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## Anesthesia for gynecological cancer surgery

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**Abstract:** Malignant neoplasms are currently a severe medical challenge and the second leading cause of death worldwide. The modern anesthesia applied may improve the patient outcome. This paper presents a review of anesthesia management related to patients with gynaecologic malignancies. It includes the influence of the type of anesthesia on cancer recurrence, application of regional anesthesia in gynaecologic oncologic surgery, and selected aspects of anesthesia for robotic surgery. 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 the topics related to anesthesia in gynecological oncology. The authors also contributed through individual, independent literature searches.

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### Introduction

Malignant neoplasms are currently a serious medical challenge. It is the leading cause of premature death in most countries worldwide. Breast cancer and gynecological malignancies are common causes of death in the female population [1]. Anesthesia is an inseparable element of modern surgical treatment. The modern anesthesia applied as a part of perioperative care influences the patient outcome. Additional patient benefits may result from novel regional anaesthesia techniques, if applicable [2–7]. Some retrospective studies suggest different oncologic outcomes related to the an-



esthesia type used in surgical treatment [8, 9]. Robotic surgery is getting more popular in gynaecologic oncology surgery and requires modification in anesthetic management. The review aims to present current knowledge in different aspects of anesthetic management and related topics in patients with gynaecologic malignancies.

## Materials and Methods

In this paper, we present a review of anesthesia management related to patients with gynaecologic malignancies, the influence of the type of anesthesia on cancer recurrence, the application of regional anesthesia in gynaecologic oncologic surgery, and selected aspects of anesthesia for robotic surgery. 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 the topics related to anesthesia for gynecological oncologic surgery. The authors also contributed through individual, independent literature searches.

### **Volatile anesthesia vs. total intravenous anesthesia — influence of anesthesia technique on cancer recurrence in gynecologic oncology**

Surgery is an essential treatment for the majority of solid organ cancers. Gynecologic oncology patients often require procedures under general anesthesia, providing sedation, amnesia, analgesia, and usually neuromuscular block. Either inhalational or intravenous techniques may accomplish induction and maintenance of general anesthesia. Volatile anesthesia (VA) is performed using anesthetic agents such as sevoflurane, desflurane, or isoflurane. Total intravenous anesthesia (TIVA) employs a sedative-hypnotic anesthetic agent — typically propofol. Both methods provide analgesia using opioid or non-opioid analgesic agents and sometimes various types of regional anesthesia.

#### *Laboratory studies — volatile anesthetics*

Some laboratory studies have suggested potential mechanisms whereby volatile anesthetics could enhance metastasis through changes in the immune response, modulation of the neuroendocrine stress response to surgery, or through effects on cancer cell signaling. However, the molecular mechanisms for such effects are not entirely understood, and there is conflicting evidence of the influence of volatile agents on different cancer cell lines. In ovarian cancer lines, Luo *et al.* found that isoflurane increases the malignant potential of ovarian cancer cells through the up-regulation of markers associated with the cell cycle, proliferation, and angiogenesis: insulin-like growth factor (ILGF), vascular endothelial growth factor (VEGF), angiopoietin-1 and matrix

metalloproteinases (MMP) [10]. Iwasaki *et al.* investigated the metastatic potential of isoflurane, sevoflurane, and desflurane on ovarian cancer cells. They found that amount of ribonucleic acid (mRNA) for VEGF-A, MMP11, chemokine receptor CXCR2, and tumor growth factor  $\beta$  (TGF- $\beta$ ) is significantly increased after exposure to volatile anesthetics, indicating the activation of cancer cell transformation, basement membrane degradation, and angiogenesis [11]. Another study published in 2017 by Guo *et al.* demonstrated a metabolic switch in ovarian cancer cells under isoflurane treatments contributing to the malignancy of cancer cells [12]. Two studies were published in 2019 with conflicting evidence in cervical cancer lines. Ding *et al.* found that sevoflurane increased chemosensitivity in cervical cancer cells does not affect apoptosis of these cells nor inhibit proliferation or migration, which would suggest its inhibitory effects on cervical cancer growth and metastasis [13].

In breast cancer lines, Liu *et al.* found that sevoflurane significantly suppresses the proliferation of breast cancer cells and further confirmed the influence of cell cycle regulation of the G1 phase and cell cycle-related gene expression [14]. On the other hand, Xue *et al.* found that sevoflurane did not attenuate the chemosensitivity of cisplatin in cervical cancer cells. It promotes the proliferation and migration of cervical cell lines and exerts an inhibitory function on cell apoptosis [15].

### *Laboratory studies — propofol*

In contrast, laboratory studies demonstrate that propofol has anti-inflammatory, anti-oxidative, and antitumor effects by directly regulating key ribonucleic acid pathways and signaling in cancer cells [16]. Propofol regulates both microRNAs and long non-coding RNAs and regulates different signaling pathways [16]. Propofol can also induce apoptosis and preserve natural killer (NK) cell activity [17, 18]. In breast cancer lines, propofol induces cell death in breast cancer cells via the inactivation of miR-24, activates the p27 signal pathway, activates the endogenous apoptotic pathway, and induces reactive oxygen species [19, 20]. However, there are conflicting results about propofol's impact on migration and invasion of human breast cancer cell lines [21–23]. In endometrial cancer lines, Du *et al.* found that propofol significantly decreased cell proliferation, migration, and invasion and promoted apoptosis by regulating sex-determining region Y-box 4 (regulatory factor involved in tumorigenesis and tumor progression, overexpressed in endometrial cancer) [24].

### *Retrospective studies*

Retrospective studies comparing intravenous and inhalation agents have reported ambiguous results. A survey of 7,030 patients who had elective cancer surgery and required general anesthesia, published in 2016 by Wigmore *et al.*, showed that mor-

tality was approximately 50% greater with volatile than intravenous anesthesia. The majority of cancer types included in this study were: breast, gastrointestinal tract, gynecologic, sarcoma, and urologic [25]. The impact of these results is limited by heterogeneity concerning the types of cancers and other limitations associated with the study's retrospective nature. Several studies have focused on the link between anesthesia technique and the risk of recurrence and overall survival in breast cancer. In a study of 325 patients conducted by Lee *et al.*, recurrence-free survival of TIVA patients compared with the VA group was significantly higher [8].

Additionally, a retrospective, multicenter database analysis of 6,305 patients has found that TIVA may have a survival advantage compared with VA among breast cancer patients [9]. These results differ considerably from those reported by Yoo *et al.* and Huang *et al.* in retrospective analyses of 5,331 and 976 breast cancer patients. They found no significant difference between TIVA and VA groups in recurrence-free survival and overall survival [26, 27].

### *Prospective studies*

Few prospective studies have explored the effects of VA and TIVA on the perioperative immune response in cancer patients. Liu *et al.* compared the effects of propofol and sevoflurane anesthesia in 60 patients undergoing radical laparoscopic hysterectomy for cervical cancer. The patients were randomized into TIVA and VA groups, and peripheral venous blood was collected at five-time points. The T lymphocyte subsets and CD4+/CD8+ ratio, natural killer (NK) cells, and B lymphocytes were measured. In terms of protecting circulating lymphocytes, TIVA was superior to VA; however, there were no differences between groups in short-term adverse consequences, such as infection rate and hospital stay [28]. In vivo studies of the effects of TIVA versus VA on cancer regulatory factors in patients undergoing breast cancer surgery have reported conflicting results. Yan *et al.* compared the impact of TIVA and VA on the release of VEGF-C and TGF- $\beta$  and recurrence-free survival rates in the 80 patients undergoing breast cancer surgery. They found that TIVA can effectively inhibit the increases of VEGF-C concentrations after surgery compared with VA.

In contrast, these two anesthetic methods had a similar influence on TGF- $\beta$  concentration. The short-term recurrence rate did not differ [29]. In a study published by Woo *et al.*, patients undergoing breast cancer surgery were randomly assigned to receive propofol or desflurane anesthesia. Blood samples were collected at three-time points for total and differential white blood cell counts with lymphocyte subpopulations, and plasma concentrations of interleukin (IL)-2 and IL-4 were measured. Both propofol and desflurane anesthesia induces a favorable immune response to preserve IL-2/IL-4 and CD4+/CD8+ T cell ratio in the perioperative period. Concerning leukocytes and NK cells, desflurane anesthesia was associated with fewer adverse immune

responses than propofol anesthesia. Unfortunately, the authors did not evaluate the long-term clinical outcome of the patients [30].

In contrast, a study published by Oh *et al.* of 201 patients who underwent breast cancer surgery who received VA versus TIVA reported no difference in counts of NK cells, helper T lymphocytes, cytotoxic T lymphocytes (CTL), in the concentration of serum cytokines or in the expression of regulatory T cell enzymes that promote cancer recurrence [31]. A similar study of 44 patients also found that TIVA was not superior to VA on NK and CTL cell counts with apoptosis rate in breast cancer surgery [32]. In the large randomized control trial published in 2019, Sessler *et al.* compared different anesthetic regimens for breast cancer surgery. Two thousand one hundred thirty-two women younger than 85 years old having a potentially curative primary mastectomy due to breast cancer were randomized to either TIVA with paravertebral block or VA and opioid analgesia. Cancer recurrence, either local or metastatic, was similar, occurring in 10 percent of patients in each group over a median follow-up of 36 months (HR 0.97, 95% CI 0.74–1.28) [33]. This is the only large randomized control trial explicitly designed to assess cancer recurrence in different anesthetic techniques.

### Meta-analyses

In a meta-analysis published in 2019, Jin *et al.* summarized clinical studies on long-term outcomes after cancer surgery under VA and TIVA. The included outcomes were all-cause mortality, recurrence, and recurrence-free survival. TIVA was associated with slightly lower mortality after cancer surgery, while recurrence and recurrence-free survival were inconclusive. There was, however, considerable heterogeneity amongst the studies. The authors conducted a subgroup analysis for the other organs' involvement, but this did not demonstrate any significant difference between TIVA and VA (Breast cancer: HR 1.14 [0.92–1.40], Colorectal cancer: HR 0.57 [0.23 to 1.41]) [34]. Another large meta-analysis published by Yap *et al.* has shown that TIVA compared to VA was associated with lower mortality in patients with gastric (HR 0.61 [0.55–0.69];  $p < 0.01$ ), mixed gastrointestinal (HR 0.68 [0.60–0.78];  $p < 0.01$ ) and esophageal cancer (HR 0.63 [0.50–0.81];  $p < 0.01$ ), while in not in patients with breast (HR 1.12 [0.90–1.39];  $p = 0.32$ ) colon (HR 0.58 [0.23–1.49];  $p = 0.26$ ) or rectal cancer (HR 0.83 [0.52–1.31];  $p = 0.43$ ) [35]. Some authors suggest TIVA's beneficial effect in patients requiring significant surgical procedures that cause considerable tissue injury and provoke substantial neural and inflammatory responses [36].

The scientific evidence presented above does not allow drawing clear conclusions. However, many perioperative factors may influence the course of oncologic illness in gynecology patients. Several ongoing prospective RCTs with oncological outcomes as primary endpoints may help us answer this question [37–39].

## Regional anesthesia vs. general anesthesia

Perioperative optimization of patient care remains challenging due to many factors such as coexisting morbidities, progression of cancer disease, and an increasing number of elderly patients undergoing surgeries. A multimodal approach is required to provide an enhanced recovery pathway and improve patient outcomes. For years, general anesthesia with traditional opioid-based analgesia was the only option for most gynecological and breast oncology surgeries. The advances in anesthesiology and the development of novel RA techniques have provided an opportunity to tailor an individual analgesic plan to the patient and the surgery. This part of the article compares the benefits of different anesthesia strategies and reveals various regional technique options.

Although GA is considered a safe procedure, it is not without risk. Potential complications related to GA range from minor, temporary events such as PONV or sore throat to significant, life-threatening complications including myocardial infarction, heart failure, pulmonary aspiration, postoperative cognitive dysfunction, accidental awareness, or even cardiac arrest [40]. The GA-related morbidity affects most commonly elderly patients with underlying comorbidities after major surgeries. Implementation of novel anesthetic approaches allows for minimizing that risk.

Regional anesthesia aims to provide selective, reversible sensation loss in a specific body part. It is a crucial element in the multimodal anesthetic management of many types of surgery. In parallel, with the increasing availability of ultrasonography, it has stopped being an arcane art limited to a narrow group of anesthesiologists. What has begun as a simple method of numbing body parts has evolved into a highly selective blockade of neural structures.

Implementing regional techniques offers several benefits. First, it may decrease systemic exposure to anesthetic drugs, provide hemodynamic stability, and decrease postoperative adverse effects such as PONV [41]. Moreover, it may be beneficial in metastatic recurrence. In addition, recent studies suggest better pain control, reduced analgesic requirement, and prolonged time to first rescue opioids compared to GA only [42].

## Regional analgesia for gynecological oncology

### *Neuraxial anesthesia*

The development of minimally invasive surgery made laparoscopic procedures more popular than ever. However, gas insufflation into the abdominal cavity may induce many significant pathophysiological effects. Pneumoperitoneum affects preload, systemic vascular resistance, and myocardial function. Increased intraabdominal pressure and Trendelenburg position reduce the functional residual capacity (FRC), re-

sulting in atelectasis and ventilation-perfusion mismatch and may increase the risk of regurgitation. Thus laparoscopic surgeries are conventionally performed under general anesthesia due to cardiovascular stability provision, reasonable ventilation control, and airway protection. However, it is not the only option. Several studies suggest that spinal anesthesia may be a reliable alternative to GA for laparoscopy. Results reported by Sinha *et al.* summarize data of 4645 patients who underwent laparoscopic abdominal surgery under spinal anesthesia over 11 years, indicating better postoperative pain control with less PONV. The need for conversion to GA was required only in 24 patients [43]. Another paper by Sinha, after an analysis of 3492 patients, suggests that spinal technique should be the anesthesia of choice in laparoscopic cholecystectomy [44]. A study comparing spinal and general anesthesia in gynecologic laparoscopic surgery demonstrated no difference in hemodynamic and respiratory parameters and patient or surgeon satisfaction [45].

In their 2020 paper, Spannella *et al.* have presented an alternative approach to anesthesia of major abdominal surgery [46]. In 1 year, the authors have enrolled 90 high-risk patients who underwent thoracic continuous spinal anesthesia and analgesia for procedures such as colectomy, cholecystectomy, gastrectomy, nephrectomy, cystoprostatectomy, and others. They have reported no severe complications related to the procedure, highlighting the potential advantage of this method in some groups of patients. However, considering the retrospective character of the study and patients' heterogeneity, future research is needed to evaluate this strategy.

Epidural anesthesia has been proven to provide excellent pain control after major surgeries and may be associated with a lower incidence of postoperative complications. A meta-analysis of 125 studies reported that epidural anesthesia reduces postoperative mortality and improves cardiovascular, respiratory, and gastrointestinal morbidity endpoints compared to systemic analgesia [47]. However, this technique may be associated with side effects such as hypotension, urinary retention, and pruritus [47]. The study by Huepenbecker has shed more light on epidural anesthesia in gynecologic oncologic patients [48]. The work compared the incidence of postoperative complications and opioid use after exploratory laparotomy with and without epidural anesthesia. The results confirmed improved pain control, shorter hospitalizations, no difference in venous thromboembolism, lower wound complications but more prolonged urinary catheter use, and higher postoperative hypotension.

Although epidural anesthesia is considered the cornerstone in ERAS pathways, its role is currently questioned. This neuraxial technique is beneficial in general, but it has some limitations. It is contraindicated in patients on anticoagulants, coagulation disorders, or hemodynamic instability. The incidence of severe complications is rare, including troublesome events such as epidural hematoma, epidural abscess, or postoperative neurologic deficits. In the laparoscopic technique, the surgical approach is less invasive; incisional pain is lower than open surgery and does not require such



extensive analgesic methods. The specific context is essential to calculating the risk-benefit ratio. The development of novel, easy-to-perform, increasingly safe, and comparably efficient regional techniques makes epidural anesthesia less and less popular.

### *Transverse abdominal plane block*

Transversus abdominis plane (TAP) block is one of the most common regional fascial techniques for abdominal surgery. Rafi first described it in 2001 as a land-marked technique [49]. A few years later, it has become widely implemented into anesthetic management through the increased availability of ultrasound guidance. A TAP block aims to deposit a local anesthetic (LA) into a plane between the internal oblique and transversus abdominis muscles. Depending on the injection site, we can achieve various distributions of the somatic blockade. The classical lateral approach targets the TAP compartment in the lateral abdominal wall covering the Th10–Th12 dermatomes unilaterally. Deposition of LA at the posterior end of the plane is commonly called the posterior TAP block and provides wider Th9–Th12 analgesia. Next, subcostal TAP is applied to cover more cephalic areas of the abdominal wall, resulting in the involvement of Th6–Th10 dermatomes. Finally, injection into the plane above the inguinal ligament leads to an ilioinguinal and iliohypogastric block, called anterior TAP block, which provides the innervation inhibition of the inguinal area.

Many trials have examined the efficacy of TAP block. The meta-analysis found that this technique reduces opioid consumption postoperatively independently of the type of surgery [50]. However, the second outcome of this study includes no additional benefit in patients after spinal anesthesia with intrathecal opioid administration. Another meta-analysis from 2017 confirmed previous findings, indicating that TAP block is opioid-sparing and delays the time to first analgesic request [51]. Cai *et al.* have provided an analysis of the comparison between TAP block and wound infiltration with LA showing that TAP results in a more effective and steady analgesic effect [52]. Though this technique is characterized by efficacy, technical simplicity, and minimal side effect rate, it is not devoid of disadvantages, including a lack of visceral pain coverage and the need for bilateral injections for midline incisions. In contrast to most current literature, the meta-analysis of Shin *et al.* reveals data not supporting the benefit of TAP block to reduce pain or opioid use after laparoscopic and robotic hysterectomies compared to either placebo with saline or no block [53].

### *Quadratus lumborum block*

Though many studies show positive effects of TAP block, researchers tried developing techniques to widen the analgesia range and provide additional visceral pain coverage. Since Blanco described the quadratus lumborum block (QLB) in 2007 [54], it has



developed significantly. Current data report four variants of this interfascial plane technique. In reference to LA deposition concerning quadratus lumborum muscle, we can mention: lateral — QLB1, posterior — QLB2, anterior — QLB3, and intramuscular QLB injected directly into the quadratus lumborum muscle. Most studies indicate that QLB provides somatic and visceral analgesia, but the mechanism of this technique is still unclear. It is believed that the LA spreads along thoracolumbar and endothoracic fascia blocking such structures as intercostal, subcostal, iliohypogastric, and ilioinguinal nerves and reaching the paravertebral spaces. The distribution of blockade is broad and varies in each approach. Most studies indicate a large area of sensory blockade of Th7–L1 dermatomes and long-lasting effects exceeding 24 hours [55].

A recent meta-analysis published in 2021 has reviewed 27 studies and concluded that QLB has the opioid-sparing effect, prolongs the time to the first rescue opioid analgesic, and lowers the incidence of PONV after abdominal surgery [56]. Another large meta-analysis of 42 RCTs demonstrated that QLB provided analgesic benefits comparable to placebo [57]. Likewise, QLB is associated with a significant reduction of postoperative pain following laparoscopic gynecologic surgery [58, 59]. Furthermore, bi-lateral QLB provided better intra- and postoperative analgesia in patients undergoing total abdominal hysterectomy than bilateral TAP [60]. A systematic review also confirmed these findings demonstrating that QLB provides a greater opioid-sparing and long-lasting effect than TAP block after abdominal surgery [61].

### *Erector spinae plane block*

Erector spinae plane (ESP) block, first introduced by Forero in 2016 as the analgesic technique for chronic thoracic neuropathic pain [62], was soon widely implemented in anesthetic management. This novel method aims to deposit LA in the plane deep into erector spinae muscles and superficial transverse processes. The spread range of LA is not consistent in studies. Still, current literature suggests wide cephalocaudal distribution along with several levels and into paravertebral space anteriorly and laterally in the intercostal spaces. ESP block can be administered along the spine, making it a valuable part of multimodal anesthesia in many procedures. Injection at the level of Th5 is most commonly performed for thoracic surgery, Th10 for abdominal indications, and L3 for lumbar spinal surgery.

A recent meta-analysis, including data from 18 RCTs, concluded that ESP block lowers pain scores at 1, 6, 12, and even 24 hours at rest and movement after surgery, reducing the incidence of PONV [63]. The study of Kamel *et al.* explored the efficacy of bilateral ESP block compared to bilateral TAP block after total abdominal hysterectomy [64]. The results indicate the superiority of ESP block, providing more potent and prolonged postoperative analgesia. In their 2019 paper, Aksu *et al.* have compared

ESP to QLB in pediatric abdominal surgeries suggesting similar postoperative analgesia in both groups [65]. Since the ESP block is a new technique, future research should assess its role in modern anesthesia management.

## **Regional anesthesia for breast surgery**

Various regional anesthesia techniques are available to provide adequate analgesia for breast surgery. In addition, the increasing accessibility to ultrasonography has led to the development of newer regional blockades of the thorax, some specially tailored for breast surgery.

### *Breast innervation*

Knowledge about innervation is mandatory to perform adequate analgesia for different types of breast surgery. Essentially the breast is a glandular organ surrounded by subcutaneous tissue which lies over the pectoral fascia associated with the musculature of the chest. Cutaneous innervation of the breast is derived from lateral and anterior cutaneous branches of thoracic intercostal nerves. They originate from the ventral rami of thoracic spinal nerves (most commonly segments Th2–Th5). In addition, a small portion of the superior area of the breast may be innervated by the supraclavicular nerves arising from the superficial cervical plexus. The intercostobrachial nerve is noteworthy in aspects of surgery involving the axillary region. It originates from a lateral cutaneous branch of the Th2 intercostal nerve and innervates the axilla and upper medial arm. Anesthesiologists should be aware that more extensive breast procedures involve the musculature of the chest, which is supplied by the brachial plexus-derived nerves. Pectoralis major muscle innervation is provided mainly by the lateral pectoral nerve (C5–7), pectoralis minor muscle by the medial pectoral nerve (C7–Th1), serratus anterior muscle by the long thoracic nerve (C5–7), and the lateral portion of the latissimus dorsi muscle by the thoracodorsal nerves (C6–8).

### *Paravertebral block*

The paravertebral block (PVB) blocks the transmission at the level of spinal nerves exiting the intervertebral foramina. Injecting the LA into the paravertebral space causes the spreading of the blockade a few levels superior and inferior, extending into the intercostal space laterally and into the epidural space. Thus, it causes unilateral somatic and sympathetic nerve blockade. Unlike thoracic epidural anesthesia, hypotension is not common because the sympathetic blockade is unilateral. The incidence of complications after PVB is relatively low and includes pleural puncture, pneumothorax, epidural, or spinal LA injection. The 2017 review of regional techniques

for breast analgesia included 31 studies on PVB. Most of them report many benefits containing lower pain scores, lower consumption of opioids intra- and postoperatively, or lower incidence of nausea and vomiting [66].

However, the innervation of the breast is complex. Thoracic PVB does not block brachial plexus-derived nerves, such as medial and lateral pectoral nerves, long thoracic and thoracodorsal nerves, resulting in a risk of inadequate analgesia in surgery involving myofascial pain.

### *Pectoral nerve blocks*

To provide anesthesia to critical nerves for breast surgery, the novel ultrasound-guided technique: pectoral nerve block (PECS), was invented and firstly described in 2011 by Blanco as the alternative to PVB or epidural anesthesia [67]. PECS I is a technique aiming to block medial and lateral pectoral nerves by injecting LA into the plane between the pectoralis muscles. Blanco described a modification of the blockade one year later, called PECS II [68], to extend the range of anesthesia. This approach includes PECS I and targets intercostal nerves (lateral cutaneous branches), long thoracic nerve, and thoracodorsal nerve by injecting the LA into the plane between the pectoralis minor and serratus anterior muscle.

Currently, only a few RCTs compare the efficacy of PVB vs. PECS, and they remain inconclusive. Some results suggest the superiority of PECS in postoperative analgesia without causing adverse effects [69], while some indicate no significant differences [70]. High-quality trials are needed to shed more light on this topic.

### *Serratus anterior plane block*

Serratus anterior plane (SAP) block is another fascial thoracic block presented in 2013 by Blanco as the progression of work with the pectoral nerve blocks [71]. This technique covers lateral cutaneous branches (Th2–9), long thoracic nerve, and thoracodorsal nerve. The aim is to spread the LA superficially or deeply to the serratus anterior muscle in the lateral aspect of the chest.

A 2019 meta-analysis shows that SAP block reduces postoperative pain scores at rest and with movement, prolongs the time to analgesic request, and lowers the incidence of PONV in breast surgery compared to non-block care [72].

### *Erector spinae plane block*

Truncal analgesia for breast surgery can also be achieved by the ESP block. A recent study by Li *et al.*, including 6 RCTs, has shown a significant decrease in pain scores and lower opioid consumption after breast surgery [73]. In their 2021 meta-analysis,

Leong *et al.* have compared 13 RCTs indicating that ESP block is opioid-sparing and lowers the pain score compared with general anesthesia alone. However, its efficacy was inferior to PECS and similar to PVB [74].

Novel regional techniques represent high efficacy, simplicity, and low-risk profile, making them valuable in perioperative management. However, further studies are required to obtain more evidence of their mechanism of action and range of clinical indications.

### **General anesthesia vs. regional anesthesia in cancer recurrence**

Although the surgery is considered the most effective treatment option in most solid cancers, some cancer cells may persist after the surgery, either locally or at distant sites [75]. The possibility that anesthetic management may impact cancer recurrence received scholarly attention a while ago. Volatile anesthetics, opioids, and surgical stress response are the most frequently suggested factors that impair host defense against cancer recurrence. Laboratory studies indicate that volatile anesthetics, i.e., sevoflurane, desflurane, and isoflurane, affect cancer cell biology, enhancing metastatic potential [11]. In addition, those agents appear to have immunosuppressive effects and up-regulate cancer cell processes like angiogenesis and proliferation in residual cells [76]. A 2016 systematic review of anesthetic drugs on metastasis in animal models reported that volatile agents might increase metastasis. However, there is no suggestion that local anesthetics are harmful to oncologic patients [77]. The mechanism of this effect is not well understood, and there are many conflicting results among the inhaled agents and different cancer cell lines [78]. In contrast, laboratory studies demonstrate a variety of anticancer effects of propofol. Underlying mechanisms remain unclear, but regulating the expression of multiple signaling pathways, downstream molecules, microRNAs, and long non-coding RNAs are most frequently mentioned [79].

#### *Opioids effect*

Opioids have been widely used in acute perioperative pain and for cancer-related pain. However, laboratory studies indicate some mechanisms which might influence tumor recurrence. For example, some opioids have been found to impair the function of natural killers, T-cells, or macrophages, promoting immunosuppression [80]. In addition, it has been shown that opioids can directly impact cancer growth via their action on mu-opioid receptors (MOR), which are overexpressed in some cancer cell lines [81]. Furthermore, a study assessing the association between MOR genotype and breast cancer survival has shown decreased mortality in patients with MOR gene polymorphism [82].

On the contrary, an animal study by Koodie *et al.* has indicated that morphine decreases leukocyte transendothelial migration, thus reducing angiogenesis associated with tumor growth [83]. A systematic review aiming to validate the data about the link between opioids and tumor dissemination in colorectal cancer could not reveal the long-term impact on cancer-related outcomes due to the heterogeneity of the different studies [84]. Therefore, whether opioid use in surgery promotes cancer recurrence remains inconclusive.

Surgical stress may cause many biologic changes, including activation of neural and inflammatory signaling pathways, suppression of cell-mediated immunity, and release of proangiogenic factors [36]. The more extensive surgery insult in animal models is, the higher the biologic perturbations are [85]. The data in many studies underlines the significance of minimizing postoperative pain. Uncontrolled pain can be a mediator of the tumor-promoting effects. The animal model study supports the hypothesis that the provision of pain relief attenuates surgery-induced metastatic susceptibility [86].

Considering *in vitro* studies results, the best regimen for anesthetic management to improve long-term oncology prognosis should be volatile agents free anesthesia alongside regional techniques combined with an opioid-sparing strategy. However, the largest RCT explicitly designed to assess cancer recurrence published in 2019 in *Lancet* does not confirm previous *in vitro* findings [33]. The authors found no cancer recurrence differences. The secondary outcome of this study revealed that the anesthetic technique does not affect the frequency and severity of chronic post-surgical breast pain.

In summary, several laboratory and animal studies have indicated that the choice of anesthetic techniques can potentially change the long-term prognosis of oncologic patients. However, few trials are in line with *in vitro* observations. Thus, there is insufficient evidence to promote specific anesthetic management, and more large-scale research is necessary to prove a link between anesthetic techniques and metastasis.

## **Robotic surgery**

Robotic surgery nowadays plays a vital role in surgical procedures. This surgical technique improves ergonomics and allows for better visualization of the surgical field with instrument stabilization, reducing the risk of tissue traumatization with a minimally invasive approach. There are, however, limitations of robotic surgery. This approach requires additional surgical training to facilitate the patient-operator interaction's haptic feedback and generates increased costs and operating room time. There are also new challenges for the anesthetic team. They include different patient's body positioning, risk of hemodynamic instability, changes in respiratory mechanics, and limited access to the patient during the procedure [87, 88].

## *Body positioning*

Most gynecological procedures require patients to be placed in the Trendelenburg position. However, a very steep Trendelenburg position (>30 degrees) should be avoided, especially in high-risk patients, because of the risk of hemodynamic changes and influence on intracranial and intraocular pressure described below.

Some evidence suggests that the degree of Trendelenburg's position does not influence surgical site access in benign gynecologic robotic-assisted surgery [89].

Most neurological complications result from prolonged patient positioning in the Trendelenburg position and include peripheral nerve injury. Compression, stretching, and ischemia appear to be possible mechanisms of the damage. Proper padding and meticulous securing of the patient in the operating room are the primary prevention measures [90]. Fortunately, gynecologic oncology patients do not represent the group of increased risk of position-related injury [91]. Using anti-skid materials prevents uncontrolled patient displacement during surgery [92]. In the steep Trendelenburg position, vessels of the upper body show retention with increased pressure which is also transferred to the intracranial vessels, causing an increase in intracranial pressure. In case of prolonged exposition, this may contribute to the development of swelling of the brain tissue. There are reports of cerebral edema in patients treated with robotic-assisted surgery [93, 94].

Ophthalmic complications include ischemic optic neuropathy and corneal abrasion. Limiting time in steep Trendelenburg and avoiding excessive fluid administration are preventive interventions [95].

Moreover, not only general body position should be the object of matter. For example, preventing heat loss during prolonged robotic-assisted surgery reduces secondary complications like surgical site infection, coagulopathy, and hemodynamic instability [96, 97].

Nursing, surgical, and anesthesia multidisciplinary team members should be involved in patient care during robotic surgery. Patients with multiple risk factors like morbid obesity, pre-existing neurological, ophthalmic, or cardiovascular disease may be in a group considered relative contraindications for robotic surgery.

## *Hemodynamic considerations*

Hemodynamic considerations in robotic-assisted surgery are similar to the laparoscopic approach, including pneumoperitoneum and the patient position. During the insufflation of the peritoneal cavity, bradycardia may be present due to the increase in vagal tone.

Increased intra-abdominal pressure [98] may initially generate an increase in preload through the pressure exerted on the visceral veins, contributing to stroke volume

and blood pressure growth early in the procedure. However, high pneumoperitoneum pressure, reaching over 15 mmHg, may decrease preload due to closure of the visceral veins and inferior vena cava. This effect may be exacerbated by vasodilation due to sympathetic tone decrease secondary to the anesthetics used, resulting in hemodynamic instability. The position changes during surgery may overlap and have an additional effect. The anti-Trendelenburg position (head upwards) due to the tendency of blood to retain in the lower body vessels leads to a decrease of venous return, which causes a reduction in cardiac output.

Proper diagnostic tools involving continuous invasive cardiovascular monitoring, neuromuscular blocking agents activity, and anesthesia depth allow for tailoring anesthesia and meeting the patient's needs. In addition, adequate management of neuromuscular blocking agents facilitates maintaining the lowest possible pneumoperitoneum pressure and increases the circulatory system's stability.

### *Pulmonary considerations*

Pneumoperitoneum combined with Trendelenburg position influence the mechanics of ventilation. Furthermore, transthoracic pressure rise reduces tidal volume (TV) and increases airways pressure. This effect may be exacerbated by direct compression of abdominal viscera, especially in the steep Trendelenburg position. The described phenomenon generates the formation of atelectasis and hypoventilation, resulting in hypoxia and carbon dioxide retention.

The protective lung ventilation strategy extrapolated from ARDS patients treated in intensive care units allows for optimizing the operating room. According to the international expert panel-based consensus recommendations, a low TV of 6–8 ml/kg predicted body weight and positive end-expiratory pressure (PEEP) of 5 cm H<sub>2</sub>O is recommended. Furthermore, when performing recruitment maneuvers, the lowest effective pressure and shortest sufficient time should be used [99].

The profound neuromuscular blockade, confirmed with the train of four monitoring devices, facilitates the compliance between pneumoperitoneum pressure, surgical field access, and optimal ventilation. In addition, anesthesia depth monitors (bispectral index or entropy) allow for avoiding unrecognized awareness episodes.

Additional respiratory problems may arise in the obese patients population. The potential challenges include upper airway obstruction, sleep apnea, decreased compliance and FRC, atelectasis, rapid oxygen desaturation, and ventilation-perfusion mismatch [100].

Protective lung ventilation is also justified in this group of patients; however, there is a need for a tailored approach to titration of TV, PEEP, the fraction of inspired oxygen (F<sub>i</sub>O<sub>2</sub>), and pneumoperitoneum pressure regarding peak inspiratory pressure and oxygenation carbon dioxide elimination, and surgical field access.



If adequate ventilation is not achieved, despite adjusting TV, PEEP,  $F_iO_2$ , and respiratory rate resulting in hypoxia or hypercarbia, there may be necessary to convert to open abdominal surgery. Obese patients may benefit from bridging respiratory support to decrease the risk of postoperative pulmonary complications. It includes non-invasive ventilation with CPAP/PEEP or high-flow nasal cannulas systems to improve the outcome in this population [101, 102].

Monitoring and diagnosing patients' respiratory well-being measures like physical examination, pulse oximetry, and capnography are essential. In addition, point of care arterial blood gas analysis allows for a quick and accurate assessment of partial pressure of oxygen and carbon dioxide and provides valuable information regarding acid-base balance. Furthermore, it will enable modifying the ventilator settings to reach satisfactory gas exchange parameters. Another useful and practical method to assess lung parenchyma is the point of care lung ultrasonography. This quick, repeatable bedside diagnostic tool identifies dynamic changes in lung aeration during surgery, facilitating proper diagnosis and treatment [103].

### *Limited access to patient*

Another challenge when dealing with robotic-assisted surgery is limited access to patients, which in some circumstances, once the robot is docked, may become a serious problem. The initial stage of robotic surgery involves installing the device and setting monitoring with a care plan during surgery, enabling relatively quick access to the patient in case of an emergency. The port sites and robotic ports application, calibration, and de-installation interfere with time spent in the operating room. All monitors, catheters, and lines should be secured before the robot is docked. Checking position and securing endotracheal tube should be confirmed. The patient must also be well secured to avoid slipping.

### *Robotic surgery in gynecological cancers*

Despite great expectations from minimal invasive robotic surgery, it is not preferred in all gynecological procedures in oncologic patients. For example, laparotomy is associated with better outcomes in early-stage cervical cancer than a minimally invasive approach [104–107]. Similar benefits can be observed for ovarian cancer [108].

A recently published meta-analysis involving endometrial cancer patients found benefits from robotic-assisted surgery, allowing for a shorter hospital stay, lowering conversion rate to laparotomy, decreasing blood loss, and overall complications with a similar duration of surgery. However, robotic surgery was associated with higher costs [109]. Beck *et al.* indicated a lower hospital readmission percentage after robotic laparoscopic surgery for endometrial cancer [110].

## Conclusions

Modern anesthesia involving novel regional techniques, if applicable in gynecology oncologic patients, may improve the patient outcome. Further prospective studies are warranted to demonstrate the relationship of the applied anesthesia technique to the oncological outcome.

## Conflict of interest

The authors declare no conflict of interest.

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