Perioperative Effects of Surgery, Anesthesia and Analgesics Associated with Cancer Progression: A Review

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Abstract: One of the most common treatments available for cancer patients is surgical removal of the malignant tumor; its long-term implications, however, are still little-known. The purpose of this review is to look at the perioperative effects and determine if there is any correlation between surgery, anesthetics and analgesics, and cancer progression, in the form of cancerous tumor growth and progression and patient survival, within the Puerto Rican population. A retrospective literature review was conducted. Current data suggest that surgery is associated with an increase in cancer proliferation and metastasis, for various reasons such as angiogenesis enhancement and bloodstream migration. Also, it was found that some anesthetics and analgesics have been associated with cancer progression, based on the peri- and postoperative immune status of the patient. Thiopental, ketamine, isoflurane, halothane and some opioids were positively correlated with cancer progression given their role in immunosuppression; while propofol, lidocaine, ropivacaine and bupivacaine were negatively correlated with tumor progression given their immune enhancement. Others, like sevoflurane, nitrous oxide, and etomidate showed inconclusive correspondence. Therefore, it was concluded that immune system boosting anesthetics and analgesics can reduce cancer progression in a patient that has undergone surgical resection. For further research and since the available data are not extensive, other variables such as age, sex, stressors and comorbidities could be considered to better understand the mechanism in which the chemicals hereby studied can cause cancer progression.

Keywords: Anesthetics, analgesics, opioids, cancer, metastasis, recurrence, immunosuppression.

INTRODUCTION

According to the World Health Organization, cancer is one of the main causes of morbidity and mortality worldwide, accounting for 8.8 million deaths each year. It is expected that within the next 20 years, the number of new cases of cancer will increase by 70%. This disease represents not only a threat to the health and well-being of the population, but also a substantial burden on health care systems.

Health care providers in the United States (US) and Puerto Rico (PR), have been concerned with cancer statistics for the past 10 years. From 2008 to 2014, 71,997 patients in PR were diagnosed with some type of invasive cancer. The sex-related distribution was 53.8% males (N=38,750) and 46.2% females (N=33,247) [1]. Moreover, age adjusted incidence rates have gradually increased over the course of the past 25 years [1]. Statistics from the Puerto Rico Cancer Registry indicate that the most frequently diagnosed cancer subtypes in female patients are breast, colon and rectum, thyroid, and corpus and uterus. Likewise, the more frequently diagnosed cancer subtypes in males are prostate, colon and rectum, lung and bronchus, and urinary bladder [1].

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An important system in the protection of an individual against cancer development or evolution is the immune system, mainly the innate immune system. Natural Killer (NK) cells are part of the innate immune system and are the main agent in the suppression of tumor development [2]. Their main function is to identify aberrant cells, which could be infected or tumorigenic cells, and eliminate them before they become harmful to the body. NK cells perform this task without the need for sensitization with a prior exposure to an antigen [2], and using cytotoxic proteins that they store in secretory lysosomes [3]. Once cancer develops, however, there is a need for additional assistance to the body's own defenses.

Currently, once cancer develops, surgery is an important part of the treatment plan. Surgery is one of the most used and effective methods to remove solid tumors; even though it has some mechanisms that could contribute to cancer recurrence. Cancer patients already have a suppressed immune system and it has been shown that the process of surgery and other associated factors, such as psychological stress, post-surgery pain and hypothermia, can increase the rate of metastasis and recurrence of tumors [4]. The type of anesthesia used for surgery can worsen the immune system's ability to attack the spreading cancer cells [5]. The release of immunosuppressive factors leading to decreased activity of NK cells and increased pro-inflammatory cytokines are major mechanisms for this effect of anesthesia [6]. Postoperative pain can also induce a decreased activity of NK cells [5]. It has been shown that perioperative procedures lead to the release of substantial amounts of catecholamines and prostaglandins (PGs) leading to postoperative low quantity of NK cells [7].

Metastasis is an important concept in a cancer patient's prognosis. It is a complex process that starts when cancer cells from a primary tumor detach, reach a non-contiguous organ and proliferate there. Metastasis requires two basic factors to spread efficiently: evading the host's immune system and developing an independent blood supply [5]. Once these two conditions are met, the metastatic cancer cells can start to invade different organs. Data have shown a possible association between metastasis and the mechanisms of action of some anesthetics used perioperatively. Immunosuppression associated with the anesthetics is thought to decrease NK cells leaving the patient helpless against cancer dissemination [8]. Although this association has been described and reported, the evidence to prove a causal relationship has been inconclusive. This review of the current literature intends to identify and emphasize on the effects that surgery and perioperative treatment have on cancer progression in cancer patients in PR.

SURGERY: PERIOPERATIVE MANAGEMENT

As mentioned earlier, cancer metastasis is a complicated process. It can be explained by the fact that for any neoplasm to spread to other tissues and organs in a successful way, it must overcome the physiological barriers that the human body itself possesses as its major defense mechanism against such uncontrolled cell proliferation. Interestingly, the perioperative management in primary surgery is known to be critical in influencing long-term outcomes for cancer patients [8]. This period extends from the preoperative day through the surgical procedure and into the postoperative recovery. Facilitation of the metastatic process following surgery has been associated with several perioperative changes, including dissemination of tumor cells during the surgical procedure, local and systemic release of growth factors, cellular immune suppression, increased cancer cell adhesion, and stimulation of angiogenesis and inflammation [9]. Even though it might seem an interesting scenario for a neoplasm to undergo metastasis, surgical excision of the primary tumor is still one of the major options in cancer treatment and the only option for certain types of cancers. In addition to representing a useful tool for eradication or progression cessation of cancer, the removal of a primary tumor through surgery is necessary to get rid of the main source of such potentially-metastatic cells [10].

However, along with its evident benefits, cancer surgery has been found to increase the risk for the development of metastasis later in life. In a study published on the British Journal of Cancer in 2001, it was found that female patients with breast cancer who underwent surgery had a spike in their risk of death after eight years following tumor removal, as compared to the group of patients who did not have surgery. Even more so, scientific evidence reports that the clinical presentation and prognosis of such metastatic cancer is usually far more serious than the one seen with the original tumor. According to some experts, these harmful effects of cancer surgery are mediated through several mechanisms that disrupt the body's defense barriers, which normally impede or slow down the spread of malignant cells to other tissues and organs [10].

One mechanism by which surgery accelerates metastasis is by enhancing the dispersion of malignant cells directly into the bloodstream and lymphatic circulation after mechanical disruption of the tumor's integrity and its vasculature. It is known that for a group of isolated neoplastic cells to spread throughout the body and form new tumors in other tissues, it must first gain access to the bloodstream. Also, surgical removal of a primary tumor has been shown to increase malignant cell proliferation and resistance to apoptosis by reducing the number of immune cells in the body and their function [10]. Specifically, one of the most vitally important cells of the immune system that has been demonstrated to play a critical role in the recognition and destruction of malignant cells is the NK cell. As part of the innate immune system, NK cells mediate the cytotoxic killing of both malignant and virally-infected cells, while triggering the production of cytokines that enhance the immune response in the presence of a physiological stress, such as cancer. To illustrate this, a study published by Tai *et al*. in 2013 found that there was a higher lung tumor clearance following surgery in the group of mice that were injected with surgically stressed NK cells, as compared to the mice that received untreated NK cells [9].

Surgery has been found to assist the ability of malignant cells of invading body tissues and organs by two major mechanisms. The first one is based on the increased release of matrix metalloproteinases (MMPs) following surgical removal of a tumor. As Gialeli *et al*. 2011 stated, the MMPs are part of a family of zinc-dependent endopeptidases which act by degrading the extracellular matrix [11]. It has been found that the MMPs play an important role during carcinogenesis by inducing tumor growth and invasion of other tissues. The second mechanism is based on the enhanced expression of adhesion molecules such as *galectin-3* on the surface of tumor cells following surgery. This makes it easier for neoplastic cells to adhere to each other and form clumps, which therefore increases the chances for metastasis formation. Also, adhesion molecules provide cancer cells the ability to attach to the endothelial tissue lining blood vessels; hence, gaining access to distant body tissues and organs.

Surgery can also affect tumor vascularity, promoting angiogenesis by reducing the levels of tumor-related anti-angiogenic factors and increasing the levels of pro-angiogenic factors [10]. Furthermore, surgical trauma initiates an inflammatory cascade consisting of elevated levels of pro-inflammatory cytokines, including TNFα and interleukin-6 (IL), and elevated levels of growth factors, such as vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF), which are considered perioperative mediators that potentiate the metastatic ability of cancer stem cells (CSCs). Inflammatory mediators interact with cancer cells and turn on signaling pathways related to self-renewal and proliferation. Tumor-associated fibroblasts and macrophages are major sources of these inflammatory mediators in CSCs. Pro-inflammatory cytokines produced by tumor-associated macrophages confer tumorigenic properties to CSCs and promote angiogenesis and metastasis by inducing the production of VEGF and NF-kB, an important regulator of signaling pathways. Surgery-induced inflammation plays an important role in angiogenesis and metastatic properties by enhancing certain signaling pathways, including Notch and Hedgehog expression [12].

Another perioperative risk factor for cancer recurrence corresponds to postoperative complications that increase physiologic stress and psychological distress. This can also be seen through anxiety, stress or depression associated with cancer diagnosis and surgery, and causes the activation of the sympathetic nervous system and hypothalamic-pituitary-adrenal axis. Animal models have shown that a single exposure to stress or stress hormones during a critical period of tumor progression may increase cancer mortality. Exposure to stress hormones, such as catecholamines, opioids and glucocorticoids, have been related to metastatic progression in certain animal models [10]. Furthermore, catecholamines increase the levels of angiogenic factors, including VEGF and MMP 2 and 9, and proinflammatory cytokines, such as IL-6 and IL-8 [8].

Given these findings, various clinical strategies have been proposed to help prevent cancer metastasis following surgical removal of the primary tumor. Strategies to prevent cancer metastasis after surgery include combating cancer cell adhesion, supporting immune health, heightening immune surveillance, inhibiting angiogenesis, minimizing inflammation and identifying appropriate surgical techniques and anesthetic agents.

A. Induction Agents

Intravenous anesthetics are used to facilitate rapid induction of anesthesia and have replaced inhalation as the preferred method of anesthesia induction in most settings, except for pediatric anesthesia. However, due to the side effects related to this type of

drugs, many studies have suggested that a balanced anesthesia, that includes inhaled anesthetics, sedative-hypnotics, opioids and neuromuscular blocking drugs, should be used to minimize unwanted effects [13].

Propofol

Propofol is the most frequently used anesthetic induction agent in clinical practice in the US. It has been used to maintain the anesthesia in preoperative and postoperative settings, and as a common choice for sedation within the monitored anesthesia care area [13]. Studies have shown that propofol can reduce the invasive potential of cancer cells by inhibiting the formation of certain factors that can otherwise increase the capacity of metastasis [14]. One of these studies demonstrated that propofol suppresses the hypoxia-inducible factor-1α (HIF-1α) protein synthesis as well as its downstream effects. Elevated levels of HIF-1α and high activation have been heavily implicated in cancer progression, and found to be directly correlated to tumor growth, angiogenesis, metastasis and poor prognosis [14]. On the same level, propofol has also been shown to significantly suppress monocytic PG E2 production via a direct effect on COX activity [15], and enhance the activity of cytotoxic T cells through other mechanisms [14]. Siddiqui *et al*. tested propofol-docosahexaenoate (propofol-DHA) and propofol-eicosapentaenoate (propofol-EPA), and discovered that these conjugates inhibited cellular adhesion, migration, and apoptosis in the MDA-MB-231 cell line of breast cancer [16].

Another study performed in the same human breast cancer cell line showed that, for primary breast cancer surgery, the use of combined propofol with paravertebral analgesia, when compared to general anesthesia alone, resulted in a reduction in the serum concentration of pro-tumorigenic cytokines and some MPPs and an increase in the serum concentration of the anti-tumorigenic cytokine IL-10 [17]. Another benefit associated with propofol is that it stimulates the activation and differentiation of T cells, a key step in anti-infective and anti-tumor immune response [18]. Based on several studies conducted in various populations, propofol has been shown to play a protective role in the immune function and to considerably reduce tumor recurrence after various types of cancer surgeries, including breast and prostate cancer [17,18]. Moreover, randomized trials conducted by the Korean Academy of Medical Sciences have shown that NK cells and leukocytes in breast cancer cells significantly decreased 1 hour after induction with propofol in comparison with desflurane, implying the possibility of impaired innate immunity [19]. However, it must be noted that the authors mentioned that NK cells are expected to significantly decrease postoperatively and that fentanyl was used in this study to provide analgesia.

Thiopental

Thiopental is a lipid-soluble barbiturate used to induce general anesthesia by acting as a $GABA_A$ receptor enhancer, which leads to greater hyperpolarization and a reduction in excitation of the target cells [20]. The enhancement of GABAergic transmission in the brainstem results in suppression of the reticular activating system, causing sedation, amnesia, and loss of consciousness. At the level of the motor neurons in the spinal cord, this GABAergic transmission leads to relaxation of different muscles and suppression of reflexes [20].

The presence of $GABA_A$ receptors in immune cells presents the possibility of barbiturates affecting immune function. Activated $GABA_A$ ion-channel currents in T cells and macrophages and GABA application resulted in decreased cytokine secretion and T cell proliferation. Drugs that increase GABA effect, such as thiopental, decreased cytokine production in macrophages [21]. Thiopental has also been associated, in human studies, to a dose-dependent decrease in T-lymphocyte proliferation and suppression of monocyte-mediated cytolysis and, in animal studies, to a significant reduction in NK cell numbers and an increase in lung tumor retention (LTR) [22]. LTR is a calculation of the ratio between the radioactivity in the lungs and the radioactivity in the injected tumor suspension [15]. An increase, such as that seen with thiopental, in the level of lung radioactivity reflects the metastatic ability of tumor cells. Melamed *et al*. 2005 studied the effect of different anesthetic agents (halothane, ketamine, propofol, and thiopental) on the number of NK cells and the studies concluded that thiopental caused the largest decrease in immune cells [7,15].

Ketamine

Ketamine is a highly lipid-soluble phencyclidine derivative that differs from most other intravenous anesthetics in that it produces significant analgesia and has a rapid onset of its effects. Ketamine's mechanism of action is complex, but the major effect is probably produced through inhibition of the NMDA receptor complex [13].

Ketamine has demonstrated immunomodulatory effects on macrophages, lymphocytes and mast cells in experimental studies [5]. In high doses, this drug limits the maturation of dendritic cells by decreasing the number of MHC II, CD40, CD80, and CD86 that are normally high in mature dendritic cells. By suppressing CD40 and CD80 expression, this drug also inhibits T-cell function, since these molecules are co-stimulators of T-cell activation [21]. Also, mature dendritic cells produce proinflammatory molecules, such as IL-12, which are necessary for the differentiation of T-cells, and cell-mediated immunity response [21]. In another study, ketamine produced inhibitory effects on the NK cell cytotoxic activity right after an in-vitro rat model surgery; and eight days after the surgery, the administration of ketamine still increased NK cell activity in comparison to non-operated ketamine-treated animals [23].

Melamed *et al*. 2005 have studied the effects of intravenous anesthetic agents on cellular immunity [7]. One of these studies showed that rats treated with ketamine had 5.5 times the number of tumor cells when compared to the control rats [16]. Melamed *et al*. 2005 also found that ketamine, thiopental, and propofol treatments suppressed NK cell activity and levels when compared to the controls [7]. This study conducted with breast cancer metastasis in a rat model demonstrated that thiopental, ketamine, and halothane, but not propofol, can significantly promote LTR or the number of MADB106 lung metastases [18,23]. In other studies, the index of LTR within 24 hours was predictive of the effects on the number of lung metastases that could develop, and ketamine had the largest effects in the increase of LTR [23].

Nevertheless, some studies performed by Oxford academy also showed that low dose ketamine during early postoperative periods may exert a beneficial effect on the post-surgical immune response via several mechanisms [24]. One of these mechanisms is ketamine acting as an analgesic, since it causes alleviation of pain, which by itself promotes proinflammatory cytokine production and suppression of IL-2 secretion [23].

Etomidate

Etomidate is a rapid onset, short duration, non-barbiturate IV anesthetic that works on $GABA_A$ receptors to produce anesthesia. The most common complication of etomidate is twitching, which limits the use of sedatives, analgesics and muscle relaxants during the surgical procedure. It can also cause adrenal suppression, but this effect is transient.

Liu *et al*. 2016 found that the levels of CD4+ cells were significantly decreased 24 hours postoperative (lung cancer resection procedure (thoracotomy)) and that the levels of CD8+ cells were higher after surgery, in comparison to the preoperative period [25]. At 72 hours, CD4+ and CD8+ levels returned to basal state. Liu *et al*. 2016 also compared etomidate effects with those of propofol for the same surgical procedure and found that etomidate effects were minimal on CD4+ cells in comparison with those of propofol [25]. The study also showed that the immune system recovered more rapidly after the use of an etomidate infusion than after a propofol infusion. However, there is a lack of compelling evidence on anesthetic drug etomidate as a potential cause for tumor recurrence or as having a clinical significant role in cancer recurrence [26].

Benzodiazepines

Benzodiazepines (BZDs), which act on the Central Nervous System (CNS), are used as sedative-anxiolytic drugs and clinically for the treatment of anxiety disorders, epilepsy, Familial paroxysmal choreoathetosis, panic disorders, sedation, light anesthesia, and anterograde amnesia, among others [27]. The BZDs work in two ways: first, they can bind to the BZD cleft composed of the subunits α1 and ɣ2 of the $GABA_A$ receptor and enhance its binding, allowing less concentration of the neurotransmitter to exert its effects on the receptor. Secondly, they can bind to the Peripheral Benzodiazepine Receptor (PBR), which consists of several subunits, among them the isoquinoline binding protein or translocator protein [27]. This receptor was found to be distributed in many peripheral organs, the CNS (in the glial cells) and other inflammatory cells [28].

It has been found that the chronic exposure to low doses of BDZ reduced cytokines IL-1, IL-2, IL-6, TNFα and IFNɣ [29]. Many theories are being studied on how these drugs exert their immunomodulatory effects; one of the theories implicates the PBR receptor, present in macrophages and lymphocytes (as well as many other organs), as responsible for the immunotoxic effects of BZDs. Another researcher points out that it could be the stimulation of these receptors in the steroidogenic tissues, that increases the glucocorticoid production, hence provoking the immune suppression and anti-inflammatory effects [30]. Researchers are considering that for the immunomodulatory and immunotoxic

effects of these drugs could be due to a combination of both the glucocorticoid elevation and the production of cytokines. Schlumpf *et al*. 1994 reported a possible change in the cytokine network of macrophages and lymphocytes after stimulation of the PBR receptor by BZDs [31]; while Ostuni *et al*. 2004 reported that blocking voltage dependent calcium channels, which are essential for T-cell activation, seems to be the direct consequence of BZDs binding to the PBR receptor [32].

Scientists believe there is an association between BZDs and an increased risk of cancer, but this is yet to be proven. Numerous studies have been conducted yielding mixed results. A specific association was found between some BZDs, like clonazepam, and the risk for brain cancer (98% risk), colorectal cancer (CRC) (25%), esophageal cancer (59%), prostate cancer (36%), bladder cancer (39%), liver cancer (18%), pancreatic cancer (41%) and lung cancer (10%) in comparison to subjects that didn't use BZDs as long term therapy. These results contrast with those of other researchers, such as Pottegard *et al*. 2013, which found that there was no association of BZDs and benzodiazepines related drugs with an overall increase of cancer risk and that the risks found were likely the result of lifestyle confounding factors, such as smoking [33].

B. Inhalation Agents

The use of certain volatile anesthetics has been implicated in the upregulation of HIF-1α [34]; a transcription factor that plays an essential role in the development and progression of tumors [35]. The gene regulation promoted by HIF-1α and HIF-2α has been acknowledged as an important determinant in tumorigenesis and metastasis [34]. A study by Wang *et al*. in 2014, revealed that HIF-1α overexpression might be a predictive factor of poor prognosis for non-small cell carcinoma of the lung (NSCLC), particularly in Asia [35]. This correlation has also been demonstrated in clinical studies of gastric, colorectal, breast, ovarian and hepatocellular carcinomas [34].

Isoflurane and Halothane

Volatile anesthetic agents like isoflurane, and the once used halothane, have been associated with properties of immunomodulation and a reduction in cell-mediated immunity [15,16]. According to Kaye *et al*. 2014, isoflurane and halothane have been shown to attenuate the interferon stimulation of NK cells in mice [16]. The immunosuppressive effects of inhalation agents have been demonstrated with *in vitro* experiments, which revealed DNA damage to human peripheral blood lymphocytes in a dose-dependent manner after exposure to halothane, isoflurane, sevoflurane, and desflurane [15].

The effects of volatile anesthetics on innate immunity are primarily observed on neutrophils, dendritic cells, NK cells, and resident tissue macrophages. Exposure to halothane was found to affect reactive oxygen species (ROS) production and chemotaxis [36]. Several studies revealed that isoflurane decreased neutrophil adhesion to human endothelial cells; and *in vitro* studies showed that isoflurane decreased the NK cell response to interferon [36]. Isoflurane inhibits immune cell adhesion by binding to lymphocyte function associated antigen-1 (LFA-1) thereby blocking the coupling of LFA-1 to intercellular adhesion molecule-1 (ICAM-1) on antigen presenting cells (APCs). Other studies have shown that in a concentration-dependent manner, isoflurane can activate p38 MAPK (mitogen-activated protein kinase) which regulates TNFα, IL-β, and IL-6 [36].

Sevoflurane

Sevoflurane, a volatile anesthetic, is associated with downregulation of the HIF-1α system. A study performed by Liang *et al*. in 2015, showed that sevoflurane could suppress hypoxia-induced growth and metastatic ability of cells [37]. It has also been showed that sevoflurane can decrease the phosphorylation levels of p38 MAPK, involved in the downregulation of MMP2, MMP9, fascin, and ezrin expression [37]. However, a study performed on glioma stem cells (GSCs) demonstrated expansion of human GSCs through HIFs *in vitro* [39]. It is important to consider that extrapolation of experimental data to the clinical situation must be done with caution. Also, the type of tumor stem cell can influence the outcome of the results.

While this aspect of sevoflurane may be beneficial for patients undergoing tumor resection to decrease the risk of metastasis, sevoflurane has also been associated to attenuation of NK cell mediated cytotoxicity by LFA-1 inhibition *in vitro* [40]. A study comparing the effects of propofol induction and maintenance versus sevoflurane induction and maintenance demonstrated decreased counts of CD3+, CD4+ T cells, NK cells, and the CD4+/CD8+ ratio in the postoperative period, leading to an extended recovery period, when compared to the propofol induction and

Table 1: Mechanism of Action and Systemic Effects of Inhaled Anesthetics

Agent	Mechanism of action	Systemic effects
Isoflurane	Inhibits activation of neutrophils Binds to LFA-1 thereby blocking the coupling of LFA-1 to ICAM-1 on APCs (Stalling *et al*., 2016) Upregulates HIF-la (Tavare *et al*., 2012)	General anesthetic effects Decreases neutrophil adhesion to human endothelial cells Decreases NK cell response to IFN HIF-1a overexpression might be a predictive factor of poor prognosis for NSCLC (Wang *et al*., 2014).
Halothane	Upregulates HIF-la (Tavare *et al*., 2012) Affects ROS production and chemotaxis (Stalling *et al*., 2016)	General anesthetic effects Decreases NK cell response to IFN
Sevoflurane	Downregulates the HIF-1a system Suppresses hypoxia-induced growth and metastatic ability of cells (Liang *et al*., 2015) Decreases the phosphorylation level of p38 MAPK, involved in the downregulation of MMP2, MMP9, fascin, and ezrin expression (Liang *et al*., 2012)	General anesthetic effects Associated with attenuation of NK cell mediated cytotoxicity by LFA-1 inhibition in vitro (Tazawa *et al*., 2017) Induces apoptosis of peripheral lymphocytes in dose- and time- dependent manners (Liu *et al*., 2016)
Nitrous Oxide	Inhibits methionine synthase due to its interaction with vitamin Bl2 Increases leukocyte adhesion to cerebral blood vessels	General anesthetic effects Thyrnidine and folate deficiency, leading to impaired DNA production (Fleischmann *et al*., 2009; Myles *et al*., 2004) Restricted formation of new cells (Fleischmann *et al*., 2009) Depression in neutrophil chemotaxis and reduced proliferation of human peripheral blood mononuclear cells (Fleischmann *et al* ., 2009; Myles *et al*., 2004)

maintenance group [25]. Other studies have demonstrated that sevoflurane can induce apoptosis of peripheral lymphocytes in dose- and time-dependent manners, further immunosuppressing the patient in the postoperative recovery period [25].

Nitrous Oxide

Modern practice of anesthesiology relies on the use of combinations of intravenous and inhaled drugs, this practice is known as balanced anesthesia technique [13]. For extensive surgical procedures, anesthesia may begin with preoperative BZDs, be induced with an intravenous agent, and maintained with a combination of inhalation such as nitrous oxide (N_2O). N_2O has been given to millions of patients and is one of the most commonly used general anesthetics. Some studies have shown that N_2O impairs numerous cellular mechanisms. One of these mechanisms is the inhibition of methionine synthase due to its interaction with vitamin B12. This inhibition leads to thymidine and folate deficiency, leading to impaired DNA production [41,42]. All these effects result in a restricted formation of new cells, such as those of the hematopoietic system, which are critical for fighting cancer [41]. Also, some animal studies have reported a depression in neutrophil chemotaxis and a reduced proliferation of human peripheral blood mononuclear cells [41,42].

Nevertheless, other investigations have found an inverse effect in the brain upon exposure to N_2O, where increased leukocyte adhesion to cerebral blood vessels was seen. Notwithstanding the contrasting results, in this study there were no harmful effects with wound infection during the postoperative period after colon surgery. However, a study with patients undergoing major colorectal surgery receiving 70% N_2O or N_2O-free anesthesia with 30% or 80% oxygen had increased DNA damage and postoperative wound infection when compared to patients who underwent nitrous-free anesthesia [43]. The difference in outcomes from both studies demonstrates the need for further research in N_2O's postoperative effects on wound infections and immunosuppression.

Fleischmann *et al*. 2009 studied the risk of cancer recurrence after colorectal surgery in a follow-up of a randomized controlled trial. The study concluded that no difference in recurrence was detected between the group that received nitrogen compared to the group that received N_2O [41]. This study was limited due to its small sample size; to determine the effects in the general human population larger clinical trials are required.

C. Local Anesthetic Agents

Local anesthetics have been implied to influence tumor suppression and *in vitro* experiments have

Table 2: Mechanism of Action and Systemic Effects of Intravenous Anesthetics

Agent	Mechanism of action	Systemic effects
Propofol	Acts on the $GABA_A$ receptor (Ruesch *et al*., 2012).	Reduces invasive potential of cancer cells and enhances cytotoxic T cell activity (Huang *et al*., 2014) NK cells and leukocytes in breast cancer cells decrease after induction with propofol (Woo *et al*., 2015) Reduces tumor recurrence after cancer surgeries (Deegan *et al*., 2009; Lee *et al*., 2016)
Barbiturates (i.e. Thiopental)	Act as a $GABA_A$ receptor enhancer	Induce general anesthesia Decreased cytokine production in macrophages (Bovill, 2010) Dose-dependent decrease in T cell proliferation and suppression of monocyte-mediated cytolysis (Gach *et al*., 2011)
Ketarnine	Highly lipid-soluble intravenous anesthetics that inhibits the NMDA receptor complex (Katzung *et al*., 2015).	Produces significant analgesia In high doses, prohibits the maturation of dendritic cells by decreasing the number of MHC II, CD40, CD80, and CD86 that are normally high in mature dendritic cells (Bovill *et al*., 2010) Inhibitory effects on NK cell cytotoxicity (Forget *et al*, 2010) Promotes LTR or the number of MADB106 lung metastases (Forget *et al*., 2010; Lee *et al*., 2016)
Etomidate	Rapid onset, short duration, non-barbiturate IV anesthetic that works on $GABA_A$ receptors	Produces anesthesia Can cause transient adrenal suppression Effects were minimal on CD4+ cells in comparison with those of propofol (Bharati *et al*., 2016)
Benzodiazepines (i.e. Midazolam)	Binds to the BZD cleft composed of the subunits a1 and g2 of the $GABA_A$ receptor and enhance its binding Binds to the PBR (Whirl-Carrillo *et al*., 2012)	Glucocorticoid elevation and production of cytokines (Ghada *et al*., 2011) Chronic exposure to low doses of BDZ reduces the cytokines IL-1, IL-2, IL-6, TNFa and IFNg (Kalashnikov *et al*., 2002)

described them to be cytotoxic at high concentrations [5,15]. The cytotoxic effects of local anesthetics on neoplastic cells depend on the duration of exposure and lipid solubility of the drug [15]. One study found that local anesthetics alter the DNA methylation status of certain cancer cell types and were also associated with reactivation of tumor suppressor genes [5]. A study by Werdehausen *et al*. in 2012 revealed that local anesthetics have cytotoxic effects on T lymphoma cells *in vitro*, with apoptosis at lower concentrations and necrosis at higher concentrations [5,44].

Lidocaine

Lidocaine, one of the most commonly used local anesthetics to treat chronic pain, is also associated with antiproliferative effects on tumor cells by inhibiting the EGF receptor (EGFR) [16]. A study performed by Sakaguchi *et al*. in 2006 demonstrated this effect of lidocaine on human tongue cancer cells. Lidocaine was found to inhibit tyrosine kinase activity of EGFR on human tongue squamous cell carcinoma CAL27 cells, which suppressed tumor proliferation [45].

In addition, lidocaine was also associated with inhibition of invasion and migration of some cancer cells. This was demonstrated in a study performed by Jiang *et al*. 2016 using transient receptor potential cation channel subfamily V member 6 (TRPV6)-expressing cancer cells [46]. Three different types of cancer cells were used in the study: human breast cancer MDA-MB-231 cells, prostatic cancer PC-3 cells and ovarian cancer ES-2 cells. The TRPV6 channels have high calcium selectivity and aid in calcium homeostasis. Lidocaine was found to downregulate TRPV6 channels, inhibiting the invasion and migration of the cancer cells, which results in the attenuation of calcium influx [46].

Ropivacaine

Ropivacaine, a long-acting local anesthetic used for postoperative pain, causes reversible inhibition of sodium ion influx which blocks impulse conduction in nerve fibers [47]. In addition to its use in pain management, ropivacaine has also been demonstrated to have suppressive effects on the growth of tumor cells. An *in vitro* study demonstrated that ropivacaine suppressed the growth of human colon adenocarcinoma cells and inhibited cancer cells in a dose-dependent manner [16].

Table 3: Mechanism of Action and Systemic Effects of Local Anesthetics

Agent	Mechanism of action	Systemic effects
Lidocaine	Fast voltage-gated Na^+ channel blocker in CNS Open and inactivated Na^+ channel blocker in heart EGFR inhibitor in cancer cells Downregulates TRPV6 expression on cancer cells (Jian *et al*., 2016)	Local and regional anesthetic/analgesic effects Antiarrhythmic effect Antiproliferative effect on EGFR- expressing cancer cells Inhibition of cell invasion and migration on TRPV6-expressing cancer cells (Jian *et al*., 2016)
Ropivacaine hydrochloride	Reversible voltage-gated Na^+ channel blocker	Long-term local anesthetic/analgesic effects Inhibition of cell growth of human NSCLC (Wang *et al*., 2016)
Bupivacaine	Reversible voltage-gated Na^+ channel blocker Inactivation of ribosomal protein S6 kinase 1 (Beigh *et al*., 2014) Induction of ROS generation and p38 MAPK in mouse neuroblastoma Neuro2a cells (Harato *et al*., 2012)	Long-term local anesthetic/analgesic effects Inhibition of cell growth (Beigh *et al*., 2014) Apoptosis in mouse neuroblastoma Neuro2a cells (Harato *et al*., 2012)

As previously mentioned, ropivacaine relieves pain by inhibiting voltage activated sodium channels (VASCs). Moreover, breast, colon, and prostate cancer cells express local anesthetic-sensitive VASCs. A study performed by Baptista-Hon *et al*. 2014 revealed that ropivacaine inhibits neonatal NaV1.5 channels, which are a variant also expressed by metastatic cancer cells derived from both colon and breast [48]. Ropivacaine was found to inhibit SW620 metastatic cells invasion in a concentration-dependent manner through inhibition of the NaV1.5 channels by stabilizing the inactivated state. This finding is particularly important since the VASCs expressed by cancer cells are more likely to be in the inactivated state, which has a higher affinity for local anesthetics [48].

In a study performed by Wang *et al*. 2016 the effect of ropivacaine on human NSCLC cells was examined *in vitro* [49]. Ropivacaine was found to inhibit cell growth and arrest the cell cycle at G0/G1 phase. In addition, ropivacaine triggered apoptosis in human NSCLC cells via apoptotic and MAPK pathways [49].

Bupivacaine

Bupivacaine is a long-acting local anesthetic used for pain management, epidural anesthesia, and nerve blockade. Its use has been associated with severe cytotoxicity, apoptosis and inhibition of cell growth and proliferation. Various studies suggest that the cell damage caused by bupivacaine may involve participation of MAPK and protein kinase B (Akt) signaling pathways. A study performed by Beigh *et al*. 2014 demonstrated the effect of bupivacaine on cell growth and proliferation by inhibition of S6K1, a ribosomal protein kinase that acts downstream of mTOR/PI3-kinase/Akt signaling pathway [50]. Bupivacaine was found to inhibit cell growth, since activation of S6K1 is essential for cell cycle progression due to its influence on protein synthesis [50]. Another study demonstrated that bupivacaine also causes apoptosis in mouse neuroblastoma Neuro2a cells by inducing ROS generation and p38 MAPK [51].

In a study performed by Xuan *et al*. 2016 the effects of bupivacaine on ovarian cancer SKOV-3 cells and prostatic cancer PC-3 cells were demonstrated. It was found that bupivacaine has cytotoxic, anti-proliferative and anti-metastatic properties in both cell lines [52]. In addition, the action of glycogen synthase kinase-3β (GSK-3β) was studied in the presence of bupivacaine. GSK-3β is a serine/threonine kinase implicated in various cell functions, including differentiation, proliferation and apoptosis. This study found that GSK-3β expression is necessary for bupivacaine induced cell death [52].

D. Regional Agents

Epidural Analgesia/Anesthesia

Thoracic epidural anesthesia (TEA) is an anesthetic technique that provides intra and postoperative analgesia. TEA has been demonstrated to significantly reduce stress and immune dysfunction in trauma patients. A study by Gu, *et al*. 2015, suggests that epidural blockade suppresses the stress-induced increase in Cor and IL-6 levels secondary to esophageal surgery [53]. This effect could be due to the epidural blockade of sympathetic nerves; decreasing the stress response after surgery, can promote tumor metastasis [54]. This type of anesthesia could play a role in downgrading immune activation, due to decreased sympathetic activity in the liver,

Table 4: Mechanism of Action and Systemic Effects of Various Types of Regional Anesthetics

Agent	Mechanism of action	Systemic effects
Epidural Anesthesia	In regional anaesthesia, local anesthetics are applied locally to interrupt the conduction of pain impulses from the site of the injury to the CNS. The action is exerted at the nerve roots (Andreae & Andreae, 2012) The anesthetic is injected in the epidural space	Inhibits or attenuates surgical stress Reduces the amount of intraoperative general anesthetic required Preserves NK cell function and Thl Cell activity better than general anesthesia (Bauer *et al*., 2012) Leads to decreased concentration of inflammatory cytokines and intestinal neutrophil accumulation and tissue edema (Enigk *et al*., 2014) Suppresses the stress induced increase in IL-6 levels (Gu *et al*., 2015)
Spinal Anesthesia	In regional anaesthesia, local anesthetics are applied locally to interrupt the conduction of pain impulses from the site of the injury to the CNS. The action is exerted at the nerve roots (Andreae & Andreae, 2012) The anesthetic is injected into the subarachnoid space	Attenuates neuroendocrine stress response to surgery Preserves NK cell function and Thl cell activity better than general anesthesia. (Bauer *et al*., 2012) More effective than general anesthesia in suppressing stress based on metabolic, hormonal and hemodynarnic response (Milosavljevic *et al*., 2014)

reducing liver immunity [55]. In a study done by Enigk, *et al*., it was concluded that TEA mediated regional sympathetic blockade was associated with decreased concentrations of inflammatory cytokines, intestinal neutrophil accumulation and tissue edema, and with less endothelial activation and leukocyte adhesion [56].

Interestingly, it has been mentioned that adding epidural anesthesia and analgesia to general anesthesia may be better than general anesthesia alone. This could be due to epidural anesthesia serving as a better agent for postoperative pain relief and reducing the incidence of side-effects [57]. By decreasing the surgical stress response and exposure to opioids, regional anesthetic techniques may suppress immune function less than opioid analgesia. However, although a study by Chen and Miao in 2013 found that there are beneficial effects of epidural use, it was not found to decrease cancer recurrence [57]. They concluded that epidural anesthesia may improve overall survival in patients with operable cancer undergoing surgery and found no association between epidural anesthesia and cancer recurrence [57]. Although studies have found that epidural anesthesia prolongs survival of cancer patients after surgery, this remains a controversial subject.

Spinal Anesthesia

Spinal anesthesia is a type of anesthesia used for laparoscopic cholecystectomy and abdominal surgeries. There are some advantages to using spinal anesthetics directly at the required heights in the body [58]. No blockade to the lower extremities means that a large portion of the body experiences no dilation of the veins and this may offer a compensatory buffer to the adverse changes in blood pressure intra-operatively. Moreover, the doses needed are very low, given that the drug is highly specific to certain nerve functions along a section of the cord; and the degree of muscle relaxation achievable without central or peripheral depression of respiration and circulation is superior to general anesthesia [58]. Milosavljevic *et al*. 2014 concluded that spinal anesthesia proved to be more effective than general anesthesia in suppressing stress based on metabolic, hormonal and hemodynamic response [59]. General anesthesia suppresses cerebral and thalamic functions while preserving the function of low brain and spinal circuits. Different to general anesthesia, regional anesthesia blocks nerves directly and stops the reflex circuit between noxious afferents and sympathetic efferents at the surgical level, thus attenuating surgical stress and immunosuppression [60]. In a study done by Tseng *et al*. in 2014 on prostate cancer, they found no difference in prostate cancer recurrence between patients who received intraoperative spinal anesthesia versus general anesthesia [61].

E. Analgesics

Opioids

Opiates are the naturally occurring analgesic alkaloids and sedative agents that contain the Opium molecule, a derivative from the poppy plant *Papaver somniferous* and *Papaveraceae album* [13]. Opioid receptor agonists are the primary drug class medically used to relieve acute or moderate to severe pain. These drugs produce their analgesic effects by acting on various receptors especially μ-opioid receptors, the

Table 5: Mechanism of Action and Systemic Effects of Analgesics

Agent	Mechanism of action	Systemic effects
Opioids	The drugs are agonist opioid receptors, especially μ opioid receptor μ opioid receptors are the major analgesic receptor on the brainstem, spinal cord and primary afferent peripheral terminals	Intraoperative and postoperative analgesia Constipation Promote metastasis of malignant cells (Shavit *et al*., 2004) Modulation of antibody production and the activity of NK cells (Shavit *et al*., 2004) Involvement in angiogenesis (Gubpta *et al*., 2002)
NSAIDs	Inhibit COX-I and COX-2 enzymes, decreasing the production of PGs and thromboxanes	Anti-inflammatory, analgesic, antiplatelet and antipyretic effects Can reduce cancer progression by inhibiting COX (Heaney & Buggy, 2012).
Gabapentin	GABA analogue Voltage-dependent calcium channel (a2d subunit) blocker	Potent anticonvulsive effects Anti-allodynic/anti-hyperalgesic effects

major analgesic opioid receptor, on the brainstem, spinal cord and primary afferent peripheral terminals [20]. Opioids have been used to treat pain associated with cancer and other terminal illnesses. They have been used to achieve intraoperative and postoperative analgesia; some of the most commonly used are morphine, fentanyl and tramadol.

Numerous studies have shown that opioids can promote metastasis of malignant cells. They stimulate angiogenesis, a key factor in growth and dissemination of cancer, in part by activating COX-2 and increasing the production of PG E2, which promotes angiogenesis and tumor progression [62]. Opioid receptors are significantly involved in signaling pathways that modulate antibody production and the activity of NK cells [62]. Morphine is a full agonist and has the greatest affinity to the μ-opioid receptors from all opioids [13]. Morphine is known as the “gold standard” for pain relieve. Currently, it is considered one of the most effective drugs available for the management of severe pain associated with cancer due to its superior efficacy when compared to other opiates [63,64]. Gupta *et al*. 2002 demonstrated that morphine promoted tumor angiogenesis in human MCF-7 cell breast tumor xenograft model in mice *in vivo*, leading to increased tumor progression [63,65]. Morphine can stimulate the MAPK/ERK signaling pathway in parallel with stimulating the proliferation of Human Dermal Microvascular Endothelial Cells, which are closely involved in angiogenesis [63]. This study also demonstrated that morphine inhibits endothelial apoptosis and promotes cell cycle progression by activating Akt and Cyclin D1.

One receptor subtype, known as μ3 receptor, is coupled to constitutive nitric oxide (NO) release pathway and this type of receptor can be expressed in human cancer cells [62]. NO mediated MAPK/ERK phosphorylation of VEGF promotes tumor growth by stimulating angiogenesis [63]. Morphine binds strongly to this receptor, μ3, whereas binding of synthetic opioids such as fentanyl and the endogenous opioid peptides is considerably weaker. This can explain why morphine is more immunosuppressive than some endogenous opioid peptides that are predominantly immunostimulatory [62].

Fentanyl is a short-acting synthetic opioid agonist that is much more potent than morphine. It is mostly used for intra-operative and peri-procedural analgesia due to its high potency and rapid onset of action. Shavit *et al*. 2004 studied breast cancer metastasis in a rat model and demonstrated that fentanyl can significantly increase LTR [62] The findings of this study indicate that a moderate dose of fentanyl increases the risk of tumor metastasis [66].

Tramadol is a centrally acting analgesic with a mechanism of action that is predominantly based on blockade of serotonin reuptake. Given the fact that tramadol has a weak opioid action and is largely independent of μ-receptor action, this drug can be used as an adjunct with pure opioid agonists in the treatment of chronic pain [13]. Tramadol was found to have less immunological effects than morphine and it was not found to cause a dose-dependent reduction in phagocytic activity of peripheral polymorphonuclear cells and monocytes, in a human *in vitro* study [22].

A review of animal models showed an increase in NK cell activity and lymphocyte proliferation following tramadol administration [22]. Sacerdote *et al*. 2000 reported that after an abdominal surgery for uterine

carcinoma, followed by tramadol administration, there was no lymphoproliferative decrease as with morphine [66]. This study also demonstrated an enhanced activity of NK cells in patients treated with tramadol, due to the increase of serotoninergic tone that has been associated with NK activity and lymphocytic proliferation [66].

Nonsteroidal Anti-Inflammatory Drugs (NSAIDS)

NSAIDs are anti-inflammatory drugs that work by inhibiting COX-1 and COX-2 enzymes, decreasing the formation of PGs and thromboxanes in the body. In addition to the classic anti-inflammatory effect, they also have analgesic, antipyretic and antiplatelet (aspirin) effects. Aspirin is the prototype NSAID; even though it is an irreversible inhibitor of both COX enzymes, while the other NSAIDs are reversible inhibitors. All NSAIDs have the same efficacy but differ in their half-life.

Studies have shown that PGs activate the inflammatory response and promote cancer adhesion, migration and invasion. PGs inhibit the activity of cytotoxic T cells and dendritic cells; they downregulate anti-neoplastic cytokines while upregulating the cytokines IL-4, IL-6 and IL-10, which have an immunosuppressive effect. Also, they have been shown to downregulate TNFα and IFNɣ. There is also evidence that COX can convert pro-carcinogens into carcinogens, inducing tumor formation. By inhibiting the COX enzymes, the pathway to produce PGs is inhibited, leading to the possible use of COX-inhibitors to reduce cancer progression [5]. A study by Ruder *et al*. in 2011 demonstrated that the use of COX inhibitors was associated with a 20% reduction in the risk for CRC. Another study, conducted by Zhao *et al*. in 2013 found that the NSAIDs aspirin and ibuprofen were associated with a decreased risk for the development of breast cancer [68].

The problematic with COX inhibitors relies on the risk of cardiovascular morbidity (except for aspirin), especially with selective COX-2 inhibitors (celecoxib), which limits their use as a possible therapy for the reduction of cancer progression. The selective COX-2 inhibitor, celecoxib, is used as adjuvant therapy in reductional surgeries of adenomatous colorectal polyps performed in individuals with Familial Adenomatous Polyposis. This drug decreases the activity of the peroxisome proliferator-activated receptor delta (PPARδ), which is a transcription factor that heterodimerizes with the RXR transcription factors that are involved in the regulation of growth. The inhibition of PPAR prevents the pathway signaling, removing the potent mitogenic stimulus that could promote the development of CRC.

Gabapentin

Gabapentin, a widely used analgesic, was initially approved as an antiepileptic agent in the 90's. It is an analogue of GABA and works on the α2δ-1 subunit of voltage-gated calcium channels [69]. Although it is used as an analgesic for neuropathic pain, including cancer-related pain; some studies suggest that gabapentin may also affect cancer cells. A study performed by Bugan *et al*. in 2015 demonstrated the effect of gabapentin on prostate cancer progression. It demonstrated that gabapentin had no effect on primary tumor development, but metastasis to the lungs was affected in a dose-dependent manner [60]. Gabapentin was associated with a decrease, followed by an increase, in metastasis. They concluded that the fact that gabapentin has multiple mechanisms of action may be the reason for both its pro- and antimetastatic effects [60].

F. Others

Antiemetics

Dexamethasone

Dexamethasone is a glucocorticoid commonly used in the perioperative process as prophylaxis for postoperative nausea and vomiting (PONV), as recommended by the PON Consensus Guidelines [70]. Nevertheless, its use has been debated due to its many side effects when used perioperatively. Dexamethasone has been shown to suppress T cell function as well as NK cell development [70].

However, a randomized study of patients who underwent emergency or elective laparotomy assessed the use of dexamethasone in association with surgical site infections or wound related complications and concluded that perioperative administration of dexamethasone was not significantly associated with surgical site infections or other wound-related complications [71].

A retrospective study performed by Merk *et al*. in 2016, considered women who underwent surgery for endometrial cancer from 2003 to 2007 and divided them in those who received dexamethasone for PONV and those who did not receive dexamethasone [72]. Dexamethasone administration was not associated

Table 6: Mechanism of Action and Systemic Effects of Antiemetic Agents and other Drugs

Agent	Mechanism of action	Systemic effects
Dexamethasone	11-0H-glucocorticoid receptor agonist	Reduced inflammation Immunosuppression Potentiation of antiemetic effect (when used with 5-HT3 receptor antagonist)
Substance P (Aprepitant)	Substance P/Neurokinin 1 receptor antagonist in CNS	High antiemetic effect
Neuromuscular blocking agents	Non-Depolarizing: Inhibition of neuromuscular transmission from nerves to muscles by competitively blocking the binding of acetylcholine to postsynaptic receptors at the motor end plate (Grosse- Sundrup *et al*., 2012). Depolarizing: Induction of depolarization of muscle cell membranes (Boiij, 2001).	Inmobility Most cause direct release of mast cell histamine (Mali *et al*., 2012) Atracurium and vecuronium induce astroglial differentiation of GSCs (Spina, *et al*., 2016) Atracurium can induce apoptosis in A549 human lung cancer cells (Sun, *et al*., 2016).
Alpha-2 adrenoceptor agonists	Stimulation of a2 receptors	Increase in cell proliferation (Shen *et al*., 2008) Reduction of NK cell activity in non-operated animals and during the first 24-hours post-surgery (Forget *et al*., 2010)

with an increased risk of recurrence in women having surgery for endometrial cancer [72]. A similar study was performed to determine the overall increase in the risk of ovarian cancer recurrence in patients given a perioperative single dose dexamethasone. The study ultimately found no significant association between perioperative dexamethasone use and ovarian cancer recurrence after primary surgical treatment [70].

Substance P Antagonist (Aprepitant)

The substance P/NK receptor complex has been associated with cancer progression. Substance P binds to the NK-1 receptor and induces tumor cell proliferation, migration of tumor cells and angiogenesis [73]. NK-1 receptor antagonists inhibit the proliferation of tumor cells and employ antiangiogenic properties; they can be considered anti-tumor drugs [73,74]. Aprepitant, an NK-1 receptor antagonist, has been evaluated as a new agent for PONV [75]. Guidelines from the American Society of Clinical Oncology recommended the use of aprepitant in addition to conventional antiemetic therapy [76].

Hatsuyama *et al*. 2015 studied the antiemetic effects of aprepitant in patients with lung cancer undergoing chemotherapy with carboplatin that developed chemotherapy-induced nausea and vomiting despite the preventive administration of 5-HT3 receptor antagonist and dexamethasone [76]. The study suggests that administration of aprepitant had high antiemetic effects in these patients who failed initial chemotherapy-induced nausea and vomiting therapy [76].

Neuromuscular Blocking Agents

Neuromuscular blocking agents (NMBA) are used to achieve immobility with lower levels of anesthetic agents. Non-depolarizing NMBA exert their function by inhibiting neuromuscular transmission from nerves to muscles, competitively blocking the binding of acetylcholine to its postsynaptic receptors at the motor end plate [77]. Depolarizing NBMA work by inducing depolarization in cell membrane of muscle cells. NMBA are the most common cause of anaphylaxis during general anesthesia or postoperatively; succinylcholine presenting the greatest risk. Most NMBAs cause the direct release of mast cell histamine [78]. In a study done by Grosse-Sundrup in 2012, *et al*., they concluded that the use of intermediate acting NMBAs during anesthesia was associated with an increased risk of clinical respiratory complications [77]. In terms of association with cancer, studies have analyzed the influence of some of these agents on the proliferation of normal human cells and their pharmacokinetic and neuromuscular effects in patients with liver problems. Still, the effects of these drugs on cancer have been poorly investigated. In the work done by Amann *et al*. in 2001, they studied the influence of atracurium, cisatracurium and mivacurium on the proliferation of human cell line hepatoma HepG2 cells and human umbilical vein endothelial cells *in vitro* [79]. Their study demonstrated that atracurium and cisatracurium progressively decreased cell proliferation in a concentration-dependent manner in both cell lines, while mivacurium did not inhibit cell proliferation [79] Also, atracurium besylate and vecuronium have been found to induce astroglial differentiation of GSCs and

the most probable mechanism is by inhibiting acetylcholine receptors [80]. Another study showed that atracurium can induce apoptosis in A549 human lung cancer cells and the apoptotic effect on these cells could be by modulation of caspase-3, p21 and p53 activities [81].

Alpha-2 Adrenoreceptor Agonists

The α2 adrenoreceptor subtype is expressed in breast cells, both in cancer and non-cancer cell lines [82]. Stimulation of these receptors has been associated with an increase in cell proliferation [83]. A study done with clonidine, an α2 agonist, increased tumor growth *in vivo* [82]. Clonidine has also been shown to reduce NK cell activity in non-operated animals and during the first 24-hours post-surgery [23]. Further studies have suggested the use of α2 antagonists in the suppression of tumor growth. A study conducted on pancreatic cells expressing α2 receptors exposed to yohimbine, an α2 antagonist, demonstrated a negative effect on inducing cell apoptosis [83]. Although the exact mechanism is not known, it is believed that yohimbine may have inhibitted pancreatic cell growth by interfering with the signal transduction pathway via MAPK or other pathways [83].

DISCUSSION

When considering cancer recurrence, it is important to consider that tumor recurrence could appear the same area of primary tumor or at another site in the body; this depends mainly on the invasive and metastatic potential of tumor cells and normal functioning of the immune defense. Disruption of the immune defenses can lead to an increase in PGs, growth factors, MMPs, catecholamines and glucocorticoids [15]. All these stressor molecules lead to increased cell migration, growth and resistance to apoptosis, characteristics strongly associated with malignant cancer cells.

During the perioperative period, the body is vulnerable to tumor spread and potentially at risk of cancer recurrence in the future. Perioperative medications as anesthetic and analgesic agents may substantially modify the systemic inflammatory processes and modulate the immunological mechanisms, which will indirectly affect tumor growth rate and recurrence [26]. Possible causes of perioperative immunosuppression include surgical stress, hypothermia, transfusion, and hypothalamic-pituitary-adrenal axis stimulation activated by postoperative pain. Surgical stress response causes NK cell function suppression, which is associated with tumor growth and metastasis. Surgery induces the formation of a microenvironment composed primarily by inflammatory cells, potent angiogenic and lymphangiogenic growth/survival factors, cytokines and proteases, which could promote neoplastic progression. According to Cassinello *et al*. 2015, postoperative immune suppression is proportional to tissue damage and lasts for several days [84]. Anesthetics and analgesic agents used as part of the perioperative management protocol have also been studied as a possible cause of surgery-induced suppression of innate tumor immunity. Some general anesthetics, including ketamine, thiopental and halothane, suppress NK cell activity, increasing the probability of tumor metastasis. N_2O has been proven to suppress neutrophil chemotaxis by reducing purine and DNA synthesis, which facilitates the spread of cancer cells. Furthermore, inhaled anesthetics have shown to up-regulates HIF-1 gene expression, which can facilitate cancer spread and contribute to cancer recurrence. It is worth noting that propofol inhibits HIF-1 expression [34]. In fact, Cassinello *et al*. 2015 states that propofol exhibits a range of protective effects, including anti-inflammatory effects, inhibition of COX-2 and reduction of PG E2 levels, enhancement of antitumor activity and preservation of NK cell function. Cassinello *et al*. 2015 also compared balanced anesthesia and maintained intravenous anesthesia [84]. Balanced anesthesia refers to the use of general anesthesia in combination with opiate analgesics, muscle relaxants and inhaled agents, while maintained intravenous anesthesia refers to the use of propofol infusions and opioids. Balanced anesthesia was associated with a decreased absolute number of CD3+, CD4+, and CD8+, decreased expression of HLA-DR, and with increased levels of IL-6 during and after surgery. Thus, balanced anesthesia seems to be related to an enhanced surgery-induced inflammatory response and inhibition of cell-mediated immunity. Propofol, in contrast, has an anti-metastatic role, promoting activation and differentiation of peripheral T-helper cells and preserving cellular immunity.

In Puerto Rico, general anesthesia is a combination of propofol, BZDs, barbiturates, and a narcotic, especially fentanyl. In the case of propofol, as mentioned before, it has been shown to cause a reduction of the invasive potential of cancer cells by inhibiting the formation of factors as HIF-1α and PG E2 that could otherwise increase the capacity for

metastasis [14]. Although propofol is most commonly used, in patients allergic to propofol and eggs, etomidate is used instead. A study by Deng *et al*. in 2016 showed that cell migration was suppressed by propofol, while etomidate promoted cell migration [85]. Etomidate also activated the PI3K/AKT pathway, known for its role in cancer progression. However, studies on the effects of etomidate on CD4+ and CD8+ T cells concluded that immune function was affected via a brief suppression, lacking a substantial inhibitory result [86]. In the case of barbiturates, they have been associated with a dose-dependent decrease in T-lymphocyte proliferation and suppression of monocyte-mediated cytolysis and, in animal studies, to a significant reduction in NK cell numbers and an increase in LTR [22]. Also, the presence of $GABA_A$ receptors in immune cells presents the possibility of barbiturates affecting immune function and decreasing cytokine production in macrophages [21], as previously mentioned in this article. BZDs have been shown to have immunomodulatory effects through different mechanisms, with some studies demonstrating an increase in glucocorticoids and therefore immunosuppression [30].

As part of the protocol, in PR, muscle relaxants can be added to the combination of perioperative management agents. Overall, muscle relaxants have no association to immunosuppression leading to metastasis or recurrence. Usually, after giving this combination of anesthetics to the patient, they are also given analgesics through inhalation gas, normally sevoflurane or isoflurane, in combination with oxygen. Studies focused on inhalation anesthetics agents found that these inhibit NK cell activity [86]. Sevoflurane was found to induce the release of IL-1 and TNF cytokines [86]. Sevoflurane is also associated with downregulation of HIF-1α system. Further studies that compared its effects on CD3+, CD4+ T cells and NK cells postoperatively, demonstrated decreased levels of these cells when compared to propofol induction and maintenance of anesthesia [86]. Isoflurane was found to increase IL-6 levels [87]. A study by Luo, *et al*, 2015 indicated that isoflurane increased the proliferative potential of ovarian cancer cells through up-regulation of markers involved in cell development, proliferation, and angiogenesis [88]. Further studies have shown the inhibition of immune cell adhesion.

The protocol in PR for perioperative pain management includes the use of opioids as the primary analgesic agent, especially morphine and meperidine. Opioids have been shown to have two paradoxical main effects: cellular and humoral immunosuppressive effects, and antiproliferative and pro-apoptotic effects on different cancer cells. Morphine exhibits the greatest suppressive effect on phagocytic cells, NK cells, B cells and T cells. Other opioids, such as hydromorphone, oxycodone, and buprenorphine, have lower suppressive activity. Furthermore, Zylla *et al*. 2013 concluded that higher mu-opioid receptor expression and higher opioid doses to treat cancer-related pain were associated with shorter survival [89]. However, administration of morphine to a mouse model given to relieve cancer pain demonstrated inhibition tumor growth and lung metastasis [90]. Analgesic agents are indispensable in the perioperative period to reduce stress response to pain and thus the effect of surgery in the immune system; however, considering the possible effects of morphine in tumor growth, the coadministration of a μ opioid peripheral antagonist may be useful to avoid the unwanted effects that could lead to cancer progression [84]. The use of antiemetic agents in the perioperative setting is usually spared in patients that lack symptoms or have previous history of surgery-induced emesis.

The use of epidural anesthetic agents like bupivacaine and ropivacaine are commonly preferred in the setting of localized colon and prostate cancer. Bupivacaine was found to have cytotoxic, anti-proliferative and antimetastatic properties on the intrinsic and extrinsic apoptotic pathways [52]. Bupivacaine also induced an important increase in ROS generation in SKOV-3 ovarian cancer cells, contrary to a decrease in ROS production in PC-3 prostatic cancer cells. However, a study performed by Ecimovic, *et al*. in 2014 on ER-positive or ER-negative breast cancer cells did not demonstrate a significant effect of bupivacaine associated anti-cancer properties [91]. Ropivacaine has been shown to impair proliferation, differentiation of mesenchymal stem cells *in vitro*. These cells have a role in tumor growth and formation of metastasis [92]. Nonetheless, an *in vitro* study showed that ropivacaine suppressed the human colon adenocarcinoma cells and inhibited cancer cells in a dose-dependent manner [16].

Although adverse immunological effects are associated with all anesthetic agents, various studies have proposed that the use of epidural anesthesia, when combined with general anesthesia, can possibly decrease the length of immunosuppression in the postoperative period [86] use of epidural anesthesia can lead to a decreased use in analgesic agents, such as opioids, which are known to cause

immunosuppression. This can lead to an overall decrease in analgesic doses and side effects, in addition to a rapid recovery, when compared to general anesthesia and postoperative analgesics alone. Epidural anesthesia can also inhibit the stress response elicited by noxious stimuli by blocking central conduction, which can ultimately reduce the stress-induced immunosuppression [86]. A combination of epidural or localized anesthesia with anesthetic agents that are known to have decreased immunosuppressive effects should be considered in future tumor resections to reduce the possibility of tumor recurrence or metastasis.

CONCLUSIONS

Considering the data previously discussed, it is evident that many of the anesthetics and analgesics used during or after a surgery can influence in the progression of tumor cells. Surgery was found to promote the dispersion of malignant cells directly into the bloodstream and lymphatic circulation after a disruption of the integrity of a tumor and its vasculature. Within the Puerto Rican population, intravenous anesthetic propofol was the most commonly used, and it behaved as an immune enhancer. Ropivacaine and bupivacaine were used as part of the perioperative anesthesia for local surgery, and caused positive immunomodulatory effects, such as cell migration inhibition. On the other hand, morphine and demerol were used for postoperative purposes, and caused tumor vascularity and angiogenesis, leading to cancer progression.

Ongoing clinical trials could focus on identifying other variables that affect the physiological stress of cancer cells, since the effects of perioperative anesthesia and analgesia on cancer cells are not completely understood. Further studies should be directed towards assessing possible correlations between the various anesthetic/analgesic drugs and the perioperative methods used, taking into consideration the tumor progression of cancer patients. Likewise, more socio-demographic variables like sex, culture, lifestyles and diet should be integrated into the analysis.

Absence of updated demographic information (eg. incidence, morbidity and mortality) in the literature analyzed proved to be a limitation to our study. Considering the fast-paced nature of technology and advances in medicine, future studies could yield more insight when considering the latest, best anesthetic agents and methods, latest surgical interventions and the long-term effects of these on cancer progression.

ABBREVIATIONS

APC = antigen presenting cell

BZD = benzodiazepine

CNS = Central Nervous System

CRC = colorectal cancer

CSC = cancer stem cells

EGF = epidermal growth factor

EGFR = epidermal growth factor receptor

GSC = glioma stem cells

GSK-3β = glycogen synthase kinase-3β

HIF-1α = hypoxia-inducible factor-1α

ICAM-1 = intercellular adhesion molecule-1

IL = interleukin

LFA-1 = lymphocyte function associated antigen-1

LTR = lung tumor retention

MAPK = mitogen-activated protein kinase

MMP = matrix metalloproteinase

NK = Natural Killer (cells)

NMBA = neuromuscular blocking agents

NO = nitric oxide

N_2O = nitrous oxide

NSCLC = non-small cell carcinoma of the lung

PBR = Peripheral Benzodiazepine Receptor

PG = prostaglandins

PONV = postoperative nausea and vomiting

PPARδ = proliferator-activated receptor delta

PR = Puerto Rico

PRCR = Puerto Rico Cancer Registry

ROS = reactive oxygen species

TEA = thoracic epidural anesthesia

TRPV6 = transient receptor potential action channel subfamily V member 6

US = United States

VASC = voltage activated sodium channel

VEGF = vascular endothelial growth factor

CONFLICT OF INTEREST STATEMENT

None declared.

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