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Review Article

Effects of Anesthesia on Cancer Surgery Outcome: A Literature Review

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Received Date: June 25, 2024; **Accepted Date:** July 08, 2024; **Published Date:** July 17, 2024

Citation: Shreyas B. Jayade, Shweta K. Tonny, Surjya P. Upadyay, (2024), Effects of Anesthesia on Cancer Surgery Outcome: A Literature Review, *Clinical Medical Reviews and Reports*, 6(6); **DOI:10.31579/2690-8794/218**

Abstract

Anesthetic management is an integral part of both short and long term outcome after onco-surgical procedures including disease free survival years and cancer recurrences. Anesthetics are integral to onco-surgical procedures, providing pain relief, maintaining physiological stability, and optimizing surgical conditions for cancer patients. Despite advancements in surgical technology and anesthetic safety, concerns persist regarding the potential impact of anesthetics on cancer progression and recurrence. Various studies have investigated these effects, revealing complex interactions between anesthetics and tumor microenvironments.

Cancer remains a leading cause of death worldwide, with its intricate nature affecting all medical fields. The choice of anesthesia—either general or local/regional—can influence cancer outcomes due to varying effects on tumor microenvironments. General anesthetics include volatile inhaled agents like isoflurane and intravenous agents such as propofol, each impacting cancer cells differently.

Keywords: anesthetics; cancer surgery; surgical outcomes; tumor microenvironment; immune response; volatile anesthetics; intravenous anesthesia; cancer recurrence

Introduction

Surgical stress triggers inflammatory, hormonal, and metabolic responses, altering immune functions and potentially contributing to cancer recurrence. Catecholamines and glucocorticoids released during surgery can suppress cell-mediated immunity by altering T-helper (Th) cell ratios. Inhaled anesthetics, like isoflurane, exacerbate this by decreasing the Th1/Th2 ratio, further compromising immunity [1].

Comparative studies suggest that total intravenous anesthesia (TIVA), especially with propofol, may lead to better outcomes in cancer surgeries compared to volatile anesthetics. Propofol has shown

anti-metastatic properties and promotes apoptosis, contrasting with the pro-metastatic effects of some volatile anesthetics. Additionally, propofol's antioxidative properties and ability to enhance drug sensitivity in cancer cells may contribute to its favorable impact on cancer outcomes [2,3].

Emerging research highlights the genotoxic effects of inhaled anesthetics, which can cause DNA damage and potentially lead to malignant transformations. Isoflurane, for example, is associated with increased tumor cell proliferation and migration, potentially enhancing cancer growth [4].
Other anesthetics like dexmedetomidine and lidocaine also exhibit distinct impacts on cancer progression. Dexmedetomidine may promote tumor growth through immunosuppressive and pro-angiogenic effects, while lidocaine shows promise in inhibiting cancer cell behaviors and enhancing chemotherapeutic efficacy [5-7].

Opioids, commonly used for pain management, present mixed effects, with some studies suggesting immunosuppressive and pro-metastatic actions, while others indicate anti-proliferative and pro-apoptotic properties [8,9]. The influence of blood transfusions and perioperative care on cancer outcomes further complicates the overall impact of anesthetics [10].
Although TIVA appears to offer benefits in cancer surgery, volatile anesthetics remain prevalent in clinical practice. Ongoing research is essential to clarify these interactions and optimize anesthetic protocols for cancer patients.

Methods:

The scientific papers used in this review were retrieved from the PubMed and Google Scholar databases using various combinations of the following search keywords: volatile anesthetics, cancer outcome, and prognosis, total intravenous anesthetics (TIVA), propofol, desflurane, isoflurane, sevoflurane, local and regional anesthesia. Articles were carefully chosen from the year 1974 to 2022. Papers were restricted to the English language. All the studies in this review have recently been peer-reviewed and published in academic journals.

Discussion:

Anesthetics play a crucial role in onco-surgical procedures by providing surgical analgesia, maintaining patients' physiology and homeostasis and

optimal operative conditions for the surgeon with a goal for optimal surgical outcome in cancer patients. Surgical interventions as disease eradicating therapy have been proven beyond doubt in many solid tumors. Optimal surgical outcome depends on many factors in perioperative period. With the advent of technology, an increasing number of cancer patients are subjected to surgical intervention. Though modern anesthesia is considered very safe, there is growing concern about the potential impact of anesthetics on cancer progression and recurrence. Several studies have explored this connection and have identified potential mechanisms through which anesthetics could also influence cancer recurrence and surgical outcomes.

Cancer is one of the leading causes of death worldwide despite the advances in medicine [11]. Cancer being a systematic disease bridges all fields of medicine making it one of the most catastrophic diseases known to mankind. The disease is so intricate that even the types of anesthesia used can be a factor in determining the outcomes, as the drugs used can have varied effects on the microenvironment of the tumor. There are various types of anesthesia. It can be broadly classified into general, local and regional anesthetics. The two main categories of general anesthetics are volatile inhaled anesthetics like isoflurane, desflurane, or sevoflurane, and TIVA, which typically uses propofol and strong opioids.

Surgery alone puts the body under stress which elicits various physiologic effects. The stress that the body undergoes during surgery can be categorized as inflammatory, hormonal and metabolic. Under inflammatory response, there is an elevation of proinflammatory cytokines and activation of immune cells. The hormonal stress response during surgery involves activation of the hypothalamic-pituitary-adrenal axis leading to a surge of cortisol, catecholamine and glucagon secretions [12]. Under metabolic stress due to surgery, there is a rise in gluconeogenesis and glycogenolysis and protein catabolism. Due to the stress induced by surgery, there is also a nutrient shift and development of insulin resistance. The nutrient shift is defined as a hypermetabolic state that diverts nutrients away from immune cells, causing immune cell dysfunction and inability to initiate an effective immune response. Insulin resistance is also developed leading to an inability to properly utilize glucose, causing protein breakdown for energy production [13, 14].

When there is a combination of anesthesia and surgery, the effects on the physiology of cellular function may be amplified. Various effects of anesthesia can be classified based on the effect it has on the immune cells and tumor microenvironment. These effects will be well discussed in the paper.

Catecholamines and glucocorticoids, released in response to surgical stress, have been found to increase the number of Th2 cells while decreasing Th1 cells, thereby reducing the Th1/Th2 ratio. This imbalance in Th cells subsets contribute to the compromised cell-mediated immunity post-surgery. It was also shown that inhaled anesthetics like isoflurane demonstrated decreased Th1/Th2 ratio and increased catecholamines and glucocorticoids following surgery, which further compromises cellular immunity and could potentially lead to cancer recurrence/progression [1].

Studies conducted to compare the overall effects of anesthesia on cancer resection surgery and the recurrence of cancer have suggested that TIVA may have slightly better surgical outcome, especially in patients with breast cancers [2]. Volatile anesthetics may be linked to cancer recurrence by promoting pro-metastatic conditions and compromising cellular immunity, whereas propofol has anti-metastatic qualities and prevents apoptosis.

When surgery is undertaken, there is now increasing work suggesting a direct interaction between anesthetic agents utilized intraoperatively and long-term cancer outcomes, resulting from the effect that these agents have on the immune system and the inflammatory milieu in which cancer cells exist, including micrometastatic disease [15].

Although much of our understanding of these potential interactions comes from either in vitro cell lines or xenograft models, there is also clinical data demonstrating an association with improved long-term survival for both regional [16,17] and intravenous anesthesia [18].

Volatile anesthetics also showed pro-apoptotic properties. Inhaled anesthetics such as sevoflurane and isoflurane, induced apoptosis of CD3+ T lymphocytes by increased mitochondrial membrane permeability and caspase-3 activation [19]. These inhaled anesthetics were also implicated in apoptosis of peripheral lymphocytes in vitro [20]. Some studies suggest that isoflurane exhibited a pro-apoptotic effect by inhibiting opioid peptide dynorphin-mediated cytotoxicity [21].

It could be speculated that apoptosis of CD3+ T lymphocytes could lead to a lack of Th cell signaling and thus T cell activation [22]. This could explain lymphocytopenia after surgery, thus suppressing cellular immunity and possibly leading to cancer progression.

Studies have revealed an imbalance in Th cell subsets in tumor patients, characterized by a predominance of Th2 cells at the tumor site and a higher presence of Th1 cells in noncancerous tissues. This Th1/Th2 imbalance serves as a common mechanism for immune evasion by tumor cells and is closely associated with cancer progression and prognosis [23].

Although the recurrence rate of cancers when volatile anesthetic agents are used can be significant, several other factors such as perioperative care, postoperative care, and extent of surgery play a determinant role in the recurrence and outcome of cancers. For example, in breast cancers, with TIVA, although there is a reduction rate in the recurrence of cancers, the factors such as type of surgery act as a variable leading to inconsistent results [24].

One study demonstrated the genotoxic effects of inhalation anesthetics, namely sevoflurane, and desflurane, on bronchoalveolar cells in lumbar discectomy surgery patients were examined [25]. Evidence of DNA damage, characterized by strand breaks or alkali-labile sites, was observed in bronchoalveolar cells post-exposure to these anesthetics. Moreover, there was an increase in plasma 8-Hydroxy-2'-deoxyguanosine levels, indicative of oxidative DNA damage. The study concluded that inhalation anesthetics could induce DNA damage in bronchoalveolar cells, with no significant disparity noted between sevoflurane and desflurane [25].

In a study, the association between micronucleus and chromosomal aberration frequencies and oxidative stress resulting from exposure to high concentrations of inhalation anesthetics was examined [26].

Individuals exposed to high cumulative nitrous oxide levels exhibited significantly elevated micronucleus frequency, suggesting DNA damage likely due to cumulative exposure. Moreover, operating room personnel displayed diminished total antioxidant capacity and superoxide dismutase levels but elevated malondialdehyde levels, indicating heightened oxidative stress [26].

Investigations have shown the potential impact of volatile anesthetics on cancer cells, suggesting varied effects on cellular behavior and signaling pathways. One study demonstrated that volatile anesthetics can modulate gene expression and alter the mRNA expression in breast and brain tumor cells [12].

These findings underline the genotoxic effect of inhaled anesthetics, signifying DNA/chromosomal damage to cells. Such damage could potentially precipitate malignant transformation, thereby contributing to cancer development. This assertion aligns with the observation that over 90% of IARC (International Agency for Research on Cancer) Group 1 chemical carcinogens are genotoxic [28].

Isoflurane, a commonly used volatile anesthetic agent in cancer surgery, has been implicated in stimulating cell signaling pathways involving hypoxia-inducible factors (HIFs), which are heavily associated with tumorigenesis. There is evidence that suggests isoflurane enhances proliferation, cytoskeletal rearrangement, migration, and angiogenesis in renal cancer cells [4].

There was proof suggesting that isoflurane, a volatile general anesthetic agent commonly used in cancer surgery, stimulated a cell signaling pathway involving HIFs, which have been heavily implicated in tumorigenesis, and enhanced several cellular activities associated with a malignant phenotype [4,29]. Having exposed renal cell carcinoma stage 4 cells to clinically relevant concentrations of isoflurane, there was proof of increased proliferation, cytoskeletal rearrangement, and migration of cells across different components of the extracellular matrix. There were statistically significant higher levels of the proangiogenic vascular endothelial growth factor A (VEGF). Together, this data revealed that isoflurane enhanced renal cancer cell growth and had noteworthy effects on the cells' malignant potential [4].

Additionally, some studies have shown contrasting effects of volatile anesthetics on different cancer types. One had demonstrated that sevoflurane increases proliferation, migration, and invasion in estrogen receptor positive (ER+) breast cancer cells, while another found that sevoflurane inhibits invasion and migration in lung cancer cells by downregulating the expression of matrix metalloproteinases (MMPs) and cytoskeletal proteins through inactivation of the p38 mitogen activated protein kinase (MAPK) signaling pathway [30,31].

The former *in vitro* cell culture study showed that sevoflurane increases proliferation, migration, and invasion functions in ER+ breast cancer cells and only proliferation and migration in ER− breast cancer cells [30]. As previously mentioned, isoflurane was shown to facilitate renal cancer cell migration *via* the Hypoxia-inducible factor cell signaling pathway progression in an *in vitro* model[4]. This supported the present data suggesting that frequently used volatile anesthetics can exert pro-tumorigenic effects on human cancer cell lines. In contrast, cell culture studies on lung cancer cells have indicated that sevoflurane actually inhibits migration and invasion by inactivating the p38 MAPK signaling pathway. This discrepancy in the effect shown for sevoflurane between breast cancer cell data and lung cancer cell data raises the question of whether the effect of anesthetic agents on cancer varies with cancer type. This seems a plausible explanation, given the widely recognized fact that different tumor types behave differently in the clinical environment [30].

The latter study indicated that sevoflurane was able to inhibit the invasion and migration of A549 cells and to downregulate the expression of MMP-2, MMP-9, fascin, and ezrin. They also suggest that the effects of sevoflurane in downregulating the expression of MMP-2, MMP-9, fascin, and ezrin occur in part through inactivation of the p38 signaling pathway[31]. Metastasis of cancer cells consists of a series of complex, continuous, and multi-step processes that include the separation of the tumor cells from the primary site, the degeneration of the extracellular matrix, and penetration of the cells through the blood vessel walls.

All of these processes are associated with the invasive and migration characteristics of cancer cells. It has been demonstrated that surgical procedures may add to the invasion and migration potential of cancer cells and thus promote their ability to disseminate during the perioperative period. Inhibition of the invasion and migration potential of cancer cells would thus have better outcomes on lung cancer mortality rates [31].

On the other hand, TIVA has different effects on tumor cells and its microenvironment. Most commonly used, propofol, has a mixed effect on tumor cells. It has an inhibitory effect on certain tumors like lung adenocarcinoma, colon cancer, and hepatocellular carcinoma. In cases of breast and gallbladder, there are no inhibitory effects. Propofol can cause either tumor growth or tumor suppression by regulating the microenvironment of the tumor and regulating the expression of microRNAs and long non-coding RNAs. Propofol can either upregulate or downregulate signaling pathways such as nuclear factor E2-related factor-2, extracellular signal-regulated kinases (ERK) 1 and 2, nuclear factor-kappa B (NF-kB), mammalian target of rapamycin (mTOR), wingless and proto-oncogene integration-1/β-catenin, phosphoinositide 3-kinase/protein kinase B, and others, leading to inhibition of cell proliferation, migration, invasion, and promotion of apoptosis [2].

One of the advantages of propofol is that it has shown antioxidative properties by three mechanisms. Firstly, it acts as a scavenger for free radicals and peroxynitrite due to its shared phenol structure with α-tocopherol. It may also suppress the biosynthesis and function of nitric oxidase and nicotinamide

adenine dinucleotide phosphate hydrogen oxidase, reducing oxidative stress. Finally, propofol may induce the expression of antioxidant enzyme heme oxygenase-1 and superoxide dismutase, thus facilitating the removal of oxidative stress [3]. A retrospective study conducted suggested the same. However, there were multiple confounders such as emergency surgeries and RBC blood transfusions. RBC blood transfusions were found to have some impact but there was very little evidence to substantiate it. Morphine used postoperatively showed impairment of immunity and use of Nitric Oxide had similar effects along with DNA production impairment but there was not enough evidence to substantiate either of these effects [32]. Propofol also minimized the effect of hypoxic drug resistance in cancer cells, i.e. it increased the sensitivity of drugs such as cisplatin, thereby killing tumor cells [2].

Another study explored the impact of propofol anesthesia on tumor angiogenesis, shedding light on its potential anti-angiogenic effects [33]. Previous studies had hinted at propofol's beneficial effects on cancer outcomes, but its influence on angiogenesis, particularly in the tumor microenvironment, had not been extensively investigated. The research had demonstrated that clinically achievable concentrations of propofol inhibit the biological functions of tumor-associated endothelial cells, suggesting anti-angiogenic activity. Notably, propofol disrupted tumor angiogenesis microenvironment by decreasing the expression and secretion of pro-angiogenic growth factors like VEGF, platelet derived growth factor (PDGF-AA), and basic fibroblast growth factor. This aligns with clinical observations showing reduced serum VEGF levels in patients receiving propofol anesthesia during cancer surgery [2].

The study further revealed that propofol targeted key signaling pathways involved in angiogenesis, including VEGFR2/PLCg/PKCz and mTOR/eIF4E pathways. By inhibiting these pathways, propofol effectively suppressed the translation of VEGF mRNA and downstream angiogenic processes [33]. These findings suggested that propofol's modulation of angiogenesis contributed to its beneficial effects in cancer patients and better outcomes.

Ketamine has been reported to reduce the inflammatory response after cancer surgery, which could inhibit the suppression of natural killer (NK) cell activity and thus immunosuppression following surgery. It also exhibits blocking of the N-methyl-D-aspartate receptor in various subsets of cancer cells, specifically colon adenocarcinoma cells [34,35].

Dexmedetomidine, an α2-adrenoceptor agonist, is widely used in perioperative settings due to its sedative, analgesic, and sympatholytic properties. However, evidence suggests that it may influence cancer recurrence and metastasis, especially in breast cancer surgeries. Further investigation has shown that dexmedetomidine can activate a2-adrenoceptor/extracellular signal-regulated kinase pathway, leading to increased proliferation, migration, and invasion of tumor cells [36].

This is supported by various animal studies demonstrating enhanced tumor growth and metastasis following dexmedetomidine administration.

A study conducted on lung cancer patients who were administered with dexmedetomidine, demonstrated its immunosuppressive effects, including the proliferation of monocytic myeloid-derived suppressor cells and increased VEGF production, further contributing to its potential pro-tumorigenic effects [5]. A retrospective study utilizing propensity score-matched analysis to examine patients with Stage I through IIIa non-small cell lung cancer. The study found that intraoperative use of dexmedetomidine

was associated with decreased overall survival and recurrence-free survival [37]. Despite its known anti-inflammatory and opioid-sparing properties, dexmedetomidine has been suggested to potentially promote tumor growth by directly stimulating cancer cell proliferation and altering the tumor microenvironment.

Lidocaine has been shown to inhibit cancer cell behavior in vitro. It can enhance the cytotoxic effects of chemotherapeutic agents on cancer cells and inhibit DNA damage repair, potentially sensitizing cancer cells to treatment[6]. Lidocaine has been found to modulate signaling pathways involved in cancer cell proliferation, invasion, and metastasis. For example, it can inhibit the NF-kB and Mitogen-activated protein kinase kinase/ERK pathways in gastric cancer cells, leading to antineoplastic effects [7]. Lidocaine has anti-inflammatory effects, reducing the inflammation that occurs during tumor cell progression. This helps in making the environment less conducive to cancer cell growth and metastasis. Other effects of lidocaine include immune modulation and enhancing immune system response to identify and eliminate cancer cells. It also prevents angiogenesis, a process known to help tumor cell progression and metastasis and has also shown to impede the process of metastasis itself as an added bonus [7, 38].

Opioids such as morphine, have been shown to demonstrate immunosuppressive effects by decreasing the activity of NK cells, which are essential for eliminating tumor cells. One possible mechanism through which morphine promotes metastasis is that it binds to the μ-opioid receptor and upregulates urokinase plasminogen activator expression and secretion, promoting extracellular matrix degradation and metastasis. They also have the effect of transactivating VEGF receptors, inducing angiogenesis and have also been involved in the suppression of T lymphocytes [8]. Contradicting the pro-tumor effects of morphine, there have been additional studies which show that it has direct anti-proliferative and pro-apoptotic effects on different cancer cells through various mechanisms, some involving the activation of p53 and by induction of apoptosis and inhibition of tumor necrosis factor α gene expression associated with inhibition of NF-kB activation [9, 39–41]. There have been no clinical studies with sufficient evidence to show that morphine has a direct effect of cancer recurrence or metastasis.

Fentanyl has shown disputable results with regards to its impact on cancer survival and recurrence. For instance, one study demonstrated that it had no impact in patients after curative colorectal cancer resection [42]. However, in case of non-small cell lung cancer, fentanyl showed decreased overall survival rate, particularly during the early stages of cancer [43].

Other factors that determine cancer surgery outcomes are blood products given during perioperative periods. Blood transfusions can cause immune suppression leading to negative impact on long term surgery outcomes, it can also lead to stimulation of tumor growth as a lot of blood products contain soluble products such as transforming growth factor β which can lead to stimulation of cancer growth [10]. Many studies have suggested that cancer growth and recurrence can be seen in patients who have had transfusions, especially red blood cell transfusions. This can also lead to shorter recurrence free periods and shorter overall survival rate. This was mostly seen in patients who had colorectal cancer [44].

Therefore, in order to prevent blood transfusion during surgeries, anesthetists play a significant role in blood conservation and reducing intraoperative blood loss by employing various blood-preserving techniques. These techniques include induced hypotension, the judicious use of antifibrinolytics such as tranexamic acid, and maintaining a high threshold for transfusions [45].

Although research favors TIVA, the majority of clinical practice still leans towards volatile anesthetics. Understanding these mechanisms improves our knowledge of propofol's potential benefits for cancer patients, particularly in the context of anesthesia management during cancer surgery [33]. There is still a large amount of scope for trials to confirm otherwise [11].

Conclusion

The field of onco-anesthesiology holds immense potential for improving cancer surgery outcomes by understanding the impact of anesthetic agents on cancer progression and recurrence. Emerging evidence suggests that different types of anesthetics, particularly volatile inhaled anesthetics and total intravenous anesthesia, have varying effects on the immune system and tumor microenvironment, influencing cancer cell behavior and long-term patient survival. Further studies in this area are crucial to improve anesthetic protocols, potentially enhancing the effectiveness of cancer treatments and improving patient prognosis.

Conflicts of Interest

There is no potential conflict of interest.

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