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Recurrence And Metastasis Of Breast Cancer After Volatile Inhalation Agents For Primary Cancer Resection

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Abstract

Surgical resection of a breast tumor is frequently a treatment option for cancer, and in some cases can be curative (Hurtado et al., 2021). Multiple factors increase the risk of metastasis or recurrence including the neuroendocrine stress response to surgery and manipulation of the tumor itself (Kim, 2018). Additional factors include depression of cell-mediated immunity including sympathetic nervous system (SNS) stimulation, hypothalamic-pituitary-adrenal (HPA) axis stimulation, and pain (Hurtado et al., 2021). Research suggests that anesthetic selection, particularly total intravenous anesthesia versus volatile inhalation anesthesia (IA), has an impact on cancer recurrence and metastasis in breast cancer patients, however it remains unclear if one is superior to the other.

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Breast cancer is the second most prevalent cause of cancer death among women (American Cancer Society, 2023). The American Cancer Society (2023) estimates that nearly 298,000 women will be diagnosed with invasive breast cancer and nearly 44,000 women will die from breast cancer in the United States in 2023. The current average risk of a woman developing breast cancer at some point in her life is approximately 13% (American Cancer Society, 2023). Though the trend in breast cancer detection rates is increasing 0.5% per year, the death rate from breast cancer in women has been on the decline since 1989, and is currently approximately 2.5% (American Cancer Society, 2023). Earlier detection of breast cancer through enhanced screening, public awareness, and improved cancer treatments are responsible for this trend (American Cancer Society, 2023).

Although the chance a woman will die as a result of breast cancer has decreased significantly since 1989, the decline has plateaued recently (American Cancer Society, 2023). As surgical excision is frequently part of the breast cancer patient's treatment plan, examination of the impact of surgical technique as well as anesthetic technique is crucial as we seek to improve breast cancer survival rates related to recurrence and metastasis. This paper seeks to explore the impact of anesthetic choice, specifically inhaled volatile anesthetic agents compared to total intravenous anesthetic, on recurrence and metastasis of breast cancer.

Background

Cancer Pathophysiology

It is widely recognized that cancer is likely caused by mutation or abnormal activation of cell genes controlling growth and mitosis. These mutations or activations are triggered by many

factors including ionizing radiation, chemical exposure, physical irritants, hereditary tendency, and exposure to oncoviruses (Hall & Hall, 2021). Under normal conditions, mutated cells most simply die. Those that survive often retain normal feedback control mechanisms that prevent excessive cell growth, or the immune system destroys the mutated cells before they become cancerous. (Hall & Hall, 2021).

When cells become cancerous, they receive nutrients for continued growth from local vasculature. Frequently, cancerous cells do not have the same growth factors or feedback mechanisms that normal cells do, allowing them to grow and proliferate beyond the size and number of normal, healthy cells (Hall & Hall, 2021). Once the malignant cells have depleted the local vasculature of nutrients, effectively killing the healthy tissues, they release vascular endothelial growth factor (VEGF) and prostaglandin E_2 (PGE_2) to stimulate angiogenesis and increase perfusion (Hurtado et al., 2021). When cell proliferation is left unchecked, embolization may occur, leading to migration through the vasculature and lymphatic system (Hurtado et al., 2021). Cancer cells are far less adherent than healthy cells are, which contributes to migration and seeding. (Hall & Hall, 2021). If untreated, the malignant cells continue to grow, killing local healthy cells and disrupting cell function by this cycle of angiogenesis, migration, and proliferation (Hurtado et al., 2021).

Immunologic Response to Cancer Cells

The immune system response to cancer cells includes the detection and destruction of the malignant cells through complex actions of the innate and acquired immune systems (Adam et al., 2003). The innate immune system is comprised of numerous cell populations, including monocytes, macrophages, natural killer (NK) cells, and multiple types of lymphocytes. The acquired immune system is comprised of B and T-lymphocytes. T-lymphocytes instruct host

cells to stop the synthesis of proteins or undergo apoptosis. B-lymphocytes differentiate into plasma cells, which then synthesize and secrete antibodies or immunoglobulins (Jenkins et al., 2007). T-lymphocytes differentiate into cell types which are distinguished by their surface proteins, the majority of which are either cytotoxic CD8 or CD4 cells (Adams et al., 2003).

T-lymphocytes play many important roles within the acquired immune system. Most T-lymphocytes that display the CD4 protein differentiate into helper T-cells, which play an important role in the destruction of cancer cells (Grossman & Porth, 2014). T-helper cells constitute over 75% of all T-lymphocytes and have regulatory actions over many immune system functions. Regulatory actions are initiated when the activated T-helper cell manufactures lymphokines, which are protein mediators that act on other immune cells and bone marrow cells (Hall & Hall, 2021). Lymphokines are required for the effective function of the immune system (Adams et al., 2003). Interleukin-2 (IL2) is a lymphokine secreted by CD4 cells. Interleukin-2 stimulates the growth and differentiation of CD8 cells as well as the cytotoxic action of NK cells (Jenkins et al., 2007).

Cytotoxic NK cells are particularly important in the innate immune response to cancer. Natural killer cell function is increased by cytokines and IL2, and inhibited by catecholamines (Hurtado et al., 2021). Of note, interleukins have both desirable and undesirable effects on cancer cells as they not only enhance NK cells, but they can also stimulate angiogenesis, proliferation, metastasis, and immune resistance of cancer cells (Hurtado et al., 2021).

Transforming growth factor-β (TGF-β) is an important cytokine produced by immune and non-immune cells. Transforming growth factor-β signaling plays an important role in regulation of T-cells, particularly CD4 cells (Travis & Sheppard, 2014). Like IL2, TGF-β effects can both impede and promote proliferation of cancer cells. Transforming growth factor-β has

anti-tumor effects in the early stages of malignancy, but it exhibits pro-oncogenic effects later in the disease process (Travis & Sheppard, 2014).

Tumor cell immune resistance is caused by cyclooxygenase-2 (COX-2) induction. The COX enzymes have a complex role in the immune system (Hurtado et al., 2021). Cyclooxygenase enzymes are derived from arachidonic acid, which is released from the cell membrane as a result of tissue trauma and inflammation (Barash et al., 2015). The COX pathway forms prostaglandins, including thromboxane A_2 (TXA_2) and PGE_2 (Barash et al., 2015). Elevated levels of COX-2 and PGE_2 have been associated with multiple cancers (Hurtado et al., 2021).

Breast Cancer Treatment

Most newly diagnosed breast cancers are non-metastatic and are categorized into early stage and locally advanced subgroups (Taghian & Merajver, 2022). Only 5% of newly diagnosed breast cancers are metastatic at the time of detection (Taghian & Merajver, 2022). A multidisciplinary approach is typically utilized in the treatment of new breast cancers, including chemotherapy, immunotherapy, radiation, and surgical intervention (Taghian & Merajver, 2022). Treatment is individualized based on the specific type and stage of the breast cancer. Breast cancers may be treated with primary surgical excision, primary surgical excision followed by neoadjuvant therapies, or with primary neoadjuvant therapies followed by secondary surgical intervention (Taghian & Merajver, 2022).

Surgical Approaches

A common approach to surgical excision of breast cancer is mastectomy. Mastectomy is the complete removal of the breast tissue and is the only surgical option for risk reduction for women at high risk of developing breast cancer (Kwong & Sabel, 2022). The indications for

mastectomy include unsuccessful breast-conserving therapy, inflammatory breast cancer, breast cancer with two or more primary tumors in separate breast quadrants (multicentric disease), unknown extent of disease due to microcalcifications on mammography, history of radiation therapy, inability to achieve persistently clear margins, and patient preference (Kwong & Sabel, 2022).

Mastectomy approaches include total simple mastectomy, modified radical mastectomy, and radical mastectomy (Kwong & Sabel, 2022). Total simple mastectomy involves the removal of the breast tissue and the underlying pectoralis major fascia. Total mastectomy may be performed using the nipple-sparing technique, where the nipple and areola are preserved while breast tissue and pectoralis major fascia are removed. Another method for total mastectomy is the skin-sparing technique where the underlying breast tissue and pectoralis major fascia are removed but the skin is left in situ. Modified radical mastectomy is a total mastectomy with dissection of level I and II axillary lymph nodes. Rarely indicated, radical mastectomy includes the removal of breast tissue, pectoralis major and minor muscles, all axillary lymph nodes, and the overlying skin (Kwong & Sabel, 2022).

Breast-conserving surgery (BCS) includes lumpectomy and is often coupled with radiation therapy. This approach to surgical excision requires complete removal of the tumor and enough surrounding tissue to achieve negative surgical margins. The goal is to preserve enough breast tissue to be cosmetically acceptable to the patient and achieve a low rate of recurrence (Taghian & Marajver, 2022). Taghian and Marajver (2022) reference recent observational studies that suggest breast-conserving therapy is associated with equivalent survival to mastectomy.

Immunologic and Physiologic Response to Surgery.

Cancer cells that escape death exist in a microenvironment that includes local non-malignant stromal cells, immune cells, extracellular matrix, chemokines, cytokines, and numerous other complex components (Wall et al., 2019). The tumor microenvironment is delicate and easily disturbed by tissue trauma induced by surgical intervention. Disruption may lead to seeding and proliferation of cancer cells in local or distant sites (Wall et al., 2019). In addition to the physical disruption of the microenvironment, surgery also induces physiologic changes to the body including tissue hypoxia, the activation of the neuroendocrine stress response, immunosuppression, angiogenesis, and inflammation which all play a role in proliferation and metastasis of malignancy (Wall et al., 2019).

Many factors in the perioperative period impact the behavior of cancer cells (Eden et al., 2018). The anesthesia provider can potentially impact several key areas of concern through choice of anesthetic or analgesic agents. These factors include the neuroendocrine stress response due to SNS and HPA axis activation, and resulting function of immune cells (Eden et al., 2018).

Painful stimuli results in activation of the HPA axis and SNS, which both increase circulating inflammatory mediators (Wall et al., 2019). Surgical tissue trauma causes an initial pro-inflammatory phase increasing the circulating levels of inflammatory mediators such as PGE_2, COX-1, COX-2, glucocorticoids, cytokines and catecholamines (Selby et al., 2021). Pro-inflammatory mediators during the intra-operative period suppress the immune system's ability to identify and destroy cancer cells. This is achieved by suppression of the cytotoxic action of NK cells and differentiation of anti-tumor T-helper cells to tumor-promoting T-helper cells (Selby et al., 2021).

Concurrently, the intraoperative tissue environment promotes the migration, invasion of tissue, and proliferation of cancerous cells (Wall et al., 2019). Tissue hypoxia causes increased release of pro-angiogenic factors including hypoxia-inducible factor (HIF) and VEGF which contribute to the invasion and proliferation of cancer cells (Wall et al., 2019). Hypoxia-inducible factor is not only activated by tissue hypoxia, but also by hypotension and hypovolemia, and is a known contributor to cancer recurrence (Hurtado et al., 2021).

After surgery, neutrophils, macrophages, and fibroblasts migrate to the wound leading to upregulation of cytokines and growth factors to promote surgical site healing (Wall et al., 2019). Consequently, these factors also promote proliferation, migration, and angiogenesis of new metastatic sites (Selby et al., 2021). It has been postulated by researchers that HIF and VEGF expression can be altered by several drugs, including analgesic and anesthetic agents (Wall et al., 2019).

Anesthetic Techniques

Surgical excision for breast cancer requires anesthesia, usually general. General anesthetics (GA) can be divided into inhalation anesthetic (IA) or total intravenous anesthesia (TIVA). Both methods modulate the physiologic and immune response to surgical stress and have been postulated to impact recurrence and metastasis in breast cancer patients (Eden et al., 2018).

Volatile Inhalation Agents

The mechanism of action of volatile inhalation agents are not fully known, they have been in use to maintain general anesthesia since the 1950s with the advent of halothane (Barash et al., 2015). Frequently administered modern volatile anesthetic agents include sevoflurane, isoflurane and desflurane. Benefits to using volatile anesthetics include ease of administration,

reliable blockade of surgical stimulation, bronchodilation, decreased cerebral metabolic rate, and the ability to reliably monitor anesthetic depth through end-tidal anesthetic concentration (Khorsund et al., 2022). Disadvantages to IA include dose dependent decrease in systemic blood pressure due to a decrease in systemic vascular resistance, dose dependent myocardial depression, increased risk of postoperative nausea and vomiting, and potential to induce malignant hyperthermia in pre-disposed patients (Khorsund et al., 2022). Isoflurane and desflurane cause sympathetic nervous system stimulation (Barash et al., 2015). As discussed previously, activation of the SNS and hypotension are both factors that may negatively affect the immune system's ability to locate and destroy cancer cells.

There is conflicting evidence related to the effects of volatile IAs on the immune system and neuroendocrine stress response (Wall et al., 2019). Animal models have shown that volatile anesthetics inhibit NK cell activity (Cata et al., 2020). Halothane, though not used in North America, decreases cytotoxic NK cell activity, and increases secretion of HIF-1 (Kim et al., 2018). Sevoflurane increases apoptosis of T-lymphocytes and secretion of HIF-1 (Kim et al., 2018). A study by Fan et al. (2020) stated that sevoflurane anesthesia was associated with inferior clinical outcomes in breast, rectal, colon and gastric cancers. A review by Cata et al. (2020) noted that breast cancer cells from patients receiving sevoflurane were more likely to survive than those of patients receiving propofol-based anesthesia. Interestingly, high concentrations of sevoflurane (5% and 10%) showed antimetastatic effects in *in vitro* and animal studies, though these concentrations would not be used for human patients (Cata et al., 2020). Sevoflurane administration has also been shown to result in much higher concentrations of VEGF in patients who underwent lung cancer surgery (Cata et al., 2020).

Most of the literature available to review focused on sevoflurane, though isoflurane and desflurane are also used clinically. Isoflurane is more potent than sevoflurane or desflurane, and is inexpensive (Khorsund et al., 2022). Isoflurane is an airway irritant, which can be of particular detriment during induction and emergence of anesthesia. Emergence may be protracted especially after prolonged administration of isoflurane (Khorsund et al., 2022). The study by Fan et al. (2020) noted that isoflurane increased the secretion of HIF-1, HIF-2, VEGF, and the proliferation of renal carcinoma cells while also inhibiting colon cancer cell apoptosis. This suggests that isoflurane may promote proliferation and metastasis of multiple types of cancer. Jing et al. (2022) found that at clinical concentrations (1.2%) isoflurane increased migration of glioblastoma cells. Additionally, isoflurane has an inhibitory effect on NK cells, and stimulates apoptosis of T-lymphocytes (Jing et al., 2022).

Desflurane is costly and requires a much higher end-tidal concentration to maintain adequate surgical anesthesia due to its low blood tissue solubility. Desflurane is also a potent airway irritant (Khorsund et al., 2022). Desflurane is rapidly eliminated which results in rapid emergence from anesthesia. Desflurane may promote metastasis through degradation of the basement membrane in ovarian cancer cells by increased expression of MMP-11 mRNA (Jing et al., 2022). Interestingly, use of desflurane decreased the occurrence of metastasis in colon cancer cells (Jing et al., 2022). Desflurane may increase secretion of VEGF and TGF-β in ovarian cancer cells (Fan et al., 2020). It is the only volatile IA currently in use that does not induce apoptosis of T-lymphocytes (Kim et al., 2018).

Total Intravenous Anesthesia

Total intravenous anesthesia involves the use of only intravenous anesthetic agents, with no inhaled anesthetic. It is important to note, the mechanisms of action of intravenous anesthetics

are well known (Barash et al., 2015). Multiple intravenous agents may be used to both induce and maintain anesthesia, including propofol, benzodiazepines, barbiturates, etomidate, dexmedetomidine, and ketamine. Arguably, propofol is most frequently used as the primary anesthetic in TIVA though it does not provide any analgesic effects (Barash et al., 2015). As such, it is frequently necessary to administer opioid analgesics when propofol is used as the primary anesthetic (Barash et al., 2015). Due to the observed effects on the immune system and cancer cells of volatile IA agents, researchers postulate that propofol may be a better anesthetic choice for cancer patients (Hurtado et al., 2021).

Propofol is classified as a sedative-hypnotic that has many indications for use as the primary maintenance anesthetic, such as patient or family history of malignant hyperthermia, substantial risk for post operative nausea and vomiting, or surgical procedures in which neuromonitoring must be utilized (Khorsund et al., 2022). Propofol has antiemetic and bronchodilatory properties and facilitates rapid induction and emergence. Propofol, like IA, causes a dose dependent reduction in systemic vascular resistance, leading to hypotension. There are currently no reliable methods to monitor depth of anesthesia during TIVA as blood concentrations of intravenous (IV) agents are not easily obtained, however it may be argued that neuromonitoring may be used for this purpose (Khorsund et al., 2022). It is difficult to monitor for infiltration or extravasation when the IV cannulation site is tucked or otherwise not visible during surgery (Khorsund et al., 2022).

Propofol has been widely researched for its potential effects on cancer cells, including anti-inflammatory and immune function stimulatory properties (Wall et al., 2019). Propofol decreased proliferation and migration and increased apoptosis rates in pancreatic cancer cells (Bonvini, 2022). Propofol was observed to modulate microRNA in ovarian cancer cells, which

resulted in decreased cell proliferation and increased apoptosis rates (Bonvini, 2022). It has also shown effects in non-small cell lung cancer cells, decreasing inflammation within the tumor microenvironment, and reducing HIF-1α (Bonvini, 2022). Hurtado et al. (2021) noted that propofol inhibited tumor progression, VEGF secretion and NK cell inhibition by its upregulating effect on lymphocytes and decreased COX-2 activity, leading to decreased production of PGE_2.

Anesthetic Adjuncts

Propofol lacks analgesic properties. As such, adjunct medications are required to provide a balanced anesthetic and blunt the response to surgical stimulation. Commonly used adjuncts include ketamine, dexmedetomidine, opioids, and non-steroidal anti-inflammatory drugs (NSAIDs; Hurtado et al., 2021). These adjuncts have been studied in terms of their impact on immunologic response of cancer cells with varied outcomes.

Ketamine is an N-methyl-d-aspartate (NMDA) receptor antagonist with anesthetic and analgesic effects that works synergistically with other anesthetic agents (Khorsund et al., 2022). Ketamine binds to NMDA, monoaminergic, muscarinic, opioid, neuronal nicotinic acetylcholine, voltage-sensitive sodium, and L-type calcium channel receptors (Flood et al., 2015). Ketamine decreases the production of inflammatory mediators by neutrophils (Flood et al., 2015). The administration of ketamine is of particular benefit in patients with opioid dependence. It provides analgesia while preserving the respiratory drive and airway reflexes. Ketamine is also a potent bronchodilator. Disadvantages to ketamine use include SNS activation and psychotropic effects such as nightmares, hallucinations and disturbing vivid dreams during and shortly after emergence (Khorsund et al., 2022). In a study on rats, lung cancer metastasized after intravenous and intraperitoneal injection (Hurtado et al., 2021). In a dog study, white blood cell cultures were mixed with ketamine, resulting in an upregulation of PGE_2 (Hurtado et al., 2021).

Dexmedetomidine is a sedative with analgesic, anxiolytic, and sympatholytic properties that acts on alpha-2 receptors in the brain and spinal cord (Hurtado et al., 2021; Khorsund et al. 2022). One of the key advantages to dexmedetomidine administration is synergism with other hypnotics and sedatives, which reduces the amount of primary anesthetic required to maintain adequate anesthetic depth. Other advantages include its analgesic properties, which reduces opioid requirement (Khorsund et al., 2022), decreased incidence of emergence delirium, and potential suppression of the neuroendocrine stress response to surgery (Schwenk, 2023). Dexmedetomidine can result in prolonged emergence due to its context-sensitive half-time and may also cause hypotension and bradycardia due to its sympatholytic properties (Khorsund et al., 2022). Researchers postulated that due to its sympatholytic effects, administration of perioperative dexmedetomidine would diminish postoperative metastasis. Instead, they found that dexmedetomidine depressed NK cell cytotoxicity in mouse and rat models (Hurtado et al., 2021). Hurtado et al. (2021) reported a retrospective human study of patients with non-small cell lung carcinoma in which patients who received dexmedetomidine experienced a significantly lower 5-year survival rate.

Opioids are a class of analgesic drugs derived from opium (Flood et al., 2015). They agonize mu (μ), kappa (κ), and delta (δ) opioid receptors in the brain and spinal cord, and to a lesser degree the periphery. Opioid receptors are also activated by enkephalins, endorphins, and dynorphins, which are endogenous opioid peptides and ligands that result in modulation of pain (Flood et al., 2015). In the periphery, opioid receptors are located on both sensory neurons and immune cells. Pain modulation occurs when immune cells are recruited to sites of inflammation and they secrete opioid peptides to provide analgesia (Flood et al., 2015).

Opioids are commonly used to attenuate surgical pain stimulus and are frequently part of the anesthetic plan. Advantages to administration of opioids include reduced requirement of other anesthetic agents, attenuation of the sympathetic response to painful stimulation, blunting of airway reflexes during instrumentation, and effective analgesia (Khorsund et al., 2022). Despite the frequent use of opioids, enhanced recovery after surgery (ERAS) protocols stress judicious use of opioid medications due to many potential adverse effects (Khorsund et al., 2022). Disadvantages related to perioperative opioid administration include hypotension, chest wall rigidity, delayed emergence, bradycardia, nausea and vomiting, urinary retention, delirium, constipation, urinary retention, and hyperalgesia (Khorsund et al., 2022). Opioids can also cause the release of histamine, which may result in hypotension in some patients (Flood et al., 2015).

The impact of opioids on the immune system and cancer cells has been researched, and results are contradictory (Hurtado et al., 2021). Initially, it was thought that since painful stimuli activates the neuroendocrine stress response and inhibits the immune system, treatment of painful stimuli with opioids could modulate these responses. However, synthetic opioids including fentanyl, alfentanil, sufentanil, and remifentanil were found to depress NK cell activity (Hurtado et al., 2021). In contrast, fentanyl, and sufentanil were found to inhibit cancer cell migration by increasing proinflammatory white blood cells (WBCs; Hurtado, et al., 2021).

Morphine, a natural opioid, is associated with the greatest immunosuppressive effects of all the opioids. Natural killer cell and lymphocyte suppression are related to morphine's action on the μ3-receptor, which is not activated by the synthetic opioid, fentanyl (Hurtado et al., 2021). Morphine causes release of glucocorticoids due to HPA activation, inhibits cancer cell apoptosis, and activates VEGF receptors leading to increased angiogenesis (Hurtado et al., 2021). Several

in vitro studies of breast and lung cancers showed that morphine promoted migration of cancer cells (Hurtado et al., 2021).

Non-steroidal anti-inflammatory drugs are frequently used analgesics, given intraoperatively or in the postoperative period. Non-steroidal anti-inflammatory drugs include aspirin, ibuprofen, ketorolac, diclofenac, and meloxicam, among others (Flood et al., 2015). These drugs are both selective and nonselective COX inhibitors whose effects are due to the inhibition of prostaglandin synthesis by blocking arachidonic acid from binding to the COX enzyme active site (Flood et al., 2015). Ketorolac is frequently given intraoperatively, and has been found to have effects including increased NK cell activity and antagonism of β-adrenergic receptors responsible for the SNS response of tachycardia (Hurtado et al., 2021). It is also hypothesized that ketorolac administration may modulate tumor angiogenesis and metastasis in the postoperative period (Hurtado et al., 2021). Several retrospective studies showed that intraoperative NSAID administration during breast cancer surgery may result in greater overall survival (OS) and recurrence free survival (RFS; Sherwin et al., 2022). A study specific to ketorolac showed patients were five times less likely to experience recurrence within four years after surgery (Hurtado et al., 2021).

Literature Review

Methods

A literature search was conducted using the following databases: PubMed, CINHAL, EMBASE, Cochrane Collection Plus, Google Scholar, and SCOPUS. Systematic reviews, randomized control trials (RCT), meta-analyses, and experimental studies with publication dates from 2017 to 2022 were selected. Initially, the key words searched included “breast cancer and anesthesia,” which yielded results comparing general anesthesia to regional anesthesia,

anesthetic impact on chronic pain, as well as total intravenous anesthesia (TIVA) compared to inhalation anesthesia (IA). The search terms were refined to include “breast cancer + TIVA vs inhalation anesthesia,” as well as “recurrence” and “metastasis.”

The resulting studies were examined and studies that did not include a primary or secondary outcome of overall survival or recurrence free survival were excluded. Common themes examined in the following literature review include OS, RFS, locoregional recurrence (LRR), immunologic response, and metastasis. Overall survival and recurrence free survival were the most heavily analyzed endpoints.

Overall Survival

Improved Overall Survival

Eleven of the studies included in this literature review investigated OS as a primary or secondary outcome. Six of those studies were retrospective cohorts, four were systematic reviews and/or meta-analyses, and one was an RCT. Chang et al. (2021) conducted a systematic review and meta-analysis of nineteen independent RCT and observational studies of newly diagnosed adult cancer patients of all types who underwent surgery. Overall survival of the patients was compared between those who received propofol-based TIVA and those who received desflurane or sevoflurane-based volatile inhalation anesthesia. From this review, Chang et al. (2021) demonstrated, with statistical significance, that cancer patients who received propofol based TIVA during cancer surgery experienced improved overall survival (p=0.008).

Enlund et al. (2020) performed a retrospective cohort study of 6305 patients anesthetized with IA or TIVA for breast cancer surgery between 2006 and 2012 to compare one and five-year post-surgical survival rates as well as overall mortality. The IA group received sevoflurane maintenance anesthesia, whereas the TIVA group received propofol and remifentanil or other

opioid maintenance. Multiple statistical adjustments were applied to the data, which resulted in discrepancies in their findings. Without statistical adjustments made for possible confounding factors, Enlund et al. (2020) found that the one and five-year survival rates for the propofol-based TIVA group was statistically higher than the sevoflurane group (98.1% and 97.7% vs 88.7% and 86.6%; $p = 0.24$). When centers were included in the propensity score (PS) matched cohorts, the difference was statistically significant (99.0% and 96.4% vs 91.0% and 81.8%; $p = 0.010$; Enlund et al., 2020). Enlund et al. (2020) found an increased risk of overall mortality for the group that received IA when compared to TIVA ($p = 0.0236$). Similar to the unmatched results, when centers were introduced in the PS matching cohort a significant increase in risk of mortality was revealed in patients who received IA versus TIVA ($p = 0.0096$; Enlund et al., 2020).

No Improvement in Overall Survival

When subgroup analysis was conducted by cancer type in Chang et al.'s (2021) study, it was determined that there was no significant difference in OS among breast cancer patients who received TIVA versus IA ($p = 0.382$; Chang et al., 2021). Similarly, Enlund et al. (2020) found no statistically significant increased risk of mortality ($p = 0.1019$) when PS matching was introduced with different thresholds. Enlund et al. (2020) found, when PS matching was applied but centers were not included, that the one and five-year survival rates did not reach statistical significance ($p = 0.102$).

Another retrospective cohort study by Hong et al. (2019) examined five-year survival rates of patients who underwent surgical resection for lung, liver, colon, breast, or gastric cancer. Hong et al. (2019) found no statistically significant difference in OS among patients who received IA versus TIVA regardless of cancer type ($p = 0.291$). A study by Huang et al. (2019)

examined overall survival as well as locoregional recurrence in patients with breast cancer who received desflurane IA compared to those who received propofol-based TIVA. Huang et al.'s (2019) retrospective cohort study found no statistically significant difference in overall survival between the IA and TIVA cohorts after PS matching ($p = 0.475$). Yet another retrospective cohort study by Yoo et al. (2019) examined 3532 breast cancer patients in groups of propofol-based TIVA with remifentanil or IA with either enflurane, isoflurane, sevoflurane, or desflurane. The type of anesthetic was determined by the attending anesthesiologists. Yoo et al. (2019) found that there was no statistically significant difference in OS between TIVA and IA groups ($p = 0.805$).

Zhang et al. (2022) performed a retrospective cohort study of 1414 patients diagnosed with invasive ductal carcinoma (IDC) who underwent total mastectomy. Overall survival was investigated as a secondary outcome. The patients were matched into cohorts of IA with sevoflurane or propofol-based paravertebral block-regional anesthesia (PB-RA). Although the PB-RA with propofol anesthetic was classified as "conscious sedation," no method of monitoring depth of sedation was discussed. Zhang et al. (2022) also report no difference in OS between cohorts (no *p* value reported).

Jin et al. (2019) conducted a systematic review and meta-analysis of 12 studies examining the all-cause mortality, recurrence rates and RFS in patients with breast cancer as well as in patients with colorectal cancer, bladder cancer, esophageal cancer, lung cancers, and glioma. Jin et al. (2019) reported significantly less risk of all-cause mortality in patients who received TIVA vs IA ($p = 0.78$). Subgroup analysis was then performed. Findings did not reveal a significant difference between IA and TIVA in breast cancer patients (no *p* value reported; Jin et al., 2019). Another systematic review and meta-analysis by Lv et al. (2022) examined seven

studies including 9781 female patients who received TIVA versus IA for primary resection of breast cancer with the primary outcome of RFS and secondary outcome of OS. Lv et al. (2022) did not delineate what constituted TIVA or IA in the review and meta-analysis, which revealed no statistically significant difference in OS ($p = 0.49$; Lv et al., 2022).

Yet another meta-analysis by Yap et al. (2019) included eight studies of patients with breast, colorectal, gastric, esophageal, non-small cell lung, and mixed cancer types, with a total of 18,778 patients. Patients who received propofol-based anesthesia with or without remifentanil were placed in the TIVA group, and patients who received enflurane, desflurane, isoflurane or sevoflurane were allotted to the IA group. This study reported improvement of OS in the patients who received TIVA over IA (pooled $p < 0.01$), however when statistical analysis was applied to the breast cancer subgroup (n = 4 studies), there was no statistically significant difference between the TIVA and IA groups ($p = 0.54$; Yap et al., 2019)

The only prospective, randomized controlled trial in this literature review that examined OS was performed by Yan et al. (2018). This study included 80 female patients undergoing modified radical mastectomy or breast conserving surgery for primary breast cancer. The patients were randomized into propofol and remifentanil-based TIVA or sevoflurane-based IA cohorts. Reported OS at 28 months was equivalent between cohorts, at 97.5% (Yan et al., 2018).

Yoon et al. (2022) performed a retrospective cohort study and meta-analysis of published data, the manuscript of which has yet to be printed but has been accepted by the *Annals of Surgery*. This study included 241,128 patients who underwent resection for primary cancers including breast, gastric, lung, liver, kidney, colorectal, pancreatic, esophageal and bladder cancers. Patients were evaluated one and five-years post-operatively for survival, and overall survival was also examined. The patients were allocated into two cohorts by type of anesthetic

received: propofol-based TIVA or IA with sevoflurane, desflurane, isoflurane or enflurane. Subgroup analysis by cancer type revealed no statistically significant difference in OS between the TIVA and IA group for breast cancer patients (inverse probability of treatment weighted p = 0.340; Yoon et al., 2022). Additionally, this study showed no significant difference in one or five-year survival rates between cohorts (p = 0.43; Yoon et al., 2022). Yoon et al.'s (2022) meta-analysis included 19 retrospective studies and four RCTs. The meta-analysis found no significant difference in OS between TIVA and IA cohorts in the breast cancer subgroup (p = 0.04; Yoon et al., 2022).

Limitations to Studies Examining OS

The discussed studies looked at OS in such a way that cause of death was not categorized by its relationship to the patient's cancer diagnosis or treatment. All cause death was not categorized in any study by patient demographics including ASA physical classification, clinical staging of the tumor, or other comorbidities. Surveillance periods, if reported, were also different lengths among the studies. None of the studies made recommendations favoring the use of either TIVA or IA over the other for improvement of OS.

Recurrence-Free Survival

Improved Recurrence-Free Survival (RFS)

Seven of the studies included in this literature review examined recurrence or RFS as an endpoint, with five systematic review and meta-analyses, two retrospective cohort studies and one RCT. The studies did not share a common duration of surveillance post-operatively. As such, each study defined RFS based on length of post-operative surveillance.

Merely two of the studies included in this literature review found improvement in RFS among breast cancer patients who received TIVA over IA for primary breast cancer surgery. Jin

et al. (2019) conducted a systematic review and meta-analysis of 12 studies, including five breast cancer specific studies. Though there was no statistically significant difference in OS between the propofol-based TIVA and IA groups, Jin et al. (2019) did find results in support of TIVA over IA in three of the breast cancer subgroup studies for RFS, though statistical significance was not reached ($p = 0.48$). Yap et al. (2019) performed a meta-analysis of six studies including 7886 patients with breast, esophageal and non-small cell lung cancer. Findings were consistent with improved RFS associated with TIVA compared to IA, though not statistically significant (pooled $p < 0.01$; breast cancer specific $p = 0.17$; Yap et al., 2019).

No Improvement in Recurrence-Free Survival

Five of the included studies found no statistically significant difference in RFS. The study by Chang et al. (2021) included 8980 patients in the assessment of RFS, 6502 of which were breast cancer patients. This study revealed no significant difference in breast cancer RFS between IA and TIVA groups ($p = 0.347$; Chang et al., 2021). Similarly, the systematic review and meta-analysis by Lv et al. (2022) revealed no significant difference in breast cancer RFS between the groups ($p = 0.54$).

Shiono et al. (2020) conducted a single center, retrospective study of primary breast cancer surgery patients. This study included 1026 patients, with 212 in the sevoflurane-based IA group and 814 in the propofol-based TIVA group. Median surveillance time was 59 months. Recurrence occurred in 9.25% of patients in the IA group, and 9.33% of the TIVA group ($p = 0.574$; Shiono et al., 2020). Furthermore, this study revealed no statistically significant difference in RFS after PS matching was applied. After matching, the recurrence rate in the IA group (n = 12) was 7.5% and 8.2% in the TIVA group (n = 13; $p = 0.995$; Shiono et al., 2020).

Two- year RFS was examined by Yan et al. (2018) in a single center, prospective RCT of 80 female patients who underwent modified radical mastectomy or breast conserving surgery. This study revealed two-year RFS of 78% in the IA group, and 95% in the TIVA group, which, despite a difference of 17%, was deemed statistically insignificant ($p = 0.221$; Yan et al., 2018). A single-center retrospective cohort study by Yoo et al. (2019) examined five-year RFS among 3532 patients who underwent breast cancer surgery. This study yielded no statistically significant difference in RFS between the IA and TIVA groups ($p = 0.782$; Yoo et al., 2019). Selby et al. (2021) conducted a systematic review of 35 published studies, of which 14 were clinical studies. Their review suggested, after multivariate adjustments, there was no significant difference in RFS between IA and TIVA groups for breast cancer. Selby et al. (2021) concluded that many of the studies included in their systematic review were underpowered to detect a difference in RFS based on length of post-operative surveillance.

Limitations to Studies Examining RFS

Limitations in analysis of RFS include inadequate sample size, with n = 80 in Yan et al.'s (2018) RCT, and n = 25 after PS-matching was introduced in the study by Shiono et al. (2020). Shiono et al. (2020) and Yan et al. (2018) were also single-center studies. Shiono et al. (2020) admitted to the risk of type II errors and incomplete adjustment of propensity scoring, bias due to retrospective design, as well as an underpowered analysis of breast cancer subtypes. Additionally, the patients were not randomized and there was no protocol for administration of anesthetic in place. All the studies except Yan et al. (2018) were retrospective in nature, which may increase the risk of bias.

Locoregional Recurrence (LRR) and Metastasis

Decreased Recurrence or Metastasis

The previously discussed study by Zhang et al. (2022) examined the primary endpoint of locoregional recurrence in patients who underwent total mastectomy for IDC. The results of this study were highly variable within multivariate analysis groupings. The most significant decrease of locoregional recurrence occurred in patients who received PB-RA-TIVA compared to IA grouped by clinical staging ($p = 0.0012$), differentiation ($p = 0.0099$), pathological tumor stage ($p = 0.0260$), and pathological nodal stage ($p = 0.0022$; Zhang et al., 2022). The fundamental endpoint of LRR showed lower rates of LRR in patients who received PB-RA-TIVA compared to IA ($p = 0.0110$).

No Change in Recurrence or Metastasis

Four studies included in this review examined the endpoint of locoregional recurrence (LRR) and/or metastasis. Huang et al. (2019) performed a retrospective cohort study of 888 patients who underwent breast cancer by one surgeon and compared locoregional recurrence, distant metastasis, and OS endpoints between the desflurane-based IA and propofol-based TIVA groups. They found no difference in LRR between the cohorts, with 4% of each IA and TIVA group experiencing recurrence within five years. Additionally, they found no significant difference in distant metastasis between the cohorts with 8% and 6% of the IA and TIVA groups, respectively, experiencing distant metastasis within five years post-operatively (matched patients: locoregional and distant metastasis $p = 0.707$; Huang et al., 2019).

Cho et al. (2017) conducted a prospective, randomized study of 50 patients who underwent primary total mastectomy, partial mastectomy, or radical mastectomy under either sevoflurane-based IA with remifentanil or propofol-based TIVA with ketorolac. This study did

not reveal any significant difference in LRR, with only one patient in the IA group experiencing recurrence within 18 months post-operatively (no *p* -value reported). Furthermore, no patients in either group experienced metastasis by the end of the two-year surveillance period (Cho et al., 2017).

Though the study by Zhang et al. (2022) showed decreased rates of LRR, it did not show a statistically significant difference in distant metastasis between the IA and PB-RA-TIVA groups (IA: 11.6%; PB-RA-TIVA: 8.6%; $p = 0.0521$). The surveillance times were variable among patients; follow-up duration for the IA and PB-RA-TIVA groups were 43.3 months and 55.9, respectively (Zhang et al., 2022).

Limitations to Studies Examining LRR

The studies examining LRR and metastasis discussed above were vastly different in study design. The surveillance periods varied drastically between studies, and amongst study subjects as noted in the study by Zhang et al. (2022). In addition, the study by Zhang et al. (2022) was ethnically homogeneous, with an Asian-only patient population. This could have skewed results due to a possible unknown ethnic susceptibility. However, Zhang et al. (2022) indicated there was no evidence to support differences in oncological outcomes between Asian and non-Asian patients with IDC. The study by Huang et al. (2019) was retrospective in nature. This eliminated the ability to closely control aspects of the study including choice of anesthetic and surgical technique, as well as patient factors such as ASA classification, cancer stage and chemotherapy, which could all introduce bias (Huang et al., 2019).

Immunologic Response

Change in Immunologic Response

Several studies included in this literature review examined immunologic response as either the primary or secondary endpoint. The prospective RCT by Yan et al. (2018) primarily examined the difference in serum vascular endothelial growth factor concentrations (VEGF-C) before and 24-hours post-operatively in patients who received propofol and remifentanil TIVA compared to those who received sevoflurane-based IA. This study showed that VEGF-C in the IA group increased significantly more than those in the TIVA group at 24-hours post-surgery (pre-post changes: IA = 50; TIVA = 12; $p = 0.008$; Yan et al., 2018). Of note, when subgroup analysis was completed on patients who underwent breast conserving surgery there was no statistically significant difference in VEGF-C levels pre- or post-surgery (pre-post changes: IA = 4; TIVA = 7; $p = 0.817$; Yan et al., 2018). These findings suggest that different surgical procedures could result in varying intensities of the physiologic stress response (Yan et al., 2018). Selby et al. (2021) completed a systematic review of 35 studies comprised of *in vitro*, animal, translational and clinical studies, to examine the immunologic response to TIVA to IA in cancer patients. Though independent statistical analysis was not completed, this review supported Yan et al.'s (2018) findings with *in vitro* and translational study evidence that suggested that IAs promote immunosuppression and tumorigenesis, whereas propofol-based TIVA showed anti-inflammatory and anti-tumorigenic properties (Selby et al., 2021).

The study by Cho et al. (2017) examined the primary endpoint of natural killer cell cytotoxicity (NKCC) and interleukin-2 (IL-2) levels among breast cancer resection patients. The patients were randomized to sevoflurane-remifentanil IA or propofol-ketorolac TIVA groups. Statistical analysis showed that the baseline NKCC (%) was not significantly different among the

two groups ($p = 0.082$), however the change of NKCC (%) over time between groups did reach statistical significance ($p = 0.048$; Cho et al., 2017). The mean NKCC (%) increased from the pre-operative baseline of 15.2 (3.2) to the 24-hour level of 20.1 (3.5; $p = 0.048$) in the TIVA group, whereas levels decreased in the IA group from 19.5 (2.8) to 16.4 (1.9; $p = 0.032$; Cho et al., 2017).

Selby et al. (2021) referenced several studies whose translational data suggested that propofol based anesthesia increased NK cell tumor infiltration and *in vitro* NK cell activity in women who underwent breast cancer surgery. This systematic review also referenced a rat model study of breast cancer and NK cell activity, which found that all anesthetics, excluding propofol, reduced NK cell activity (Selby et al., 2021). Selby et al. (2021) also addressed a translational study that found that intra-tumor CD4 counts were higher in patients who underwent PB-RA with propofol than those who received sevoflurane-based IA.

No Change in Immunologic Response

One of the secondary outcomes examined by Yan et al. (2018) was pre- and post-operative TGF-β levels. Neither the IA or TIVA groups showed statistically significant changes in pre- or post-operative TGF-β levels (pre-post changes: IA = 3; TIVA = 13; $p = 0.582$; Yan et al., 2018). No other studies in the available literature provided data on TGF-β levels.

The study by Cho et al. (2017) also analyzed serum concentrations of IL-2 pre-operatively and at 24-hours post-operatively. Though IL-2 is an important activator of NK cells, there was no significant difference in 24-hour IL-2 levels in either the TIVA or IA groups ($p = 0.620$; Cho et al., 2017).

An *in vitro* study by Levins et al. (2018) examined the NK cell counts (CD56 and CD57) of pre-operative biopsies and intraoperative specimens of 20 patients who had been randomized

to receive either PB-RA-TIVA or sevoflurane-based IA. The specimens were previously collected and randomly chosen from patients enrolled in Sessler et al.'s (2019) study while it was ongoing. Two independent investigators were blinded to randomization. This study found that, as in Cho et al.'s (2017) study, pre-operative biopsy specimens CD56 and CD57 counts were equally low between the PB-RA-TIVA and IA groups. However, there was no statistically significant difference in pre-operative biopsy and intra-operative specimen CD56 or CD57 counts between the PB-RA-TIVA and IA groups ($p = 0.4$, $p = 0.8$, respectively; Levins et al., 2018).

Levins et al. (2018) also examined CD4 counts in the same manner as CD56 and CD57 counts: pre-operative biopsy levels and intra-operative tumor specimen were measured in both the PB-RA-TIVA and IA groups. This study found that, like CD56 and CD57 counts, the pre-operative biopsy CD4 levels were zero in both groups. Though intra-operative tumor specimen CD4 counts were higher (mean = 10) in the PB-RA-TIVA group than the IA group (mean = 8), statistical significance was not achieved ($p = 0.7$; Levins et al., 2018).

Limitations to Studies Examining Immunologic Response

The sample sizes in three out of the four studies examining immunologic response were small. In the study by Levins et al. (2018), the results could have been impacted by morphine administration. Selby et al. (2021) examined not only clinical studies, but *in vitro* and animal models as well. Additionally, no independent statistical analysis was performed by Selby et al. (2021); this was merely a review of previously reported data. In the study by Yan et al. (2018), the patients in the TIVA group also received remifentanil, which could have impacted the immune response to anesthesia. Cho et al.'s (2017) study was of small sample size and the OR staff was not blinded to group allocation (although the post-op follow-up investigators were

blinded to allocation). Due to study design, the respective effects of each drug administered on NKCC and inflammatory response could not be discerned.

Discussion

Despite a large body of research that points to IA promoting tumor recurrence and metastasis through various mechanisms, it remains unclear if there is reliable clinical evidence to suggest that TIVA is superior to IA in breast cancer patients. Nine of the ten studies examining OS determined there was no statistically significant difference between the IA and TIVA groups. Five of the seven studies examining RFS determined there was no statistically significant difference between the groups. Two of the three studies that examined LRR determined there was no difference between the groups. Neither of the two studies that examined metastasis found a difference between the groups (Appendix A).

The variety of medications given during anesthesia for breast cancer surgery interact with one another, the tumor microenvironment, the patient's immune system, and the hormonal systems in a complex manner. This makes it exceedingly difficult to determine whether the observed results in immune response, LRR, OS, or RFS are due to the primary anesthetic chosen or to the compound effects of the patient's physiology, co-administered medications, and many other confounding variables. For example, Hurtado et al. (2021) discussed one study of breast cancer surgery patients who received TIVA with remifentanil. The TIVA group experienced decreased VEGF concentrations compared to patients who received sevoflurane-based IA. It was unclear whether the decrease in VEGF and resultant decreased tumor angiogenesis was due to the propofol, the remifentanil, or the combination of the two (Hurtado et al., 2021).

The more substantial the surgical stress and longer duration of anesthetic administration, the greater the impact of the primary anesthetic agent (Selby et al., 2021). This could change the

outcomes of studies. For example, patients who underwent radical mastectomy would experience far greater surgical stress and longer anesthetic duration than those who underwent breast lumpectomy. Though this is a significant confounder, none of the studies included in the literature review adjusted analysis based on type of surgical intervention.

Limitations

Adequate large, prospective RCTs published in the last five years are lacking.to thoroughly examine the effect of IA or TIVA on breast cancer recurrence and metastasis. The available research varies widely in study design, blinding, randomization, surgical technique, and concurrent drugs administered. Patients in several studies received ketorolac, while others received fentanyl or intravenous lidocaine. These factors make it difficult to discern if the impact observed by the researchers was due to the anesthetic or other factors. Additionally, surgical techniques must be considered due to the impact of surgical trauma on recurrence and metastasis.

Several of the studies included in this literature review were ethnically homogeneous, which decreases universality. In addition, several of the studies included ASA II and III patients with multiple comorbidities which may have impacted their risk of recurrence and metastasis. Staging and subtype of breast cancers were confounders in many studies that were unable to be adjusted. The study by Sessler et al. (2019) was conducted over the course of 12 years, during which treatment options for breast cancer improved, potentially impacting the findings. The majority of the included studies were retrospective in nature, which increases the risk of bias due to lack of control of confounding factors including smoking and eating habits, body weight, estrogen therapy, socioeconomic factors, and other comorbidities that impact the postoperative prognosis of breast cancer patients. Additionally, retrospective studies cannot prove causation, only correlation.

Conclusion

Given the tremendous number of variables involved in the delivery of anesthesia, the behavior of breast cancer cells, and the litany of comorbidities among breast cancer patients, it is difficult to discern whether TIVA is beneficial over IA for limiting recurrence and metastasis. Research suggests volatile anesthetics may negatively impact the immune response, but clear high-quality evidence that TIVA provides more favorable outcomes is lacking (Hurtado et al., 2021). The anesthetic plan for breast cancer patients should be individualized and based on the patient's comorbidities and risk factors.

While TIVA may be a more costly anesthetic, it may be beneficial to patients undergoing breast cancer surgery. If not to decrease risk of recurrence and metastasis, then to prevent post operative nausea and vomiting (PONV) as well as other perioperative complications. Post operative nausea and vomiting is a prevalent concern in breast surgeries (Macksey, 2018). Propofol-based TIVA is a safe anesthetic, and is associated with earlier return to bowel function, decreased post-operative cognitive impairment and potentially decreased opioid requirements in the immediate post-operative period than IA (Selby et al., 2021).

There is a need for larger, randomized controlled prospective studies with clearly delineated IA groups and propofol-based TIVA groups with consistent medication regimens between the groups. Also, studies should focus on a specific surgical intervention, for example simple mastectomy, rather than including multiple surgical interventions in the same study. Variables must be controlled to determine if the anesthetic technique is causal to outcomes of recurrence and metastasis.

In conclusion, the provider may impact risk of recurrence or metastasis of breast cancer through anesthetic choice. However, the lack of data proving anesthetic causation of recurrence

or metastasis leaves providers to choose anesthetic based on their own preferences. The best course of action is to tailor the anesthetic plan to the patient at hand by including risk factors and comorbidities in the decision-making process.

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Appendix A

Synthesis of Outcomes

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
OS	↔		↑	↔	↔	↔						↔	↔	↔	↔	↔
RFS	↔					↑			↔		↔	↔	↑	↔		
LRR		↔			↔											↓
Metastasis		↔														↔

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