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The Influence of Analgesic Modalities on Postoperative Cancer Recurrence

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Abstract

The potential for cancer cells to grow and to metastasize depends on complex interactions between inflammatory signals and pathways, immune cells, and elements of the stromal tissue in which they invade. Related to the nature of many cancers, the probability of recurrence can potentially be quite high for some patients. Immunology, lifestyle modifications, timing of disease, genetics, age, gender, and race are only a handful of ways the likelihood of cancer recurrence can be influenced. The quantity, or density, of certain immunological cells or factors, plays a role in the propagation of cancer cells. Opioids are often used in cancer patients for acute postoperative and chronic pain management. While they can produce significant pain relief, the type of analgesic utilized is important, as it may influence cancer propagation. In this regard, certain opioids have been found to increase T regulatory cells while suppressing NK cell function. Morphine may promote tumor neovascularization and expansion. Fentanyl administration significantly diminishes NK-cells and CD8+ cytotoxic T-cells. In a recent meta-analysis, propofol-based anesthesia improved both cancer-free survival and overall survival. COX inhibitors have also shown promise in persevering cancer immune function, as in literature involving ketorolac and celecoxib. In summary, inhaled anesthesia and opioids may contribute to a pro-tumor metastasis environment also known as cancer propagation; whereas propofol and COX inhibitors may provide a better alternative to reduce cancer recurrence and propagation.

Keywords: Opioids, Volatile, Morphine, Tramadol, Fentanyl, Recurrence, Cancer, COX Inhibitors

1. Introduction

Cancer is essentially an abnormal or unregulated growth of cells (1). The potential for cancer cells to grow and metastasize depends on many factors, a few including the complex interactions between inflammatory signals and pathways, immune cells, and elements of the stromal tissue in which they invade. Most cancer cells have the ability to induce the expression of tumor-promoting metabolic factors that lead to tumor invasion as well (2).

Cancer is currently the second leading cause of death in the United States, with an estimated incidence of 1.9 million new cases per year (3). Cancer screening has also played a very important role in identifying cancers, with some obvious examples being colorectal, cervical, breast, and lung cancers (3). Unlike the past, new modes of screening, detection, and treatment have given many patients hope for survival and a much better chance at a life of longevity.

Cancer is a systemic disease that impacts patients' lives in many ways. A vast number of individuals often encounter analgesics and anesthetics throughout their course of treatment, whether it is indicated for surgery or pain relief. The effects of these treatment modalities on the nature of the body and tumor cells are actively being investigated to discover the most optimal way to treat a patient with a cancer diagnosis.

2. Current Treatment of Cancer

It is essential to create a treatment plan with the patient to best target the cancer while minimizing the harm to the patient. There are multiple cancer treatment options available (4, 5). Combination therapy is an option for some patients as it is meant to provide a superior effect by working synergistically or on the same pathway to kill cancerous cells (6). This includes the combination of surgery with therapies such as chemotherapy or radiation. If the treatment is inadequate or complete surgical resection is not possible, cancer cells may be left behind and become dormant. This allows them to form adaptations to evade the immune system (7).

2.1. Surgery

Size and location are important factors influencing if a surgical procedure can be performed. In cases that the complete removal of the cancer is not possible, leftover cells can multiply and continue to spread (8). Patients with early diagnosis or lower grade tumors can have higher rates of favorable outcomes with tumor resection (9). Minimally invasive surgery has demonstrated to be an effective treatment modality while minimizing the amount of blood loss, need for hospital stay, and blood transfusions (10).

2.2. Radiation Therapy

The goal of radiation therapy is to safely deliver a therapeutic dose of radiation while limiting the harm to the surrounding tissues (11). Treatment may be done through internal radiation or external beam radiation. Advances in the field have allowed for magnetic resonance imaging to be used with radiation for improved delivery of treatment (12). It is a form of cancer treatment that additionally provides the advantage of recruiting antigen-specific T cells, making it an effective modality to combine with immunotherapy (13).

2.3. Chemotherapy

Chemotherapy drugs can inhibit DNA replication and signaling cascade leading to cell damage (14). Delivery of chemotherapy may be done orally, by injections, or intravenously. Common side effects include nausea, vomiting, hair loss, and fatigue that can often cause significant distress, making the continuation of treatment more difficult for the patients (15). Chemotherapy provides the advantage of creating combination therapies for direct and more effective cancer treatment.

2.4. Molecular Targeted Therapy

Molecular-targeted therapy blocks cancer cell growth by targeting specific molecules. This may be done with the use of small molecules, monoclonal antibodies, therapeutic cancer vaccines, or gene therapy which function to ultimately promote cell death (16). Molecular targeted therapy rarely produces adverse side effects due to its personalization towards the patients' genetic profile (17). Patients may benefit from a combination of chemotherapy and molecular targeted therapy and increase the effectiveness of treatment.

2.5. Cancer Immunotherapy

The immune system normally functions to identify and destroy abnormalities in cells, such as those that are cancerous (18). Immunotherapy uses this same method but enhances its effects through the use of cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), programmed death 1 (PD-1), programmed death-ligand 1 (PD-L1), and chimeric antigen receptors (CARs) (19). This type of therapy allows for the immune system to target specific cells while keeping toxicity to a minimum.

3. Cancer Recurrence

Related to the nature of many cancers, the probability of recurrence can potentially be quite high for some patients. Outcomes from cancer recurrences can be influenced by the initial staging at the time of detection and time-to-recurrence (20). These two factors have wide-ranging effects in regard to the multitude of different cancers, with some being colorectal, breast, and lung cancers, to name a few. Immunology, lifestyle modifications, timing of disease, genetics, age, gender, and race are only a handful of ways the likelihood of cancer recurrence can be influenced. At times there may not even be a clear explanation for its return. Typically, patients with cancer recurrence, even after complete resection, tend to have worse outcomes in comparison to their primary occurrence (21).

3.1. Immunologic Factors

Cancer is highly efficient in the way that it can communicate with various cells and parts of the human body to make its growth prosperous. Common interactions with non-cancerous cells can be located in the lymphatic system, bloodstream, immune system, bone marrow, stroma, and many others (22). Tumor cells are able to alter their tumor microenvironment to flourish and progress, and it is with these changes that the risk of future recurrences

can be augmented (23). The quantity, or density, of certain immunological cells or factors, plays a role in a cancer's prosperity. On the contrary, a negative correlation exists between the outcomes of patients with non-small cell lung cancer and the amount of their own tumor-infiltrating lymphocytes (TIL) (24). As for researchers, identifying these immunologic markers with the use of newer methods like flow cytometry and multi-omics have been enormously useful to assess the likelihood of cancer recurrence, as the field of pathology is becoming more technologically advanced (22).

3.2. Physical Factors

With improvements in modern-day science and medicine, numerous patients are able to beat their cancer diagnosis. With that, there has concomitantly been an increase in a concept known as fear of recurrence in cancer survivors. One way a person can play a role in their chance of recurrence is through their lifestyle choices and risk modifications. It is noted that eating a wholesome diet and partaking in physical activity has proven to be a benefit in reducing one's risk of developing cancer. However, the implementation of a healthy lifestyle is actively being studied to determine if it has a strong positive effect on the risk of cancer recurrence (25).

4. Opioids and Cancer Recurrence

There are various factors that may influence a patient's vulnerability and increase their likelihood for cancer recurrence, such as the organ affected, lymph node metastasis, seeding, proliferation of residual cells, and surgical stress (26). For those with cancer that require surgical intervention, it places them at increased risk for recurrence as the secretion of inflammatory cytokines during the postoperative phase allows for tumor cells to escape and cancer propagation (27).

Opioids are often used in cancer patients during perioperative period, and for chronic pain control (28-30). While they can produce significant pain relief, the type of opioid used is important as it may influence cancer recurrence. Certain opioids have been found to increase T regulatory cells, while suppressing NK cell function (31). The μ- and κ-opioid receptors have been studied and shown to decrease NK cell activity. Morphine, a commonly used opioid, may promote tumor neovascularization and expansion (32, 33). Its use in IV and epidural injections inhibit an immune response by targeting the production of IFN-γ by CD8 cells (34, 35). Similarly, buprenorphine and methadone reduce the function of NK cell activity (31, 36). In a study by Zhang et al., looking at fentanyl's effect on tumor growth in colorectal cancer, it was found to inhibit cell invasion and tumor growth, making its use to be effective for reducing the risk of colorectal cancer recurrence (37). Tramadol functions similarly to morphine but may produce the opposite effect and instead increase the activation of NK cells for patients undergoing surgical tumor resection (38, 39). The use of opioids and their effect on cancer remains a central topic of discussion as not all produce the same effect, and some may place patients at higher risk of immunosuppression, leading to the recurrence of cancer.

5. Clinical Studies

Breast cancer remains the leading cause of death in women, and surgical treatment often provides the best prognosis. Even despite surgical removal, tumor recurrence and distant metastasis still pose a major challenge (40, 41). It is known that the risk of metastasis is both dependent on the metastatic potential of the tumor and the ability of the host immune response to fight it off (42). With the "surgical stress response" (or perioperative immune response) and a dampened immune system due to general anesthesia, there is an increased chance that the host immune system is not able to fend off these potentially metastatic breast cancer cells (42). To understand how different anesthesia techniques may contribute to breast cancer recurrence, it is first important to understand the perioperative immune response.

5.1. Surgical Stress Response

Cell-mediated immunity is damped for several days after major surgery, with the lowest immunosuppression occurring around the third day (43). This third day may serve as the pivotal day when the tumor cells are in an environment favorable for the growth of disseminated tumor colonies. It is also possible that the environment allows the growth of undetected metastases that were previously held in check by the immune system (44). During this time, there is a detectable decrease in IL-2, IL-12, and INF-y, which are all key cytokines involved in cell-mediated immunity and shifting to an increased, anti-tumor Th1/Th2 ratio (42). Furthermore, there is an increase in IL-10, which is involved in inhibiting the Th1 response (42). As expected from the shift in these cytokines, there is a decrease in cytotoxic T-lymphocytes, natural killer (NK) cells, dendritic cells, and T-helper cells.

An increase in local and systemic growth factors, such as VEGF and TGF-B, may also contribute to the metastatic potential of residual tumor cells (45). VEGF, TGF-B, and prostaglandin E2 (PGE2) are all important mediators in angiogenesis, which must occur for tumors to grow beyond 2-mm in diameter to meet oxygen and nutrient demand (46). Other perioperative factors, such as pain and anxiety, increase inflammatory mediators (COX) that lead to increased PGE2 levels pain and anxiety also increase immunosuppression by decreasing NK cell levels, further hindering the host's ability to recognize and combat tumor cells (44). It has also been shown that, with increased surgical trauma and patient anxiety, there is an increase in β-adrenoceptor signaling, which contributes to increased metastasis and tumor recurrence (47, 48).

These factors may all synergize to provide the optimal environment for tumor growth and metastasis. While these factors have been shown to result in immune dysfunction during surgery, it is now widely recognized that different anesthetic techniques may alter the immune response, either further contributing to a pro-tumorigenic environment or possibly ameliorating this "surgical stress response." This brief overview of perioperative/pro-tumorigenic factors will serve as a foundation to understand how different anesthesia techniques may interact and influence breast cancer recurrence.

5.2. Problem with Inhaled Anesthetics and Opioids: Current in vitro and Animal Studies

Halogenated and inhaled anesthetics (isoflurane and sevoflurane) can inhibit the interferon α/β-induced NK-cell function in mice (49). Sevoflurane has also been shown to decrease the release of cytokines from NK and NK-like cells in vitro (50). Furthermore, Elena et al. found that volatile anesthetics alter Th1/Th2 ratios in mice, shifting toward the tumor favorable Th2 response (51). Given that the tumor stage is indirectly related to NK-cell levels, it is plausible that inhaled anesthetics contribute to a tumor-conducive environment where tumors are prone to grow and/or metastasize (52).

The effects of opioids on immune dysfunction are also well studied, and not all opioids have similar effects. For example, morphine has been shown to suppress NK-cell cytotoxicity in a dose-dependent manner in mice studies. It was also shown to increase angiogenesis and growth of breast tumors in mice (32). In contrast, several other studies found that morphine administration was a way to reduce tumor metastasis and suppress tumor growth in rat and mouse models (53). A study in humans found that the decline in postoperative T-lymphocyte proliferation may be prolonged by morphine administration (38). Overall, the effects of morphine on the perioperative period are debated, and it is not clear whether or not morphine administration increases the odds of cancer recurrence (54).

Fentanyl administration, another commonly used analgesic agent, significantly diminishes NK-cells and CD8+ cytotoxic T-cells (54, 55). For instance, Yeager et al. found there was a dose-dependent decline in NK-cell activity when given to healthy human volunteers (56). This decline in critical tumor-fighting cells has been shown in both animal and human models (54). Others have also demonstrated that fentanyl suppresses NK-cell levels (57). However, they also found that, at low doses, fentanyl does not suppress immune resistance to cancer (58). In a rat study that examined the effects of fentanyl on lung metastasis, the authors showed that fentanyl had a dose-dependent suppression of NK-cells and an increase in metastatic cells (59).

It is generally agreed that volatile anesthetics, morphine, and fentanyl pose a recognizable risk when administered during surgical removal of tumors, especially during procedures that have a high risk of disseminating residual tumor cells such as during breast cancer removal. Thankfully, several anesthetic options may exist to replace the general anesthetic techniques (ie, sevoflurane, fentanyl, morphine) with alternative techniques that prevent or preserve the surgical stress response associated with a pro-tumorigenic environment (60-63).

5.3. Propofol, Paravertebral Block, and NSAIDS: Techniques of Promise?

Propofol, an already widely used alternative to inhaled anesthetics, shows promise for preserving NK-cell cytotoxicity and suppressing the surgical stress response (64, 65). It has been shown to suppress inflammatory cytokines and prostaglandins in several studies (66). Melamed et al. found that only propofol maintained NK-cell cytotoxicity when testing the effects of propofol, ketamine, thiopental, and halothane (67). Another study found that propofol can reduce the production of COX-2 and PGE-2, thus indirectly attenuating the decreased NK-cell levels seen in general anesthesia (27). In a recent meta-analysis, propofol-based IV anesthesia improved both cancer-free survival and overall survival (68). Further, COX inhibitors have also shown promise in persevering cancer immune function (69). Ketorolac can potentially reverse the NK-cell cytotoxicity compared to morphine (70). Celecoxib was also shown to reverse the immune suppressive and

angiogenesis-promoting effects of morphine in a mouse model (71). Findings such as these have led many to believe there are better anesthetic options for cancer surgery.

Furthermore, the paravertebral block is another potential option to preserve immune function and is an effective anesthetic technique (72). Importantly, paravertebral blocks reduce the need for opioid analgesia, which, as mentioned previously, cause immune dysfunction (73). Deegan et al. clearly showed that propofol/paravertebral block did not increase VEGF levels and attenuated MMP-2, MMP-9, and IL-1 compared to sevoflurane/opioid anesthesia (74).

6. Conclusions

Many cancer survivors struggle with fear of recurrence, which can be psychologically difficult to deal with. Once a person has dealt with cancer, their body is no longer the same in the way that it reacts to various medications and stressors, and the basic everyday worries that life brings. COX inhibitors have shown promise in helping with the prevention of cancer recurrence. Celecoxib has been shown to reverse the immune suppressive and angiogenesis-promoting effects of morphine in a mouse model. Propofol has been shown to improve both cancer-free survival and overall survival. Fentanyl, on the other hand, can significantly diminish NK-cells and CD8+ cytotoxic T cells. This shows that the selection of both pain medications and even anesthetic agents can affect cancer reoccurrence.

Footnotes

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