Spring 4-30-2024

Final Scholarly Project: Development of Evidenced-Based Practice Guidelines for Female Patients Undergoing Anesthesia for Breast Cancer Surgery

Alexa High
high1@otterbein.edu

Spring 4-30-2024

Final Scholarly Project: Development of Evidenced-Based Practice Guidelines for Female Patients Undergoing Anesthesia for Breast Cancer Surgery

Alexa High

Final Scholarly Project: Development of Evidenced-Based Practice Guidelines for Female Patients Undergoing Anesthesia for Breast Cancer Surgery

Alexa J. High, BSN, RN

Department of Nursing, Otterbein University

2023

In Partial Fulfillment of the Requirements for the Degree

Doctor of Nursing Practice

DNP Final Scholarly Project Team:

Dr. Brian Garrett, DNP, CRNA – Project Team Leader

Dr. Joy Shoemaker, DNP, APRN-CNP – Team Member

Kerrie Rodgers, MSN, CRNA

Mrs. Kerrie Rodgers, MSN, CRNA – Team Member

Development of Evidenced-Based Practice Guidelines for Female Patients Undergoing Anesthesia for Breast Cancer Surgery

Abstract

In the United States, the rate at which cancer is diagnosed is on the rise. In women, breast cancer is the second most common cancer diagnosis, following skin cancer, with approximately one in eight women developing breast cancer in their lifetime. When a patient receives a breast cancer diagnosis, the oncologic team will discuss the most suitable treatment plan for the patient, this often includes chemotherapy, radiation therapy, and surgery. Within the last few decades, research has shown that there may be a correlation between anesthetic medications and breast cancer metastasis. This project aims to create an evidence-based anesthesia guideline for patients undergoing breast cancer surgery. Interventions will include a paravertebral block, total intravenous anesthesia (TIVA), and non-opioid analgesics; evidence has shown that volatile agents and opioids can decrease natural killer cell activity and increase postoperative metastasis. The Johns Hopkins Evidence-Based Practice Guideline Model for Nurses and Healthcare Professionals will be used to guide this process.

Keywords: breast cancer, anesthesia, natural killer cells, opioids, metastasis

Problem Identification

Introduction of Problem

Breast cancer is a growing cause of concern in healthcare. The American Cancer Society estimates that in 2023, approximately “297,790 new cases of invasive breast cancer will be diagnosed in women… about 55,720 new cases of ductal carcinoma in situ (DCIS) will be diagnosed… [and] about 43,700 women will die from breast cancer” (American Cancer Society, 2023, para. 2). Aside from skin cancer, breast cancer is the most common form in the United States (U.S.), comprising approximately 30% of new cancers in women yearly (American Cancer Society, 2023). The risk of a woman in the U.S. developing breast cancer at some point in her lifetime is approximately 13%, which equates to almost one out of every eight women developing breast cancer (American Cancer Society, 2023). The prevalence of breast cancer in America has caused medical centers across the nation to turn to a variety of treatment regimens. To aggressively treat breast cancer, patients commonly receive chemotherapy, radiation, and surgery; however, newer advances in breast cancer treatment include hormone therapy, targeted drug therapy, and immunotherapy (American Cancer Society, n.d.). Oh et al. (2018) states, "worldwide, breast cancer is the most common cancer and the second most common cause of death in females. Surgical removal of breast cancer is the first-line treatment [while other types of therapies] continue to play important roles" (p. 921). Some of the most common surgeries for breast cancer include breast cancer biopsies, needle localization surgery for breast-conserving surgeries, and mastectomies, either partial or total (American Cancer Society, n.d.). Additionally, during breast cancer surgery, the breast surgeon may perform sentinel lymph node dissection to see if the cancer has spread to other areas of the body.

If the patient chooses surgery as a treatment, a few different anesthetic techniques may be employed. The first is a general anesthetic, which usually includes a variety of drugs, including but not limited to opioids, benzodiazepines, muscle relaxants, and volatile anesthetics. The second option is regional anesthesia. Regional anesthesia may include a neuraxial block (spinal or epidural blockade), a paravertebral block (an approach of injecting local anesthetic alongside the thoracic vertebra close to the spinal nerves), as well as a variety of local blockades, including the pectoralis nerve block (Pecs I or Pecs II block, which includes injection of a local anesthetic into the fascial sheath between the pectoralis major and minor muscles) (Karmakar et al., 2022; Blanco & Barrington, 2022). Regional anesthetics can be used with a general anesthetic or a total intravenous anesthetic (TIVA). A total intravenous anesthetic may include medications such as propofol, a sedative agent which potentiates GABA-A receptors, or dexmedetomidine, a sedative agent which is an alpha-2 receptor agonist (Solt & Forman, 2007; Sanders & Maze, 2011). All of the agents listed above can be used safely in a patient in the right context, however an anesthesia provider's judgement should be used prior to administration.

Unfortunately, anesthesia can cause incredibly harmful side effects in breast cancer surgery patients. When a patient has cancer, the risk of metastasis is always a concern. There has been recent research that links breast cancer metastasis and suppressed natural killer cells with the use of volatile anesthetics and opioids. This problem should encourage certified registered nurse anesthetists (CRNAs) and anesthesiologists to seek the safest anesthetic practice for breast cancer patients.

Background

The use of anesthetic drugs causing breast cancer metastasis is of growing concern. One of the earliest journals highlighting the concerns of anesthesia and postoperative cancer

metastasis was by Shapiro et al. (1981). These researchers studied the effects of postoperative growth of tumors in mice after four different anesthetics were implemented (Shapiro et al., 1981). The researchers found that when anesthesia was employed for the surgical removal of a tumor, spontaneous lung and liver metastases occurred in the mice, where spontaneous tumors were not associated with the mice's specific types of cancers (Shapiro et al., 1981). Since 1981, hundreds of studies were completed on anesthetics and their effects on cancer metastasis, including breast cancer metastasis. However, in everyday practice, anesthesia providers are not well educated on how anesthesia can cause cancer metastasis.

The human body functions with numerous mechanisms to protect itself from foreign substances, viruses, and bacteria. The human immune system contains two categories – the innate or natural immune system and the adaptive or acquired immune system (Chaplin, 2010). The innate immune system is acquired and is the "first-line of defense to an invading pathogen" (Nagelhout & Elisha, 2017, p. 959). The innate response does not require a person to be exposed to a prior antigen, and the response to a foreign invader will be the same every time (McCance & Huether, 2014a). The adaptive or acquired immune system is activated when a person is exposed to an antigen. Initially, the response is slow, but the adaptive immune system has memory cells, and with repeated exposure to an antigen, the response is much faster (McCance & Huether, 2014b). Therefore, it is essential that the body maintains healthy, functional innate and adaptive immune systems to fight pathogens immediately and to trigger this response in the future.

NK cells are a part of the innate immune system. “Natural killer cell activity has been identified as one method by which the body attacks tumor cells and thereby prevents metastasis” (Welden et al., 2009, p. 287). NK cells recognize other foreign cells from the host’s cells and target the non-self cells for attack (Welden et al., 2009). When NK cells recognize a cell that

does not have a normal self-MHC protein, they approach the foreign cell and release perforin that damages and destroys the foreign cell membrane, thereby killing the foreign invader (Nagelhout & Elisha, 2017). There are also natural killer T (NKT) cells, a specialized type of T cell with properties of both NK and T cells (Nagelhout & Elisha, 2017). These cells recognize MHC proteins typically seen on antigens and target them for destruction. However, they also "rapidly produce cytokines, including IFN, macrophage stimulating factor, IL, chemokines, and TNP that can destroy bacterial and viral pathogens" (Nagelhout & Elisha, 2017, p. 967). Therefore, NK cells, T cells and NKT cells all significantly enhance the body's ability to fight pathogens.

Surgery is a mainstay treatment for breast cancer patients. However, "surgery and anesthesia are associated with a variety of metabolic and endocrine responses which cause a generalized state of immunosuppression that can result in a reduced resistance to infection, development of postoperative septic complications and tumor metastasis" (Nagelhout & Elisha, 2017, p. 978). Additionally, surgical excision of the tumor can interrupt the blood supply to the tumor and allow tumor cells to enter systemic circulation (Heaney & Buggy, 2012). If anesthesia or opioids suppress NK cells during surgery, this prevents the body from attacking these foreign cells. Immunosuppression, the stress response of surgery, and natural killer cell activity must be taken into consideration when using surgery as a treatment option for breast cancer.

Significance of Problem to Nurse Anesthesia

Breast cancer is a well-known disease both outpatient and in the operating room. These patients are seen daily in the operating room, as surgery is a mainstay treatment in removing breast cancer tumors. The most current edition of *Nurse Anesthesia* states that "approximately 80% of cancer patients require anesthesia and analgesia for a variety of diagnostic and

therapeutic procedures" (Elisha et al., 2022, p. 1072). However, many of the medications given by the anesthesia provider for induction and pain management during surgical intervention for breast cancer can impact metastasis and NK cell activity (Oh et al., 2018).

As previously mentioned, an assortment of systems protect the human body from foreign invaders, primarily the innate and acquired immune systems. Elisha et al. (2022) states:

> The surgical induced activation of the [hypothalamic-pituitary-adrenal or HPA] axis and the [sympathetic nervous system] increases the release of cortisol and catecholamines, which inhibit the proliferation of NK cells and CD8+ T cells that are necessary to destroy cancer cells" (p. 1072).

Additionally, evidence has shown that inhalational anesthetics and opioids may contribute to cancer metastasis, while local anesthetics, propofol, and dexmedetomidine show possible "chemo-preventative" effects (Chen & Miao, 2013). These “chemo-preventative” effects may help the immune system when it comes to protecting against cancer metastasis.

Though there may be many contraindications to drugs given by nurse anesthetists, the possibility that volatile anesthetics and opioids may decrease a patient’s innate immunity and cause cancer metastasis is not common knowledge in the operating room. Research on this topic is new in the anesthesia field, and education on this is in the beginning stages in the classroom. Therefore, it is important for nurse anesthetists to understand the potential cause anesthetics and opioids have on the development of breast cancer metastasis. CRNAs must fulfill an anesthetic plan that will create adequate anesthetic and amnesic conditions for surgery while minimizing the patient's potential harm and decreasing the risk of cancer metastasis.

PICOT Question

In female patients undergoing breast cancer surgery, how would the development and implementation of evidence-based practice anesthesia guidelines versus a traditional anesthetic approach affect NK cell activity and metastasis rates?

The following is a further description of how the PICOT question will guide the project:

- The population evaluated for the intent of this project will be female breast cancer patients undergoing surgery for breast cancer.
- The intervention for this project is alternative anesthesia and pain modalities, including but not limited to total intravenous anesthesia (TIVA), regional blockades, and non-opioid pain medications.
- The author will compare new anesthesia guidelines and metastasis rates to previous anesthesia guidelines or general anesthesia.
- The outcomes that will be monitored for these patients are NK cell activity and metastasis rates.
- NK cell activity will be measured directly prior to surgery, immediately postoperatively, at 12 hours, 24 hours, and 48 hours postoperatively. Metastasis rates for breast cancer will be monitored at six months, one year, two years, five years, and ten years following the interventions outlined in this project.

Project Objectives

The following are objectives to be used to direct the scholarly project:

- develop anesthesia evidence-based guidelines for breast cancer patients undergoing breast surgery,

- apply the Johns Hopkins Evidence Based Practice Model for Nurses and Healthcare Professionals to develop an implementation plan,
    - increase anesthesia awareness and provide knowledge of metastasis rates related to anesthetic technique with breast cancer patients to anesthesia providers,
- monitor and measure outcomes regarding NK cell activity and metastasis rates in correlation to new anesthesia guidelines for breast cancer patients,
- refer to the Johns Hopkins Evidence Based Practice Model for Nurses and Healthcare Professionals to redirect project if the initial outcomes are less than desirable.

Literature Review

A systematic literature search was conducted. Databases included CINAHL Plus with full text, Cochran Database of Systematic Reviews, PubMed, and Academic Search Complete. These databases were searched from conception to January 2022. The strategy of these searches included a combination of the following search terms, searching all fields or titles: "Anesthesia" or "Breast Cancer" or "Natural Killer Cells" or "Opioids" or "Metastasis" or "Breast Cancer Metastasis." The Boolean search included "AND" to group the search terms for a more concise search. Inclusion criteria for this literature review included the following:

- Randomized control trials (RCTs), meta-analyses/Systematic reviews, literature reviews, and expert opinions
- articles supplied with full text or those that could be secured via the Otterbein librarian
- studies including adult patients
- studies including patients undergoing breast cancer surgeries
- studies including patients undergoing regional anesthesia or general anesthesia

- studies assessing postoperative outcomes, including natural killer cell function, immune function, or metastasis rates

Exclusion criteria for this study included studies written in foreign languages, pediatric studies, and animal studies (except for the use of human studies that referenced animal studies in the past). Using the criteria listed above, the author yielded 371 articles in her search. Most of the studies that were not focused on breast cancer were eliminated. Papers before 2015 were reviewed but only included if data was deemed remarkable. The author's goal was to use the most relevant, fresh, and pertinent data she could find. The author found the CINAHL database to provide the best, focused studies relevant to the topic. The author found the Cochran database to be the least helpful, yielding only a few articles and only one about breast cancer, anesthetics, and metastasis. Once the articles were narrowed down, the author completed a literature review table that can be found in Appendix A. The articles were then scored on their level of evidence using a table by Melnyk and Fineout-Overholt (2019).

Literature Supporting Propofol or Alternate Modalities of Anesthesia

Buckley et al. (2014) completed a randomized control trial to determine the effects of two different types of anesthetics on natural killer cell function in breast cancer surgery patients. The researchers used a sample size of ten patients randomly selected for either a propofol-paravertebral block (PPA) or sevoflurane-opioid (GA) anesthesia. Paravertebral blocks were used in many of the studies reviewed by the author. A "thoracic paravertebral block (TPVB) is the technique of injecting local anesthetic alongside the thoracic vertebra close to where the spinal nerves emerge from the intervertebral foramen" (Karmakar et al., 2022, para. 1). The thoracic paravertebral block is useful for breast cancer surgeries as well as other thoracic surgeries such as renal surgery, cholecystectomies, and appendectomies.

The study by Buckley et al. (2014) was based on the hypothesis that "regional anesthesia and avoidance of volatile agents and opioids could contribute to reduced perioperative residual disease" (p. i61). The researchers excluded patients under 18 years of age, patients with inflammatory breast cancer, previous breast cancer surgery, other types of cancer, an ASA status greater than IV or patients who were unable to receive a paravertebral block or allergies to medications to be used for this study (Buckley et al., 2014).

Patients in the PPA group received a paravertebral block with 20mL of 0.25% levobupivacaine, a propofol drip targeted to 4 mg ml^{-1} throughout surgery and maintenance with oxygen and air (Buckley et al., 2014). The paravertebral block was used until 24 hours after surgery, and rescue analgesia was provided for a pain score greater than three. This rescue analgesia included a bolus of levobupivacaine, and if the pain was not alleviated within 15 minutes, a bolus of 0.1 mg kg^{-1} morphine was provided (Buckley et al., 2014). Patients in "the GA group received 1-3 mg kg^{-1} fentanyl, 2-4 mg $^{kg-1}$ propofol and maintenance with sevoflurane and oxygen/air to maintain arterial pressure and heart rate withing 20% of preoperative baseline values" (Buckley et al., 2014, p. i57). Postoperatively, subjects were treated with patient-controlled analgesia pumps or IM with morphine (0.1 mg kg-1) (Buckley et al., 2014).

The subjects in this study had blood specimens drawn preoperatively and 24 hours postoperatively. "The serums were then co-cultured with HCC1500 and healthy primary NK cells. NK cell activating receptors (NKp30, NKp44, 2b4, CD16, NKG2D), cytokine production, NK CD107a expression, and cytotoxicity towards HCC1500 were examined" (Buckley et al., 2016, p. i56). After the tests were completed on patient serums, the researchers found the serum from women in the PPA group to have maintained healthy NK anti-tumor cell activity compared to the women who received the GA anesthetic (Buckley et al., 2014). Limitations for this study

included the use of morphine, which has been shown to minimize the effects of natural killer cells in previous literature. Although the PPA group in this study maintained healthy NK cell levels with the use of morphine, had the researchers avoided opioids entirely, this may have yielded different results.

The author found an article by Chhabra et al. (2021) very inclusive of evidence regarding paravertebral anesthesia and general anesthesia. This systematic review encompassed nine randomized control trials, including 614 participants. Chhabra et al. (2021) found paravertebral anesthesia helpful in decreasing postoperative nausea and vomiting, decreasing 24-hour postoperative opioid use, and decreasing postoperative pain at rest and on movement at 6 hours and 24 hours postop. Chhabra et al. (2021) analyzed their data thoroughly using the P value, odds ratio, confidence interval, SWiM analysis, and mean difference. However, Chhabra et al. (2021) did not find any of the articles to include details on quality of life after surgery, disease-free survival, chronic pain, or mortality rates in their review of the nine studies. Unfortunately, this study did not provide information related to the interventions, however, the article highlights the other benefits of paravertebral anesthesia.

An article by Cho et al. (2017) differs from the others in that the researchers did not study paravertebral anesthesia; instead, this study compared two groups - intraoperative propofol and remifentanil anesthesia with postoperative ketorolac analgesia against intraoperative sevoflurane, and remifentanil anesthesia with postoperative fentanyl analgesia. The researchers analyzed the serum from the two groups before breast cancer surgery and 24 hours after surgery to determine natural killer cell cytotoxicity (NKCC); the researchers also evaluated cancer recurrence or metastasis via ultrasound and whole-body bone scans every six months for two years post-surgery (Cho et al., 2017).

Based on previous research, the authors of this article hypothesized that avoiding volatile anesthetics and opioid analgesics might decrease immunosuppression in the perioperative period (Cho et al., 2017). The researchers studied 50 patients between 20 and 65 years old with ASA scores between I and III. The researchers excluded patients with renal disease, those with a BMI > 35 kg/m2, those on immunosuppressive therapy, those on steroid therapy within the last six months, and those with immune disorders (Cho et al., 2017). The patients were randomly assigned (25 patients in each group) to either the propofol-ketorolac group or the sevoflurane-fentanyl group.

The researchers used the following guidelines: for the propofol-ketorolac group they used targeted amounts of propofol and increased the concentration if the patient required more (Cho et al., 2017). In the sevo-fentanyl group they administered 1.5-2 μg/kg of fentanyl and maintained sedation with sevoflurane throughout the case (Cho et al., 2017). Both groups in this study were given remifentanil intraoperatively; additionally, rocuronium was given as a paralytic agent to facilitate tracheal intubation (Cho et al., 2017). For emergence from anesthesia, the researchers reversed the neuromuscular blocker with 40 μg/kg of neostigmine and 5 μg /kg of glycopyrrolate, 0.3 mg of ramosetron was also given at the end of surgery to prevent postoperative nausea and vomiting (Cho et al., 2015). "At the end of surgery, the Propofol-ketorolac group received ketorolac 60 mg and the Sevo-fentanyl group received fentanyl 50 mg for acute pain relief" (Cho et al., 2017, p. 971).

At the conclusion of the study, two patients were ruled out (one from each group) due to concurrent breast reconstruction surgery (Cho et al., 2017). The researchers did not find a statistically different baseline NKCC between the two groups. Compared to the baseline, the NKCC (%) increased in the propofol-ketorolac group from 15.2 to 20.1 (preoperatively to

postoperatively), and it decreased in the sevoflurane-fentanyl group from 19.5 to 16.4 (Cho et al., 2017). Pain scores were comparable in each group, and only one patient had cancer recurrence in the contralateral breast 18 months after surgery in the Sevo-fentanyl group (Cho et al., 2017). Neither group had a patient with metastasis within two years of surgery (Cho et al., 2017). The researchers found their study consistent with their hypothesis that "avoiding volatile anesthetics and opioids could reduce the immunosuppression during surgery" (Cho et al., 2017, p. 976). This study included five limitations, including 1) that operating room staff could not be blinded to group allocation, 2) remifentanil and tramadol were used in both study groups, which may have made an impact on NKCC, 3) the researchers "could not discriminate the respective effects of each drug on NKCC and inflammatory responses," 4) the researchers did not isolate NK cells and used peripheral blood mononuclear cells (PBMCs) as effector cells instead and finally 5) the study was limited to a follow up of two years when further long-term monitoring would have been beneficial to monitor cancer recurrence and metastasis (Cho et al., 2017, p. 975).

A retrospective study by Desmond et al. (2015) reviewed the effects of propofol-paravertebral anesthesia versus a balanced general anesthetic with opioid analgesia on breast cancer patients (Desmond et al., 2015). A total of 30 patients were selected for this study. The researchers re-stained the 30 patients' breast cancer tissue specimens to look for "differential expression markers of immunocyte infiltration" (Desmond et al., 2015, p. 1313). Two of the 30 specimens were unusable due to difficulties with staining; therefore, 16 samples were used from the PPA group, and 12 were used from the GA group. Analyzing the data via a P value, the researchers found the PPA group had increased levels of natural killer cells and T helper cell infiltration in the breast cancer tissue samples compared to the general anesthetic samples (Desmond et al., 2015). However, the PPA group did not show an increased level of T

suppressor cells, macrophages, or other important immune cells in battling breast cancer or other foreign invaders (Desmond et al., 2015).

A critical point to note for this study that the propofol-paravertebral group used intraoperative fentanyl for pain control (0-125 mcg) but did not use morphine, whereas the general-opioid anesthetic group used fentanyl intraoperatively for pain control (100-300 mcg) and morphine postoperatively for pain control (4-15 mg) (Desmond et al., 2015). Many studies reviewing anesthetics for cancer recurrence also review opioids as there may be a correlation between the type of opioid used and immune cell function. The researchers also noted that there had been recent evidence showing that amide local anesthetics, which were used in the PPA group of this study, may have anti-inflammatory or anti-metastatic properties, which could contribute to the higher NK cell and T cell infiltration rates (Desmond et al., 2015). The author also believes it would have been helpful if this article included serum samples of the subjects in addition to the tissue samples that were studied. Further studies are warranted.

An expert opinion article was found that supported the claims related to breast cancer and metastatic disease. Hurtado et al. (2021) discussed how anesthetics and analgesics could influence cancer metastasis and recurrence. Although Hurtado did not conduct his own study, he reviewed twenty-eight articles relevant to anesthesia and cancer metastasis rates. Hurtado et al. (2021) discussed how surgery is a means of curative treatment, surgery and the human stress response may promote perioperative cancer cell proliferation. He also found that the immune response during the perioperative period can lead to angiogenesis or the formation of new blood cells to the tumor, leading to postoperative cancer recurrence (Hurtado et al., 2021).

Hurtado et al. (2021) found that "surgical manipulation of tumors… has been found to result in shedding of tumor cells into systemic circulation, promoting metastasis" (p. 222).

Hurtado et al. (2021) also went into extensive detail regarding natural killer (NK) cells and their importance in cytotoxicity to tumor cells. The researcher also found the following drugs and factors to *inhibit* NK cell activity: Hypoxia-inducible factor, hypothermia, Vitamin B2 agonism, Cyclooxygenase-2, Isoflurane, Sevoflurane, Dexmedetomidine, Fentanyl, Remifentanil, Alfentanil, Sufentanil, and Morphine; he also found the following drugs and factors to *promote* NK cell activity, or in other words assist the body in fighting cancer cells: desflurane, beta-blockers, propofol, local anesthetics, cyclooxygenase inhibitors, Ketorolac and Celecoxib (Hurtado et al., 2021). In Hurtado et al.'s (2021) final discussion, they found that "surgical stress combined with anesthetic agents promote an environment favorable to malignancy… 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" (p. 224).

Le-Wendling et al. (2018), the final study in this section, aimed to conduct a literature review studying the effects of regional anesthesia on various types of cancer. Regional anesthesia is a valuable tool in the operating room, helpful in decreasing postoperative opioid consumption and decreasing the patient's overall pain level after surgery. In the oncology population, regional anesthetics can also be helpful by "attenuating the sympathetic nervous system's stress response to surgery, reducing opioid requirements thus reducing their immunosuppressant effects, and providing anti-tumor and anti-inflammatory effects directly through systemic local anesthetic action" (Le-Wendling et al., 2018, p. 756). These researchers found a positive correlation between regional anesthetics and decreased cancer metastasis rates, including breast cancer. The researchers specifically found an article by Exadaktylos that included the use of paravertebral anesthesia to decrease breast carcinoma cell proliferation from 73% to 24%, a remarkable change

(Le-Wendling et al., 2018). Articles such as this are essential to consider when it comes to anesthetic management for breast cancer surgery.

Literature Opposing the Use Propofol or Alternate Modalities of Anesthesia

In 2020, The American Society of Anesthesiologists published an article titled *Anesthesia and Circulating Tumor Cells in Primary Breast Cancer Patients.* In this article, the authors completed a randomized control trial with 210 participants comparing the effects of sevoflurane anesthesia and propofol-based anesthesia on circulating tumor cell counts (Hovaguimian et al., 2020). The researchers found that circulating tumor cell counts are "independently associated with a higher risk of disease recurrence and with reduced survival, both in nonmetastatic and metastatic breast cancer" (Hovaguimian et al., 2020, p. 549).

For their study, Hovaguimian et al. (2020) divided the patients randomly, 1:1, into an intravenous anesthesia group using propofol or an inhalational anesthetic group using sevoflurane. For induction, in both groups, the researchers used fentanyl (2-3 μg/kg), thiopental (4-6 mg/kg), and rocuronium as a muscle relaxant (0.6 mg/kg) (Hovaguimian et al., 2020). Following induction, if fentanyl was further required, it was given following a standard protocol including 2 μg/kg, totaling 5-10 μg/kg (Hovaguimian et al., 2020). For the propofol patients, a propofol drip was maintained and targeted to a bispectral index (BIS) value of 40-60; the sevoflurane group also had sevoflurane targeted to a BIS value between 40-60 (Hovaguimian et al., 2020). The researchers gave antiemetics and perioperative analgesia following standardized protocols; however, they did not list which medications were used in their study.

Hovaguimian et al. (2020) drew blood samples from the subjects at four different intervals, before induction of anesthesia (their baseline), after anesthesia but before removing the airway (0h), 48 hours after surgery, and 72 hours postoperatively. Circulating tumor cell counts

were then conducted on the samples. The researchers found no difference in circulating tumor cell counts between the sevoflurane and propofol groups**.** This study was the first found by the author that did not support non-volatile anesthesia in decreasing tumor cell rates; however, it is essential to note that there were no harmful effects of using propofol based/ total intravenous anesthetic.

Jeong-Ae et al. (2018) completed a randomized control trial to study the effects of propofol or sevoflurane-based anesthesia techniques on different types of immune cells in patients undergoing breast cancer surgery. This study, based in Korea, analyzed venous samples from 44 patients to determine the apoptosis rates of cancer cells, analyze natural killer cells, cytotoxic T cells, cytokines tumor necrosis factor-alpha, and interleukin (IL)-6 and IL-10 (Jeong-Ae et al., 2018). These researchers were forthright in explaining that cancer surgery has been shown to impact a patient's immunity which may allow cancer recurrence or metastasis, "however, recent studies have demonstrated conflicting results and did not show any definite effects of anesthetic agents on cancer immunity" (Jeong-Ae et al., 2018, p. 2).

Based on the information found, the researchers went forward with creating a standardized technique for anesthesia for breast cancer surgery. The patients in both groups did not receive pre-anesthetic medication and were induced with anesthesia after basic monitoring and BIS monitoring were applied (Joeng-Ae et al., 2018). The researchers initiated propofol intravenously at a target concentration of 4 μg/ml using a target-controlled infusion device (Joeng-Ae et al., 2018). Thiopental sodium, a barbiturate, was administered (5 mg/kg) to induce anesthesia in the sevoflurane group (Joeng-Ae et al., 2018). "After loss of consciousness, mask ventilation was confirmed and 0.6 $mg \cdot kg^{-1}$ rocuronium was administered intravenously. The fixed target concentration of remifentanil was 5.0 $ng \cdot kg^{-1}$… which was administered

intravenously and maintained until the end of surgery" (Joeng-Ae et al., 2018, p. 2). After the patient was tracheally intubated, propofol was given to the propofol group, and sevoflurane was applied to the sevoflurane group with both medications titrated to a BIS of 40-60, similar to previous studies (Joeng-Ae et al., 2018). Mean blood pressure was maintained within 20% of the patient's baseline blood pressure, or a MAP > 60mmHg with anesthesia (Joeng-Ae et al., 2018).

Upon completion of surgery, both medications (propofol or sevoflurane with the administration of remifentanil) were discontinued, and ketorolac (0.5 mg/kg) was given for postoperative pain control (Joeng-Ae et al., 2018). The researchers gave 0.03 mg/kg of neostigmine and 0.008 mg/kg of glycopyrrolate to reverse postoperative residual muscular paralysis (Joeng-Ae et al., 2018). As previously stated, the researchers collected blood samples in preop, one hour postoperatively, and 24 hours postoperatively. Blood samples were then analyzed in the laboratory, and the results were compared.

The researchers concluded that "the effect of propofol-based anesthesia on cancer cell, NK cell and CTL [cytotoxic T lymphocytes] did not differ from that of sevoflurane-based anesthesia in breast cancer surgery" (Joeng-Ae et al., 2018, p. 7). However, this study did include a few limitations. The researchers recognized that propofol was used with both the propofol-only anesthetic group and the sevoflurane group, which may have led to different outcomes in immune cell counts and apoptosis rates. Additionally, "the types of opioid administered varied without consideration of their potency" (Joeng-Ae et al., 2018, p. 6). However, it was beneficial for the researchers to use the same opioid, remifentanil, and not to mix different opioids within the groups for consistency.

Additionally, remifentanil tends to be an opioid with little effect on intraoperative inflammation compared to alfentanil or fentanyl (Joeng-Ae et al., 2018). The author found a

limitation of this study to be a lack of follow-up with the participants. The last blood sample was drawn 24 hours postoperatively; therefore, there is no way to know if there was metastasis in any of these patients six months, one year, two years, or five years later.

Oh et al. (2018) completed a RCT to determine the effects of propofol versus sevoflurane-based anesthesia on regulatory T cells. The researchers recognized that clusters of differentiation, or enzymes, which appear on regulatory T cells, are a key component in immunosuppression; this immunosuppression can cause cancer recurrence. This RCT, based in Korea, analyzed 201 women randomly allocated to either the sevoflurane or propofol group. The health care personnel responsible for the patients were blinded to the study goals and instructed to follow a protocol, and the research assistant collecting the blood samples was blinded to the allocation of the study participants (Oh et al., 2018).

The anesthetic procedure was as follows: the patients were not premedicated prior to surgery (Oh et al., 2018). The patients were given anesthesia after monitoring systems, including the BIS monitor, were applied (Oh et al., 2018). All patients were given lidocaine (0.5 mg/kg) intravenously; the propofol group then received 4 mg/mL intravenously using a target-controlled infusion device (Oh et al., 2018). The sevoflurane group received thiopental sodium as an induction agent (5 mg/kg) (Oh et al., 2018). "After loss of consciousness, adequate mask ventilation was confirmed and 0.6 mg/kg rocuronium was administered intravenously for muscle relaxation under the guidance of peripheral neuromuscular transmission monitoring. A fixed target concentration of 5.0 ng/ml remifentanil… was administered intravenously and maintained until the end of surgery" (Oh et al., 2018, p. 922). Once the patient's train of four count was zero, the patient would then be tracheally intubated (Oh et al., 2018).

From induction, the patients in both groups were administered 0.3 mg of ramosetron intravenously to prevent postoperative nausea and vomiting (Oh et al., 2018). The propofol group anesthetic was maintained via target-controlled infusion, and the sevoflurane group was maintained with sevoflurane vapor anesthetic; both groups were maintained within a target range of 40-60 on the BIS monitor to maintain an adequate depth of anesthetic (Oh et al., 2018). At the conclusion of surgery, propofol, sevoflurane, and remifentanil were stopped, and both groups received 0.5 mg/kg ketorolac for postoperative pain control (Oh et al., 2018). Neuromuscular paralysis was reversed with 0.03 mg/kg of neostigmine and 0.008 mg/kg of glycopyrrolate (Oh et al., 2018). Patient-controlled analgesia (PCA) pumps were initiated for patients undergoing radical mastectomies, which contained a volume of "200 ml, consisting of 2,000 mg (40 ml) fentanyl, 0.6 mg (4 ml) ramosetron, and 156 ml normal saline" (Oh et al., 2018, p. 922). After the patients' endotracheal tube was removed, they were transferred to the postoperative care unit (Oh et al., 2018).

Blood samples were obtained from the subjects at three intervals – immediately before induction of anesthesia, on arrival to the postoperative care unit, and 24 hours after the conclusion of the surgery (Oh et al., 2018). The researchers examined the serum to determine the "frequency of cluster of differentiation 39 and 73 expression on circulating regulatory T cells, as well as the frequency of circulating immune cells, such as types 1 and 17 helper T cells. In addition, the frequency and apoptosis of circulating natural killer cells and cluster of differentiation 8+ T cells were explored" (Oh et al., 2018, p. 922). The researchers' results found "similar effects on the frequency of cluster differentiation 39 and 73 expression on circulating regulatory T cells" for both the sevoflurane and propofol groups (Oh et al., 2018, p. 925). Effects on the frequency of other immune cells, including helper T cells and NK cells, remained similar

between the two groups as well (Oh et al., 2018). Overall, the researchers found a lack of definitive evidence supporting the use of propofol in immune cell protection for breast cancer surgery (Oh et al., 2018). However, the study did include several limitations. One of the most important limitations was that the use of opioids, both remifentanil and fentanyl, and the anti-inflammatory drug ketorolac, were used in both groups. These drugs "could mask the pure effect of propofol or sevoflurane on the immunity of patients with cancer, although they were used similarly" (Oh et al., 2018, p. 928). Research has shown a correlation between opioid use and immunosuppressant properties, so a study without the use of opioids would be beneficial (Oh et al., 2018). Additionally, this study drew their last blood specimen at 24 hours postoperatively; it would have been advantageous to study the serum of these patients at six months, one year, two years, and five years postoperatively to determine the effects these anesthetics had on immune cell function at later intervals.

The largest, most comprehensive, and one of the more recent studies was conducted by Sessler et al. (2019). This RCT was completed in 13 hospitals across eight countries over 12 years. This study included women between the ages of 18- and 85-years old undergoing curative primary breast cancer surgery (Sessler et al., 2019). The researchers' primary outcome was to compare metastasis rates in patients receiving regional anesthesia-analgesia with the use of paravertebral blocks and propofol and compare the effects with patients receiving general anesthesia with sevoflurane and opioid analgesia (Sessler et al., 2019). The second outcome was comparing the two groups' incisional pain at six months and 12 months postoperatively (Sessler et al., 2019).

Sessler et al.’s (2019) study scope was more extensive than any of the other studies reviewed by the author. Over 12 years, 2132 women were selected to participate in the clinical

trial; prior to surgery, 24 participants were excluded for various reasons (Sessler et al., 2019). A total of 1065 women were allocated to the general anesthesia group and 1043 women to the PVB-propofol group; these women were randomly assigned via computer-randomization software (Sessler et al., 2019). The researchers restricted the study to women under the age of 85 "with primary breast cancer without known extension beyond the breast and axillary nodes… who were scheduled either for unilateral or bilateral mastectomy, with or without implants, or for wide local excision with node dissection" (Sessler et al., 2019, p. 1808). The researchers excluded patients who had previous breast cancer surgery (not including those who had biopsies or guide-wire insertion), those who had inflammatory breast cancer, those with an ASA score of IV or greater, and those scheduled for free-flap reconstruction (Sessler et al., 2019).

The procedures varied slightly between the different study sites; generally, a paravertebral block was completed between the thoracic vertebrae of T1-T5 using ultrasound guidance and using 5 mL of local anesthetic at each vertebral level (Sessler et al., 2019). "Morphine was the first-line postoperative analgesic in both study groups. After approximately 24 h, patients in both study groups were transitioned to paracetamol, tramadol, non-steroidal anti-inflammatory drugs, or a combination of these analgesics; oral opioids were also permitted if necessary" (Sessler et al., 2019, p. 1809). This study differed from others in that the exact amount of propofol, sevoflurane, and opioid varied from patient to patient, and the authors admitted to over 100 missing data points regarding crystalloid intake, colloid intake, estimated blood loss, allogenic blood loss, mean arterial pressure, heart rate, bispectral index, core temperature and sevoflurane MAC (minimal alveolar concentration) hours (Sessler et al., 2019).

The mean data for the regional anesthesia group is as follows: the patients kept a bispectral index of 51, 17% of the regional group received some amount of sevoflurane, most

patients received 4 mg of Ondansetron to prevent postoperative nausea and vomiting, a mean of 525 mg of propofol was used, a mean of 1mg of Versed, a mean of 20 mg of rocuronium was used for muscle relaxation, 100 mcg of fentanyl, and approximately 10 mg of intraoperative morphine equivalents were used (Sessler et al., 2019).

The mean data for the general anesthesia group is as follows: most patients kept a bispectral index of 55, most received 0.9 MAC hours of sevoflurane, and 97% of the general anesthesia group received sevoflurane. Most subjects received 4 mg of Ondansetron, 120 mg of propofol, 1 mg of Midazolam, 1 mg of neostigmine, 20 mg of rocuronium, 200 mcg of fentanyl, and 20 mg of intraoperative morphine equivalents (Sessler et al., 2019). Five patients had unsuccessful paravertebral blocks and were converted to the general anesthetic group, and one patient who was in the general anesthesia group received a paravertebral block (Sessler et al., 2019). "27 patients assigned regional anaesthesia-analgesia and 40 allocated general anesthesia were lost to follow up… Both groups had a median follow up of 36 months" (Sessler et al., 2019, p. 1811).

The researchers found the result of this study to be that the type of anesthetic, PVB-propofol versus general anesthesia, does not reduce breast cancer recurrence (Sessler et al., 2019). Limitations of this study include the lack of data points for multiple cases, limiting the non-general anesthesia group to just paravertebral blocks, and that 17% of the PVB-propofol group still used sevoflurane in some capacity. There has also been a correlation between the use of opioids and immune-cell suppression. Further research would be warranted to include a study that eliminates the use of opioids. The researchers in this study stated, "Additional trials are needed to assess potential benefits of regional analgesia in patients having larger operations that provoke more surgical stress, cause more pain, and require more opioid analgesia" (Sessler et al.,

2019, p. 1808). However, the results should be weighed heavily due to the sheer size of this study compared to the other studies evaluated.

Inconclusive or Mixed Result Literature Regarding Propofol or Alternate Modalities of Anesthesia

The author reviewed four articles that had inconclusive or mixed responses on the use of propofol-paravertebral anesthesia (PPA) versus the use of a general anesthetic. Chen et al. (2015), a literature review, found that PPA is a pain-resistant technique in surgery that may enhance breast cancer prognosis; however, there are "only a few convincing reports [which] have stated that PPA improves the prognosis of breast cancer in patients, and whether there is a better pattern to implement PPA is not clear" (Chen et al., 2015, p. 8262). A literature review by Li et al. (2018) found a positive correlation between the use of propofol and increased NK cell activity, however, the evidence stopped there. The researchers determined that there was not sufficient evidence, with the retrospective studies, to recommend a change in anesthetic practice (Li et al., 2018). Therefore, both studies recommended that further research be done before recommending the use of PPA anesthesia in breast cancer patients.

Two other studies by Pérez-González et al. (2017) and Yan et al. (2018), a systematic review and a randomized control trial (RCT) respectively, could not support or deny the use of PPA or a TIVA anesthetic instead of a general anesthetic. Pérez-González et al. (2017) claimed that based on their studies, there was not enough evidence to support or contest the use of paravertebral block "for reduction of cancer recurrence or improvement of cancer-related survival. Although the data suggest that PVB may decrease perioperative inflammation and prevent immune suppression and diminish angiogenesis, further evidence is required because we found that in most studies PVBs were used in combination with propofol" (Pérez-González et al.,

2017, p. 755). The researchers also recommend following a study by Sessler et. al., 2019 that was not yet complete at the time of their publishing but can be reviewed earlier in this document. Yan et al. (2018) performed a RCT studying the effects of propofol/remifentanil-based anesthesia (also known as TIVA or total intravenous anesthesia) versus sevoflurane-based inhalational anesthesia and its effects on vascular endothelial growth factor (VEGF-C) and transforming growth factor-b (TGF-b), which have been shown to correlate with metastasis and tumor growth in patients (Yan et al., 2018). There was no substantial difference in cancer recurrence rates between the two anesthetic groups (Yan et al., 2018). Consequently, these articles suggest that further studies be complete before promoting alternative anesthesia modalities for breast cancer surgery.

Summary of Evidence/Interpretation

The results of this literature review were nonunanimous. Several articles by Buckley et al. (2014), Cho et al. (2017), Desmond et al. (2015), Hurtado (2021) and Le-Wendling et al. (2018) all supported using TIVA and regional anesthesia versus a traditional anesthetic, showing decreased metastasis rates or increased NK cell activity postoperatively. Unfortunately, some of those studies included the use of opioids in their experimental group. Other articles, including one of the most extensive and most recent studies by Sessler et al. (2019), did not show a decrease in metastasis rates with a paravertebral block and propofol versus the Sevoflurane and opioids. Furthermore, the last group of articles were inconclusive or represented mixed results with an experimental TIVA group versus a traditional anesthetic approach, not finding substantial differences between TIVA and Sevo groups and metastasis rates.

There are a few essential points to consider when interpreting these articles. First, none of the studies reviewed showed poor outcomes or increased metastasis rates regarding a TIVA,

regional anesthesia, or opioid-free anesthetic in breast cancer patients. Second, many of these studies did not have a prolonged follow-up period with the patients. Therefore, one could not deduce how these anesthetic plans may affect the participants five to ten years postoperatively. Lastly, there are other significant patient benefits regarding the use of TIVA, regional anesthesia and/or opioid-free anesthesia. A regional anesthetic, like a paravertebral block, can help decrease the patient's postoperative pain levels and decrease inflammation, and TIVA and an opioid-free anesthetic can help reduce postoperative nausea and vomiting (PONV) in a patient population that is typically high risk for PONV (Chhabra et al., 2021).

Furthermore, if anesthesia providers can provide an anesthetic that can decrease someone's metastasis rates without known harm to the patient, and with pharmaceuticals that are already on the formulary, they should do so. Implementing an anesthetic guideline that can decrease patient metastasis rates in the future, decrease PONV and postoperative pain, increases a patient's quality of life and saves the patient time on future doctors' visits and treatment, and relieves a financial burden, is essential.

Model for Project Framework

Due to the ever-changing amount of research and advances in the medical field, the most updated scientific evidence must be used to guide us in healthcare. Evidence-based practice uses heavily researched data to create the safest outcomes for patients and providers. "Evidence-based practice (EBP) enhances healthcare quality, improves patient outcomes, reduces cost, and empowers clinicians; this is known as the quadruple aim in healthcare" (Melnyk & Fineout-Overholt, 2019, p. 36). Evidence-based practice integrates external evidence from data, clinical expertise, and patient and clinician preference to guide clinical decision-making (Melnyk & Fineout-Overholt, 2019). Due to the significance of evidence-based practice in health systems

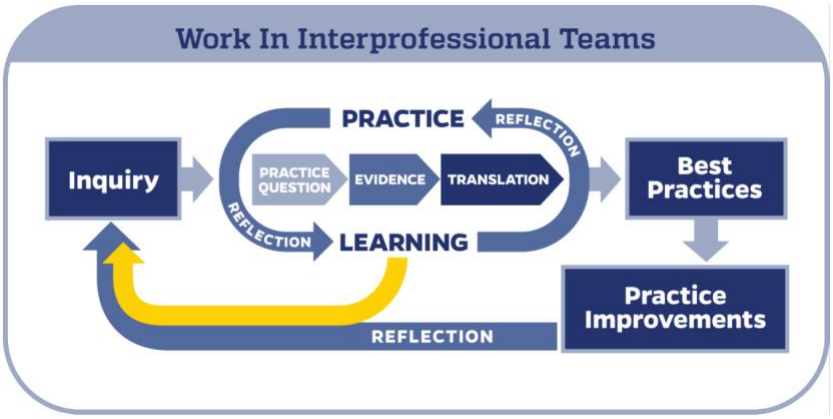
nationwide, The Johns Hopkins Evidence-Based Practice Model for Nurses and Healthcare Professionals (JHEBP) is best to guide this project. The author received permission to use The Johns Hopkins Evidence-Based Practice Model for Nurses and Healthcare Professionals for this project, which can be found in Appendix A.

Clinical inquiry guided this process. When reviewing the literature, it was evident that there is a need for breast cancer surgery guidelines to reduce cancer metastasis. Based on clinical inquiry, the PET process (Practice Question, Evidence, Translation) allows the development of study a question, research for the best available scientific evidence, and then allows the researcher to translate the data into practice (Melnyk & Fineout-Overholt, 2019). If further questions or new evidence arises throughout the review, the author will refine the PICOT question and move back through the previous steps of the JHEBP model (Melnyk & Fineout-Overholt, 2019). The JHEBP Model will be integrated into this project using the following questions and statements:

1. Practice question: In patients undergoing breast cancer surgery, how would the development and implementation of evidence-based practice anesthesia guidelines versus a traditional anesthetic approach affect metastasis rates?
2. Evidence: What does evidence-based literature show regarding anesthetic technique and metastasis rates in breast cancer surgery patients?
3. Best Practices: What anesthetic techniques should be implemented to promote best practice guidelines to reduce metastasis rates?
4. Practice Improvements: Create and implement EBP guidelines for a central Ohio hospital for multimodal anesthesia and non-opioid analgesia for breast cancer patients.

5. Reflect: Through monitoring outcomes from the literature, did the EBP guidelines have an impact on patient outcomes?

Figure 1



Note. The Johns Hopkins Evidence-Based Practice Model for Nurses and Healthcare Professionals

Project Method

Thus far, following the JHEBP Model, the practice question and evidence through the literature search have been addressed. Literature has shown that there are benefits for breast cancer patients using an anesthetic technique including an anesthetic without the use of volatile gases or opioids; therefore, a practice improvement should be implemented. Due to time constraints, the project will not be implemented; however, the following evidence-based best-practice anesthesia guidelines (located in Appendix C) should be applied.

Project Team

The project would be fulfilled by the project team leader and Chief CRNA of a hospital. They would be responsible for educating anesthesia staff members, including anesthesiologists,

CRNAs, anesthesia associates (AAs), and student registered nurse anesthetists (SRNAs). The project team leader would also be responsible for contacting the pharmacy and following up with the Quality Improvement (QI) department as results populate.

Other significant team members are the stakeholders. Stakeholders can include anyone from the initial oncologists who see the patients, the surgeons, the chief anesthesiologist or chief CRNA at the hospital, the bedside anesthesiologists, CRNAs or residents, pharmacists, the hospital QI department, and the hospital budgeting department. This project requires support, permission, and funding from various key stakeholders. Once the stakeholders have a thorough understanding of the method of this project and the projected outcomes, project implementation can occur.

Target Population and Setting

The ideal setting for this guideline development and implementation would be a mid-sized inpatient hospital or cancer hospital in the Mid-Western region of the United States. This hospital should see routine breast cancer surgeries with a minimum of six cases per week.

The target population for staff education includes anesthesiologists, anesthesiology residents, CRNAs, AAs, and student registered nurse anesthetists. The patient population includes female patients undergoing breast cancer surgery. Examples of surgeries to be included in the guideline are breast tissue lumpectomy, single or double mastectomy, and lymph node dissections (lymphadenectomy). Other appropriate inclusion criteria include female patients between the ages of 18-65 and those with ASA Physical Status Classification scores between I and III.

Patient populations that should be excluded from the anesthesia guideline include patients under the age of 18, male gender, patients with inflammatory breast cancer, previous breast

cancer surgery, another type of cancer, an ASA status greater than IV, patients who are unable to receive a paravertebral block or are allergic to local anesthetics or propofol. Patients should also be excluded if they have renal disease, asthma, a BMI > 40 kg/m^2, those on immunosuppressive therapy, and those with immune disorders. The anesthesia provider should also consider excluding patients undergoing breast reconstruction; depending on the invasiveness of reconstruction, opioid use may be inevitable.

Project Intervention/Implementation

First, the project team leader and Chief CRNA will need to connect with the IT department, QI department and pharmacy. The IT department will be needed to create a "pop-up" alert with the anesthesia guidelines within *Epic*. The QI department will be needed to create metrics based on the outcomes of this project and anesthesia provider compliance of the guideline. Pharmacy will need to be contacted to ensure that the medications required are readily available to anesthesia staff.

Next, the Chief CRNA and project team leader will hold a one-hour educational information session for the hospital anesthesia team. This education session will include a PowerPoint presentation outlining the new breast cancer anesthesia guidelines' benefits compared to a traditional anesthetic approach. The guideline will be e-mailed to staff; therefore, no additional costs for printing are required. Once the anesthesia staff is educated, and preparations are made, the guideline can be implemented.

Upon opening the "Intraprocedure" tab within *Epic* for every breast cancer surgery, the anesthesia provider should receive a "pop-up" alert to consider using the recommended EBP guidelines. Once the anesthesia provider considers the indications and contraindications for the

patient, and the patient is deemed an appropriate candidate for the anesthesia guideline, the anesthesia provider can proceed with guidelines.

Monitoring/Data Collection

Plasma levels should be drawn by the preoperative nurse 1 hour prior to surgery, immediately postoperatively (within the first hour) in the post-anesthesia care unit, 12 hours, 24 hours, and 48 hours postoperatively. These plasma levels would determine natural killer cell counts. Follow-up with patients should occur at three months, six months, one year, two years, five years, and ten years postoperatively. During these follow-up visits, a complete blood count with differential should be drawn (at all follow-up appointments); a PET scan and a mammogram should be completed to evaluate for metastasis (at 6 months, one year, two year, five year and ten year visits).

Outcome Analysis Plan

Data, Instruments, and Tools

As previously mentioned, data collection includes regular intervals of serum plasma collection from study participants, blood tests, and imaging at several post-surgical follow-up appointments. All data will need to be methodically accounted for and interpreted. All quantitative data should be imported into the *Epic* software/charting system. Examples of the quantitative data used include the patient's age, medication dosages, ASA status, and natural killer cell counts from serum samples. Other examples of quantitative data include ethnic origin, initial tumor site, and tumor staging prior to surgery.

Epic will be the primary software program used for guideline implementation. The QI department for the hospital will be utilized to measure the outcomes of the guideline. The initial tests to monitor are histograms to illustrate the distribution frequency (Moran et al., 2019). The

distribution frequency will give the project leader and chief CRNA initial results regarding natural killer cell rates in some of the first patients. Moran et al. (2019) explain that if the distribution frequency is normal, parametric analyses can then be completed. If the distribution frequency is not normal, adjustments to the interventions should be made immediately and not postponed.

The next series of data analyses should be descriptive data. The descriptive analysis includes common data entry points to find the mean, median, and mode, as well as data variation, including range and standard deviation (Moran et al., 2019). The next set of data should come from the hospital's statistical software. This data should include a hazard ratio, confidence interval, and P-value for NK cells and metastasis rates. Reliability should be tested using the hospital's statistical software.

When the data analysis is complete, the project team leader and the chief CRNA should interpret the data related to the PICOT question – did the new anesthesia guideline provide decreased metastasis rates and increased natural killer cell activity? As data is collected throughout the study period, data should be analyzed. As part of the JHEBP model, the research team should constantly evaluate results and outcomes and reflect upon them. If the immediate results show undesired outcomes, including decreased NK cell rates or recurrence of metastasis, the research team should pause the research and reevaluate their interventions. Intervention changes may include changing the anesthetic medications or changing from a paravertebral block to a PECs block.

Limitations/Barriers

There are a variety of limitations or barriers to this study. A primary limitation may be anesthesia staff compliance with the new guidelines. These guidelines may take more time and

effort than a traditional anesthetic, including a preoperative paravertebral nerve block. This change from a traditional anesthetic, may cause pushback from anesthesia. Another barrier includes patients who may not be eligible for the guideline due to opioid requirements. In this case, it should be recommended that the anesthesia staff continue using TIVA rather than volatile anesthetics and supplement low-dose opioids in addition to non-opioid analgesics. Another barrier may be getting Ofirmev or other non-opioid analgesics in the pharmacy formulary. Finally, due to the length of this study, there is a possibility for a lack of patient follow-up. Patients who miss appointments should be contacted by the project team leader or by the hospital scheduling department to reschedule, however, there is still a chance that patients will not participate.

Outcome Measurement

The project will be successful if either natural killer cell activity is increased in the immediate postoperative period (0-48 hours) or if metastasis rates decrease from use of the new guidelines. NK cell counts will be measured by the QI department and reported back to the research team. If cancer metastasis or breast cancer recurrence is found during postoperative visits, the oncologist should report it to the research team, and data on metastasis location and timing should be accounted for. Again, initiatives should be reevaluated by the research team if there is any point at which the outcomes are unsuccessful or undesirable.

Timeline and Budget

Timeline

The projected time frame for anesthesia guideline implementation is two years. The additional follow up for metastasis monitoring may take an additional 10 years. The first six months of the project will be for anesthesia guideline preparation. This period includes

connecting with the pharmacy and QI departments to ensure that the desired medications are available and that the appropriate tests and software are available. The IT department should be consulted to insert the “pop-up” window in *Epic* to notify the anesthesia provider to consider utilizing the new guideline. This time also includes educating anesthesia providers on the new breast cancer anesthesia guideline.

Following the education and preparation phase, is the data collection phase which includes NK cell count collection and metastasis monitoring. The collection period contains preoperative serum lab draws, immediate postoperative lab draws, and lab draws at 12 hours, 24 hours, and 48 hours for each patient postoperatively. Labs will be drawn by the pre-op and PACU nurses and the nurses on the surgical floor where the patient stays postoperatively. If the patient returns home the same day of surgery, they should be instructed to go to the outpatient laboratory for blood draws at 24- and 48-hours post-operation. The blood samples will be collected by the nurse and run by the laboratory, and data will then be entered within *Epic* and the hospital’s statistical software. Then each patient will undergo postoperative follow-up appointments with their oncologist. The patients will give another blood sample, a mammogram, and a PET scan at regular intervals – three months, six months, 12 months, two years, five years, and ten years postoperatively. The study will end at the 12-and-a-half-year mark with the last patient's follow-up visit and data collection. Following the last data collection point, the researchers will have approximately one month to finalize the data entry points and measure the outcomes. Since there should be adequate amounts of time within the project's last eight to ten years, the research team should collect and analyze most of their data before the patients' final follow-up visits.

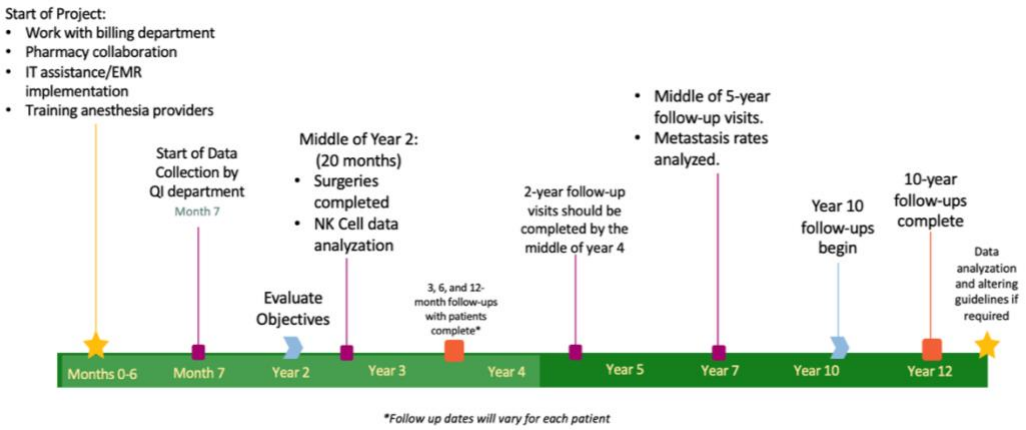


Figure 2

Note. Project timeline

Budget

The total cost for development and implementation of the guideline is approximately $29,438. These costs include purchasing a new ultrasound for the paravertebral blocks, the one-hour costs for anesthesia education for 15 CRNAs and eight anesthesiologists, and poster supplies for the project team leader or chief CRNA. This cost may be lower if there are functioning ultrasounds owned by the hospital and if the anesthesia department already has educational time built into the providers' salary.

Figure 3

Item	Description	Project Cost
TE7 Mindray Ultrasound		$26,377
Anesthesiologist Education	Average salary of $401,000 => $192/hr x 8 anesthesiologists	$1,536
CRNA Education	Average salary of $197,000 => $94/hr x 15 CRNAs	$1,410
Lab Supplies for Poster		$115
		$29,438

When evaluating the cost of the project, one needs to consider other factors. For example, a retrospective study completed by Stokes et al. (2008) found that "Expected 10-year costs

attributable to distant recurrence, local recurrence, and contralateral breast cancer were $11,450, $19,596, and $19,183, respectively" (p. 213). These costs do not account for inflation in the U.S. since 2008. The cost attributable to recurrence for one patient is approximately two-thirds of how much it costs for this entire project.

Another factor to consider is medical malpractice settlements. According to *Calculating Medical Malpractice Settlement Damages* (2022), “the average medical malpractice settlement in the United States awards $242,000. Those that go to trial average around $1,000,000” (para. 7). Other, more severe cases that cause pain and suffering can have settlements that average between $100,000-$500,000 (*Calculating Medical Malpractice Settlement Damages*, 2022). In conclusion, although the cost of this project is considerable, if patients file for medical malpractice related to their anesthetic and cancer recurrence, the hospital may have to pay a substantial amount to the affected patient.

Conclusion

In conclusion, the literature shows benefits of using regional and total intravenous anesthesia versus opioids and volatile anesthetics in treating breast cancer surgery patients. Using a regional anesthetic combined with TIVA can reduce metastasis rates and increase natural killer cells postoperatively. The use of the John Hopkins EBP Model guides this process in order to continually assess postoperative metastasis rates and NK cell activity based on the aforementioned interventions. Utilizing evidence-based practice guidelines outlined in the project can assist hospitals in achieving a consistent anesthetic for breast cancer patients with the best post-operative outcomes. The researcher hopes that implementation of the guidelines will assist breast cancer patients in quick cancer remission and long-term prevention of cancer metastasis.

References

American Cancer Society. (n.d.). *Breast Cancer Treatment | Treatment Options for Breast Cancer*. Retrieved February 22, 2023, from https://www.cancer.org/cancer/breast-cancer/treatment.html

American Cancer Society. (2023, January 12). *Breast Cancer Statistics | How Common Is Breast Cancer?* Retrieved February 22, 2023, from https://www.cancer.org/cancer/breast-cancer/about/how-common-is-breast-cancer.html

Blanco, R., & Barrington, M. J. (2022, April 26). *Pectoralis and Serratus Plane Nerve Blocks*. NYSORA. Retrieved February 22, 2023, from https://www.nysora.com/topics/regional-anesthesia-for-specific-surgical-procedures/thorax/pectoralis-serratus-plane-blocks/

Buckley, A., McQuaid, S., Johnson, P., & Buggy, D. J. (2014). Effect of anaesthetic technique on the natural killer cell anti-tumour activity of serum from women undergoing breast cancer surgery: A pilot study. *BJA: The British Journal of Anaesthesia*, 113, i56-i62. https://doi.org/10.1093/bja/aeu200

Calculating Medical Malpractice Settlement Damages. (2022, February 23). The Knowles Group. Retrieved September 11, 2022, from https://www.theknowlesgroup.org/blog/calculating-medical-malpractice-settlement-damages/#:%7E:text=The%20average%20medical%20malpractice%20settlement,out%2Dof%2Dpocket%20expenses.

Chaplin D. D. (2010). Overview of the immune response. *The Journal of allergy and clinical immunology*, 125(2), S3–S23. https://doi.org/10.1016/j.jaci.2009.12.980

Chen, W. K., & Miao, C. H. (2013). The effect of anesthetic technique on survival in human cancers: a meta-analysis of retrospective and prospective studies. *PloS one*, *8*(2), e56540. https://doi.org/10.1371/journal.pone.0056540

Cheng, G. S., & Ilfeld, B. M. (2016). An Evidence-Based Review of the Efficacy of Perioperative Analgesic Techniques for Breast Cancer-Related Surgery. *Pain Medicine*, pnw172. https://doi.org/10.1093/pm/pnw172

Chhabra, A., Roy Chowdhury, A., Prabhakar, H., Subramaniam, R., Arora, M. K., Srivastava, A., & Kalaivani, M. (2021). Paravertebral anaesthesia with or without sedation versus general anaesthesia for women undergoing breast cancer surgery. *The Cochrane Database of Systematic Reviews*, *2*(2), CD012968. https://doi.org/10.1002/14651858.CD012968.pub2

Cho, J. S., Lee, M.-H., Kim, S. I., Park, S., Park, H. S., Oh, E., Lee, J. H., & Koo, B.-N. (2017). The effects of perioperative anesthesia and analgesia on immune function in patients undergoing breast cancer resection: A prospective randomized study. *International Journal of Medical Sciences, 14*(10), 970-976. https://doi.org/10.7150/ijms.20064

Dang, D., Dearholt, S., Bissett, K., Ascenzi, J., & Whalen, M. (2022). Johns Hopkins evidence-based practice for nurses and healthcare professionals: Model and guidelines. 4th ed. Sigma Theta Tau International

Desmond, F., McCormack, J., Mulligan, N., Stokes, M., & Buggy, D.J. (2015). Effect of anaesthetic technique on immune cell infiltration in breast cancer: A follow-up pilot analysis of a prospective, randomised, investigator-masked study. *Anticancer Res. 2015 Mar*; *35*(3):1311-1319. PMID: 25750280.

Elisha, S., Heiner, J. S., & Nagelhout, J. J. (2022). *Nurse Anesthesia* (7th ed.). Saunders.

Elshanbary, A. A., Zaazouee, M. S., Darwish, Y. B., Omran, M. J., Elkilany, A. Y., Abdo, M. S., Saadeldin, A. M., Elkady, S., Nourelden, A. Z., & Ragab, K. M. (2021). Efficacy and safety of pectoral nerve block (pecs) compared with control, paravertebral block, erector spinae plane block, and local anesthesia in patients undergoing breast cancer surgeries: A systematic review and meta-analysis. *Clinical Journal of Pain, 37*(12), 925-939. https://doi.org/10.1097/AJP.0000000000000985

Fancellu, A., Perra, T., Ninniri, C., Cottu, P., Deiana, G., Feo, C. F., & Porcu, A. (2020). The emerging role of pectoral nerve block (PECS block) in breast surgery: A case-matched analysis. *Breast Journal, 26*(9), 1784-1787. https://doi.org/10.1111/tbj.13939

Heaney, A., & Buggy, D. J. (2012). Can anaesthetic and analgesic techniques affect cancer recurrence or metastasis?. *British journal of anaesthesia*, *109 Suppl 1*, i17–i28. https://doi.org/10.1093/bja/aes421

Hovaguimian, F., Braun, J., Z'graggen, B. R., Schläpfer, M., Dumrese, C., Ewald, C., Dedes, K. J., Fink, D., Rölli, U., Seeberger, M., Tausch, C., Papassotiropoulos, B., Puhan, M. A., & Beck-Schimmer, B. (2020). Anesthesia and circulating tumor cells in primary breast cancer patients: A randomized controlled trial. *Anesthesiology, 133*(3), 548-558. https://doi.org/10.1097/ALN.0000000000003409

Hurtado, C., Bendure, J., & Bennetts, P. (2021). Anesthetic and Analgesic Influence on Cancer Recurrence and Metastasis. *AANA journal*, *89*(3), 221–226.

Jeong-Ae Lim, Chung-Sik Oh, Tae-Gyoon Yoon, Ji Yeon Lee, Seung-Hyun Lee, Young-Bum Yoo, Jung-Hyun Yang, & Seong-Hyop Kim. (2018). The effect of propofol and sevoflurane on cancer cell, natural killer cell, and cytotoxic T lymphocyte function in

patients undergoing breast cancer surgery: an in vitro analysis. *BMC Cancer, 18*(1), 1-8. https://doi.org/10.1186/s12885-018-4064-8

Karmakar, M. K., Greengrass, R. A., Latmore, & Levin, M. (2022, May 3). *Thoracic and Lumbar Paravertebral Block – Landmarks and Nerve Stimulator Technique*. NYSORA. Retrieved February 22, 2023, from https://www.nysora.com/topics/regional-anesthesia-for-specific-surgical-procedures/abdomen/thoracic-lumbar-paravertebral-block/

Le-Wendling, L., Nin, O., & Capdevila, X. (2016). Cancer recurrence and regional anesthesia: The theories, the data, and the future in Outcomes. *Pain Medicine, 17*(4), 756-775. https://dx.doi.org/10.1111/pme.12893

Li, R., Liu, H., Dilger, J. P., & Lin, J. (2018). Effect of propofol on breast cancer cell, the immune system, and patient outcome. *BMC Anesthesiology, 18*(1), 1-8. https://doi.org/10.1186/s12871-018-0543-3

McCance, K. L., & Huether, S. E. (2014a). Innate Immunity. *Pathophysiology: The Biologic Basis for Disease in Adults and Children* (7th ed.). Elsevier Health Sciences. 191-223.

McCance, K. L., & Huether, S. E. (2014b). Adaptive Immunity. *Pathophysiology: The Biologic Basis for Disease in Adults and Children* (7th ed.). Elsevier Health Sciences. 224-261.

Melnyk, B. M., & Fineout-Overholt, E. (2019). *Evidence-Based Practice in Nursing & Healthcare, International Edition* (4th ed.). Wolters Kluwer.

Moran, K. J., Burson, R., & Conrad, D. (2019). *The Doctor of Nursing Practice Project: A Framework for Success* (3rd ed.). Jones & Bartlett Learning.

Nagelhout, J. J., & Elisha, S. (2017). *Nurse Anesthesia, 6e* (6th ed.). Saunders.

Oh, C.-S., Lee, J., Yoon, T.-G., Seo, E.-H., Park, H.-J., Piao, L., Lee, S.-H., & Kim, S.-H. (2018). Effect of equipotent doses of propofol versus sevoflurane anesthesia on

regulatory T cells after breast cancer surgery. *Anesthesiology, 129*(5), 921-931. https://doi.org/10.1097/ALN.0000000000002382

Pérez-González, O., Cuéllar-Guzmán, L. F., Soliz, J., & Cata, J. P. (2017). Impact of regional anesthesia on recurrence, metastasis, and immune response in breast cancer surgery: A systematic review of the literature. *Regional Anesthesia & Pain Medicine, 42*(6), 751-756. https://doi.org/10.1097/AAP.0000000000000662

Sanders R.D. & Maze, M. (2011). Anesthetic Pharmacology: Basic Principles and Clinical Practice. Cambridge University Press. 478-492. https://doi.org/10.1017/CBO9780511781933.031

Sessler, D. I., Pei, L., Huang, Y., Fleischmann, E., Marhofer, P., Kurz, A., Mayers, D. B., Meyer-Treschan, T. A., Grady, M., Tan, E. Y., Ayad, S., Mascha, E. J., & Buggy, D. J. (2019). Recurrence of breast cancer after regional or general anaesthesia: a randomised controlled trial. *Lancet, 394*(10211), 1807-1815. https://doi.org/10.1016/S0140-6736(19)32313-X

Shapiro, J., Jersky, J., Katzav, S., Feldman, M., & Segal, S. (1981). Anesthetic drugs accelerate the progression of postoperative metastases of mouse tumors. *The Journal of clinical investigation, 68*(3), 678–685. https://doi.org/10.1172/jci110303

Singleton P.A., & Moss J. (2010). Effect of perioperative opioids on cancer recurrence: A hypothesis. *Future Oncology, 6*(8), 1237-1242. https://doi.org/10.2217/fon.10.99

Solt, K., & Forman, S. A. (2007). Correlating the clinical actions and molecular mechanisms of general anesthetics. *Current opinion in anaesthesiology*, 20(4), 300–306. https://doi.org/10.1097/ACO.0b013e32816678a5

Stokes, M. E., Thompson, D., Montoya, E. L., Weinstein, M. C., Winer, E. P., & Earle, C. C. (2008). Ten-year survival and cost following breast cancer recurrence: estimates from SEER-medicare data. *Value in health: the journal of the International Society for Pharmacoeconomics and Outcomes Research*, *11*(2), 213–220. https://doi.org/10.1111/j.1524-4733.2007.00226.x

Welden B., Gates G., Mallari R., & Garrett N. (2009). Effects of anesthetics and analgesics on natural killer cell activity. *AANA Journal*, *77*(4), 287-292.

Yan, T., Zhang, G.-H., Wang, B.-N., Sun, L., & Zheng, H. (2018). Effects of propofol/remifentanil-based total intravenous anesthesia versus sevoflurane-based inhalational anesthesia on the release of VEGF-C and TGF-β and prognosis after breast cancer surgery: A prospective, randomized and controlled study. *BMC Anesthesiology*, *18*(1), 1-9. https://doi.org/10.1186/s12871-018-0588-3

Yeager M.P., & Rosenkranz K.M. (2010). Cancer recurrence after surgery: a role for regional anesthesia? *Regional Anesthesia & Pain Medicine*, *35*(6), 483-484. https://doi.org/10.1097/AAP.0b013e3181fa11a9

Appendix A

Citation, Author & Year	Conceptual Framework	Design/ Method	Setting/Sample Size	Major Variables Definitions (Independent Variables, dependent variables)	Outcome Measurement	Data Analysis [what stats used?]	Findings [Statistical findings or qualitative findings]	Level of Evidence
Buckley, A., McQuaid, S., Johnson, P., & Buggy, D. J. (2014). Effect of anaesthetic technique on the natural killer cell anti-tumour activity of serum from women undergoing breast cancer surgery: A pilot study. BJA: The British Journal of Anaesthesia, 113, i56-i62. https://doi.org/10.1093/bja/aeu200	The purpose was for researchers to evaluate patient serum before operation and 24hrs after breast cancer surgery to determine NK cell activity between patients who received PPA or sevo-opioid (GA) anesthetic.	RCT	n = 10	Independent Variables: propofol-paravertebral block (PPA) or sevoflurane-opioid (GA) anesthetic techniques. Dependent variable = Natural killer cell function/cytotoxicity.	Serum from the 10 subjects (PPA = 5; GA = 5), were obtained before operation and 24 hours after operation. The serums were then co-cultured with HCC1500 and health primary NK cells. NK cell activating receptors (NKp30, NKp44, 2b4,CD16, NKG2D), cytokine production, NK CD107a expression, and cytotoxicity towards HCC1500 were examined.	P value	Serum from women with breast cancer undergoing surgical excision who were randomized to receive a PA anaesthetic technique led to greater human donor NK cell cytotoxicity *in vitro* compared with serum from women who received GA.	2

Chen, X., Lu, P., Chen, L., Yang, S. J., Shen, H. Y., Yu, D. D., Zhang, X. H., Zhong, S. L., Zhao, J. H., & Tang, J. H. (2015). Perioperative propofol-paravertebral anesthesia decreases the metastasis and progression of breast cancer. *Tumour biology: the journal of the International Society for Oncodevelopmental Biology and Medicine*, *36*(11), 8259–8266. https://doi.org/10.1007/s13277-015-4027-5	Determining the effects of propofol plus paravertebral anesthesia on metastasis rates versus a traditional anesthetic approach.	Literature Review	N/A	Independent Variables: propofol-paravertebral block (PPA) or general anesthetic techniques. Dependent variable = Natural killer cell function, serum nitrous oxide levels, tumor growth factor (TGF) and HER2 pathways	N/A	N/A	It was found that PPA elevated nitrous oxide expression and caused perioperative pain depression. However, only a few consistent reports have shown the benefits of PPA anesthesia versus the traditional approach, further studies are required.	5
Chhabra, A., Roy Chowdhury, A., Prabhakar, H., Subramaniam, R., Arora, M. K., Srivastava, A., & Kalaivani, M. (2021). Paravertebral anaesthesia with or without sedation versus general anaesthesia for women undergoing breast cancer surgery. The Cochrane Database of Systematic Reviews, 2(2), CD012968. https://doi.org/10.1002/14651858.CD012968.pub2	To assess the effects of paravertebral anaesthesia with or without sedation compared to general anaesthesia in women undergoing breast cancer surgery, with important outcomes of quality of recovery, postoperative pain at rest, and mortality.	Systematic Review	9 studies; 614 participants	The authors only reviewed RCTs in which paravertebral anesthesia (PPA) with or without sedation was compared to general anesthesia. PPA could not be used in conjunction with general anesthesia. Independent Variables = PPA or general anesthesia techniques. Dependent variables = quality of recovery, postoperative pain at rest and mortality.	Postoperative analgesic requirement Assessed with: number of patients who required postoperative analgesia [Follow-up: 1 day]Postoperative nausea and vomiting (PONV)Assessed with: number of patients who had persistent nausea or retching or vomiting requiring treatment [Follow-up: 1 day]Postoperative pain at 2 hours - Assessed with: VAS 0 to 10 scalePostoperative pain at 24 hours on rest - Assessed	P value Odds ratio Confidence Interval SWiM analysis Mean difference	PPA may reduce 24h postop analgesic use (61/1000 vs. 480/1000 in the GA group)Probably reduces the incidence of PONV (72/1000 vs. 340-1000)Probably reduces pain at 2 hours (by 2.95 points on a 0-10 pt. scale) and may reduce pain at 24h rest (0.21 pts. on a 0-10 pt. scale compared to GAMay reduce pain on movement at 6hrs and at 24hrs post surgery (at 6 hrs by 2.57 pts; at 24hrs by 2.12 pts. on a scale of	1

					with: 0 to 10 VAS scalePostoperative pain at 6 hours on movement - Assessed with: 0 to 10 VAS scalePostoperative pain at 24 hours on movement - Assessed with: 0 to 10 VAS scaleMortality		0-10) compared to GANo study reported on death with each anesthetic technique. No studies reported on disease-free survival, chronic pain or quality of life after breast CA surgery	
Cho, J. S., Lee, M.-H., Kim, S. I., Park, S., Park, H. S., Oh, E., Lee, J. H., & Koo, B.-N. (2017). The effects of perioperative anesthesia and analgesia on immune function in patients undergoing breast cancer resection: A prospective randomized study. International Journal of Medical Sciences, 14(10), 970-976. https://doi.org/10.7150/ijms.20064	To assess natural killer (NK) cell function in patients undergoing breast cancer surgery, comparing two different types of anesthetic techniques (propofol-remifentanil anesthesia with postoperative ketorolac analgesia vs. sevoflurane-remifentanil anesthesia with postoperative fentanyl anesthesia).	RCT	n = 50	Independent Variables: propofol-remifentanil anesthesia with postoperative ketorolac analgesia & sevoflurane-remifentanil anesthesia with postoperative fentanyl anesthesia Dependent Variables: NK cell cytotoxicity	Serum from the 50 patients was obtained prior to surgery and 24 hours after surgery. Post-surgical pain scores and inflammatory responses measured by WBC, neutrophil and lymphocyte counts were assessed. Cancer recurrence or metastasis was evaluated with ultrasound and whole-body bone	P value	The baseline NKCC (%) was comparable between the two groups (*P* = 0.082). Compared with the baseline value, NKCC (%) increased in the Propofol-ketorolac group [15.2 (3.2) to 20.1 (3.5), *P* = 0.048], whereas it decreased in the Sevoflurane-fentanyl group [19.5 (2.8) to 16.4 (1.9), *P* = 0.032]. The change of NKCC over time	2

					scan every 6 months for 2 years after surgery.		was significantly different between the groups (*P* = 0.048). Pain scores during 48 h after surgery and post-surgical inflammatory responses were comparable between the groups. One patient in the Sevoflurane-fentanyl group had recurrence in the contralateral breast and no metastasis was found in either group.	
Desmond, F., McCormack, J., Mulligan, N., Stokes, M., & Buggy, D.J. (2015). Effect of anaesthetic technique on immune cell infiltration in breast cancer: A follow-up pilot analysis of a prospective, randomised, investigator-masked study. *Anticancer Res. 2015 Mar*; *35*(3):1311-1319. PMID: 25750280.	This retrospective study assessed two groups of women undergoing breast cancer surgery. The first group had a propofol-paravertebral block for their anesthetic, the second group had a general anesthetic including volatile gases and opioids for pain control. The authors then interpreted the results by reviewing the patients' natural killer cells and T helper cell infiltration rates.	Retrospecti ve Study	n = 30	Independent Variables include: propofol-paravertebral block (PPA) or general anesthetic techniques. Dependent Variables include: immune cell infiltration including NK cells, CD4 cells, CD8 cells and CD68 cells (macrophages)	Breast cancer specimens from 30 patients previously enrolled in a randomized control trial were analyzed. The researchers compared Natural Killer cell and T helper cell infiltration between the two groups of patients.	P value	Propofol-paravertebral anesthetic with continuing analgesia (PPA) induces increased levels of NK cells and T helper cell infiltration into breast cancer tissue compared with GA but not T suppressor cells or macrophages.	3

Hovaguimian, F., Braun, J., Z'graggen, B. R., Schläpfer, M., Dumrese, C., Ewald, C., Dedes, K. J., Fink, D., Rölli, U., Seeberger, M., Tausch, C., Papassotiropoulos, B., Puhan, M. A., & Beck-Schimmer, B. (2020). Anesthesia and circulating tumor cells in primary breast cancer patients: A randomized controlled trial. *Anesthesiology, 133*(3), 548-558. https://doi.org/10.1097/ALN.0000000000003409	This randomized control trial compared a group of women receiving sevoflurane-based anesthesia versus propofol based anesthesia in breast cancer surgery. Circulating tumor cell counts were sampled from both groups.	RCT	n = 210	Independent Variables: sevoflurane anesthesia or propofol anesthesia Dependent Variable: circulating tumor cell counts	Serum from 210 subjects was analyzed at the end of surgery (0hrs), 48hrs after surgery and at 72 hours after surgery to analyze tumor cell counts overtime.	Interquartile range P value	In this randomized controlled trial investigating the effect of anesthesia on an independent prognostic factor for breast cancer, there was no difference between sevoflurane and propofol with respect to circulating tumor cell counts over time.	2
Hurtado, C. (2021). Anesthetic and analgesic influence on cancer recurrence and metastasis. *AANA Journal*, *89*(3), 221-226.	This expert opinion piece discusses the way that anesthetics may be harmful to the patient, causing immunosuppression and angiogenesis which may cause future cancer metastasis.	Expert Opinion	N/A	N/A	N/A	N/A	The author found that avoiding volatile anesthetics and using propofol-based TIVA, COX inhibitors, and regional anesthesia may prevent immune suppression; however, further research is needed to deter-mine the associated effects on cancer recurrence.	7

Jeong-Ae Lim, Chung-Sik Oh, Tae-Gyoon Yoon, Ji Yeon Lee, Seung-Hyun Lee, Young-Bum Yoo, Jung-Hyun Yang, & Seong-Hyop Kim. (2018). The effect of propofol and sevoflurane on cancer cell, natural killer cell, and cytotoxic T lymphocyte function in patients undergoing breast cancer surgery: an in vitro analysis. *BMC Cancer, 18*(1), 1-8. https://doi.org/10.1186/s12885-018-4064-8	This randomized control trial allocated women receiving breast cancer surgery into two groups - one group receiving propofol based anesthesia and the other receiving sevoflurane based anesthesia. The researchers then counted and detected apoptosis rates in cancer cell, NK cell and cytotoxic T lymphocyte counts for both groups.	RCT	n = 44	Independent Variables: sevoflurane anesthesia or propofol anesthesia Dependent Variable: apoptosis in cancer cells, NK cell and Cytotoxic T cells & changes in the cytokines tumor necrosis factor-alpha, interleukin (IL)-6 and IL-10	Venous blood samples were collected from the patients after inducing anesthesia and at 1 and 24h postoperatively in patients undergoing breast cancer surgery. 44 patients' serum was analyzed.	two-tailed *t*-test Mann-Whitney *U* test Friedman's test Chi-square test P value	This study revealed that propofol- and sevoflurane-based anesthesia during breast cell cancer surgery did not affect breast cancer cell, NK cell or CTL counts, or the rate of apoptosis.	2
Le-Wendling, L., Nin, O., & Capdevila, X. (2016). Cancer recurrence and regional anesthesia: The theories, the data, and the future in Outcomes. *Pain Medicine, 17*(4), 756-775. https://dx.doi.org/10.1111/pme.12893	The researchers of this article aimed to review recent literature and discuss how regional anesthesia may affect cancer metastasis rates.	Literature Review	N/A	Independent Variables: regional anesthesia techniques versus general anesthesia Dependent Variables: NK cell count and cancer metastasis rates	The researchers used the PubMed database using a variety of search terms regarding stress, surgery, and anesthetic techniques. A total of 30 human studies and 5 animal studies were included in the final review.	N/A	This study found that in vitro, animal, and human retrospective studies support the hypothesis that in certain types of cancer, regional anesthesia may be associated with lower recurrence rates.	8
Li, R., Liu, H., Dilger, J. P., & Lin, J. (2018). Effect of propofol on breast cancer cell, the immune system, and patient outcome. BMC Anesthesiology, 18(1), 1-8. https://doi.org/10.1186/s12871-018-0543-3	The researchers reviewed literature regarding propofol, breast cancer cells and immune cells. They aimed to discuss what current literature has shown regarding anesthetic practice and its affect on breast cancer cell biology, the immune system and postoperative pain.	Literature Review	N/A	N/A	The researchers used the PubMed database using the search terms "propofol" and "breast cancer." Their limitations included articles written in English.	N/A	The researchers found a positive correlation between the use of propofol and an increased NK cell function, however the evidence stopped here. Further research was warranted.	8

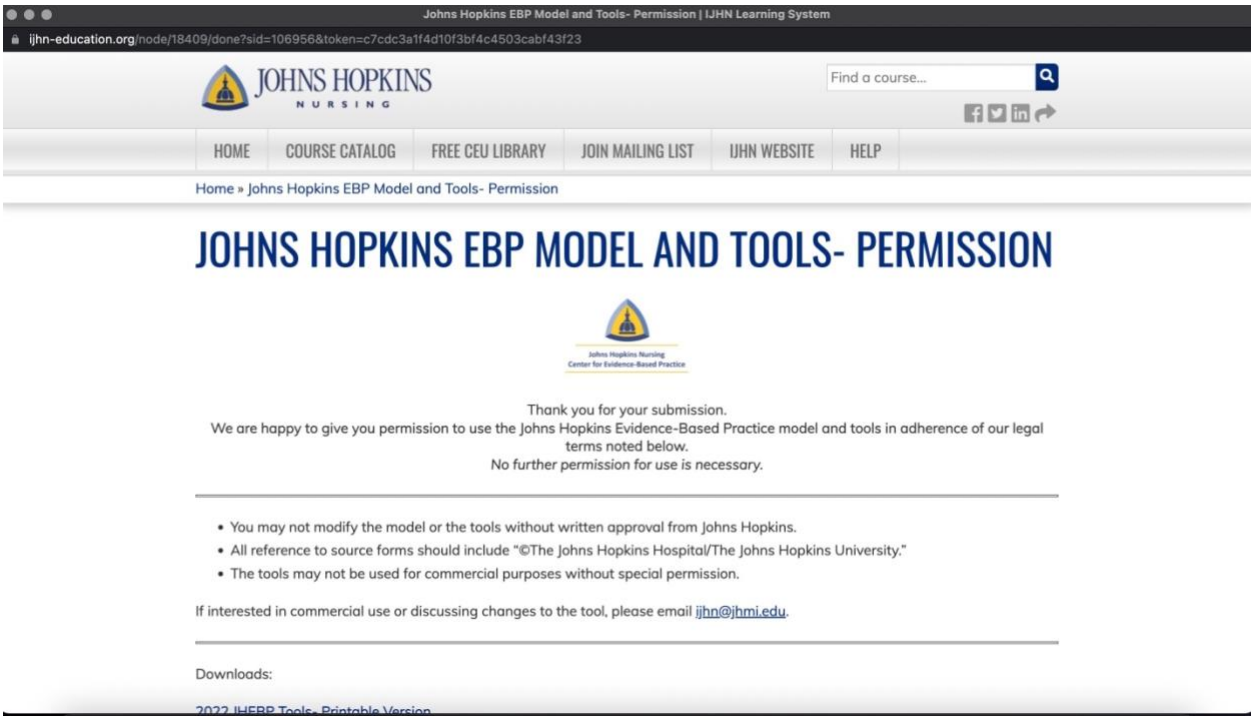
Oh, C.-S., Lee, J., Yoon, T.-G., Seo, E.-H., Park, H.-J., Piao, L., Lee, S.-H., & Kim, S.-H. (2018). Effect of equipotent doses of propofol versus sevoflurane anesthesia on regulatory T cells after breast cancer surgery. *Anesthesiology, 129*(5), 921-931. https://doi.org/10.1097/ALN.0000000000002382	Comparing propofol versus sevoflurane anesthesia and its effects on regulatory T cells (the cells that control NK cells) and their effect on patients/cancer progression and metastasis.	RCT	n = 201	Independent Variables: propofol-based versus sevoflurane-based anesthesia group Dependent Variables: cluster of differentiation 39 and 73 expression	The researchers reviewed the frequency of cluster of differentiation 39 and 73 expression on circulating regulatory T cells (primary outcome) and the frequency of circulating type 1 and type 17 helper T cells, natural killer cells, and cytotoxic T cells.	P value confidence interval [CI]	There was a "lack of a definitive conclusion regarding choice of propofol or sevoflurane for cancer surgery."	2
Pérez-González, O., Cuéllar-Guzmán, L. F., Soliz, J., & Cata, J. P. (2017). Impact of regional anesthesia on recurrence, metastasis, and immune response in breast cancer surgery: A systematic review of the literature. Regional Anesthesia & Pain Medicine, 42(6), 751-756. https://doi.org/10.1097/AAP.0000000000000662	To study the immune response of patients who received a paravertebral block for breast cancer surgery as well as recurrence and metastasis rates.	Systematic Review	15 studies	Independent Variables: paravertebral block with propofol based anesthesia versus sevoflurane-opioid anesthesia Dependent Variables: immune cell function, recurrence and metastasis rates	The researchers reviewed 15 articles which compared PVB-propofol anesthesia with sevoflurane-opioid anesthesia. The researchers then compared results of the studies which included incidence of metastatic spread, recurrence rate, immune cell function, apoptosis rates and cancer cell proliferation.	P value confidence interval [CI]	PVB does not reduce breast cancer recurrence or metastasis however it assists with inflammation and has improved immune response compared to GA & opioid-based anesthesia	1

Sessler, D. I., Pei, L., Huang, Y., Fleischmann, E., Marhofer, P., Kurz, A., Mayers, D. B., Meyer-Treschan, T. A., Grady, M., Tan, E. Y., Ayad, S., Mascha, E. J., & Buggy, D. J. (2019). Recurrence of breast cancer after regional or general anaesthesia: a randomised controlled trial. Lancet, 394(10211), 1807-1815. https://doi.org/10.1016/S0140-6736(19)32313-X	Breast cancer recurrence and incisional pain were evaluated comparing the use of regional anesthesia-analgesia (paravertebral block) versus traditional volatile anesthesia (sevoflurane) and opioids.	RCT	n = 2108	Independent Variables: regional anesthesia-analgesia (paravertebral block and propofol) versus general anesthesia (sevoflurane) and opioids Dependent Variables: breast cancer recurrence and incisional pain	The researchers trialed women undergoing breast cancer surgery in 13 hospitals across 8 countries over the course of 12 years; 2132 women were enrolled in the study, 24 excluded prior to surgery. 1065 were allocated to the general anesthesia group, 1043 were assigned to the regional anesthesia group. The patients were then followed at 6-month intervals until recurrence was reported, 5-6 years had elapsed, or study enrollment ended.	hazard ratio P value confidence interval [CI]	Regional anaesthesia-analgesia by paravertebral blocks and propofol did not reduce breast cancer recurrence after potential curative surgery compared with general anesthesia with the volatile anaesthetic sevoflurane and opioids for analgesia. The incidence and severity of persistent incisional breast pain was unaffected by anaesthetic technique.	2
Yan, T., Zhang, G.-H., Wang, B.-N., Sun, L., & Zheng, H. (2018). Effects of propofol/remifentanil-based total intravenous anesthesia versus sevoflurane-based inhalational anesthesia on the release of VEGF-C and TGF-β and prognosis after breast cancer surgery: A prospective, randomized and controlled study. *BMC Anesthesiology, 18*(1), 1-9. https://doi.org/10.1186/s12871-018-0588-3	Vascular endothelial growth factor (VEGF-C) and transforming growth factor-β were evaluated to determine tumor cell growth and metastasis in women undergoing breast cancer surgery. The subjects were divided into two groups - a propofol/remifentanil based total intravenous anesthesia (TIVA) group and a	RCT	n = 80	Independent Variables: propofol/remifentanil-based anesthesia versus sevoflurane-based anesthesiaDependent Variables: VEGF and TGF-β concentrations and cancer recurrence rates	Serum was drawn from the two groups of patients before surgery and 24 hours after surgery and VEGF-C and TGF-β concentrations were measured. Patients were then followed up for 2 years to evaluate recurrence-free survival (RFS) rates.	P value	In comparison with sevoflurane-based inhalational anesthesia, propofol/remifentanil-based total intravenous anesthesia can effectively inhibit the release of VEGF-C induced by breast surgery but didn't seem to be beneficial	2

	sevoflurane-based inhalational anesthesia group.						in the short-term recurrence rate of breast cancer.	

Appendix B

JHEBP Model Permission



OhioHealth	GUIDELINE DRAFT
TITLE: Evidence-Based Practice Guidelines for Female Patients Undergoing Anesthesia for Breast Cancer Surgery	**NUMBER:**
ISSUE DATE:	**EFFECTIVE DATE:**
DEVELOPED / REVISED BY: Alexa High, BSN, SRNA	
REVIEWED BY:	**DATE REVIEWED:**
APPROVED BY:	

SCOPE - This guideline is in effect for the following OhioHealth system business units: Grant Medical Center

STATEMENT OF PURPOSE:

The purpose of this guideline is to provide evidence-based practice recommendations regarding anesthesia for female breast cancer surgery patients. Breast cancer surgery patients are seen routinely in operating rooms across the nation. Evidence has shown that anesthetic agents have the potential to decrease natural killer cell rates and increase metastasis rates in breast cancer patients who undergo surgery as a treatment option. Selection of certain anesthetic agents may help prevent cancer spread or metastasis and increase natural killer cell rates. Selection of an appropriate anesthetic includes assessing the patient's indications and contraindications, risks and benefits, type of breast cancer surgery and institution of corrective measures to address for any complications. Consideration generally includes:

a) Obtaining appropriate pre-op assessment of the patient
b) Addressing patients' consents and surgeons' preferences
c) Availability and cost of pain adjuncts and local anesthetics
d) Technical aspect of providing a paravertebral nerve block
e) Availability of medications to address any potential complications
f) Availability of anesthesiologists or CRNAs to address complications

DEFINITIONS:

- **Natural killer cells:** a type of immune cell that contains enzymes which can kill tumor cells or cells infected with a virus
- **Metastasis:** development of secondary malignant growths located separately from the primary site of cancer
- **Paravertebral block:** a peripheral nerve block performed by injecting local anesthetic into the thoracic paravertebral space

POLICY:

The guideline applies to female breast cancer patients undergoing surgery for breast cancer and assists anesthesia providers in the selection, administration, and management of anesthesia for this patient population. It is intended to provide the most current, relevant evidence-based practice without guaranteeing a specific patient outcome. This guideline is not a substitute for clinical judgement, and it does not establish legally enforceable requirements or responsibilities.

Appendix C

GUIDELINE

1. Intravenous Access
    a. One to two large bore peripheral IVs, two if arms are being tucked for procedure
2. **Paravertebral Block**
    a. Dose:
        i. 25mL of 0.5% ropivacaine
        ii. PPV block should be completed at thoracic levels 1 through 5 using ultrasound guidance with 5mL of local anesthetic placed at each level.
        iii. 1-2mg of Versed may be given prior to the block for patient comfort; avoid use of fentanyl.
    b. Type:
        i. Ropivacaine is the recommended type of local anesthetic:
            1. Rationale for recommending Ropivacaine:
                a. Ropivacaine has a high potency and long duration of action
                b. Ropivacaine has a lower risk of cardiac toxicity versus bupivacaine.
                c. Ropivacaine is less lipophilic than bupivacaine and is cleared more rapidly in the liver
        ii. Bupivacaine and/or lidocaine and ropivacaine combinations can also be used
    c. Recommended criteria:
        i. Common inclusion criteria:
            1. Patients between the ages of 18-65 years old, those with ASA scores between I and III, and those receiving primary breast cancer surgery
        ii. Common exclusion criteria:
            1. Allergy to amide local anesthetic
3. **Anesthetic Selection**
    a. Recommended Medications:
        i. Lidocaine
        ii. Propofol
        iii. Rocuronium
        iv. Neostigmine
        v. Glycopyrrolate
        vi. Ketorolac
        vii. Ofirmev
    b. Route:
        i. Intravenous
    c. Dose:
        i. Lidocaine: 1 mg/kg can be given prior to propofol to help with IV pain of propofol and to blunt cardiovascular response to laryngoscopy
        ii. Propofol:
            1. Initial induction dose of propofol should be 1-2 mg/kg
            2. Once endotracheal intubation is achieved, a maintenance drip (Total Intravenous Anesthesia/TIVA) of propofol should be continued. The maintenance rate should be started at 100mcg/kg/min and titrated in increments of 10mcg/kg/min to achieve a Bispectral Index Score of 40-60.
        iii. Rocuronium: 0.6 – 1.2 mg/kg should be utilized for muscle paralytic prior to endotracheal intubation
            1. Should the patient necessitate, or the surgeon request continued paralytic throughout the case, Rocuronium should be re-dosed at 0.1mg/kg.
        iv. Neostigmine:
            1. 0.02-0.08 mg/kg with a maximum of 5mg for paralytic reversal
        v. Glycopyrrolate:
            1. 0.2 mg per 1mg of Neostigmine should be given to prevent bradycardia

vi. Ketorolac
    1. 60mg on emergence should be given for pain management
vii. Ofirmev
    1. 1000 mg IV q6hr, not to exceed 4g/day in recovery

d. Recommended criteria:
    i. Common inclusion criteria:
        1. Patients between the ages of 18-65 years old, those with ASA scores between I and III, and those receiving primary breast cancer surgery
    ii. Common exclusion criteria:
        1. Allergy to any of the medications listed above; should the patient have a strong response to pain, or an unsuccessful paravertebral block and the patient necessitates opioids the patient can be switched to a general anesthetic.

REFERENCES:

American Cancer Society. (n.d.). *Breast Cancer Treatment | Treatment Options for Breast Cancer*. Retrieved February 22, 2023, from https://www.cancer.org/cancer/breast-cancer/treatment.html

American Cancer Society. (2023, January 12). *Breast Cancer Statistics | How Common Is Breast Cancer?* Retrieved February 22, 2023, from https://www.cancer.org/cancer/breast-cancer/about/how-common-is-breast-cancer.html

Blanco, R., & Barrington, M. J. (2022, April 26). *Pectoralis and Serratus Plane Nerve Blocks*. NYSORA. Retrieved February 22, 2023, from https://www.nysora.com/topics/regional-anesthesia-for-specific-surgical-procedures/thorax/pectoralis-serratus-plane-blocks/

Buckley, A., McQuaid, S., Johnson, P., & Buggy, D. J. (2014). Effect of anaesthetic technique on the natural killer cell anti-tumour activity of serum from women undergoing breast cancer surgery: A pilot study. *BJA: The British Journal of Anaesthesia*, 113, i56-i62. https://doi.org/10.1093/bja/aeu200

Calculating Medical Malpractice Settlement Damages. (2022, February 23). The Knowles Group. Retrieved September 11, 2022, from https://www.theknowlesgroup.org/blog/calculating-medical-malpractice-settlement-damages/#:%7E:text=The%20average%20medical%20malpractice%20settlement,out%2Dof%2Dpocket%20expenses.

Chaplin D. D. (2010). Overview of the immune response. *The Journal of allergy and clinical immunology*, 125(2), S3–S23. https://doi.org/10.1016/j.jaci.2009.12.980

Chen, W. K., & Miao, C. H. (2013). The effect of anesthetic technique on survival in human cancers: a meta-analysis of retrospective and prospective studies. *PloS one*, *8*(2), e56540. https://doi.org/10.1371/journal.pone.0056540

Cheng, G. S., & Ilfeld, B. M. (2016). An Evidence-Based Review of the Efficacy of Perioperative Analgesic Techniques for Breast Cancer-Related Surgery. *Pain Medicine*, pnw172. https://doi.org/10.1093/pm/pnw172

Chhabra, A., Roy Chowdhury, A., Prabhakar, H., Subramaniam, R., Arora, M. K., Srivastava, A., & Kalaivani, M. (2021). Paravertebral anaesthesia with or without sedation versus general anaesthesia for women undergoing breast cancer surgery. *The Cochrane Database of Systematic Reviews, 2*(2), CD012968. https://doi.org/10.1002/14651858.CD012968.pub2

Cho, J. S., Lee, M.-H., Kim, S. I., Park, S., Park, H. S., Oh, E., Lee, J. H., & Koo, B.-N. (2017). The effects of perioperative anesthesia and analgesia on immune function in patients undergoing breast cancer resection: A prospective randomized study. *International Journal of Medical Sciences, 14*(10), 970-976. https://doi.org/10.7150/ijms.20064

Dang, D., Dearholt, S., Bissett, K., Ascenzi, J., & Whalen, M. (2022). Johns Hopkins evidence-based practice for nurses and healthcare professionals: Model and guidelines. 4th ed. Sigma Theta Tau International

Desmond, F., McCormack, J., Mulligan, N., Stokes, M., & Buggy, D.J. (2015). Effect of anaesthetic technique on immune cell infiltration in breast cancer: A follow-up pilot analysis of a prospective, randomised, investigator-masked study. *Anticancer Res. 2015 Mar*; *35*(3):1311-1319. PMID: 25750280.

Elisha, S., Heiner, J. S., & Nagelhout, J. J. (2022). *Nurse Anesthesia* (7th ed.). Saunders.

Elshanbary, A. A., Zaazouee, M. S., Darwish, Y. B., Omran, M. J., Elkilany, A. Y., Abdo, M. S., Saadeldin, A. M., Elkady, S., Nourelden, A. Z., & Ragab, K. M. (2021). Efficacy and safety of pectoral nerve block (pecs) compared with control, paravertebral block, erector spinae plane block, and local anesthesia in patients undergoing breast cancer surgeries: A systematic review and meta-analysis. *Clinical Journal of Pain, 37*(12), 925-939. https://doi.org/10.1097/AJP.0000000000000985

Fancellu, A., Perra, T., Ninniri, C., Cottu, P., Deiana, G., Feo, C. F., & Porcu, A. (2020). The emerging role of pectoral nerve block (PECS block) in breast surgery: A case-matched analysis. *Breast Journal, 26*(9), 1784-1787. https://doi.org/10.1111/tbj.13939

Heaney, A., & Buggy, D. J. (2012). Can anaesthetic and analgesic techniques affect cancer recurrence or metastasis?. *British journal of anaesthesia*, *109 Suppl 1*, i17–i28. https://doi.org/10.1093/bja/aes421

Hovaguimian, F., Braun, J., Z'graggen, B. R., Schläpfer, M., Dumrese, C., Ewald, C., Dedes, K. J., Fink, D., Rölli, U., Seeberger, M., Tausch, C., Papassotiropoulos, B., Puhan, M. A., & Beck-Schimmer, B. (2020). Anesthesia and circulating tumor cells in primary breast cancer patients: A randomized controlled trial. *Anesthesiology, 133*(3), 548-558. https://doi.org/10.1097/ALN.0000000000003409

Hurtado, C., Bendure, J., & Bennetts, P. (2021). Anesthetic and Analgesic Influence on Cancer Recurrence and Metastasis. *AANA journal*, *89*(3), 221–226.

Jeong-Ae Lim, Chung-Sik Oh, Tae-Gyoon Yoon, Ji Yeon Lee, Seung-Hyun Lee, Young-Bum Yoo, Jung-Hyun Yang, & Seong-Hyop Kim. (2018). The effect of propofol and sevoflurane on cancer cell, natural killer cell, and cytotoxic T lymphocyte function in patients undergoing breast cancer surgery: an in vitro analysis. *BMC Cancer, 18*(1), 1-8. https://doi.org/10.1186/s12885-018-4064-8

Karmakar, M. K., Greengrass, R. A., Latmore, & Levin, M. (2022, May 3). *Thoracic and Lumbar Paravertebral Block – Landmarks and Nerve Stimulator Technique*. NYSORA. Retrieved February 22, 2023, from https://www.nysora.com/topics/regional-anesthesia-for-specific-surgical-procedures/abdomen/thoracic-lumbar-paravertebral-block/

Le-Wendling, L., Nin, O., & Capdevila, X. (2016). Cancer recurrence and regional anesthesia: The theories, the data, and the future in Outcomes. *Pain Medicine, 17*(4), 756-775. https://dx.doi.org/10.1111/pme.12893

Li, R., Liu, H., Dilger, J. P., & Lin, J. (2018). Effect of propofol on breast cancer cell, the immune system, and patient outcome. *BMC Anesthesiology, 18*(1), 1-8. https://doi.org/10.1186/s12871-018-0543-3

McCance, K. L., & Huether, S. E. (2014a). Innate Immunity. *Pathophysiology: The Biologic Basis for Disease in Adults and Children* (7th ed.). Elsevier Health Sciences. 191-223.

McCance, K. L., & Huether, S. E. (2014b). Adaptive Immunity. *Pathophysiology: The Biologic Basis for Disease in Adults and Children* (7th ed.). Elsevier Health Sciences. 224-261.

Melnyk, B. M., & Fineout-Overholt, E. (2019). *Evidence-Based Practice in Nursing & Healthcare, International Edition* (4th ed.). Wolters Kluwer.

Moran, K. J., Burson, R., & Conrad, D. (2019). *The Doctor of Nursing Practice Project: A Framework for Success* (3rd ed.). Jones & Bartlett Learning.

Nagelhout, J. J., & Elisha, S. (2017). *Nurse Anesthesia, 6e* (6th ed.). Saunders.

Oh, C.-S., Lee, J., Yoon, T.-G., Seo, E.-H., Park, H.-J., Piao, L., Lee, S.-H., & Kim, S.-H. (2018). Effect of equipotent doses of propofol versus sevoflurane anesthesia on regulatory T cells after breast cancer surgery. *Anesthesiology, 129*(5), 921-931. https://doi.org/10.1097/ALN.0000000000002382

Pérez-González, O., Cuéllar-Guzmán, L. F., Soliz, J., & Cata, J. P. (2017). Impact of regional anesthesia on recurrence, metastasis, and immune response in breast cancer surgery: A systematic review of the literature. *Regional Anesthesia & Pain Medicine, 42*(6), 751-756. https://doi.org/10.1097/AAP.0000000000000662

Sanders R.D. & Maze, M. (2011). Anesthetic Pharmacology: Basic Principles and Clinical Practice. Cambridge University Press. 478-492. https://doi.org/10.1017/CBO9780511781933.031

Sessler, D. I., Pei, L., Huang, Y., Fleischmann, E., Marhofer, P., Kurz, A., Mayers, D. B., Meyer-Treschan, T. A., Grady, M., Tan, E. Y., Ayad, S., Mascha, E. J., & Buggy, D. J. (2019). Recurrence of breast cancer after regional or general anaesthesia: a randomised controlled trial. *Lancet, 394*(10211), 1807-1815. https://doi.org/10.1016/S0140-6736(19)32313-X

Shapiro, J., Jersky, J., Katzav, S., Feldman, M., & Segal, S. (1981). Anesthetic drugs accelerate the progression of postoperative metastases of mouse tumors. *The Journal of clinical investigation*, *68*(3), 678–685. https://doi.org/10.1172/jci110303

Singleton P.A., & Moss J. (2010). Effect of perioperative opioids on cancer recurrence: A hypothesis. *Future Oncology, 6*(8), 1237-1242. https://doi.org/10.2217/fon.10.99

Solt, K., & Forman, S. A. (2007). Correlating the clinical actions and molecular mechanisms of general anesthetics. *Current opinion in anaesthesiology*, 20(4), 300–306. https://doi.org/10.1097/ACO.0b013e32816678a5

Stokes, M. E., Thompson, D., Montoya, E. L., Weinstein, M. C., Winer, E. P., & Earle, C. C. (2008). Ten-year survival and cost following breast cancer recurrence: estimates from SEER-medicare data. *Value in health: the journal of the International Society for Pharmacoeconomics and Outcomes Research*, *11*(2), 213–220. https://doi.org/10.1111/j.1524-4733.2007.00226.x

Welden B., Gates G., Mallari R., & Garrett N. (2009). Effects of anesthetics and analgesics on natural killer cell activity. *AANA Journal*, *77*(4), 287-292.

Yan, T., Zhang, G.-H., Wang, B.-N., Sun, L., & Zheng, H. (2018). Effects of propofol/remifentanil-based total intravenous anesthesia versus sevoflurane-based inhalational anesthesia on the release of VEGF-C and TGF-β and prognosis after breast cancer surgery: A prospective, randomized and controlled study. *BMC Anesthesiology, 18*(1), 1-9. https://doi.org/10.1186/s12871-018-0588-3

Yeager M.P., & Rosenkranz K.M. (2010). Cancer recurrence after surgery: a role for regional anesthesia? *Regional Anesthesia & Pain Medicine, 35*(6), 483-484. https://doi.org/10.1097/AAP.0b013e3181fa11a9