

FOLIA MEDICA CRACOVIENSIA

Vol. LXII, 4, 2022: 25–33

PL ISSN 0015-5616

DOI: 10.24425/fmc.2022.144080

Perioperative management of patients with gynecological cancers

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Abstract: Oncological surgery is the primary treatment for gynecological malignancies and is inseparably linked with anesthesia. The modern approach to interdisciplinary and multidisciplinary perioperative care in gynecologic oncological patients improves the outcome. This paper presents a review of perioperative management of patients with gynecologic oncology related to enhanced recovery after surgery and cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. We performed a literature search on MEDLINE, EMBASE, Google Scholar, the Cochrane Central Register of Controlled Trials, and Clinical Trials. The database search focused on selected topics related to perioperative gynecological oncology care. The authors also contributed through individual, independent literature searches.

Keywords: gynecological oncology, cancer, HIPEC, ERAS, CRS, perioperative management, review.

Submitted: 12-Oct-2022; **Accepted in the final form:** 11-Nov-2022; **Published:** 29-Dec-2022.

Introduction

In 2018, more than 9.5 million people died from cancer. It is the leading cause of premature death in most countries worldwide. Implementing appropriate preventive interventions and action strategies can reduce these deaths in the future [1]. The most frequently diagnosed malignant neoplasms are lung cancer (11.6% of all cases), female breast cancer (11.6%), and colorectal cancer (10.2%). Breast cancer is the leading malignancy (24.2%) in the female population. Gynecological cancers take the following places: 4th for cervix uteri (6.6%), 6th for corpus uteri (4.4%), and 8th for ovary (3.4%). Preventive interventions that can significantly reduce the incidence of certain



cancers in the female population include vaccinations against human papillomavirus, covering over 90% of the population, and screening for cervical cancer with over 70% [1]. Preferably with HPV genotyping or with liquid-based cytology.

Oncological surgery is the primary treatment for gynecological malignancies. It is inseparably linked with modern anesthesia [2] and multidisciplinary and interdisciplinary perioperative care. Oncological surgery may be introduced at different stages of the disease in staging, cure, or palliation, including new surgical techniques and technical devices involving reconstructive surgery. Therefore, healthcare providers should stratify the risks and benefits of surgery from the perspective of possible radio- and systemic adjuvant therapy. The review aims to present current knowledge in terms of optimal perioperative care for gynecological oncologic patients.

Materials and Methods

We present a review of perioperative management of patients with gynecologic oncology related to Enhanced Recovery After Surgery (ERAS) and cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC). We performed a literature search in MEDLINE, EMBASE, Google Scholar, the Cochrane Central Register of Controlled Trials, and Clinical Trials. The database search focused on selected topics related to perioperative gynecological oncology care. The authors also contributed through individual, independent literature searches.

Enhanced Recovery After Surgery

The Enhanced Recovery After Surgery program facilitates recovery after surgery [3]. It refers to several perioperative interventions to improve patient outcomes and optimize resource use. The ERAS protocol originates from the change of the original perioperative care procedure used in colon surgery, first described at the end of the twentieth century by Kehlet and colleagues [4]. They proposed this treatment to attenuate the physiological and psychological stress associated with surgery. As a result, it shortened patients' hospital stay without increasing the number of complications and effectively performed the surgery. The current form of the ERAS protocols results from improving prehospital, intraoperative, and postoperative care based on current knowledge and published evidence.

Prehospital management includes proper patient counseling, optimization with risk stratification, and education prior to hospital admission. All patients should be offered medical optimization before surgery and be screened early to detect preoperative abnormalities such as malnutrition or anemia. The involvement of appropriate interventions can improve the outcome [5]. If necessary, an assessment of general medical conditions should include a medical history and extended physical examina-

tion to assess vital organ activity properly. Furthermore, frailty in older adults generates additional risks [6].

The preparation for surgery should include the avoidance of routine bowel preparation and sedatives used as pre-anesthetic medication. Oral liquids are allowed and encouraged until 2 hours and solids up to 6 hours before anesthesia and surgery. Oral carbohydrate solutions are preferred. Gynecologic oncologic patients are at increased risk of venous thromboembolism with increased rates of up to 3–4% in cervical cancer, 4–9% in endometrial cancer, and 17–38% in ovarian cancer due to multiple mechanisms involved in cancer-associated thrombosis, as well as thrombosis associated directly with surgical treatment and postoperative recovery [7–9].

Both non-pharmacological (compression stockings, intermittent pneumatic compression) and pharmacological (low molecular weight heparin — LMWH) thromboprophylaxis measures should be routinely used when relevant. Modifiable risk factors should be eliminated, including discontinuing hormone replacement therapy, oral contraception prior to surgery, and switching to another form. Using cognitive aids such as venous thromboembolism risk scales allows for stratifying the risk and implementing proper prophylaxis. The prophylactic use of antibiotics should be administered 60 minutes before the skin incision. In addition, healthcare providers should consider a multimodal approach to postoperative nausea and vomiting (PONV) treatment before surgery based on a standardized PONV risk assessment.

Intraoperative management includes the avoidance of routine use of drains and a nasogastric tube. Additionally, surgical techniques should involve laparoscopy-assisted surgery or open surgery with the shortest appropriate surgical incisions. Prevention of hypothermia and optimal fluid management by avoiding high volume and sodium load are essential elements of the intraoperative ERAS strategy.

Modern anesthesia practice has a significant impact on ERAS. Therefore, anesthesia should include lung-protective ventilation with low tidal volume and positive end-expiratory pressure. In addition, the use of short-acting anesthetic agents and multimodal pain therapy facilitates faster recovery. Opioid dosing reduction (i.e., non-opioid drug use, short-acting opioids use, and regional analgesia involvement) and the proper prevention of PONV reduce side effects and the surgical stress response [10]. Postoperative management should include the continuation of multimodal opioid-sparing analgesia and prevention of PONV. In addition, oral fluid supply should be preferred to avoid postoperative fluid overload. Postoperatively, patients should be mobilized early, including early removal of urinary catheters and avoidance of nasogastric tubes. Stimulation of intestinal motility and early enteral feeding prevent postoperative ileus. The ERAS team should perform a systematic audit of protocol compliance and outcomes.

After the initial publication of ERAS [4], followed by further official ERAS recommendations [11], the ERAS guidelines are available for most medical disciplines.

However, its implementation in oncological gynecology was only discussed in 2016 [12]. These publications were followed by two extensive documents focusing on enhanced recovery after surgery in gynecological oncology [13, 14].

One of the challenges in introducing guidelines is the implementation process [15], which can delay the use of all principles of the protocol [16]. Proposing practical solutions can facilitate the translation of the guidelines into practice [17]. However, the implementation of ERAS elements in gynecologic oncology is still unsatisfactory. In 2018, the International Federation of Gynecology and Obstetrics (FIGO) recognized ERAS strategies. This document focused on improving the outcomes resulting from the use of the protocol and discouraged the use of interventions without evidence of benefit. The publication also highlights the need for engagement and education of a multidisciplinary team that cares for the patient to grant successful implementation [18]. The researchers analyzed the patients' satisfaction with using the ERAS protocol in oncological gynecology. Patients reported comparable satisfaction and quality of life using ERAS protocols; however, this audit indicated the challenge of postoperative pain management in selected types of open surgery [19]. In 2019, the ERAS oncologic gynecology guidelines were updated based on the current literature. The update introduced new topics of prehabilitation, site infection prevention, patient-reported outcomes, cytoreductive pelvic surgery, HIPEC, audit, and reporting [20]. Improvements in compliance with the ERAS protocol in gynecological oncology resulted in the reduction in adjusted length of stay and cost savings, indicating that the audit tool facilitates implementation [21].

The ERAS protocol for gynecological cancers is also safe and feasible for the elderly. The benefit may be even more significant in the aging population of oncological gynecology patients [22]. ERAS programs have improved clinical outcomes in gynecologic oncology, and most published reports originate from a small number of specialized centers. It is unclear to what extent ERAS is implemented in hospitals worldwide. The international survey by Bhandoria *et al.* investigated the status of implementation of the ERAS protocol in open gynecologic oncology surgery to provide a worldwide perspective on perioperative practice patterns. While some practices are consistent with the guideline recommendations, many contradict the established evidence. Efforts are required to decrease the variation in perioperative care to improve clinical outcomes for patients with gynecologic cancer worldwide [23].

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

Hyperthermic intraperitoneal chemotherapy (HIPEC) is a therapeutic option for cytoreductive surgery (CRS) in peritoneal-based malignancies. Treatment involves cytostatic, chemotherapeutic, and high-temperature effects on malignant tissue; however, the result is limited by the ability to penetrate tissue below 2.5 mm [24].

This approach may be an optional treatment for advanced (stage III) epithelial ovarian cancer (EOC). A recently published multicenter randomized trial provided evidence supporting the involvement of this treatment regimen showing longer recurrence-free survival and overall survival without a higher side effect rate [25]. It should be noted that a general implementation of HIPEC in the surgical treatment of all patients with advanced EOC is still not recommended [26].

However, the combination of CRS and HIPEC is associated with a high complication rate. The severe complication rate after CRS with HIPEC ranges between 12 and 54% and includes gastrointestinal (4.5–19%), pulmonary (10–16%), hematological (4–39%), renal (2–4%), metabolic, thromboembolic (4–4.4%), hemorrhagic, and infectious complications [27].

Gaining experience in CRS and HIPEC treatment and the role of the learning curve influence the improvement of the perioperative outcome, reducing complications rate, patient morbidity, and mortality [28].

A recently published paper by Charo *et al.* aimed to compare the frequency of HIPEC use in ovarian cancer treatment as a result of the publication of van Driel *et al.* [25]. Data from 550 US hospitals revealed a relative increase in HIPEC use; however, this was accompanied by an increase in hospital length of stay, cost, admissions to the ICU, and rates of complication [29].

Despite the data showing the benefit of CRS and HIPEC in the treatment of advanced EOC, there is an ongoing debate on a different aspect of this therapy, including a higher risk of complications, especially when establishing the HIPEC center [30].

There are still questions about the use of HIPEC in advanced EOC [31]. Previous studies have failed to address optimal patient selection, drug choice, dose, and duration of HIPEC. Several ongoing phase III randomized clinical trials aim to answer the questions [24].

Several interventions can guide the implementation and facilitate improving the outcomes of a HIPEC program. In 2020, Chambers *et al.* presented their evidence-based recommendations following experience in a high-volume tertiary care center. They indicated the need to build a multidisciplinary team (gynecologists, oncologists, anesthesia team, nurses, perfusionists, and pharmacists) and to effectively educate the team members about the protocols used and the safety of the staff, including emergencies. Furthermore, the article indicates the need to use diagnostic tools during the HIPEC phase to monitor glycemia, electrolyte level, and metabolic changes, including lactic acidosis and renal- and cardiotoxicity, according to the cytostatic and hyperthermia protocol used [32].

The specific approach to HIPEC patients was reflected in the ERAS Society guidelines for CRS and HIPEC [33, 34]. In addition to the general ERAS rules described above, the recommendations indicated that specific interventions play an essential role in care during CRS and HIPEC.

The assessment of cardiac risk, screening for obstructive sleep apnea, and frailty should be a part of the preoperative assessment. Laboratory testing should screen for abnormalities that may be corrected before surgery and influence the intended outcome. During the HIPEC phase, strict temperature and glucose control should prevent hyperthermia and keep normoglycemia. CRS and HIPEC management should involve an early diagnostic approach to screen and identify anemia and coagulopathy, triggering proper management. Intraoperative normothermia is an essential element influencing the outcomes during CRS and HIPEC. All measures should be involved during CRS to monitor core temperature and prevent hypothermia. Conversely, when initiating the HIPEC phase, prevention of hyperthermia plays an important role. Minimally invasive cardiac output monitoring should guide fluid therapy, vasopressors, and catecholamine use. It reduces postoperative complications resulting from fluid shifts, vasodilation, and hemodynamic changes during the HIPEC phase [35]. Routine administration of loop diuretics and dopamine to maintain urine output is not recommended. Coagulopathy can often be present perioperatively. Modern technologies like thromboelastography and rotational thromboelastometry can allow titration of blood products and prothrombotic treatment according to the patient's needs focusing on the point of care management.

Postoperative management recommends early oral feeding from the first postoperative day. It should focus on the identification of patients with insufficient intake. In some patients, pre-emptive enteral nutrition could be indicated. In addition to oral and enteral nutrition, parenteral nutrition is recommended in selected patients [36]. Postoperative management should include prevention, early detection, and treatment of HIPEC complications involving modification of treatment protocols (antiangiogenic medications, dose of cisplatin, dose of Mitomycin C, use of sodium thiosulfate, and administration of granulocyte colony-stimulating factor). Routine post-discharge care should address nutritional care and physiotherapy issues.

Conclusions

The modern approach to perioperative care in gynecologic oncological patients improves the outcome; however, further studies are warranted to demonstrate the relationship of the applied anesthesia technique with the oncological outcome. The multidisciplinary and interdisciplinary team approach to treatment allows for a better outcome.

Conflict of interest

None declared.

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