 342 000 deaths annually[(1)].

Surgical management

Surgery is suitable for early stages, where cervical conization, simple hysterectomy, or radical hysterectomy may be selected according to the stage of disease.

Endometrial cancer

Endometrial cancer represents the sixth most common malignant disorder worldwide. An estimated 382 000 new cases were diagnosed with this malignancy in 2018[(2)]**.** High-income countries have a greater incidence of endometrial cancer (11.1 per 100 000 females) compared with low-resource countries (3.3 per 100 000 females). This might be attributable to high rates of obesity and physical inactivity, and to ageing of the population. Specifically, elevated estrogen levels are known to be the most likely cause of the increased risk of endometrial cancer for postmenopausal obese women[(3)]**.**

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 07, 2021

Cytoreductive (debulking) surgery for advanced stage disease:

1 Primary debulking

At least two-thirds of patients with ovarian cancer present with Stage III or IV disease. This may affect the performance status and fitness for surgery. However, the most important prognostic indicator in patients with advanced stage ovarian cancer is the volume of residual disease after surgical debulking. Therefore, patients whose medical condition permits should generally undergo a primary laparotomy with total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and maximal attempt at optimal cytoreduction. This may necessitate bowel resection, and occasionally, partial or complete resection of other organs. Based on recent data from the randomized Lymphadenectomy in Ovarian Neoplasm (LION) trial, the removal of clinically negative lymph nodes during cytoreductive surgery does not increase the progression-free or overall survival and should not be undertaken[(4)].

2 Interval debulking

In selected patients with cytologically proven Stage IIIC and IV disease who may not be good surgical candidates, 3–4 cycles of neoadjuvant chemotherapy (NACT) may be given initially, followed by interval debulking surgery and additional chemotherapy[(5)].

Vulvar cancer:

Vulvar cancer is a malignant, invasive growth in the vulva, or the outer portion of the female genitals. The disease accounts for only 0.6% of cancer diagnoses but 5% of gynecologic cancers in the United States. The labia majora are the most common sites involved representing about 50% of all cases, followed by the labia minora. The clitoris and Bartholin glands may rarely be involved. Vulvar cancer is separate from vulvar intraepithelial neoplasia (VIN), a superficial lesion of the epithelium that has not invaded the basement membrane or a pre-cancer. VIN may progress to carcinoma-in-situ and, eventually, squamous cell cancer.

Surgical management

Surgery may involve a wide local excision, radical partial vulvectomy, or radical complete vulvectomy with removal of vulvar tissue, inguinal and femoral lymph nodes. In cases of early vulvar cancer, the surgery may be less extensive and consist of wide excision or a simple vulvectomy. Surgery is significantly more extensive when the cancer has spread to nearby organs such as the urethra, vagina, or rectum. Complications of surgery include wound infection, sexual dysfunction, edema and thrombosis, as well as lymphedema secondary to dissected lymph nodes.

Sentinel lymph node (SLN) dissection is the identification of the main lymph node(s) draining the tumor, with the aim of removing as few nodes as possible, decreasing the risk of adverse effects. Location of the sentinel node(s) may require the use of technetium(99m)-labeled nano-colloid, or a combination of technetium and 1% isosulfan blue dye, wherein the combination may reduce the number of women with "missed" groin node metastases compared with technetium only[(6)].

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Vaginal cancer:

Vaginal cancer isa malignant tumor thatformsin the tissues of the vagina. Primary tumors are most usually squamous cell carcinomas. Primary tumors are rare, and more usually vaginal cancer occurs as a secondary tumor. Vaginal cancer occurs more often in women over age 50, but can occur at any age, even in infancy. It often can be cured if found and treated in early stages.

Surgical management

The role of surgery is limited in primary vaginal cancer since the primary tumor is near the bladder, urethra, and rectum. In general, primary treatment with surgery is limited to early and small lesions confined to the vaginal mucosa (less than 2 cm). There are no RCTs and most of the literature is retrospective in nature. There may be a role for surgical treatment in certain additional situations beyond early disease, as listed below.

1) Surgical management of Stage I disease (early disease)
   a) Upper vaginal disease
      i) The tumor is limited to the mucosa in Stage I disease.
      ii) If the uterus is in situ, radical hysterectomy, vaginectomy aiming for 1 cm disease-free margins, and pelvic lymphadenopathy should be offered. If the uterus has been removed, radical vaginectomy as above with pelvic lymphadenopathy can be performed[(7)].
   b) Lower vaginal disease
      i) Radical wide local excision with 1 cm margins can be offered, in addition to bilateral groin node dissection.

1. Ovarian transposition during surgery and preradiation

In young women with vaginal cancer requiring radiation as primary treatment, ovarian transposition can be offered prior to definitive radiation treatment to prevent the adverse effects of radiation-induced menopause. In selected cases, laparoscopic or extraperitoneal removal of bulky lymph nodes can be offered as part of staging and treatment planning.

3. Central recurrence after radiation treatment

   Pelvic exenteration is a possibility if the recurrence is central and isolated. These patients require extensive counselling regarding the risks and morbidity of surgery, as well as the impact on quality of life and body image.

4. Palliative management of recurrent or advanced disease

   In women with advanced or recurrent disease who present with vesicovaginal or rectovaginal fistula, a palliative urinary diversion or colostomy can be offered to improve quality of life before definitive management with radiation treatment.

Enhanced Recovery After Surgery (ERAS) is now firmly established as a global surgical quality improvement initiative that results in both clinical improvements and cost benefits to the healthcare system[(8)]. ERAS guidelines are based on the highest quality evidence available and as such require updating on a regular basis[(9)].

ERAS pathways were initially introduced in colorectal surgery. They have since been successfully implemented in many surgical specialties, including cardiac, thoracic,

vascular surgery, urology, and orthopedics. A growing body of evidence suggests that it is both a safe and effective perioperative care approach allowing for shorter length of hospital stay, decreased morbidity, and significant cost reduction without increasing postoperative complication and readmission rates while maintaining high patient satisfaction[(10)].

The main ERAS elements differ drastically from traditional care and can be divided into preoperative, intraoperative, and postoperative interventions.

Preoperative:

Pre-admission Information, Education, and Counseling

The goal of pre-operative counseling is to set expectations about surgical and anesthetic procedures, as well as provide information regarding a care plan in the post-operative period. Pre-operative education and psychological preparation can reduce anxiety and increase patient satisfaction, which may improve fatigue and facilitate early discharge[(11)].

Pre-operative education is also effective in reducing pain and nausea and improving well-being when added to an existing ERAS protocol. Studies have shown that patients with gynecologic cancer prefer to be well informed, and support from a nurse at the time of diagnosis can reduce stress levels for up to 6 months[(12)].

Venous Thromboembolism Prophylaxis

Venous thromboembolism (VTE) is a major risk in gynecologic oncology patients with rates up to 3–4% in cervical cancer, 4–9% in endometrial cancer, and 17–38% in ovarian cancer. Approximately 3% of women with a new ovarian cancer diagnosis will have a concomitant VTE diagnosed before they start cancer treatment; the risk of VTE approaches 12% during neoadjuvant chemotherapy **Greco et al.** [(13)]and extends through at least the full course of primary therapy. The presence of malignancy, higher body mass index, age, pelvic surgery, extra-pelvic disease, histology, pre-operative corticosteroids, receipt of chemotherapy, immobility, and a hypercoagulable state have all been identified as independent risk factors for VTE and are common among women undergoing gynecologic surgery, especially for cancer. All gynecologic oncology patients who undergo major surgery lasting longer than 30 min should receive dual VTE mechanical prophylaxis and chemoprophylaxis with either low molecular weight heparin or unfractionated heparin and dual prophylaxis should continue throughout the hospital stay[(14)].

Importantly, prophylactic anticoagulation has not been shown to increase the risk of intraoperative bleeding, thrombocytopenia, and epidural hematoma. Therefore, epidural catheter placement and removal should be timed according to the last dose of heparin[(15)].

The use of mechanical prophylaxis, specifically pneumatic compression devices, has been shown to decrease the rate of VTE when compared with no prophylaxis within the first 5 post-operative days. The efficacy of mechanical prophylaxis is equivalent to heparin alone and leads to the greatest VTE risk reduction when combined with heparin in gynecologic oncology[(16)].

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 07, 2021

Preemptive analgesia:

In ERAS pathways, pain management begins before incision. This theory is based on the concept of preemptive analgesia, in which pain medications block activation of pain receptors before they are activated by the presence of noxious stimuli, resulting in superior pain control and a decrease in pain medication requirements. A multimodal approach incorporating the preoperative use of Gabapentin, oral or intravenous (IV) cyclo-oxygenase (COX) -2 inhibitors (celecoxib or parecoxib), and oral or IV paracetamol, has been associated with decreased use of opioids postoperatively and is typically used in ERAS protocols[17].

Intraoperative:

Surgical Site Infection Reduction Bundles:

Surgical site infections are defined as infections of the surgical incision or organ space that develop within 30 days of surgery. Surgical site infections are associated with increased patient morbidity, mortality, and healthcare expenditures and occur in up to 20–30% of gynecologic oncology patients undergoing a laparotomy Surgical site infection reduction bundle have been demonstrated to decrease the risk of developing a surgical site infection in an additive fashion[18]. Surgical site infection bundle elements include antimicrobial prophylaxis, skin preparation, avoiding hypothermia, avoiding surgical drains, and reducing perioperative hyperglycemia.

Antimicrobial Prophylaxis:

Appropriate antibiotic prophylaxis includes administration of a first-generation cephalosporin to cover skin flora. Cephalosporins have relatively broad coverage, are low cost, have a low allergenic potential, and are the recommended prophylaxis for simple hysterectomy Additional anaerobic coverage is recommended if the bowel is entered during pelvic surgery for cancer. Dosage may need to be adjusted based on patient weight. Most antibiotics should be administered within 1 hour of incision to obtain the highest drug serum levels at incision. Antibiotic redosing should be monitored for compliance based on operative time and blood loss. Several surgical site infection reduction bundles include an emphasis on antibiotic dosing and timing of administration[19].

Skin Preparation

Skin preparation is intended to decrease the amount of bacterial flora present on the skin before incision. This can be accomplished through pre-operative bathing at home as well as use of a skin preparation in the operating room before incision[20]. Most surgical site infection reduction bundles have incorporated pre-operative bathing with a chlorhexidine-based antimicrobial soap and chlorohexidine-alcohol skin preparation before surgery[21].

Prevention of Hypothermia

Intra-operative hypothermia has been linked to an increased risk of surgical site infections and cardiac events. Various methods to avoid intraoperative hypothermia have been evaluated including forced air blanket devices, underbody warming mattresses, and warmed intravenous fluid administration. In a randomized clinical trial comparing

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 07, 2021

intraoperative warming only (control group) versus additional warming 2 hours before and after surgery (warming group) among patients undergoing major abdominal surgery, the rate of surgical site infections was decreased by half among those who were normothermic[(22)].

Avoidance of Drains/Naso-GastricTubes

High quality evidence is lacking to address the role of subcutaneous or peritoneal drains in decreasing surgical site infections and evidence exists that drain biofilm colonization can be detected as early as 2 hours after placement[(23)]. One surgical site infection reduction bundle implemented among gynecologic oncology patients included use of subcutaneous drains in obese patients. However, this surgical site infection reduction bundle also included other interventions with stronger surgical site infection reduction evidence[(24)].

At this point, there is insufficient evidence to recommend inclusion of a subcutaneous drain or peritoneal drain as part of a surgical site infection reduction bundle and there may be harm by introducing a foreign body conduit for bacteria to travel into a surgical wound.

Nasogastric intubation increases the risk of post-operative pneumonia after elective abdominal surgery and does not reduce the risk of wound dehiscence or intestinal leaks[(25)].As such, the use of drains should be tailored according to the surgical procedure and rationale for individualized drain placement.

Control of Perioperative Hyperglycemia

Perioperative hyperglycemia has been associated with increased risk of developing surgical site infections, in both diabetic and non-diabetic patients undergoing surgery, and the CDC recommends (category 1A) blood glucose levels be maintained at <200 mg/dL regardless of whether a patient is diabetic or not[(26)]. Importantly, glucose management must avoid hypoglycemia as well as hyperglycemia as both extremes have been associated with higher mortality risk[(27)].It should be noted that other interventions that decrease insulin resistance are part of the ERAS protocol, including oral carbohydrate loading, minimally invasive surgery, early feeding, and thoracic epidural analgesia.

Standard Anesthetic Protocol

High dose or long-acting opioids should be avoided to reduce post-operative opioid-related side effects. Short-acting opioid analgesics such as remifentanil may allow a consistently rapid recovery, but there is concern it may induce hyperalgesia. Nitrous oxide as well as being minimum alveolar concentration additive has analgesic properties but is associated with an increased rate of post-operative nausea and vomiting in a patient population with a high baseline risk. Both laparoscopic procedures and gynecological surgery are independent predictors of post-operative nausea and vomiting; therefore, it is reasonable to omit nitrous oxide during laparoscopic gynecologic surgery to prevent post-operative nausea and vomiting, and prophylaxis with a combination of at least two anti-emetics should be standard[(28)].

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 07, 2021

Postoperative:

Early postoperative feeding:

Maintenance of appropriate nutritional status post-operatively has led to improvements in return of bowel activity, reduced length of hospital stays, and equivalent complication rates as measured by wound healing, anastomotic leaks, or pulmonary complications. In colorectal patients, delivery of post-operative nutrition on day 1 is an independent prognostic factor of 5-year survival and mortality. Higher post-operative protein intake is also associated with earlier discharge. Currently there are no definitive guidelines for surgical patients as it pertains to protein needs; however, in the acute care setting guidelines have recommended up to 2.0 g of protein/kg/day and 25–30 kcal/kg/day. It appears that a high protein diet post-operatively may reduce complications and the role of immune nutrition and arginine supplementation continues to evolve[(29)].

Early mobilization:

Early mobilization is a key component in ERAS protocols. It has been stipulated that it protects against muscle loss and deconditioning by avoiding prolonged bed rest and immobility, helps reduce pulmonary and venous thromboembolic complications, improves insulin resistance, and contributes to shortening hospitalizations.

Early urinary catheter removal:

ERAS protocols call for removal of urinary catheters within 24 hours following surgery, with some advocating for even earlier removal. An argument toward routine removal immediately after surgery in laparotomies does not appear to be substantiated based on a recent study comparing removal of urinary catheter immediately after surgery, 6 hours, or 24 hours postoperatively following uncomplicated total abdominal hysterectomy. The intermediate removal group (removal of catheter 6 hours postoperatively) was superior to the immediate group (removal at the end of surgery) in terms of less frequent need for recatheterization and superior to the delayed group (removal within 24 hours postoperatively) in terms of less frequent urinary tract infections, earlier ambulation, and shorter hospital LOS[(30)].

Opioid Sparing Multimodal Post-Operative Analgesia:

Post-operative pain after gynecologic surgery plays a major role in patient quality of life and it may also be associated with higher rates of complications, longer hospital stays, increased readmission rates, and higher cost[(31)]. When patients rely on opioid alone for post-operative analgesia, this may cause nausea, sedation, and fatigue while increasing the risk of addiction, thus leading to associated financial and social costs. Avoiding opioid use within a multimodal post-operative analgesia pathway, with greater emphasis on non-opioid medications, preserves or improves patient experience and functional recovery after surgery[(32)]. Non-opioid alternatives include non-steroidal anti-inflammatory drugs, acetaminophen, gabapentin, and dexamethasone. Pre-operative education should stress the use of non-opioid alternatives as first-line therapy and set expectations for post-operative pain control.

Health-Related Quality of Life and Patient Satisfaction:

ERAS pathways have been associated with improvement in patient-reported outcomes, improved quality of life, and excellent patient satisfaction. De Groot and colleagues considered successful functional recovery to have been achieved when the patient was able to tolerate general diet, mobilize independently, and have good control of postoperative pain with oral analgesia. They noted that the ERAS protocol resulted in earlier independent mobilization by 3 days, earlier oral fluid intake and ability to tolerate general diet by 2 days, as well as ability to have good control of postoperative pain with oral medication by 1 day. Based on these criteria, return to functional recovery was achieved 3 days earlier with the ERAS pathway compared with traditional perioperative care (3 days vs 6 days; P<.001). Meyer and colleagues did not observe any change in the most highly rated patient-reported symptoms, which include fatigue, abdominal pain, and overall surgical pain. Specifically, pain scores were no different between pre-ERAS and post ERAS patients despite a significant reduction in the amount of opioid medication required to treat postoperative pain. In contrast, they observed improvement in the severity of nausea, sleep disturbance, constipation, urinary urgency, and difficulty with memory during hospitalization. These findings are consistent with previously published studies on ERAS pathway in gynecologic surgery[(33)].

Patient satisfaction following ERAS-associated perioperative care has consistently been reported as high. In one study by Ottesen and colleagues, 92.7% of the patients stated that their hospitalization was “as expected,” “easier than expected,” or “much easier than expected.” Most patients were satisfied with their hospital LOS; only a small percentage of patients of less than 5% (2/41) reported feeling “a little pressure put on them toward discharge,” among which one was discharged on postoperative day 8. In a 0 to 10 scale of “how acceptable the program and advice had been,” the median score was 10. Patient satisfaction rates have universally been reported high ranging from 75% to 95% across studies[(34)].

High-quality data support the safety and efficacy of ERAS pathways in enhancing postoperative recovery of patients undergoing gynecologic surgery. ERAS pathways have been consistently associated with improved postoperative outcomes including earlier return of gastrointestinal function, adequate pain management with reduced opioid use, shorter length of hospital stay, excellent patient satisfaction, and substantial cost reductions with no increase in complication or readmission rates. Successful implementation of an ERAS pathway requires a multidisciplinary and collaborative approach between surgeons, anesthesiologists, pharmacists, nursing staff, and physicians in training as well as active engagement of patients in the enhancement of their recovery. Systematic efforts are needed for active diffusion of the ERAS perioperative care model and should be considered standard of care in gynecologic surgery.

CONCLUSIONS

Implementation of the policy of enhanced recovery after surgery (ERAS) in gynecologic oncology was associated with an overall improvement in postoperative outcomes. The implementation of a successful ERAS policy lead to early movement, early

postoperative feeding, earlier return of bowel movement, decreasing time of urinary catheterization, decreasing incidence of DVT and paralytic ileus, pain control with reduced opioids using, reducing length of hospital stay with decrease of readmission and morbidity rates with early return to normal daily activity.

Current study recommendsthat we should exert efforts that are needed for implementation of the ERAS perioperative care policy and should be considered as standard of gynecological oncology surgery care.

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