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Total Intravenous Anesthesia to Reduce Metastasis and Recurrence Rates in Patients Presenting for Breast Cancer Surgery: An Educational Intervention

A DNP Project Presented to the Faculty of the
Nicole Wertheim College of Nursing and Health Sciences

Florida International University

In partial fulfillment of the requirements
for the Degree of Doctor of Nursing Practice

By

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Table of Contents

Abstract

Background: Surgical intervention for breast malignancy is the treatment of choice for the breast cancer patient population. Extensive research has established the correlation between the mode of anesthetic delivery and breast cancer recurrence and metastasis in patients undergoing surgical intervention for breast cancer. Researchers have identified the implications of volatile anesthetic agents (VAA), or inhalational agents, on the suppression of the immune response throughout the perioperative period; thus, cultivating an environment that is ideal for cancer cell proliferation, migration, and eventual metastasis via systemic circulation. Although the standardization of the anesthetic management for this patient population has not been declared, total intravenous anesthesia (TIVA) has been identified as the optimal anesthetic method to reduce the risk of breast cancer recurrence and metastasis in patients undergoing breast surgery, due to the immunologic protectant effects proffered by the drugs utilized in TIVA anesthetic administration.

Methods: PubMed, Google Scholar, and the Cumulative Index of Nursing and Allied Health Literature (CINAHL) search engines were accessed via the Florida International University (FIU) library database to compose a comprehensive search for peer-reviewed research studies within the last 10 years that examined the effects of VAA or TIVA anesthetic on breast cancer recurrence and metastasis in patients undergoing surgical intervention for breast cancer.

Results: Eight high-level research articles were selected for appraisal and inclusion of this review due to novelty and relevance. The articles included in this review evaluate the long-term effects of VAA or TIVA anesthetic delivery on breast cancer recurrence and metastasis in the breast cancer patient surgical population and identify the existing research-to-practice gap that must be addressed in the anesthesia community to yield the best possible outcomes for the aforementioned target population.

Conclusion: Current evidence-based research has illuminated the impactful role that anesthesia providers may have on the long-term outcomes of patients with breast malignancy presenting for surgical intervention via the selection of a TIVA-based anesthetic approach. It is anticipated that the implementation of a QI project will enhance the anesthesia providers' capacity to improve the quality of life and reduce the risk of life-altering implications with the selection of their anesthetic approach in breast cancer patients.

Keywords: Inhalational Agents, Volatile Anesthetic Agents, Breast Cancer Surgery, Breast Cancer Recurrence, Breast Cancer Metastasis, Total Intravenous Anesthesia

I. Introduction

Problem Identification

Breast malignancy is one of the most prevalent and aggressive forms of cancer that continues to usurp the lives of a vast number of women in the United States (US). Documented as the second most common form of cancer and leading cause of cancer-related mortality among women in the US, up to 284,200 new cases of breast cancer diagnoses and approximately 44,000 breast cancer associated deaths occur in the US each year.[1-2] Metastasis is documented as the primary culprit for mortality in the breast cancer patient population with alarming statistics as high as 25%.[3-6] As breast malignancy diagnoses persist in a steady state, the number of women undergoing surgical resection of breast malignancies to manage their diagnosis have paralleled as the recommended treatment; thus, presenting anesthesia providers with the dilemma of selecting an anesthetic technique that can maximize the resistance to breast cancer cell proliferation.

Current research suggests that the perioperative anesthetic technique of a patient undergoing breast cancer surgery may be associated with cancer recurrence and metastasis through varying mechanisms that may potentiate or mitigate the spread of cancerous cells, particularly the administration of volatile anesthetic agents (VAA) compared with total intravenous anesthesia (TIVA), respectively.[3, 7-13] Although many high-level studies have demonstrated the direct and indirect benefits of utilizing TIVA to reduce the prevalence of cancer recurrence and metastasis in patients who underwent surgical interventions for breast malignancy, the standardization of a TIVA-based anesthetic approach for the aforementioned patient population to eradicate the risk of recurrence has not been established.[3, 7-13] As on-going

comprehensive research continues to solidify the existing evidence that connects TIVA technique to a reduction in cancer recurrence in breast cancer patients to pave the way for a gold standard of anesthetic care, it is the responsibility of anesthesia providers to keep abreast modern clinical findings and tailor the anesthetic approach to optimize this patient population and provide a favorable long-term outcome based on available evidence.[14]

Implementation of a TIVA-based anesthetic technique in the breast cancer patient population is pivotal to anesthetic practice, as the choice of anesthetic may determine the difference between a subsequent cancer diagnosis or a cancer-free life for breast cancer survivors post-surgical intervention.[7] The aim of this Quality Improvement project is to enhance the knowledge of anesthesia providers regarding the correlation between TIVA and reduced breast cancer recurrence and metastasis compared with VAA via a comprehensive educational module to initiate a paradigm shift in the anesthetic management of surgical patients with breast cancer presenting for surgery.

Background

Surgical intervention is considered a curative method for breast cancer; however, it is well-documented that resection of malignant tissue during breast surgery is associated with systemic proinflammatory alterations that support cancer cell proliferation, a precursor for recurrence and metastasis.[7,9] Additional research has linked various anesthetic agents and techniques to the promotion or prevention of the various immunologic and inflammatory systemic responses to surgical stress that are responsible for cancer metastasis.[3-7] Understanding the mechanisms by which cancer cells thrive, as well as, the body's natural immunologic defense is a critical component to grasping the severity of anesthesia technique in relation to long-term outcomes in patients presenting for breast cancer surgery.

Similar to healthy cell tissue, malignant cells rely on nutrients from blood supply that is provided from adjacent vasculature.[6] Increased nutrients requirements results in the activation of angiogenesis by cancer cells via stimulation of vascular endothelial growth factor (VEGF) and prostaglandin E_2 (PGE2) to create additional circulation pathways; thus, an increase in perfusion to the malignant tissue.[6,9] Malignant cell-mediated angiogenesis coupled with the embolization of upregulated cancer cells facilitates migration of the cancerous cells to localized and distal regions via the circulatory and lymphatic systems.[6] A vicious cycle of cancer cell nutrient requirements, proliferation, angiogenesis, and mobilization persists as malignant cells invade healthy tissue, resulting in increased severity of the cancer and metastasis to other organs.[5-6,9,17]

In response to the physiological changes produced by the cancerous cells, the body activates a cell-mediated immune response within the circulatory and lymphatic systems that involves the recruitment of white blood cells (WBCs) to combat cancerous cells through identification and destruction.[6,17] Natural Killer (NK) cells are cytotoxic lymphocytes that are vital to and primarily responsible for the body's natural line of defense against malignancy.[6-7,10,17] The NK cytotoxicity against tumor cells is strengthened by the presence of interleukins, or proinflammatory cytokines; however, interleukins have the capacity to promote stimulation of cancer cell proliferation, angiogenesis, and metastasis of cancerous tissue, as well as immunologic resistance.[6,17] Additionally, catecholamines are often released in the body's response to stress and have demonstrated inhibition of cancer-fighting NK cells.[17]

The aforementioned physiology of cancer cell proliferation response is further exacerbated by surgical and anesthetic conditions.[3] Research suggests that surgical resection of cancerous tissue results in metastasis due to the inadvertent shedding of malignant cells via the systemic vasculature. Additional immunosuppressive responses secondary to surgical conditions

that promote metastasis during the perioperative period include sympathetic nervous system (SNS) stimulation, pain, hypovolemia, hypoxia, and hypotension; most of these responses can be blunted or corrected with careful anesthetic intervention by the anesthesia provider.[17]

Several studies have identified a time-sensitive and dose-dependent immunosuppressive effects of VAA on NK cells and lymphocytes. Suppression of NK cell activity cultivates an environment that favors an increased risk for cancer cell proliferation, as the body is unable to combat the circulating cancerous cells exacerbated by tumor resection intraoperatively.[3,6-7,12-13,16] Various studies have evaluated the effects of VAA on immunologic suppression compared with TIVA and identified an increase in breast cancer cell proliferation, migration, and decreased immunologic response in patients that received VAA anesthesia.[3,7-13,19] In fact, TIVA-based anesthetic demonstrated an increase in NK cell response and suppressed malignant cell metastasis in vitro.[3-4,7-13,16-17,19] In a recent study by Yan et al, propofol-based TIVA was also associated with decreased cyclooxygenase-2 (COX-2) activity, which is a foundational component to the production of the aforementioned tumor-progression hormone, PGE_2.[11]

MicroRNAs (miRNAs), single-stranded, noncoding RNA molecules, which are responsible for transcriptional gene regulation have also been identified as tumor suppressants via various mechanisms of cell biology.[4-5,18] Researchers have identified that anesthetic agents may directly or indirectly modulate cancer cell biology pathways, as well as, anti-cancer immunity via alterations in miRNA expression.[4,18] MiRNA is critical to the control of cell proliferation, inflammation, and metabolism; therefore, anesthetic management may have serious implications on the malignant cell activity in the perioperative period. For example, Ishikawa et al compared the effects of VAA and TIVA on miRNA expression in rats, which highlighted the pro-cancer effects of VAA on miRNA expression.[18]

Given the available evidence, the choice of anesthetic may have serious implications that impact the long-term outcomes in the breast cancer patient population. Anesthesia providers are in the unique position to tailor an anesthetic plan of care that may influence the future of patients presenting for breast cancer surgery; it is prudent to bridge the gap between new research and current anesthetic practice to optimize this patient population and contribute to a paradigm shift toward proactive cancer management in reducing breast cancer reoccurrence and metastasis.

Scope of the Problem

According to the American Cancer Society,[2] the estimated number of new invasive breast cancer diagnoses in women in the US is approximately 281,550 for the current year, 2021. Compared to previous years, the incidence of breast cancer has continued to climb steadily at a rate of 0.5% despite advancements in breast malignancy detection and treatment.[2] Breast cancer is a death sentence for 1 in 39 women, or 2.6%, which mirrors the American Cancer Society's estimated 43,600 incidences of breast malignancy-associated deaths projected in 2021.[2] Compared to the most recent Centers for Control and Disease (CDC) annual breast cancer case report in 2018, breast cancer diagnoses have increased by 26,806 in the US in less than three years.[15] Breast cancer survival and recurrence rates are monitored over a 5-year period, as recurrence is probable depending on the severity of the breast cancer in relation to location and metastasis to other tissues; proliferation of malignant breast cells is associated with as low as a 28% survival rate.[2]

The physiological stress response activated during surgery poses many risk factors that determine the behavior of cancerous cells and immunologic cell function; for example, surgical resection of malignant tissue may potentiate the proliferation and circulation of tumor cells

resulting in residual cancer and a consequential increased risk for recurrence.[10] Various anesthetic agents, such as VAA and opioids have been implicated in impairing immunologic function and contributing to cancer metastasis via inhibition of the immunocompetent cells, which are vital to the modulation of the stress response elicited in surgery.[3-4,6-9,11-13] TIVA anesthetic coupled with a multi-modal approach has demonstrated preservation of immunocompetent cell function, which is responsible for the resistance to cancer cell implantation, a well-documented precursor to cancer metastasis. [3-5, 7-13] The aforementioned statistics and existing knowledge regarding the altered behavior of immunologic function secondary to anesthetic method underscores the necessity for anesthesia providers to adopt anesthetic techniques that have demonstrated a reduced risk in breast cancer cell proliferation and associated recurrence; however, a knowledge deficit regarding the anesthetic management of patients presenting for breast cancer surgery persists.

Consequences of the Problem

Millions of cancer-related deaths occur each year, primarily as a result of recurrence or metastasis.[1-2,4] While research regarding cancer prevention and treatment is a continual feat of trial and error in the healthcare arena, it is crucial for all interdisciplinaries to take ownership for their potential role in cancer prevention as it relates to modifiable risk factors. Growing evidence demonstrates a correlation between various anesthetic techniques and recurrence in breast cancer patients presenting for breast surgery, which highlights the critical role that the anesthesia provider may have in optimizing the long-term outcomes of this patient population via their anesthesia plan of care. [3-4,6-9,11-13] Breast cancer morality is primarily associated with breast cancer recurrence and metasasis; therefore, identification of methods for recurrence preventions is critical to reduce mortality rates in this patient population. Given that high-quality research has

implicated the definitive association between VAA and opioid anesthetic techniques with recurrence and metastasis in breast cancer patients, an educational module that presents the optimal technique to mitigate recurrence and metastasis is warranted to allow anesthesia providers to be proactive in providing evidenced based medicine in utilizing the current empirical evidence. [3-4,6-9,11-13] Informing anesthesia providers of the benefits of implementing a TIVA-based anesthetic plan of care to reduce the risk of recurrence and metastasis in breast cancer patients presenting for surgical intervention can lead to a pivotal break-through in the anesthetic management, as well as, a potential life-changing advancement in healthcare.

Knowledge Gaps

Although various studies have evaluated the effects of anesthetic management on breast cancer recurrence and metastasis, knowledge gaps have been identified and have delayed the standardization of the anesthetic care. In 2019, Yap and colleagues conducted a meta-analysis to evaluate the current research regarding the correlation between anesthetic technique and cancer outcomes, which included eight studies.[20] Six of the eight studies evaluated the effects of anesthetic agent on recurrence-free survival following breast, esophageal, and non-small cell lung cancer, while all eight studies examined the effects of anesthetic agents on overall cancer survival.[20] In all eight studies, TIVA-based anesthesia was associated with improved recurrence-free survival and/or improved overall cancer survival, indicating TIVA is the anesthetic of choice for cancer patients presenting for surgery.[20]

Although Yap and colleagues identified a positive correlation between TIVA and optimal cancer patient outcomes, the researchers acknowledged that a propensity toward VAA anesthesia exists in the anesthesia arena and TIVA is rarely utilized.[20] Anesthesia provider preference for VAA administration has taken precedence over existing data, as a result of conflicting

conclusions of some studies.[20] Additional knowledge gaps that have impacted the standardization of anesthetic management in breast cancer patients includes the unknown molecular mechanisms behind the clinical findings that associate anesthetics with direct and indirect immunomodulation and cellular effects.[5] Equally challenging, the lack of randomized control trials in comparison to retrospective analysis studies complicates and delays the translation of current research to standardized anesthetic management .[20]

Proposed Solution

Currently, there is no standardized anesthetic plan of care for the management of patients undergoing surgical intervention for breast malignancy despite existing research that has connected breast cancer metastasis and recurrence with VAA technique; therefore, anesthesia providers continue to incorporate VAA and other anesthetic agents with propensity to cancer cell proliferation into their anesthesia regimen. TIVA-based anesthetic proffers a higher probability of favorable long-term, recurrence-free outcomes and an educational module should be presented to anesthesia providers in an effort to shift the anesthetic plan of care for this vulnerable patient population.

The prevalence and fatal effects of breast cancer metastasis necessitates the identification for preventative methods; the standardization of an anesthetic approach to minimize the risk of recurrence and metastasis in breast cancer patients is paramount. The aforementioned studies underscore that the administration of TIVA-based anesthesia to breast cancer patients undergoing breast surgery resists tumor cell proliferation and yields an associated reduced rate of metastasis, compared to patients that receive a VAA-based anesthetic.[3-13,16-20] TIVA anesthetic technique in patients with breast malignancy is the most efficacious, safest anesthetic method to optimize the long-term outcomes of breast cancer patients via the reduction in recurrence and

metastasis and the ultimate quality of life. It is anticipated that the positive implications of TIVA-based anesthesia on long-term patient outcomes will reflect life-saving advancements and a standardization of anesthetic management for the breast cancer patient population with the adoption of a TIVA approach; therefore, an educational module will inform anesthesia providers and position them as leaders at the forefront of breast cancer surgery to utilize the best empirical evidence and reduce the potential for breast cancer reoccurrence and metastasis through anesthetic delivery.

Objective, Purpose, and PICO Question

The purpose of this literature review is to thoroughly analyze current research that elucidates the probable benefits of a TIVA-based anesthetic approach, compared with VAA, to prevent breast cancer recurrence and metastasis; thus, promoting favorable long-term outcomes in breast cancer patients undergoing surgical intervention. Currently, there is no standardized anesthetic plan of care for the management of patients undergoing surgical intervention for breast malignancy despite various high-level studies that have connected breast cancer metastasis with VAA technique; therefore, anesthesia providers continue to incorporate VAA and other anesthetic agents with propensity to cancer cell proliferation into their anesthesia regimen, respectively. This literature critique aims to close the existing research and knowledge-to-clinical practice gap in the anesthesia realm with emphasis on the adoption of a TIVA-based anesthetic approach to proffer a higher probability of favorable long-term, recurrence-free outcomes in patients with breast malignancy presenting for breast surgery. In congruence with the primary objectives of this literature review, the ultimate goal of this quality improvement initiative is to cultivate a positive cultural transformation in regard to the anesthesia providers' knowledge and attitude in the anesthetic care of this vulnerable patient population.

The following PICO (Population, Intervention, Comparison, and Outcome) question was formulated based on elements depicted by Dang & Dearholt[21] to evaluate this topic: (P) In anesthesia providers (I) does an educational module on the utilization of a TIVA-based anesthetic approach and avoidance of Volatile Anesthetic Agents (VAA) to reduce breast cancer recurrence and metastasis (C), compared to no educational module (O) improve the knowledge and attitude regarding the anesthetic management of patients presenting for breast cancer surgery? The population involved in this topic includes patients with breast malignancy that underwent radical mastectomy, while the intervention will incorporate the delivery of one of two anesthetic methods, TIVA or VAA, utilized for the surgical procedure of those in the investigative population. The effects of immunologic suppression and cancer cell proliferation, as well as, recurrence and metastasis rates will be compared for each group and the respective outcomes will be evaluated based on recurrence and metastasis occurrence. The aforementioned question will be thoroughly examined through the literature appraisal and analysis of eight fundamental peer-reviewed research articles.

II. Literature Search Methodology

Eligibility Criteria

The peer-reviewed articles included in this literature review were elected through careful consideration of exclusion and inclusion criteria established to best delineate the previously outlined objectives. Articles written within the English language published within the last ten years with full-text availability were considered for evaluation. Articles were eliminated for underwhelming sample size, insufficient relevance to the topic, focus on regional anesthetic technique and other anesthetic drugs extraneous to TIVA or VAA administration, or omission of discussion regarding the relationship of anesthetic technique to suppression of the immunologic

response. Inclusion criteria comprised of studies that accentuated the direct effects of VAA and/or TIVA based anesthetic methods for patients with breast cancer presenting for surgical intervention and their subsequent influence on NK cell suppression and cancer cell dissemination and implantation, as evidence by markers and recurrence rates. The Florida International University (FIU) Library Database was utilized to access professional search engines to conduct research congruent with the clinical question. The following key terms were exercised in a comprehensive search with the proper Boolean operators and search symbols: Inhalational Agents, Volatile Anesthetic Agents, Breast Cancer Surgery, Breast Cancer Recurrence, Breast Cancer Metastasis, and Total Intravenous Anesthesia.

Information Sources

The Cumulative Index of Nursing and Allied Health Literature (CINAHL), Google Scholar, and PubMed search engines were accessed via the Florida International University (FIU) library database to compose comprehensive research. The literature review and study selection were further directed and confined by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Search Strategy

The keyword search conducted within the CINAHL and PubMed databases included the following terms: (“Inhalational Agents” OR “Volatile Anesthetic Agents”) AND/OR (“Total Intravenous Anesthesia”) AND (“Breast Cancer” OR “Breast Malignancy” OR “Breast Cancer Surgery” OR “Breast Cancer Recurrence” OR “Breast Cancer Metastasis”). The keywords were utilized independently or collectively and with the Boolean operators “OR” and “AND” interchangeably in the literature search to yield a total of 869 articles, 517 from PubMed and 352 from CINAHL. The results produced from the aforementioned search were further refined via the

application of a publication date filter to generate current peer-reviewed studies from the years 2011 to 2021, yielding 80 relevant articles. Duplicate articles and those written in alternative languages were immediately eliminated from consideration, reducing the article count to 65.

Studies with inadequate sample size, lack of relevance to the topic, emphasis on regional anesthetic technique and other anesthetic drugs unspecific to TIVA or VAA administration, or failure to discuss the correlation of anesthetic technique to suppression of the immunologic response were disqualified. Inclusion criteria consisted of studies that evaluated the direct effects of VAA and/or TIVA based anesthetic methods for patients with breast cancer presenting for surgical intervention and their effects on NK cell suppression and cancer cell dissemination and implantation, as evidence by markers and recurrence rates. Following the modifications and thorough assessment, twenty articles were selected and approved for analysis; however, further evaluation of the full text resulted in the final selection of eight high-level articles for appraisal due to their currency in relevance to present clinical practice and support of the abovementioned outlined objectives.

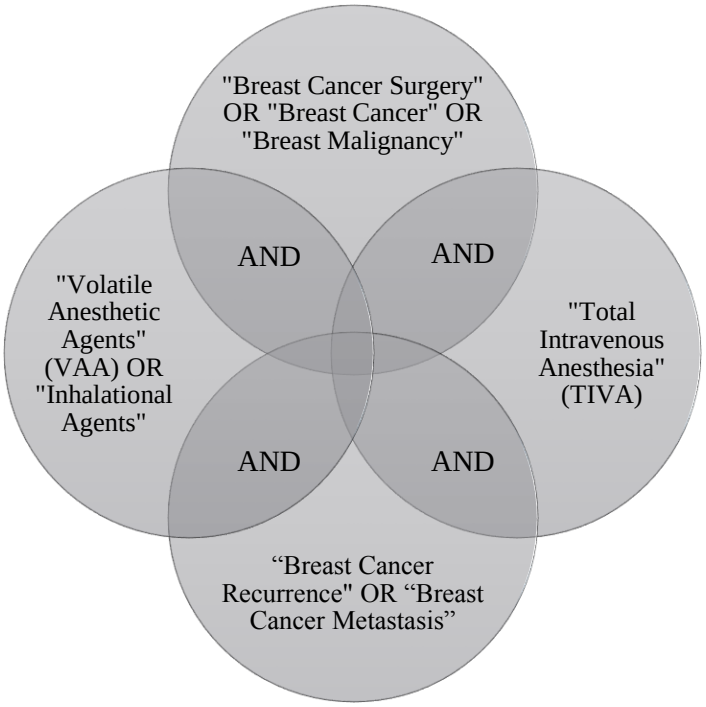

Diagram 1: Keywords Search

III. Results of Literature Related to the Clinical Question Study Characteristics

Thorough evaluation of the eight elected articles revealed a consistency in themes that guided the organization of this review and illuminated the significance of anesthetic technique in the management of the investigative patient population. Cho, Lee, and Kim[7], Lee et al[10], and Yan et al[11] investigated a pivotal theme detailing the attenuating impact of VAA on immunologic response and facilitation of cancer cell proliferation compared with the efficacy of TIVA in suppressing the perioperative stress response. These researchers highlight the impact of anesthetic method of the immunologic function and subsequent breast cancer recurrence and metastasis, which intertwines with a second pertinent theme. Authors Enlund et al[8] and Kim et al[16] echo the findings of the aforementioned researchers with an emphasis on reduced breast cancer recurrence and metastasis rates in patients that received TIVA-based anesthetic compared to those that received VAA.[7-8.10-11,20]

All eight of the articles focused on the implications of the mode of anesthetic delivery in regard to long-term cancer outcomes in patients with breast cancer presenting for surgical intervention, with an emphasis on the adoption of a TIVA-based anesthetic approach to mitigate the risk anesthesia-associated breast cancer recurrence or metastasis; thus, an improved quality of life and overall survival. Two of the studies were randomized, prospective clinical trials,[7,11] two were retrospective database analyses,[8,10] and the remaining study was based on a retrospective cohort design.[7] Participants in the retrospective studies were grouped into VAA versus TIVA-based anesthetic and the immunologic function and recurrence rates were analyzed in the immediate post-operative and long-term period up to 5 years following surgical intervention.[7,11] The database analyses aimed to examine and compare the recurrence, metastasis, and survival rates of breast cancer patients that received VAA compared with those that received TIVA anesthesia during surgical intervention.[8,10] The retrospective cohort analysis sought to identify the feasibility, safety, and efficacy of a combined local infiltration and TIVA-based anesthetic for outpatient breast-conserving surgery (BCS) in breast cancer patients in regard to reduced recurrence and increased survival compared to existing data implicating the detrimental effects of VAA in breast cancer patients.[16]

Immunological Function Preservation Secondary to TIVA-Based Anesthetic

In a study by Cho, Lee, and Kim,[7] the authors evaluated the effects of propofol-remifentanil based anesthesia with postoperative ketorolac analgesia (propofol-ketorolac group) compared with sevoflurane-remifentanil based anesthesia with postoperative fentanyl analgesia (sevoflurane-fentanyl group) on NK cell cytotoxicity (NKCC) in patients with breast cancer undergoing breast cancer surgery. NKCC secondary to VAA anesthetic technique and excessive opioid administration has been designated as the culprit of increased breast cancer recurrence

and metastasis rates in breast cancer patients that underwent surgical intervention for breast cancer treatment; thus, the researchers initiated this prospective randomized study to evaluate the veracity of this trending finding from current retrospective analyses.[7] Following approval by the Institutional Review Board and Hospital Research Ethics Committee of Severance Hospital, Yonsel University Health System, Seoul, Korea in February of 2014, the study was registered at clinicaltrial.gov in March 2014 as NCT02089178.[7] The researchers included patients aged 20-65 years old who underwent elective surgery for breast cancer with an American Society of Anesthesiologists (ASA) physical status classification ranged I-III, whereas patients with renal or hepatic deficiency; body mass index (BMI) exceeding 35 kg/m^2; immunosuppressive disorders or recipients of immunosuppressive therapy, including steroids within six months of surgical intervention; existing metastatic disease; or recipients of radiation or chemotherapy were excluded.[7] Written consent was obtained from a sample of 50 patients ($n = 50$) and random assignment to the propofol-ketorolac or sevoflurane-fentanyl groups was established utilizing a computer-generated random number table, yielding 25 subjects in each group ($n = 25$).[7] Patients in the propofol-ketorolac group were anesthetized with propofol and remifentanil intra-operatively and treated with ketorolac for analgesia in the post-operative period, while patients in the sevoflurane-fentanyl group were anesthetized with sevoflurane and remifentanil with fentanyl-based analgesia post-operatively.[7] The ultimate aim of the researchers of this study was to compare the effects of each anesthesia-analgesia method on immune function (assessed by NKCC measurement) in the preoperative and 24-hour postoperative period; secondary outcomes evaluated included postoperative pain scores, interleukin-2 assay (IL-2), and inflammatory responses evidenced by white blood cell (WBC), neutrophil, and lymphocyte counts.[7] The incidence of breast cancer recurrence or metastasis were assessed utilizing ultra-sound guided

breast and abdomen examinations, in addition to full-body bone scans every six months following surgery.[7] Statistical analysis of the aforementioned variables was achieved utilizing IBM SPSS20.0 (IBMCorp-Armonk, NY, USA) and SAS9.2 (SAS Institute Inc., Cary, NC, USA) and continuous variables were evaluated utilizing an independent t-test or Mann-Whitney U test following confirmation of normality of distribution with the Kolmogorov-Smirnov test; categorical variables were assessed utilizing the X^2 test or Fisher exact test.[7] Variables requiring repeated measurements including the NKCC, IL-2, total leukocyte, neutrophil, and lymphocyte counts, as well as neutrophil-lymphocyte-ratio (NLR) were evaluated utilizing a linear mixed model with randomized patient indicators and fixed group, time, and group-by-time effects, which assessed the whether a change-over-time difference occurred between the two groups.[7] Lastly, the researchers performed a post-hoc analysis with Bonferroni corrections to obtain multiple comparisons and verify significant differences in the measurements between each group and established a *P*-value of < 0.05 as statistically significant.[7] The results of the researchers' study indicated that while the baseline NKCC (%) was comparable between the two groups ($P = 0.082$), 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), $P = 0.032$]; this indicates that the sevoflurane-fentanyl based anesthetic squelched the NK cell cancer-fighting capacity in the intra- and post-operative periods and facilitated an environment ideal for cancer cell migration and proliferation. Researchers also found that the change of NKCC over time was significantly different between the groups ($P = 0.048$), indicating that the debilitating effects of sevoflurane-fentanyl anesthetic on immunologic cytogenic function of sevoflurane-fentanyl anesthetic can progress into the later stages of the post-operative period.[7] One patient in the sevoflurane-fentanyl cohort developed recurrence in

the contralateral breast.[7] While pain scores and post-surgical inflammatory responses remained competitive between both cohorts, the researchers underline that ketorolac has been identified as an analgesic that supports NK cell function.[7] The researchers concluded that a TIVA-based anesthetic with propofol and remifentanil and postoperative ketorolac analgesia supports immunological function and; thus, reduces the risk of breast cancer recurrence and improved chance of survival.[7] The researchers identified some limitations to their study including: inability to blind the operating room staff; the discriminative effects of each individual drug could not be ascertained; and the post-surgical recurrence and metastasis follow-up period was restricted to two years.[7] The researchers advocate for additional studies with similar design to evaluate the long-term effects on breast cancer recurrence and metastasis rates beyond a two year post-operative period.[7] Studies that evaluate recurrence rates in 5-to-10 years following surgery would be invaluable to the identification of the anesthetic implications for this patient population and aid in the transition to standardized practice.

Similar to Cho, Lee, and Kim,[7] a study conducted by Lee et al[10] incorporated a single-center retrospective study design to assess the long-term effects of propofol-based TIVA anesthetic technique on breast cancer recurrence and overall survival in patients that underwent modified radical mastectomy for breast malignancy secondary to immunological compromise. The researchers exercised a quantitative data collection which included rates of recurrence-free survival and overall survival in the VAA and TIVA group, respectively, and facilitated statistical analysis.[10] Lee et al[10] utilized an electronic database to access all patients that underwent modified radical mastectomy from January 2007 to December 2008 to yield an adequate sample size of 363 modified radical mastectomy cases, 173 of which were TIVA-based with propofol and 152 that were VAA-based with sevoflurane. The exclusion criteria were clearly defined, as

well as, demographic data and the methodology of instituting a power 0.3 software to validate that the sample size was sufficient to accurately reflect the impact of anesthetic technique on recurrence.[10] The primary outcomes of the study included recurrence-free survival and overall survival during the initial 5 years following modified radical mastectomy (MRM) for breast cancer.[10] The researchers delineated recurrence-free as from the date of surgery to the date of first recurrence, which was further deciphered as locoregional recurrence or distant metastases confirmed via clinical evidence or radiological examination, whereas overall survival was defined as the date of surgery to the date of death.[10] The researchers' statistical analytical methods mirrored those of Cho, Lee, and Kim;[7] however, recurrence-free survival and overall survival rates were estimated utilizing the Kaplan Meier log-rank test and Cox proportional hazards regression was exercised to uni- and multivariate analysis of perioperative and clinically pathologic variables that influence recurrence-free survival.[10] Variables with a P-value less than 0.25 ($P < 0.25$) from the univariate analysis were considered meaningful and incorporated in the multivariate analysis to identify statistically significant outcomes with a $P < 0.05$.[10] The results demonstrated statistical significance, as the propofol TIVA-based anesthetic group was associated with lower rate of recurrence-free survival with a *P*-value of 0.037 and an estimated hazard ratio of 0.550, a 95% CI 0.311-0.973.[10] Alternate results of this study evaluated the pain management of each of the respective cohorts. Unlike the comparability of pain management identified by Cho, Lee, and Kim[7] between the sevoflurane and propofol-based cohorts, Lee et al[10] found that the TIVA-based propofol group required more opioid administration in the peri-operative period. In alignment with the conclusion of Cho, Lee, and Kim,[7] Lee et al[10] the authors concluded that propofol-based TIVA significantly reduced breast cancer recurrence after modified radical mastectomy due to the immunologic-protective effects. The authors

acknowledged study limitations, which included the retrospective design, lack of randomization, and single-site evaluation in an effort to eliminate inconsistencies in surgical and medical methods that may have altered the results.[10] Although the authors recommend additional multi-center prospective studies to validate their findings, the endorsement of TIVA-based anesthetic approach in breast cancer patients presenting for breast surgery is strongly supported to reduce the inherent risk of immunologic suppression and associated potentiation of recurrence and metastasis.

Yan et al[11] evaluated the implications of a TIVA-based anesthetic for breast cancer resection due to its correlation with decreased tumor growth and metastasis compared to an VAA approach utilizing a comprehensive, randomized controlled clinical study design. The researchers randomly assigned 80 (n =80) patients undergoing breast cancer resection to either a propofol/remifentanil-based or sevoflurane-based anesthetic technique via an envelope reveal on arrival to the operating room (OR). Vascular endothelial growth factor (VEGF) and transforming growth factor (TGF), markers associated with tumor growth and proliferation, were analyzed 24 hours following surgery and recurrence-free survival (RFS) rates were assessed over a two-year follow-up period.[11] The statistical findings were significant as evidence by preoperative and postoperative great difference in VEGF between the VAA (50) and TIVA (12) groups, reflective of a P-value of 0.008.[11] Additionally, the two-year recurrence-free survival rates were 78% and 95% in the VAA and TIVA groups, respectively.[11] These results led the researchers to conclude that TIVA-based anesthetic technique can "effectively inhibit the increases" in cancer marker concentrations after surgery compared with VAA; thus, potentiating the possibility of recurrence and metastasis secondary to anesthetic mode of delivery.[11] Limitations included a limited sample size, failure to conduct the study with a multi-center design, and the desire for a longer term

follow-up period to clarify the roles of each anesthetic modes on recurrence and metastasis of breast cancer.[11] An additional limitation addressed the fact that a small bolus of propofol and fentanyl were administered to each cohort upon induction of anesthesia; however, the effects of single-dose propofol administered to the sevoflurane-based group would have dissipated within ten minutes and anesthesia was maintained with sevoflurane throughout the intra-operative period. The results obtained from Yan et al[11] echo the findings of the previously mentioned studies and highlight the significance of anesthetic approach in the quality of life for breast cancer patients undergoing surgical intervention.

In an effort to demonstrate the direct effects of anesthetic agents on recurrence and metastasis, Connolly et al[4] completed a retrospective analysis to evaluate the association between genetic expression of anesthetic-analgesic receptor targets and recurrence and metastasis, utilizing a repository of malignant breast tissue gene expression and correlating clinical data. The researchers included 23 genes with the most prominent anesthetic-analgesic receptor targets frequented in the current anesthetic management of patients with breast malignancy presenting for surgery. Connolly et al[4] utilized an algorithm via *Breastmark*, to integrate the gene expression data from approximately 17,000 samples and clinical data from greater than 4,500 breast cancer samples. The gene expression data was dichotomized according to disease-free survival, or survival without recurrence, and distant disease-free survival, or survival without metastasis; whereas, hazard ratios were achieved via a Cox-regression analysis for each group, respectively. Prognostic markers were determined via the randomized selection from the 23-member gene lists from all available genes, in addition to, a calculation for each occurrence in which more than 5 significant markers were observed.[4] After 10,000 repetitions of the aforementioned process, the researchers calculated an empirical P-value to determine statistical significance. The researchers

identified that 9 of the 23 genes were significantly associated with altered rates of metastasis and 4 of 23 with recurrence. Although a P-value of 0.07 failed to demonstrate statistical significance for metastasis after adjustments for multiple testing, the researchers emphasize that several anesthetic and analgesic agents, such as VAA and opioids, utilized in the management of breast cancer patients demonstrated a propensity for the metastatic spread of breast cancer compared to others anesthetic agents, including propofol.[4] Connolly et al[4] highlight that the effects of anesthetic agents may potentiate or mitigate the proliferation and metastasis of breast cancer on a molecular level; therefore, having drastic implications on the long-term outcomes in patients with breast malignancy presenting for surgical intervention.

Breast Cancer Recurrence and Metastasis Secondary to Anesthetic Technique

Enlund et al[8] conducted a retrospective, multicenter database analysis from seven Swedish hospitals to evaluate and compare the effects of TIVA propofol-based and VAA sevoflurane-based anesthetic delivery in breast cancer surgery patients in regard to long-term recurrence and breast cancer survival. The researchers distinguished all breast cancer patients that underwent breast cancer surgery from 2006 to 2012, which were matched to the Swedish Breast Cancer Quality Register to ascertain specific tumor characteristics, prognostic factors, adjuvant therapies, and date of expiry.[8] A total of 6305 patients (n = 6305) were included in the database analysis; 3096 subjects (n = 3096) received propofol-based anesthesia intraoperatively, while 3209 subjects (n = 3209) received a sevoflurane-based anesthetic.[8] The survival rates for the sample were assessed at 1- and 5-years following surgical intervention utilizing the multiple Cox regression models adjusted accordingly for demographic, oncological, and multi-control variables, as well as, propensity score (PS) matching for the same variables including a separate analysis to accommodate the participating hospitals as a cofactor.[8] The researchers exercised two

Cox regression models for each of the anesthetic delivery groups; propofol or sevoflurane-based cohorts, respectively. Each regression model were concisely adjusted for age, classification, histopathology, adjuvant therapies, and specific intervention (total or partial mastectomy, sector resection, with or without axillary clearance, and supplemental breast surgery).[8] PS were calculated with an emphasis of the treatment for each cohort as the dependent variable and adjusted for the aforementioned criteria, yielding a five PS matching cohorts for estimation.[8] Following the application of a Cox regression model, the authors identified a *P*-value less than 0.05 ($P < 0.05$) as statistically significant.[8] Enlund et al[8] identified that the survival rates for the cohorts were 81.8% and 91.0% for the sevoflurane and propofol cohorts, respectively; yielding a *P*-value of 0.126 ($P = 0.126$). The researchers delineated that different results obtained fluctuated depending on the application of the varying statistical adjustment methods utilized; however, a proposed and determined difference in survival favored the propofol-based anesthetic across the board with up to a 9.2 percentage increase in survival rate at 5-years following surgical intervention.[8] The increased 5-year survival rate of the propofol-based cohort is reflected by a hazard ratio of 1.46, 95% CI 1.10-1.95.[8] Congruent with the findings of the researchers in the above mentioned studies, Enlund et al[8] determined that general anesthesia with a TIVA propofol-based anesthetic approach is beneficial regarding long-term outcome following primary breast cancer surgery compared with VAA sevoflurane-based anesthesia, in terms of overall survival.[8] The authors acknowledge that the retrospective nature of their study as a limitation and urge the completion of randomized control trials to further establish the validity of their findings.[8]

A retrospective analysis conducted by Enlund et al[13] focused on the correlation between anesthetic technique and patient survival following radical cancer surgery.[13] Similar to the previous researchers, Enlund et al[13] compared the differences in the overall 1- and 5-year

survival rates of patients that underwent surgical intervention for breast, colon, or rectal malignancy and received either a propofol-based TIVA anesthetic or sevoflurane-based VAA anesthetic. The researchers accessed a database to select 2,838 patients (n= 2,838) that underwent breast (n= 1,837), colon (n= 695), or rectal (n= 306) cancers and were record-linked to regional clinical quality registers.[13] Cumulative 1- and 5-year overall survival rates were achieved utilizing the Kaplan-Meier method, and estimates were compared between patients that received a propofol-based anesthetic (n = 903) or sevoflurane-based anesthetic (n = 1,935).[13] The researchers incorporated Cox proportional hazard models to calculate and assess the risk of death adjusted for potential effect modifiers and confounders for accuracy.[13] The results from the statistical analysis reflected an obvious advantage of a propofol-based anesthetic in the management of cancer patients presenting for surgery with in the overall 1- and 5-year survival rate of 4.7% (P = 0.004) and 5.6% (P < 0.001), respectively for all cancer types combined.[13] Enlund et al[13] advocate that TIVA anesthetic technique with propofol improves the overall quality of life and chance of survival in cancer patients presenting for surgery.

Safety, Efficacy, and Feasibility of TIVA-based Anesthetic

Kim et al[16] in 2020, conducted a retrospective cohort analysis to examine the safety, efficacy, and feasibility of a combined local and TIVA anesthetic and/or sedation in relation to the overall effects of this less-immunosuppressive anesthetic approach on reduced breast cancer recurrence and survival.[16] The researchers underscore that the administration of inhalational anesthetic agents in breast cancer patients undergoing surgical intervention is an associated trigger for increased mortality secondary to breast cancer recurrence linked to VAA anesthetic-associated immunosuppression during the perioperative period. Kim et al[16] explored this alternate anesthetic approach to circumvent the jeopardy of an ineffective cytotoxic response.

The researchers' study was comprised of 456 patients (n = 456) diagnosed with stage 0-III breast cancer who underwent outpatient breast conserving surgery (BCS) or axillary lymph node (ALN) management with a combined local-TIVA based anesthetic from March 2008 to January 2020.[16] Of the 456 patients included, the ages ranged from 27 to 91 years and the clinical stages dispersed among the subjects were as follows: 267 (58.4%) patients were diagnosed with stage 0 or I malignancy, 165 (36.1%) patients with stage II malignancy, and 24 (5.2%) patients with stage III malignancy.[16] The researchers established a median follow-up period of 2259 days during the 11.4 year-period of their study to evaluate the overall survival and breast cancer-specific survival rates of the patients included in the study.[16] Survival rates included the pathological tumor size, ALN metastasis, or no metastasis (pN0); 1.9% with complete tumor reduction following NAC, 36.1% of patients, and 76.5% of patients, respectively.[16] Tumor subtypes accounted for this study yielded a total of 325 of patients with hormone receptor–positive and human epidermal growth factor receptor 2 (HER2)-negative tumors, 58 patients with HER2-positive tumors, and 17 (3.7%) patients with triple negative (TN) breast cancer.[16] Unlike the samples in the previously mentioned studies, Kim et al[16] included patients that received adjuvant chemotherapy and/or endocrine and radiotherapy following surgical intervention based on tumor subtype and the primary pathological tumor findings.[16] Patients that requiring radiation for salvaged breast tissue received standard dosing with or without additional boosters as needed; 3-4 weeks for hypofractionated doses or 4-5 weeks post-operatively. Those that required neoadjuvant treatment with chemo or endocrine therapy were treated 6 months prior to surgical intervention, while all patients with stage II and stage III malignancy received neoadjuvant therapy.[16] Statistical analysis was achieved utilizing a Statcel 4 (OMS Publishing Inc., Saitama, Japan) to ascertain cumulative overall survival (OS) and breast-cancer specific

survival (BCSS) rates; Kaplan-Meier method was employed to determine survival rates according to pathological stage (pStage) and tumor subtype.[16] Kim et al[16] compared the data between each group utilizing the log-rank test and elected *P*-values less than 0.05 ($P < 0.05$) as statistically significant. The researchers' statistical analysis revealed OS and BCSS rates of 92.3% and 94.7%, respectively. The OS rates for pStages 0–III disease were 93.5%, 94.1%, 90.0%, and 71.4%, respectively ($P = 0.017$), while the OS rates for L, L- HER2, HER2, and TN breast cancers were 93.4%, 93.1%, 83.3%, and 64.2%, respectively ($P = 0.002$).[16] The BCSS rates for pStages 0–III disease were 97.9%, 95.9%, 92.7%, and 71.4%, respectively ($P = 0.001$), while the BCSS rates for L, L-HER2, HER2, and TN breast cancers were 94.8%, 93.1%, 83.3%, and 83.3%, respectively ($P = 0.130$).[16] Overall, the researchers observed a recurrence rate as low as 5.4%, or 25 patients. The results supported the original hypothesis that outpatient surgery for breast cancer patients requiring BCS and ALN management under a combined local-TIVA anesthetic delivery model is an immunologic protective anesthetic method to reduce breast cancer recurrence and improve overall survival, in contrast to VAA-based anesthesia.[16]

Ní Eochagáin et al[3] conducted a retrospective analysis of an on-going randomized control trial (RCT) NCT00418457 to evaluate and compare the effects of a propofol-paravertebral and inhalational agent-opioid anesthetic technique on the neutrophil-lymphocyte ratio (NLR) during the post-operative period in patients that underwent breast cancer surgery. The researchers accentuate that the administration of a propofol-paravertebral technique may be the safest, most efficacious anesthetic technique to optimize the post-operative immune response in breast cancer patients presenting for surgical intervention, thus reducing the risk of long-term breast cancer recurrence and metastasis.[3] Ní Eochagáin et al[3] included 116 participants ($n = 116$), which were randomly assigned to either the propofol-paravertebral anesthesia ($n = 59$) or inhalational agent-

opioid anesthesia (n = 57) groups.[3] The propofol-paravertebral group received a thoracic epidural catheter with an initial test dose consisting of 1.5% lidocaine and 1:200,000 epinephrine and a 10-20mL bolus of 0.5% bupivacaine or 0.5% ropivacaine, followed by a supplementary intravenous propofol infusion titrated to effect with a range of 60-90 mcg/kg/min.[3] A continuous epidural infusion of 0.5% bupivacaine or 0.5% ropivacaine at a rate of 6-10 mL/hour was initiated toward the end of surgery and continued up to 48 hours post-operatively, where additional analgesia via the administration of non-steroidal anti-inflammatory (NSAID) or paracetamol medications served as adjuvants for breakthrough pain.[3] The inhalational agent-opioid anesthesia group received general anesthesia that consisted of induction via the administration of 1-3 mcg/kg of fentanyl and 2-4 mg/kg of propofol and maintenance with sevoflurane, titrated to maintain the heart rate and blood pressure within 20% of baseline values and an adequate anesthetic plane.[3] Toward the end of surgery, 0.1 mg/kg of intravenous morphine was administered toward the end of surgery and long-acting intravenous opioid analgesics were administered as needed in the post-operative period via nurse-controlled or patient-controlled analgesia.[3] Both groups were transitioned to paracetamol and NSAIDs approximately 24 hours post-operatively. Complete blood count (CBC) was drawn for the patients in each group in both the pre- and post-operative periods and the NLR were compared to identify a baseline, as well as, deviation from the baseline NLR following intervention.[3] While the pre-operative NLR for the patients in each group were comparable, the post-operative NLR was significantly lower in the propofol-paravertebral anesthesia group (3.0 (2.4-4.2) compared to the inhalational-opioid anesthesia group (4.0 (2.9-5.4), reflecting a P-value of P = 0.001.[3] Ní Eochagáin et al[3] underscore that existing data suggests an NLR greater than 3.0 in the post-operative period is associated with an increased risk of breast cancer recurrence and metastasis;

therefore, the selection of a propofol-paravertebral anesthetic for breast cancer patients undergoing surgical intervention is likely to yield more favorable long-term, recurrence-free outcomes compared to an inhalational agent-opioid anesthetic.[3]

Authors	Purpose	Methodology/ Research Design	Intervention(s)/ Measures	Sampling/ Setting	Primary Results	Relevant Conclusions
Ní Eochagáin et al[3]	Inflammation and immunosuppression contribute to the pathogenesis of cancer. An increased neutrophil–lymphocyte ratio reflects these processes and is associated with adverse cancer outcomes. Whether anesthetic technique for breast cancer surgery influences these factors, and potentially cancer recurrence, remains unknown. Researchers conducted a secondary analysis in patients enrolled in an ongoing trial of anesthetic technique on breast cancer recurrence. The primary hypothesis was that postoperative neutrophil–lymphocyte ratio is lower in patients allocated to receive propofol-paravertebral rather than inhalational agent-opioid anesthesia for primary breast cancer surgery.[3]	Retrospective Analysis of on-going Randomized Control Trial: NCT00418457	Patients were randomly allocated to receive either a propofol-paravertebral anesthetic with propofol-based TIVA and paravertebral block or an inhalational agent-opioid anesthetic with sevoflurane and morphine. The Pre- and Post-operative neutrophil–lymphocyte ratio (NLR) was compared for each group.[13]	A total of 397 participants were enrolled in NCT 00418457 up to 31 October 2016 at the Mater University Hospital. Among these, 10 participants withdrew from the study, four had incomplete records and 267 lacked both a pre-operative and a postoperative full blood count within three days of their primary surgery. Therefore, the charts of 116 participants were included in this retrospective analysis, with 59 randomly allocated to propofol-paravertebral anesthesia and 57 to inhalational agent-opioid anesthesia.[3]	Among 397 patients, 116 had differential white cell counts performed pre-operatively and postoperatively. Pre-operative neutrophil–lymphocyte ratio was similar in the propofol-paravertebral 2.3 (95% CI 1.8–2.8) and inhalational agent-opioid anesthesia 2.2 (1.9–3.2) groups, P = 0.72. Postoperative neutrophil–lymphocyte ratio was lower (3.0 (2.4–4.2) vs. 4.0 (2.9–5.4), p = 0.001) in the propofol-paravertebral group.[3]	The propofol-paravertebral group demonstrated statistically significant results for attenuating post-operative increase in the NLR.[3]

Connolly et al[4]	Evaluate the association between the genetic expression of anesthetic-analgesic receptor targets and recurrence and metastasis in breast cancer tissue.[4]	Retrospective Analysis	A list of 23 genes encoding for the most prominent anesthetic-analgesic receptor targets were compiled. and processed via *Breastmark*, an algorithm integrating gene expression data from ~17,000 samples and clinical data from >4,500 breast cancer samples. Gene expression data was dichotomized utilizing disease-free survival, or survival without recurrence, and distant disease-free survival, or survival without metastasis as end points. Hazard ratios were calculated by Cox-regression analysis. Enrichment for prognostic markers was determined by randomly choosing 23-member gene lists from all available genes, calculating how often >5 significant markers were observed and adjusting p-values for multiple testing. This was repeated 10,000 times and an empirical p-value calculated.[4]	A total of 23 genes were evaluated in the gene expression data from 17,000 samples and clinical data from more than 4,500 breast tumor samples.[4]	Of 23 selected genes, 9 were significantly associated with altered rates of metastasis and 4 with recurrence on univariate analysis. Adjusting for multiple testing, 5 of these 9 genes remained significantly associated with metastasis.[4] This ratio of genes (5/23) was not significantly enriched for markers of metastasis ($p = 0.07$); however, a trend of metastasis was observed specific to several anesthetic-analgesic agents.[4]	Several anesthetic-analgesic receptor genes were associated with metastatic spread in breast cancer. Overall there was no significant enrichment in prognostic markers of metastasis, although a trend was observed.[4]

Cho, Lee, and Kim[7]	Compare the effects of two different anesthesia and analgesia methods [propofol-remifentanil anesthesia with postoperative ketorolac analgesia (Propofol-ketorolac groups) VS sevoflurane-remifentanil anesthesia with postoperative fentanyl analgesia (Sevoflurane-fentanyl group)] on the NK cell cytotoxicity (NKCC) in patients undergoing breast cancer surgery.[7]	Prospective Randomized Study	Fifty patients undergoing breast cancer resection were randomly assigned to either the Propofol-Ketorolac or Sevoflurane-Fentanyl anesthesia groups. The primary outcome was NKCC, which was measured before and 24 h after surgery. Post-surgical pain scores and inflammatory responses measured by white blood cell, neutrophil, and lymphocyte counts were assessed. Cancer recurrence or metastasis was evaluated with ultrasound and whole-body bone scan every 6 months for 2 years after surgery.[7]	A total of 50 patients (20-65 years old) who underwent elective surgery for breast cancer and had an American Society of Anesthesiologists (ASA) physical status classification of I to III were randomly assigned into one of the study groups (25 patients each) using a computer-generated random number table and assignments were concealed in an envelope. The Propofol-ketorolac group, patients were anesthetized with propofol and remifentanil and received ketorolac after surgery, whereas the Sevoflurane-fentanyl group, patients were anesthetized with sevoflurane and remifentanil and received fentanyl postoperatively.[7]	The baseline NKCC (%) was comparable between the two groups (P = 0.082). Compared with the baseline value, NKCC (%) increased in the Propofol-ketorolac group and decreased in the Sevoflurane-fentanyl group [15.2 (3.2) to 20.1 (3.5), P = 0.048] and [19.5 (2.8) to 16.4 (1.9), P = 0.032], respectively. The change of NKCC over time 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.[7]	Propofol anesthesia with postoperative ketorolac analgesia demonstrated a favorable impact on immune function by preserving NKCC compared with sevoflurane anesthesia and postoperative fentanyl analgesia in patients undergoing breast cancer surgery.[7]

Enlund et al[8]	Retrospective studies indicate that the mode of anesthetic impacts long-term cancer survival secondary to the reduction in breast cancer recurrence. Researchers gathered a large cohort of breast cancer surgery patients from seven Swedish hospitals and hypothesized that general anesthesia with propofol would be superior to sevoflurane anesthesia regarding long-term breast cancer survival.[8]	Retrospective, Multicenter Database Analysis	Researchers identified all patients that were anaesthetized for breast cancer surgery between 2006 and 2012. The patients were matched to the Swedish Breast Cancer Quality Register, to retrieve tumor characteristics, prognostic factors, and adjuvant treatment, as well as, date of death. Overall survival between patients that underwent sevoflurane and propofol anesthesia was analyzed with different statistical approaches: (a) multiple Cox regression models adjusted for demographic, oncological, and multiple control variables, (b) propensity score matching on the same variables, but also including the participating centers as a cofactor in a separate analysis.[8]	All patients anesthetized for primary breast cancer surgery between 1998 and 2012 were retrieved from each participating hospital's database (Borås, Kalmar, Lund, Sundsvall, Uppsala, Västerås, and Örebro hospital). The database analysis identified 6305 patients.[8]	The 5-year survival rates were 91.0% and 81.8% for the propofol and sevoflurane group, respectively, in the final model (P = .126). Depending on the statistical adjustment method used, different results were obtained, from a non-significant to a "proposed" and even a "determined" difference in survival that favored propofol, with a maximum of 9.2 percentage points higher survival rate at 5 years (hazard ratio 1.46, 95% CI 1.10-1.95).[8]	General anesthesia with propofol is beneficial regarding long-term outcome following primary breast cancer surgery compared with general anesthesia with sevoflurane, in terms of overall survival.[8]

Lee et al[10]	Examine the link between propofol-based total intravenous anesthesia (TIVA) and recurrence or overall survival in patients undergoing modified radical mastectomy (MRM), compared to patients that received sevoflurane-based anesthetic.[10]	Single-Center, Retrospective Cohort Analysis	A retrospective analysis of the electronic database of all patients undergoing MRM for breast cancer between January 2007 and December 2008 was undertaken. Patients received either propofol-based TIVA (propofol group) or sevoflurane-based anesthesia (sevoflurane group). We analyzed prognostic factors of breast cancer and perioperative factors and compared recurrence-free survival and overall survival between propofol and sevoflurane groups.[10]	Researchers reviewed the electronic medical records of 363 patients who underwent MRM for invasive ductal carcinoma of the breast between January 2007 and December 2008; 325 cases were suitable for analysis (173 cases of propofol group, and 152 cases of sevoflurane group). There were insignificant differences between the groups in age, weight, height, histopathologic results, surgical time, or postoperative treatment (chemotherapy, hormonal therapy, and radiotherapy).[10]	The use of opioids during the perioperative period was greater in propofol group than in sevoflurane group. Overall survival was no difference between the two groups. Propofol group showed a lower rate of cancer recurrence ($P = 0.037$), with an estimated hazard ratio of 0.550 (95% CI 0.311–0.973).[10]	This retrospective study provides the possibility that propofol-based TIVA for breast cancer surgery can reduce the risk of recurrence during the initial 5 years after MRM.[10]

Yan et al[11]	Vascular endothelial growth factor (VEGF) and transforming growth factor-β (TGF-β) have been involved in tumor growth and metastasis. Sevoflurane may promote angiogenesis, whereas propofol can present an anti-angiogenic effect. In this study, researchers compared the effects of propofol/remifentanil-based total intravenous anesthesia (TIVA) and sevoflurane-based inhalational anesthesia on the release of VEGF-C and TGF-β, as well as, recurrence- free survival (RFS) rates in the patients undergoing breast cancer surgery.[11]	Prospective, Randomized, Controlled Parallel-Group Clinical Trial	Eighty female patients undergoing breast cancer resection were enrolled and randomized to receive either sevoflurane-based inhalational anesthesia (SEV group) or propofol/remifentanil-based TIVA (TIVA group). The serum concentrations of VEGF-C and TGF-β before and 24 h after surgery were measured and RFS rates over a two-year follow-up were analyzed in both groups. The postoperative pain scores assessed using a visual analogue scale (VAS) and the use of perioperative opioids were also evaluated.[11]	After taking written informed consent, adult female patients aged 18 to 80 years, ASA physical status I and II, undergoing MRM or BCS for confirmed breast cancer were enrolled in the study. The patients were randomly assigned to receive propofol/ remifentanil -based TIVA (TIVA group) or sevoflurane- based inhalational anesthesia (SEV group). Randomization was done using a sealed envelope system. A physician (Dr. Liu) not involved in the study randomly inserted 50 of each two anesthetic designations to 100 sequentially numbered envelopes. The allocation sequence was generated using a random number generator. The envelop was opened before anesthetic induction by the investigators to determine which anesthetic technique was going to be performed.[11]	Although VAS scores at 2 h and 24 h after surgery were comparable between the two groups, there were more patients receiving postoperative fentanyl in the TIVA group (16[40%]) compared with the SEV group (6[15%], p = 0.023). VEGF-C serum concentrations increased after surgery from 105 (87–193) pg/ml to174 (111–281) pg/ml in the SEV group (P = 0.009), but remained almost unchanged in the TIVA group with 134 (80–205) pg/ml vs.140(92–250) pg/ml(P = 0.402). The preoperative to postoperative change for VEGF-C of the SEV group (50 pg/ml) was significantly higher than that of the TIVA group (12 pg/ml) with a difference of 46 (− 11–113) pg/ml (P = 0.008). There were also no significant differences in the preoperative and postoperative	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.[11]

					TGF-β concentrations between the two groups. The two-year RFS rates were 78% and 95% in the SEV and TIVA groups (P = 0.221), respectively.[11]	

Enlund et al[13]	Several clinical studies have illuminated that commonly used inhalational agents, such as sevoflurane, are pro-inflammatory, whereas the intravenously administered hypnotic agent propofol is anti-inflammatory and anti-oxidative. This retrospective analysis examined the possible association between patient survival after radical cancer surgery and the use of sevoflurane or propofol anesthesia.[13]	Retrospective Analysis	Demographic, anesthetic, and surgical data from 2,838 patients registered for surgery for breast, colon, or rectal cancers were included in a database. This was record-linked to regional clinical quality registers. Cumulative 1- and 5-year overall survival rates were assessed utilizing the Kaplan-Meier method, and estimates were compared between patients given propofol (n = 903) or sevoflurane (n = 1,935). In a second step, Cox proportional hazard models were calculated to assess the risk of death adjusted for potential effect modifiers and confounders.[13]	A database was accessed to retrieve surgical data from 2,838 patients that underwent surgical intervention for breast, colon, or rectal cancers. The sample size was further analyzed to compare the 1- and 5-year overall survival rates between the propofol-based TIVA group (n= 903) or sevoflurane-based VAA group (n= 1,935).[13]	Differences in overall 1- and 5-year survival rates for all three sites combined were 4.7% ($p = 0.004$) and 5.6% ($p < 0.001$), respectively, in favor of propofol.[13]	Propofol-based TIVA suggests favorable long-term outcomes in patients undergoing radical cancer surgery, compared with VAA-based anesthetic.

Kim et al[16]	The use of general anesthesia (GA) with inhalational anesthetics for breast cancer surgery may be associated with breast cancer recurrence and increased mortality due to the immunosuppressive effects of these drugs. Less-immunosuppressive anesthetic techniques may reduce breast cancer recurrence. We evaluated the feasibility, safety, and efficacy of outpatient breast-conserving surgery (BCS) for breast cancer in a breast clinic in terms of the anesthetic technique used, complications occurring, recurrence, and survival utilizing local and intravenous anesthesia and/or sedation.[16]	Retrospective Cohort Analysis	The sample comprised 456 consecutive patients with stage 0–III breast cancer who underwent BCS/axillary lymph node (ALN) management using local and intravenous anesthesia and/or sedation between May 2008 and January 2020. Most patients received adjuvant chemotherapy and/or endocrine therapy and radiotherapy after surgery. Patient outcomes were evaluated retrospectively.[16]	Breast cancer recurrence and associated mortality were examined in a sample of 456 consecutive patients with breast cancer undergoing BCS and ALN management under local and IV anesthesia and/or sedation in the outpatient setting of a breast clinic. The researchers hypothesized that the use of less-immunosuppressive anesthetic approaches with local and IV anes-thesia and/or sedation with the maintenance of spontaneous breathing would improve the survival of patients with breast cancer.[16]	All patients recovered and were discharged after resting for 3–4h postoperatively. No procedure-related severe complication or death occurred. The median follow-up period was 2259 days (range, 9–4190 days), during which disease recurrence was observed in 25 (5.4%) patients. The overall survival and breast cancer–specific survival rates were 92.3% and 94.7%, respectively.[16]	Outpatient surgery for breast cancer involving BCS and ALN management under local and intravenous anesthesia and/or sedation can be performed safely, without serious complication or death. Less-immunosuppressive anesthetic techniques with spontaneous breathing may reduce the recurrence of breast cancer and improve survival relative to GA.[16]

IV. Summary of the Supporting Evidence

Current research strongly suggests a direct correlation between VAA-based anesthetic and immunologic suppression and ultimate contribution to morality secondary to anesthesia-associated breast cancer recurrence.[3-13,16-22] Despite existing evidence, a standardization for the anesthetic management of breast cancer patients undergoing surgical interventions has yet to be implemented; thus, researchers continue to pursue studies to heighten awareness amongst anesthesia providers to encourage the professional, evidence-based decision to employ a TIVA-based anesthetic for this patient population to maximize their opportunity at cancer-free survival following surgery.[7-8,10-11,16] All authors of the abovementioned studies concluded that TIVA-

based anesthesia lacks the immunosuppressive effects identified with VAA administration in breast cancer patients.[7-8,10-11,16]

While all eight of the studies shared consistent themes, Ní Eochagáin et al,[3] Connolly et al,[4] Cho, Lee, and Kim,[7] Lee et al,[10] and Yan et al,[11] placed emphasis on the effects of anesthesia with inhalational anesthetics on immunologic function compared to TIVA in patients with breast malignancy undergoing surgical intervention. All authors identified that VAA-based anesthesia resulted in immunologic suppression via various mechanisms that led to an impaired cytotoxic environment; thus, facilitating cancer cell migration and proliferation and ultimate recurrence and metastasis.[7,10-11] Enlund et al,[8] Enlund et al,[13] and Kim et al[16] constructed their studies with a foundational purpose on recurrence, metastasis, and survival rates in breast cancer patients that underwent breast cancer surgery with either a VAA or TIVA-guided anesthetic; this was a secondary theme addressed in the previously mentioned studies.[7,10-11] The authors from each study identified a statistically significant reduction in breast cancer recurrence, metastasis, and/or survival rates in patients that received a TIVA-based anesthetic during their surgical intervention.[7-8,10-11,16]

The results from the eight studies included in this review underscore the significance of increasing anesthesia provider knowledge in regard to the implications of anesthetic delivery on the long-term outcomes of the target patient population. Eliminating the knowledge deficit and bridging the gap between current evidence-based research and clinical practice in the anesthesia arena with an educational module will provide anesthesia providers with the tools necessary to

provide the safest, efficacious TIVA-based anesthetic to breast cancer patients presenting for surgery, ultimately fostering a greater chance at breast cancer survival.

V. Primary DNP Project Goal

Metastasis is documented as the primary cause of mortality in the breast cancer patient population with rates as high as 25%.[3-6] As a result of increased breast malignancy diagnoses, the number of women undergoing surgical resection of breast malignancies to manage their diagnosis are frequent in operating rooms at a higher rate; thus, forcing anesthesia providers into the difficult position of constructing an individualized anesthetic plan of care that maximizes the resistance to breast cancer cell proliferation.

Current literature suggests that the administration of VAA to breast cancer patients undergoing breast cancer surgery may be associated with cancer recurrence and metastasis through varying mechanisms that may potentiate the spread of cancerous cells, compared with total intravenous anesthesia (TIVA). [3, 7-13] Although many high-level studies have demonstrated the direct and indirect benefits of utilizing TIVA to reduce the prevalence of cancer recurrence and metastasis in patients who underwent surgical interventions for breast malignancy, the standardization of a TIVA-based anesthetic approach for the aforementioned patient population to mitigate the risk of anesthesia-associated recurrence has not been established.[3, 7-13] Since the standardization of anesthetic management for this vulnerable patient population has yet to be established, it is critical for anesthesia providers to familiarize themselves with current clinical findings and tailor the anesthetic approach to optimize this patient population and provide a favorable long-term outcome based on available empirical evidence.[14]

The primary goal of this Quality Improvement Project is to enhance the knowledge of anesthesia providers regarding the correlation between TIVA and reduced breast cancer

recurrence and metastasis compared with VAA via a comprehensive educational module to initiate a paradigm shift in the anesthetic management of surgical patients with breast cancer presenting for surgery. The objective of the development of a TIVA-based anesthetic protocol for patients with breast malignancy presenting for breast surgery is to reevaluate current practices and substitute a standardized approach that is based on empirical evidence to achieve optimal recurrence and metastasis-free breast cancer patient outcomes. The implementation of a TIVA-based anesthetic technique in the breast cancer patient population may be paramount to anesthetic practice, as the choice of anesthetic may influence the long-term quality of life and survival for breast cancer patients post-surgical intervention.[7]

VI. Goals and Outcomes

The acronym SMART was utilized to direct the development of the goal objectives for this educational module. The SMART model articulates that objectives must be specific, measurable, achievable, realistic, and time-limited; thus, ensuring the project will advance toward the ultimate goal when completed.[23-24]

Specific

Anesthesia providers will have a standardized, evidence-based TIVA anesthetic management protocol to mitigate the risk of anesthesia-associated breast cancer recurrence and metastasis in patients with breast cancer presenting for surgical intervention.

Measurable

The efficacy of the TIVA anesthetic management protocol will be evaluated via the analysis of a questionnaire that will be provided to the recipients before and after the delivery of the educational intervention. Outcomes will be calculated through the evaluation of the anesthesia providers' knowledge and comprehension of the physiologic causes of breast cancer

recurrence and metastasis secondary to surgical and anesthetic conditions; consequences of VAA and TIVA anesthetic on immunologic function; long-term consequences of VAA and TIVA on breast cancer outcomes; and the optimal multi-modal anesthetic plan of care for the breast cancer patient population based on current evidence-based research. Qualtrics® software will be utilized to generate surveys, analyze and synthesize the data, and yield results.

Achievable

The surgeons and anesthesia providers will collaborate to ensure that the anesthetic plan is tailored to optimize each individual patient, while maintaining the integrity of a TIVA-based anesthetic delivery to reduce the risk of breast cancer recurrence and metastasis secondary to anesthetic technique in breast cancer patients undergoing breast surgery. Additionally, the patient will be an active participant with a complete understanding of the interventions and steps taken to provide the best possible long-term breast cancer-free outcome.

Realistic

Anesthesia providers will be educated on the recommended TIVA-based anesthetic approach for breast cancer patients undergoing surgical intervention by the leader of this educational initiative.

Timely

The TIVA-based anesthetic protocol for breast cancer patients presenting for breast surgical intervention will be completed and available to anesthesia providers to access within a 6-month time period. The outcome of this initiative is designated as follows: within a 6-month timeframe, anesthesia providers will have access to an evidence-based TIVA-anesthetic management protocol for breast cancer patients presenting for breast surgical intervention that will reduce the risks of anesthetic-associated breast cancer recurrence and metastasis and

ultimately serve as the foundation for anesthesia providers to optimize long-term breast cancer-free outcomes for this patient population.

VII. Program Structure

The development of the TIVA-based anesthetic protocol for breast cancer patients presenting for breast surgical intervention will require a paradigm shift in attitude and knowledge with the collaborative effort of all stakeholders. Zaccagnini and White[23] emphasize that the conduction of a comprehensive assessment is critical to identify foreseeable roadblocks to the implementation of educational module and respective potential solutions, as well as, the establishment of a direction for the project that corresponds with the values and relevance to the stakeholders involved. The utilization of the strengths, weaknesses, opportunities, and threats (SWOT) assessment tool, will aid in the identification of internal and external characteristics that serve as supportive or detrimental qualities to the success and sustainability of the educational protocol implementation.[23-24]

Strengths

Breast cancer is one of the most prevalent variations of malignancy among women in the US and has resulted in a paralleled influx of patients with breast malignancy undergoing surgical intervention; thus, anesthesia providers are required to develop an anesthetic plan of care that is optimal for breast cancer patients.[1-2,22] Currently, there is no standardized anesthetic plan of care for breast cancer patients presenting for breast surgery; however, research has associated TIVA-based anesthetic with favorable long-term patient outcomes evidenced by reduced breast cancer recurrence and metastasis rates compared to patients that received VAA-based anesthesia.[3, 7-13] It is anticipated that a foundational strength of the development and successful implementation of a TIVA-based anesthetic protocol for breast cancer patients undergoing surgical intervention is its

congruence with each pillar of the organization's mission and values: research, teaching, and high-quality care. The organization of interest accentuates the significance of keeping abreast current research to ensure a continuum of learning across disciplines in order to provide holistic, optimal patient-centered care that is supported by evidence-based research and best practice recommendations.

Developing and implementing a TIVA-based anesthetic management educational module to guide the surgeon and anesthesia provider to work collectively to ensure that patients with breast malignancy presenting for surgical intervention will have a reduced risk of breast cancer recurrence and metastasis secondary to anesthesia technique; and ultimately, an optimal long-term outcome, aligns with the organization's commitment to provide high-quality patient care that fosters lifelong health and healing. Respectively, the goal of the educational module will be to provide anesthesia providers with the knowledge necessary to tailor a TIVA-based anesthetic plan of care that optimizes the long-term outcomes of breast cancer patients presenting for breast surgery; thus, mitigating anesthesia-associated causes of recurrence and metastasis. Additionally, it is important to note that the surgeons are equally committed to achieving the best possible long-term outcomes for their patients and working together with the anesthesia provider to ensure adequate surgical conditions are achieved with meticulous anesthetic management via immunologic supportive methods.

Weaknesses

Zaccagnini & White[23] define weaknesses as identified areas for improvement and might include the performance of the organization or unit, perceived weak areas according to the patients, and the availability, or potential, of resources to overcome the weaknesses. Parallel to current literature, an internal problem observed is the existing attitude amongst several

anesthesia providers regarding the perceived ease and efficiency of VAA-based anesthetic compared to the preparation and administration of a TIVA-based approach.[25] Lim et al[25] articulate that anesthesia providers associate TIVA-based anesthesia with a longer set-up time, increased risk for equipment failure and subsequent medical errors, and complicated anesthetic management compared to the administration and titration of inhalational agents; however, knowledge deficits regarding the aforementioned perceptions and concerns can be alleviated with educational modules and training.

Additional weakness identified in the organization of interest include the different methodology regarding the anesthetic care amongst anesthesiologists and nurse anesthetists, as well as, the surgeons. For example, while a nurse anesthetist may advocate to proceed with a combined regional anesthetic technique and TIVA-based approach, the anesthesiologist and surgeon may settle for general anesthesia because the surgeon plans to administer local anesthesia intra-operatively; thus, the competing modes of anesthetic and analgesic management may result in inconsistency in patient management and subsequent barriers to successful implementation of a standardized anesthetic protocol. The benefits of a TIVA-based anesthetic with or without additional adjuvants must be considered and accepted by each stakeholder to ensure the successful initiation of a practice and culture change related to the anesthetic care of breast cancer patients presenting for breast surgery.

Opportunities

The implementation of a TIVA-based anesthetic management protocol for breast cancer patients presenting for surgery provides an opportunity for anesthesia providers to be leaders at the forefront of breast cancer surgical patient management to utilize the best empirical evidence and reduce the potential for breast cancer reoccurrence and metastasis through anesthetic

delivery. Anesthesia providers will be integral to the promotion of long-term cancer free outcomes of this patient population and potentially initiate transitional change to anesthetic practice that impacts the anesthetic approach for breast cancer patients, as well as, patients with other known malignancies presenting for surgical intervention.

The initiation of a TIVA-based anesthetic protocol also provides an opportunity for the anesthesia provider and surgeon to work collectively in the continuous reassessment and evaluation for on-going improvement, while deepening the provider-patient rapport and relationship. The collaborative efforts of the stakeholders to tailor an anesthetic that supports the surgical plan of care to optimize the patient for surgery, as well as, the patients' long-term breast cancer outcome strengthens the relationship between disciplines and cultivates an environment conducive to best-practice advancements. The anesthesia chief and anesthesia clinical coordinator will be responsible for the approval of the program and select champions within the department to lead the implemented practice change. The elected champions will provide an educational module and determine the competency via meetings and observation. The anesthesia providers will be responsible for development of a TIVA-based anesthetic plan of care based on each individual patient with breast cancer presenting for breast cancer surgery. Lastly, the surgeons will be expected to communicate their needs and plan with the anesthesia provider through all stages of the operative period to ensure that the patient receives the anesthesia that is both conducive to the surgical conditions and favorable long-term breast cancer outcomes.

Threats

The standardization of evidence-based practice has been universally recognized as a key-driver of high-quality patient care and optimal outcomes; however, barriers, or threats, to implementation of evidence-based practice or quality improvement initiatives persist.[26] Threats,

which include obstacles to successful project implementation and sustainability, should be evaluated to provide the project leader with a sense of direction and plan for the project's best chance for success.[23-24] Interference with the programs' ability to achieve its objectives may include the anesthesia providers' negative feelings toward the adoption of a standardized anesthetic technique, which may be perceived as an infringement on their anesthetic "art" or individuality. Lim et al[25] found that anesthesia providers perceive TIVA-based anesthesia to be a more time-consuming anesthetic approach involving a longer set-up time and requiring more complicated titration. The researchers also discovered that despite the existing evidence that TIVA-based anesthetic reduces the risk of breast cancer recurrence and metastasis compared to VAA, anesthesia providers are reluctant and resistive to the adoption of a standardized TIVA-based anesthetic protocol, for it may jeopardize their anesthetic freedom and autonomy regarding the anesthetic management of their patients.[25] Ost et al[26] identify that a major barrier to the implementation of evidence-based practice or quality improvement initiatives is the readiness, or preparedness, and culture of the staff.[26] Ost et al[26] stress that stakeholders must be willing and ready to participate in projects aimed to institute change; this will eliminate inconsistency and create an supportive environment conducive to a successful quality improvement initiative; thus, it is critical for anesthesia providers to develop an understanding and appreciation of the impact of the their anesthetic management on the long-term breast cancer outcomes of this patient population to become active participants dedicated to the suggested transition to practice, eliminate existing practice gaps, and ensure project success.[23-24]

Organizational Factors

The implementation of the TIVA-based anesthetic protocol for breast cancer patients presenting for breast surgery will be conducted via a collaborative effort amongst disciplines.

First, the author will determine the steps necessary to develop a TIVA-based anesthetic protocol. A flowchart will be developed to provide visualization of the process steps, as well as, options for anesthetic drug selection to individualize the anesthetic plan for each patient. Each patient will have a form that the anesthesia provider can utilize to document the anesthetic plan and selected drugs to facilitate analysis of the data in follow-up periods proceeding surgery to correlate with recurrence and metastasis rates. Additionally, anesthesia providers will receive an identical questionnaire and test before and after receipt of an educational module via Zoom PowerPoint presentation to ascertain existing knowledge deficits and gauge understanding of the implications of anesthetic administration and breast cancer outcomes; the results will be compared to determine the success of the educational module pre- and post- implementation. In the evaluation phase, the post-implementation surveys, as well as, the educational module post-test will be compared to the educational module pre-test to assess an improvement in knowledge and attitude regarding the impact, feasibility, and efficacy of a TIVA-based anesthetic approach in breast cancer patient undergoing surgical intervention. The stakeholders will be responsible for a summary detailing the core findings resulted from their evaluation of the protocol and must include: a concise description of the protocol, purpose statement, applied interventions, methods utilized for data collection and analysis, background history surrounding the clinical issue, tools utilized to collect and analyze data, pertinent results and conclusions, unanticipated and unexpected outcomes, identified design flaws, and protocol improvement recommendations.

VIII. Conceptual Underpinning and Theoretical Framework

Middle range theories provide a foundation for healthcare professionals to seek an understanding of their patients and their health complications from which appropriate interventions are derived; thus, allowing healthcare professionals to provide a higher quality of

care while simultaneously elevating the professional's standards, accountability, and autonomy.[23,27] Peterson & Bredow[27] emphasize that middle-range theories are less abstract and more exact for practice implementation as the scope of the study is focused within the parameters of a narrowed spectrum; therefore, a middle-range theory will be utilized to guide this process. Kurt Lewin's Change Theory models how groups process change and involves three phases: unfreezing, change, and freezing.[23] The change theory suggests that successful implementation of change involves the preparation of those undergoing change via the "unfreezing" of their current view of the issue, followed by the application of the change, and "freezing" the new process into place.[23] The application of the Change Theory is essential to overcome the identified weaknesses and threats of the organization of interest surrounding the existing anesthesia providers' perception and attitude regarding standardized anesthetic management and TIVA-based anesthetic administration. As the Change Theory suggests, "unfreezing" current attitudes and beliefs facilitates an environment that is receptive to change and the sustainability of the implemented change to practice will be favorable.

IX. Methodology

To successfully achieve the overall goal of this educational intervention, a series of steps will be executed following the dissemination of the intervention to a specific group of participants. The series of actions involving the target group will be detailed in the following sections. Each of the following methodology sections are critical to the determination of the educational module outcomes , as well as, the overall impact of anesthesia provider role in reducing breast cancer recurrence and metastasis secondary to anesthetic mode of delivery to breast cancer patients undergoing surgical intervention.

Settings and Participants

The study will take place at Mount Sinai Medical Center (MSMC) located in Miami Beach, Florida, which is a private hospital. The primary study participants will include anesthesia providers of Miami Beach Anesthesia Associates (MBAA) and will range from physicians to advanced practice nurses in the anesthesia profession. The participants will be recruited voluntarily via an anonymous link distributed from an email within Qualtrics. If the recruit consents to participate in the educational intervention, an anonymous link will redirect the participant to a pre-educational module survey, followed by a video educational module, and a post-educational module survey. The educational module was distributed to a total of 29 individuals; it is anticipated that the sample size will include approximately 5-10 participants.

Description of Approach and Educational Module Procedures

The primary objective of this proposed study is to distribute an online educational intervention to anesthesia providers that emphasizes the implications of administering a TIVA-based anesthetic to patients with breast malignancy presenting for surgical intervention to mitigate the risk of breast cancer recurrence and metastasis secondary to anesthetic delivery. The initial phase of the project will involve an online pre-educational module assessment to ascertain the participants' baseline knowledge regarding the effects of anesthetic delivery on breast cancer recurrence and metastasis, the effects of anesthetics on cytotoxic physiology, and the best mode of anesthetic delivery to reduce the risk of breast cancer recurrence and metastasis in breast cancer patients presenting for breast cancer surgery. The pre-educational module assessment will also serve as a gauge to assess the anesthesia providers' attitude regarding the adoption of a TIVA-based approach for the anesthetic management of patients with breast malignancy undergoing surgical intervention. The existing knowledge of the participating anesthesia

providers in the selected clinical setting will be distinguished utilizing this preassessment tool; thus, providing a baseline for comparison to the post-educational module assessment and allow the researchers to evaluate the impact of the educational intervention on the improved knowledge and attitude of anesthesia providers regarding the anesthetic management of breast cancer patients presenting for breast cancer surgery.

Following a pre-educational module test, the participants will be directed to a 10-15 Voiceover PowerPoint presentation (VPP) that discusses the implications of anesthetic delivery on breast cancer recurrence and metastasis in breast cancer patients presenting for surgical intervention. The primary learning objective of the educational module will underscore the detrimental effects and mechanism of action (MOA) of VAA on breast cancer recurrence and metastasis via cytotoxic effects, compared to the benefits and MOA of TIVA on the mitigation of breast cancer recurrence and metastasis via immunologic protectant effects. In order to eliminate the existing research-to-clinical practice gap regarding the optimal anesthetic management of this patient population, it is essential for anesthesia providers to acquire a keen awareness and thorough comprehension of the magnitude of anesthetic management on the long-term outcomes of patients with breast malignancy undergoing surgical intervention for treatment.[25] The provision of the VPP will inform anesthesia providers of the significance of utilizing a TIVA-based anesthetic for breast cancer patients presenting for breast cancer surgery to reduce the risk of breast cancer recurrence and metastasis; thus, promoting favorable long-term outcomes and an improved quality of life for this patient population. The research supports the need for an educational intervention with comprehensive content regarding the impact of anesthetic delivery on breast cancer recurrence and metastasis in breast cancer patients presenting for breast cancer surgery.

The final phase of the project will include an online post-educational module assessment that serves to evaluate the knowledge gained by the anesthesia provider after successful completion of the educational module. Additionally, the post-educational module test will assess the aptitude for anesthesia provider support regarding a standardized TIVA approach for the anesthetic management of the aforementioned patient population and help researchers determine the next steps required to navigate a standardized anesthetic practice change to optimize the long-term outcomes in the breast cancer surgical population. The pre-/post-test comparison will provide pertinent data regarding the efficiency of the online educational intervention and promote the adoption of a TIVA-based approach for the anesthetic management of breast cancer patients undergoing breast cancer surgery.

Protection of Human Subjects

For this project, the recruitment population will include anesthesia providers who administer anesthetic care to patients at MSMC including anesthesiologists and certified registered nurse anesthetists (CRNAs). This population is significant due to their direct role in the development of an anesthetic plan of care and the administration of anesthesia to patients undergoing breast cancer surgery; thus, anesthesia providers will benefit from increased knowledge regarding the optimal anesthetic mode of delivery to mitigate the risk of anesthesia-associated breast cancer recurrence and metastasis and promote the best possible outcomes for the breast cancer surgical population. Recruitment activities will be conducted via email invitation through Qualtrics to all anesthesia providers of MSMC, which will provide an anonymous link to the pre-educational module assessment that requires their voluntary consent to participate. There will be no penalty should any participant elect to withdraw from the educational intervention. There are no perceived risks associated with this project; however,

elective participation requires 15-20 minutes of the anesthesia providers' time to complete the educational intervention phases to their entirety.

Data Collection

The primary tools utilized to determine the efficacy of this educational intervention include a pre- and post-educational module assessment. The tests will be identical and conducted in an anonymous survey format on Qualtrics; thus, comparison of the results from the pre- and post-tests will elucidate if an improvement to the participants' knowledge and attitude regarding the administration of a TIVA-based anesthetic to reduce breast cancer recurrence and metastasis to patients presenting for breast cancer surgery has occurred. The survey will consist of 12 questions that concentrate on the comprehension of anesthesia-associated breast cancer recurrence and metastasis; the MOA of anesthetic agents on cytotoxic physiology; and the optimal anesthetic delivery to optimize long-term outcomes in breast cancer patients undergoing breast cancer surgical intervention. Additionally, the questions will assess the participants' willingness to adopt the selection of a TIVA anesthetic for the management of the target patient population.

The pre-test will allow the researchers to gauge anesthesia provider interest in the educational intervention and existing baseline knowledge of the topic, while the post-test will evaluate knowledge gain and the participants' aptitude for applying this new knowledge to their clinical practice. The reliability and validity of this data collection method will be measured relative to the intervention and its overall impact on anesthesia providers. Confidentiality of the participants and the data collected will be maintained and no subject identifiers will be recorded throughout any component of this project.

Data Management and Analysis Plan

The DNP student will be co-investigator of this project and responsible for dissemination of the survey. The Qualtrics Stat-IQ software will be utilized to generate data based on the responses submitted by the participants on the pre- and post-assessment and facilitate the investigators' ability decipher if an improvement to anesthesia provider knowledge and attitude has occurred. The responses to each question will be recorded and measured to evaluate the knowledge base before and after the educational intervention, in addition to, the identification of aptitude adjustment following the completion of the module. The confidentiality of each participant will be maintained, and all recorded responses will be anonymous without any personal identifiers to preserve the unbiased integrity of the results collected from the pre- and post-test data collection tools. The investigators anticipate that statistical analysis of the study results will reflect the effectiveness of the educational module regarding the improvement of anesthesia provider knowledge and attitude regarding the administration of a TIVA-based anesthetic to prevent anesthesia-associated breast cancer recurrence and metastasis in breast cancer patients presenting for breast cancer surgery. The data collected in this study is classified and will be stored and secured by the co-investigator on a password-protected laptop computer.

X. Results

Pre-Test Demographics

The educational module pre-test demographics are outlined below in Table 1. It is important to note that the post-test demographics are identical to the pre-test demographics; an anonymous link redirected the participant to the post-test for completion following the educational intervention VPP.

Table 1

Pre-Test Participant Demographics

Demographic	***n* (%)**
Total Participants	5 (100.00%)
Gender	
Male	1 (20.00%)
Female	4 (80.00%)
Age (Free Response)	
20-29	1 (20.00%)
30-39	2 (40.00%)
40-49	1 (20.00%)
No Response	1 (20.00%)
Ethnicity	
Caucasian	3 (60.00%)
Hispanic	1 (20.00%)
Asian	1 (20.00%)
Position/Title (Free Response)	
CRNA	4 (80.00%)
No Response	1 (20.00%)
Level of Education	
Doctorate	5 (100.00%)
Experience as an Anesthesia Provider	
5-10 years	1 (20.00%)
2-5 years	1 (20.00%)
1-2 years	3 (60.00%)

There were 5 participants (*n*= 5) in this study. The majority of participants were female (*n*= 4, 80.00%), compared to male (*n*=1, 20.00%). Participants were able to enter a free response to report their age; however, for the purpose of data analysis are divided according to decade: age 20-29 (*n*=1, 20.00%), age 30-39 (*n*=2, 40.00%), age 40-49 (*n*=1, 20.00%), and one participant omitted their response (*n*=1, 20.00%). Ethnicities of the participants in this study varied: Asian (*n*=1, 20.00%), Caucasian (*n*=3, 60.00%), and Hispanic (*n*=1, 20.00%). CRNAs represented the majority of participants (*n*=4, 80.00%); one participant omitted their response (*n*=1, 20.00%). All 5 of the participants reported a doctorate level of education (*n*=5, 100.00%).

Lastly, the representatives were questioned about their years of experience in the field, which demonstrated the following: 1-2 years (*n*=3, 60.00%), 2-5 years (*n*=1, 20.00%), and 5-10 years (*n*=1, 20.00%).

Pre-Test Knowledge of Breast Cancer Recurrence Secondary to Anesthetic Delivery

This section contains questions that assess the participants' knowledge of the anesthetic effects on breast cancer recurrence and metastasis. The majority of participants (60.00%) were aware that VAA-based anesthesia increases the risk of breast cancer recurrence and metastasis rates in breast cancer patients presenting for surgical intervention; however, one participant (20.00%) elected that both TIVA and VAA-based anesthesia have been associated with increased risk of breast cancer recurrence and metastasis. Alternately, one participant (20.00%) selected that neither TIVA or VAA-based anesthesia have implications on breast cancer recurrence and metastasis.

The second question within this category examined the participants' knowledge of the VAA association to increased pro-cancer markers in the miRNA of rats compared to the anesthetic agents utilized in a TIVA-based anesthetic. The majority of surveyors identified that VAA are linked to increased pro-cancer markers in the MiRNA of rats (80.00%), while one participant lacked knowledge of this topic (20.00%). Only 2 out of 5 participants (40.00%) recognized that breast cancer recurrence and metastasis secondary to surgical intervention is a result of the impairment of immunological function by VAA during the perioperative period, while 2 out of 5 surveyors (40.00%) believed breast cancer recurrence and metastasis secondary to surgical intervention was multifactorial involving VAA and inadequate margins by the surgeon. One participant (20.00%) believed the result of breast cancer recurrence and metastasis secondary to surgical intervention was only attributed to inadequate margins by the surgeon.

Lastly, the participants were least versed on the overall implications of the mode of anesthetic delivery on breast cancer recurrence and metastasis. Most surveyors (60.00%) selected that it was true that anesthetic selection only posed a minimal risk for breast cancer recurrence and metastasis in breast cancer patients undergoing surgical intervention; however, 2 out of 5 participants (40.00%) identified the magnitude of anesthetic selection on long-term breast cancer outcomes.

Pre-Test Knowledge of Mechanism of Action of Anesthetics on Cytotoxic Physiology

This series of questions serves to elucidate the anesthesia providers' knowledge of anesthetic agent effects on cytotoxic and immunologic function in the perioperative period. The majority of participating anesthesia providers (80.00%) were aware that anesthetic agents may impair and/or support immunologic function, while 1 out of the 5 anesthesia providers (20.00%) answered that the aforementioned statement was false. The next two questions required the participants to select more than one answer; however, 2 out of 5 participants only selected one option. For the aforementioned reason, it is significant to note that only the selection of both correct answer choices selected by the surveyor were deemed correct.

Only 2 out of 5 participants (40.00%) accurately identified NK-1 cells and MiRNA as the primary culprits for the cytotoxic effects that contribute to the prevention of cancer cell migration and proliferation in the perioperative period. As previously stated, 2 out of 5 (40.00%) participants failed to select two answer choices as directed in the question and 1 out 5 (20.00%) only selected one correct option. All of the participating anesthesia providers demonstrated a knowledge deficit regarding the NK-1 cell immunological functions, reflected by the 0 out of 5 participants (0.00%) that answered the question correctly; however, 2 out of 5 (20.00%) of participants failed to select 2 answer choices as instructed in the question.

Only 1 out of 5 (20.00%) participating anesthesia providers were aware of the impact of VAA on overall immunological function in the perioperative period including the proliferation and migration of cancerous cells and the direct impairment of the cytotoxic effects of NK-1 cells; thus, leading to breast cancer recurrence and metastasis. An obvious knowledge deficit regarding the MOA of anesthetic agents on cytotoxic physiology exists among the participating anesthesia providers in this study, as evidenced by the recorded responses to the pre-educational module assessment questions in this category.

Pre-Test Knowledge of TIVA to Prevent Breast Cancer Recurrence and Metastasis

There was a notable knowledge deficit amongst participants (0.00%) regarding TIVA as the optimal anesthetic approach to prevent breast cancer recurrence and metastasis relative to the immunologic pathophysiology and MOA; however, 2 out of 5 participants (40.00%) failed to select 3 answer choices as directed in the question. Most surveyors (60.00%) were able to distinguish that a combined TIVA-based anesthetic with regional and multimodal adjuvants is the best anesthetic method to reduce the risk of breast cancer recurrence and metastasis. The majority of participants (60.00%) knew that breast cancer patients that underwent breast cancer surgery and received TIVA had reduced 1- and 5-year breast cancer recurrence and metastasis rates, compared to those that received VAA.

Pre-Test Aptitude for Standardized TIVA for Breast Cancer Patients Undergoing Surgery

There were varying responses regarding the anesthesia providers' attitude and willingness toward the administration of TIVA for the anesthetic management of breast cancer patients presenting for surgical intervention. There were equal responses (40.00%) where participating anesthesia providers would either most likely use or somewhat likely use TIVA in the anesthetic

management of breast cancer patients undergoing breast cancer surgery. Only one respondent reported (20.00%) that they are somewhat unlikely to use.

Post-Test Knowledge of Breast Cancer Recurrence Secondary to Anesthetic Delivery

Post-test knowledge of breast cancer recurrence secondary to anesthetic delivery incorporates data regarding the participants' knowledge of the anesthetic effects on breast cancer recurrence and metastasis following the completion of the educational intervention. All of the surveyors (100.00%) successfully identified that VAA-based anesthesia increases the risk of breast cancer recurrence and metastasis rates in breast cancer patients undergoing surgical intervention. Equally favorable results demonstrated a thorough comprehension that VAA are implicated in the increased pro-cancer markers in the MiRNA of rats, compared to TIVA (100.00%). There was no improvement among participants regarding the knowledge of breast cancer recurrence and metastasis causes during surgical intervention (40.00%); surveyors attributed inadequate margins by the surgeon as an additional cause of breast cancer recurrence and metastasis among the breast cancer patients. Finally, most participants (60.00%) acknowledged that there is a great risk of breast cancer recurrence and metastasis associated with the mode of anesthetic delivery and the selection of anesthetic agents utilized in the anesthetic management of patients with breast cancer that undergo surgical intervention. Table 2 illustrates the differences in responses from the pre- and post-tests, as well as, the improvement percentage.

Table 2
Difference in Pre- and Post-Test (Knowledge of Breast Cancer Recurrence Secondary to Anesthetic Delivery)

True Responses	*Pre-test*	*Post-test*	*Difference*
Which type of anesthesia increases the risk of breast cancer recurrence and metastasis rates in breast cancer patients presenting for surgical intervention?	60.00%	100.00%	**40.00%**
Volatile anesthetic agents (VAA) are linked to increased pro-cancer markers in the miRNA of rats compared to total intravenous agents (TIVA), such as propofol; true or false?	80.00%	100.00%	**20.00%**
Breast cancer recurrence and metastasis secondary to surgical intervention is:	40.00%	40.00%	**0.00%**
Patients with breast cancer that undergo surgical intervention are at a MINIMAL risk for breast recurrence and metastasis secondary to the mode of anesthetic delivery and the selection of anesthetic agents; true or false?	40.00%	60.00%	**20.00%**

In Table 2 shown above, there was an overall increase in anesthesia provider knowledge of breast cancer recurrence and metastasis secondary to anesthetic delivery. There was notable improvement (40.00% increase) in the participant knowledge of VAA implications on increased risk for breast cancer recurrence and metastasis rates in breast cancer surgical patients. There was also a knowledge improvement regarding VAA effects on pro-cancer markers in the MiRNA of rats (20.00%) and the severe impact of the mode of anesthetic delivery and selection of anesthetic agents on breast cancer recurrence and metastasis (20.00%); however, participants continue to report inadequate margins as the culprit for increased breast cancer recurrence and metastasis rates in breast cancer patients undergoing surgical intervention (reflected by a 0.00% increase).

Post-Test Knowledge of Mechanism of Action of Anesthetics on Cytotoxic Physiology

Post-test knowledge of the mechanism of action of anesthetics on cytotoxic physiology improved the anesthesia providers' knowledge of anesthetic agent effects on cytotoxic and immunologic function in the perioperative period following the completion of the educational

module. While only a 20.00% increase, all of the participating anesthesia providers (100.00%) knew that anesthetic agents may impair and/or support immunological function. There was no improvement of knowledge demonstrated between the pre- and post-test (40.00%) regarding the fact that NK-1 cells and MiRNA cytotoxic cells responsible for the prevention of cancer cell migration and proliferation in the peri-operative period; however, 2 out of 5 participants (40.00%) failed to select 2 answer choices and instructed in the question. A knowledge increase (40.00%) regarding the immunological function and MOA of NK-1 cells in the peri-operative period is acknowledged, as none of the anesthesia providers answered this question correctly in the pre-test. Lastly, the greatest knowledge improvement in this series includes the detrimental effects and MOA of

VAA on immunological function and is evidenced by a 60.00% difference.

Table 3 outlines the differences in responses from the pre- and post-tests, as well as, the improvement percentage for the knowledge of anesthesia providers in this question theme.

Table 3

True Responses	***Pre-test***	***Post-test***	***Difference***
Anesthetic agents may impair and/or support immunologic function; true or false?	80.00%	100.00%	**20.00%**
Which of the following are primarily credited for the cytotoxic effects responsible for the prevention of cancer cell migration and proliferation in the perioperative period? (Select 2).	40.00%	40.00%	**0.00%**
Natural Killer Cells (NK-1) are responsible for which of the following immunological functions in the peri-operative period? (Select 2)	0.00%	40.00%	**40.00%**
Which of the following accurately describes the impact of volatile anesthetic agents (VAA) on immunological function?	20.00%	80.00%	**60.00%**

Difference in Pre- and Post-Test (Knowledge of Mechanism of Action of Anesthetics on Cytotoxic Physiology)

It is acknowledged that there was a knowledge improvement following completion of the educational module, except for 1 out of 4 questions. This suggests that the educational module successfully increased the anesthesia providers' knowledge of anesthetics on cytotoxic physiology.

Post-Test Knowledge of TIVA to Prevent Breast Cancer Recurrence and Metastasis

Post-test knowledge of TIVA to prevent breast cancer recurrence and metastasis details the increased knowledge amongst participating anesthesia providers that TIVA is the optimal mode of anesthetic to prevent breast cancer recurrence and metastasis in patients with breast malignancy presenting for breast cancer surgery. There was a congruent increase of anesthesia provider knowledge (40.00%) for each question within this category. It is important to note that all 5 (100.00%) of participants were able to correctly identify that a combined TIVA-based anesthetic with regional and multimodal adjuvants is the optimal anesthetic approach for the aforementioned patient population following the completion of the educational module. Additionally, 100.00% of surveyors were able to report that breast cancer patients that underwent breast cancer surgery and received TIVA had reduced 1- and 5-year breast cancer recurrence and metastasis rates, compared to those that received VAA. The comparison of pre- and post-module knowledge is demonstrated below in Table 4.

Table 4

True Responses	*Pre-test*	*Post-test*	*Difference*
The mechanism of action and/or pathophysiology by which total intravenous anesthetic (TIVA) agents support immunological function includes: (Select 3)	0.00%	40.00%	**40.00%**
The best anesthetic method to REDUCE the risk of breast cancer recurrence and metastasis is:	60.00%	100.00%	**40.00%**
Breast cancer patients that underwent breast cancer surgery and received a total intravenous anesthetic (TIVA) had reduced 1- and 5-year breast cancer recurrence and metastasis rates, compared to those that received volatile anesthetic agents (VAA); true or false?	60.00%	100.00%	**40.00%**

Difference in Pre- and Post-Test (Knowledge of TIVA to Prevent Breast Cancer Recurrence and Metastasis)

Table 4 delineates an increase in anesthesia provider knowledge that a TIVA-based anesthetic is the optimal mode of anesthetic delivery to prevent anesthesia-associated breast cancer recurrence and metastasis in breast cancer patients undergoing breast cancer surgery.

Post-Test Aptitude for Standardized TIVA for Breast Cancer Patients Undergoing Surgery

The final section of the data collection analyzes the participants' attitude toward the adoption of a standardized TIVA-based anesthetic care of breast cancer patients presenting for surgical intervention following the completion of the educational module. Although the researchers of this study hoped that all participants of this study would opt to utilize a TIVA-based anesthetic due to the implications of VAA, only 4 out of 5 (80.00%) of participating anesthesia providers stated that they would most likely use TIVA in the anesthetic management of the aforementioned surgical patient population. There was an overall improvement of the anesthesia provider attitude toward a TIVA-based anesthetic approach (40.00%) increase from the pre- to post- educational module assessments, as reflected in Table 5.

Table 5

Difference in Pre- and Post-Test (Aptitude for Standardized TIVA for Breast Cancer Patients Undergoing Surgery)

True Responses	*Pre-test*	*Post-test*	*Difference*
What is your attitude in utilizing total intravenous anesthesia (TIVA) for the anesthetic management of breast cancer patients presenting for surgical intervention?	40.00%	80.00% ….	**40.00%**

Summary

Overall, the results reflect that there was a degree of improvement in correct answers from the pre- to post-educational module assessment. There was an increase in knowledge and attitude amongst the participating anesthesia providers following the completion of this educational intervention.

XI. Discussion

Limitations

Limitations of this study include the small sample size (n= 5). This project was disseminated to the anesthesia group at a large private hospital. A multi-center study that incorporates additional anesthesia groups would have been ideal and likely strengthen the validity of the study results. Time was an additional barrier to the study, as the candidates had only two weeks to initiate and complete all phases of the educational module. The researchers believe that a longer timeframe would have solicited greater participation from anesthesia providers; thus, adding value to the project with a larger sample size. Lastly, the online delivery

method of the project may have impacted the overall participation from anesthesia providers due to the asynchronous format and a two-week deadline to complete the survey.

Future Implications for Advanced Practice Nursing

While many variations of malignancy fall under the looming cancer umbrella, breast cancer is reportedly the most aggressive and prevalent origins of cancer and the primary cause of cancer-related death among women in the US.[1-2,22] As breast malignancy diagnoses continue to climb, the requirement for the recommended treatment involving surgical intervention to eradicate the cancerous tissue grows, respectively. Research suggests that the mortality associated with breast cancer diagnosis is triggered by recurrence, or metastasis, that occurs after resection of the primary tumor secondary to the circulation of tumor cells throughout the peri-operative period and concurrent suppression of the patient's immune system under surgical conditions, particularly in relation to VAA delivery. [3, 7-13] Current evidence-based research has illuminated the impactful role that anesthesia providers may have on the long-term outcomes of patients with breast malignancy presenting for surgical intervention via the selection of a TIVA-based anesthetic approach.[22]

The high-level research studies included as the basis of this study echo the recurring themes regarding the correlation between TIVA anesthesia and reduced breast cancer recurrence and metastasis in the surgical breast cancer patient population with supporting evidence and statistics; however, standardization of the anesthetic management of the target patient population has yet to be established. Since the evidence-based research-to-clinical practice gap exists, it is critical to inform anesthesia providers of the implications of anesthetic delivery in breast cancer patients to overcome the knowledge deficit and initiate a cultural shift toward the adoption of a TIVA-based anesthetic for patients with breast malignancy presenting for breast surgery. All

eight of the studies included in research for this project emphasized the significance of anesthetic technique in the management of the investigative patient population: the detrimental impact of VAA on the immunologic response and cancer cell proliferation; the efficacy of TIVA in suppressing the peri-operative stress response; and reduced breast cancer recurrence rates in patients that received TIVA-based anesthetic compared to those that received VAA. The purpose of this educational intervention was to unite the identified themes to facilitate a positive change to anesthetic practice that optimizes the quality of life of patients with breast cancer presenting for surgical intervention.

In summary, the evidence ascertained from the eight aforementioned studies solidified the foundation for this quality improvement (QI) project, which serves as a catalyst to standardize the adoption of a TIVA-based approach for the anesthetic management of patients with breast malignancy presenting for surgical intervention. The author of this QI project aimed to bridge the knowledge-to-clinical practice gap among anesthesia providers regarding the optimal anesthetic management to reduce the risk of breast cancer recurrence and promote long-term survival in this vulnerable patient population. The outcomes of this educational intervention are critical to the identification of the strategies required to enhance the anesthesia providers' capacity to improve the quality of life and reduce the risk of life-altering implications with the selection of their anesthetic approach in breast cancer patients.

It is evident that the administration of this educational module expounds the anesthesia providers' knowledge of anesthesia-associated breast cancer recurrence and metastasis in breast cancer patients presenting for surgical intervention. Overall, the data demonstrates that the educational intervention was efficacious in increasing the anesthesia providers' knowledge and propensity regarding the administration of a TIVA-based anesthetic to reduce breast cancer

recurrence and metastasis in breast cancer patients undergoing breast cancer surgery. It is prudent to present the success of this educational intervention with other clinical settings in an attempt to initiate a paradigm shift in the anesthetic care of the breast cancer patient population undergoing surgical intervention. Additional research that focuses on the best anesthetic selection to optimize the breast cancer patient population, as well as, the dissemination of this educational module to other clinical settings is recommended to substantiate our findings and prompt a universal practice change.

Appendix

Appendix A

Protocol Title: "Total Intravenous Anesthesia to Reduce Metastasis and Recurrence Rates in Patients Presenting for Breast Cancer Surgery: An Educational Intervention"

The Florida International University Office of Research Integrity has reviewed your research study for the use of human subjects and deemed it Exempt via the **Exempt Review** process.

IRB Protocol Exemption #: IRB-22-0176 **IRB Exemption Date:** 04/27/22
TOPAZ Reference #: 111546

As a requirement of IRB Exemption you are required to:

1) Submit an IRB Exempt Amendment Form for all proposed additions or changes in the procedures involving human subjects. All additions and changes must be reviewed and approved prior to implementation.
2) Promptly submit an IRB Exempt Event Report Form for every serious or unusual or unanticipated adverse event, problems with the rights or welfare of the human subjects, and/or deviations from the approved protocol.
3) Submit an IRB Exempt Project Completion Report Form when the study is finished or discontinued.

Special Conditions: N/A

For further information, you may visit the IRB website at http://research.fiu.edu/irb.

MMV/em

Appendix B

Miami Beach Anesthesiology Associates, Inc.

Mount Sinai Medical Center • Division of Anesthesia

S. Howard Wittels MD
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Hector Davila MSS, MD
Executive Director

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Vice Chairman

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Co-Assistant Director

Flor Marin MD

Gerald Rosen MD
Residency Program
Director

Jason Wigley MD
Residency Program
Co-Assistant Director

Alexander Volsky MD

Jennifer Wright MD

J.P. Mato DNP, CRNA
CRNA Director & SRNA
Coordinator

Paula Schultz DNP, CRNA
OB-Chief CRNA

February 1, 2022

Dr. Ann Miller, DNP, CRNA, APRN
Associate Professor
Department of Nurse Anesthesiology
Florida International University

Dr.Miller

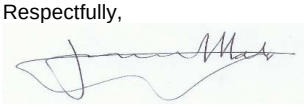
Thank you for inviting Mount Sinai Medical Center to participate in Doctor of Nursing Practice (DNP) project conducted by Kiersten De La Vega entitled “Total Intravenous Anesthesia to Reduce Metastasis and Recurrence Rates in Patients Presenting for Breast Cancer Surgery: An Educational Intervention” in the Nicole Wertheim College of Nursing and Health Sciences, Department of Nurse Anesthesiology at Florida International University. I have given the student permission to conduct the project using our providers.

Evidence-based practice's primary aim is to yield the best outcomes for patients by selecting interventions supported by the evidence. This proposed quality improvement project seeks to investigate and synthesize the latest evidence.

We understand that participation in the study is voluntary and carries no overt risk. All Division of Anesthesia providers are free to participate or withdraw from the study at any time. The educational intervention will be conveyed by a 15-minute virtual PowerPoint presentation, with a pretest and posttest questionnaire delivered by a URL link electronically via Qualtrics, an online survey product. Responses to pretest and posttest surveys are not linked to any participant. The collected information is reported as an aggregate, and there is no monetary compensation for participation. All collected material will be kept confidential, stored in a password encrypted digital cloud, and only be accessible to the investigators of this study: Kiersten De La Vega and Dr. Miller.

Once the Institutional Review Board's approval is achieved, this scholarly project's execution will occur over two weeks. Kiersten De La Vega will behave professionally, follow standards of care, and not impede hospital performance. We support the participation of our Division of Anesthesia providers in this project and look forward to working with you.

Respectfully,



Jampierre (J.P.) Mato, DNP, CRNA, APRN
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SRNA Coordinator/Supervisor
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Appendix C

Proposed Method for Data Collection

Pre-Survey and Post-Survey

INTRODUCTION

The primary aim of this Quality Improvement Project is to enhance the knowledge of anesthesia providers regarding the correlation between TIVA and reduced breast cancer recurrence and metastasis compared with VAA via a comprehensive educational module to initiate a paradigm shift in the anesthetic management of surgical patients with breast cancer presenting for surgery. Please answer the question below to the best of your ability. The questions are either in multiple choice or true/false format and are meant to measure knowledge and perceptions on anesthetic selection for breast cancer patients presenting for surgical intervention and the effects of anesthetics on breast cancer patient long-term outcomes.

I. DEMOGRAPHICS

1. Gender:
    A. Male
    B. Female
    C. Prefer Not to Answer
2. Age: _____
3. Ethnicity:
    A. Hispanic
    B. Caucasian
    C. African American
    D. Asian

E. Other

F. Prefer not to answer

4. Position/Title: _____

5. Level of Education

A. Certificate

B. Bachelors

C. Masters

D. Doctorate

E. Other

6. How many years have you been an anesthesia provider?

A. Over 10

B. 5-10 years

C. 2-5 years

D. 1-2 years

II. KNOWLEDGE ACCURACY

1. Which type of anesthesia increases the risk of breast cancer recurrence and metastasis rates in breast cancer patients presenting for surgical intervention?

A. Total Intravenous Anesthesia (TIVA)

B. Volatile Anesthetic Agents (VAA)

C. Both A and B

D. Neither A nor B

2. Volatile anesthetic agents (VAA) are linked to increased pro-cancer markers in the miRNA of rats compared to total intravenous agents (TIVA), such as propofol?

A. True

B. False

3. Anesthetic agents may impair and/or support immunologic function; true or false?

    A. True

    B. False

4. Which of the following are primarily credited for the cytotoxic effects responsible for the prevention of cancer cell migration and proliferation in the perioperative period? (Select 2).

    A. Natural Killer Cells (NK-1)

    B. Neutrophils

    C. T & B Lymphocytes

    D. miRNA

5. Natural Killer Cells (NK-1) are responsible for which of the following immunological functions in the peri-operative period? (Select 2)

    A. Inhibition of adrenergic activation associated with surgical stress

    B. Prevention of cancer cell migration and proliferation

    C. Inhibition of cancer cell marker concentrations in the post-operative period

    D. Prevention of cancer cell migration, but not proliferation

    E. Prevention of cancer cell proliferation, but not migration

6. The mechanism of action and/or pathophysiology by which total intravenous anesthetic (TIVA) agents support immunological function includes: (Select 3)

    A. Increased natural killer (NK-1) cell response

B. Increased cyclooxygenase-2 (COX-2) activity, thus increased production of the foundational tumor-progression hormone, PGE2

C. Decreased cyclooxygenase-2 (COX-2) activity, thus decreased production of the foundational tumor-progression hormone, PGE2

D. Suppression of malignant cell metastasis in vitro throughout the peri-operative period

E. Suppression of malignant cell metastasis in vitro in the post-operative period

7. Breast cancer recurrence and metastasis secondary to surgical intervention is:

   A. A result of inadequate margins surgically removed by the surgeon in the intra-operative period

   B. Environmental exposures and lifestyle

   C. The impairment of immunological function by inhalational agents (VAA) during the perioperative period

   D. A&C

8. The best anesthetic method to REDUCE the risk of breast cancer recurrence and metastasis is:

   A. TIVA anesthetic with 0.5 MAC of inhalational agents and non-opioid analgesics

   B. Combined TIVA-based anesthetic with regional and other multi-modal adjuvants

   C. Any mode of anesthetic is acceptable, as long as there are no contraindications

   D. VAA maintained at 1.3 MAC

9. Which of the following accurately describes the impact of volatile anesthetic agents (VAA) on immunological function?

A. VAAs impair the cytotoxic effects of immunocompetent cells, such as natural killer (NK-1) cells; thus, contributing to breast cancer cell migration

B. VAAs impair the cytotoxic effects of immunocompetent cells, such as natural killer (NK-1) cells; thus, contributing to breast cancer cell proliferation

C. VAAs impair the cytotoxic effects of immunocompetent cells, such as natural killer (NK-1) cells; thus, reducing the body's resistance to cancer cell implantation, resulting in recurrence and metastasis

D. All of the above

10. Patients with breast cancer that undergo surgical intervention are at a MINIMAL risk for breast recurrence and metastasis secondary to the mode of anesthetic delivery and the selection of anesthetic agents; true or false?

    A. True

    B. False

11. Breast cancer patients that underwent breast cancer surgery and received a total intravenous anesthetic (TIVA) had reduced 1- and 5-year breast cancer recurrence and metastasis rates, compared to those that received volatile anesthetic agents (VAA); true or false?

    A. True

    B. False

III. ATTITUDE TOWARD PRACTICE CHANGE

12. What is your attitude in utilizing total intravenous anesthesia (TIVA) for the anesthetic management of breast cancer patients presenting for surgical intervention?

    A. Will most likely use

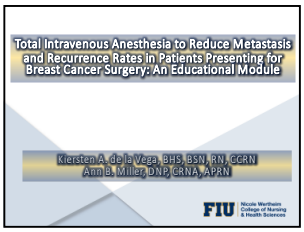
    B. Will somewhat likely use

    C. Somewhat unlikely to use

    D. Most unlikely to use

Appendix D

Educational Module



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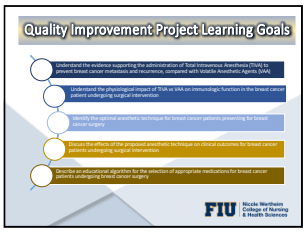

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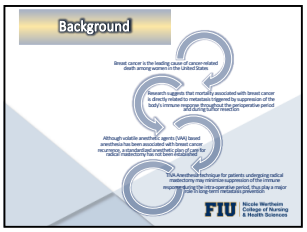

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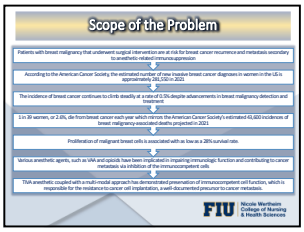

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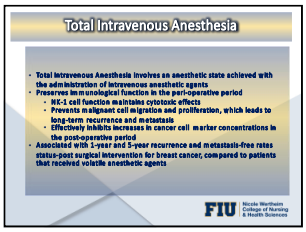

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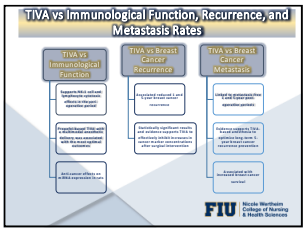

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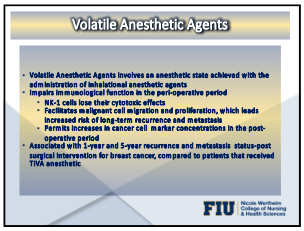

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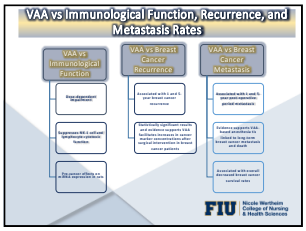

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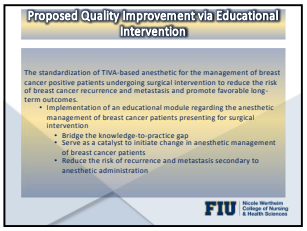

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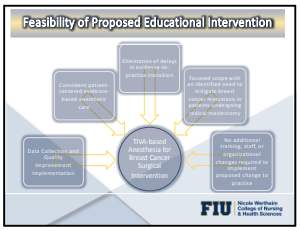

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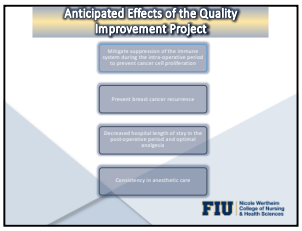

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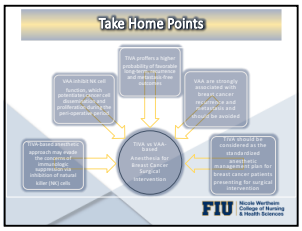

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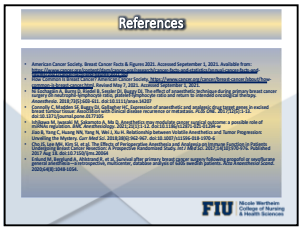

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