Anesthetic and Analgesic Influence on Cancer Recurrence and Metastasis

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Cancer is one of the leading causes of death in the United States. Total resection of tumors can be curative; however, investigators have speculated that inflammatory, metabolic, neuroendocrine, and immunologic changes that occur perioperatively may be promoted or induced by anesthetics. The influence of anesthetic choice on cancer recurrence and metastasis has yet to be definitively linked. Retrospective, animal model, and in vitro studies investigating volatile anesthetics, local anesthetics, and intravenous analgesics have resulted in contradicting findings. Results ranged from no association between type of anesthetic used and cancer recurrence, to immune-protective effects inhibiting tumor cell growth, or immune-suppressive effects promoting tumor cell growth or metastasis. It has yet to be confirmed whether volatile anesthetics, intravenous anesthetics, and analgesics are causal factors for cancer metastasis or recurrence. There are increasing data suggesting the immunosuppressant effects of anesthesia can be circumvented by avoiding opioids and volatile anesthetics. Further evaluation is required to determine the implications of regional anesthesia and propofol-based total intravenous anesthesia on cancer recurrence. Several ongoing randomized controlled trials are studying this link. Changes to clinical practice cannot definitively be recommended until the results of these studies can be examined.

Keywords: Analgesics, cancer recurrence, intravenous anesthesia, volatile anesthetics.

In the United States, there will be an estimated 1,898,160 newly diagnosed cancer cases and 608,570 cancer-related deaths in 2021. One hundred years ago, surgery was first hypothesized to promote local recurrence and distant spread of cancer cells, with the suggestion that residual tumor cells were disseminated from tumor manipulation and activating dormant tumors into a proliferative state. In the 1980s, postoperative cancer outcomes in a mouse model were linked to anesthetic agents. In 2006 researchers reported a correlation between anesthetic technique in breast cancer surgery and cancer recurrence or metastasis. Total resection of tumors can be curative; however, systemic proinflammatory changes may be responsible for tumor upregulation. Recently, investigators have speculated that perioperative inflammatory, metabolic, neuroendocrine, and immunologic changes may be promoted or induced by anesthetics. Surgery and anesthesia have been suggested to suppress the immune system, resulting in perioperative promotion of cancer cell proliferation and metastasis. With the modern anesthetics and analgesic choices available, anesthesia providers may be in a unique position to positively affect the long-term success of surgical resection of cancers and the prevention of tumor metastasis.

Cancer Physiology and Immune Response
Cancer cells receive their nutrient supply from the surrounding vasculature. Once nutrient demand has exceeded supply, cancer cells promote angiogenesis with the release of vascular endothelial growth factor (VEGF) and prostaglandin E2 (PGE2) to increase perfusion to these cells via newly formed vasculature. This process of angiogenesis has been linked to postoperative cancer recurrence and metastasis. The unregulated proliferation of cancer cells can result in embolization, allowing them to migrate to local and distal tissues via the blood and lymphatics. Once introduced to new tissue, the cancer cells continue their cycle of acquiring nutrients, proliferating, stimulating angiogenesis, and mobilizing.

The body forms a cell-mediated immune response involving lymphocytic and white blood cell (WBC) detection and destruction of cancer cells once presented. Natural killer (NK) cells are lymphocytes of importance in the defense against cancer. Natural killer cells are cytotoxic to tumor cells; their effects are enhanced by proinflammatory cytokines (interleukins) and inhibited by catecholamines. Although this immune response is important in combating cancer cells, the involvement of interleukins can also be a hindrance. Interleukins can enhance NK cell activity, but they can also interact with tumor cells to stimulate cell proliferation, angiogenesis, lymphangiogenesis, metastasis, and immune resistance.

Surgical Effects on Tumor Metastasis
Surgery is a common treatment option for patients with
solid tumors. Surgical manipulation of tumors, however, has been found to result in shedding of tumor cells into systemic circulation, promoting metastasis.\(^5\) Surgery contributes to tumor cell resistance by inhibiting anti-inflammatory factors and decreasing tumor cell apoptosis secondary to anti-inflammatory factor inhibition.\(^3,5\) In addition to surgical effects on tumors, secondary factors are also responsible for cell-mediated immunity depression and metastasis. Such factors include hypotension, hypoxia, hypothermia, blood transfusion, pain, hypovolemia, hypothalamic-pituitary-adrenal (HPA) axis stimulation, and sympathetic nervous system (SNS) stimulation.\(^5\)

Researchers have identified hypoxia-inducible factor (HIF-1\(\alpha\)) and hypothermia as contributors to cancer recurrence. Hypotension, hypovolemia, and hypoxia activate HIF-1\(\alpha\). These hypoxia-inducible factors are responsible for NK cell and WBC suppression and increased VEGF secretion, and they act as DNA transcription factors to promote tumor cell replication and survival.\(^3,4\) Hypothermia promotes inflammation and reduced NK cell activity.

Studies have reported increased risk of cancer recurrence and metastasis with allogenic blood transfusion. Although the mechanism is unclear, it is hypothesized to be the result of recipient lymphocyte suppression through induction of regulatory T cells (Tregs).\(^4\) Tregs are immune-suppressive cells that promote tumor formation, growth, and advancement by inhibiting immune responses against cancer.\(^5\)

The stress response associated with surgery also plays a role in tumor cell survival. Immune and lymphoid organs are innervated by the SNS. When stimulated, pain receptors activate the SNS. \(\beta_2\)-Adrenergic receptor agonism results in NK cell inhibition and production of leukotrienes. Activation of the HPA stimulates release of glucocorticoids from the adrenal glands. Immune cell glucocorticoid receptor activation prevents anti-inflammatory cytokine production and stimulates lymphocyte apoptosis in the thymus.\(^4\) Destruction of lymphocytes reduces the cell-mediated immune response to tumors, further promoting tumor survival. Perioperative influences and cancer metastasis are illustrated in the Figure.

### Anesthetics and Analgesic Effects on Cancer

- **Inhaled Anesthetics.** Volatile anesthetics exhibit a dose-dependent and time-dependent suppressive effect on immune cells, particularly NK cells and lymphocytes.\(^4\) Studies of volatile anesthetic effects on cancer have yielded contradicting results related to tumor type. Isoflurane and sevoflurane have been shown to suppress NK cell activity, inhibit lymphocyte proliferation and cytokine production, and induce lymphocyte apoptosis.\(^4,6\) Isoflurane has been found to upregulate HIF-1\(\alpha\) among human hepatoma and prostate cancer cells in in vitro studies.\(^7,8\) In addition to HIF-1\(\alpha\) upregulation, isoﬂurane appears to enhance tumor cell migration.\(^7\) Unlike isoﬂurane, sevoflurane suppressed HIF-1\(\alpha\) and lung adenocarcinoma metastases in one in vitro study.\(^9\) In an in vitro breast cancer study, sevoflurane and intravenous (IV) fentanyl/morphine combinations were compared with propofol and paravertebral regional anesthesia. The sevoflurane group was found to have increased proliferation, migration, and invasion of estrogen receptor–positive or negative breast cancer cells. The group receiving propofol infusion in conjunction with regional anesthesia did not demonstrate a proliferation of cancer cells.\(^10\)

The volatile anesthetic desflurane has also been implicated in cancer recurrence and metastasis. In a study of desflurane anesthesia for cytoreductive ovarian cancer surgery, desflurane was found to preserve lymphocyte and NK cell function. However, SNS stimulation that is commonly associated with the use of desflurane has been found to promote proinflammatory cytokines and to inhibit cell-mediated immune response.\(^11\)

Nitrous oxide (\(\mathrm{N}_2\mathrm{O}\)) has been suggested to contribute to cancer metastasis. Nitrous oxide impairs DNA, purine, and thymidylate synthesis (involved in DNA synthesis), which can stimulate oncogenesis and potentially facilitate the spread of cancer.\(^5,3,6\) Studies have shown \(\mathrm{N}_2\mathrm{O}\) to be contributory to cancer cell metastasis; however, no significant correlation was demonstrated between \(\mathrm{N}_2\mathrm{O}\) exposure and tumor relapse in a randomized controlled trial of patients with colon cancer.\(^5,12\)

- **Intravenous Anesthetics.** Propofol may be a superior anesthetic choice for patients with cancer. In contrast to volatile anesthetics, propofol increased NK cell activity and suppressed cancer cell metastasis in vitro.\(^2,4,13\) Propofol was found to increase lymphocyte activity and decrease cyclooxygenase-2 (COX-2) activity. Cyclooxygenase-2 is necessary for the production of PGE\(_2\), which promotes tumor progression, VEGF secretion, and NK cell inhibition. Malignant cell activity, such as isoﬂurane-induced HIF-1\(\alpha\) activation, has

### Table. Anesthetic Impact on Natural Killer (NK) Cells

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been shown to be inhibited by propofol. In a breast cancer study by Lee et al, 5-year recurrence rates were investigated comparing patients receiving propofol-based total IV anesthesia (TIVA) or sevoflurane. The authors suggested that propofol-based TIVA could reduce the risk of recurrence; however, Yoo et al questioned the study results because of a small sample size of 325 cases. Because of the retrospective nature of the study, Lee et al conducted a power analysis before data collection to minimize effect size, enabling them to detect a 2-fold difference in risk of recurrence between the groups. In 2019, Yoo et al published the results of a retrospective cohort study of 5,331 cases, showing no association between anesthetic type used and prognosis of breast cancer comparing propofol-remifentanil TIVA and enflurane, isoflurane, sevoflurane, or desflurane. In this study, the researchers could not exclude the possibility that the lack of statistical significance resulted from inadequate statistical power because the sample size was determined on the data available between January 2005 and December 2013. Based on the results of in vivo, in vitro, and retrospective studies, an understanding of cancer outcomes in this scenario is unclear.

Ketamine, often used as a sedative and adjunct analgesic, and the anxiolytic drug midazolam may not be suitable drugs for patients with cancer. In a rat model study, intraperitoneal and IV injection of ketamine (80 mg/kg) led to lung metastasis. In dog models, WBC cultures mixed with ketamine were found to have an upregulation of PGE2, further promoting tumor growth. In mice models, dendritic cell cultures mixed with midazolam were shown to have suppressed antigen-presenting capability. Unlike morphine, fentanyl does not stimulate the μ3-receptor, thereby diminishing the immune suppression cascade. A recent in vitro study found sufentanil did not affect apoptosis rates or cell cycle distribution of colon and pancreatic cancer cells compared with ropivacaine and bupivacaine when the cancer cells were exposed to the drugs dissolved in standard growth media. Another study, of breast cancer surgical patients, found propofol and remifentanil-based TIVA could inhibit the increases of VEGF compared with sevoflurane, but it is unclear whether the decreased tumor angiogenesis is a result of the propofol or the

Figure. Cancer Surgery Influences on Cancer Recurrence and Metastasis
Abbreviations: HPA, hypothalamic-pituitary-adrenal axis; SNS, sympathetic nervous system.
remifentanil, or a synergistic effect of both. Studies of fentanyl and remifentanil, nevertheless, have not led to definite conclusions about their effects on cell proliferation and metastases, raising questions about the mechanism of these effects. The greatest immunosuppressive effects have been associated with morphine’s μ3-receptor stimulation. Morphine has been found to suppress NK cells and lymphocytes via μ3-receptor stimulation. In vitro studies of breast and lung cancer, morphine was also found to promote migration of cancer cells via upregulation of matrix metalloproteinases. Morphine also increases glucocorticoids (HPA stimulation), stimulates angiogenesis via VEGF receptors, and inhibits tumor cell apoptosis. The timing of morphine administration may also affect cancer proliferation. Intraoperative administration caused immunosuppression, yet preoperative and postoperative administration decreased surgery-induced glucocorticoid release in rat models. Although there are no prospective clinical trials focused on demonstrating the angiogenic, proliferative, and metastatic actions of morphine, compared with other analgesic drugs, there is adequate evidence in vitro and in vivo evidence to support employing alternative strategies to control perioperative pain and reduce opioid consumption.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs). Cyclooxygenase-2 induction by cancer cells is responsible for tumor cell immune resistance. Prostaglandin E2, a product of the COX pathway, suppresses the cell-mediated immune response while promoting a proinflammatory response beneficial to tumor cell growth. Increased levels of COX-2 and PGE2 have been associated with various cancers. Therefore, COX-2 inhibitors such as ketorolac and celecoxib, by inhibiting the production of PGE2, can be useful in preventing cancer metastasis. Ketorolac has been found to increase NK cell activity and antagonize β-adrenergic receptors. In previous studies, preoperative ketorolac administration was associated with a 5-fold decrease in cancer recurrence within 4 years after surgery. Celecoxib was found to prevent morphine-induced tumor growth and metastasis, and to increase survival by counteracting the immunosuppressant effects of morphine. Tumor angiogenesis and metastasis following surgery and the associated systemic inflammation may be attenuated by administration of NSAIDs.

Regional Anesthesia. Regional anesthetics are useful in the prevention of surgical pain and limiting surgery-induced HPA and SNS immune suppression. Use of regional anesthetics minimize opioid and volatile anesthetic requirements. Although benefits of using regional anesthesia to avoid opioids have been suggested, it is unclear whether those benefits result from withholding opioids or from another mechanism related to regional anesthesia. Mechanisms by which regional anesthesia protects the immune system intraoperatively and postoperatively are multifactorial. Local anesthetics are responsible for stimulating lymphocytes and NK cells, reducing VEGF, and in clinically related concentrations, inducing apoptosis. In one study, the apoptotic actions of local anesthetics were more pronounced in malignant breast cancer cells than healthy breast epithelial cells. The DNA destruction found among estrogen receptor–positive breast cancer cells exposed to lidocaine inhibited tumor cell replication and prevented cancer progression. Ongoing prospective clinical trials are investigating the influence of regional anesthesia on survival after breast, lung, and colorectal tumor surgery. In a retrospective study of 129 patients with breast cancer, the use of paravertebral block for breast cancer surgery was associated with a reduced risk of recurrence and metastasis during the initial 3 years of follow-up. In addition to the previously noted studies, others have resulted in contradicting conclusions. In 2013, a meta-analysis of retrospective and prospective studies concluded that epidural anesthesia and/or analgesia was associated with improved overall survival in patients undergoing surgical treatment of colorectal cancer; however, the analysis did not support an association between epidural anesthesia and cancer recurrence. In a randomized trial of 446 patients undergoing major abdominal cancer surgery, researchers found that epidural block was not associated with improved cancer-free survival. Another colorectal cancer study, with 669 participants, found a benefit with epidural anesthesia only in older patients. The authors of this study concluded that the benefit of regional anesthesia on cancer recurrence may be contingent on specific tumor types.

Discussion Research has highlighted the importance of optimal perioperative management of oncologic patients. It has been noted that surgical stress combined with anesthetic agents promote an environment favorable to malignancy. Yan et al stated that cancer recurrence and death were related to breast cancer subtype, nonadherence to cancer therapy, and poor ASA status. Yoo et al noted that a limitation of retrospective studies is the inability to measure inflammatory biomarkers that could explain a causal relationship between anesthesia and cancer recurrence. Use of volatile anesthetics has been criticized because of their immunosuppressant effects and stimulation of tumor-promoting factors HIF–1α and VEGF. Avoiding volatile anesthetics and using propofol-based TIVA, COX inhibitors, and regional anesthesia may prevent immune suppression; however, further research is needed to determine the associated effects on cancer recurrence. Tumor cell metastasis occurs through different mechanisms that may be attenuated by inhibition of the SNS or HPA.

The role of opioids in cancer surgery is controversial because of the contradicting data. Whereas preoperative
and postoperative morphine administration decreases surgical stress immune suppression, there is dose-dependent tumor cell attenuation or accentuation. It remains unclear whether synthetic opioids or morphine enhances cancer metastasis or recurrence after surgery. Therefore, current evidence does not support a change in practice.

Regional anesthesia has been thought to be beneficial by reducing use of volatile anesthesia, inhibiting SNS stimulation, and decreasing opioid use; however, there currently is inadequate evidence to determine the role of regional anesthesia in cancer recurrence. Regional anesthesia studies have mostly been retrospective, making them vulnerable to selection bias and confounding variable influences. Among the various studies, confounding variables ranged from varying drug doses, cancer subtypes, and use of different opioids to different techniques with general or regional anesthesia. Patient temperature, blood transfusions, and psychological stress are additional confounding variables among the studies that potentially contribute to the differing results related to cancer recurrence and metastasis. There is an increasing amount of data suggesting the immunosuppressant effects of anesthesia can be circumvented by avoiding opioids and volatile anesthetics; however, further evaluation is required to determine the implications of regional anesthesia and cancer recurrence.

It has yet to be confirmed whether volatile anesthetics, IV anesthetics, and analgesics are the causal factor for the cancer recurrence. There are several ongoing randomized controlled trials studying this link. With conflicting conclusions from the studies, one might ask, what should we do? Some anesthesia providers have begun to change their practice by avoiding volatile anesthetics in patients with cancer and by opting for an opioid-analgesic TIVA approach. Although randomized controlled studies are still in progress, there are enough animal models and in vitro studies resulting in favorable and unfavorable outcomes with choice of anesthetic or analgesic. It may be prudent to err on the side of caution by avoiding HIF-inducing volatile anesthetics. Propofol may be a favorable choice due to its HIF-suppressive and NK cell–inducing effects. Opioids have shown variable effects on cancer progression, and it would be premature to rule out the administration of opioids completely. Limiting the use of intraoperative opioids in favor of alternative analgesic strategies such as regional anesthesia and NSAIDs is reasonable given their ability to reduce surgical stress and immunosuppression as well as the inhibition of tumor cell angiogenesis compared with volatile anesthetics and opioids.

REFERENCES


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**DISCLOSURES**

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