

The Impact of Anesthetic Choice to Decrease Cancer Recurrence and Morbidity

Sun hee Kim, BSN, SRNA and Jean I. Morrison, BSN, SRNA, CCRN-CSC

Nurse Anesthesia Program, Adventist University of Health Sciences

Project Mentor: Matthew Newbern, MD, Anesthesiologist, USAP-JLR Medical Group

Project Chair: Sarah Snell, DNP, CRNA, ADU-NAP Department Instructor

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Abstract

The number of cancer patients worldwide is increasing, and surgical resection is often the first choice for removal of the primary tumor. The perioperative period is a crucial time to promote or prevent tumor recurrence by incorporating evidenced-based research into practice. There is ongoing research that inhalational anesthesia can depress the immune system, while intravenous anesthesia with propofol can inhibit tumor growth and enhance cell-mediated immunity. A thorough literature review and synthesis was completed regarding the effects of inhalational versus the intravenous anesthetic propofol in preventing cancer recurrence. The aim of this scholarly project was to increase the 2019 Advent University of Health Sciences (ADU) student registered nurse anesthetists (SRNAs) cohort's knowledge base regarding anesthetic selection. After informed consent was obtained, a 30-minute PowerPoint presentation was conducted, and an identical pre- and post-test were given to assess for an increase in the 2019 ADU SRNAs knowledge base. A paired sample t test showed a statistically significant ($p < 0.0001$) increase in test scores from 30.9% to 83.6%. The results of this scholarly project suggest that the 2019 ADU NAP cohort had a statistically significant increase in knowledge regarding the appropriate perioperative anesthetic selection to promote overall survival and decrease cancer relapse.

Keywords: anesthesia, anesthesia, anesthetic agents, cancer, cancer recurrence, circulating tumor cells, desflurane, immunosuppression, inhalational anesthetics, isoflurane, oncologic surgery, propofol, total intravenous anesthesia, tumor removal, and sevoflurane.

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Anesthesia and Cancer Recurrence

Cancer recurrence following primary removal of a cancerous tumor is dismally high (Cassinello, Prieto, del Olmo, & Strichartz, 2015; Gottshalk, Sharma, Ford, Durieux, & Tiouririne, 2010; Tavare, Perry, Benzonana, Takata, & Ma, 2012). The perioperative period is an important time period for enhancing the immune system and mitigating the stress response to prevent cancer recurrence (Hiller, Brodner, & Gottschalk, 2013; Horowitz, Neeman, Sharon, & Ben-Eliyahu, 2015; Kim, 2018; Piegler, & Beck-Schimmer, 2016). A knowledge gap exists on the current subject with the student ADU SRNA 2019 cohort. A thorough literature review and synthesis was conducted on the effects of perioperative period interventions to prevent cancer recurrence focusing on volatile anesthetics versus the intravenous anesthetic propofol.

Problem

Cancer is a leading cause of death worldwide and will more than double its impact from 12.7 million cases with a mortality of 7.6 million in 2008 to 26.4 million cases with 17 million deaths per year by 2030 (Huang et al., 2014). This globally affects more than one-quarter of the world's population (Tohme, Simmons, & Tsung, 2017). First line treatment for cancer therapy is often surgical removal of the primary malignant tumor (Cassinello et al., 2015; Kim, 2018; Piegler et al, 2016; Tavare et al., 2012). However, even in well-localized cancer with negative stations, tumor recurrence can occur from micrometastasis of circulating tumor cells (Cassinello et al., 2015; Piegler et al, 2016). The stress response during the tumor removal and the medications utilized by the anesthesia provider can influence the possibility of recurrence and overall mortality. Recently, a great variety of clinical research has been published that implies a high correlation between specific anesthetic technic and cancer recurrence after surgery (Benzonana et al., 2013; Buckley, McQuaid, Johnson, & Buggy, 2014; Huang et al., 2014; Liang

et al.,2015).

Anesthetic medications can contribute to a cascade of events that lead to circulating tumor cell dissemination such as angiogenesis at the primary site, invasion of the tissues, and proliferation at a distal site. Surgery activates the sympathetic nervous system and inhibits natural killer cells (NK cells) and natural cell-mediated immunity which normally abate the metastatic cells (Luo et al., 2015). The reoccurrence of cancer can have a higher rate of mortality than the original tumor and is often difficult to treat with resistance to medications (Huang et al., 2014).

It is essential for SRNAs to realize the perioperative period is crucial for choosing the appropriate anesthetic technique to prevent tumor recurrence and enhance the immune system. Inhalational anesthetics such as sevoflurane and isoflurane may decrease NK cell activity and cell-mediated immunity leading to tumor recurrence following surgery whereas propofol does not suppress NK cells (Buckley, McQuaid, Johnson, & Buggy, 2014). Propofol-based anesthesia technique reduces surgical stress, decreases angiogenesis and keeps the immune system in balance in the perioperative period (Kim, 2018). We therefore recommend that the ADU SRNA 2019 cohort receive an educational PowerPoint regarding the potential impact of inhalational agents and propofol on cancer recurrence.

Project Questions

Two research questions were asked that guided the literature review regarding anesthetic use and the effect on cancer recurrence as well as the education of student registered nurse anesthetists (SRNAs) regarding current research and best practices.

PICOT: In patient's undergoing primary tumor resection for cancer (P), how does the use of inhalational anesthetics (I) compare to the intravenous anesthetic propofol (C) during the

perioperative period (T) impact cancer recurrence (O)?

PICOT: In the ADU SRNA 2019 cohort (P), does a 30-minute (T) PowerPoint presentation regarding anesthetic choice to decrease cancer recurrence (I) lead to a significant increase in knowledge base (O)?

Literature Review and Synthesis

The evolution of tumor recurrence begins with the dissemination of circulating tumor cells (CTCs) prior to surgery, and with primary tumor removal (Benzonana et al., 2012; Buckley et al., 2014; Huang et al., 2014; Piegler et al., 2016). During surgical removal of the primary tumor, recurrence can occur in two different ways. CTCs are comprised of a complex milieu both coexisting within the primary tumor and located at distal sites left in dormancy with the normal immune system. The removal of the primary tumor can cause micro metastasis of CTCs from disruption of the neoplasm at the primary site during surgical resection. Distal CTCs can activate with surgical immunosuppression, leading to the trigger and spread of malignant cells (Cassinello et al., 2015; Kim, 2018; Gottshalk et al. 2010; Tavare et al., 2012). Most cancer related deaths after the primary tumor removal are related to metastasis (Horowitz et al., 2015; Liang et al., 2015; Shi et al., 2014). The number of CTCs is a prognostic indicator for the severity of cancer, sequelae, and survivability (Lim et al., 2015; Masuda et al., 2016; Piegler & Beck-Schimmer, 2016; Tavare et al., 2012; Tohme et al., 2017). Recent research indicates that survivability from tumor removal is unfortunately low at 8.5-60% depending on the location of the primary tumor (Center for Disease Control [CDC], 2018; Liu et al., 2016; Luo et al., 2015). This has led to research about the perioperative period being crucial for impacting the survivability of cancer patients (Kim, 2018; Horowitz et al., 2015; Piegler et al., 2016). Inhalational anesthetics versus total intravenous anesthesia with propofol has been a specific

target of this research. This literature review will therefore focus on the differences between inhalational anesthetics and the intravenous anesthetic propofol regarding immunosuppression, hypoxia induced factors (HIFs), angiogenesis, and metastasis with long-term survivability.

Immunosuppression

The tumor may shed cancerous cells into circulation, which leads to micro metastasis despite careful surgical resection (Hiller et al., 2013 ; Horowitz et al., 2015; Tavare et al., 2011). NK cells, which are part of the innate immune system, are a first line of defense in destroying tumor cells, micro metastasis, and infected cells. NK cells would normally attack and destroy cancerous cells, but the surgically induced stress response decreases the typical response and function of the NK cells (Buckley et al., 2014; Liu et al., 2016). This is a direct result of sympathetic nervous system (SNS) and hypothalamic-pituitary-adrenal (HPA) activation.

The SNS activation increases malignant cell propagation and angiogenesis by stimulating the beta receptors and suppressing the NK cells (Gottshalk et al., 2010; Horowitz et al., 2015; Kim, 2018). The SNS releases catecholamines and prostaglandins that cause inflammation, suppress cell mediated immunity, and increase circulation to the tumor itself (Cassinello et al., 2015; Horowitz et al., 2015; Luo et al., 2015). The HPA system is activated by pain, and the stress response releases glucocorticoids which lead to inflammation and the spread of tumor cells. Controlling perioperative pain is important to reducing the surgical stress response and SNS activation. However, specific agents may affect cell mediated immunity positively or negatively, but paradoxically, pain control will attenuate surgical stress and improve the NK cell count (Meserve, Kaye, Parbhakar, & Urman, 2014). Inhalational anesthetics have been shown to decrease NK cell count promoting metastasis, whereas propofol has been shown to have anti-inflammatory properties by increasing NK cells and suppressing tumor growth (Buckley et al.,

2014; Luo et al., 2015; Wigmore, Mohammed, & Jhani, 2016; Zheng et al., 2018). A decreased immune response and inflammation leads to a hypoxic environment that increases cancer proliferation and metastasis through cell signaling from hypoxic induced factors (HIFs).

Cell Signaling, Angiogenesis, and Metastasis

Hypoxia increases the proliferation of cancer cells, and HIFs lead to a cascade of inflammatory mediators decreasing the host immune defenses. HIFs are transcription factors that regulate more than 60 target genes, causing decreased immunity by controlling angiogenesis, metabolism, pH regulation, proliferation, and metastasis (Liang et al., 2015; Tavaré et al., 2012). Higher levels of HIFs have been associated with poorer prognosis and survivability as they stimulate the growth of tumor cells over normal cells (Huang et al., 2014). Tissue inflammation caused by the tumor removal can set the environment up for the neoplastic disease to thrive. Volatile anesthetics cause upregulation of HIFs and create an environment of decreased immune surveillance (Luo et al., 2015). Sevoflurane and isoflurane upregulate hypoxia-induced factors and can cause tumor cell growth and migration (Benzonana et al., 2013; Huang et al., Liang et al., 2015; Shi et al., 2015).

Propofol suppressed HIFs via impaired translation of messenger RNA (Tavaré et al., 2012) decreases tumor seeding and CTC implantation (Du et al., 2018; Liang et al., 2015; Quin, Shen, Chen & Chen, 2018; Shi et al., 2015)). Long-term survival with inhalational versus intravenous anesthesia with propofol has been compared. Propofol showed improved long-term survivability over sevoflurane (Wigmore, Mohammed, & Jhanji, 2016; Zheng et al., 2018). It is important to note that some other investigations showed no statistical improvement for long-term oncologic outcomes between inhalational anesthetics and intravenous agents (Enlund et al., 2014; Kim et al., 2017; Oh et al., 2018). For the anesthetic provider, it is important to understand

the impact of HIFs on anesthetic selection during the perioperative period. The hypoxic environment sets up conditions for angiogenesis, cell proliferation, and metastasis (Cassinello et al., 2015; Huang et al., 2015; Lee et al., 2016; Luo et al., 2015; & Tavare et al., 2012).

Neovascularization of the tumor is controlled by angiogenic factors, such as vascular endothelial growth factor (VEGF), and angiopoietin-1 and 2 (Ang-1 and Ang-2) (Benzonana et al., 2013; Liu et al., 2015; Shi et al., 2015). Cancer cell growth is potentiated with angiogenic factors VEGF, Ang-1, and Ang-2 which decrease oxygen and nutrients, an ideal environment for cancer growth (Cassinello et al., 2015; Gottschalk et al., 2010; Huang et al., 2014; Kim, 2018; Piegeler, & Beck-Schimmer, 2016). These growth factors support an environment of tumor growth and the increased tumor size evolves into metastasis (Luo et al., 2014). Metastasis is affected by matrix metalloproteinase-2 and 9 (MMP-2 and MMP-9) by relaxing the cellular matrix to allow for cancer cells to spread into circulation and potentiate distal invasion (Luo et al., 2015; Zhang, Zhang, Wu, Feng, and Zhu, 2013). Pain and catecholamines increase MMPs and lead to the malignant cell proliferation and metastasis (Gottshalk et al., 2010; Horowitz et al., 2015). Cancer cells exposed to isoflurane showed a five-fold increase of MMP-2 and MMP-9, which are important enzymes that promote metastasis by breaking down the basement membrane (Benzonana et al., 2013; Luo et al., 2015). This indicates the inhalational agent's capability to increase malignancy. In contrast, propofol downregulated MMP-9 expression, which reduced the tumor cells' ability to metastasize and spread (Zhang et al., 2013). Propofol has shown anticancer effects on cell lines with the KRAS gene mutation, which functions as a cell signaling pathway (Song, Shen, Zhang, & Lian, 2014).

There is increased interest in the perioperative period and impact of inhalational anesthetic versus the intravenous anesthetic choice to enhance innate immunosuppression,

prevent tumor recurrence, and improve overall survivability. HIFs lead to a cascade of inflammatory mediators, and it is important to prevent their activation. Propofol seems to have a promising effect on preventing HIF activation. Multimodal anesthesia presents a challenge for future research with the isolation of different anesthetics to make equivalent comparisons. Future studies should include prospective randomized controlled studies with adequate power to confirm the anesthetic selection for decreased tumor recurrence, the promotion of natural immunity, and the attenuation of the SNS. When using similar multimodal interventions, it is imperative to isolate them to demonstrate efficacy of the controls (Liu et al., 2016). Several randomized control trials are currently in progress (Cassinello et al., 2015) and need to correlate data regarding the beneficial effects of propofol and intravenous anesthesia over inhalational anesthetics for practical implementation to occur.

A few confounding factors associated with propofol use were the need to use a Bispectral index (BIS) monitor for amnesia reference and the potential for a slower wakeup from anesthesia due to redistribution. Evidence has been presented supporting propofol as a possible anesthetic choice over inhalational anesthetics to support the immune system; although, large-scale multicenter randomized studies are needed to confirm the validity of these results.

Contribution and Dissemination/Justification

This project increased knowledge by utilizing an educational PowerPoint regarding recent research on how inhalational anesthetic agents and the intravenous propofol anesthetic affects immunosuppression, HIFs, and long-term cancer survival rates. A 30-minute PowerPoint presentation was implemented on October 4th, 2018 for the MSNA 504 course. Pre- and post-tests assessed for an increase in knowledge base in response to the educational PowerPoint. Dissemination of results, in the form of a poster board presentation will occur at the Spring 2019

research day.

Project Aims

The aim of this scholarly project was to increase the 2019 ADU SRNA cohort's knowledge base regarding how the perioperative use of inhalational anesthetics compared to the intravenous anesthetic propofol affects cancer recurrence in patients undergoing primary tumor resection. The primary aim was met as evidenced by a statistically significant increase in pre-test scores as compared to post-test scores.

Project Methods

This scholarly project had a quantitative design, utilized a convenience sample of 22 SRNAs from the 2019 ADU MSNA NAP cohort. In fall 2018, an educational PowerPoint was presented to 22 senior SRNAs of the MSNA NAP. The scholarly project team members educated all participants, 22 senior SRNAs, of informed consent, pre-and post-test before the PowerPoint presentation. All cohort 2019 SRNAs in attendance were given informed consent and asked to sign. Inclusion criteria were the senior SRNAs who signed the informed consent. Exclusion criteria included: the two senior SRNAs that were giving the presentation, those students who were absent or delayed, and those who refused to sign the informed consent. There were no senior SRNAs who refused to sign an informed consent or were late or absent. The participants were given an anonymous pretest before the PowerPoint presentation to protect their identity, which was collected before the PowerPoint presentation began. After the PowerPoint presentation, an opportunity for questions or comments on the scholarly presentation was provided. Finally, the scholarly project team members passed out the post-test, which was identical to the pre-test, to participants and collected them before participants left the presentation. Like the pretest, the post-test was taken anonymously. The key was shared between

the project chair and two authors of the project until the results of the pre-and post-test were compiled. The results were then entered into an Excel spread sheet and submitted to Dr. Roy Lukman for statistical analysis using the SPSS program. All pre- and post-tests were deidentified. The information was saved to a password protected One Drive which was only accessed by the scholarly project team members and the project chair. Once statistical analysis was completed, physical data was shredded, and the electronic record was deleted.

Timeline

The timeline for this scholarly project began May 11, 2018 and ends April 4, 2019. It will be divided over three academic trimesters. Trimester one was the foundation for the project. The scholarly project team's primary duty was to find a project topic and a partner and gain NAP approval. With the approval of the NAP office, the researchers applied to the Scientific Review Committee (SRC) and the Institutional Review Board (IRB) by July 16, 2018, with required documentations. Trimester two was for proceeding project implementation along with a PowerPoint presentation and data analysis for pre-and post-test by November 16, 2018. By April 2019, this project will be ended by completing a final draft of the scholarly project paper and exhibiting the poster of the project to faculties and students at ADU.

Data Collection Plan

Data collection occurred during the PowerPoint presentation on October 4, 2018. The pre-and post-tests were composed of the same ten multiple choices of questions approved by IRB. The scholarly project team members put 22 pre-and 22 post-tests in an envelope separately, the total of 44 envelopes. All participants took these two tests anonymously to protect their identity. The pre-test was done before the PowerPoint presentation, and post-test was completed directly after the PowerPoint presentation ended and all questions were answered. All

participants had adequate time, 10-15 minutes, to finish the tests. The scholarly project team members made sure there was no communication while participants were taking pre-and post-tests. There was a total of six exchanges between researchers and participants. The first two exchanges occurred when the scholarly project team members handed over consent to the individual participants and the participants returned the consent to the scholarly project team members individually after signing it. Two more exchanges occurred when the scholarly project team members gave the pre-test to the participant individually and when participants returned the pre-test to the scholarly project team members after completion. The last two exchanges were when the scholarly project team members gave the post-test to the participants and the participants submitted the post-test before leaving the classroom. Data compilation occurred one week later with anonymity of the participants maintained. The test results were then submitted to Dr. Roy Lukman at ADU to analyze statistically.

Evaluation Plan

The pre- and post-tests consisted of 10 questions evaluating the senior SRNAs' basic knowledge of anesthetic agents with both inhalational and intravenous agents related to tumor recurrence. A paired sample t-test with a significance threshold of $p < 0.05$ was utilized.

Limitations

There were several limitations to this scholarly project. The sample size was limited to 22 SRNAs from a single academic institution. Given the restricted sample size, replication may not be possible and may affect the validity of the results. Retention could not be measured by a post-test following a 30-minute Power Point presentation. Finally, the pre-and post-test were not validated or proven reliable.

Results

A paired sample t-test was conducted by Dr. Roy Lukman and the mean pre- and post-test scores were compared. The average pre-test scores were 30.9% with a standard deviation of 1.74 and a standard error mean of 0.37. The average post-test scores were 83.6% with a standard deviation of 2.05 and a standard error of 0.44. Mean test scores improved by 52.7% overall. The paired sample t-test showed a mean of -5.27 with a standard deviation of 1.31 and a mean standard error of 0.28. The 2-tailed significance was calculated at 0.0001. Therefore, the aim of this study was met as a statistical significance of 0.0001 was achieved between the pre- and post-test scores.

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre Test	3.0909	22	1.74326	.37166
	PostTest	8.3636	22	2.05971	.43913

Paired Samples Test									
		Paired Differences					t	df	
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference		t	df	Sig. (2-tailed)
					Lower	Upper			
Pair 1	PreTest PostTest	-5.27273	1.31590	.28055	-5.85617	-4.68929	-18.794	21	.000

Conclusion

The pre- and post-test scores were significantly increased ($p < 0.001$) suggesting effective communication and dissemination of information occurred and the 2019 ADU SRNA cohort's knowledge base regarding anesthetic selection to decrease cancer reoccurrence was improved. Limitations of this include not measuring long term retention since the posttest was given the same day as the presentation and a small convenient sample size.

The aim of this scholarly project was to increase the 2019 ADU SRNA cohort's knowledge base regarding anesthetic selection. Several large multicenter randomized trials

confirming anesthetic selection for improved survivability are currently in progress. The increase in the 2019 ADU NAP cohort's knowledge of appropriate anesthetic technique to promote survivability will positively lead to a clinical change in practice as more large scale trials become available.

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Appendix A Informed Consent

ADU NAP CAPSTONE PROJECT – INFORMED CONSENT

This is a Capstone Project called *The Impact of Anesthetic Choice to Decrease Cancer Recurrence and Morbidity* and is being completed by two students in the Nurse Anesthesia Program (NAP) at Adventist University of Health Sciences (ADU). This scholarly project is being supervised by a ADU faculty sponsor. We would like to invite you to participate in this project. The main purpose of this form is to provide information about the project, so you can decide about whether you want to participate.

WHAT IS THE PROJECT ABOUT?

The purpose of this project is to increase the SRNAs knowledge base regarding cancer recurrence in patient's undergoing primary tumor resection and how the perioperative use of inhalational anesthetics compares to the intravenous anesthetic propofol. The primary aim will be considered met if there is a statistically significant improvement in knowledge base from pre-test scores to post-test scores.

WHAT DOES PARTICIPATION IN THIS PROJECT INVOLVE?

If you decide to participate in this project, you will be asked to complete an anonymous pre-assessment, attend a classroom presentation, and then complete an anonymous post-assessment. The assessment will address an increase in knowledge from the lecture. Your participation by attendance at the presentation and completion of the survey is anticipated to take approximately 30 minutes.

WHY ARE YOU BEING ASKED TO PARTICIPATE?

Your participation in this study is voluntary. You may choose to not to participate. The decision to participate or not participate in this research study is completely up to you. If you choose not to participate your refusal to participate in this research study will involve no penalty or loss of benefits to you. If you choose to participate, you can change your mind later and withdraw your consent and discontinue participation from this study at any time. If you chose to withdraw informed the Primary Investigator (PI) of your wishes.

WHAT ARE THE RISKS INVOLVED IN THIS PROJECT?

Although no project is completely risk-free, we don't anticipate that you will be harmed or distressed by participating in this project.

ARE THERE ANY BENEFITS TO PARTICIPATION?

We don't expect any direct benefits to you from participation in this project. The possible indirect benefit of participation in the project is the opportunity to gain additional knowledge about in the perioperative period and impact of inhalational anesthetic versus the intravenous anesthetic choice to enhance innate immunosuppression, prevent tumor recurrence, and improve overall survivability.

HOW WILL THE INVESTIGATORS PROTECT PARTICIPANTS' CONFIDENTIALITY?

The results of the project will be published, but your name or identity will not be revealed. To maintain confidentiality of assessments, the investigators will conduct this project in such a way to ensure that information is submitted without participants' identification. Participants will be issued pre-testing and post-testing forms that will not include any identifiable information. A lettering system will correspond to the pre-and post- test belonging to the test taker, but it will not identify the test taker themselves. All paper materials will be stored in an unlabeled sealable folder to maintain anonymity. Forms will be kept at a secure location. After statistical information aggregation, and graduation of both researchers from the Nurse Anesthesia Program at ADU, testing forms will be disposed of appropriately according to SRC and IRB standards. Thus, the investigators will not have access to any participants' identities. Thus, the investigators will not have access to any participants' identities.

WILL IT COST ANYTHING OR WILL I GET PAID TO PARTICIPATE IN THE PROJECT?

Your participation will cost approximately one hour of your time but will require no monetary cost on your part. You will not be paid to participate.

VOLUNTARY CONSENT

You do not have to participate in this research study and choosing not to participate in this study will not involve any penalty or loss of benefit to you. The decision to participate or not participate in this research study is completely up to you. If you choose to participate, you can change your mind later and withdraw your consent and discontinue participation from this study at any time. If you chose to withdraw from the study informed the PI of your wishes.

By signing this form, you are saying that you have read this form, you understand the risks and benefits of this project, and you know what you are being asked to do. The investigators will be happy to answer any questions you have about the project. If you have any questions, please feel free to contact the Nurse Anesthesia Program at (407) 303-9331. If you have concerns about the project process or the investigators, please contact the Nurse Anesthesia Program at (407) 303-9331.

Participant Signature/ Participant Name (PRINTED LEGIBLY)

Date _____

Participant Name (PRINTED LEGIBLY)

Appendix B**Pre and Post Test**

Please mark the correct answer regarding anesthesia and cancer recurrence.

1. In well-localized cancer with negative stations, tumor recurrence can occur from
 - a. NK cells being released
 - b. micrometastasis of circulating tumor cells
 - c. macrometastasis of circulating tumor cells
 - d. tertiary site cell dissemination
2. SNS activation:
 - a. decreases malignant cell propagation and angiogenesis by stimulating the beta receptors and suppressing the NK cells
 - b. releases NK cells
 - c. increases malignant cell propagation and angiogenesis by stimulating the beta receptors and suppressing the NK cells
 - d. decreases the beta receptors
3. The HPA system is activated by pain, and the stress response releases
 - a. glucocorticoids which lead to inflammation and the spread of tumor cells.
 - b. insulin which decrease blood glucose.
 - c. NK cells
 - d. inhibitory cells
4. Inhalational anesthetics have been shown to _____ NK cell count promoting metastasis, whereas propofol has been shown to have anti-inflammatory properties by _____ NK cells and suppressing tumor growth
 - a. decrease, increasing
 - b. increase, decreasing
 - c. insulin, glucagon
 - d. glucagon, insulin
5. HIFs are transcription factors that regulate more than
 - a. one million target genes, causing increasing immunity
 - b. one million genes, causing decreased immunity
 - c. 60 target genes, caused increased immunity
 - d. 60 target genes, causing decreased immunity
6. The reoccurrence of cancer has a _____ rate of mortality compared to the original tumor.
 - a. lower
 - b. higher
 - c. the same
 - d. slower

7. What is angiogenesis and how does it play a role in cancer treatment?
 - a. A multistep biological process that stimulates the development of new blood vessels and tumor metastases while maintaining existing blood vessels.
 - b. A substance that inhibits the growth of new blood vessels that inhibits tumor metastases.
 - c. Good blood supply to provide itself with food and oxygen and to stop tumor blood vessel growth.
 - d. An anticoagulation activity that is associated with a reduction in metastasis of tumor
8. Most cancer-related deaths after the primary tumor removal are related to?
 - a. Infection
 - b. Bleeding
 - c. Metastasis
 - d. Drug toxicity
9. According to CDC 2018, what is the survivability from tumor removal surgery?
 - a. 8.5-60% depending on the location of the primary tumor
 - b. 20-75% depending on the location of the primary tumor
 - c. 40-85% depending on the location of the primary tumor
 - d. 50-95% depending on the location of the primary tumor
10. Sevoflurane and isoflurane _____ hypoxia-induced factors and can cause tumor cell growth and migration. In contrast, Propofol _____ HIFs via impaired translation of messenger RNA decreases tumor seeding and CTC implantation
 - a. upregulates, suppressed.
 - b. downregulates, upregulate.
 - c. downregulates, neutralized
 - d. upregulates, neutralized.

Answers:

1. a. Micrometastasis of circulating tumor cells
2. b. Increases malignant cell propagation and angiogenesis by stimulating the beta receptors and suppressing the NK cells
3. a. Glucocorticoids which lead to inflammation and the spread of tumor cells.
4. a. Decrease, increasing
5. d. 60 target genes, causing decreased immunity
6. b. Higher
7. a. A multistep biological process that stimulates the development of new blood vessels and tumor metastases while maintaining existing blood vessels.
8. c. Metastasis
9. a. 8.5-60% depending on the location of the primary tumor
10. a. Upregulates, suppressed.

Appendix C PowerPoint Presentation Slides

THE IMPACT OF ANESTHETIC CHOICE TO DECREASE CANCER RECURRENCE AND MORBIDITY

Sun hee Kim, BSN, SRNA
 Jean I. Morrison, BSN, SRNA, CCRN-CSC
 Project Mentor: Matthew Newbern, MD, Anesthesiologist, USAP Medical Group
 Project Chair: Sarah Snell, DNAP, CRNA, ADU-NAP Department Instructor
 Nurse Anesthesia Program, Adventist University of Health Sciences

Objectives

By the end of the presentation, the audience members should be able to:

- Recognize the perioperative period as an important time for choosing appropriate anesthetic techniques to prevent tumor recurrence.
- Understand the possibility of potential negative impact of inhalational agents may have on cancer recurrence by depressing the immune system.
- Understand that Propofol and total intravenous anesthesia (TIVA) may offer antitumor properties by inhibiting tumor growth and enhancing cell mediated immunity (CMI).

Problem

- Cancer is a leading cause of death worldwide with 12.7 million cancer patients in 2008 and 7.6 million mortality rate. By 2030 these figures are estimated to more than double (Huang et al., 2014).
- **The survivability from primary tumor removal is estimated at only 8.5-60% depending on the location of the primary tumor** (CDC, 2018).
- **Even in well-localized cancer with negative stations, tumor recurrence can occur from micro metastasis of circulating tumor cells** (Cassinello, Prieto, del Olmo, & Strichartz, 2015).
- **The recurrence of cancer has a higher rate of mortality than the original tumor and is often difficult to treat with resistance to medications** (Huang et al., 2014).

Problem

- The high rate of mortality has led to research about the perioperative period as an important step to prevent cancer recurrence and promote survivability.
- The stress response during the tumor removal and the medications utilized by the anesthesia provider can influence the possibility of recurrence and overall mortality.
- Anesthetic medications can contribute to a cascade of events that lead to tumor cell migration such as angiogenesis at the primary site, invasion of the tissues, and proliferation at the distal site.
- Surgery activates the sympathetic nervous system (SNS), inhibits natural killer cells (NK cells), and natural CMI which normally stops the metastatic cells.
- **Most cancer-related deaths after the primary tumor removal are related to metastasis.**

CASE STUDY

- A 40 year old female patient presents for wide excision of a left sided breast tumor with sentinel node identification and excision. The patient underwent GETA with the inhalational anesthetic Sevoflurane for the surgery. 10-months later the patient presents to her primary caregiver with visual disturbances and frequent headaches. The patient is found to have a tumor in the left frontal lobe which was diagnosed as a metastatic lesion; primary: breast tumor.
- Could Sevoflurane for the breast tumor excision have caused micrometastasis of cancer?
- What is the most appropriate anesthetic technique for this patient?
- Can certain anesthetic techniques facilitate the metastasis and recurrent of cancer?

Aim

- The aim of this study was to investigate the influence of inhalational anesthetics such as sevoflurane, desflurane, and isoflurane versus total intravenous anesthesia (TIVA) with propofol for patients undergoing primary tumor resection.

Project Questions

- In patient's undergoing primary tumor resection for cancer, how does the use of inhalational anesthetics compare to the intravenous anesthetic Propofol during the perioperative period impact cancer recurrence?
- In the ADU SRNA 2019 cohort, does a 30 minute PowerPoint presentation regarding anesthetic choices to decrease cancer recurrence lead to significant increase in knowledge base?

■ Themes emerged from the literature

- Immunosuppression
- Hypoxia Induced Factors
- Angiogenic Factors
- Metastasis

Literature Review

- Tumor recurrence can occur from the tumor shedding complex circulating tumor cells (CTCs) which lead to micro metastasis (Benzonana et al., 2012; Buckley, McQuaid, Johnson, & Buggy, 2014; Huang et al., 2014; Piegler & Beck-Schimmer, 2016), even with well localized cancer with negative stations (Cassinello et al., 2015; Piegler et al., 2016).
- Distally, CTCs can activate with surgical immunosuppression, leading to the trigger and spread of malignant cells (Cassinello et al., 2015; Kim, 2018; Gottshalk, Sharma, Ford, Durieux, & Tiourrine, 2010; Tavare, Perry, Benzonana, Takata & Ma, 2012).

Literature Review

- The number of CTCs is a prognostic indicator for the severity of cancer, sequelae, and survivability (Lin, Spring, de Souza, MacKenzie & Bokey, 2015; Masuda, Hayashi, Iguchi, Ito, Eguchi & Mimori, 2016; Piegler et al., 2016; Tavare et al., 2012; Tohme, Simmons & Tsung, 2017).
- Perioperative period has been recently studied as a crucial time for impacting survivability of cancer patients (Kim, 2018; Horowitz, Neeman, Sharon & Ben-Elizahu, 2015; Piegler et al., 2016) with inhalational anesthetics versus intravenous anesthetics being a specific target.

Immunosuppression and NK Cells

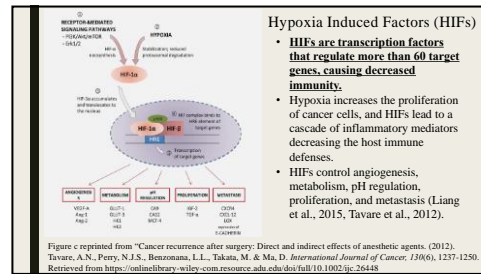
- Natural Killer (NK) cells, part of the innate immune system, normally are the first line of defense in destroying tumor cells, but surgical stress can inhibit the function of NK cells.
- **Sympathetic Nervous System (SNS) activation increases malignant cell propagation and angiogenesis by stimulating the beta receptors and suppressing the NK cells.**
- The SNS releases catecholamines and prostaglandins that cause inflammation, suppress cell mediated immunity (CMI), and increase circulation to the tumor itself (Cassinello et al., 2015; Horowitz et al., 2015; Luo et al., 2015).

Immunosuppression and HPA system

- **The Hypothalamic Pituitary Adrenal Axis (HPA) system is activated by pain, and the stress response releases glucocorticoids leading to inflammation and tumor cell spread.**
- Specific pain agents may affect CMI positively or negatively, but paradoxically pain control will attenuate surgical stress and improve the NK cell count (Meserve, Kaye, Parbhakar, & Urman, 2014).

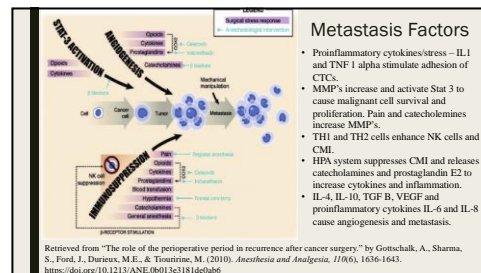
Immunosuppression

- **Inhalational anesthetics have been shown to decrease NK cell count promoting metastasis, whereas propofol has been shown to have anti-inflammatory properties by increasing NK cells and suppressing tumor growth.** (Buckley et al., 2014; Liao et al., 2015; Wigmore, Mohammed & Jhoni, 2016; Zheng et al., 2018).
- A decreased immune response and inflammation leads to a hypoxic environment that increases cancer proliferation and metastasis through cell signaling from hypoxic induced factors (HIFs).



Hypoxic Induced Factors (HIFs)

- Higher levels of HIFs are associated with poorer prognosis and survivability as they stimulate the growth of tumor cells over normal cells.
- **Inhalational anesthetics-sevoflurane and isoflurane upregulate hypoxia-induced factors and can cause tumor cell growth and migration.** (Benzonana et al., 2013; Huang et al., 2014; Liang et al., 2015; Shi et al., 2015).

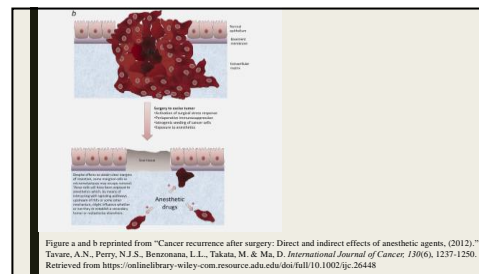
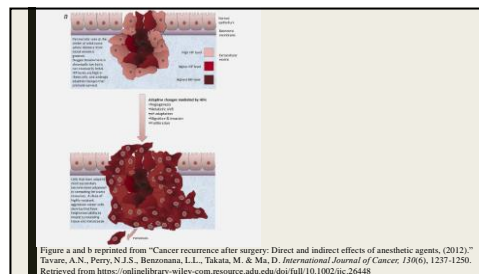


Hypoxic Induced Factors

- **In contrast, propofol suppresses HIFs via impaired translation of messenger RNA decreases tumor seeding and CTC implantation.** (Du et al., 2018; Liang et al., 2015; Quin, Shen, Chen & Chen, 2018; Shi et al., 2015).
- Higher HIF's sets up conditions for angiogenesis, cell proliferation, and metastasis.

Angiogenic Factors

- **Angiogenesis is a multistep biological process that stimulates the development of new blood vessels and tumor metastasis while maintaining existing blood vessels.**
- Angiogenic factors include: Vascular endothelial growth factor (VEGF), Angiopoietin-1 and Angiopoietin-2 (Ang-1 and Ang-2).
- Cancer cell growth is potentiated with VEGF, Ang-1, and Ang-2 which decrease oxygen and nutrients, and provide an ideal environment for cancer growth and increased tumor size (Cassinello et al., 2015; Gottschalk et al., 2010; Huang et al., 2014; Kim, 2018; Piegler et al., 2016).



Metastasis

- Metastasis is affected by Matrix Metalloproteinase-2 and 9 (MMP-2 and MMP-9) by: relaxing the cellular matrix and breaking down the basement membrane to allow for cancer cells to spread into circulation and potentiate distal invasion.
- Cancer cells exposed to isoflurane showed a five-fold increase MMP-2 and MMP-9 which promotes metastasis (Benzonana et al., 2013; Luo et al., 2015).
- Propofol downregulated MMP-9 expression, which reduced the tumor cells' ability to metastasize and spread (Zhang et al., 2013).
- Propofol has also shown anticancer effects on cell lines with the KRAS gene mutation (Song, Shen, Zhang, & Lian, 2014).

Case Study

- Theorized that the brain tumor could have been caused by micrometastasis of the primary breast tumor from the inhalational anesthetic Sevoflurane and activation of the sympathetic nervous system.
- It is possible if TIVA with propofol were used instead of Sevoflurane that no metastasis may have occurred.

Results

- Surgery-induced stress responses and surgical manipulation enhance tumor metastasis via release of angiogenic factors and suppression of NK cells and cell-mediated immunity.
- Intravenous agent, propofol, does not suppress NK cell activity versus volatile anesthetics suppressing NK cell activity, inducing T-lymphocyte apoptosis, and enhancing angiogenesis through HIF activation.
- Intravenous anesthetic agents decrease surgery-induced neuroendocrine responses through the HPA-axis and SNS suppression, and may cause less immunosuppression and recurrence of certain types of cancer compared to volatile anesthetics.

Summary: Impact of Inhalational Agents and Propofol on Cancer Recurrence

- The perioperative period is important for choosing the appropriate anesthetic technique to prevent tumor recurrence and enhance the immune system.
- Inhalational anesthetics may decrease NK cell activity and CMI leading to tumor recurrence following surgery.
- Propofol-based anesthesia may reduce surgical stress, decrease angiogenesis and keeps the immune system in balance in the perioperative period. Propofol shows promising effects on preventing HIF activation.

Limitations

- Research studies are mostly in vitro or retrospective studies with only a few prospective small randomized controlled trials.
- Different multimodal medications utilized could affect outcomes and studies need to be controlled to account for these.

Future Research

- Studies need to control for different multimodal medications.
- Prospective randomized controlled studies with adequate power to confirm the anesthetic selection are needed.
- Several multicenter large randomized control trials are currently in progress.

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Questions?

Appendix D Research Results

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre Test	3.0909	22	1.74326	.37166
	PostTest	8.3636	22	2.05971	.43913

Paired Samples Test									
		Paired Differences						t	df
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference		t	df	Sig. (2-tailed)
					Lower	Upper			
Pair 1	PreTest PostTest	-5.27273	1.31590	.28055	-5.85617	-4.68929	-18.794	21	.000

Note. According to Dr. Roy Lukman: A paired samples t-test was conducted to analyze the data and the obtained t value of – 18.794 is associated with $p < 0.001$ which is statistically significant. Therefore, it can be concluded that the average scores between pre-test and post-test increased significantly.