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Research Article

Narrative Review: The Effect of Anesthetic Choice on Cancer Recurrence and Metastasis

Robert G DeVito MD[1], Ashley M Shilling MD[2] and John T Stranix MD[1]*

[1]*Department of Plastic Surgery, University of Virginia Health System, USA*

[2]*Department of Anesthesiology, University of Virginia Health System, USA*

***Corresponding author:** John T Stranix MD, Department of Plastic Surgery, University of Virginia Health System, USA.

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Abstract

Introduction: Almost two in five people will be diagnosed with cancer in their lifetime. These patients will commonly undergo surgical procedures requiring anesthesia. Recently, investigation has begun into whether different methods and agents of anesthesia effect the cancer disease process. The objective was to investigate different common anesthetic agents and current data on their possible effects on the cancer disease process relating to recurrence and metastasis. A literature search of utilizing common search engines and databases of PubMed, Cochrane, and Google Scholar was performed. There were no specific date inclusions and exclusion parameters. Studies were required to be relevant to the clinical question of how anesthetic agents effect the cancer disease process and progression.

Findings: There has been a significant amount of research into the topic of anesthetic agents and their specific effects on the cancer disease process as it relates to recurrence and metastasis. In this project specific agents investigated include morphine, fentanyl, propofol, sevoflurane, regional anesthesia, and local anesthesia. Morphine and Sevoflurane potentially have negative effects on cancer pathology whereas regional anesthesia and local anesthesia have been shown to have some positive effects on the cancer disease process. Agents such as propofol and fentanyl require more investigation.

Conclusion: There has been a significant amount of research into the topic of anesthetic agents and cancer recurrence and metastasis. There is data that shows some anesthetic agents may pose more risks than others when being utilized in a patient with a cancer diagnosis. More research is needed into this topic so providers can best care for patients undergoing cancer surgeries.

Keywords: Anesthesia; Morphine; Fentanyl; Propofol; Sevoflurane; Regional; Local; Cancer; Recurrence; Metastasis

Abbreviations: TSP-1: Thrombospondin-1; EGF: vascular endothelial growth factor; TGF-B: Tumor growth factor beta; IL-2: Interleukin-2; NSAIDs: Non-steroidal anti-inflammatory; COX-2: Cyclooxygenase-2; NF-Kb: Nuclear factor – kappa beta; PTEN: Phosphatase and tensin homolog; Nrf-2: Nuclear factor erythroid 2-related factor 2; MMP: Matrix metalloproteinase; NSCLC: Non-small cell lung cancer; MTOR: Mammalian target of rapamycin; GABAAR: Gamma aminobutyric acid A receptor; TRIM21: Tripartite motif-containing protein 21; Her-2: Human epidermal growth factor receptor 2; CCI Score: Charlson comorbidity index score; PT: Pathologic tumor stage; PN: Pathologic nodal stage; PCA: Patient-controlled analgesia

Introduction

Around 39.5% of men and women will be diagnosed with cancer at some point in their life [1]. Because patients with cancer commonly undergo surgical procedures and require various forms of anesthesia, the drugs used in the peri-operative period have been scrutinized for their potential role in cancer progression or protection. A debated topic in recent years has been whether

different agents and delivery methods of anesthesia can positively or negatively impact cancer recurrence, metastasis, and patient survival. Multiple studies and reviews have examined whether there are correlations or associations with anesthetic agents and cancer outcomes. The most commonly researched agents on this topic include morphine, propofol, and sevoflurane. Nonetheless, while the clinical relevance of these specific agents remains poorly understood, the in vitro data shows the potential for significant effects on cancer progression. Therefore, we feel it is worth reviewing the potential effects of specific anesthetics on cancer recurrence in patients in hopes of raising awareness and instigating further interest and research. The objective of this project was to examine multiple commonly used anesthetic agents and their possible effects on cancer disease progression as it relates to recurrence and metastasis. This objective is important because of the significant number of individuals who will be diagnosed with and undergo an operation for a cancer diagnosis. A literature review utilizing databases and search engines commonly used in medical research including PubMed, Cochrane Review, and Google Scholar was utilized. There was no specific date parameter relevant for inclusion or exclusion. Each article was reviewed by the authors for its relevance as it relates to the stated objective of this project.

Findings

Morphine, a commonly used opioid, is hypothesized to affect both cancer recurrence and metastasis. Studies have shown that morphine can affect microvascular endothelium proliferation and angiogenesis. Mechanistically, evidence has suggested this is related to Thrombospondin-1 (TSP-1). TSP-1, an angiogenesis suppressor which is thought to be down-regulated by morphine, therefore allowing for increased angiogenesis via vascular endothelial growth factor (VEGF). The increase in angiogenesis is postulated to be a contributing factor in the increase in distant metastasis in patients treated with morphine [2,3]. Local recurrence of cancers may be affected by morphine through its effects on the function of regulatory T-cells. It is proposed that morphine's effects on regulatory T cells directly influences immune response through tumor growth factor-beta (TGF-B) and interleukin-2 (IL-2) [4]. Interestingly, a study in 2020 by Liu et al published in Life Sciences examined these effects of morphine on a cellular signaling level and found that co-administration of Ketorolac, which has been found to increase secretion of TSP-1, negated the effects of morphine on TSP-1. NSAIDs, namely Celecoxib, had previously been hypothesized to prevent metastasis by inhibiting cyclooxygenase-2 (COX-2) and prostaglandins [3]. Specific to triple negative breast cancer, a study was published in 2021 in the British Journal of Anesthesia examining the association between intra-operative opioids (including fentanyl, hydromorphone, and morphine) and recurrence-free survival. The study included over 1100 patients, and in contrast to the theories above, found that higher doses of intra-operative opioids were associated with increased recurrence-free survival, but not overall survival [5]. In a recent 2021 study specific to lung adenocarcinoma, the authors found that opioid exposure was found to be associated with a worse overall survival [6] While most of the research has focused on morphine, the questions exist whether certain opioids carry a greater risk. With the risks of opioids in general, it is prudent to consider multi-modal analgesia for all patients with consideration of regional techniques as mentioned below. Whether opioids and specifically morphine negatively influence cancer outcomes is still undetermined, but avoidance seems prudent.

Fentanyl is a mu-agonist opioid commonly used for pain control, especially in surgical procedures and also in patients with malignancies. It has been well studied in patient populations including those with moderate to severe cancer-related pain and found to be safe, effective, and related to improvements in patients' quality of life. It has been found that fentanyl can affect tumor growth in a variety of different types of cells [7]. A 2012 study published in Oncology Research specifically examined the effects fentanyl could have on in vitro Gastric carcinoma cells. Utilizing a human gastric cancer cell line MGC-803 it was found that through downregulating NF-kB and PTEN fentanyl inhibited cell growth and proliferation. It was also found that cells incubated with fentanyl exhibited higher apoptotic rates, theoretically giving it the ability to halt progression of disease [8]. While the overall topic of anesthetic effect on cancer recurrence and metastasis has a paucity of literature in many ways, there are a scarce amount studies examining fentanyl and its effects on cancer outcomes. Two studies that were applicable were found. The first, examining patients undergoing major abdominal surgery for cancer, compared 132 patients who received either a bupivacaine thoracic epidural and general anesthesia versus general anesthesia with fentanyl followed by continuous subcutaneous morphine. There was found to be no statistically significant difference between the two groups when examining recurrence-free survival or overall survival, however authors did note a trend in favor of the epidural group [9]. Another study examined patients undergoing radical prostatectomy for cancer compared two groups of patients. One group received general anesthesia with systemic opioids or epidural anesthesia with epidural fentanyl analgesia. The authors found no statistically significant differences in prostate cancer recurrence, systemic tumor progression, cancer specific mortality, or overall mortality [10]. There has been less investigation into fentanyl as an agent associated with cancer outcomes as compared to agents such as morphine, propofol, or sevoflurane making it more difficult to pass judgment on its possible effects in cancer outcomes.

Propofol, used for induction of anesthesia and maintenance of anesthesia and sedation, is a second agent that has been

studied regarding its effects on cancer and cancer progression. On a cellular level, it has been theorized that propofol affects cancer by multiple pathways (or mechanisms). First, propofol affects signaling pathways by both promoting and suppressing oncogenesis in cancer cells. There are studies demonstrating that in both gallbladder cancer and breast cancer, propofol can promote oncogenesis via activation of Nrf-2 (nuclear factor erythroid 2-related factor 2), a transcription factor, and specifically in breast cancer via down regulation of p53. However, other studies have shown that specifically in breast cancer, via propofol's effects on matrix-metalloproteinases (MMP's) and suppression of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) pathways, propofol can inhibit cell invasion and migration, thus decreasing oncogenesis. The review article, published by Xu et al in-Cell Proliferation in 2020, examined multiple types of cancer including breast, colon, gallbladder, cervical, glioma, non-small cell lung cancer (NSCLC), thyroid, gastric and other cancers. It was found that propofol affects a wide array of cell signaling pathways, including MMP's, NF-kB, mammalian target of rapamycin (mTOR), and Wnt, amongst others. Affecting these signaling pathways leads to the propofol-induced suppression of oncogenesis by mechanisms including inhibiting cell invasion in colon and breast cancer, and inducing apoptosis in cervical cancer, NSCLC, and cholangiocarcinoma. There were also effects on other types of cancer through signaling pathways resulting in similar mechanisms of suppressing oncogenesis. In short, through various mechanisms, previous studies have shown propofol to have both positive and negative effects on cancer cells [11]. Another study, published in Advanced Science in 2021, examined propofol's specific effects on tumor metastasis in mice with lung cancer. The authors found that through an upregulation in the protein Src, which is associated with cell adhesion, propofol induced more lung tumor metastasis than in control groups. The exact mechanism behind this was found to be related to the interplay between GABAAR, TRIM21, and Src [12]. It is therefore difficult to know if propofol plays a protective or detrimental role in cancer recurrence, though as seen below, may offer benefits as it allows the avoidance of halogenated volatile anesthetics when general anesthesia is required for cancer surgeries.

Halogenated volatile anesthetics are typically used for maintenance of anesthesia, with sevoflurane being the most common due to its cardiovascular and respiratory safety profile. Sevoflurane has been proposed to affect cancer progression due to its pro-inflammatory characteristics and by inhibition of natural killer cells [13,14]. It has also thoughts been proposed that sevoflurane leads to an increase in metastasis related gene expression. Multiple studies have attempted to compare sevoflurane to propofol using endpoints of cancer outcomes [15]. A study out of Sweden in 2014 including patients diagnosed with colon, breast, or rectal cancers compared propofol to sevoflurane and found that both 1-year and 5-year survival rates favored patients receiving propofol. In fact, the 1-year survival rate in colon cancer was 9% higher in the propofol group. However, after adjusting for confounding variables including date of surgery, the use of nitrous oxide, the group found no statistical difference between the propofol and sevoflurane groups [13]. Another 2020 retrospective study of more than 6000 patients with breast cancer was performed by some of the same authors in Sweden; When comparing patients receiving general anesthesia with propofol or sevoflurane, the authors found that the five-year survival rates were 91.0% and 81.2% in the propofol and sevoflurane groups respectively. However, these results were not found to be statistically significant when "statistical adjustment" occurred. The authors concluded that there "seems" to be a benefit in using propofol over sevoflurane in breast cancer patients [16]. Another 2020 study published in Anesthesiology comparing sevoflurane to propofol as the anesthetic included 210 patients and found that there was no difference in circulating tumor cell counts over time. The authors used the outcome of circulating tumor cell counts due to an independent association between high tumor counts and a higher risk of disease recurrence and reduced survival [14].

Regional anesthesia typically includes both neuraxial techniques and peripheral nerve techniques. This procedure involves the injection of local anesthetics in proximity to nerves with the goal of providing analgesia or surgical anesthesia for hours up to days with the use of an indwelling catheter. When a surgical nerve block, spinal, or epidural is performed, patients can frequently undergo surgery without the need for a general anesthetic. Common sedation includes a propofol infusion or other anxiolytics. Significant research has focused on the association between regional anesthesia and cancer recurrence or metastasis. A study published in 2021 in Biomedicine & Pharmacotherapy based out of China and Taiwan specifically examined patients undergoing paravertebral regional anesthetic blockade with propofol sedation compared to patients receiving volatile inhalation general anesthesia without propofol. This study specifically examined loco-regional recurrence in invasive ductal carcinoma breast cancer patients undergoing breast conserving therapy. Each arm of the study included 1395 patients (2760 patients total), and the authors performed propensity score matching considering age, diagnosis year, differentiation, clinical stage, adjuvant radiation therapy, hormone-receptor status, Her-2 status, nodal surgery, menopausal status, CCI score, pT, and pN. At a mean follow-up of 62.1 months in the regional blockade group and 61.2 months in the volatile inhalation anesthetic group, the Hazard ratio (HR) for loco-regional recurrence in the regional blockade group was found

to be 0.67 (0.46 – 0.99) as compared to the volatile inhalational anesthetic group. The rates of loco-regional recurrence were found to be 6.5% in the volatile inhalation anesthetic group and 4.3% in the regional blockade group (p = 0.0120). This study also examined distant metastasis outcomes in the studied patient population, and while they did not find a statistically significant difference between the two groups (p = 0.0541), the rates were found to be 10.8% distant metastasis in the volatile inhalational anesthetic group, as compared to 8.5% in the regional nerve blockade group [15]. Mechanistically, decreases in loco-regional recurrence and distant metastasis in patients undergoing regional nerve blockade has been proposed by researchers from H. Lee Moffitt Cancer Center and the University of Texas Southwestern Medical Center to be related to a reduction in the surgical stress response, reduction in surgical inflammation, and decreased or avoidance of volatile anesthetic requirement during surgery. The authors from these institutions hypothesize that surgical resection of a tumor triggers cancer dissemination by shedding of tumor cells, enhancement of motility, invasion, and proliferation from proinflammatory factors, disruption of immunosurveillance, and an alteration of the equilibrium that exists between the immune system and circulating tumor cells [17]. Multiple other studies have attempted to examine the effects that regional nerve blockade have on cancer recurrence or metastasis without resolution. A meta-analysis published in Regional Anesthesia and Pain Medicine in 2015 examined twenty eligible studies and found that regional anesthesia may improve overall survival but not reduce cancer recurrence after oncologic surgery [18]. A meta-analysis performed in 2020 published in the International Journal of Surgery examined six randomized control trials and found that regional nerve blockade did not impart any benefit as compared to general anesthesia with regard to cancer recurrence rate [2]. Another study in 2020 published in the Journal of Clinical Anesthesia performed a meta-analysis with "trial sequential analysis", however despite including ten retrospective observational studies the authors felt that given the low level of evidence and underpowered trial sequential analysis, their study could not support or reject that regional nerve blockade was associated with a decrease in cancer recurrence in cancer resection surgery [19]. A study published in Lancet in 2019 examined over 2000 women with breast cancer undergoing resection and found equal recurrence rates of roughly 10% at an average of 36 months post-operatively in both regional blockade groups and general anesthetic groups [20]. Lastly, a study published in Anesthesia and Analgesia in 2017 examining specifically lung cancer patients undergoing resection found that paravertebral blocks were not beneficial with regard to cancer recurrence, but they did find that patients who underwent a paravertebral block had greater overall survival when compared to PCA or thoracic epidural anesthesia [21].

Local anesthetic agents are commonly used analgesic agents in any surgical patient. As previously stated, many if not most patients diagnosed with a malignancy will undergo a surgical intervention. The mechanism by which local anesthetic agents work is producing both use- and voltage-dependent inhibition of voltage-gated sodium channels, blocking those channels in resting, open, and inactivated states [22]. In addition to being beneficial for pain management, local anesthetics also decrease post-operative opioid consumption [23]. As these agents are very commonly used, there has been some substantial research into their effects on patients with malignancy with regard to recurrence and metastasis. The most studied and popular agents in research have been lidocaine, bupivacaine, and ropivacaine [24]. Studies specifically examining lidocaine have found that lidocaine either decreases cancer cell viability or has no effect on cell viability. This varies specifically by cell line, the most sensitive cancer cell lines were found to be SW480 colon cancer cells which had a 30% decrease in viability, and other cell lines, including subtypes of melanoma and glioma were found to have no significant changes in cell viability after lidocaine exposure. It should be noted that there has been conflicting research on the topic as other studies have failed to prove the decrease in viability in the SW480 colon cancer cells. Another interesting point made in the literature is that there seemed to be a time-related component in some studies in the decrease in cell viability after local anesthetic exposure. While there are differences between cell lines, some cell lines in studies have shown decreases in viability in the first 24 hours of lidocaine exposure and very little change afterwards, whereas other cell lines showed steady decreases in cell viability for two to five days after exposure and then a tapering of changes. Bupivacaine has been studied for its effects on ovarian and prostate cancer specifically. It was found in a study by Xuan et al that bupivacaine has "direct anti-cancer properties" by increasing apoptosis rates by activating intrinsic and extrinsic apoptosis pathways in ovarian cancer cells, and by activating the intrinsic apoptosis pathway in prostate cancer cells [25]. The last commonly studied local anesthetic agent is ropivacaine. Ropivacaine has been found to block channels implicated in colon cancer specifically related to cell invasion in a dose-dependent fashion [24]. Specific to breast cancer, Ropivacaine was found to affect the cell signaling axis miR-27b-3p/YAP. Prior studies examining miR-27b-3p have found it to be a micro-RNA with a crucial function in suppressing cancer, and the Yes-associated protein (YAP) is a transcriptional co-activator that has been found to abnormally expressed in cancer, as well as been found to be an oncogene contributing to breast cancer. This study, published in the journal Aging, found that Ropivacaine attenuates tumor growth in breast cancer in vivo [25]. Specific to cancer metastasis, it has been in found through in vivo studies with mice that lidocaine injected mice have decreased cancer metastasis after surgical resection [22]. While many of these studies have in

vitro and in vivo components, and there is not a broad generalizable effect, it can be reasonably concluded that local anesthetic agents do affect cancer cell physiology, and the majority of the research has shown that commonly used local anesthetic agents have detrimental effects on cancer cells, inhibiting their growth and invasion [22-25]. The research done on these agents does bring up an interesting hypothesis that intravenous local anesthetic injections, particularly lidocaine, could be beneficial in patients undergoing cancer surgery not only for pain control and decreasing opioid use, but also for their anti-cancer properties [22].

Based on the data presented above and the ambiguity of findings, the relationship between anesthetic agents and cancer recurrence or progression is an area of great interest that requires further research. However, the data that is available does supply interesting clues as to how these agents can affect patients. Basic science (or in vitro) studies have provided useful information as to how, at a cellular level, these agents can affect signaling mechanisms that affect cell functions such as adhesion, proliferation, and apoptosis. There are also immune system considerations in which anesthetic agents have been implicated in potentially dulling the immune response to cancer through various mechanisms which could theoretically result in negative consequences of recurrence and metastasis. It is critical that we continue to prospectively study how commonly used anesthetic agents affect both normal and cancer cell functions. It is also important that the clinical research in cancer outcomes and anesthetic agents continues. "Cancer", however, is likely too broad of a term for the purposes of this clinical question. Targeting specific cancer types and narrowing study focus provides us with the most accurate and specific data. The 2021 study by Zhang et al. is a nice example of a specific cancer in a specific patient population and a specific clinical outcome. Retrospective reviews lack standardization and have significant limitations. Therefore, prospective studies are needed to a new perspective on the effect anesthetics can have on cancer recurrence and metastasis. However, this study would likely need to have very strict inclusion criteria, because other studies examining this topic have had statistically significant results undone by confounding variables [13]. When considering the amount and quality of research currently relevant to this clinical question it is important that practitioners are mindful when considering their anesthetic choices such as morphine, propofol, or sevoflurane. It is also important that regional techniques are considered for multiple outcomes benefits including also malignancy potential benefits.

Conclusion

In conclusion, there has been a significant amount of interest and research into the topic of anesthetic methods and their effects on cancer recurrence and metastasis. The basic science of this clinical consideration cites anesthetic effects on cancer cells via affecting cell proliferation, adhesion, apoptosis and other cell functions. Anesthetic agents have also been hypothesized to affect immune system function by affecting regulatory T cells and natural killer cells [4,11,17]. The agents used and techniques such as avoidance of general anesthesia and addition of regional techniques may decrease cancer recurrence and distant metastasis by various methods including affecting stress response to surgery and immune response. Even with clinical data lacking, it seems prudent to consider the potential for anesthetic agents and modalities to affect cancer patient outcomes. Our hope is to have better understanding of mechanisms so that we can best care for patients undergoing cancer surgeries.

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Conflict of Interest

No funding was received or utilized in the development of this project. Dr. DeVito, Dr. Shilling, and Dr. Stranix have no relevant disclosures related to the topic presented and discussed.

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