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Short Note

Malignancy and Inhaled Anesthetics

Filiz Uzumcugil* and Meral Kanbak

Department of Anesthesiology and Reanimation, Hacettepe University School of Medicine, Turkey

***Corresponding author**

Filiz Uzumcugil, Department of Anesthesiology and Reanimation, Hacettepe University School of Medicine, Ankara, Turkey, Tel: 905325659393; Email: filizuzumcugil@hotmail.com

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Abstract

Surgery is the most commonly used treatment for cancer patients, particularly in cases of solid tumors. The perioperative period includes various factors that could adversely affect tumour progression. Tumor growth, progression and recurrence depends on the invasive and metastatic potential of the tumor cells, as well as a normal functioning immune system. It has been demonstrated that surgery and anesthesia exert inhibitory effects on cellular immunity favoring metastasis. Inhalational anesthetics reportedly promote tumorigenesison cancer cells *in vitro*. However, depending on secondary analyses of randomized controlled trials addressing different outcomes and retrospective cohorts, clinical data supportthe use of regional anesthesia/analgesia as a supplement or alternative to general anesthesia with inhalational anesthetics. It is well known that regional anesthesia/analgesia reduces stress responses and reduces the requirement for anesthetic agents and opioids, thereby providing beneficial effects for oncologic patients. Currently available data do not definitively suggest any avoidance or preference for any anesthetic agent or technique for these patients. There are, however, ongoing randomized controlled trials promising definitive results on the subject. It is most likely that simple changes will probably not significantly improve patient survival.

INTRODUCTION

Concern over the effects of anesthetic/analgesic techniques on the outcomes of oncologic patients is not new. While there is enough information to develop some hypotheses on the subject, to date there have been no definitive answer on the cause and effect link to change current clinical practices. Moreover, it is likely that simple changes will not change the outcomes of these patients. The exact mechanism and link are unclear; the relationship is complicated, and the mechanism spectrum is wide. The immune system plays a major role in cancer development, progression and spread. The effects of anesthesia and surgery on the immune system (i.e. suppression) are well known; however, it is difficult to prefer one technique to another.

PATHOGENESIS

Cancer develops with DNA damage and somatic alterations leading to abnormal and unregulated cell proliferation, which can potentially invade other organ systems and lymphatics [1-3]. The damage and consequent alterations can lay dormant until a promoting event occurs. The promoting event may be caused by inflammation, injury, irritation or exposure to other stimulants, all of which result in the recruitment of inflammatory cells, release of chemical mediators, oxidative damage and failure in apoptosis. The defense against these developments primarily provided by the innate immune system, which is already functioning in a healthy host. Cell-mediated immunity, which constitutes this primary defense, include natural killer (NK) cells, cytotoxic T-lymphocytes, dendritic cells and macrophages which destroy the tumor cells to a level of 0.1% viable cells within 24 hours [1-4]. Inflammatory mediators, such as IL-2, IL-4, IL-10, IFN-ɤ and T_H-1 cytokines, enhance the cytotoxic potential of T and NK cells. NK cells constitute the major defense mechanism against tumor cells, thus their decrease in number or function result in metastatic spread and tumor recurrence [1,4-6]. However, even with an intact immune defense, some of these cells evade the immune system. The tumor cells that evade this defense can be kept dormant by the adaptive immune system, which includes both humoral and cell-mediated immunity. However, tumor cells establish a new microenvironment, which actually constitutes an inflammatory state by leukocytes and lymphocytes, secreting cytokines and chemokines [e.g. vascular endothelial growth factor [VEGF] and tumor growth factor [TGF]-β]. The inflammatory cells in this microenvironment may not function properly to eradicate the tumor cells. Moreover, the release of inflammatory mediators can tip the balance towards tumor progression resulting in clinically apparent growth [2,3].

Metastatic cells detach from the primary tumor and proliferate within a distant organ to form a secondary tumor site. Metastasis depends on the evasion of the immune system and the development of new vessels [angiogenesis]. VEGF and PGE_2 released from the tumor microenvironment induce the process of angiogenesis [1-3]. The metastatic cells that detach from the primary site penetrate through the thin walls of the newly developed capillary network to gain access to systemic

circulation, through which they migrate to form a secondary tumor site. Angiogenesis is crucial for metastasis, which is why it has been the target of many treatment protocols [7].

Surgery is accepted as the primary treatment for most solid tumors, however, when the primary tumor is removed, the balance is disrupted and circulating tumor cells are activated. Pro-angiogenic and anti-angiogenic factors are secreted from the microenvironment of the primary tumor, leading to angiogenesis when the pro-angiogenic factors overcome the inhibitors. After the migration to circulation, the inducers rapidly fall and more stable inhibitors [e.g. angiostatin, endostatin and thrombospondin] lead to a more anti-angiogenic environment for newly formed secondary tumor sites. However, when the primary tumor is removed, the inhibitor levels fall, resulting in a pro-angiogenic environment throughout the system. In addition, stress hormones and pro-inflammatory mediators increase with surgery and remain elevated for 3-5 days afterwards. The experimental and clinical data show that surgery inhibits NK cell, B-cell and T-cell function, and decreases the level of dendritic cells, thereby suppressing the cell-mediated-immunity for days after surgery, during which the system will determine whether to establish or eradicate a potential metastasis [4,8,9]. Surgery and the anesthesia-stimulated hypothalamic-pituitary-adrenal axis, as well as the sympathetic nervous system, lead to the well-known stress response, which downregulates cell-mediated immunity, including the primary defense. Pro-inflammatory and anti-inflammatory responses cause immunosuppression, leading to detrimental tumor progression effects [7] [Figure 1]. The stimulation of VEGF, matrix metalloproteinases [MMPs] and NK-cell activity is highlighted in this process because these are the most commonly addressed parameters used to evaluate the relationship between anesthesia and cancer outcomes [10-14].

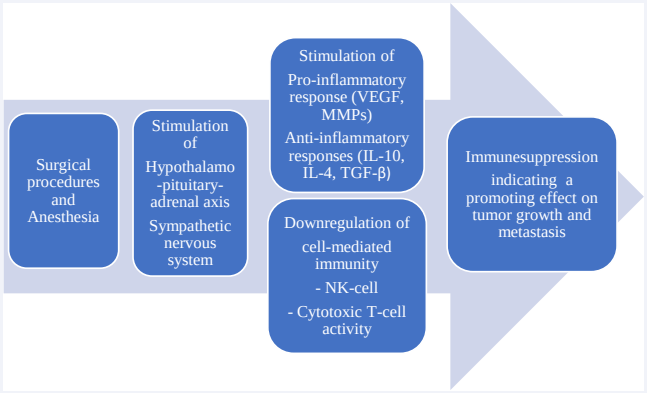

Figure 1 The suggested mechanism of surgery and anesthesia induced immune suppresion promoting tumor growth and metastasis (1,2). (VEGF; vascular endothelial growth factor, MMP; matrix metalloproteinase, NK; natural killer, IL; ınterleukine, TGF; tumor growth factor).

EXPERIMENTAL DATA

During the perioperative period, various factors may result in cancer progression, metastasis and recurrence. Numerous valuable reviews on the subject have addresseddifferent anesthetics, analgesics and techniques in cancer patients [1,5,15-17]. The most problematic anesthetic agents seem to be inhalational agents, although the currently available data are not definitive enough to suggest avoidance. *In vitro* studies and animal studies addressing inhalational anesthetics are summarized in Table 1. The results of these studies primarily describe suppression of the immune defense mechanism against cancer cells [9,18-27]. In an *in vitro* study, Benzonana et al. have reported that isoflurane enhanced the malignant potential of some cells, indicating its protumorigenic effect on the human renal cancer cell line [28]. In a similar *in vitro* study of ovarian cancer, Luo et. al, have reported that isoflurane increased MMP 3 and 9 by five-fold, leading to cell migration and increased VEGF, which led to angiogenesis. In addition, isoflurane increased insulin-like growth factor [IGF] and IGF-1 receptor expression, leading to cell-cycle progression and cell proliferation; and when the IGF-1 receptor signaling was blocked, these effects were reported to disappear [25]. Inhalational anesthetics have also been reported to upregulate hypoxia-inducible factors [HIFs],which mediate pro-angiogenic factors, such as VEGF and platelet-derived growth factor [PDGF], and promote extravasation and chemotaxis [16,29,30]. In an *in vitro* study of prostate cancer cell lines, Huang et al., have investigated the effect of isoflurane, propofol and their combinations on HIF-1α. Isoflurane reportedly upregulated HIF-1α, and propofol reportedly inhibited the HIF-1αinduced by hypoxia, as well as by isoflurane [31]. The serum of patients who have been recruited for a still ongoing clinical trial [NCT00418457], was used for two *in vitro* studies for the effects on oestrogene receptor-negative breast cancer cell lines [32,33]. The sera of patients who received propofol+paravertebral blocks induced apoptosis and inhibited proliferation and migration more than the sera of patients who received sevoflurane+opioid [32,33]. Despite being few in number, some *in vitro* studies have described favorable effects of inhalational anesthetics. Muller-Edenborn et al., have reported that neutrophils pretreated with either desflurane or sevoflurane inhibited MMP-9, leading to the inhibition of migration in colon cancer cell lines [34]. In a similar *in vitro* study by Kvolik et al., sevoflurane reportedly increased apoptosis in colon cancer cells but not in laryngeal cancer cells [21] [Table 1]. However, Xenon demonstrated an inhibitory effect on the migration and release of angiogenic factors in breast carcinoma cells, indicating that all inhalational agents may not exert similar effects on the same cancer types [35].

N_2O is known to have an immune suppressive effect, however, there is no evidence of any aggravating effect on cancer recurrence [36,37].

Inhalational agents have been investigated for their effects on the immune system, and most experimental studies[both animal and *in vitro*] have reported the various aspects of immune system suppression demonstrated by these agents [9,18,19,20,22,23,25,26,36,38]. However, some data indicate that the effects of inhalational agents may depend on the type of cancer being treated [21,34,35].

CLINICAL DATA

Human clinical data primarily depends on the secondary analysis of previous randomized controlled trials, which were actually designed to address different hypotheses, and retrospective cohorts. The types of studies matter, however, ther

Table 1: Experimental data on the relationship between inhalational anesthetics and cancer. IGF; insulin like growth factor, IP3; inositol triphosphate, MMP; matrix metalloproteinase, NK; natural killer.

Reference	Type of study	Cell Type	Inhalational Agent	Outcome
Markovic et al. 1993	Animal (mice)	NK cell	Halothane Isoflurane	Decreased interferone mediated NK cell cytotoxicity
Melamed et al. 2003	Animal (rat)	Breast cancer	Halothane	Decreased NK cell activity
Loop et al. 2005	*In vitro*	Human T-lymphocytes	Sevoflurane Isoflurane	Induction of apoptosis in T-lymphocytes
Wei et al. 2008	*In vitro*	Chicken-derived B-lymphocytes	Isoflurane	Induction of apoptosis in B-lymphocytes via activation of IP_3
Kvolik et al. 2009	*In vitro*	Colon adenocarcinoma Laryngeal cancer cells	Sevoflurane	Increased apoptosis via expression of P53 and caspase-3 in colon cancer cells. Decreased the expression in laryngeal cancer cells.
Deegan et al. 2009	*In vitro* (serum of patients undergoing breast cancer surgery was used)	Breast cancer cells (Oestrogene receptor negative)	Sevoflurane	Serum of patients receiving propofol+paravertebral block inhibited proliferation but not migration, compared to patients' receiving sevoflurane+opioid
Yuki et al. 2010	*In vitro*	Lymphocyte function-associated antigen-1 (LFA-1).	Sevoflurane Isoflurane	Block activation-dependent conformational changes of LFA-1 (May be one of the pathways of immunomodulation induced by anesthesia)
Huitink et al. 2010	*In vitro*	Breast Carcinoma Neuroblastoma	Enflurane Isoflurane Desflurane Halothane Sevoflurane N_2O	Modulation in gene expression
Kawaraguchi et al. 2011	*In vitro*	Human colon cancer cells	Isoflurane	Resistance to apoptosis via caveolin-1 (Cav-1) dependent mechanism
Jun et al. 2011	*In vitro*	Head and Neck squamous cell carcinoma cells	Isoflurane	Enhancement in tumour development and promote metatasis
Muller-Edenborn et al. 2012	*In vitro*	Colon cancer cells	Sevoflurane Desflurane	Neutrophils pretreated by inhalational agents inhibited MMP-9 leading to inhibition of migration
Benzonana et al. 2013	*In vitro*	Renal Cancer cells	Isoflurane	Enhance migration via HIF
Ash et al. 2014	*In vitro*	Breast adenocarcinoma	Xenon Sevoflurane	Xenon, but not sevoflurane, reduced migration and release of pro-angiogenic factors.
Buckley et al. 2014	*In vitro* (serum of patients undergoing breast cancer surgery was used-NCT00418457)	Breast cancer cells (Oestrogen and progesterone receptor-positive) Healthy primary NK cells	Sevoflurane	Serum of patients receiving propofol+paravertebral block showedgreater human donor NK cell cytotoxicity*in vitro* more than patients' receiving sevoflurane+opioid analgesia
Jaura et al. 2014	*In vitro* (serum of patients undergoing breast cancer surgery was used-NCT00418457)	Breast cancer cells (Oestrogene receptor negative)	Sevoflurane	Serum of patients receiving propofol+paravertebral block induced apoptosis *in vitro* more than patients' receiving sevoflurane+opioid analgesia
Huang et al. 2014	*In vitro*	Prostate cancer cells	Isoflurane	Isoflurane upregulates HIF-1α
Shi QY, et al. 2015	*In vitro*	Glioma stem cells	Sevoflurane	Increased proliferation and renewal capacity of cancer cells via HIF
Luo et al. 2015	*In vitro*	Ovarian cancer cells	Isoflurane	Increased tumorigenic (IGF-1 and IGF-1 rec.) and angiogenic markers (VEGF, angiopoietin-1) Increased MMP 2 and 9
Xu et al. 2016	*In vitro* (serum of patients undergoing colon cancer surgery was used)	LoVo colon cancer cell culture	Sevoflurane	Serum of patients receiving propofol+thoracal epidural inhibited proliferation and invasion and induced apoptosis *in vitro* more than patients' receiving sevoflurane+opioid analgesia
Iwasaki et al. 2016	*In vitro*	Ovarian cancer	Isoflurane Desflurane Sevoflurane	Inhalational anesthetics enhanced metastatic potential via increasing VEGF-C, MMP-11, TGF-β

Table 2: Clinical data comparing general anesthesia maintained by an inhalational anesthetics with either regional anesthesia/analgesia or general anesthesia maintained by total intravenous anesthesia.

Reference	Type of study	Cancer Type	Anesthetic techniques using Inhalational Anesthetics	Outcome
Deegan et al. 2010	RCT	Breast Carcinoma	Sevoflurane+opioidvs Propofol+PVB	Propofol+PVB reduced IL-1β and MMP 3 and 9, and increased IL-10
Looney et al. 2010	RCT	Breast Carcinoma	Sevoflurane+morphine vs Propofol+paravertebral block	Sevoflurane+morphine increased VEGF-C
Ismail et al. 2010	Retrospective	Brachytherapy for cervix carcinoma	Neuroaxial anesthesia vs GA	No difference in tumor recurrence or survival
Lin et al. 2011	Retrospective	Ovarian serous adenocarcinoma	Epidural anesthesia and analgesia (AA) vs Sevoflurane+ fentanyl PCA	Epidural AA increased 3 and 5-year overall survival
Gottschalk et al. 2012	Retrospective	Lymph node dissection for malignant melanoma	Spinal anesthesia vs Sevoflurane+sufentanyl vs Propofol+remifentanil (TIVA)	No significant but better cumulative survival rate for patients receiving spinal anesthesia
Lai et al. 2012	Retrospective	Radiofrequency ablation of small hepatocellular carcinoma	Epidural anesthesia vs GA	GA reduced the recurrence No difference in overall survival
Xu et al. 2014	RCT	Colon Carcinoma	Sevoflurane vs propofol+epidural anesthesia	Volatile-based anesthesia increased VEGF-C and TGF-β1
Desmond et al. 2015	RCT (specimens of patients undergoing breast cancer surgery was used-NCT00418457)	Breast Carcinoma	Sevoflurane+opioid vs propofol+paravertebral block	Specimens of patients receiving propofol+paravertebral block were infiltrated by NK and T helper cell, , than patients' receiving sevoflurane+opioid analgesia
Cho et al. 2017	RCT	Breast Carcinoma	Sevoflurane+remifentanil+postoperative fentanyl vs propofol+remifentanil+postoperative ketorolac	Propofol+remifentanil+postoperative ketorolac preserved NK-cell cytotoxicity

Table 3: The ongoing trials comparing inhalational anesthetics with intravenous anesthetics in terms of their effects on cancer.

NCT Number	Type of Cancer	Interventions	Primary Outcome	Secondary Outcome
03034096	Cancer resection surgery	Inhalational Anesthetic (Isoflurane, sevoflurane or desflurane) vs Propofol	All cause mortality	Recurrence-free survival (RFS)
02335151	Pancreatic adenocarcinoma	Desflurane vs Propofol	Circulating tumor cells (CTC)	Kinetics of CTC Months to tumor recurrence Number of surviving patients (1 year)
02839668	Breast cancer	Sevoflurane vs Sevoflurane+lidocaine vs Propofol vs Propofol+lidocaine	VEGF-A	Pain score Survival (5-year) VEGFR-1 and VEGFR-2 density
01975064	Breast cancer Colon cancer Rectal cancer	Sevoflurane vs Propofol	Overall survival (OS) (5-year)	OS (1 year)
00418457	Breast cancer	GA (mostly sevoflurane)+opioid vs RA (either epidural or paravertebral)+propofol	Recurrence rate (10-year)	Postsurgical pain
02567929	Breast cancer	Sevoflurane vs Propofol	NK cell activity	Changes of percentage of CD39 and CD73 T_H activity
02567942	Colon cancer	Sevoflurane vs Propofol	NK cell activity	Changes of percentage of CD39 and CD73 T_H activity
02660411	Cancer surgery	Sevoflurane vs Propofol	3-year survival	Survival rates (1^{st}, 2^{nd}, 3^{rd} year) 3-year RFS RFS rates (1^{st}, 2^{nd}, 3^{rd} year) Quality of life
02758249	Breast cancer	Sevoflurane vs Propofol	NK cell and CD8+ T cell	Cancer cell (MCF-7) apoptosis
02005770	Breast cancer	Sevoflurane vs Propofol	Cirulating tumor cells (CTC)	-

are also numerous confounders, such as the stage of cancer at the time of surgery, underlying tumor biology, surgical skill of the clinicians and effects of the perioperative adjuvant therapies. General anesthesia, with or without regional anesthesia and/or analgesia, was compared in these studies. Inhalational anesthetics were usually combined with an opioid or local anesthetic; few trials have suggested an independent effect of inhalational anesthetics on human cancer cells [39-47] [Table 2].

In studies addressing breast carcinoma, sevoflurane was compared with total intravenous anesthesia in patients undergoing surgery [39,40,47]. Sevoflurane was reported to induce pro-angiogenic factors,such as MMP and VEGF [39,40]. There is a large multi-center international ongoing trial [NCT00418457] investigating patients with Stage 1-3 breast cancer undergoing mastectomy;cancer recurrence is the primary end-point [48]. The specimens of these patients were examined for their effects on immunity. Propofol combined with PVB was found to show a greater infiltrationof cancer specimens with NK-cells and $T_H$cell compared to general anesthesia with sevoflurane combined with an opioid [46]. In a small RCT, Xu et al. have reported that sevoflurane increased VEGF-C and TGF-β1 in patients undergoing surgery for colon cancer [45]. Recently, Cho et al., have reported that anesthesia maintained by total intravenous agents preserved NK-cell toxicity more than sevoflurane-based general anesthesia in colon cancerpatients[47].

ONGOING CLINICAL TRIALS

Currently, we do nothave definitive evidence on the cause and effect link between anesthesia and/or analgesia techniques and cancer outcomes. However, ongoing randomized controlled trials will provide results within a few years. These trials can be placed in two groups: one group evaluating a volatile agent against propofol and another group evaluating regional anesthesia/analgesia during and after surgery[15,48]. The ongoing clinical trials comparing inhalational agents with intravenous anestheticswere obtained from ClinicalTrials gov [using the search items of 'cancer; sevoflurane, desflurane, propofol, regional anesthesia] and are summarized in Table 3. The trials that did not specify general anesthesia as intravenous or inhalational anesthetics or used both in their general anesthesia groups were not included, and only the trials that have started recruiting patients were included in our summary in Table 3.

CONCLUSION

Until we gain definitive answers, we know that there is some evidence supporting the use of regional anesthesia alone or general anesthesia with propofol supplemented with regional anesthesia in oncologic patients over general anesthesia with inhalational anesthetics.

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